Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE

INVENCIÓN

TITULO: SALES COMPUESTOS DE TETRAHIDROPIRIDO-PIRIDINA Y TETRAHIDROPIRIDO-PIRIMIDINA Y SU USO COMO MODULADORES DE RECEPTORES DE C5A

SOLICITANTE: NOVARTIS AG,

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-014580- -00000-0000

Fecha: 2014-01-24 17:17:07 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 6

DIRECCIÓN: Lichtstrasse 35 CH-4056 Basel, Zuisa

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 22 de enero de 2014

P2014/000011

OLARTEMOURE

OLARTE MOURE & ASOC

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-014580- -00000-0000

Fecha: 2014-01-24 17:17:07 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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Industria y Comercio
SUPERINTENDENCIA

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2014/000011**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-4056 Basel
Nacionalidad o Domicilio: Suiza
Lugar de Constitución: Suiza
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

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

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

INVENTOR (ES) (72)

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2012/047617 Fecha Julio 20, 2012

Publicación Internacional No. WO 2013/016197 A1 Fecha Enero 31, 2013

(6) **Título (54) COMPUESTOS DE TETRAHIDROPIRIDO-PIRIDINA Y TETRAHIDROPIRIDO-PIRIMIDINA Y SU USO COMO MODULADORES DE RECEPTORES DE C5A**

Clasificación Internacional (51) C07D 471/04, A61K 31/4375, A61K 31/519, A61P 27/02, A61P37/00

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Julio 22, 2011	61/510,643
US	Septiembre 27, 2011	61/539,732

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

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.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Declaraciones. Declaración bajo la regla 4.17 (ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

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Nacionalidad: Estadounidense

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

6

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 008098

Bogotá D.C., Enero 24 de 2014 - 11:49:38

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	601308934	24/01/2014	8.186.700.00

*** Conceptos Pagados ***

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

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

Responsable: _____
-*****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-014580- -00000-0000

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Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: 2014 01 24 (AAAA MM DD)	Recorrido:
2020	2014	4

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

Radicador: | Planilla:

ID	No. Radicación	Consecutivo	Item
1	14-14580	0	7
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

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

Observaciones:
EL CD ANEXO CONTIENE UN TOTAL DE 7 ARCHIVOS
7 EN PDF, LOS CUALES FUERON PROCESADOS.

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2014/000011**

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

[X] Capítulo I. [ ] Capítulo II.

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Nacionalidad o Domicilio: Suiza
Lugar de Constitución: Suiza
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Nacionalidad: Estadounidense

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250 Massachusetts Avenue
Cambridge, MA 02139
Estados Unidos de America
Nacionalidad: Estadounidense

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

Nota del traductor:

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

CERTIFICACIÓN NOTARIAL

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

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

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

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

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

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

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

Mi licencia vence el 11 de Marzo de 2009.

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

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

Certificación:

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

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

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

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

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

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

Signature/Firma:

Arthur Canonica

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

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

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

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

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

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

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

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

M. Staehelin Notar

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

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

Leg.Prot.Nr. 975 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

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

Certified 24. May. 2006

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. 2'049'13'389
9. Seal / stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 January 2013 (31.01.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/016197 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 27/02* (2006.01)
A61K 31/4375 (2006.01) *A61P 37/00* (2006.01)
A61K 31/519 (2006.01)

(21) International Application Number:
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(22) International Filing Date:
20 July 2012 (20.07.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/510,643 22 July 2011 (22.07.2011) US
61/539,732 27 September 2011 (27.09.2011) US

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(72) Inventors; and

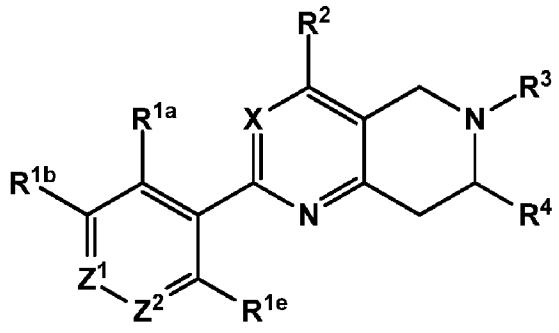
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[Continued on next page]

(54) Title: TETRAHYDROPYRIDO-PYRIDINE AND TETRAHYDROPYRIDO-PYRIMIDINE COMPOUNDS AND USE THEREOF AS C5A RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention provides a compound of formula I: (I) a method for manufacturing the compounds of the invention, and its therapeutic uses. The present invention further provides a combination of pharmacologically active agents and a pharmaceutical composition.

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TETRAHYDROPYRIDO-PYRIDINE AND TETRAHYDROPYRIDO-PYRIMIDINE COMPOUNDS AND USE THEREOF AS C5A RECEPTOR MODULATORS

FIELD OF THE INVENTION

This invention relates generally to tetrahydropyrido-pyridine, tetrahydropyrido-pyrimidine and related heterocyclic compounds that act as modulators of mammalian complement C5a receptors, and to pharmaceutical compositions comprising such modulators. The present invention further relates to the use of such modulators in treating a variety of inflammatory and immune system disorders and as probes for the localization of C5a receptors.

BACKGROUND OF THE INVENTION

The complement system is a crucial component of the innate immunity system and comprises a group of proteins that are normally present in an inactive state. These proteins are organized in three activation pathways: the classical, the lectin, and the alternative pathways (V. M. Holers, In Clinical Immunology: Principles and Practice, ed. R.R. Rich, Mosby Press; 1996, 363-391). Molecules from microorganisms, antibodies or cellular components can activate these pathways resulting in the formation of protease complexes known as the C3-convertase and the C5-convertase. The classical pathway is a calcium/magnesium-dependent cascade, which is normally activated by the formation of antigen-antibody complexes. It can also be activated in an antibody-independent manner by the binding of C-reactive protein complexed to ligand and by many pathogens including gram-negative bacteria. The alternative pathway is a magnesium-dependent cascade which is activated by deposition and activation of C3 on certain susceptible surfaces (e.g., cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials).

C5a, a 74 amino acid peptide, is generated in the complement cascade by the cleavage of the complement protein C5 by the complement C5 convertase enzyme. C5a has both anaphylatoxic (*e.g.,* bronchoconstricting and vascular spasmogenic) and chemotactic effects. Therefore, it is active in engendering both the vascular and cellular phases of inflammatory responses. Because it is a plasma protein and, therefore, generally almost instantly available at a site of an inciting stimulus, it is a key mediator in terms of initiating the complex series of events that results in augmentation and amplification of an initial inflammatory stimulus. The anaphylatoxic and chemotactic effects of the C5a peptide are believed to be mediated through its interaction with the C5a receptor (CD88 antigen), a 52 kD membrane bound G-protein coupled receptor (GPCR). C5a is a potent chemoattractant for polymorphonuclear leukocytes, bringing neutrophils, basophils, eosinophils and monocytes to sites of inflammation and/or cellular injury. C5a is one of the most potent chemotactic agents known for a wide variety of inflammatory cell types. C5a also "primes" or prepares neutrophils for various antibacterial functions

(*e.g.,* phagocytosis). Additionally, C5a stimulates the release of inflammatory mediators (*e.g.,* histamines, TNF-α, IL-1, IL-6, IL-8, prostaglandins, and leukotrienes) and the release of lysosomal enzymes and other cytotoxic components from granulocytes. Among its other actions, C5a also promotes the production of activated oxygen radicals and the contraction of smooth muscle.

Macular degeneration is a clinical term that is used to describe a family of diseases that are characterized by a progressive loss of central vision associated with abnormalities of Bruch's membrane, the choroid, the neural retina and/or the retinal pigment epithelium. In the center of the retina is the macula lutea, which is about 1/3 to ½ cm in diameter. The macula provides detailed vision, particularly in the center (the fovea), because the cones are higher in density and because of the high ratio of ganglion cells to photoreceptor cells. Blood vessels, ganglion cells, inner nuclear layer cells, and the plexiform layers are all displaced to the side (rather than resting above the photoreceptor cells), thereby allowing light a more direct path to the cones. Under the retina is the choroid, a part of the uveal tract, and the retinal pigmented epithelium (RPE), which is between the neural retina and the choroid. The choroidal blood vessels provide nutrition to the retina and its visual cells.

Age-related macular degeneration (AMD), the most prevalent form of macular degeneration, is associated with progressive loss of visual acuity in the central portion of the visual field, changes in color vision, and abnormal dark adaptation and sensitivity. Two principal clinical manifestations of AMD have been described as the dry, or atrophic, form and the neovascular, or exudative, form. The dry form is associated with atrophic cell death of the central retina or macula, which is required for fine vision used for activities such as reading, driving or recognizing faces. About 10-20% of these AMD patients progress to the second form of AMD, known as neovascular AMD (also referred to as wet AMD).

Neovascular AMD is characterized by the abnormal growth of blood vessels under the macula and vascular leakage, resulting in displacement of the retina, hemorrhage and scarring. This results in a deterioration of sight over a period of weeks to years. Neovascular AMD cases originate from intermediate or advanced dry AMD. The neovascular form accounts for 85% of legal blindness due to AMD. In neovascular AMD, as the abnormal blood vessels leak fluid and blood, scar tissue is formed that destroys the central retina.

The new blood vessels in neovascular AMD are usually derived from the choroid and are referred to as choroidal neovascularizaton (CNV). The pathogenesis of new choroidal vessels is poorly understood, but such factors as inflammation, ischemia, and local production of angiogenic factors are thought to be important. A published study suggests that CNV is caused by complement activation in a mouse laser model (Bora P.S., J. Immunol. 2005;174; 491-497).

Human genetic evidence implicates the involvement of the complement system, particularly the alternative pathway, in the pathogenesis of Age-related Macular Degeneration (AMD). Significant

associations have been found between AMD and polymorphisms in complement factor H (CFH) (Edwards AO, et al. Complement factor H polymorphism and age-related macular degeneration. Science. 2005 Apr 15;308(5720):421-4; Hageman GS, et al A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A. 2005 May 17;102(20):7227-32; Haines JL, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005 Apr 15;308(5720):419-21; Klein RJ, et al Complement factor H polymorphism in age-related macular degeneration. Science. 2005 Apr 15;308(5720):385-9; Lau LI, et al. Association of the Y402H polymorphism in complement factor H gene and neovascular age-related macular degeneration in Chinese patients. Invest Ophthalmol Vis Sci. 2006 Aug;47(8):3242-6; Simonelli F, et al. Polymorphism p.402Y>H in the complement factor H protein is a risk factor for age related macular degeneration in an Italian population. Br J Ophthalmol. 2006 Sep;90(9):1142-5; and Zareparsi S, et al Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. Am J Hum Genet. 2005 Jul;77(1):149-53.), complement factor B (CFB) and complement C2 (Gold B, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet. 2006 Apr;38(4):458-62 and Jakobsdottir J, et al. C2 and CFB genes inage-related maculopathy and joint action with CFH and LOC387715 genes. PLoS One. 2008 May 21;3(5):e2199), and most recently in complement C3 (Despriet DD, et al Complement component C3 and risk of age-related macular degeneration. Ophthalmology. 2009 Mar;116(3):474-480.e2; Maller JB, et al Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet. 2007 Oct;39(10):1200-1 and Park KH, et al Complement component 3 (C3) haplotypes and risk of advanced age-related macular degeneration. Invest Ophthalmol Vis Sci. 2009 Jul;50(7):3386-93. Epub 2009 Feb 21.). Taken together, the genetic variations in the alternative pathway components CFH, CFB, and C3 can predict clinical outcome in nearly 80% of cases.

Currently there is no proven medical therapy for dry AMD and many patients with neovascular AMD become legally blind despite current therapy with anti-VEGF agents such as Lucentis. Thus, it would be desirable to provide therapeutic agents for the treatment or prevention of complement mediated diseases and particularly for the treatment of AMD.

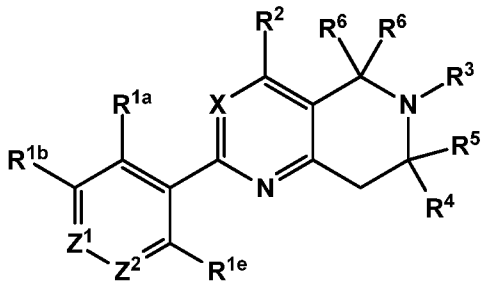
SUMMARY OF THE INVENTION

The present invention provides compounds that modulate, and preferably inhibit, C5a receptor activation and/or C5a receptor-mediated signal transduction. Such C5a receptor modulators are preferably high affinity C5a receptor ligands and act as antagonists (*e.g.,* inverse agonists) of complement

C5a receptors, such as human C5a receptors. Within certain aspects, C5a receptor modulators provided herein are tetrahydropyrido-pyridines and tetrahydropyrido-pyrimidines.

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

Within certain aspects, C5a receptor_modulators provided herein are compounds of Formula I and salts thereof:



(I)

wherein

X is N or CH;

Z^1 is N or CR^{1c};

Z^2 is N or CR^{1d}, wherein at least one of Z^1 and Z^2 is not N;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy, cyano or halogen;

R^{1b} is selected from the group consisting of hydrogen, amino, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and mono- and di-C_1-C_4alkylamino;

R^{1c} is hydrogen, halogen or C_1-C_6alkyl;

R^{1d} is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{1e} is selected from hydrogen, halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy and haloC_1-C_6alkoxy; or

R^{1a} and R^{1b} taken in combination form a 5 member saturated or unsaturated heterocyclic ring having one or two ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 independently selected C_1-C_6alkyl or halogen substituents;

wherein at least one of R^{1a} and R^{1e} is not hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl and $(CH_2)_pNR^{2a}R^{2b}$, wherein each alkyl and alkoxy group is substituted with 0 or 1 substituents selected from the group consisting of hydroxy, halogen, and C_1-C_4alkoxy;

p is 0 or 1;

R^{2a} is hydrogen, C_1-C_6alkyl or hydroxyC_1-C_6alkyl;

R^{2b} is hydrogen, C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_4alkyl, wherein each alkyl is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxycarbonyl, or heterocycle wherein the heterocycle is a saturated, unsaturated or aromatic five or six member ring having 1 or 2 ring heteroatoms selected from N, O or S and is unsubstituted or substituted with 1 or 2 independently selected C_1-C_4alkyl substituents; or

$NR^{2a}R^{2b}$ taken in combination form a 4 to 8 member saturated heterocyclic ring system having 1 or 2 rings and 0 or 1 additional ring heteroatoms selected from N, O or S, the saturated heterocyclic ring system is unsubstituted or substituted with 1-4 substituents independently selected from the group consisting of C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxyC_1-C_4alkyl, hydroxyC_1-C_4alkyl, halogen, amino, mono- and di-C_1-C_4alkylamino, C_1-C_4alkoxycarbonyl, C_1-C_4alkanoyl, $S(O)_2C_1$-C_4alkyl, and $CH_2C(O)NH_2$;

R_3 is selected from the group consisting of substituted phenyl, substituted heteroaryl, and phenylC_1-C_3alkyl, wherein the heteroaryl is selected from pyridyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, and isoxazolyl, and wherein each phenyl or heteroaryl group is substituted with 1, 2 or 3 substituents which are independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, C_3-C_6cycloalkyl, and saturated oxacycle having 4, 5, or 6 ring atoms and one ring oxygen, which oxacycle is unsubstituted or substituted with 1 or 2 independently selected C_1-C_4alkyl substituents, and wherein each phenyl or heteroaryl comprises at least one non-hydrogen substituent *ortho* to the point of attachment to the remainder of the compound of formula (I);

R_4 is hydrogen or C_1-C_4alkyl;

R^5 is hydrogen; or

R^4 and R^5 taken in combination are oxo; and

R^6 is hydrogen at each occurrence or CR^6_2, taken in combination, form a divalent carbonyl.

In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the definition of formula (I) or sub formulae thereof and one or more pharmaceutically acceptable carriers.

In another embodiment, the invention provides a combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to the definition of formula (I) or sub formulae thereof and one or more therapeutically active agents.

The invention further provides methods of treating or preventing complement mediated diseases, the method comprising the steps of identifying a patient in need of complement modulation therapy and

administering a compound of Formula (I) or a sub formulae thereof. Complement mediated diseases include ophthalmic diseases (including early or neovascular age-related macular degeneration and geographic atrophy), autoimmune diseases (including arthritis, rheumatoid arthritis), Respiratory diseases, cardiovascular diseases.

Other aspects of the invention are discussed *infra*.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. illustrates the x-ray powder diffraction patterns of Example 19-F from MTBE.

FIG. 2. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 19-F from MTBE.

FIG. 3. illustrates the x-ray powder diffraction patterns of Example 19-F from Me-THF.

FIG. 4. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 19-F from Me-THF.

FIG. 5. illustrates the x-ray powder diffraction patterns of Example 19-F of the initial precipitate (upper pattern) and dried material (lower pattern) from Me-THF.

FIG. 6. illustrates the x-ray powder diffraction patterns of Example 19-F from toluene.

FIG. 7. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 19-F from toluene.

FIG. 8. illustrates the x-ray powder diffraction patterns of Example 19-F from EtOAc.

FIG. 9. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 19-F from EtOAc.

FIG. 10. overlays the x-ray powder diffraction patterns of Example 19-F solid forms.

FIG. 11. illustrates the x-ray powder diffraction patterns of Example 19-F Hydrochloride Form A.

FIG. 12. illustrates the thermogravimetric analysis (TGA) of Example 19-F Hydrochloride Form A (5°C/min heating rate).

FIG. 13. illustrates the non-hermetic differential scanning calorimetry (DSC) of Example 19-F Hydrochloride Form A: (5°C/min heating rate).

FIG. 14. illustrates the hermetic differential scanning calorimetry (DSC) of Example 19-F Hydrochloride Form A (5°C/min heating rate).

FIG. 15. illustrates the x-ray powder diffraction patterns of two scans of Example 19-F Hydrochloride Form B compared to one scan of Form A.

FIG. 16. illustrates the thermogravimetric analysis (TGA) of Example 19-F Hydrochloride Form B (5°C/min heating rate).

FIG. 17. illustrates the non-hermetic differential scanning calorimetry (DSC) of Example 19-F Hydrochloride Form B (5°C/min heating rate).

FIG. 18. illustrates the x-ray powder diffraction patterns of Example 19-F Phosphate Form A.

FIG. 19. illustrates the hermetic differential scanning calorimetry (DSC) of Example 19-F Phosphate Form A (10°C/min heating rate).

FIG. 20. illustrates the x-ray powder diffraction patterns of Example 19-F Phosphate Form B with Example 19-F Phosphate Form A for comparison.

FIG. 21. illustrates the hermetic differential scanning calorimetry (DSC) of Example 19-F Phosphate Form B (10°C/min heating rate).

FIG. 22. illustrates the x-ray powder diffraction patterns of Example 19-F Phosphate Form C.

FIG. 23. illustrates the non-hermetic differential scanning calorimetry (DSC) of Example 19-F Phosphate Form C (10°C/min heating rate).

FIG. 24. illustrates the thermogravimetric analysis (TGA) of Example 19-F Phosphate Form C (10°C/min heating rate).

FIG. 25. Comparison of amorphous, hydrochloride and phosphate forms of Example 19-F of Plasma AUC measured after rat PK.

FIG. 26. illustrates the x-ray powder diffraction patterns of Example 55-G from 10% EtOAc in heptane.

FIG. 27. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 55-G from 10% EtOAc in heptane.

FIG. 28. illustrates the x-ray powder diffraction patterns of Example 55-G from 50% MeOH in water.

FIG. 29. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 55-G from 50% MeOH in water showing 6.6% weight loss.

FIG. 30. illustrates sealed pan differential scanning calorimetry (DSC) of Example 55-G from 50% MeOH in water showing true melting point.

FIG. 31. illustrates the x-ray powder diffraction patterns of Example 55-G sulfate.

FIG. 32. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 55-G sulfate.

FIG. 33. illustrates the x-ray powder diffraction patterns of Example 55-G tosylate.

FIG. 34. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 55-G tosylate.

FIG. 35. illustrates the x-ray powder diffraction patterns of Example 55-G besylate.

FIG. 36. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 55-G besylate.

FIG. 37. illustrates the x-ray powder diffraction patterns of Example 55-G MTBE solvate.

FIG. 38. illustrates the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of Example 55-G MTBE solvate.

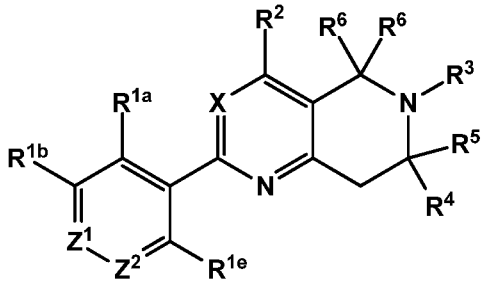
FIG. 39. illustrates a comparison of different forms of Example 55-G of Plasma AUC measured after rat PK.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention provides tetrahydropyrido-pyrimidines, tetrahydropyridopyridines and related heterocyclic compounds that modulate C5a receptor activation and/or C5a receptor-mediated signal transduction. Such compounds may be used *in vitro* or *in vivo* to modulate (preferably inhibit) C5a receptor activity (sometimes referred to hereinafter as C5aR) in a variety of contexts.

In a first embodiment, the invention provides compounds of Formula I and pharmaceutically acceptable salts thereof, which modulate the complement system. More particularly, the compounds of the invention modulate the C5a mediated response induced by activation of any one of the classical, alternative or lectin pathways of the complement system.

In a first embodiment, compounds of Formula I and salts thereof are provided which are represented by the structure:



(I)

wherein

X is N or CH;

Z^1 is N or CR^{1c};

Z^2 is N or CR^{1d}, wherein at least one of Z^1 and Z^2 is not N;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy, cyano or halogen;

R^{1b} is selected from the group consisting of hydrogen, amino, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and mono- and di-C_1-C_4alkylamino;

R^{1c} is hydrogen, halogen or C_1-C_6alkyl;

R^{1d} is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{1e} is selected from hydrogen, halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy and haloC_1-C_6alkoxy; or

R^{1a} and R^{1b} taken in combination form a 5 member saturated or unsaturated heterocyclic ring having one or two ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 independently selected C_1-C_6alkyl or halogen substituents;

wherein at least one of R^{1a} and R^{1e} is not hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl and $(CH_2)_pNR^{2a}R^{2b}$, wherein each alkyl and alkoxy group is substituted with 0 or 1 substituents selected from the group consisting of hydroxy, halogen, and C_1-C_4alkoxy;

p is 0 or 1;

R^{2a} is hydrogen, C_1-C_6alkyl or hydroxyC_1-C_6alkyl;

R^{2b} is hydrogen, C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_4alkyl, wherein each alkyl is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxycarbonyl, or heterocycle wherein the heterocycle is a saturated, unsaturated or aromatic five or six member ring having 1 or 2 ring heteroatoms selected from N, O or S and is unsubstituted or substituted with 1 or 2 independently selected C_1-C_4alkyl substituents; or

$NR^{2a}R^{2b}$ taken in combination form a 4 to 8 member saturated heterocyclic ring system having 1 or 2 rings and 0 or 1 additional ring heteroatoms selected from N, O or S, the saturated heterocyclic ring system is unsubstituted or substituted with 1-4 substituents independently selected from the group consisting of C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxyC_1-C_4alkyl, hydroxyC_1-C_4alkyl, halogen, amino, mono- and di-C_1-C_4alkylamino, C_1-C_4alkoxycarbonyl, C_1-C_4alkanoyl, $S(O)_2C_1$-C_4alkyl, $CH_2C(O)(C_1$-C_4alkoxy) and $CH_2C(O)NH_2$;

R_3 is selected from the group consisting of substituted phenyl, substituted heteroaryl, and phenylC_1-C_3alkyl, wherein the heteroaryl is selected from pyridyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, and isoxazolyl, and wherein each phenyl or heteroaryl group is substituted with 1, 2 or 3 substituents which are independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, C_3-C_6cycloalkyl, and saturated oxacycle having 4, 5, or 6 ring atoms and one ring oxygen, which oxacycle is unsubstituted or substituted with 1 or 2 independently selected C_1-C_4alkyl substituents, and wherein each phenyl or heteroaryl comprises at least one non-hydrogen substituent *ortho* to the point of attachment to the remainder of the compound of formula (I);

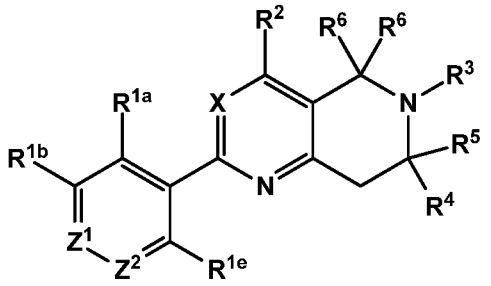
R_4 is hydrogen or C_1-C_4alkyl;

R^5 is hydrogen; or

R^4 and R^5 taken in combination are oxo; and

R^6 is hydrogen at each occurrence or CR^6_2, taken in combination, form a divalent carbonyl.

In another embodiment, compounds of Formula I and salts thereof are provided which are represented by the structure:



(I)

wherein

X is N or CH;

Z^1 is N or CR^{1c};

Z^2 is N or CR^{1d}, wherein at least one of Z^1 and Z^2 is not N;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy, cyano or halogen;

R^{1b} is selected from the group consisting of hydrogen, amino, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and mono- and di-C_1-C_4alkylamino;

R^{1c} is hydrogen, halogen or C_1-C_6alkyl;

R^{1d} is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{1e} is selected from hydrogen, halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy and haloC_1-C_6alkoxy, sulfone, C_3-C_7cycloalkyl; or

R^{1a} and R^{1b} taken in combination form a 5 member saturated or unsaturated heterocyclic ring having one or two ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 independently selected C_1-C_6alkyl or halogen substituents;

wherein at least one of R^{1a} and R^{1e} is not hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl and $(CH_2)_pNR^{2a}R^{2b}$, wherein each alkyl and alkoxy group is substituted with 0 or 2 substituents selected from the group consisting of hydroxy, halogen, and C_1-C_4alkoxy, amino, mono- and di-C_1-C_4 alkylamino;

p is 0 or 1;

R^{2a} is hydrogen, C_1-C_6alkyl or hydroxyC_1-C_6alkyl;

R^{2b} is hydrogen, C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_4alkyl, wherein each alkyl is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxycarbonyl, or heterocycle wherein the heterocycle is a saturated, unsaturated or aromatic five or six member ring having 1 or 2 ring heteroatoms selected from N, O or S and is unsubstituted or substituted with 1 or 2 independently selected C_1-C_4alkyl substituents; or

$NR^{2a}R^{2b}$ taken in combination form a 4 to 8 member saturated heterocyclic ring system having 1 or 2 rings and 0 or 1 additional ring heteroatoms selected from N, O or S, the saturated heterocyclic ring system is unsubstituted or substituted with 1-4 substituents independently selected from the group consisting of C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxyC_1-C_4alkyl, hydroxyC_1-C_4alkyl, halogen, amino, mono- and di-C_1-C_4alkylamino, C_1-C_4alkoxycarbonyl, C_1-C_4alkanoyl, $S(O)_2C_1$-C_4alkyl, $CH_2C(O)(C_1$-C_4alkoxy) and $CH_2C(O)NH_2$;

R_3 is selected from the group consisting of substituted phenyl, substituted heteroaryl, and phenylC_1-C_3alkyl, wherein the heteroaryl is selected from pyridyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, and isoxazolyl, and wherein each phenyl or heteroaryl group is substituted with 1, 2 or 3 substituents which are independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy, halogen, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, C_3-C_6cycloalkyl, and saturated oxacycle having 4, 5, or 6 ring atoms and one ring oxygen, which oxacycle is unsubstituted or substituted with 1 or 2 independently selected C_1-C_4alkyl substituents, and wherein each phenyl or heteroaryl comprises at least one non-hydrogen substituent *ortho* to the point of attachment to the remainder of the compound of formula (I);

R_4 is hydrogen or C_1-C_4alkyl;

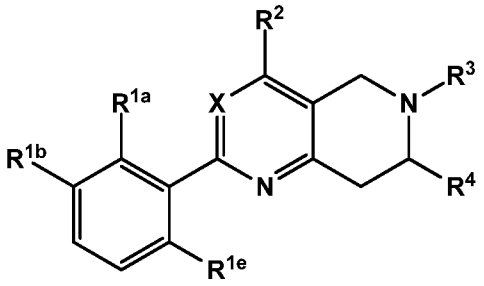
R^5 is hydrogen; or

R^4 and R^5 taken in combination are oxo; and

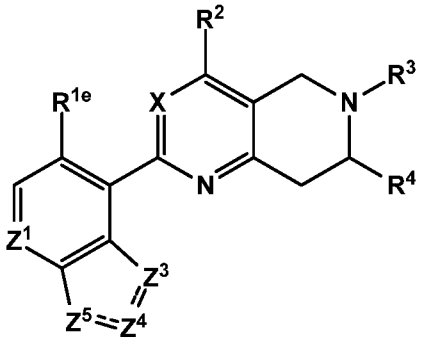
R^6 is hydrogen at each occurrence or CR^6_2, taken in combination, form a divalent carbonyl.

The language "wherein each phenyl or heteroaryl comprises at least one non-hydrogen substituent *ortho* to the point of attachment to the remainder of the compound of formula (I)" shall mean that the phenyl or heteroaryl ring bears at least one substituent ortho to the tetrahydropyrido-pyridine or tetrahydropyrido-pyrimidine ring of Formula (I).

In a second embodiment, a compound of Formula (I) of embodiment one is provided, which compound is a compound of formula (II) or formula (III), or a salt thereof:



(II)



(III)

wherein

Z^1 is N or CH;

Z^3 is N(H), N(C_1-C_4alkyl), or C(R^{1f});

Z^4 is N or CH;

Z^5 is N(H), N(C_1-C_4alkyl) or C(R^{1g}), wherein one or two of Z^3, Z^4 and Z^5 is nitrogen;

R^{1f} is hydrogen, C_1-C_4alkyl or halogen; and

R^{1g} is hydrogen or C_1-C_4alkyl.

In a third embodiment, a compound of embodiment one or two is provided in which R^3 is phenyl or 1H-pyrazolyl, each of which is substituted with 1 or 2 independently selected C_1-C_4alkyl groups and 0, 1 or 2 additional substituents selected from the group consisting of halogen, cyano, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy, cyclopropyl, oxetanyl or 1-methyl-oxetanyl. In certain compounds of the third embodiment, R^3 is phenyl or 1H-pyrazolyl, each of which is substituted with 1 or 2 independently selected C_1-C_4alkyl groups and 0 or 1 additional substituents selected from the group consisting of halogen, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy, cyclopropyl, oxetanyl or 1-methyl-oxetanyl.

In a fourth embodiment, a compound of embodiment two or three is provided in which R^{1a} is hydrogen or methyl;

R^{1e} is hydrogen, methyl or trifluoromethyl, wherein at least one of R^{1a} and R^{1e} is not hydrogen;

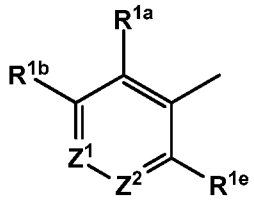
Z^3 is C(R^{1f});

Z^4 is N or CH;

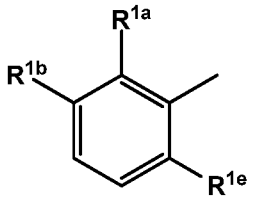
Z^5 is N(H); and

R^{1f} is hydrogen or methyl.

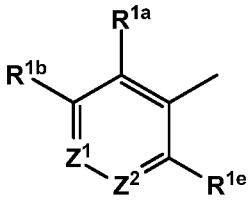
In a fifth embodiment, a compound of any one of embodiments one to three is provided in which



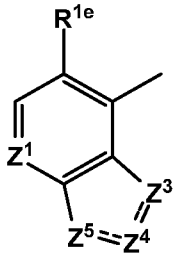
the fragment of Formula (I) or the



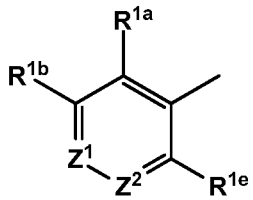
fragment of Formula (II) is 2,6-dimethylphenyl or 2,6-diethylphenyl;



Or the fragment of Formula (I) or the



fragment of Formula (III) is 5-methyl-1*H*-indazol-4-yl, 3-methyl-1*H*-indol-4-yl, 3,5-dimethyl-1*H*-indazol-4-yl, 3,5-dimethyl-1*H*-indol-4-yl, 3,5-dimethyl-1*H*-indol-4-yl, or 3,5-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl, 5-trifluoromethyl-3*H*-pyrrolo[2,3-*b*]pyridin-4-yl.



In certain aspects of the fifth embodiment, the fragment of Formula (I) is 2,6-dimethylphenyl, 2,6-diethylphenyl 5-methyl-1*H*-indazol-4-yl, 3-methyl-1*H*-indol-4-yl, 3,5-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl or 5-methyl-1*H*-indazol-4-yl.

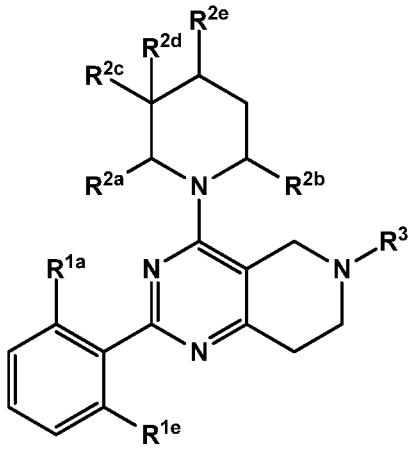
In a sixth embodiment, a compound of any one of embodiments one to five is provided in which R^4 is hydrogen.

In a seventh embodiment, a compound of any one of embodiments one to five is provided in which X is N.

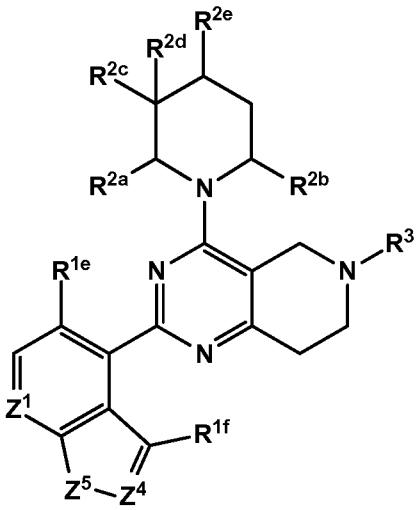
In certain aspects, compounds of any one of embodiments one to seven include those compounds in which R^2 is methyl, methoxy, or methoxy-piperidin-1-yl which are further substituted with one or two methyl groups. In certain compounds, R^2 is selected from methyl, methoxy, 2-methyl-4-methoxy-

piperidin-1-yl, 3,3-dimethyl-4-methoxy-piperidin-1-yl, 2,5-dimethyl-4-methoxy-piperidin-1-yl and 2,5,5-trimethyl-4-methoxy-piperidin-1-yl.

In an eighth embodiment, a compound of any one of embodiments one to seven is provided which compound is a compound of Formula (IV) or (V), or a salt thereof:



(IV)



(V)

wherein

R^{2a}, R^{2b}, R^{2c}, and R^{2d} are independently selected from hydrogen and C_1-C_4alkyl; or

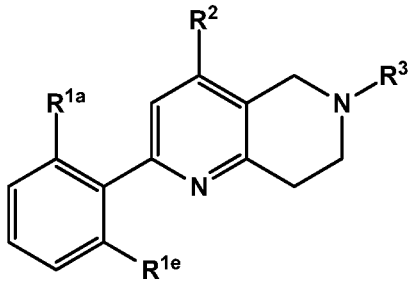
R^{2a} and R^{2b}, taken in combination, form a divalent C_1-C_3alkylene group; and

R^{2e} is hydroxy or C_1-C_4alkoxy.

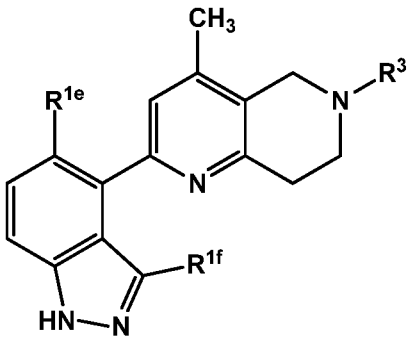
In a ninth embodiment, a compound of any one of embodiments one to five is provided in which X is CH.

In a tenth embodiment, a compound of any one of embodiments one to five or nine is provided in which R^2 is hydrogen or methyl.

In an eleventh embodiment, a compound of any one of embodiments one to five, nine or ten is provided which compound is a compound of Formula (VI) or (VII), or a salt thereof:



(VI)



(VII)

wherein

in Formula (VI), R^{1a} and R^{1e} are methyl or ethyl; or

in Formula (VII), R^{1e} and R^{1f} are hydrogen or methyl, wherein at least one R^{1e} or R^{1f} is methyl.

In a twelfth embodiment, a compound or a salt thereof according to Formula (I), in which R^6 is deuterium.

In yet another embodiment, compounds of any one of embodiments 9 to 11 are provided in which R^3 is phenyl or 1H-pyrazolyl, each of which is substituted with 1 or 2 independently selected C_1-C_4alkyl groups and 0 or 1 additional substituents selected from the group consisting of halogen, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy, cyclopropyl, oxetanyl or 1-methyl-oxetanyl.

In certain other embodiments according to any one of embodiments one to twelve R^3 is 2-methyl-5-trifluorophenyl, 2-methyl-5-chlorophenyl, 2-methyl-5-isopropyl-phenyl, 3-cyclopropyl-1*H*-pyrazol-5-yl, 3-propyl-1*H*-pyrazol-5-yl, 4-chloro-3-cyclopropyl-1*H*-pyrazol-5-yl, or 4-chloro-3-propyl-1*H*-pyrazol-5-yl.

In a thirteenth embodiment, individual compounds according to the invention are those listed in the Examples section below. In certain aspects the compound is selected from the group consisting of:

racemic 1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-4-ol;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

*racemic*1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-4-ol;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3-methoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(1,3-dimethyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-N-(2-methoxyethyl)-N-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

1-((2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(3-(2-methoxyethyl)-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(tetrahydrofuran-2-yl)-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

N-cyclopentyl-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-*N*-methyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-amine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

*racemic*1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

(*R*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(2-methylpyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-*N*-methyl-*N*-((tetrahydrofuran-2-yl)methyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-amine;

racemic 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(3-(methoxymethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(4-(methoxymethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*S*)-1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.;

1-((2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol;

ethyl 1-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidine-3-carboxylate;

2,2'-((2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)azanediyl)diethanol;

2-(2,6-dimethylphenyl)-N-propyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

methyl 2-((2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)acetate;

(*R*)-2-((6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)amino)-3-methylbutan-1-ol;

4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2R,4S)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*S*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2*S*,4*S*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-N,N-dimethyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

2-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-N-methyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-(4-methoxypiperidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpyrrolidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,2-dimethylmorpholine;

4-(azetidin-1-yl)-2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(4-methoxypiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-chloro-2-methylphenyl)-4-(4-methoxypiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-methyl-1-(methyl(2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)amino)propan-2-ol;

1-((6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol;

6-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,2-dimethylmorpholine;

6-(5-isopropyl-2-methylphenyl)-N,N-dimethyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3,3-dimethylpiperidin-4-ol;

6-(5-isopropyl-2-methylphenyl)-N-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

N-isopropyl-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

4-(azetidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-4-ol;

6-(5-isopropyl-2-methylphenyl)-N-(2-methoxyethyl)-N-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)azetidin-3-ol;

racemic 6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3-fluoroazetidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3,3-dimethylpiperidin-4-ol;

(*S*)-4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylmorpholine;

(*S*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

(*R*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;

6-(5-isopropyl-2-methylphenyl)-4-((3*R*,4*R*)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-(1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)pyrrolidin-2-yl)methanol;

(*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*S*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylazetidin-3-ol;

6-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-oxa-6-azaspiro[3.3]heptane;

6-(5-isopropyl-2-methylphenyl)-4-(3-methoxyazetidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine;

(3-*endo*)-8-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol;

(*S*)-2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*S*)-6-(5-chloro-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.;

2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(1-methyl-1H-indazol-7-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(1-methyl-1H-indazol-7-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-chloro-2-methoxyphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-2-(5-fluoro-2-methylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5- Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,5-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*R*)-2-(2,4-dimethylpyridin-3-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,5-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(3,5-dimethylpyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(5-methoxy-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3,5-dimethyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,4-dimethylpyridin-3-yl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(5-fluoro-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(4-fluoro-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-cyclopropyl-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(4-(2-(2,5-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(2-(2,6-dimethylphenyl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide;

(*R*)-2-(4-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-(trifluoromethyl)phenyl)-5,6,7,8 tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(4-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide.;

(*R*)-2-(4-(6-(3-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(2,4-difluorophenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-cyclopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone;

1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone;

(*R*)-1-(3-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone;

racemic 1-(4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)ethanone;

racemic 1-((*trans*)-4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,5-dimethylpiperazin-1-yl)ethanone;

racemic 2-(-4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)acetamide;

racemic 2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)acetamide;

(*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(methylsulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-;

methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-4-(4-ethyl-3-methylpiperazin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-;

tetrahydropyrido[4,3-d]pyrimidine;

2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-isopropyl-1H-indazol-4-yl)-4-methoxy-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3-chloro-5-methyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8 tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(3-chloro-5-methyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic 2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-((*S*)-1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic 2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-((R) 1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*R*)-4-methyl-1-(2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)pentane-1,3-dione;

(*R*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(4-(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*S*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-((3R,4R)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic 1-(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-4-ol;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-4-methyl-6-(o-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(1,3-dimethyl-1H-pyrazol-5-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(5-methoxy-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(2,5-dimethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(1-ethyl-3-methyl-1H-pyrazol-5-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(2,4-dimethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(5-cyclopropyl-2-methylphenyl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(5-chloro-2-methylphenyl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(5-fluoro-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(3-methyl-1H-indol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro($^2H_2$)-1,6-naphthyridine.;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2-chloro-5-methoxyphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

4-methyl-2-(5-methyl-1H-indazol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-diethylphenyl)-4,7-dimethyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4,7-dimethyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(2,4-dimethylpyridin-3-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(3-methyl-1H-indol-4-yl)-6-(2,6-dimethylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine ;

6-(5-methoxy-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(3-methyl-1H-indol-4-yl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(2,6-diethylphenyl)-4-methyl-6-(1-methyl-1H-tetrazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy 5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy 5,6,7,8-tetrahydro(5,5-^{2}-1,6-naphthyridine;

(*S*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

2-(2,6-dimethylphenyl)-4-((2-hydroxy-2-methylpropyl)(methyl)amino)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

4-((cyclopropylmethyl)(propyl)amino)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2-methoxyethyl)(methyl)amino)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

(*S*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

1-((2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)(methyl)amino)-2-methylpropan-2-ol;

N-(cyclopropylmethyl)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-N-propyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-amine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-N-(2-methoxyethyl)-N-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-amine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-ethoxy-2-methylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(4-chloro-3-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-ethoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-methyl-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(S)-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(R)-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine; and

(R)-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(S)-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic (cis)-3-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane;

(R)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-cyclopropyl-2-(2-(3,5-dimethyl-1H-indazol-4-yl)-4-((4*S*,6*R*)-6-methyl-1-oxa-7-azaspiro[3.5]nonan-7-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)benzonitrile;

(R)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

(R)-6-(4-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(R)-6-(3-(difluoromethyl)-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(R)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(4-fluoro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-fluoroethoxy)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(2,2-difluoroethoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)ethanamine;

2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-N-methylethanamine;

(S)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)ethyl)morpholine;

(*R*)-3-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)propane-1,2-diol;

1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine;

(*R*)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3,3-difluoropiperidin-4-ol;

(*R*)-1-(2-(3,5-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

(3S,4S)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(3R,4R)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(3R,4R)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(3S,4S)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(*R*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-4-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine;

2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-(methylsulfonyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-(2,2-difluoroethoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(3-ethoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

(R)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(S)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(3R,4R)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(3S,4S)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

racemic (trans)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylazetidin-3-ol;

racemic 6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((*trans)*-3-methoxy-2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2,4-dimethylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic (1*S**,6*S**)-3-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane;

racemic (*cis*)-3-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-7-oxa-3-azabicyclo[4.2.0]octane;

(*R*)-4-(6-(4-Chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-4-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine;

1-(6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine;

(*R*)-6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-cyclopropyl-1-ethyl-4-fluoro-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-3-(difluoromethyl)-5-(2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbonitrile

Racemic (1*S**,6*S**)-3-(6-(3-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane;

(*R*)-4-(6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine;

(R)-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine; and

(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

In a fourteenth embodiment, a pharmaceutical composition is provided which comprises one or more pharmaceutically acceptable carriers and a therapeutically effective amount of a compound of any one of embodiments 1 to 13.

In a fifteenth embodiment, a combination, in particular a pharmaceutical combination, is provided which comprises a therapeutically effective amount of the compound according to any one of embodiments 1 to 13 and a second therapeutically active agent.

In a sixteenth embodiment, a method of inhibiting C5a induced anaphalaxis in a subject is provided, the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of embodiments 1 to 13.

In a seventeenth embodiment, a method of treating a disorder or a disease in a subject mediated by complement activation, in particular mediated by C5a activation is provided, the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of embodiments 1 to 13.

In an eighteenth embodiment, the method of embodiment seventeen is provided in which the disease or disorder is selected from the group consisting of age-related macular degeneration, geographic atrophy, diabetic retinopathy, uveitis, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyanagi-Harada syndrome, intermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular cicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, retinal vein occlusion, neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome (ARDS), myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration, neural regeneration, dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, pulmonary fibrosis, asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, antiphospholipid syndrome, glomerulonephritis and obesity.

In a nineteenth embodiment, a method of treating age related macular degeneration is provided, the method comprising administering to a subject in need thereof an effective amount of a composition comprising a compound of any one of claims 1 to 14.

In a twentieth embodiment, a compound according to any one of embodiment 1 to 13 is provided for use as a medicament.

In a twenty first embodiment the use of a compound according to any one of embodiments 1 to 13 is provided in the manufacture of a medicament for the treatment of a disorder or disease in a subject mediated by complement activation or activation of the complement alternative pathway.

In a twenty second embodiment, the use of a compound according to any one of embodiments 1 to 13 is provided for the treatment of age-related macular degeneration

In another embodiment, pharmaceutical compositions are provided which comprise one or more pharmaceutically acceptable carriers and a therapeutically effective amount of a compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra*.

In another embodiment, combinations, in particular pharmaceutical combinations, are provided which comprise a therapeutically effective amount of the compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra*.

In another embodiment, methods of modulating complement activity in a subject are provided which methods comprise administering to the subject a therapeutically effective amount of the compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra*.

In yet other embodiments, methods of treating a disorder or a disease in a subject mediated by complement activation, in particular mediated by activation of the complement system, are provided, which methods comprise administering to the subject a therapeutically effective amount of the compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra*.

In another embodiment, methods of treating age related macular degeneration in a subject are provided which methods comprise administering to the subject a therapeutically effective amount of the compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra*.

In another aspect, the invention provides for the use of compounds of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra,* for use in the preparation of a medicament and more particularly

for use in the manufacture of a medicament for the treatment of a disorder or disease in a subject mediated by complement activation or activation of the complement system. In certain other aspects, the invention provides for the use of a compound according to any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra,* in the treatment of age-related macular degeneration.

In one embodiment, the invention provides a combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to the definition of formula (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra,* or any one of the specifically disclosed compounds of the invention and one or more therapeutically active agents (preferably selected from those listed *infra*).

In twenty third embodiment, the invention is a solvate form of Example 19-F isolated from MTBE.

In a twenty fourth embodiment, the invention is a solvate form of Example 19-F isolated from MTBE characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 6.369±0.2°, 7.058±0.2°, 9.306±0.2°, 10.522±0.2°, 11.908±0.2°, 12.511±0.2°, 13.434±0.2°, 15.527±0.2°, 16.385±0.2°, 17.390±0.2°, 18.883±0.2°, 20.285±0.2°, 22.351±0.2° and 23.297±0.2°, at a temperature of about 22°C.

In a twenty fifth embodiment, the invention is a solvate form of Example 19-F isolated from MTBE characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 6.369±0.2°, 7.058±0.2°, 9.306±0.2°, 10.522±0.2°, 11.908±0.2°, 12.511±0.2°, 13.434±0.2°, 15.527±0.2°, 16.385±0.2°, 17.390±0.2°, 18.883±0.2°, 20.285±0.2°, 22.351±0.2° and 23.297±0.2°, at a temperature of about 22° C.

In a twenty sixth embodiment, the invention is a solvate form of Example 19-F isolated from MTBE having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 1.

In a twenty seventh embodiment, the invention is a solvate form of Example 19-F isolated from MTBE having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 2.

In a twenty eighth embodiment, the invention is a solvate form of Example 19-F isolated from MTBE having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 2.

In a thirtieth embodiment, the invention is a solvate form of Example 19-F isolated from Me-THF.

In a thirty first embodiment, the invention is a solvate form of Example 19-F isolated from Me-THF characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 6.959±0.2°, 8.629±0.2°11.310±0.2°, 13.387±0.2°, 16.778±0.2°, 17.287±0.2°, 17.865±0.2°, 18.849±0.2°, 19.452±0.2°, 22.353±0.2°, 22.830±0.2° and 26.312±0.2° at a temperature of about 22° C.

In a thirty second embodiment, the invention is a solvate form of Example 19-F isolated from Me-THF characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 6.959±0.2°, 8.629±0.2°11.310±0.2°, 13.387±0.2°, 16.778±0.2°, 17.287±0.2°, 17.865±0.2°, 18.849±0.2°, 19.452±0.2°, 22.353±0.2°, 22.830±0.2° and 26.312±0.2° at a temperature of about 22° C.

In a thirty third embodiment, the invention is a solvate form of Example 19-F isolated from Me-THF having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 3.

In a thirty fourth embodiment, the invention is a solvate form of Example 19-F isolated from Me-THF having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 4.

In a thirty fifth embodiment, the invention is a solvate form of Example 19-F isolated from Me-THF having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 4.

In a thirty sixth embodiment, the invention is a solvate form of Example 19-F isolated from Toluene.

In thirty seventh embodiment, the invention is a solvate form of Example 19-F isolated from Toluene characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 7.431±0.2°, 9.970±0.2°, 10.975±0.2°, 11.562±0.2°, 12.209±0.2°, 13.632±0.2°14.448±0.2°, 15.032±0.2°, 15.865±0.2°, 16.974±0.2°, 17.280±0.2°, 18.829±0.2°, 22.402±0.2° and 23.165±0.2°, at a temperature of about 22° C.

In a thirty eighth embodiment, the invention is a solvate form of Example 19-F isolated from Toluene characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 7.431±0.2°, 9.970±0.2°, 10.975±0.2°, 11.562±0.2°, 12.209±0.2°, 13.632±0.2°14.448±0.2°, 15.032±0.2°, 15.865±0.2°, 16.974±0.2°, 17.280±0.2°, 18.829±0.2°, 22.402±0.2° and 23.165±0.2°, at a temperature of about 22° C.

In a thirty ninth embodiment, the invention is a solvate form of Example 19-F isolated from Toluene having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 6.

In a fortieth embodiment, the invention is a solvate form of Example 19-F isolated from Toluene having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 7.

In a forty first embodiment, the invention is a solvate form of Example 19-F isolated from Toluene having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 7.

Ina forty second embodiment, the invention is a solvate form of Example 19-F isolated from EtOAc.

In a forty third embodiment, the invention is a solvate form of Example 19-F isolated from EtOAc characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 7.430±0.2°, 9.171±0.2°, 10.048±0.2°, 11.070±0.2°, 11.555±0.2°, 12.318±0.2°, 13.778±0.2°, 14.490±0.2°, 15.972±0.2°, 17.394±0.2°, 19.025±0.2° and 23.283±0.2°, at a temperature of about 22° C.

In a forty fourth embodiment, the invention is a solvate form of Example 19-F isolated from EtOAc characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 7.430±0.2°, 9.171±0.2°, 10.048±0.2°, 11.070±0.2°, 11.555±0.2°, 12.318±0.2°, 13.778±0.2°, 14.490±0.2°, 15.972±0.2°, 17.394±0.2°, 19.025±0.2° and 23.283±0.2°, at a temperature of about 22° C.

In a forty fifth embodiment, the invention is a solvate form of Example 19-F isolated from EtOAc having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 8.

In a forty sixth embodiment, the invention is a solvate form of Example 19-F isolated from EtOAc having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 9.

In a forty seventh embodiment, the invention is a solvate form of Example 19-F isolated from EtOAc having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 9.

In a forty eighth embodiment, the invention is a crystalline Hydrochloride Form A of Example 19-F.

In a forty ninth embodiment, the invention is a crystalline Hydrochloride Form A of Example 19-F characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 6.928±0.2°, 7.630±0.2°, 9.394±0.2°, 10.875±0.2°, 12.252±0.2°, 14.236±0.2°, 15.378±0.2°, 17.227±0.2°, 18.146±0.2°, 19.187±0.2° and 26.521±0.2°, at a temperature of about 22°C.

In a fiftieth embodiment, the invention is a crystalline Hydrochloride Form A of Example 19-F characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 6.928±0.2°, 7.630±0.2°, 9.394±0.2°, 10.875±0.2°, 12.252±0.2°, 14.236±0.2°, 15.378±0.2°, 17.227±0.2°, 18.146±0.2°, 19.187±0.2° and 26.521±0.2°, at a temperature of about 22°C.

In a fifty first embodiment, the invention is a crystalline Hydrochloride Form A of Example 19-F having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 11.

In a fifty second embodiment, the invention is a crystalline Hydrochloride Form A of Example 19-F having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG's. 13 and 14.

In a fifty third embodiment, the invention is a crystalline Hydrochloride Form A of Example 19-F having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 12.

In a fifty fourth embodiment, the invention is a crystalline Hydrochloride Form B of Example 19-F.

In a fifty fifth embodiment, the invention is a crystalline Hydrochloride Form B of Example 19-F characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 7.407±0.2°, 8.041±0.2°, 8.368±0.2°, 9.681±0.2°, 9.983±0.2°, 13.252±0.2°, 15.006±0.2°, 15.554±0.2°, 19.271±0.2° and 20.137±0.2°, at a temperature of about 22°C.

In a fifty sixth embodiment, the invention is a crystalline Hydrochloride Form B of Example 19-F characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 7.407±0.2°, 8.041±0.2°, 8.368±0.2°, 9.681±0.2°, 9.983±0.2°, 13.252±0.2°, 15.006±0.2°, 15.554±0.2°, 19.271±0.2° and 20.137±0.2°, at a temperature of about 22°C.

In fifty seventh embodiment, the invention is a crystalline Hydrochloride Form B of Example 19-F having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 15.

In a fifty eighth embodiment, the invention is a crystalline Hydrochloride Form B of Example 19-F having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 17.

In a fifty ninth embodiment, the invention is a crystalline Hydrochloride Form B of Example 19-F having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 16.

In a sixtieth embodiment, the invention is a crystalline Phosphate Form A of Example 19-F.

In a sixty first embodiment, the invention is a crystalline Phosphate Form A of Example 19-F characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 4.730±0.2°, 7.956±0.2°, 9.584±0.2°, 10.644±0.2°, 13.588±0.2°, 14.548±0.2°, 16.287±0.2°, 17.266±0.2°, 11.835±0.2° and 18.948±0.2°, at a temperature of about 22°C.

In a sixty second embodiment, the invention is a crystalline Phosphate Form A of Example 19-F characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 7.956±0.2°, 9.584±0.2°, 10.644±0.2°, 13.588±0.2°, 14.548±0.2°, 16.287±0.2°, 17.266±0.2°, 11.835±0.2° and 18.948±0.2°, at a temperature of about 22°C.

In a sixty third embodiment, the invention is a crystalline Phosphate Form A of Example 19-F having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 18.

In a sixty fourth embodiment, the invention is a crystalline Phosphate Form A of Example 19-F having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 19.

In a sixty fifth embodiment, the invention is a crystalline Phosphate Form B of Example 19-F.

In a sixty sixth embodiment, the invention is a crystalline Phosphate Form B of Example 19-F characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 5.873±0.2°, 7.086±0.2°, 7.993±0.2°, 10.188±0.2°, 11.865±0.2°, 13.382±0.2°, 14.434±0.2°, 16.946±0.2°, 18.742±0.2°, 20.709±0.2°, 21.718±0.2° and 22.728±0.2°, at a temperature of about 22°C.

In a sixty seventh embodiment, the invention is a crystalline Phosphate Form B of Example 19-F characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 5.873±0.2°, 7.086±0.2°, 7.993±0.2°, 10.188±0.2°, 11.865±0.2°, 13.382±0.2°, 14.434±0.2°, 16.946±0.2°, 18.742±0.2°, 20.709±0.2°, 21.718±0.2° and 22.728±0.2°, at a temperature of about 22°C.

In a sixty eighth embodiment, the invention is a crystalline Phosphate Form B of Example 19-F having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 20.

In a sixty ninth embodiment, the invention is a crystalline Phosphate Form B of Example 19-F having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 21.

In a seventieth embodiment, the invention is a crystalline Phosphate Form C of Example 19-F.

In a seventy first embodiment, the invention is a crystalline Phosphate Form C of Example 19-F characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the

group consisting of 7.93±0.2°, 8.65±0.2°, 10.63±0.2°, 12.00±0.2°, 13.85±0.2°, 15.35±0.2°, 16.06±0.2°, 17.65±0.2° and 18.82±0.2°, at a temperature of about 22°C.

In a seventy second embodiment, the invention is a crystalline Phosphate Form C of Example 19-F characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 4.50±0.2°, 7.93±0.2°, 8.65±0.2°, 10.63±0.2°, 12.00±0.2°, 13.85±0.2°, 15.35±0.2°, 16.06±0.2°, 17.65±0.2° and 18.82±0.2°, at a temperature of about 22°C.

In a seventy third embodiment, the invention is a crystalline Phosphate Form C of Example 19-F having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 22.

In a seventy fourth embodiment, the invention is a crystalline Phosphate Form C of Example 19-F having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 23.

In a seventy fifth embodiment, the invention is a crystalline Hydrochloride Form C of Example 19-F having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 24.

In a seventy sixth embodiment, the invention is a solvate form of Example 55-G isolated from EtOAc in Heptane.

In a seventy seventh embodiment, the invention is a solvate form of Example 55-G isolated from EtOAc in Heptane characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 7.752±0.2°, 8.750±0.2°, 10.211±0.2°, 10.909±0.2°, 11.635±0.2°, 12.485±0.2°, 12.972±0.2°, 14.159±0.2°, 14.831±0.2°, 15.714±0.2°, 16.227±0.2°, 17.249±0.2°, 17.899±0.2°, 18.411±0.2°, 19.351±0.2°, 20.094±0.2°, 22.443±0.2°, 23.089±0.2°, 23.813±0.2°, 24.303±0.2°, 25.326±0.2°, 25.809±0.2°, 27.193±0.2°, 27.973 and 28.863±0.2°, at a temperature of about 22°C.

In a seventy eighth embodiment, the invention is a solvate form of Example 55-G isolated from EtOAc in Heptane characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 7.752±0.2°, 8.750±0.2°, 10.211±0.2°, 10.909±0.2°, 11.635±0.2°, 12.485±0.2°, 12.972±0.2°, 14.159±0.2°, 14.831±0.2°, 15.714±0.2°, 16.227±0.2°, 17.249±0.2°, 17.899±0.2°, 18.411±0.2°, 19.351±0.2°, 20.094±0.2°, 22.443±0.2°, 23.089±0.2°, 23.813±0.2°, 24.303±0.2°, 25.326±0.2°, 25.809±0.2°, 27.193±0.2°, 27.973 and 28.863±0.2°, at a temperature of about 22°C.

In a seventy ninth embodiment, the invention is a solvate form of Example 55-G isolated from EtOAc in Heptane having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 26.

In an eightieth embodiment, the invention is a solvate form of Example 55-G isolated from EtOAc in Heptane having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 27.

In an eighty first embodiment, the invention is a solvate form of Example 55-G isolated from EtOAc in Heptane having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 27.

In an eighty second embodiment, the invention is a tri-hydrate form of Example 55-G isolated from 50% MeOH in Water.

In an eighty third embodiment, the invention is a tri-hydrate form of Example 55-G isolated from 50% MeOH in Water characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 8.161±0.2°, 9.746±0.2°, 12.689±0.2°, 13.109±0.2°, 13.910±0.2°, 14.544±0.2°, 16.441±0.2°, 16.999±0.2°, 17.517±0.2°, 19.318±0.2°, 21.222±0.2°, 22.710±0.2°, 23.065±0.2°, 24.253±0.2°, 25.351±0.2° and 27.787±0.2°, at a temperature of about 22°C.

In an eighty fourth embodiment, the invention is a tri-hydrate form of Example 55-G isolated from 50% MeOH in Water characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 6.602±0.2°, 8.161±0.2°, 9.746±0.2°, 12.689±0.2°, 13.109±0.2°, 13.910±0.2°, 14.544±0.2°, 16.441±0.2°, 16.999±0.2°, 17.517±0.2°, 19.318±0.2°, 21.222±0.2°, 22.710±0.2°, 23.065±0.2°, 24.253±0.2°, 25.351±0.2° and 27.787±0.2°, at a temperature of about 22°C.

In an eighty fifth embodiment, the invention is a tri-hydrate form of Example 55-G isolated from 50% MeOH in Water having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 28.

In an eighty sixth embodiment, the invention is a tri-hydrate form of Example 55-G isolated from 50% MeOH in Water having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG.'s 29 and 30.

In an eighty seventh embodiment, the invention is a tri-hydrate form of Example 55-G isolated from 50% MeOH in Water having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 30.

In an eighty eighth embodiment, the invention is a crystalline Sulfate Form of Example 55-G.

In an eighty ninth embodiment, the invention is a crystalline Sulfate Form of Example 55-G characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 6.198±0.2°, 8.648±0.2°, 10.047±0.2°, 11.452±0.2°, 12.769±0.2°, 14.551±0.2°, 16.203±0.2°, 17.059±0.2°, 17.827±0.2°19.214±0.2° and 19.952±0.2°, at a temperature of about 22°C.

In a ninetieth embodiment, the invention is a crystalline Sulfate Form of Example 55-G characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 6.198±0.2°, 8.648±0.2°, 10.047±0.2°, 11.452±0.2°, 12.769±0.2°, 14.551±0.2°, 16.203±0.2°, 17.059±0.2°, 17.827±0.2°19.214±0.2° and 19.952±0.2°, at a temperature of about 22°C.

In a ninety first embodiment, the invention is a crystalline Sulfate Form of Example 55-G having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 31.

In a ninety second embodiment, the invention is a crystalline Sulfate Form of Example 55-G having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 32.

In a ninety third embodiment, the invention is a crystalline Sulfate Form of Example 55-G having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 32.

In a ninety fourth embodiment, the invention is a crystalline Tosylate Form of Example 55-G.

In a ninety fifth embodiment, the invention is a crystalline Tosylate Form of Example 55-G characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 6.405±0.2°, 8.264±0.2°, 9.769±0.2°, 12.366±0.2°, 13.724±0.2°, 14.639±0.2°, 16.026±0.2°, 18.069 and 18.889±0.2°, at a temperature of about 22°C.

In a ninety sixth embodiment, the invention is a crystalline Tosylate Form of Example 55-G characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 6.405±0.2°, 8.264±0.2°, 9.769±0.2°, 12.366±0.2°, 13.724±0.2°, 14.639±0.2°, 16.026±0.2°, 18.069 and 18.889±0.2°, at a temperature of about 22°C.

In a ninety seventh embodiment, the invention is a crystalline Tosylate Form of Example 55-G having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 33.

In a ninety eighth embodiment, the invention is a crystalline Tosylate Form of Example 55-G having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 34.

In a ninety ninth embodiment, the invention is a crystalline Tosylate Form of Example 55-G having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 34.

In a one hundredth embodiment, the invention is a crystalline Besylate Form of Example 55-G.

In a one hundred first embodiment, the invention is a crystalline Besylate Form of Example 55-G characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 7.624±0.2°, 8.215±0.2°, 9.196±0.2°, 10.674±0.2°, 11.177±0.2°, 11.715±0.2°,

13.324±0.2°, 13.710±0.2°, 14.352±0.2°, 14.912±0.2°, 15.358±0.2°, 16.169±0.2°, 16.706±0.2°, 17.160±0.2°, 17.465±0.2°, 17.737±0.2°, 18.952±0.2°, 19.915±0.2°, 21.568±0.2°, 22.119±0.2°, 22.422±0.2°, 23.656±0.2°, 24.450±0.2°, 25.535±0.2°, 27.668±0.2°, 28.393±0.2°, 29.209±0.2°, 29.832, 30.595 and 33.143±0.2°, at a temperature of about 22°C.

In a one hundred second embodiment, the invention is a crystalline Besylate Form of Example 55-G characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 7.624±0.2°, 8.215±0.2°, 9.196±0.2°, 10.674±0.2°, 11.177±0.2°, 11.715±0.2°, 13.324±0.2°, 13.710±0.2°, 14.352±0.2°, 14.912±0.2°, 15.358±0.2°, 16.169±0.2°, 16.706±0.2°, 17.160±0.2°, 17.465±0.2°, 17.737±0.2°, 18.952±0.2°, 19.915±0.2°, 21.568±0.2°, 22.119±0.2°, 22.422±0.2°, 23.656±0.2°, 24.450±0.2°, 25.535±0.2°, 27.668±0.2°, 28.393±0.2°, 29.209±0.2°, 29.832, 30.595 and 33.143±0.2°, at a temperature of about 22°C.

In a one hundred third embodiment, the invention is a crystalline Besylate Form of Example 55-G having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 35.

In a one hundred fourth embodiment, the invention is a crystalline Besylate Form of Example 55-G having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 36.

In a one hundred fifth embodiment, the invention is a crystalline Besylate Form of Example 55-G having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 36.

In a one hundred sixth embodiment, the invention is a solvate form of Example 55-G isolated from MTBE.

In a one hundred seventh embodiment, the invention is a solvate form of Example 55-G isolated from MTBE characterized by a x-ray powder diffraction pattern comprising four or more 2θ values selected from the group consisting of 6.728±0.2°, 7.659±0.2°, 8.627±0.2°, 10.148±0.2°, 10.853±0.2°, 11.418±0.2°, 12.313±0.2°, 12.889±0.2°, 14.043±0.2°, 14.684±0.2°, 15.969±0.2°, 16.689±0.2°, 17.149±0.2°, 17.842±0.2°, 18.338±0.2°, 19.119±0.2°, 19.752±0.2°, 23.113±0.2°, 24.397±0.2°, 25.187±0.2°, 25.794±0.2° and 27.159±0.2° , at a temperature of about 22°C.

In a one hundred eighth embodiment, the invention is a solvate form of Example 55-G isolated from MTBE characterized by a x-ray powder diffraction pattern comprising five or more 2θ values selected from the group consisting of 6.728±0.2°, 7.659±0.2°, 8.627±0.2°, 10.148±0.2°, 10.853±0.2°, 11.418±0.2°, 12.313±0.2°, 12.889±0.2°, 14.043±0.2°, 14.684±0.2°, 15.969±0.2°, 16.689±0.2°, 17.149±0.2°, 17.842±0.2°, 18.338±0.2°, 19.119±0.2°, 19.752±0.2°, 23.113±0.2°, 24.397±0.2°, 25.187±0.2°, 25.794±0.2° and 27.159±0.2° , at a temperature of about 22°C.

In a one hundred ninth embodiment, the invention is a solvate form of Example 55-G isolated from MTBE having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 37.

In a one hundred tenth embodiment, the invention is a solvate form of Example 55-G isolated from MTBE having a differential scanning calorimetry (DSC) thermogram substantially the same as that shown in shown in FIG. 38.

In a one hundred eleventh embodiment, the invention is a solvate form of Example 55-G isolated from MTBE having a thermo gravimetric analysis (TGA) diagram substantially the same as that shown in shown in FIG. 38.

For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa.

As used herein, the term "alkyl" refers to a fully saturated branched or unbranched hydrocarbon moiety having up to 20 carbon atoms. Unless otherwise provided, alkyl refers to hydrocarbon moieties having 1 to 12 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

As used herein, the term "alkylene" refers to divalent alkyl group as defined herein above having 1 to 20 carbon atoms. It comprises 1 to 20 carbon atoms, Unless otherwise provided, alkylene refers to moieties having 1 to 12 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkylene include, but are not limited to, methylene, ethylene, *n*-propylene, *iso*-propylene, *n*-butylene, *sec*-butylene, *iso*-butylene, *tert*-butylene, *n*-pentylene, isopentylene, neopentylene, *n*-hexylene, 3-methylhexylene, 2,2- dimethylpentylene, 2,3-dimethylpentylene, *n*-heptylene, *n*-octylene, *n*-nonylene, *n*-decylene and the like.

As used herein, the term "haloalkyl" refers to an alkyl as defined herein, that is substituted by one or more halo groups as defined herein. The haloalkyl can be monohaloalkyl, dihaloalkyl or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Dihaloalky and polyhaloalkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Typically the polyhaloalkyl contains up to 12, or 10, or 8, or 6, or 4, or 3, or 2 halo groups. Non-limiting examples of haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. A perhaloalkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms.

The term "aryl" refers to an aromatic hydrocarbon group having 6-20 carbon atoms in the ring portion. Typically, aryl is monocyclic, bicyclic or tricyclic aryl having 6-20 carbon atoms.

Furthermore, the term "aryl" as used herein, refers to an aromatic substituent which can be a single aromatic ring, or multiple aromatic rings that are fused together.

Non-limiting examples include phenyl, naphthyl or tetrahydronaphthyl, each of which may optionally be substituted by 1-4 substituents, such as alkyl, trifluoromethyl, cycloalkyl, halogen, hydroxy, alkoxy, acyl, alkyl-C(O)-O-, aryl-O-, heteroaryl-O-, amino, thiol, alkyl-S-, aryl-S-, nitro, cyano, carboxy, alkyl-O-C(O)-, carbamoyl, alkyl-S(O)-, sulfonyl, sulfonamido, phenyl, and heterocyclyl.

As used herein, the term "alkoxy" refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, hexyloxy, cyclopropyloxy-, cyclohexyloxy- and the like. Typically, alkoxy groups have about 1-7, more preferably about 1-4 carbons.

As used herein, the term "heterocyclyl" or "heterocyclo" refers to a saturated or unsaturated non-aromatic ring or ring system, *e.g.*, which is a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic ring system and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. The heterocyclic group can be attached at a heteroatom or a carbon atom. The heterocyclyl can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1, 4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, and the like.

The term "heterocyclyl" further refers to heterocyclic groups as defined herein substituted with 1 to 5 substituents independently selected from the groups consisting of the following:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo, i.e., =O;

(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxyl;

(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;

(j) alkyl-O-C(O)-;

(k) mercapto;

(l) nitro;

(m) cyano;

(n) sulfamoyl or sulfonamido;

(o) aryl;

(p) alkyl-C(O)-O-;

(q) aryl-C(O)-O-;

(r) aryl-S-;

(s) aryloxy;

(t) alkyl-S-;

(u) formyl, i.e., HC(O)-;

(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term "cycloalkyl" refers to saturated or unsaturated monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms. Unless otherwise provided, cycloalkyl refers to cyclic hydrocarbon groups having between 3 and 9 ring carbon atoms or between 3 and 7 ring carbon atoms, each of which can be optionally substituted by one, or two, or three, or more substituents independently selected from the group consisting of alkyl, halo, oxo, hydroxy, alkoxy, alkyl-C(O)-, acylamino, carbamoyl, alkyl-NH-, $(alkyl)_2N$-, thiol, alkyl-S-, nitro, cyano, carboxy, alkyl-O-C(O)-, sulfonyl, sulfonamido, sulfamoyl, and heterocyclyl. Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like. Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like. Exemplary tricyclic hydrocarbon groups include adamantyl and the like.

As used herein, the term “aryloxy” refers to both an -O-aryl and an -O-heteroaryl group, wherein aryl and heteroaryl are defined herein.

As used herein, the term "heteroaryl" refers to a 5-14 membered monocyclic- or bicyclic- or tricyclic-aromatic ring system, having 1 to 8 heteroatoms selected from N, O or S. Typically, the heteroaryl is a 5-10 membered ring system (e.g., 5-7 membered monocycle or an 8-10 membered bicycle) or a 5-7 membered ring system. Typical heteroaryl groups include 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5- pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-,

4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2, 3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, and 2-, 4-, or 5-pyrimidinyl.

The term "heteroaryl" also refers to a group in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include 1-, 2-, 3-, 5-, 6-, 7-, or 8- indolizinyl, 1-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-indazolyl, 2-, 4-, 5-, 6-, 7-, or 8-purinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliyl, 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl, 2-, 3-, 4-, 5-, or 6-naphthyridinyl, 2-, 3- , 5-, 6-, 7-, or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl, 2-, 4-, 6-, or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-4aH carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-carbazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-carbolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl, 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridinyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 8-, 9-, or 10-phenathrolinyl, 1-, 2- , 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl, 1- , 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl, 2-, 3-, 4-, 5- , 6-, or l-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- benzisoqinolinyl, 2-, 3-, 4-, or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, or 11-7H-pyrazino[2,3-c]carbazolyl,2-, 3-, 5-, 6-, or 7-2H- furo[3,2-b]-pyranyl, 2-, 3-, 4-, 5-, 7-, or 8-5H-pyrido[2,3-d]-o-oxazinyl, 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl, 2-, 4-, or 54H-imidazo[4,5-d] thiazolyl, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5-, or 6- imidazo[2,1-b] thiazolyl, 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10, or 11-4H-pyrido[2,3-c]carbazolyl, 2-, 3-, 6-, or 7-imidazo[1,2-b][1,2,4]triazinyl, 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 4-, 5-, 6-, or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9- benzoxapinyl, 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-1H-pyrrolo[1,2-b][2]benzazapinyl. Typical fused heteroaryl groups include, but are not limited to 2-, 3-, 4-, 5- , 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, and 2-, 4-, 5- , 6-, or 7-benzothiazolyl.

A heteroaryl group may be substituted with 1 to 5 substituents independently selected from the groups consisting of the following:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo, i.e., =O;

(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxyl;

(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;

(j) alkyl-O-C(O)-;

(k) mercapto;

(l) nitro;

(m) cyano;

(n) sulfamoyl or sulfonamido;

(o) aryl;

(p) alkyl-C(O)-O-;

(q) aryl-C(O)-O-;

(r) aryl-S-;

(s) aryloxy;

(t) alkyl-S-;

(u) formyl, i.e., HC(O)-;

(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term "halogen" or "halo" refers to fluoro, chloro, bromo, and iodo.

As used herein, the term "optionally substituted" unless otherwise specified refers to a group that is unsubstituted or is substituted by one or more, typically 1, 2, 3 or 4, suitable non-hydrogen substituents, each of which is independently selected from the group consisting of:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo, i.e., =O;

(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxyl;

(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;

(j) alkyl-O-C(O)-;

(k) mercapto;

(l) nitro;

(m) cyano;

(n) sulfamoyl or sulfonamido;

(o) aryl;

(p) alkyl-C(O)-O-;

(q) aryl-C(O)-O-;

(r) aryl-S-;

(s) aryloxy;

(t) alkyl-S-;

(u) formyl, i.e., HC(O)-;

(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. The asterisk (*) indicated in the name of a compound designate a racemic mixture. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- lngold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using

conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, , hydroiodide/iodide, isothionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, palmoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base

forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

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

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

incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

In certain embodiments, selective deuteration of compounds of Formula (I) include those compounds in which R^6 is deuterium. In certain additional embodiments, compounds of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a sub formulae thereof, e.g., a compound of any one of embodiments one to eleven listed *supra* may be bis-deuterated at the 5 position of either the tetrahydropyrido-pyridine or tetrahydropyrido-pyrimidine ring system.

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

The compounds of the present invention may inherently or by design form solvates with solvents (including water). Therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to a recipient, e.g., water, ethanol, dimethylsulfoxide, acetone and other common organic solvents. The term "hydrate" refers to a molecular complex comprising a compound of the invention and water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

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

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as

any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder, or a disease or biological process (e.g., tissue regeneration and reproduction) (i) mediated by C5a receptor activity, or (ii) associated C5a receptor activity, or (iii) characterized by activity (normal or abnormal) of the complement system; or (2) reducing or inhibiting the activity of C5a receptor activity; or (3) reducing or inhibiting activation of the complement system and particularly reducing or inhibiting the interaction of C5a and it's receptor.

In another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity C5a receptor and/or the complement system.

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

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

As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat", "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat", "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, "treat", "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

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

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

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

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

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

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

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

Compounds of the present invention are either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention may also form internal salts, e.g., zwitterionic molecules.

The present invention also provides pro-drugs of the compounds of the present invention that converts *in vivo* to the compounds of the present invention. A pro-drug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a subject. The suitability and techniques involved in making and using pro-drugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds, which are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity.

Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of (a) hydroxyl groups with lipophilic carboxylic acids (e.g., a carboxylic acid having at least one lipophilic moiety), or (b) carboxylic acid groups with lipophilic alcohols (e.g., an alcohol having at least one lipophilic moiety, for example aliphatic alcohols).

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl derivatives of thiols and *O*-acyl derivatives of alcohols or phenols, wherein acyl has a meaning as defined herein. Suitable prodrugs are often pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester

and the like conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem.* 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (*e.g.* by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known to those skilled in the art. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by

treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralization of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers.

Salts can be converted into the free compounds in accordance with methods known to those skilled in the art. Metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallization, or by chromatography over optically active column materials.

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

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

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

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

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic

ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, methycyclohexane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

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

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

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

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

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

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

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

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

e) absorbents, colorants, flavors and sweeteners.

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

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

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

Suitable compositions for transdermal application include an effective amount of a compound of the invention with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example,

transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for ophthalmic application, *e.g.*, for the treatment of eye diseases *e.g.*, for therapeutic or prophylactic use in treating age related macular degeneration and other complement mediated ophthalmic disorders. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

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

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be desirable.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

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

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

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

Prophylactic and Therapeutic Uses

The compounds of Formula I in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. C5a receptor modulating properties, complement pathway modulating properties and modulation of the complement system, e.g. as indicated in *in vitro* and *in vivo* tests as provided in the next sections and are therefore indicated for therapy.

The present invention provides methods of treating a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the compounds of Formula (I) of the invention. In certain aspects, methods are provided for the treatment of diseases associated with increased activity of the C3 amplification loop of the complement pathway. In certain embodiments, methods of treating or preventing complement mediated diseases are provided in which the complement activation is induced by antibody-antigen interactions, by a component of an autoimmune disease, or by ischemic damage.

In a specific embodiment, the present invention provides a method of treating or preventing age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of the compound of Formula (I) of the invention. In certain embodiments, patients who are currently asymptomatic but are at risk of developing a symptomatic macular degeneration related disorder are suitable for administration with a compound of the invention. The methods of treating or preventing AMD include, but are not limited to, methods of treating or preventing one or more symptoms or aspects of AMD selected from formation of ocular drusen, inflammation of the eye or eye tissue, loss of photoreceptor cells, loss of vision (including loss of visual acuity or visual field), neovascularization

(including CNV), retinal detachment, photoreceptor degeneration, RPE degeneration, retinal degeneration, chorioretinal degeneration, cone degeneration, retinal dysfunction, retinal damage in response to light exposure, damage of the Bruch's membrane, and/ or loss of RPE function.

The compound of Formula (I) of the invention can be used, *inter alia*, to prevent the onset of AMD, to prevent the progression of early AMD to advanced forms of AMD including neovascular AMD or geographic atrophy, to slow and/or prevent progression of geographic atrophy, to treat or prevent macular edema from AMD or other conditions (such as diabetic retinopathy, uveitis, or post surgical or non-surgical trauma), to prevent or reduce the loss of vision from AMD, and to improve vision lost due to pre-existing early or advanced AMD. It can also be used in combination with anti-VEGF therapies for the treatment of neovascular AMD patients or for the prevention of neovascular AMD. The present invention further provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compound(s) of the invention, wherein said disease or disorder is selected from uveitis, adult macular degeneration, diabetic retinopathy, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyanagi-Harada syndrome, intermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular cicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, and retinal vein occlusion.

In some embodiments, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compounds of the invention. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration and neural regeneration. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (*e.g.*, silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gases and chemicals,

e.g., chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (*e.g.*, burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, uveitis (including Behcet's disease and other sub-types of uveitis), antiphospholipid syndrome.

In a specific embodiment, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compounds of the invention, wherein said disease or disorder is asthma, arthritis (*e.g.*, rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions, atypicaly hemolytic uremic syndrome (aHUS), glomerulonephritis (including membrane proliferative glomerulonephritis), blistering cutaneous diseases (including bullous pemphigoid, pemphigus, and epidermolysis bullosa), ocular cicatrical pemphigoid or MPGN II.

In a specific embodiment, the present invention provides methods of treating glomerulonephritis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the present invention. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen--BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention with or without concomitent administration of a complement C5 inhibitor or C5 convertase inhibitor such as Soliris.

In a specific embodiment, the present invention provides methods of reducing the dysfunction of the immune and/or hemostatic systems associated with extracorporeal circulation by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention. The compounds of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures

involving the introduction of an artificial or foreign organ, tissue, or vessel into the blood circuit of a patient. More particularly, such procedures include, but are not limited to, transplantation procedures including kidney, liver, lung or heart transplant procedures and islet cell transplant procedures.

In other embodiments, the compounds of the invention are suitable for use in the treatment of diseases and disorders associated with fatty acid metabolism, including obesity and other metabolic disorders.

In another embodiment, the compounds of the invention may be used in blood ampules, diagnostic kits and other equipment used in the collection and sampling of blood. The use of the compounds of the invention in such diagnostic kits may inhibit the ex vivo activation of the complement pathway associated with blood sampling.

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

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

The activity of a compound according to the present invention can be assessed by the following *in vitro & in vivo* methods.

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

In one embodiment, the invention provides a product comprising a compound of formula (I) and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by

complement activation. Products provided as a combined preparation include a composition comprising the compound of formula (I) and the other therapeutic agent(s) together in the same pharmaceutical composition, or the compound of formula (I) and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

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

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

The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

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

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

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

also provides a compound of formula (I) for use in a method of treating a disease or condition mediated by the complement system and/or C5a mediated inflammation, wherein the compound of formula (I) is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition mediated by the complement system and/ or C5a mediated inflammation, wherein the other therapeutic agent is administered with a compound of formula (I).

The invention also provides the use of a compound of formula (I) for treating a disease or condition mediated by the complement system and/or C5a mediated inflammation, wherein the patient has previously (*e.g.* within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by the complement system and/ or C5a mediated inflammation wherein the patient has previously (*e.g.* within 24 hours) been treated with a compound of formula (I).

The pharmaceutical compositions can be administered alone or in combination with other molecules known to have a beneficial effect on retinal attachment or damaged retinal tissue, including molecules capable of tissue repair and regeneration and/or inhibiting inflammation. Examples of useful, cofactors include anti-VEGF agents (such as an antibody or FAB against VEGF, e.g., Lucentis or Avastin), basic fibroblast growth factor (bFGF), ciliary neurotrophic factor (CNTF), axokine (a mutein of CNTF), leukemia inhibitory factor (LIF), neurotrophin 3 (NT-3), neurotrophin-4 (NT-4), nerve growth factor (NGF), insulin-like growth factor II, prostaglandin E2, 30 kD survival factor, taurine, and vitamin A. Other useful cofactors include symptom-alleviating cofactors, including antiseptics, antibiotics, antiviral and antifungal agents and analgesics and anesthetics. Suitable agents for combination treatment with the compounds of the invention include agents known in the art that are able to modulate the activities of complement components.

A combination therapy regimen may be additive, or it may produce synergistic results (*e.g.*, reductions in complement pathway activity more than expected for the combined use of the two agents). In some embodiments, the present invention provide a combination therapy for preventing and/or treating AMD or another complement related ocular disease as described above with a compound of the invention and an anti-angiogenic, such as anti-VEGF agent (including Lucentis and Avastin) or photodynamic therapy (such as verteporfin).

In some embodiments, the present invention provide a combination therapy for preventing and/or treating autoimmune disease as described above with a compound of the invention and a B-Cell or T-Cell modulating agent (for example cyclosporine or analogs thereof, rapamycin, RAD001 or analogs thereof, and the like). In particular, for multiple sclerosis therapy may include the combination of a compound of the invention and a second MS agent selected from fingolimod, cladribine, tysabri, laquinimod, rebif, avonex and the like.

In one embodiment, the invention provides a method of modulating activity of the complement system in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to the definition of formula (I). The invention further provides methods of modulating the activity of the complement system in a subject by modulating the activity of C5a receptor, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to the definition of Formula (I).

In one embodiment, the invention provides a compound according to the definition of formula (I), (Ia), (VII) or any sub formulae thereof, for use as a medicament.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), (VII) or any sub formulae thereof, for the treatment of a disorder or disease in a subject mediated by complement activation. In particular, the invention provides the use of a compound according to the definition of formula (I), (Ia), (VII) or any sub formulae thereof, for the treatment of a disorder or disease mediated by activation of the complement system.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), in the manufacture of a medicament for the treatment of a disorder or disease in a subject characterized by activation of the complement system. More particularly in the manufacture of a medicament for the treatment of a disease or disorder in a subject characterized by over activation of the complement system.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), or sub formulae thereof for the treatment of a disorder or disease in a subject characterized by activation of the complement system. More particularly, the invention provides uses of the compounds provided herein in the treatment of a disease or disorder characterized by over activation of the complement system or the C3 amplification loop of the system. In certain embodiments, the use is in the treatment of a disease or disorder is selected from retinal diseases (such as age-related macular degeneration).

The present invention provides use of the compounds of the invention for treating a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the compounds of Formula (I) of the invention. In certain aspects, uses are provided for the treatment of diseases associated with increased activity of the C3 amplification loop of the complement pathway. In certain embodiments, uses of treating or preventing complement mediated diseases are provided in which the complement activation is induced by antibody-antigen interactions, by a component of an autoimmune disease, or by ischemic damage.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating or preventing age-related macular degeneration (AMD). In certain embodiments, patients

who are currently asymptomatic but are at risk of developing a symptomatic macular degeneration related disorder are suitable for administration with a compound of the invention. The use in treating or preventing AMD include, but are not limited to, uses in treating or preventing one or more symptoms or aspects of AMD selected from formation of ocular drusen, inflammation of the eye or eye tissue, loss of photoreceptor cells, loss of vision (including loss of visual acuity or visual field), neovascularization (including CNV), retinal detachment, photoreceptor degeneration, RPE degeneration, retinal degeneration, chorioretinal degeneration, cone degeneration, retinal dysfunction, retinal damage in response to light exposure, damage of the Bruch's membrane, and/ or loss of RPE function.

The compound of Formula (I) of the invention can be used, *inter alia*, to prevent the onset of AMD, to prevent the progression of early AMD to advanced forms of AMD including neovascular AMD or geographic atrophy, to slow and/or prevent progression of geographic atrophy, to treat or prevent macular edema from AMD or other conditions (such as diabetic retinopathy, uveitis, or post surgical or non-surgical trauma), to prevent or reduce the loss of vision from AMD, and to improve vision lost due to pre-existing early or advanced AMD. It can also be used in combination with anti-VEGF therapies for the treatment of neovascular AMD patients or for the prevention of neovascular AMD. The present invention further provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compound(s) of the invention, wherein said disease or disorder is selected from uveitis, adult macular degeneration, diabetic retinopathy, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyanagi-Harada syndrome, intermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular cicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, and retinal vein occlusion.

In some embodiments, the present invention provides uses for treating a complement related disease or disorder. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration and neural regeneration. In addition, other known

complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (*e.g.*, silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gases and chemicals, *e.g.*, chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (*e.g.*, burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, uveitis (including Behcet's disease and other sub-types of uveitis), antiphospholipid syndrome.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating a complement related disease or disorder, wherein said disease or disorder is asthma, arthritis (*e.g.*, rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions, atypicaly hemolytic uremic syndrome (aHUS), glomerulonephritis (including membrane proliferative glomerulonephritis), blistering cutaneous diseases (including bullous pemphigoid, pemphigus, and epidermolysis bullosa), ocular cicatrical pemphigoid or MPGN II.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating glomerulonephritis. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen--BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention with or without concomitent administration of a complement C5 inhibitor or C5 convertase inhibitor such as Soliris.

In a specific embodiment, the present invention provides use of the compounds of the invention for reducing the dysfunction of the immune and/or hemostatic systems associated with extracorporeal circulation. The compounds of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte

adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures involving the introduction of an artificial or foreign organ, tissue, or vessel into the blood circuit of a patient. More particularly, such procedures include, but are not limited to, transplantation procedures including kidney, liver, lung or heart transplant procedures and islet cell transplant procedures.

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

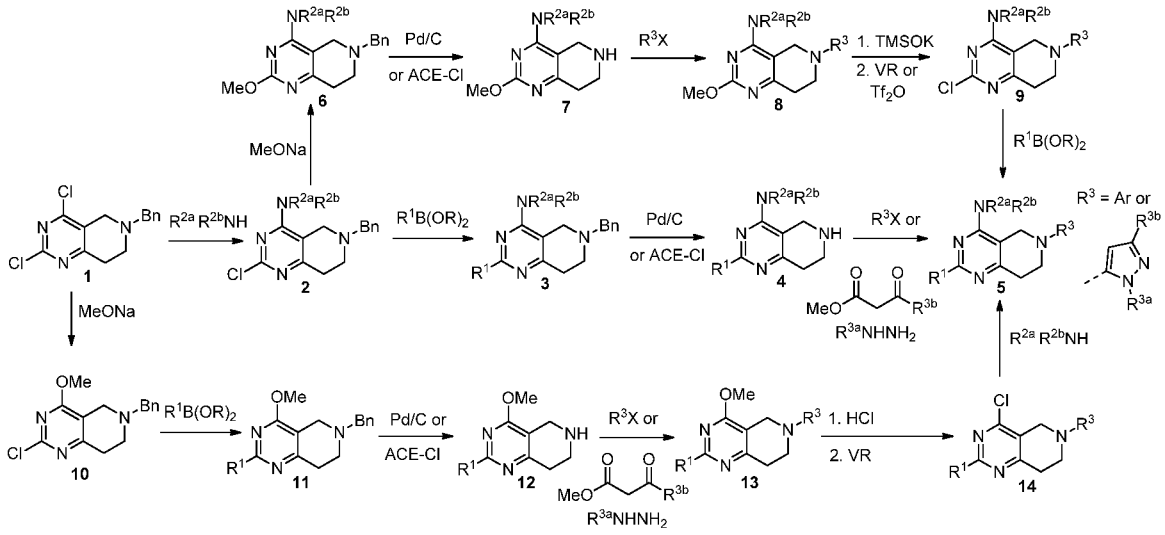
All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl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

The following Examples serve to illustrate the invention without limiting the scope thereof.

GENERAL SYNTHETIC ASPECTS

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

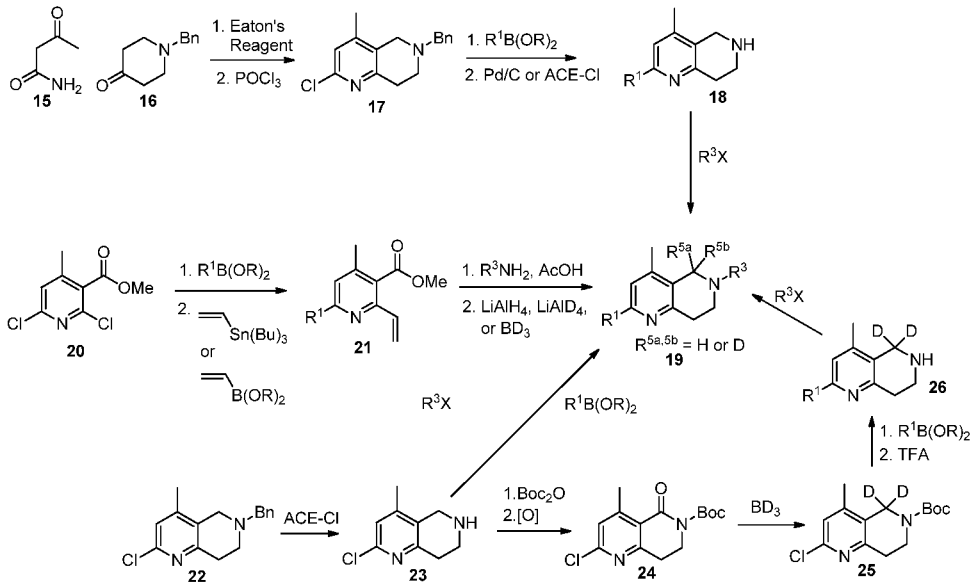
Scheme 1



Amination of the pyrimidine core, to provide intermediates such as **2**, can be accomplished by treatment of dichloropyrimidine **1** with either primary or secondary amines ($R^{2a}R^{2b}NH$), and DIEA or TEA in

solvents such as DMA or IPA at elevated temperature. In a similar manner treatment of dichloropyrimidine **1** with MeONa in MeOH provides methoxy derivative **10**. Installation of R^1 into either intermediate **2** or **10** can be accomplished with palladium catalyzed cross-coupling of boronic acids or the corresponding borate esters to give **3** and **12** respectively. Alternatively, **2** can be reacted with MeONa at elevated temperature to give methoxy intermediate **6**. Removal of the benzyl protecting group from **3**, **11**, or **6** can be accomplished upon treatment with ACE-Cl or palladium catalyzed hydrogenolysis to give the corresponding secondary amines **4**, **7**, or **12**. The R^3 group can then be installed by a palladium catalyzed amination with the appropriate aryl triflate or aryl halide and one of **4**, **7**, or **12** to give **5**, **8** or **13**. Alternatively, an R^3 pyrazole can be constructed by the reaction of amines **4**, **7**, or **12** with the appropriate β-ketoester and then subsequent condensation the β-ketoamide intermediate with alkylhydrazine facilitated by Lawesson's reagent. The methoxy group of **8** can be removed upon treatment with TMSOK at elevated temperature and the hydroxyl pyrimidine is then converted to the chloride upon reaction with Vilsmeier Reagent, $POCl_3$, PPh_3/CCl_4 or the like. An analogous sequence is employed with methoxy intermediate **13** to provide the 4-chloropyrimidine **14**. The 2-chloropyrimidine **9** can then undergo installation of the R^1 group as described above to provide **5**. The 4-chloropyrimidine **14** can undergo nucleophilic displacement either primary or secondary amines ($R^{2a}R^{2b}NH$), and DIEA or TEA in solvents such as DMA or IPA at elevated temperature to provide **5**.

Scheme 2



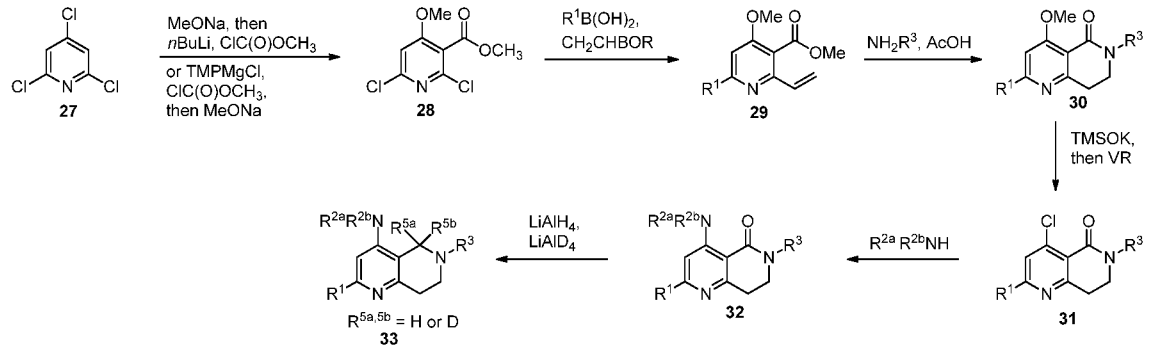
The pyridine core **17** can be prepared by the condensation of **15** and **16** in Eaton's Reagent at elevated temperature followed by chlorination of the resulting hydroxypyridine with $POCl_3$. Palladium catalyzed

cross-coupling reaction of chloropyridine **17** with the appropriate R^1 boronic acid or ester enables installation of R^1. Removal of the benzyl protecting group from **17** can be accomplished upon treatment with ACE-Cl or palladium catalyzed hydrogenolysis to give the corresponding secondary amines **18**. The R^3 group can then be installed by a palladium catalyzed amination with the appropriate aryl triflate or aryl halide and **18** to provide **19**. Alternatively, an R^3 pyrazole can be constructed by the reaction of amines **18** with the appropriate β-ketoester and then subsequent condensation the β-ketoamide intermediate with alkylhydrazine facilitated by Lawesson's reagent to provide **19**.

Intermediate **19** can also be prepared from **20** palladium catalyzed cross-coupling reaction with the appropriate R^1 boronic acid or ester to install R^1, a second palladium catalyzed cross-coupling reaction with either a vinyl borate ester or vinyl stannane reagent to give **21**. Heating of the appropriate R^3 amine with **21** in AcOH facilitates ring formation to give the intermediate lactam corresponding to **19**. The lactam can then be reduced with $LiAlH_4$, $LiAlD_4$, or BD_3 to give the desired compounds **19**. An alternative approach to **19** utilizes a selective palladium catalyzed amination of **23** with an appropriate aryl triflate or aryl bromide followed by palladium catalyzed cross-coupling to install R^1.

Deuterated intermediate can be accessed by the protection, oxidation, and reduction sequence from **23**-**25**. The R^1 group is installed as above on intermediate **25** and then deprotection provides **26**. Palladium catalyzed amination as described above provides **19**.

Scheme 3



Treatment of **27** with MeONa and then *n*butyllithim and methyl chloroformate provides dichloropyridine **28**. Alternatively, **28** can be prepared from **27** by metallation with TMPMgCl, esterification, and then methanolysis with MeONa. The R^1 group can be installed with palladium catalyzed cross-coupling with the corresponding boronic acid or ester. In a second cross-coupling step the vinyl group can be installed to give **29**. As described above, **29** undergoes cyclization upon reaction with the corresponding amine in acetic acid at elevated temperature to provide lactam **30**. The 4-methoxypyridine is then converted to a 4-chloropyridine **31** by treatment with TMSOK and then Vilsmeier Reagent. Displacement of the chloro

group is facilitated by heating **31** with the appropriate primary or secondary amine to give the intermediate lactam, which then undergoes reduction as described above to provide **33**.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known *per se*.

With the groups of preferred compounds of formula I mentioned hereinafter, definitions of substituents from the general definitions mentioned hereinbefore may reasonably be used, for example, to replace one or more up to all more general definitions with more specific definitions or especially with definitions characterized as being preferred.

Compounds of formula I are prepared analogously to methods that, for other compounds, are in principle known in the art, but are novel when applied in the manufacture of the compounds of the present invention, and are especially prepared according to the methods described hereinbelow under 'Examples' or by analogous methods.

Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999. Corresponding protecting groups can be introduced, used and removed at appropriate stages at any stage in the manufacture of a compound of the formula I.

Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as acetonitrile, methanol, ethanol, ethyl acetate, heptane, or tetrahydrofuran..

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

Abbreviations

ACECl	2-chloroethyl chlroformate

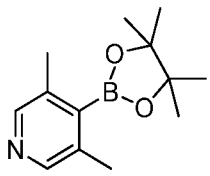
app	apparent
aq	aqueous
atm	atmosphere
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Bn	benzyl
BOC	*tert*iary butyl carboxy
br	broad
BSA	bovine serum albumin
Cbz	carbobenzyloxy
C5aR	C5a receptor
d	doublet
D	deuterium
DCE	1,2-dichloroethane
dd	doublet of doublets
DCM	dichloromethane
DEA	diethylamine
DIEA, DIPEA	diisopropylethylamine
DMA	N,N-dimethylacetamide
DMAP	4,4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMEM	Dulbecco's Modified Eagle Medium
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
ESI	electrospray ionization
EtOAc	ethyl acetate
FACS	fluorescence-activated cell sorting
FCC	flash column chromatography
FITC	fluorescein isothiocyanate
FLIPR	Fluorescent Imaging Plate Reader
g	grams
h	hour(s)
HBSS	Hanks' Balanced Salt Solution

HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC	high pressure liquid chromatography
IR	infrared spectroscopy
LAD	lithium aluminum deuteride
LAH	lithium aluminum hydride
Lawesson's reagent	2,4-bis-(4-methoxyophenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide
LCMS	liquid chromatography and mass spectrometry
LTMP	lithium 2,2',6,6'-tetramethylpiperidine
M	molar
m	multiplet
MeCN, CH_3CN	acetonitrile
MeOH	methanol
Me-THF	2-Methyl Tetra Hydro Furan
MTBE	Methyl tert-butyl ether
min	minutes
mL	milliliter(s)
mmol	millimoles
MS	mass spectrometry
MsOH	methanesulfonic acid
MW	microwave
m/z	mass to charge ratio
N	normal
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
obs	obscured; partially obscured
PBS	phosphate buffer solution
Pd/C	palladium on carbon
ppm	parts per million
rac	racemic
rt	room temperature
R_t	retention time
s	singlet
sat	saturated
SFC	Supercritical Fluid Chromatography

S-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
TBSCl	*tert*-butyldimethylsilyl chloride
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts, Tos	tosyl
VR	Vilsmeier Reagent; (Chlormethylene)dimethylammonium chloride
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Example 1

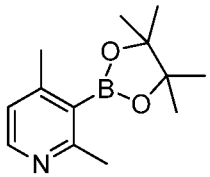
3,5-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine.



To a solution of 4-bromo-3,5-dimethylpyridine (600 mg, 2.70 mmol) in dioxane (9 mL) was added bis(pinocolato) diboron (1.37 g, 5.39 mmol), potassium acetate (1.06 g, 10.8 mmol), S-phos (221 mg, 0.539 mmol) and $PdCl_2(MeCN)_2$ (35 mg, 0.14 mmol). Reaction was heated at 95 °C for 16 h. Water was added and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified via FCC (40-60% EtOAc/heptane) to give the title compound. MS (ESI+) *m/z* 234.1 $(M+H)^+$.

Example 2

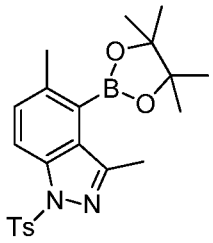
2,4-Dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine.



To a solution of 3-bromo-2,4-dimethylpyridine (476 mg, 2.56 mmol) in DMSO (14 mL) was added bis(pinocolato) diboron (3.25 g, 12.8 mmol), potassium acetate (1.26 g, 12.8 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (209 mg, 0.256 mmol). Reaction was heated at 95°C for 16 h. Water was added and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduce pressure. The residue was purified via FCC (40-70% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.35 (d, *J*=5.1 Hz, 1 H), 6.91 (d, *J*=5.1 Hz, 1 H), 2.64 (s, 3 H), 2.42 (s, 3 H); 1.43 (s, 12 H); MS (ESI+) *m/z* 234.1 $(M+H)^+$.

Example 3

3,5-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indazole.



A solution of 1-(2-chloro-6-fluoro-3-methylphenyl)ethanone (10 g, 53.6 mmol) and hydrazine (5.05 mL, 161 mmol) in DMSO (50 mL) was heated at 80 °C overnight. The reaction mixture was then partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to provide crude 4-chloro-3,5-dimethyl-1H-indazole as a white solid, which was used in the next step directly. MS (ESI+) *m/z* 180.9 $(M+H)^+$.

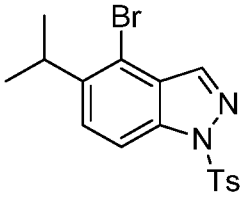
NaH (60% dispersion in mineral oil, 3.87 g, 97 mmol) was added portion wise to a solution of crude 4-chloro-3,5-dimethyl-1H-indazole (9.7 g, 53.7 mmol) in THF (200 mL) at -20 °C. The mixture was allowed to warm to 0 °C and stir for 20 min, then TsCl (14.33 g, 75 mmol) was added. The reaction mixture was allowed to warm to rt and stir overnight. The reaction mixture was cooled to -20 °C and sat. NH_4Cl aqueous solution was added to quench excess base. The resulting mixture was extracted with CH_2Cl_2 (2X). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The residue was triturated with EtOAc and filtered to provide 4-chloro-3,5-dimethyl-1-tosyl-1H-indazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98 (d, *J*=8.34 Hz, 1 H) 7.84 (m, *J*=8.34 Hz, 2 H) 7.39 (d, *J*=8.59 Hz, 1 H) 7.25 (m, *J*=7.83 Hz, 2 H) 2.73 (s, 3 H) 2.46 (s, 3 H) 2.38 (s, 3 H); MS (ESI+) *m/z* 334.7 $(M+H)^+$.

A mixture of 4-chloro-3,5-dimethyl-1-tosyl-1H-indazole (1.5 g, 4.48 mmol), dioxaborolane (3.41 g, 13.44 mmol), S-Phos palladacycle (CAS: 1028206-58-7, 0.151 g, 0.224 mmol), and K_3PO_4 (2.85 g, 13.44 mmol) in DMSO (20 mL) was heated at 110 °C for 70 min. The reaction mixture was then partitioned

between DCM and water. The aqueous layer was extracted with DCM (2X). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by FCC (0-30% EtOAc/heptanes) to provide 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.09 (d, *J*=8.59 Hz, 1 H) 7.78 (m, *J*=8.34 Hz, 2 H) 7.35 (d, *J*=8.84 Hz, 1 H) 7.19 (m, *J*=8.08 Hz, 2 H) 2.59 (s, 3 H) 2.54 (s, 3 H) 2.35 (s, 3 H) 1.44 (s, 12 H); (ESI+) *m/z* 426.9 $(M+H)^+$.

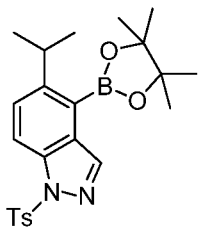
Example 4

4-A. 4-Bromo-5-isopropyl-1-tosyl-1H-indazole.



NaH (60% dispersion in mineral oil, 241 mg, 6.02 mmol) was added to a solution of 4-bromo-5-isopropyl-1H-indazole (720 mg, 3.01 mmol) in THF (15 mL) at 0 °C. After 10 min, TsCl (861 mg, 4.52 mmol) was added and the resulting mixture was stirred at 0 °C for 1 h, then at room temperature overnight. Saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc (2X). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. Ther residue was purified by silica gel chromatography (0-30% EtOAc/heptanes) to provide 4-bromo-5-isopropyl-1-tosyl-1H-indazole. MS (ESI+) *m/z* 394.8 $(M+H)^+$.

4-B. 5-Isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indazole.

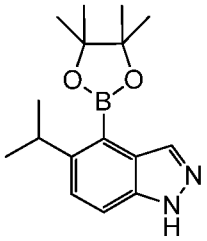


A mixture of 4-bromo-5-isopropyl-1-tosyl-1H-indazole (550 mg, 1.398 mmol), bis(pinacolato)diboron (710 mg, 2.80 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (91 mg, 0.112 mmol) and potassium acetate (412 mg, 4.20 mmol) in DMSO (8 mL) was heated at 110 °C for 24 h. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (0-30% EtOAc/heptane) to provide 5-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)-1-tosyl-1H-indazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.57 (s, 1 H) 8.24 (d, *J*=8.84 Hz, 1 H) 7.87 (d, *J*=8.59 Hz, 2 H) 7.57 (d, *J*=8.84 Hz, 1 H) 7.24 (d, *J*=8.59 Hz, 2 H) 3.71 - 3.88 (m, 1 H) 2.38 (s, 3 H) 1.41 (s, 12 H) 1.29 - 1.32 (m, 6 H); MS (ESI+) *m/z* 440.9 $(M+H)^+$.

Example 5

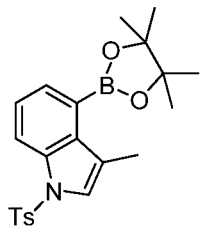
5-Isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole.



A suspension of 4-bromo-5-isopropyl-1*H*-indazole (396 mg, 1.656 mmol), bis(pinacolato)diboron (841 mg, 3.31 mmol), KOAc (488 mg, 4.97 mmol), $PdCl_2(CH_3CN)_2$ (21.48 mg, 0.083 mmol) and S-Phos (136 mg, 0.331 mmol) in DMSO (6 mL) was allowed to stir at 110 °C for 23 h under nitrogen. The reaction mixture was cooled to rt, and diluted with EtOAc and half-saturated brine. The products were extracted three times with EtOAc. The combined organic layer was washed with brine, and concentrated. After the residue was diluted with THF (10 mL) and MeOH (1.5 mL), 1 M aq LiOH (4.5 mL) was added. After stirring for 0.5 h, the reaction was quenched with sat aq NH_4Cl, and diluted with EtOAc and brine. The mixture was extracted twice with EtOAc. The combined organic layer were washed with a 1:1 solution of sat aq NH_4Cl and saturated brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on 40 g of silica gel (0-20% EtOAc/heptane) to give 5-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole along with 20 mol% of debromonated product (345 mg) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, the desired boronic ester) δ ppm 9.93 (br s, 1 H), 8.39 (d, *J* = 1.01 Hz, 1 H), 7.50 – 7.52 (m, 1 H), 7.41 (d, *J* = 8.84 Hz, 1 H), 3.75 – 3.85 (m, 1 H), 1.42 (s, 12 H), 1.28 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 287.30 $(M+H)^+$. The obtained material was used without further purification.

Example 6

6-A. 3-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indole.

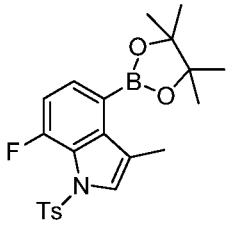


To a solution of 4-bromo-1H-indole-3-carbaldehyde (7.5 g, 66.9 mmol) in THF (125 mL) was added $LiAlH_4$ (40 mL, 1.0 M THF) dropwise at rt. The mixture was then heated at reflux for 2 h and was then cooled to 0 °C. At that point 15% NaOH (2 mL) and water (7 mL) were added in sequence and the mixture was stirred vigorously for 1 h. At that point the suspension was filtered over Celite® and the filtrate was concentrated to provide crude 4-bromo-3-methyl-1H-indole, which was taken to the next step. A solution of crude 4-bromo-3-methyl-1H-indole (14.0 g, 66.9 mmol) in THF (50 mL) was added to a suspension of NaH (2.94 g, 73.6 mmol, 60% in mineral oil) in THF (200 mL) at 0 °C. The mixture was stirred for 0.5 h at that temperature before a solution of *p*-toluene sulfonylcholoride (13.4 g, 70.2 mmol) in THF (50 mL) was added. After stirring for an additional 1 h sat aq NH_4Cl was added slowly. The reaction mixture was then diluted with EtOAc and sat aq NH_4Cl and the layers were separated. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was then purified by FCC (0-50% EtOAc/heptane) to give 4-bromo-3-methyl-1-tosyl-1H-indole.

To a solution of 4-bromo-3-methyl-1-tosyl-1H-indole (8.66 g, 23.8 mmol) in DMSO (100 mL), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.85 g, 30.9 mmol), potassium acetate (3.50 g, 35.7 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.97 g, 1.19 mmol) were added. The reaction mixture was placed under a nitrogen atmosphere and then heated at 100 °C for 4 h. The mixture was then allowed to cool to rt and then poured into ice water (600 mL). The precipitate was filtered and the solid was then purified by FCC (0-25% EtOAc/heptanes) to give 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indole. MS (ESI+) *m/z* 412.2 $(M+H)^+$.

The following compounds were prepared in a similar manner.

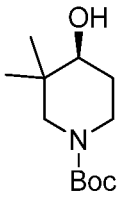
6-B. 7-Fluoro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-indole



MS (ESI+) *m/z* 429.8 $(M+H)^+$. Prepared as described for **Example 6-A** from 4-bromo-7-fluoro-1H-indole-3-carbaldehyde which was prepared by the following method. POCl3 (0.85 mL, 9.11 mmol) was added to DMF (4.4 ml, 56.1 mmol) which had been cooled in an ice bath. After stirring for 15 min a solution of 4-bromo-7-fluoro-1H-indole (1.50 g, 7.01 mmol) in DMF (1.5 mL) was added and the mixture was then heated at 35 °C for 1.25 h. The reaction mixture was then cooled in an ice bath and treated with ice and 20%w/w aq NaOH to pH 14 and heated at reflux for 8 h. After allowing the reaction to cool to rt the mixture was neutralized with HCl to pH 7 and extracted with EtOAc (2 x). The combined organic layers were then concentrated under reduced pressure and the residue was purified with FCC to give 4-bromo-7-fluoro-1H-indole-3-carbaldehyde.

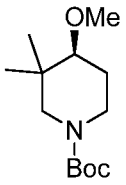
Example 7

7-A. (*S*)-Tert-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate.



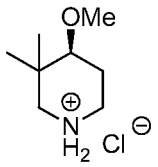
To a solution of *tert*-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (10.0 g, 44.0 mmol) in THF (45 mL) at 0 °C was added dropwise (–)-DIP-Chloride (50-65 wt. % in heptane, 48.9 mL, 79.0 mmol), and the reaction mixture was stirred at 5 °C for 4 days. The reaction mixture was then diluted with Et_2O (250 mL) and diethanol amine (8.0 g) was added to give a massive amount of white precipitate. The resulting mixture was vigorously stirred at room temperature for 3 h. The heterogeneous mixture was then filtered through a Buchner funnel packed with Celite®, and the resulting filtrate was concentrated to give a yellow residue. The residue was purified by silica gel chromatography (25-70% EtOAc/heptane) to provide (*S*)-*tert*-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate. (90% ee). Enantiomeric excess determined by Mosher ester analysis. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.79 - 3.94 (m, 1 H), 3.53 (d, *J*=13.4 Hz, 1 H), 3.42 (dd, *J*=9.2, 4.2 Hz, 1 H), 3.05 (ddd, *J*=13.2, 9.8, 3.5 Hz, 1 H), 2.74 (d, *J*=13.1 Hz, 1 H), 1.69 - 1.80 (m, 2 H), 1.58 (m, 1 H), 1.46 (s, 9 H), 0.97 (s, 3 H), 0.90 (s, 3 H).

7-B. (*S*)-Tert-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate.



To a solution of (*S*)-*tert*-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate (6.43 g, 28.0 mmol) in DMF (100 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 2.24 g, 56.1 mmol), and the reaction mixture was stirred at room temperature for 15 min. Then, MeI (3.16 mL, 50.5 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was then cooled to 0 °C and sat. aq. NH_4Cl was added slowly and stirred for 5 min. The solution was warmed to room temperature and diluted with water (250 mL) and extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (5-30% EtOAc/heptane) to provide (*S*)-tert-butyl 4-methoxy-3,3-dimethylpiperidine-1-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.75 (br. s., 1 H), 3.41 (d, *J*=13.1 Hz, 1 H), 3.35 (s, 3 H), 3.09 (ddd, *J*=13.3, 9.3, 3.7 Hz, 1 H), 2.86 (dd, *J*=8.5, 3.7 Hz, 1 H), 2.80 (d, *J*=13.1 Hz, 1 H), 1.74 - 1.85 (m, 1 H), 1.48 - 1.59 (m, 1 H), 1.46 (s, 9 H), 0.94 (s, 3 H), 0.88 (s, 3 H).

7-C. (*S*)-4-Methoxy-3,3-dimethylpiperidin-1-ium chloride.

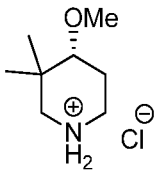


To neat (*S*)-tert-butyl 4-methoxy-3,3-dimethylpiperidine-1-carboxylate (5.87 g, 24.1 mmol) was added 4.0 M HCl in dioxane (24.1 mL, 96.0 mmol), and the reaction mixture was stirred at room temperature for 16 h. Then, the reaction mixture was diluted with heptanes (60 mL) and Et_2O (10 mL) and stirred at room temperature until a white solid crashed out. The heterogeneous mixture was then filtered and the white solid was collected to afford (*S*)-4-methoxy-3,3-dimethylpiperidin-1-ium chloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.58 (br. s., 1 H), 9.23 (br. s., 1 H), 3.34 (s, 3 H), 3.09 - 3.24 (m, 2 H), 3.05 (t, *J*=10.0 Hz, 1 H), 2.97 (dd, *J*=5.4, 2.4 Hz, 1 H), 2.76 (d, *J*=13.1 Hz, 1 H), 2.04 - 2.17 (m, 1 H), 1.84 - 1.96 (m, 1 H), 1.19 (s, 3 H), 1.05 (s, 3 H).

The corresponding TFA salt was also prepared with a similar method using TFA in DCM.

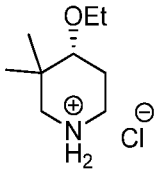
The following compounds were prepared in a similar manner.

7-D. (*R*)-4-Methoxy-3,3-dimethylpiperidin-1-ium chloride.



^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.62 (br. s., 1 H) 9.36 (br. s., 1 H) 3.33 (s, 3 H) 3.15 (d, *J*=8.84 Hz, 1 H) 2.90 - 3.08 (m, 3 H) 2.65 - 2.77 (m, 1 H) 1.98 - 2.11 (m, 1 H) 1.81 - 1.93 (m, 1 H) 1.15 (s, 3 H) 1.04 (s, 3 H).

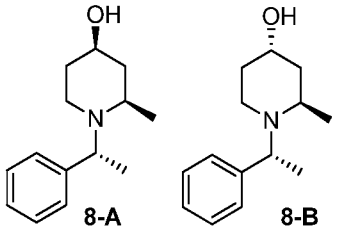
7-E. (*R*)-4-Ethoxy-3,3-dimethylpiperidin-1-ium chloride.



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.56 (br. s., 1 H) 9.14 (br. s., 1 H) 3.53 - 3.65 (m, 1 H) 3.30 - 3.40 (m, 1 H) 3.10 - 3.27 (m, 2 H) 3.06 (d, *J*=4.93 Hz, 2 H) 2.75 (d, *J*=12.25 Hz, 1 H) 2.01 - 2.16 (m, 1 H) 1.79 - 1.92 (m, 1 H) 1.20 (s, 3 H) 1.18 (t, *J*=5.40 Hz, 3 H) 1.04 (s, 3 H).

Example 8

8-A. (2*R*,4*R*)-2-Methyl-1-((*R*)-1-phenylethyl)piperidin-4-ol and 8-B. (2*R*,4*S*)-2-Methyl-1-((*R*)-1-phenylethyl)piperidin-4-ol.



Preparation of (*R*)-2-methyl-1-((*R*)-1-phenylethyl)piperidin-4-one and (*S*)-2-methyl-1-((*R*)-1-phenylethyl)piperidin-4-one done done as described in WO2004/94380. The mixture of diastereomers was separated by FCC (0-15% EtOAc/heptane) to provide (*R*)-2-methyl-1-((*R*)-1-phenylethyl)piperidin-4-one as the first eluting diastereomer. Analytical data for (*R*)-2-methyl-1-((*R*)-1-phenylethyl)piperidin-4-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.46 (d, *J*=7.07 Hz, 2 H) 7.35 (t, *J*=7.45 Hz, 2 H) 7.23 - 7.28 (m, 1 H) 4.02 (q, *J*=6.57 Hz, 1 H) 3.39 (m, 1 H) 2.73 - 2.83 (m, 1 H) 2.61 - 2.72 (m, 2 H) 2.30 - 2.40 (m, 1 H) 2.16 - 2.30 (m, 2 H) 1.35 (d, *J*=6.82 Hz, 3 H) 1.15 (d, *J*=6.57 Hz, 3 H); $[\alpha]^{25}_D$ +46.28 (c 1.0, MeOH).

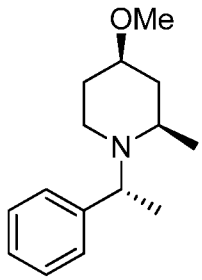
To a precooled (0 °C) solution of (*R*)-2-methyl-1-((*R*)-1-phenylethyl)piperidin-4-one, prepared as above, (2.64 g, 12.1 mmol) in EtOH (50 mL) was added sodium borohydride (551 mg, 14.6 mmol). After 2 h, reaction was quenched with a saturated solution of ammonium chloride and allowed to warm to room temperature. The pH was then adjusted to 9 by the addition of 4 N NaOH and then extracted with EtOAc

(3 x). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The diasteromers **8-A** and **8-B** were then purified by FCC (0-50% EtOAc/heptane) with **8-A** being the major product and the first eluting diastereomer followed by **8-B** as the minor diastereomer product.

8-A : ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (d, *J*=8.1 Hz, 2 H), 7.31 - 7.40 (m, 2 H), 7.21 - 7.28 (m, 1 H), 4.34 (q, *J*=6.8 Hz, 1 H), 3.62 (tq, *J*=10.5, 5.1 Hz, 1 H), 2.60 - 2.72 (m, 1 H), 2.47 (dt, *J*=11.8, 3.7 Hz, 1 H), 2.13 (td, *J*=11.9, 2.3 Hz, 1 H), 2.00 (ddt, *J*=11.9, 4.7, 2.5 Hz, 1 H), 1.74 - 1.85 (m, 1 H), 1.36 - 1.45 (m, 1 H), 1.30 - 1.36 (m, 2 H), 1.23 - 1.30 (m, 6 H); MS (ESI+) *m/z* 220.2 $(M+H)^+$; $[\alpha]^{25}_D$ –51.66 (c 1.0, MeOH).

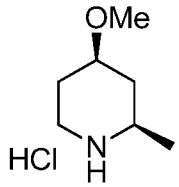
8-B : ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 - 7.46 (m, 2 H), 7.33 (t, *J*=7.6 Hz, 2 H), 7.21 - 7.27 (m, 1 H), 3.99 (br. s., 1 H), 3.89 (q, *J*=6.7 Hz, 1 H), 3.32 (sxt, *J*=6.0 Hz, 1 H), 2.48 - 2.58 (m, 1 H), 2.32 (ddd, *J*=12.1, 8.5, 3.4 Hz, 1 H), 1.77 (t, *J*=5.6 Hz, 2 H), 1.66 - 1.74 (m, *J*=12.6, 3.4, 3.4 Hz, 1 H), 1.47 (dtd, *J*=12.3, 8.1, 3.8 Hz, 1 H), 1.29 - 1.35 (m, 4 H), 1.13 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 220.2 $(M+H)^+$.

8-C. (2*R*,4*R*)-4-Methoxy-2-methyl-1-((*R*)-1-phenylethyl)piperidine.



Sodium hydride (710 mg, 17.7 mmol; 60% dispersion in mineral oil) was added to a solution of (2*R*,4*R*)-2-methyl-1-((*R*)-1-phenylethyl)piperidin-4-ol (1.95 g, 8.87 mmol) in DMF (47 mL) at 0°C. After 15 min, iodomethane (666 µL, 10.7 mmol) was added and the solution was allowed to warm to room temperature. After 1h, water was slowly added at 0° C. The aqueous phase was extracted with a 4:1 mixture of EtOAc/n-heptane (3 x). The combined organic layers were washed with brine (3 x), dried over anhydrous sodium sulfate, filtered, and concentrated under reduce pressure. The residue was purified via FCC (0-30% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (d, *J*=7.8 Hz, 2 H), 7.35 (t, *J*=7.6 Hz, 2 H), 7.21 - 7.28 (m, 1 H), 4.33 (q, *J*=6.8 Hz, 1 H), 3.36 (s, 3 H), 3.11 - 3.22 (m, 1 H), 2.59 - 2.71 (m, 1 H), 2.49 (dt, *J*=11.9, 3.8 Hz, 1 H), 1.99 - 2.16 (m, 2 H), 1.85 (d, *J*=12.1 Hz, 1 H), 1.33 - 1.42 (m, 1 H), 1.28 (d, *J*=7.1 Hz, 4 H), 1.25 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 234.2 $(M+H)^+$; $[\alpha]^{25}_D$ –49.17 (c 1.0, MeOH).

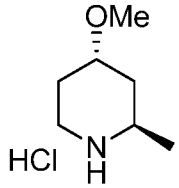
8-D. (+)-(2*R*,4*R*)-4-Methoxy-2-methylpiperidine hydrochloride.



Palladium on carbon (5%) (857 mg, 0.403 mmol) and HCl (concentrated) (734 µL, 24.3 mmol) were added to (2*R*,4*R*)-4-methoxy-2-methyl-1-((*R*)-1-phenylethyl)piperidine (1.88 g, 8.05 mmol) in MeOH (80 mL). Hydrogen was bubbled through the reaciton mixture for 15 min. After 1h, the reaction mixture was filtered through Celite®. The filtrate was washed with a solution of DCM/MeOH (4:1) and concentrated in vacuo to give the title compound. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.40 - 3.51 (m, 2 H), 3.38 (s, 3 H), 3.19 - 3.28 (m, 1 H), 3.01 (td, *J*=13.5, 2.7 Hz, 1 H), 2.19 - 2.36 (m, 2 H), 1.48 (tdd, *J*=13.7, 10.7, 4.5 Hz, 1 H), 1.35 (d, *J*=6.6 Hz, 3 H), 1.25 - 1.33 (m, 1 H); $[\alpha]^{25}_D$ +15.03 (c 1.0, MeOH).

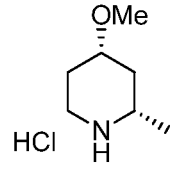
The following compounds were prepared in a similar manner.

8-E. (2*R*,4*S*)-4-Methoxy-2-methylpiperidine hydrochloride.



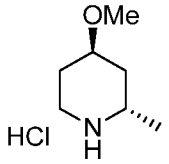
^{1}H NMR (400 MHz, MeOD) δ ppm 3.66 (quin, *J*=2.9 Hz, 1 H), 3.39 - 3.47 (m, 1 H), 3.35 (s, 3 H), 3.16 - 3.23 (m, 2 H), 2.03 - 2.18 (m, 2 H), 1.69 - 1.82 (m, 1 H), 1.53 - 1.63 (m, 1 H), 1.29 (d, *J*=6.6 Hz, 3 H).

8-F. (2*S*,4*S*)-4-Methoxy-2-methylpiperidine hydrochloride..



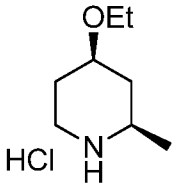
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.88 (br. s., 1 H), 9.41 (br. s., 1 H), 3.54 (br. s., 1 H), 3.38 (s, 3 H), 3.38 (obs m, 1 H) 3.21 (br. s., 1 H), 2.88 (br. s., 1 H), 2.21 (d, *J*=11.9 Hz, 2 H), 1.91 (br. s., 1 H), 1.71 (br. s., 1 H), 1.61 (br. s., 3 H).

8-G. (2*S*,4*R*)-4-Methoxy-2-methylpiperidine hydrochloride..



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.50 (br. s., 1 H), 9.17 (br. s., 1 H), 3.77 (q, *J*=7.0 Hz, 1 H), 3.66 (br. s., 1 H), 3.48 - 3.61 (m, 1 H), 3.35 (s, 3H), 3.26 (br. s., 1 H), 2.06 (d, *J*=8.8 Hz, 2 H), 1.17 - 1.34 (m, 3 H).

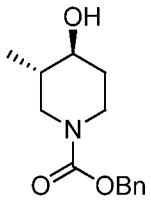
8-H. (2*R*,4*R*)-4-Ethoxy-2-methylpiperidine hydrochloride.



^{1}H NMR (400 MHz, MeOD) δ ppm ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (br. s., 1 H) 8.80 (br. s., 1 H) 3.46 (q, *J*=6.99 Hz, 3 H) 3.19 - 3.30 (m, 1 H) 3.03 - 3.16 (m, 1 H) 2.75 - 2.90 (m, 1 H) 1.98 - 2.14 (m, 2 H) 1.40 - 1.55 (m, 1 H) 1.28 - 1.37 (m, 1 H) 1.25 (d, *J*=6.57 Hz, 3 H) 1.09 (t, *J*=6.95 Hz, 3 H).

Example 9

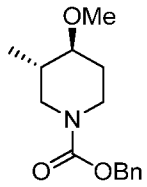
9-A. (3*S*,4*S*)-Benzyl 4-hydroxy-3-methylpiperidine-1-carboxylate.



To a solution of (3*S*,4*S*)-3-methylpiperidin-4-yl pivalate [6.6 g, 33.1 mmol (CAS# 863249-31-4; prepared as described in WO 2005077932)] in THF (200 mL) at 0°C under an atmosphere of argon was added $LiAlH_4$ (2.51 g, 66.2 mmol) in 3 portions. The reaction mixture was then allowed to warm to room temperature and then heated at 55°C for ca. 14 hours. The reaction mixture was then cooled to 0°C and quenched via slow drop-wise addition of a 9:1 mixture of THF/H_2O (20 mL). Then 2 N aq. NaOH (7 mL) was added and the reaction was put at room temperature. Next, water (13.2 mL) and THF (60 mL) were added and the mixture was stirred for 10 minutes. Celite® (30 grams) was added and the heterogeneous mixture was stirred for 2 minutes and then filtered through a pad of Celite®, washing the

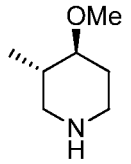
pad with 10% MeOH/THF (200 mL). The eluent was then concentrated to give a semi-solid which was dissolved in water (165 mL). To the resulting solution was added 2N aq. Na_2CO_3 (99 mL, 198 mmol), then CbzCl (9.42 mL, 66.0 mmol). The mixture was stirred at room temperature for 3.5 h. The mixture was then poured into dichloromethane and the resulting layers were separated. The aqueous layer was re-extracted with dichloromethane and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (35-80% {Et_2O(2%EtOH)}/DCM) to provide: (3*S*,4*S*)-benzyl 4-hydroxy-3-methylpiperidine-1-carboxylate. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 0.98 (d, *J*=6.6 Hz, 3 H) 1.31 - 1.53 (m, 2 H) 1.89 (dq, *J*=12.8, 3.6 Hz, 1 H) 2.54 (br. s., 1 H) 2.73 - 3.02 (m, 1 H) 3.28 (td, *J*=9.7, 4.3 Hz, 1 H) 3.89 - 4.20 (m, 2 H) 4.93 - 5.23 (m, 2 H) 7.19 - 7.47 (m, 5 H); MS (ESI+) *m/z* 250.1 $(M+H)^+$.

9-B. (3*S*,4*S*)-Benzyl 4-methoxy-3-methylpiperidine-1-carboxylate.



To a solution of (3*S*,4*S*)-benzyl 4-methoxy-3-methylpiperidine-1-carboxylate (4.45 g, 17.85 mmol) in DMF (100 mL) at 0°C was added NaH (60% dispersion in oil, 1.285 g, 32.1 mmol). The reaction mixture was then put at room temperature for 10 min and then re-cooled to 0°C. MeI (1.674 mL, 26.8 mmol) was then added and the reaction was allowed to warm to room temperature. After stirring for ca. 40 minutes the reaction mixture was cooled to 0°C and quenched with saturated aq NH_4Cl and diluted with Et_2O. The mixture was further diluted with water and the resulting layers were separated. The aqueous layer was re-extracted with Et_2O and the organic layers were combined, washed with brine, then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (50%Et_2O/Heptane) to provide: (3*S*,4*S*)-benzyl 4-methoxy-3-methylpiperidine-1-carboxylate. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 0.95 (d, *J*=6.6 Hz, 3 H) 1.25 - 1.40 (m, 1 H) 1.56 - 1.68 (m, 1 H) 1.94 - 2.05 (m, 1 H) 2.67 (br. s., 1 H) 2.87 (td, *J*=8.8, 4.0 Hz, 1 H) 2.97 (ddd, *J*=13.6, 10.8, 3.2 Hz, 1 H) 3.33 (s, 3 H) 3.79 - 4.10 (m, 2 H) 4.96 - 5.18 (m, 2 H) 7.20 - 7.46 (m, 5 H); MS (ESI+) *m/z* 264.0 $(M+H)^+$.

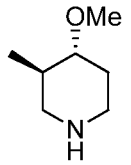
9-C. (3*S*,4*S*)-4-Methoxy-3-methylpiperidine.



To a solution of (3*S*,4*S*)-benzyl 4-methoxy-3-methylpiperidine-1-carboxylate (4.0 g, 15.19 mmol) in MeOH (150 mL) under an argon atmosphere was added wet Pd/C [(5% dry basis) (1.617 g, 0.759 mmol)] The atmosphere was replaced with hydrogen gas via a balloon. The heterogeneous mixture was stirred for 1 hour at room temperature, and then filtered through Celite®. The filter cake was washed with dichloromethane (150 mL) followed by 20%MeOH/DCM (150 mL). The eluent was concentrated to afford (3*S*,4*S*)-4-methoxy-3-methylpiperidine which was used without the need for further purification. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 0.91 (d, *J*=6.6 Hz, 3 H) 1.20 (tdd, *J*=12.2, 12.2, 10.5, 4.3 Hz, 1 H) 1.37 - 1.55 (m, 1 H) 2.03 (ddt, *J*=12.6, 4.2, 3.0, 3.0 Hz, 1 H) 2.21 (dd, *J*=12.6, 10.6 Hz, 1 H) 2.53 (td, *J*=12.4, 2.8 Hz, 1 H) 2.70 - 2.81 (m, 1 H) 2.95 (ddd, *J*=12.5, 4.3, 1.6 Hz, 1 H) 3.01 - 3.11 (m, 1 H) 3.31 (s, 3 H).

The following compounds were prepared by similar method.

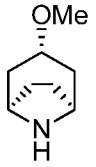
9-D. (3*R*,4*R*)-4-Methoxy-3-methylpiperidine.



The same procedures employed to synthesize (3*S*,4*S*)-4-methoxy-3-methylpiperidine **Examples 9-C** were utilized, however the starting material used was (3*R*,4*R*)-3-methylpiperidin-4-yl pivalate (CAS# 863249-35-8, prepared as described in WO 2005077932). ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 0.92 (d, *J*=6.6 Hz, 3 H) 1.22 (tdd, *J*=12.3, 12.3, 10.4, 4.3 Hz, 1 H) 1.39 - 1.55 (m, 1 H) 2.04 (dq, *J*=12.4, 3.5 Hz, 1 H) 2.23 (dd, *J*=12.6, 10.6 Hz, 1 H) 2.55 (td, *J*=12.4, 2.8 Hz, 1 H) 2.75 (td, *J*=9.7, 4.2 Hz, 1 H) 2.96 (ddd, *J*=12.6, 4.2, 1.4 Hz, 1 H) 3.02 - 3.11 (m, 1 H) 3.31 (s, 3 H).

Example 10

(3-*endo*)-3-Methoxy-8-azabicyclo[3.2.1]octane.



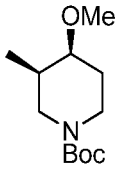
A solution of nortropine (5 g, 39.3 mmol) and Boc_2O (9.44g, 43.2 mmol) in THF (100 mL) was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the residue was triturated with heptanes to provide crude (3-*endo*)-tert-butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate as a off white solid. MS (ESI+) *m/z* 228.0 $(M+H)^+$.

NaH (60% dispersion in mineral oil, 1.5 g, 38 mmol) was added portion wise to a solution of crude (3-*endo*)-tert-butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (4.3 g, 19 mmol) in DMF (43 mL) at 0 °C. After 30 min methyl iodide (4.8 g, 34.1 mmol) was added and the mixture was allowed to warm to room temperature. After 1.5 hours the reaction mixture was cooled to 0 °C and sat. NH_4Cl aqueous solution was added slowly to quench excess base. The resulting mixture was diluted with H_2O (100 mL) and Et_2O (100 mL). The layers were mixed and then separated. The aqueous layer was further extracted with Et_2O (2 x). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated to provide crude (3-*endo*)-tert-butyl 3-methoxy-8-azabicyclo[3.2.1]octane-8-carboxylate. MS (ESI+) *m/z* 242.0 $(M+H)^+$.

A solution of (3-*endo*)-tert-butyl 3-methoxy-8-azabicyclo[3.2.1]octane-8-carboxylate (1.9 g, 8.0 mmol in DCM (20 mL) and TFA (10 mL) was stirred at room temperature for 3 h. The reaction mixture was then concentrated in vacuo to provide (3-*endo*)-3-methoxy-8-abicyclo[3.2.1]octane TFA salt. ^1H NMR (400 MHz, DMSO) δ ppm 3.91 (s, 2 H) 3.46 (t, J=2.78 Hz, 1 H) 3.22 (s, 3 H) 2.10 (d, J=7.33 Hz, 2 H) 2.00 (t, J=3.03 Hz, 4 H) 1.84 - 1.92 (m, 2 H).

Example 11

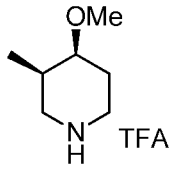
11-A. *Racemic* (*cis*)-tert-butyl 4-methoxy-3-methylpiperidine-1-carboxylate



To a solution of *racemic* (*cis*)-tert-butyl 4-hydroxy-3-methylpiperidine-1-carboxylate (310 mg, 1.44 mmol) (CAS# 955028-93-0; prepared as described in US 20070249589)] in DMF (5 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 75 mg, 1.87 mmol). The reaction mixture was stirred at 0°C for 10 minutes and MeI (0.13 mL, 2.02 mmol) was added. After 2 h the reaction was quenched with

saturated aqueous NH_4Cl. The aqueous phase was washed three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (0-100% EtOAc/heptanes) to provide *racemic* (*cis*)-tert-butyl 4-methoxy-3-methylpiperidine-1-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.36 - 3.50 (m, 6 H), 3.34 (dt, *J*=6.6, 3.3 Hz, 1 H), 3.22 - 3.29 (m, 1 H), 1.78 - 1.96 (m, 2 H), 1.49 (s, 9 H), 0.95 (d, *J*=6.8 Hz, 3 H).

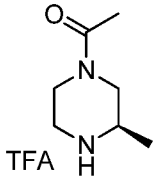
11-B. *Racemic* (*cis*)-4-methoxy-3-methylpiperidine 2,2,2-trifluoroacetate.



A solution of *racemic* (*cis*)-tert-butyl 4-methoxy-3-methylpiperidine-1-carboxylate (230 mg, 1.0 mmol) in DCM (2 mL) with TFA (0.23 mL, 3.01 mmol) was stirred at room temperature overnight. The reaction mixture was then concentrated to give racemic (*cis*)-4-methoxy-3-methylpiperidine 2,2,2-trifluoroacetate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.27 (s, 3 H), 3.01 - 3.09 (m, 1 H), 2.93 - 3.00 (m, 1 H), 2.81 - 2.93 (m, 1 H), 2.69 - 2.77 (m, 1 H), 1.90 - 2.08 (m, 2 H), 1.57 - 1.67 (m, 1 H), 0.90 (d, *J*=7.1 Hz, 3 H).

Example 12

(*R*)-1-(3-Methylpiperazin-1-yl)ethanone 2,2,2-trifluoroacetate.



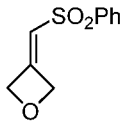
A mixture of (*R*)-tert-butyl 2-methylpiperazine-1-carboxylate (4.8 g, 23.97 mmol), Ac_2O (3.39 mL, 36.0 mmol) and pyridine (3.88 mL, 47.9 mmol) in DCM (30 mL) was stirred at rt for 30 min. Reaction was diluted with EtOAc, washed with diluted HCl, brine and sat $NaHCO_3$, brine, and dried over Na_2SO_4, concentrated. Resulting residue was treated with 1N NaOH in ether, extracted with ether, washed with brine, dried over Na_2SO_4, concentrated and purified by FCC (0-10% MeOH in DCM) to give (*R*)-tert-butyl 4-acetyl-2-methylpiperazine-1-carboxylate. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 4.14 - 4.46 (m, 2 H) 3.74 - 3.91 (m, 1 H) 3.46 - 3.72 (m, 1 H) 2.92 - 3.35 (m, 2 H) 2.56 - 2.91 (m, 1 H) 2.05 (d, *J*=16.67 Hz, 3 H) 1.44 (s, 9 H) 1.03 - 1.18 (m, 3 H). MS (ESI+) *m/z* 243.2 $(M+H)^+$.

A mixture of (*R*)-tert-butyl 4-acetyl-2-methylpiperazine-1-carboxylate (1.34 g, 5.53 mmol) and TFA (10 mL, 130 mmol) in DCM (30 mL) was stirred at rt for 45 min, then concentrated, diluted with DCM, and

then concentrated again which was repeated 3 times. Dried under high vacuum at 80°C to give (*R*)-1-(3-methylpiperazin-1-yl)ethanone 2,2,2-trifluoroacetate (1.95 g). MS (ESI+) *m/z* 143.0 $(M+H)^+$.

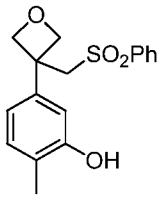
Example 13

13-A. 3-((Phenylsulfonyl)methylene)oxetane.



A solution of BuLi (2.5 M in hexanes, 22.5 mL, 56.3 mmol) was added over 10 min to a solution of methylphenylsulfone (4.00 g, 25.6 mmol) in THF (70 mL) at 0 °C. The solution went from clear to light green to a heterogeneous yellow suspension. The mixture was stirred for 30 min at 0 °C and then chlorodiethylphosphonate (4.46 mL, 30.7 mmol) was added dropwise and the stirring was continued for 30 min, at which point the solution turned clear orange. The reaction mixture was then cooled to –78 °C and oxetan-3-one (1.85 g, 25.6 mmol) was added in THF (3 mL). The reaction mixture turned pale brown/yellow in color. After stirring for another 1.5 h, the reaction mixture was filtered through a plug of silica gel. The filtrate was triturated with solid NH_4Cl until pH reached 7. The mixture was then filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography (0-60% EtOAc/heptane) to provide 3-((phenylsulfonyl)methylene)oxetane. 1H NMR (400 MHz, CD_2Cl_2) δ ppm 7.86 - 7.99 (m, 2 H) 7.68 - 7.77 (m, 1 H) 7.57 - 7.68 (m, 2 H) 6.18 (t, *J*=2.40 Hz, 1 H) 5.59 - 5.70 (m, 2 H) 5.30 (td, *J*=3.41, 2.27 Hz, 2 H)

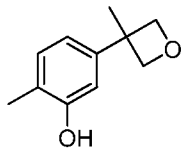
13-B. 2-Methyl-5-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenol.



A solution of KOH (1.5 M in water, 14.2 mL, 21.3 mmol) was added to a solution of $[Rh(cod)Cl]_2$ (0.525 g, 1.07 mmol) in dioxane (60 mL). The resulting yellow solution was stirred for 1 min. Then, 3-hydroxy-4-methylphenyl boronic acid (6.48 g, 42.6 mmol) and a solution of 3-((phenylsulfonyl)methylene)oxetane (4.48 g, 21.3 mmol) in dioxane (40 mL) were added in that order. After 1 h, a solution of KOH (1.5 M in water, 14.2 mL, 21.3 mmol) was added. After another 10 min, $[Rh(cod)Cl]_2$ (0.525 g, 1.07 mmol) was added. The resulting mixture was stirred at room temperature overnight, and then partitioned between Et_2O and aqueous NH_4Cl. The aqueous layer was extracted with Et_2O (3X). (During extractions, some

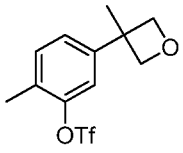
solids crashed out in the organic layer, but went back into solution over time). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The dark orange residue was purified by silica gel chromatography (30-100% EtOAc/heptane) to provide 2-methyl-5-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.52 - 7.63 (m, 3 H) 7.41 (t, *J*=7.71 Hz, 2 H) 6.99 (d, *J*=7.83 Hz, 1 H) 6.57 (dd, *J*=7.83, 1.77 Hz, 1 H) 6.50 (d, *J*=2.02 Hz, 1 H) 4.99 (d, *J*=6.57 Hz, 2 H) 4.91 (d, *J*=6.57 Hz, 2 H) 4.03 (s, 2 H) 2.20 (s, 3 H)

13-C. 2-Methyl-5-(3-methyloxetan-3-yl)phenol.



Magnesium (granulate) (8.70 g, 358 mmol) was added to a solution of crude 2-methyl-5-(3-((phenylsulfonyl)methyl)oxetan-3-yl)phenol (7.6 g, 23.9 mmol) in MeOH (100 mL). The resulting mixture was stirred for 2 min in an ultrasound bath. The flask was then fitted with a condenser. Stirring was continued for 3 h, at which point the reaction mixture turned cloudy and off white in color. *The reaction was exothermic, which caused the solvent to reflux.* Water bath was added to lower the reaction mixture temperature to room temperature. The reaction mixture was then stirred overnight and became heterogeneous and pale orange in color. Et_2O (525 mL) was added, followed by $Na_2SO_4 \cdot 10H_2O$ (85 g). The resulting mixture was stirred for 2 h at room temperature and Celite® was then added. The resulting mixture was stirred for another 1 h and filtered through a Buchner funnel packed with Celite®. The cake was washed with EtOAc (2X) and MeOH (1X). The light yellow filtrate was concentrated and the residue was triturated with $CHCl_3$ (220 mL) and filtered. The filtrate was concentrated to provide 2-methyl-5-(3-methyloxetan-3-yl)phenol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.14 (d, *J*=7.83 Hz, 1 H) 6.73 (d, *J*=7.58 Hz, 1 H) 6.69 (d, *J*=1.77 Hz, 1 H) 4.92 (d, *J*=5.31 Hz, 2 H) 4.61 (d, *J*=5.56 Hz, 2 H) 2.26 (s, 3 H) 1.72 (s, 3 H)

13-D. 2-Methyl-5-(3-methyloxetan-3-yl)phenyl trifluoromethanesulfonate.

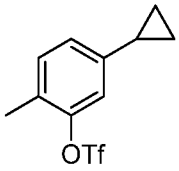


Tf_2O (3.07 mL, 18.2 mmol) was added dropwise to a solution of 2-methyl-5-(3-methyloxetan-3-yl)phenol (2.70 g, 15.2 mmol) and pyridine (1.71 mL, 21.2 mmol) in DCM (25 mL) at 0 °C. The red/orange mixture was stirred at 0 °C for 1.5 h, then partitioned between DCM and water. The aqueous layer was extracted

with DCM (2X). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (0-40% EtOAc/heptane) to provide 2-methyl-5-(3-methyloxetan-3-yl)phenyl trifluoromethanesulfonate. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.38 (d, *J*=8.08 Hz, 1 H) 7.26 (dd, *J*=7.96, 1.89 Hz, 1 H) 7.14 (d, *J*=1.77 Hz, 1 H) 4.89 (d, *J*=5.56 Hz, 2 H) 4.66 (d, *J*=5.81 Hz, 2 H) 2.41 (s, 3 H) 1.75 (s, 3 H).

Example 14

5-Cyclopropyl-2-methylphenyl trifluoromethanesulfonate.

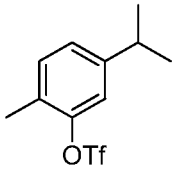


A solution of 5-bromo-2-methylphenol (2.00 g, 10.7 mmol), potassium cyclopropyltrifluoroborate (2.85 g, 19.2 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.379 g, 0.535 mmol) and K_3PO_4 (5.67 g, 26.7 mmol) in toluene (40 mL) and water (10 mL) was allowed to stir at 100 °C for 17 h under nitrogen. The reaction was monitored by ^{1}H NMR. The mixture was cooled to rt, and diluted with 1 M HCl aq (100 mL), brine and EtOAc. The products were extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO4, filtered, and concentrated to give crude as red oil (1.73 g). The crude was used without further purification.

To a solution of the crude product (1.73 g) and pyridine (1.21 mL, 15.0 mmol) in DCM (15 mL), Tf_2O (2.17 mL, 12.8 mmol) was added at 0 °C under nitrogen. The mixture was allowed to stir for 1 h. The reaction was monitored by TLC (25% EtOAc/heptane). The mixture was diluted with brine and DCM. The organic layer was separated and concentrated. The residue was purified by flash column chromatography on 40 g silica gel (with 15 g pre-column of silica gel; eluent: heptane/EtOAc =100:0 to 85:15) to give 5-cyclopropyl-2-methylphenyl trifluoromethanesulfonate. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.16 (d, *J* = 7.87 Hz, 1 H), 6.96 (dd, *J* = 1.64, 7.87 Hz, 1 H), 6.92 (d, *J* = 1.64 Hz, 1 H), 2.32 (s, 3 H), 1.85 – 1.92 (m, 1 H), 0.97 – 1.01 (m, 2 H), 0.65 – 0.69 (m, 2 H).

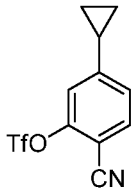
Example 15

15-A. 5-Isopropyl-2-methylphenyl trifluoromethanesulfonate.



To a solution of the carvacrol (5.0 g, 33.3 mmol) and pyridine (20 mL) in DCM (40 mL) was added Tf_2O (8.44 mL, 33.3 mmol) at 0 °C under nitrogen. The solution was stirred for 0.5 h at that temperature and then 0.5 h at room temperature.. At that point the reaction was diluted with DCM (250 mL) and 1 M HCl (250 mL). The layers were mixed and then separated. The aqueous layer was further extracted with DCM (250 mL) and the combined organic layers were then dried (Na_2SO_4), filtered, and concentrated. The residue was then purified by FCC (10-30% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.19 - 7.24 (m, 1 H) 7.12 - 7.17 (m, 1 H) 7.08 (d, *J*=1.52 Hz, 1 H) 2.92 (spt, *J*=6.91 Hz, 1 H) 2.35 (s, 3 H) 1.25 (d, *J*=6.82 Hz, 6 H).

15-B. 2-cyano-5-cyclopropylphenyl trifluoromethanesulfonate

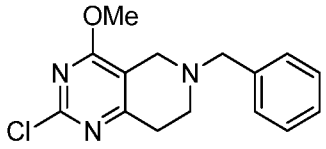


Step 1 : A solution of 4-bromo-2-hydroxybenzonitrile (1 g, 5.05 mmol), potassium cyclopropyltrifluoroborate (1.495 g, 10.10 mmol), K_3PO_4 (5.05 ml, 15.15 mmol) and $PdCl_2(Amphos)_2$ (0.358 g, 0.505 mmol) in toluene (25 mL) was allowed to stir at 100 °C under nitrogen overnight. The mixture was then cooled to room temperature, diluted with EtOAc/NH_4Cl (aq), and filtered through a pad of Celite. The organic layer was seperated, dried over Na_2SO_4, filtered and concentrated. The residue was purifed by FCC (0-50% EtOAc/heptane) to provide 4-cyclopropyl-2-hydroxybenzonitrile, ^{1}H NMR (400 MHz, CH_2Cl_2) δ 12.17 (br. s., 1H), 7.23 (d, *J* = 8.34 Hz, 1H), 6.51 - 6.58 (m, 2H), 1.82 (tt, *J* = 5.02, 8.37 Hz, 1H), 0.94 - 1.00 (m, 2H), 0.68 - 0.73 (m, 2H).

Step 2: The title compound was prepared from 4-cyclopropyl-2-hydroxybenzonitrile in a similar manner as example **15-A**. ^{1}H NMR (400 MHz, CD_3Cl) δ ppm 7.63 (d, *J* = 8.08 Hz, 1H), 7.16 (dd, *J* = 1.52, 8.08 Hz, 1H), 7.13 (d, *J* = 1.77 Hz, 1H), 2.01 (tt, *J* = 4.93, 8.34 Hz, 1H), 1.19 - 1.26 (m, 2H), 0.82 - 0.88 (m, 2H).

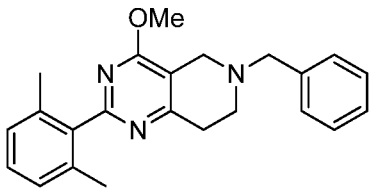
Example 16

16-A. 6-Benzyl-2-chloro-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.



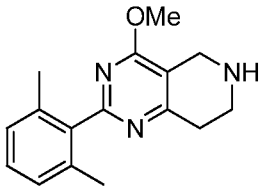
To a solution of 6-benzyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (6.38 g, 21.69 mmol) in anhydrous methanol (100 mL), was added 4.67 N sodium methoxide (5.57 mL, 26 mmol) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, then at rt for 30 min. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM and washed with brine, dried over Na_2SO_4, filtered, and concentrated to give 6-benzyl-2-chloro-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine which was used without the need for purification. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.31 - 7.40 (m, 4 H), 7.23 - 7.31 (m, 1 H), 3.95 (s, 3 H), 3.72 (br. s., 2 H), 3.43 (br. s., 2 H), 2.84 (d, *J*=4.5 Hz, 2 H), 2.78 (d, *J*=4.0 Hz, 2 H). MS (ESI+) *m/z* 290.4 $(M+H)^+$.

16-B. 6-Benzyl-2-(2,6-dimethylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.



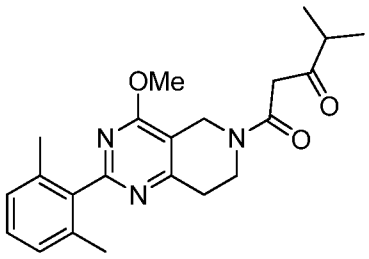
To a suspension of 6-benzyl-2-chloro-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (6.52 g, 22.5 mmol) and 2,6-dimethylphenylboronic acid (3.90 g, 26.0 mmol) in 1,2-dimethoxyethane (175 mL), was added 2 M aqueous Na_2CO_3 (35.2 mL, 70.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.751 g, 0.651 mmol). The reaction was flushed with nitrogen, then heated to 100 °C for 48 h. The reaction mixture was cooled to r.t., then ethyl acetate and brine were added. The aqueous layer was extracted by ethyl acetate twice. The combined ethyl acetate layers were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified via silica gel FCC (0-40% EtOAc/heptane) to give 6-benzyl-2-(2,6-dimethylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.23 - 7.46 (m, 5 H), 7.12 - 7.21 (m, 1 H), 7.04 - 7.10 (m, 1 H), 6.97 (d, *J*=7.6 Hz, 1 H), 3.94 (d, *J*=10.1 Hz, 3 H), 3.73 (d, *J*=16.4 Hz, 2 H), 3.36 - 3.56 (m, 2 H), 2.91 (d, *J*=4.8 Hz, 1 H), 2.84 (br. s., 2 H), 2.77 (t, *J*=5.4 Hz, 1 H), 2.35 (s, 3 H), 2.08 (s, 3 H). MS (ESI+) *m/z* 360.3 $(M+H)^+$.

16-C. 2-(2,6-Dimethylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.



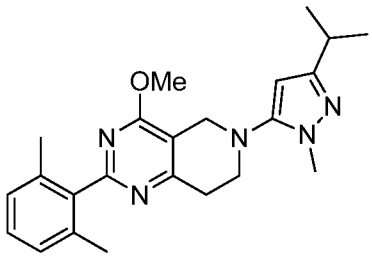
To a solution of 6-benzyl-2-(2,6-dimethylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (7.08 g, 19.70 mmol) in THF (100 mL) and H_2O (12.50 mL), was added 20% $Pd(OH)_2$ wet (50% dry basis, 2.77 g, 1.970 mmol), followed by acetic acid (2.26 mL, 39.4 mmol). The reaction was stirred at r.t. under hydrogen atmosphere for 30 min, then heated to 40 °C for 16 h. The reaction mixture was cooled to r.t. and filtered through a Celite® pad which was washed with methanol. The organic solvent in the filtrate was removed under reduced pressure. The reaction mixture was diluted by 200 mL DCM and neutralized by saturated aqueous $NaHCO_3$. The mixture was extracted twice by DCM. The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the resulting residue was purified via silica gel FCC (Methanol/DCM=0 to 10%) to provide 2-(2,6-dimethylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.22 (m, 1 H), 7.05 - 7.11 (m, 2 H), 5.75 (s, 1 H), 3.88 (s, 3 H), 3.72 (s, 2 H), 3.01 (t, *J*=5.8 Hz, 2 H), 2.68 (t, *J*=5.7 Hz, 2 H), 2.03 (s, 6 H). MS (ESI+) *m/z* 270.5 $(M+H)^+$.

16-D. 1-(2-(2,6-Dimethylphenyl)-4-methoxy-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylpentane-1,3-dione.



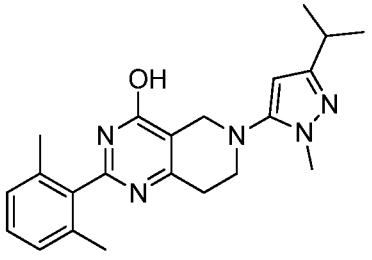
A mixture of 2-(2,6-dimethylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (4.8 g, 17.82 mmol), methyl 4-methyl-3-oxopentanoate (5.14 g, 35.6 mmol), and DMAP (0.327 g, 2.67 mmol) was dissolved in toluene (70 mL). The mixture was evenly divided into four 20 mL microwave vials. Each vial was heated to 150°C for 30 min via microwave irradiation. The reaction mixtures were combine and directly concentrated. The resulting residue was purified via silica gel FCC (0-80% EtOAc/heptane) to give 1-(2-(2,6-dimethylphenyl)-4-methoxy-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl)-4-methylpentane-1,3-dione. MS (ESI+) *m/z* 382.3 $(M+H)^+$.

16-E. 2-(2,6-Dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.



To a solution of 1-(2-(2,6-dimethylphenyl)-4-methoxy-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl)-4-methylpentane-1,3-dione (5.92 g, 15.52 mmol) in THF (80 mL) was added pyridine (5 mL). the resulting solution was evenly divided into four microwave 20 mL vials. To each microwave via was added, methyl hydrazine (0.312 mL, 5.81 mmol) and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson's reagent) (1.88 g, 4.66 mmol). The vials were immediately capped and heated to 125 °C for 10 min via microwave irradiation. The reaction vials were cooled to r.t. and the reaction mixtures were combined and diluted with brine. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the resulting residue was purified via silica gel FCC ((1% MeOH in EtOAc):n-heptane=0 to 100%) to provide 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.15 - 7.24 (m, 1 H), 7.05 - 7.12 (m, 2 H), 5.77 (s, 1 H), 4.00 - 4.04 (m, 2 H), 3.98 (s, 3 H), 3.70 (s, 3 H), 3.28 (t, *J*=5.8 Hz, 2 H), 3.05 (t, *J*=5.8 Hz, 2 H), 2.87 (dt, *J*=13.9, 6.9 Hz, 1 H), 2.12 (s, 6 H), 1.23 (d, *J*=7.1 Hz, 6 H). MS (ESI+) *m/z* 392.4 $(M+H)^+$.

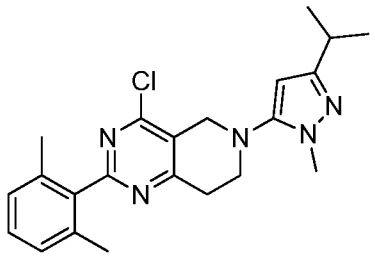
16-F. 2-(2,6-Dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ol.



To a solution of 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (3.3 g, 8.51 mmol) in EtOH (30 mL) in a 150 mL sealed tube was added concentrated hydrochloride (21 mL). The tube was sealed, stirred, and heated at 90 °C for 16 h.

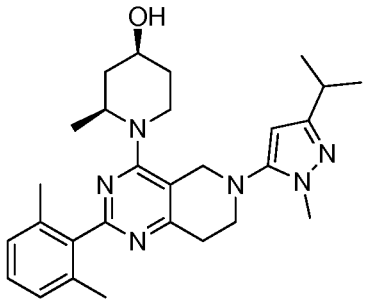
The reaction mixture was cooled to r.t. and poured onto iced-water. Solid $NaHCO_3$ was added to neutralize the mixture. The mixture was extracted by DCM three times. The combined organic layers were dried over Na_2SO_4. After filtration and concentration, the resulting residue was purified via silica gel FCC (0-100% EtOAc/heptane) to give 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.95 (br. s., 1 H), 7.21 - 7.36 (m, 1 H), 7.13 (d, *J*=7.3 Hz, 2 H), 5.76 (s, 1 H), 3.87 (s, 2 H), 3.68 (s, 3 H), 3.22 (t, *J*=5.7 Hz, 2 H), 2.77 - 2.97 (m, 3 H), 2.22 (s, 6 H), 1.22 (d, *J*=7.1 Hz, 6 H). MS (ESI+) *m/z* 378.3 $(M+H)^+$.

16-G. 4-Chloro-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.



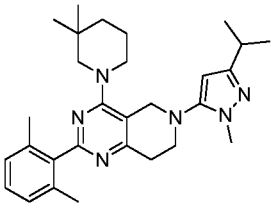
To a solution of 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-ol (2.38 g, 6.3 mmol) in DCM (50 mL) at 0 °C, was added (1-chloro-ethylidene)-dimethylammonium chloride (Vilsmeier reagent) (2.421 g, 18.91 mmol). The reaction was stirred at 0 °C for 5 min, then at r.t. for 30 min. Saturated aqueous $NaHCO_3$ was added to quench the reaction. The mxture was extracted with DCM three times. The combined organic layers was dried over Na_2SO_4. After filtration and concentration, the resulting residue was purified via silica gel FCC (0-100% EtOAc/heptane) to give 4-chloro-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.19 - 7.27 (m, 1 H), 7.11 (d, *J*=7.6 Hz, 2 H), 5.80 (s, 1 H), 4.16 (s, 2 H), 3.72 (s, 3 H), 3.32 (t, *J*=5.9 Hz, 2 H), 3.16 (t, *J*=5.8 Hz, 2 H), 2.88 (dt, *J*=13.9, 6.9 Hz, 1 H), 2.11 (s, 6 H), 1.23 (d, *J*=6.8 Hz, 6 H). MS (ESI+) *m/z* 396.3 $(M+H)^+$.

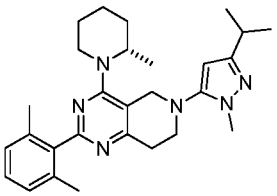
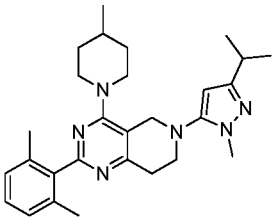
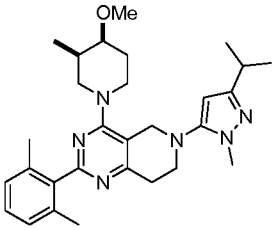
16-H. (±)-1-(2-(2,6-Dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-4-ol.

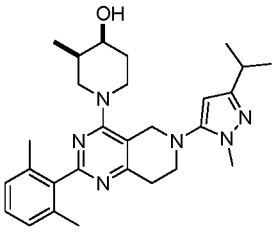
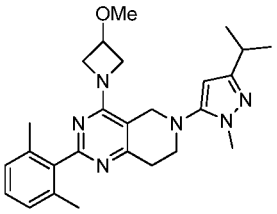
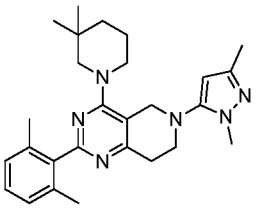
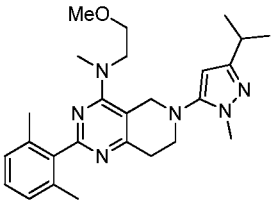


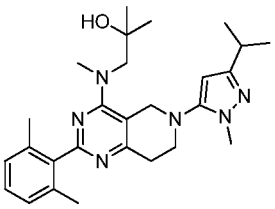
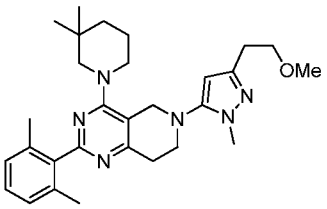
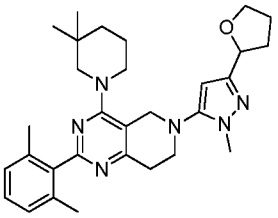
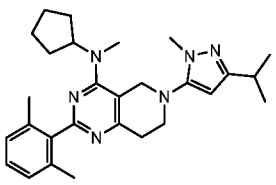
To a solution of 4-chloro-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (40 mg, 0.101 mmol) in *N,N*-dimethylacetamide (1.5 mL), was added diisopropylethylamine (0.141 mL, 0.808 mmol) and *cis* racemic-2-methylpiperidin-4-ol hydrochloride, (CAS# 344329-35-7, 30.6 mg, 0.202 mmol). The reaction was heated to 125 °C for 42 h. After cooling, the mixture was directly purified via HPLC ((0.1% ammonium hydroxide in acetonitrile/water 35%-100%) to give 26 mg of product. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.14 - 7.24 (m, 1 H), 7.04 - 7.12 (m, 2 H), 5.70 (s, 1 H), 4.15 (d, *J*=15.2 Hz, 1 H), 3.94 (d, *J*=15.4 Hz, 1 H), 3.78 - 3.91 (m, 1 H), 3.69 (s, 3 H), 3.57 - 3.67 (m, 1 H), 3.27 - 3.39 (m, 2 H), 3.19 - 3.27 (m, 1 H), 3.02 - 3.12 (m, 2 H), 2.96 (ddd, *J*=12.8, 9.3, 3.2 Hz, 1 H), 2.86 (ddd, *J*=13.8, 7.1, 6.9 Hz, 1 H), 2.09 (s, 6 H), 1.87 - 2.02 (m, 2 H), 1.82 (d, *J*=3.0 Hz, 1 H), 1.56 - 1.71 (m, 1 H), 1.49 (dt, *J*=12.9, 8.3 Hz, 1 H), 1.22 (d, *J*=7.1 Hz, 6 H), 1.14 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 475.4 $(M+H)^+$.

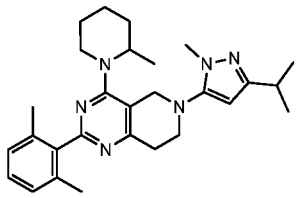
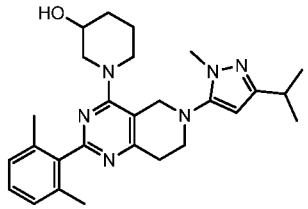
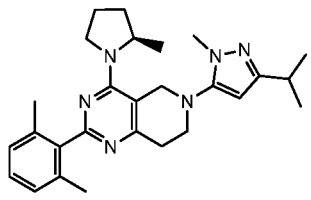
The following compounds were prepared in a similar manner.

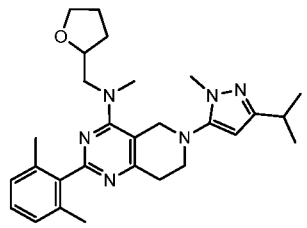
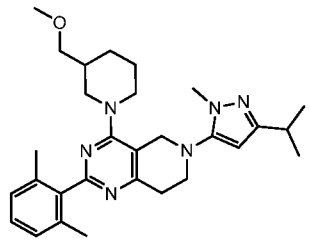
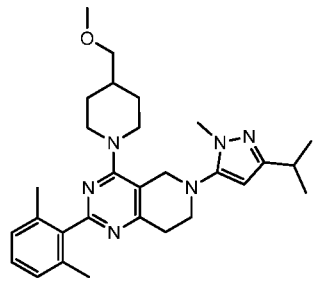
	Structure	Chemical Name & Analytical Data
16-I		2-(2,6-Dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. HCl salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 - 7.43 (m, 1 H), 7.25 (d, *J*=7.8 Hz, 2 H), 5.76 (s, 1 H), 4.15 (s, 2 H), 3.73 (br. s., 2 H), 3.61 (s, 3 H), 3.31 (t, *J*=5.8 Hz, 2 H), 3.01 (br. s., 2 H), 2.77 (spt, *J*=6.9 Hz, 1 H), 2.17 (s, 6 H), 1.68 (br. s., 2 H), 1.48 (br. s., 2 H), 1.15 (d, *J*=7.1 Hz, 6 H), 0.89 (s, 6 H); MS (ESI+) *m/z* 473.2 $(M+H)^+$.

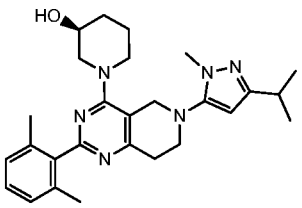
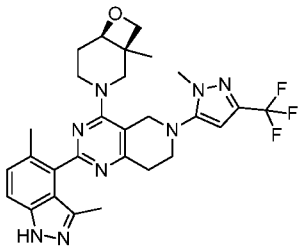
16-J		(*S*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.8 Hz, 2 H), 5.78 (s, 1 H), 4.26 (d, *J*=14.1 Hz, 2 H), 3.96 (d, *J*=14.9 Hz, 2 H), 3.62 (s, 3 H), 3.29 - 3.43 (m, 3 H), 3.18 - 3.29 (m, 1 H), 2.91 - 3.13 (m, 3 H), 2.72 - 2.82 (m, 1 H), 2.18 (s, 6 H), 1.67 - 1.82 (m, 3 H), 1.55 - 1.67 (m, 2 H), 1.50 (dd, *J*=14.9, 5.3 Hz, 1 H), 1.32 (d, *J*=6.6 Hz, 3 H), 1.16 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 459.5 $(M+H)^+$.
16-K		2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.8 Hz, 2 H), 5.83 (s, 1 H), 4.19 - 4.43 (m, 2 H), 4.11 (s, 2 H), 3.61 (s, 3 H), 3.14 - 3.33 (m, 4 H), 3.02 (t, *J*=5.7 Hz, 2 H), 2.73 - 2.83 (m, 1 H), 2.18 (s, 6 H), 1.70 - 1.83 (m, 4 H), 1.18 - 1.24 (m, 1 H), 1.16 (d, *J*=7.1 Hz, 6 H), 0.92 (d, *J*=6.1 Hz, 3 H); MS (ESI+) *m/z* 459.5 $(M+H)^+$.
16-L		(±)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.25 (d, *J*=7.8 Hz, 2 H), 5.80 (s, 1 H), 4.05 - 4.25 (m, 2 H), 3.64 - 3.84 (m, 3 H), 3.62 (s, 3 H), 3.53 - 3.61 (m, 1 H), 3.40 - 3.49 (m, 1 H), 3.22 - 3.37 (m, 5 H), 3.03 (t, *J*=5.9 Hz, 2 H), 2.72 - 2.84 (m, 1 H), 2.18 (s, 6 H), 1.99 - 2.11 (m, 1 H), 1.81 - 1.94 (m, 1 H), 1.63 - 1.77 (m, 1 H), 1.17 (d, *J*=7.1 Hz, 6 H), 0.86 (d, *J*=6.8 Hz, 3 H); MS (ESI+) *m/z* 489.5 $(M+H)^+$.

16-M		*racemic*1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-4-ol. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.6 Hz, 2 H), 5.79 (s, 1 H), 4.05 - 4.22 (m, 2 H), 3.75 - 3.98 (m, 3 H), 3.63 - 3.75 (m, 1 H), 3.61 (s, 3 H), 3.48 (dd, *J*=12.6, 9.9 Hz, 1 H), 3.21 - 3.38 (m, 2 H), 3.01 (t, *J*=5.9 Hz, 2 H), 2.77 (quin, *J*=6.9 Hz, 1 H), 2.18 (s, 6 H), 1.79 - 1.92 (m, 1 H), 1.67 - 1.78 (m, 2 H), 1.16 (d, *J*=6.8 Hz, 6 H), 0.86 (d, *J*=6.8 Hz, 3 H); MS (ESI+) *m/z* 475.5 $(M+H)^+$.
16-N		2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3-methoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.23 (d, *J*=7.6 Hz, 2 H), 5.92 (s, 1 H), 4.59 - 5.13 (m, 2 H), 4.36 - 4.59 (m, 1 H), 4.26 - 4.36 (m, 1 H), 4.18 (br. s., 2 H), 3.88 - 4.13 (m, 1 H), 3.62 (s, 3 H), 3.25 (s, 3 H), 3.18 (t, *J*=5.7 Hz, 2 H), 2.95 (t, *J*=4.3 Hz, 2 H), 2.78 (quin, *J*=6.9 Hz, 1 H), 2.17 (s, 6 H), 1.17 (d, *J*=6.9 Hz, 6 H); MS (ESI+) *m/z* 447.5 $(M+H)^+$.
16-O		6-(1,3-dimethyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. TFA salt ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.34 (t, *J*=7.6 Hz, 1 H), 7.16 (d, *J*=7.6 Hz, 2 H), 5.86 (s, 1 H), 4.05 (s, 2 H), 3.82 (s, 3 H), 3.73 (app. t, *J*=5.1 Hz, 2 H), 3.53 (s, 2 H), 3.40 (br. s., 4 H), 2.33 (s, 3 H), 2.22 (s, 6 H), 1.73 - 1.81 (m, 2 H), 1.52 - 1.58 (m, 2 H), 0.94 (s, 6 H); MS (ESI+) *m/z* 445.3 $(M+H)^+$.
16-P		2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-N-(2-methoxyethyl)-N-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine. ^{1}H NMR HCl salt (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=8.6 Hz, 1 H), 7.24 (d, *J*=7.6 Hz, 2 H), 5.88 (br. s., 1 H), 4.35 (br. s., 2 H), 3.66 (s, 3 H), 3.56 - 3.63 (m, 2 H), 3.38 - 3.45 (m, 3 H), 3.31 (br. s., 2 H), 3.23 (s, 3 H), 3.04 (br. s., 2 H), 2.81 (spt, *J*=6.6 Hz, 1 H),

		2.18 (s, 6 H), 1.18 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 449.2 $(M+H)^+$.
16-Q		1-((2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.12 - 7.19 (m, 1 H), 7.06 (d, *J*=7.6 Hz, 2 H), 5.55 (s, 1 H), 4.64 (s, 1 H), 4.15 (br. s, 2 H), 3.63 (s, 2 H), 3.60 (s, 3 H), 3.28 – 3.33 (m, 2 H), 2.84 (t, *J*=5.7 Hz, 2 H), 2.74 (spt, *J*=7.1 Hz, 1 H), 2.02 (s, 6 H), 1.11 (d, *J*=6.8 Hz, 6 H), 1.02 (s, 6 H); MS (ESI+) *m/z* 463.2 $(M+H)^+$.
16-R		2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(3-(2-methoxyethyl)-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.17 (m, *J*=7.1 Hz, 1 H), 7.08 (d, *J*=7.6 Hz, 2 H), 5.73 (s, 1 H), 4.00 (s, 2 H), 3.59 (s, 3 H), 3.51 (t, *J*=7.1 Hz, 2 H), 3.22 - 3.32 (m, 7 H), 3.04 (s, 2 H), 2.93 (t, *J*=5.9 Hz, 2 H), 2.66 (t, *J*=7.1 Hz, 2 H), 2.04 (s, 6 H), 1.58 - 1.68 (m, 2 H), 1.39 (t, *J*=5.8 Hz, 2 H), 0.91 (s, 6 H); MS (ESI+) *m/z* 489.3 $(M+H)^+$.
16-S		2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(tetrahydrofuran-2-yl)-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.17 (dd, *J*=8.6, 7.1 Hz, 1 H), 7.07 (d, *J*=7.6 Hz, 2 H), 5.80 (s, 1 H), 4.63 - 4.68 (m, 1 H), 4.02 (br. s, 2 H), 3.76 - 3.84 (m, 1 H), 3.66 - 3.74 (m, 1 H), 3.62 (s, 3 H), 3.24 - 3.32 (m, 4 H), 3.05 (d, *J*=2.8 Hz, 2 H), 2.92 (t, *J*=6.1 Hz, 2 H), 2.06 - 2.15 (m, 1 H), 2.04 (s, 6 H), 1.84 - 1.96 (m, 3 H), 1.58 - 1.67 (m, 2 H), 1.37 – 1.41 (m, 2 H), 0.90 (s, 6 H); MS (ESI+) *m/z* 501.3 $(M+H)^+$.
16-T		*N*-cyclopentyl-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-*N*-methyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-amine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.41 (t, *J*=7.8 Hz, 1 H), 7.25 (d,

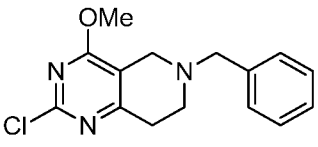
		J=7.6 Hz, 2 H), 5.79 (s, 1 H), 4.88 (br. s., 1 H), 4.25 (s, 3 H), 3.62 (s, 3 H), 3.29 (t, *J*=5.9 Hz, 2 H), 3.18 (s, 2 H), 2.94 - 3.08 (m, 2 H), 2.72 - 2.84 (m, 1 H), 2.18 (s, 6 H), 1.79 - 1.93 (m, 1 H), 1.79 - 1.94 (m, 2 H), 1.62 - 1.79 (m, 4 H), 1.46 - 1.62 (m, 2 H), 1.17 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 459.5 $(M+H)^+$.
16-U		2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.25 (d, *J*=7.6 Hz, 2 H), 5.78 (s, 1 H), 4.70 (br. s., 1 H), 3.87 - 4.37 (m, 2 H), 3.62 (s, 3 H), 3.36 (ddd, *J*=12.3, 6.1, 5.9 Hz, 2 H), 3.15 - 3.29 (m, 1 H), 2.91 - 3.15 (m, 3 H), 2.72 - 2.85 (m, 1 H), 2.18 (s, 6 H), 1.65 - 1.84 (m, 3 H), 1.54 - 1.65 (m, 2 H), 1.42 - 1.54 (m, 1 H), 1.33 (d, *J*=6.6 Hz, 3 H), 1.16 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 459.4 $(M+H)^+$.
16-V		*racemic* 1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.25 (d, *J*=7.6 Hz, 2 H), 5.81 (s, 1 H), 4.27 (d, *J*=14.7 Hz, 1 H), 4.01 (d, *J*=14.9 Hz, 1 H), 3.79 - 3.98 (m, 2 H), 3.73 (br. s., 1 H), 3.66 (br. s., 1 H), 3.61 (s, 3 H), 3.49 (br. s., 1 H), 3.18 - 3.39 (m, 2 H), 3.03 (t, *J*=5.3 Hz, 2 H), 2.71 - 2.84 (m, 1 H), 2.18 (s, 6 H), 1.85 (d, *J*=8.6 Hz, 2 H), 1.41 - 1.65 (m, 2 H), 1.16 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 461.4 $(M+H)^+$.
16-W		(*R*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(2-methylpyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.41 (t, *J*=7.6 Hz, 1 H), 7.26 (d, *J*=7.8 Hz, 2 H), 5.88 (s, 1 H), 4.52 (br. s., 1 H), 4.20 - 4.44 (m, 2 H), 3.89 - 4.18 (m, 2 H), 3.63 (s, 3 H), 3.22 - 3.36 (m, 1 H), 2.87 - 3.21 (m, 2 H), 2.73 - 2.87 (m, 1 H), 2.19 (s, 6 H), 1.78 - 2.13 (m, 4 H), 1.62 (br. s., 1 H), 1.22 (d, *J*=6.1 Hz, 3 H), 1.18 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 445.4 $(M+H)^+$.

16-X		2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-*N*-methyl-*N*-((tetrahydrofuran-2-yl)methyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-amine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.23 (d, *J*=7.6 Hz, 2 H), 5.76 (s, 1 H), 4.32 - 4.45 (m, 1 H), 4.23 (d, *J*=14.9 Hz, 1 H), 4.10 - 4.20 (m, 1 H), 3.73 - 3.86 (m, 2 H), 3.63 - 3.73 (m, 1 H), 3.55 - 3.63 (m, 4 H), 3.41 (s, 3 H), 3.26 (t, *J*=5.9 Hz, 2 H), 2.99 (t, *J*=4.9 Hz, 2 H), 2.69 - 2.83 (m, 1 H), 2.16 (s, 6 H), 1.87 - 2.01 (m, 1 H), 1.68 - 1.87 (m, 2 H), 1.43 - 1.60 (m, 1 H), 1.14 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 475.5 $(M+H)^+$.
16-Y		*racemic* 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(3-(methoxymethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.25 (d, *J*=7.6 Hz, 2 H), 5.80 (s, 1 H), 4.25 (br. s., 2 H), 4.19 (d, *J*=15.2 Hz, 1 H), 4.02 - 4.10 (m, 1 H), 3.62 (s, 3 H), 3.22 - 3.39 (m, 4 H), 3.16 - 3.22 (m, 4 H), 3.09 - 3.16 (m, 1 H), 2.93 - 3.08 (m, 2 H), 2.72 - 2.85 (m, 1 H), 2.19 (s, 6 H), 1.89 - 2.06 (m, 1 H), 1.71 - 1.86 (m, 2 H), 1.47 - 1.65 (m, 1 H), 1.28 - 1.44 (m, 1 H), 1.17 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 489.4 $(M+H)^+$.
16-Z		2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(4-(methoxymethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.8 Hz, 2 H), 5.82 (s, 1 H), 4.33 (d, *J*=13.6 Hz, 2 H), 4.12 (s, 2 H), 3.61 (s, 3 H), 3.24 - 3.34 (m, 4 H), 3.23 (s, 3 H), 3.20 (d, *J*=6.3 Hz, 2 H), 3.02 (t, *J*=5.7 Hz, 2 H), 2.77 (quin, *J*=6.9 Hz, 1 H), 2.17 (s, 6 H), 1.86 - 2.02 (m, 1 H), 1.81 (d, *J*=14.1 Hz, 2 H), 1.19 - 1.34 (m, 2 H), 1.16 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 489.5 $(M+H)^+$.

16-AA		(*S*)-1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol. TFA salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.6 Hz, 2 H), 5.80 (s, 1 H), 4.27 (d, *J*=15.2 Hz, 1 H), 4.01 (d, *J*=14.7 Hz, 1 H), 3.93 (d, *J*=14.9 Hz, 1 H), 3.78 - 3.90 (m, 1 H), 3.70 - 3.78 (m, 1 H), 3.62 - 3.70 (m, 1 H), 3.61 (s, 3 H), 3.42 - 3.55 (m, 1 H), 3.18 - 3.38 (m, 2 H), 2.97 - 3.08 (m, 2 H), 2.73 - 2.81 (m, 1 H), 2.18 (s, 6 H), 1.85 (d, *J*=11.4 Hz, 2 H), 1.42 - 1.63 (m, 2 H), 1.16 (d, 6 H); MS (ESI+) *m/z* 461.5 $(M+H)^+$.
16-AB LLN0 36		*racemic (cis)*-3-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane. ^{1}H NMR (400 MHz,CD_2Cl_2) δ ppm 9.78 (br. s, 1H), 7.27 (d, *J* = 8.59 Hz, 1H), 7.16 (d, *J* = 8.59 Hz, 1H), 6.08 (s, 1H), 4.57 (t, *J* = 3.03 Hz, 1H), 4.44 (d, *J* = 5.81 Hz, 1H), 4.23 (d, *J* = 6.06 Hz, 1H), 4.12 (q, *J* = 14.70 Hz, 2H), 3.89 - 4.00 (m, 1H), 3.73 (s, 3H), 3.65 (d, *J* = 13.64 Hz, 1H), 3.43 (td, *J* = 4.36, 11.24 Hz, 1H), 3.24 - 3.37 (m, 2H), 3.20 (d, *J* = 13.64 Hz, 1H), 2.92 - 3.09 (m, 2H), 2.19 (s, 3H), 1.88 - 1.97 (m, 2H), 1.92 (s, 3H), 1.18 (s, 3H); MS (ESI+) *m/z* 553.3 $(M+H)^+$.

Example 17

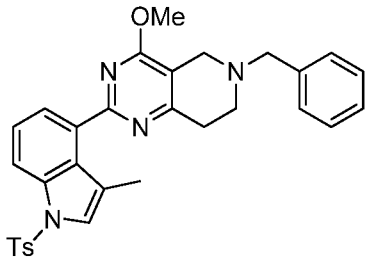
17-A. 6-Benzyl-2-chloro-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 6-benzyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (CAS# 778574-06-4 2.0 g, 6.80 mmol) in MeOH (70 mL) at 0 °C was added 25% sodium methoxide in methanol (1.9 mL, 8.2 mmol) to give a suspension. After 15 minutes the reaction became a homogeneous solution, at which time an additional aliquot of 25% sodium methoxide in methanol (0.25 mL, 1.1 mmol) was added and the

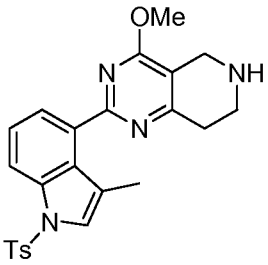
reaction was stirred for 15 minutes. The reaction was then diluted with water and diethyl ether and the resulting layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting yellow oil was used without further purification. ^1H NMR (400 MHz, CD_2Cl_2) δ ppm 2.71 - 2.91 (m, 4 H) 3.43 (m, 2 H) 3.72 (m, 2 H) 3.95 (s, 3 H) 7.24 - 7.42 (m, 5 H). MS (ESI+) *m/z* 290.2 $(M+H)^+$.

17-B. 6-Benzyl-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



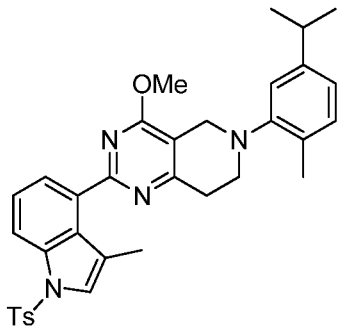
To a solution of 6-benzyl-2-chloro-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.0 g, 3.45 mmol) in DME (10.0 mL) in a 20 mL microwave reaction vial was added 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indole (1.57 g, 3.80 mmol). Then 2 M aqueous Na_2CO_3 (5.6 mL, 11.22 mmol) was added. The reaction mixture was degassed via a series of 3 argon/vacuum cycles and then placed under an atmosphere of argon. Then $Pd(Ph_3P)_4$ (0.399 g, 0.345 mmol) was added and the vial was sealed and heated via microwave irradiation at 140 °C for 90 minutes. The reaction mixture was cooled to room temperature and diluted with Et_2O and water. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (27-48% ethyl acetate/heptanes) to provide 6-benzyl-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine as a white solid. MS (ESI+) *m/z* 539.3 $(M+H)^+$.

17-C. 4-Methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



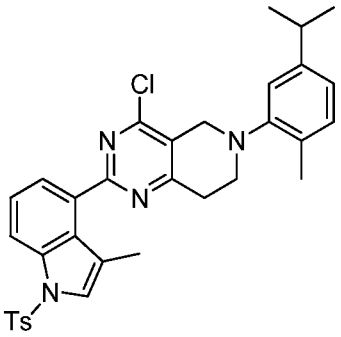
To a solution of 6-benzyl-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.1 g, 2.0 mmol) in THF (15 mL) was added water (3.75 mL) and acetic acid (0.34 mL, 5.9 mmol), then 20 mol% $Pd(OH)_2$/carbon (50% wet) (0.86 g, 0.61 mmol) was added. The reaction mixture was placed under an atmosphere of hydrogen gas via balloon. After 1.5 hours the mixture was diluted with ethyl acetate and neutralized with saturated aqueous $NaHCO_3$. The mixture was then filtered through a pad of Celite®. The eluent was then further diluted with ethyl acetate and brine and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (0-20% MeOH/DCM) to provide 4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 (d, *J*=1.0 Hz, 3 H) 2.32 (s, 3 H) 2.68 (t, *J*=5.6 Hz, 2 H) 3.00 (t, *J*=5.7 Hz, 2 H) 3.72 (s, 2 H) 3.92 (s, 3 H) 7.30 - 7.48 (m, 4 H) 7.65 (d, *J*=1.0 Hz, 1 H) 7.85 (d, *J*=8.3 Hz, 2 H) 8.04 (dd, *J*=7.3, 2.0 Hz, 1 H). MS (ESI+) *m/z* 449.2 $(M+H)^+$.

17-D. 6-(5-Isopropyl-2-methylphenyl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



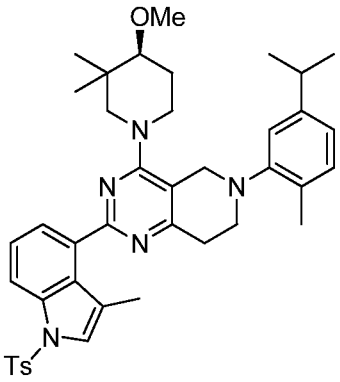
To a solution of 4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.32 g, 2.94 mmol) in THF (11 mL) in a 20 mL microwave vial was added 5-isopropyl-2-methylphenyl trifluoromethanesulfonate, prepared as described in **Example 15** (1.25 g, 4.41 mmol). Then cesium carbonate (2.4 g, 7.36 mmol) was added followed by X-Phos (CAS# 564483-18-7, 0.28 g, 0.59 mmol). The reaction mixture was degassed via several vacuum/nitrogen cycles and then $Pd(OAc)_2$ (53 mg, 0.235 mmol) was added. The vial was sealed and heated via microwave irradiation at 120 °C for 90 minutes. The reaction was then diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted two additional times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (0-50% ethyl acetate/heptanes) to provide: 6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 581.2 $(M+H)^+$.

17-E. 4-Chloro-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



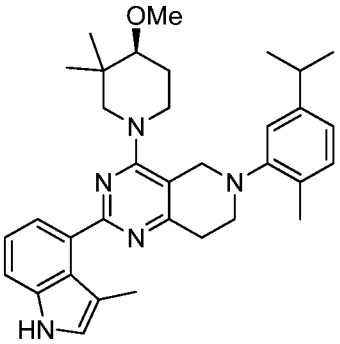
Ethanol (4 mL) was added to 6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.92 g, 1.58 mmol) and then 12 N aqueous HCl (2 mL, 24 mmol) was added and the mixture was heated to 68 °C for ca. 15 hours. The reaction was then cooled to room temperature, diluted with dichloromethane, and neutralized via the slow addition of saturated aqueous sodium bicarbonate. The resulting layers were separated and the aqueous layer was extracted two additional times with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was then dissolved in dichloromethane (20 mL) and cooled to 0 °C and N-chloromethylene-N,N-dimethyl ammonium chloride (Vilsmeier reagent) (0.41 g, 3.21 mmol) was added. The reaction was then placed at room temperature for 25 minutes. The reaction was then diluted with dichloromethane and saturated aqueous sodium bicarbonate. The resulting layers were separated and the aqueous layer was extracted one additional time with dichloromethane. The organic layers were combined, dried over Na_2SO_4 filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (0-45% ethyl acetate/heptanes) to provide 4-chloro-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 585.2 $(M+H)^+$.

17-F. (*S*)-6-(5-Isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



Isopropanol (2 mL) was added to a microwave vial containing a mixture of 4-chloro-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (150 mg, 0.256 mmol) and the trifluoroacetic acid salt of (*S*)-4-methoxy-3,3-dimethylpiperidine (120 mg, 0.461 mmol). Then diisopropylethylamine (0.32 mL, 1.8 mmol) was added and the vial was sealed and heated via microwave irradiation at 125 °C for 3.5 hours. The reaction was then cooled to room temperature and diluted with ethyl acetate and saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel chromatography (0-60% ethyl acetate/heptanes) to afford: (*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 692.5 $(M+H)^+$.

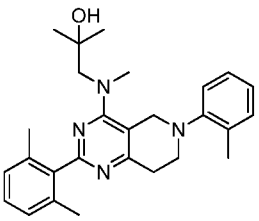
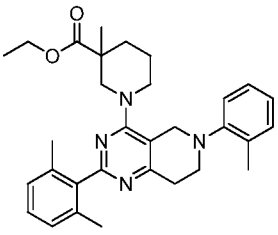
17-G. (*S*)-6-(5-Isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

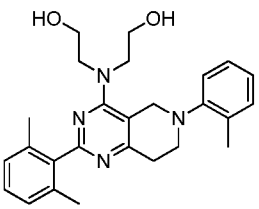
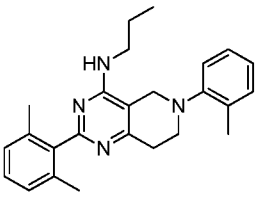
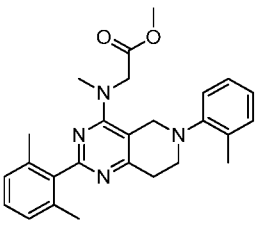
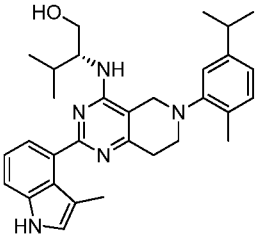


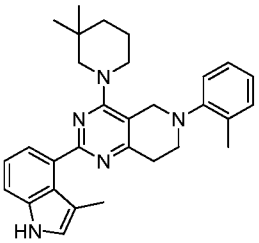
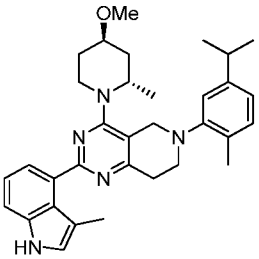
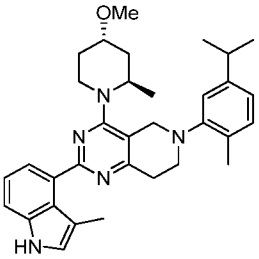
To a solution of (*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (135 mg, 0.195 mmol) in

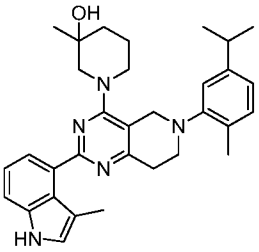
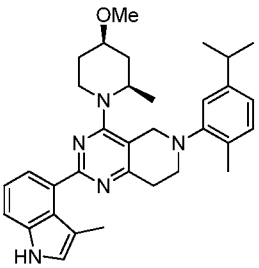
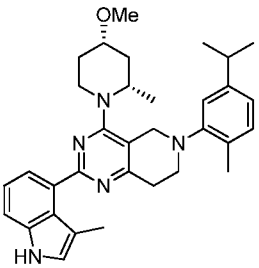
methanol (2 mL) in a microwave vial was added KOH (100 mg, 1.75 mmol) followed by 28% ammonium hydroxide in water (1 mL, 7.25 mmol). The vial was sealed and heated via microwave irradiation at 80 °C for 75 minutes. The reaction mixture was cooled to room temperature and diluted with dichloromethane and brine. The layers were separated and the aqueous layer was extracted two additional times with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (0-70% ethyl acetate/heptanes) to furnish (*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 (s, 3 H) 0.98 (s, 3 H) 1.18 (d, *J*=6.8 Hz, 6 H) 1.51 - 1.62 (m, 1 H) 1.91 - 1.99 (m, 1 H) 2.01 (s, 3 H) 2.21 (s, 3 H) 2.78 - 2.88 (m, 2 H) 2.91 - 3.08 (m, 4 H) 3.29 (s, 3 H) 3.31 - 3.41 (m, 3 H) 3.60 - 3.71 (m, 1 H) 4.07 (s, 2 H) 6.86 (d, *J*=7.3 Hz, 1 H) 6.96 (s, 1 H) 7.07 - 7.15 (m, 3 H) 7.20 (d, *J*=7.1 Hz, 1 H) 7.41 (d, *J*=7.8 Hz, 1 H) 10.89 (br. s., 1 H); MS (ESI+) *m/z* 538.4 $(M+H)^+$.

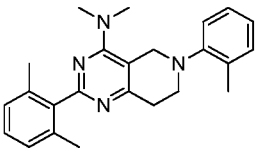
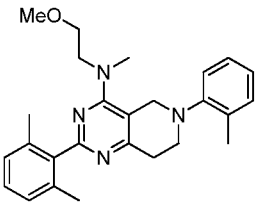
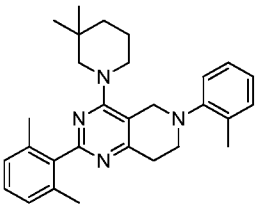
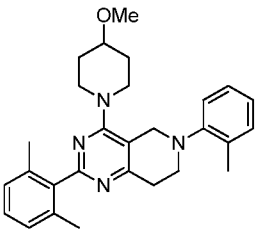
The following compounds were prepared in a similar manner.

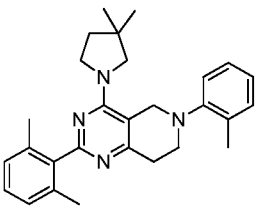
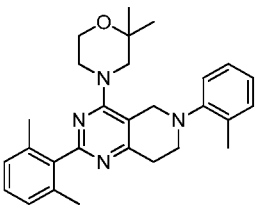
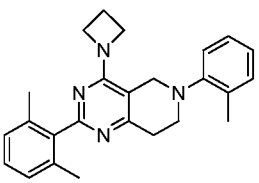
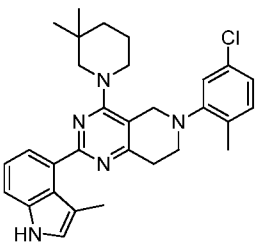
	Structure	Chemical Name&Analytical Data
17-H		1-((2-(2,6-Dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.13 - 7.26 (m, 4 H), 7.00 - 7.11 (m, 3 H), 4.17 (s, 2 H), 3.54 (s, 2 H), 3.26 - 3.32 (m, 5 H), 3.05 (t, *J*=5.8 Hz, 2 H), 2.34 (s, 3 H), 2.11 (s, 6 H), 1.14 (s, 6 H); MS (ESI+) *m/z* 431.2 $(M+H)^+$.
17-I		Ethyl 1-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidine-3-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.25 (m, 4 H), 7.08 (d, *J*=7.6 Hz, 2 H), 7.01 (t, *J*=7.1 Hz, 1 H), 4.03 - 4.15 (m, 2 H), 3.81 - 3.96 (m, 2 H), 3.77 (d, *J*=14.4 Hz, 1 H), 3.58 - 3.67 (m, 1 H), 3.19 - 3.28 (m, 1 H), 2.85 - 3.05 (m, 4 H), 2.24 (s, 3 H), 2.08 - 2.16 (m, 1 H), 2.05 (s, 6 H), 1.57 - 1.67 (m, 2 H), 1.35 - 1.44 (m, 1 H), 1.09 (s, 3 H), 0.97 (t, *J*=7.1 Hz, 3 H); MS (ESI+) *m/z* 499.2 $(M+H)^+$.

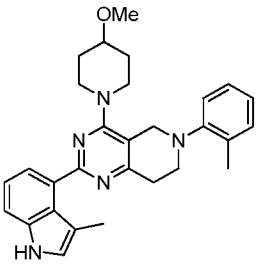
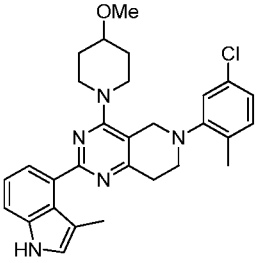
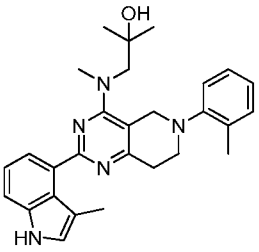
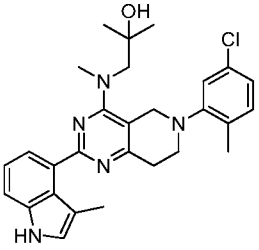
17-J		2,2'-((2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)azanediyl)diethanol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.23 (m, 4 H), 7.07 (d, *J*=7.6 Hz, 2 H), 6.97 - 7.02 (m, 1 H), 4.76 (t, *J*=5.1 Hz, 2 H), 4.11 (s, 2 H), 3.49 - 3.60 (m, 8 H), 3.23 (t, *J*=5.9 Hz, 2 H), 2.92 (t, *J*=5.7 Hz, 2 H), 2.27 (s, 3 H), 2.04 (s, 6 H); MS (ESI+) *m/z* 433.1 $(M+H)^+$.
17-K		2-(2,6-dimethylphenyl)-N-propyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.12 - 7.29 (m, 4 H), 6.98 - 7.10 (m, 3 H), 3.80 (s, 2 H), 3.19 (t, *J*=5.7 Hz, 2 H), 2.78 - 2.86 (m, 2 H), 2.31 (s, 3 H), 2.07 (br. s., 6 H), 1.53 (sxt, *J*=7.1 Hz, 2 H), 0.85 (t, *J*=7.3 Hz, 3 H); MS (ESI+) *m/z* 387.2 $(M+H)^+$.
17-L		methyl 2-((2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)acetate. ^{1}H NMR HCl salt (400 MHz, DMSO-d_6) ppm 7.39 (t, *J*=7.7 Hz, 1 H), 7.19 - 7.27 (m, 5 H), 7.02 - 7.08 (m, 1 H), 4.47 (br. s., 2 H), 4.34 (br. s., 2 H), 3.61 (s, 3 H), 3.26 (t, *J*=5.6 Hz, 2 H), 3.04 (br. s., 2 H), 2.28 (s, 3 H), 2.11 (s, 6 H); MS (ESI+) *m/z* 431.2 $(M+H)^+$.
17-M		(*R*)-2-((6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)amino)-3-methylbutan-1-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.52 (br. s., 1 H), 7.35 (d, *J*=6.6 Hz, 1 H), 7.19 - 7.23 (m, 1 H), 7.16 (d, *J*=7.8 Hz, 1 H), 7.08 - 7.14 (m, 2 H), 6.95 (dd, *J*=7.8, 1.8 Hz, 1 H), 3.72 - 3.87 (m, 3 H), 3.26 (br. s., 1 H), 3.06 (br. s., 2 H), 2.90 (spt, *J*=6.3 Hz, 1 H), 2.30 (s, 3 H), 2.13 (s, 3 H), 2.04 (spt, *J*=6.6 Hz, 1 H), 1.26 (d, *J*=7.1 Hz, 6 H), 0.99 (d, *J*=6.8 Hz, 3 H), 0.96 (d, *J*=6.8 Hz, 3 H); MS (ESI+) *m/z* 498.3 $(M+H)^+$.

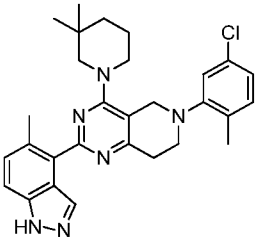
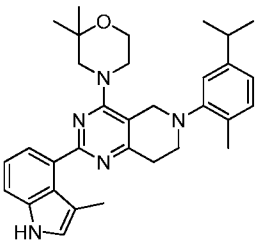
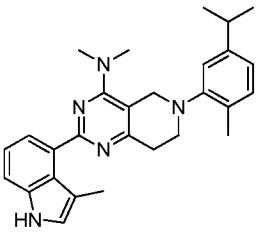
17-N		4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.46 - 7.54 (m, 1 H), 7.37 - 7.44 (m, 1 H), 7.22 - 7.30 (m, 3 H), 7.14 - 7.19 (m, 1 H), 7.09 (d, *J*=12.9 Hz, 2 H), 4.03 (s, 2 H), 3.40 (br. s., 1 H), 3.35 (t, *J*=5.9 Hz, 2 H), 3.20 (br. s., 4 H), 2.33 (s, 3 H), 2.10 (s, 3 H), 1.69 - 1.75 (m, 2 H), 1.45 - 1.51 (m, 2 H), 1.01 (s, 6 H); MS (ESI+) *m/z* 466.3 $(M+H)^+$.
17-O		6-(5-isopropyl-2-methylphenyl)-4-((2*S*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 9.96 - 10.13 (br. s., 1 H), 7.47 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.39 (dd, *J*=7.3, 1.0 Hz, 1 H), 7.13 - 7.20 (m, 3 H), 7.11 (d, *J*=1.8 Hz, 1 H), 6.92 (dd, *J*=7.6, 1.8 Hz, 1 H), 4.34 - 4.42 (m, 1 H), 4.02 - 4.20 (m, 2 H), 3.82 (dt, *J*=13.5, 4.2 Hz, 1 H), 3.62 - 3.72 (m, 1 H), 3.40 - 3.46 (m, 2 H), 3.33 (s, 3 H), 3.08 (t, *J*=6.2 Hz, 2 H), 2.91 (dt, *J*=13.9, 6.9 Hz, 1 H), 2.76 (m, 2 H), 2.30 (s, 3 H), 2.18 (s, 3 H), 1.94 - 2.01 (m, 1 H), 1.66 (ddd, *J*=12.6, 10.4, 5.3 Hz, 1 H), 1.55 (m, 1 H), 1.32 (d, *J*=6.8 Hz, 3 H), 1.26 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.
17-P		6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*S*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 9.96 - 10.13 (br. s., 1 H), 7.47 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.39 (dd, *J*=7.3, 1.0 Hz, 1 H), 7.13 - 7.20 (m, 3 H), 7.11 (d, *J*=1.8 Hz, 1 H), 6.92 (dd, *J*=7.6, 1.8 Hz, 1 H), 4.34 - 4.42 (m, 1 H), 4.02 - 4.20 (m, 2 H), 3.82 (dt, *J*=13.5, 4.2 Hz, 1 H), 3.62 - 3.72 (m, 1 H), 3.40 - 3.46 (m, 2 H), 3.33 (s, 3 H), 3.08 (t, *J*=6.2 Hz, 2 H), 2.91 (dt, *J*=13.9, 6.9 Hz, 1 H), 2.76 (m, 2 H), 2.30 (s, 3 H), 2.18 (s, 3 H), 1.94 - 2.01 (m, 1 H), 1.66 (ddd, *J*=12.6, 10.4, 5.3 Hz, 1 H), 1.55 (m, 1 H), 1.32 (d, *J*=6.8 Hz, 3 H), 1.26 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 524.3

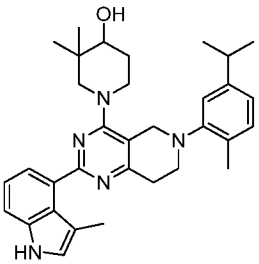
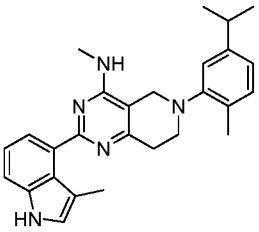
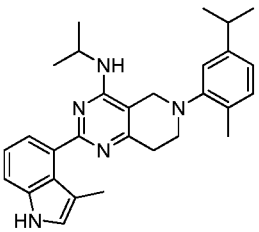
		$(M+H)^+$.
17-Q		1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.47 (d, *J*=8.1 Hz, 1 H), 7.32 (d, *J*=7.1 Hz, 1 H), 7.18 - 7.26 (m, 1 H), 7.14 (d, *J*=7.8 Hz, 1 H), 7.07 (d, *J*=1.3 Hz, 1 H), 7.00 (d, *J*=1.8 Hz, 1 H), 6.92 (dd, *J*=7.7, 1.6 Hz, 1 H), 3.98 - 4.13 (m, 2 H), 3.83 - 3.98 (m, 2 H), 3.35 - 3.46 (m, 1 H), 3.25 - 3.34 (m, 1 H), 3.12 - 3.25 (m, 2 H), 2.96 - 3.12 (m, 2 H), 2.89 (dt, *J*=13.8, 6.9 Hz, 1 H), 2.27 (s, 3 H), 2.10 (s, 3 H), 1.81 - 1.96 (m, 1 H), 1.76 (d, *J*=15.2 Hz, 1 H), 1.42 - 1.65 (m, 2 H), 1.25 (d, *J*=7.1 Hz, 6 H), 1.20 (s, 3 H); MS (ESI+) *m/z* 510.2 $(M+H)^+$.
17-R		6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.81 - 11.02 (m, 1 H), 7.33 - 7.52 (m, 1 H), 7.22 (d, *J*=1.0 Hz, 1 H), 7.07 - 7.16 (m, 3 H), 6.96 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.04 - 4.13 (m, 1 H), 3.93 - 4.02 (m, 1 H), 3.76 - 3.87 (m, 1 H), 3.41 - 3.50 (m, 1 H), 3.31 - 3.37 (m, 3 H), 3.26 (s, 3 H), 3.11 - 3.23 (m, 1 H), 2.96 (t, *J*=5.7 Hz, 2 H), 2.84 (dt, *J*=13.9, 6.9 Hz, 1 H), 2.22 (s, 3 H), 2.02 (s, 3 H), 1.84 - 1.95 (m, 2 H), 1.52 - 1.67 (m, 2 H), 1.15 - 1.23 (m, 9 H); MS (ESI+) *m/z* 524.2 $(M+H)^+$.
17-S		6-(5-isopropyl-2-methylphenyl)-4-((2*S*,4*S*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 10.07 (br. s., 1 H), 7.48 (d, *J*=9.1 Hz, 1 H), 7.41 (d, *J*=7.3 Hz, 1 H), 7.13 - 7.22 (m, 3 H), 7.10 (d, *J*=1.5 Hz, 1 H), 6.93 (dd, *J*=1.6, 7.7 Hz, 1 H), 4.03 - 4.28 (m, 2 H), 3.90 (dd, *J*=6.3, 10.9 Hz, 1 H), 3.49 (dt, *J*=3.5, 7.2 Hz, 1 H), 3.39 - 3.46 (m, 2 H), 3.35 (s, 3 H), 3.18 - 3.26 (m, 1 H), 3.06 - 3.13 (m, 2 H), 2.91 (td, *J*=6.9, 13.8 Hz, 1 H), 2.79 (d, *J*=13.6

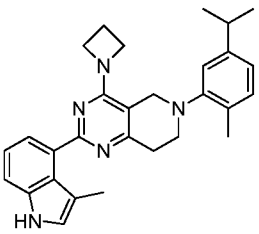
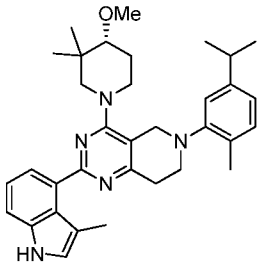
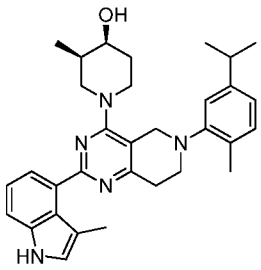
		Hz, 2 H), 2.32 (s, 3 H), 2.18 (d, *J*=0.8 Hz, 3 H), 1.98 – 2.04 (m, 1 H), 1.68 - 1.76 (m, 1 H), 1.59 - 1.68 (m, 1 H), 1.24 - 1.30 (m, 9 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.
17-T		2-(2,6-dimethylphenyl)-N,N-dimethyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.23 (m, 4 H), 7.07 (d, *J*=7.6 Hz, 2 H), 6.96 - 7.04 (m, 1 H), 4.08 (s, 2 H), 3.24 (t, *J*=5.9 Hz, 2 H), 3.01 (s, 6 H), 2.91 (t, *J*=5.8 Hz, 2 H), 2.26 (s, 3 H), 2.06 (s, 6 H); MS (ESI+) *m/z* 373.2 $(M+H)^+$.
17-U		2-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-N-methyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine. HCl salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, *J*=7.1 Hz, 1 H), 7.17 - 7.28 (m, 5 H), 6.99 - 7.09 (m, 1 H), 4.31 (br. s., 2 H), 3.89 (t, *J*=4.8 Hz, 2 H), 3.53 - 3.62 (m, 5 H), 3.19 - 3.29 (m, 5 H), 3.01 - 3.10 (m, 2 H), 2.28 (s, 3 H), 2.19 (s, 6 H); MS (ESI+) *m/z* 417.3 $(M+H)^+$.
17-V		2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. HCl salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=6.8 Hz, 1 H), 7.19 - 7.28 (m, 5 H), 7.05 (td, *J*=6.9, 2.0 Hz, 1 H), 4.16 (s, 2 H), 3.76 (br. s., 2 H), 3.59 (s, 2 H), 3.29 (t, *J*=5.6 Hz, 2 H), 3.05 - 3.14 (m, 2 H), 2.28 (s, 3 H), 2.19 (s, 6 H), 1.62 - 1.73 (m, 2 H), 1.47 (t, *J*=5.6 Hz, 2 H), 0.89 (s, 6 H); MS (ESI+) *m/z* 441.3 $(M+H)^+$.
17-W		2-(2,6-dimethylphenyl)-4-(4-methoxypiperidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.17 - 7.30 (m, 5 H), 7.01 - 7.09 (m, 1 H), 4.14 (br. s., 2 H), 3.95 - 4.06 (m, 2 H), 3.64 - 3.73 (m, 2 H), 3.21 - 3.31 (m, 4 H), 3.10 (br. s., 2 H), 2.28 (s, 3 H), 2.20 (s, 6 H), 1.88 - 2.01 (m, 2 H), 1.59 (s, 3 H); MS (ESI+) *m/z* 443.3 $(M+H)^+$.

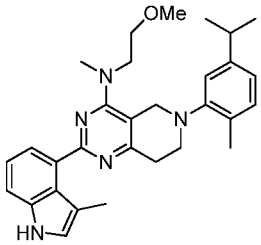
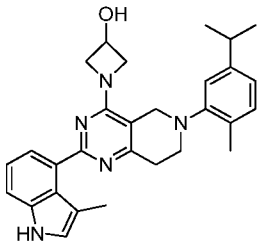
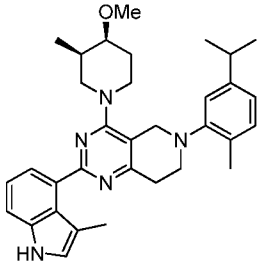
17-X		2-(2,6-dimethylphenyl)-4-(3,3-dimethylpyrrolidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.18 - 7.27 (m, 3 H) 7.14 (d, J=7.3 Hz, 1 H) 7.06 (d, J=7.6 Hz, 2 H) 7.02 (br. s., 1 H) 4.23 (s, 2 H) 3.74 (t, J=7.0 Hz, 2 H) 3.10 - 3.24 (m, 3 H) 2.87 (t, J=5.3 Hz, 2 H) 2.28 (s, 3 H) 2.07 (s, 6 H) 1.65 (t, J=7.0 Hz, 2 H) 1.05 (s, 6 H); MS (ESI+) *m/z* 427.29 $(M+H)^+$.
17-Y		4-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,2-dimethylmorpholine. HCl salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=7.8 Hz, 1 H), 7.19 - 7.29 (m, 5 H), 7.05 (dd, *J*=7.6, 6.8 Hz, 1 H), 4.16 (s, 2 H), 3.84 (br. s., 2 H), 3.71 (br. s., 4 H), 3.21 - 3.29 (m, 2 H), 3.09 (br. s., 2 H), 2.28 (s, 3 H), 2.18 (s, 6 H), 1.16 (s, 6 H); MS (ESI+) *m/z* 443.3 $(M+H)^+$.
17-Z		4-(azetidin-1-yl)-2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. HCl salt ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.18 - 7.29 (m, 5 H), 7.01 - 7.09 (m, 1 H), 4.83 - 4.92 (m, 2 H), 4.22 - 4.31 (m, 2 H), 4.20 (s, 2 H), 3.15 - 3.21 (m, 2 H), 2.92 - 2.98 (m, 2 H), 2.32 - 2.41 (m, 2 H), 2.30 (s, 3 H), 2.19 (s, 6 H); MS (ESI+) *m/z* 385.3 $(M+H)^+$.
17-AA		6-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.46 (d, *J*=7.8 Hz, 1 H), 7.33 - 7.40 (m, 1 H), 7.19 - 7.25 (m, 1 H), 7.17 (d, *J*=8.1 Hz, 1 H), 7.05 - 7.11 (m, 2 H), 7.02 (dd, *J*=8.1, 2.0 Hz, 1 H), 4.00 (s, 2 H), 3.30 - 3.46 (m, 4 H), 3.09 - 3.28 (m, 4 H), 2.29 (s, 3 H), 2.10 (s, 3 H), 1.68 - 1.77 (m, 2 H), 1.42 - 1.48 (m, 2 H), 0.98 (s, 6 H); MS (ESI+) *m/z* 500.3 $(M+H)^+$.

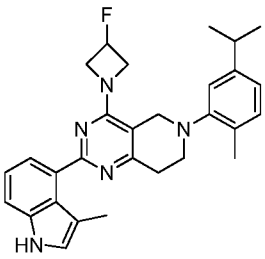
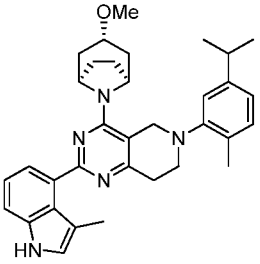
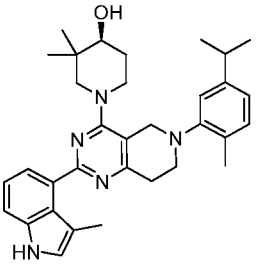
17-AB		4-(4-methoxypiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.26 (br. s., 1 H), 7.46 (d, *J*=9.3 Hz, 1 H), 7.38 (d, *J*=6.3 Hz, 1 H), 7.19 - 7.24 (m, 3 H), 7.13 (d, *J*=6.8 Hz, 1 H), 7.07 (s, 1 H), 7.02 - 7.05 (m, 1 H), 4.01 (s, 2 H), 3.76 (br. s., 2 H), 3.43 (br. s., 1 H), 3.30 - 3.37 (m, 6 H), 3.12 - 3.28 (br. s., 3 H), 2.32 (s, 3 H), 2.10 (s, 3 H), 1.93 - 2.01 (m, 2 H), 1.60 - 1.71 (m, 2 H); MS (ESI+) *m/z* 468.3 $(M+H)^+$.
17-AC		6-(5-chloro-2-methylphenyl)-4-(4-methoxypiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.20 – 8.29 (br. s., 1 H), 7.45 (d, *J*=7.8 Hz, 1 H), 7.37 (d, *J*=7.3 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.16 (d, *J*=0.5 Hz, 1 H), 7.11 (d, *J*=2.3 Hz, 1 H), 7.07 (s, 1 H), 7.02 (dd, *J*=7.8, 2.0 Hz, 1 H), 3.98 (s, 2 H), 3.69 - 3.79 (m, 2 H), 3.39 - 3.46 (m, 1 H), 3.31 - 3.37 (m, 5 H), 3.11 - 3.27 (m, 4 H), 2.28 (s, 3 H), 2.10 (d, *J*=0.8 Hz, 3 H), 1.94 - 2.02 (m, 2 H), 1.60 - 1.70 (m, 2 H); MS (ESI+) *m/z* 502.3 $(M+H)^+$.
17-AD		2-methyl-1-(methyl(2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)amino)propan-2-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.89 (br. s., 1 H), 7.37 (d, *J*=10.1 Hz, 1 H), 7.07 - 7.22 (m, 6 H), 7.00 - 7.03 (m, 1 H), 4.71 (s, 1 H), 4.09 (s, 2 H), 3.67 (s, 2 H), 3.19 (s, 3 H), 2.94 (s, 2 H), 2.26 (s, 3 H), 2.00 (s, 3 H), 1.05 (s, 6 H); MS (ESI+) *m/z* 456.2 $(M+H)^+$.
17-AE		1-((6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (br. s, 1 H), 7.39 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.23 (d, *J*=8.1 Hz, 1 H), 7.03 - 7.16 (m, 5 H), 4.71 (s, 1 H), 4.15 (s, 2 H), 3.69 (s, 2 H), 3.19 (s, 3 H), 2.91 (t, *J*=5.7 Hz, 2 H), 2.24 (s, 3 H), 1.99 (s, 3 H), 1.06 (s, 6 H); MS (ESI+) *m/z* 490.2 $(M+H)^+$.

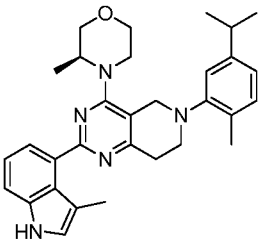
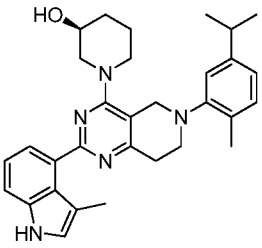
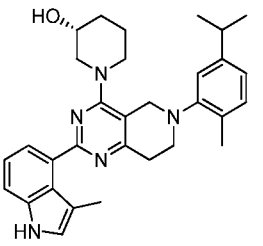
17-AF		6-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.83 - 7.87 (m, 1 H), 7.28 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.1 Hz, 1 H), 7.12 - 7.17 (m, 2 H), 7.09 (dd, *J*=8.1, 2.0 Hz, 1 H), 4.02 (s, 2 H), 3.73 - 3.78 (m, 2 H), 3.58 - 3.64 (m, 2 H), 3.55 (s, 2 H), 3.37 (t, *J*=5.8 Hz, 2 H), 2.67 (s, 3 H), 2.31 (s, 3 H), 1.75 - 1.81 (m, 2 H), 1.50 - 1.56 (m, 2 H), 0.95 (s, 6 H); MS (ESI+) *m/z* 501.2 $(M+H)^+$.
17-AG		4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,2-dimethylmorpholine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.24 (s, 3 H) 1.26 (s, 3 H) 1.28 (s, 6 H) 2.10 (s, 3 H) 2.29 (s, 3 H) 2.89 (dt, *J*=13.9, 7.0 Hz, 1 H) 3.10 - 3.21 (m, 2 H) 3.22 - 3.31 (m, 2 H) 3.37 (t, *J*=5.9 Hz, 2 H) 3.40 - 3.45 (m, 2 H) 3.78 - 3.87 (m, 2 H) 4.04 (s, 2 H) 6.91 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.97 (d, *J*=1.5 Hz, 1 H) 7.07 (s, 1 H) 7.14 (d, *J*=8.1 Hz, 1 H) 7.22 (t, *J*=7.7 Hz, 1 H) 7.36 (d, *J*=7.1 Hz, 1 H) 7.45 (d, *J*=8.1 Hz, 1 H) 8.21 (br. s., 1 H); MS (ESI+) *m/z* 510.3 $(M+H)^+$.
17-AH		6-(5-isopropyl-2-methylphenyl)-N,N-dimethyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.25 (d, *J*=6.8 Hz, 6 H) 2.12 (s, 3 H) 2.28 (s, 3 H) 2.89 (spt, *J*=6.9 Hz, 1 H) 3.06 - 3.24 (m, 8 H) 3.34 (t, *J*=5.9 Hz, 2 H) 4.09 (s, 2 H) 6.92 (dd, *J*=7.7, 1.6 Hz, 1 H) 7.01 (d, *J*=1.8 Hz, 1 H) 7.06 (d, *J*=1.0 Hz, 1 H) 7.14 (d, *J*=7.6 Hz, 1 H) 7.21 (t, *J*=7.7 Hz, 1 H) 7.38 (d, *J*=7.1 Hz, 1 H) 7.45 (d, *J*=8.1 Hz, 1 H) 8.27 (br. s., 1 H); MS (ESI+) *m/z* 440.2 $(M+H)^+$.

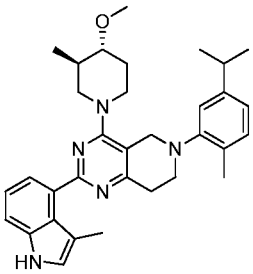
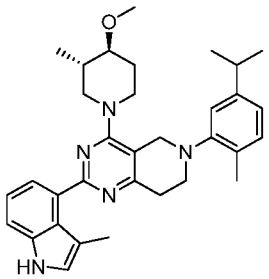
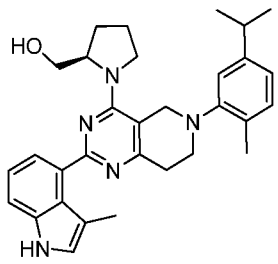
17-AI		1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3,3-dimethylpiperidin-4-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90 (s, 3 H) 0.93 (s, 3 H) 1.18 (d, *J*=6.8 Hz, 6 H) 1.52 - 1.65 (m, 1 H) 1.70 - 1.78 (m, 1 H) 2.01 (s, 3 H) 2.21 (s, 3 H) 2.74 (d, *J*=12.9 Hz, 1 H) 2.83 (dt, *J*=13.6, 6.8 Hz, 1 H) 2.90 - 3.05 (m, 3 H) 3.26 - 3.36 (m, 3 H) 3.42 (d, *J*=13.1 Hz, 1 H) 3.61 - 3.70 (m, 1 H) 4.06 (s, 2 H) 4.63 (d, *J*=4.8 Hz, 1 H) 6.86 (dd, *J*=7.6, 1.3 Hz, 1 H) 6.96 (s, 1 H) 7.07 - 7.15 (m, 3 H) 7.19 (dd, *J*=7.1, 1.0 Hz, 1 H) 7.40 (dd, *J*=8.0, 0.9 Hz, 1 H) 10.89 (br. s., 1 H); MS (ESI+) *m/z* 524.4 $(M+H)^+$.
17-AJ		6-(5-isopropyl-2-methylphenyl)-N-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.23 (br. s., 1 H), 7.42 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.34 (dd, *J*=7.3, 1.0 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.16 (d, *J*=7.8 Hz, 1 H), 7.03 - 7.07 (m, 2 H), 6.93 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.56 (br. s., 1 H), 3.85 (s, 2 H), 3.28 (t, *J*=5.7 Hz, 2 H), 3.09 (d, *J*=4.8 Hz, 3 H), 3.02 (t, *J*=5.6 Hz, 2 H), 2.89 (spt, *J*=6.9 Hz, 1 H), 2.32 (s, 3 H), 2.12 (d, *J*=1.0 Hz, 3 H), 1.26 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 426.2 $(M+H)^+$.
17-AK		N-isopropyl-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_6) δ ppm 8.23 (br. s., 1 H), 7.42 (dd, *J*=8.1, 0.8 Hz, 1 H), 7.33 (d, *J*=7.1 Hz, 1 H), 7.15 - 7.23 (m, 2 H), 7.08 (d, *J*=1.8 Hz, 1 H), 7.05 (d, *J*=1.0 Hz, 1 H), 6.94 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.48 - 4.57 (m, 1 H), 3.80 (s, 2 H), 3.28 (t, *J*=5.7 Hz, 2 H), 2.99 - 3.07 (m, 2 H), 2.90 (spt, *J*=6.9 Hz, 1 H), 2.33 (s, 3 H), 2.12 (d, *J*=1.0 Hz, 3 H), 1.23 - 1.28 (m, 12 H); MS (ESI+) *m/z* 454.2 $(M+H)^+$.

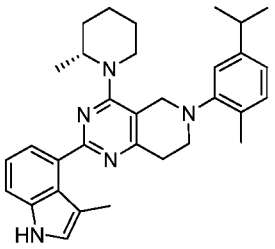
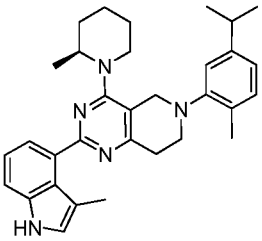
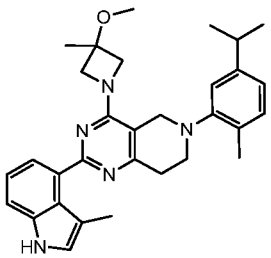
17-AL		4-(azetidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.16 - 8.22 (m, 1 H), 7.41 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.29 - 7.32 (m, 1 H), 7.16 - 7.21 (m, 1 H), 7.14 (d, *J*=7.6 Hz, 1 H), 7.02 - 7.05 (m, 1 H), 6.99 (d, *J*=1.8 Hz, 1 H), 6.90 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.29 (t, *J*=7.6 Hz, 4 H), 4.06 (s, 2 H), 3.28 (t, *J*=5.7 Hz, 2 H), 2.99 - 3.05 (m, 2 H), 2.88 (spt, *J*=6.9 Hz, 1 H), 2.29 - 2.40 (m, 5 H), 2.10 (d, *J*=0.8 Hz, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 452.1 $(M+H)^+$.
17-AM		(*R*)-6-(5-Isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 0.94 - 0.99 (m, 3 H) 1.01 (s, 3 H) 1.25 (d, *J*=7.1 Hz, 6 H) 1.63 - 1.76 (m, 1 H) 1.91 - 2.03 (m, 1 H) 2.10 (s, 3 H) 2.28 (s, 3 H) 2.81 - 3.03 (m, 3 H) 3.11 - 3.25 (m, 3 H) 3.34 (s, 3 H) 3.35 - 3.39 (m, 2 H) 3.41 - 3.53 (m, 1 H) 3.74 (dd, *J*=11.4, 6.3 Hz, 1 H) 4.05 (s, 2 H) 6.91 (dd, *J*=7.6, 1.5 Hz, 1 H) 6.97 (d, *J*=1.5 Hz, 1 H) 7.06 (d, *J*=1.0 Hz, 1 H) 7.14 (d, *J*=7.8 Hz, 1 H) 7.19 - 7.25 (m, 1 H) 7.36 (d, *J*=7.1 Hz, 1 H) 7.45 (d, *J*=8.1 Hz, 1 H) 8.27 (br. s., 1 H); MS (ESI+) *m/z* 538.4 $(M+H)^+$.
17-AN		*racemic*-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-4-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.24 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.35 (d, *J*=7.1 Hz, 1 H), 7.19 - 7.23 (m, *J*=7.6 Hz, 1 H), 7.13 (d, *J*=7.8 Hz, 1 H), 7.06 (d, *J*=1.0 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.90 (dd, *J*=8.1, 1.5 Hz, 1 H), 4.03 (d, *J*=7.1 Hz, 2 H), 3.93 (br. s., 1 H), 3.39 - 3.61 (m, 1 H), 3.35 (t, *J*=6.3 Hz, 2 H), 3.24 (app t, *J*=11.9 Hz, 1 H), 3.15 (br. s., 1 H), 2.89 (spt, *J*=7.1 Hz, 1 H), 2.27 (s, 3 H), 2.10 (s, 1 H), 1.92 - 2.00 (m, 1 H), 1.78 - 1.88 (m, 2 H), 1.25 (d, *J*=7.1 Hz, 6 H), 0.99 (d, *J*=7.1 Hz, 3 H); MS

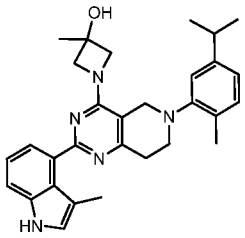
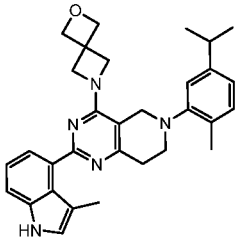
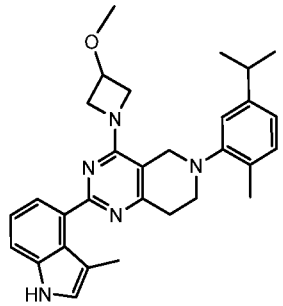
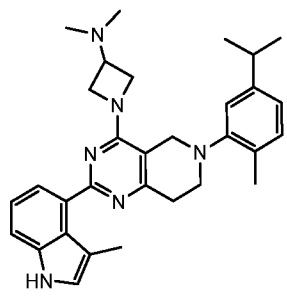
		(ESI+) *m/z* 510.2 $(M+H)^+$.
17-AO		6-(5-isopropyl-2-methylphenyl)-N-(2-methoxyethyl)-N-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.37 (br. s., 1 H), 7.43 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.36 (dd, *J*=7.1 Hz, 1 H), 7.17 - 7.23 (m, 1 H), 7.14 (d, *J*=7.6 Hz, 1 H), 7.05 (d, *J*=1.3 Hz, 1 H), 7.00 (d, *J*=1.8 Hz, 1 H), 6.91 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.11 (s, 2 H), 3.72 (br. s., 2 H), 3.62 (app. t, *J*=5.8 Hz, 2 H), 3.33 (app. t, *J*=5.8 Hz, 2 H), 3.30 (s, 3 H), 3.20 (br. s., 4 H), 2.89 (spt, *J*=7.1 Hz, 1 H), 2.27 (s, 3 H), 2.11 (d, *J*=0.8, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 484.22 $(M+H)^+$.
17-AP		1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)azetidin-3-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.43 (d, *J*=7.3 Hz, 1 H), 7.31 (d, *J*=7.3 Hz, 1 H), 7.15 - 7.19 (m, 2 H), 7.05 (s, 1 H), 6.99 (d, *J*=1.8 Hz, 1 H), 6.93 (dd, *J*=8.1, 1.5 Hz, 1 H), 4.65 - 4.74 (m, 1 H), 4.47 (dd, *J*=8.6, 6.8 Hz, 2 H), 4.14 (br. s., 2 H), 4.01 (s, 2 H), 3.25 (t, *J*=5.6 Hz, 2 H), 3.01 - 3.09 (m, 2 H), 2.89 (spt, *J*=6.6 Hz, 1 H), 2.30 (s, 3 H), 2.09 (s, 3 H), 1.26 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 468.3 $(M+H)^+$.
17-AQ		*racemic* 6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.21 (br. s., 1 H), 7.43 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.34 (d, *J*=6.6 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.13 (d, *J*=7.8 Hz, 1 H), 7.05 (dd, *J*=2.0, 1.0 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.90 (dd, *J*=7.6, 1.8 Hz, 1 H), 4.03 (AB q, *J*=6.1 Hz, 2 H), 3.41 - 3.52 (m, 1 H), 3.29 - 3.40 (m, 9 H), 3.11 (br. s., 2 H), 2.89 (spt, *J*=7.3 Hz, 1 H), 2.27 (s, 3 H), 2.09 (s, 3 H), 2.01 - 2.08 (m, 1 H), 1.89 - 1.99 (m, 1 H), 1.66 - 1.77 (m, 1 H), 1.25 (d, *J*=6.8 Hz, 6 H), 0.98 (d, *J*=6.8 Hz, 3 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.

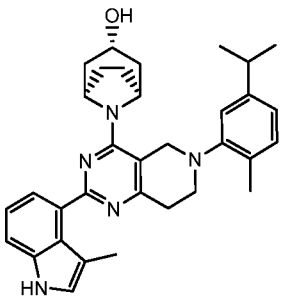
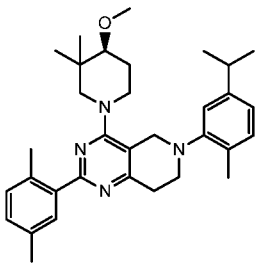
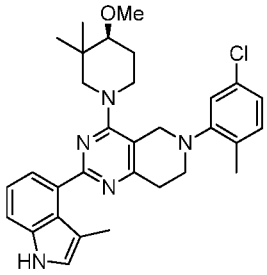
17-AR		4-(3-fluoroazetidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.92 (br. s., 1 H), 7.41 (d, *J*=8.1 Hz, 1 H), 7.21 (d, *J*=8.1 Hz, 1 H), 7.06 - 7.16 (m, 3 H), 7.02 (d, *J*=1.5 Hz, 1 H), 6.89 (dd, *J*=7.8, 1.5 Hz, 1 H), 5.35 - 5.59 (m, 1 H), 4.49 - 4.66 (m, 2 H), 4.23 - 4.38 (m, 2 H), 4.05 (s, 2 H), 3.23 (t, *J*=5.7 Hz, 2 H), 2.81 - 2.94 (m, 3 H), 2.24 (s, 3 H), 2.03 (d, *J*=0.8 Hz, 3 H), 1.20 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 470.1 $(M+H)^+$.
17-AS		6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR TFA salt (400 MHz, DMSO-d_6) δ ppm 10.88 - 10.92 (br. s., 1 H), 7.39 (dd, *J*=8.0, 1.1 Hz, 1 H), 7.19 (dd, *J*=7.2, 1.1 Hz, 1 H), 7.13 (s, 1 H), 7.07 - 7.13 (m, 2 H), 7.01 (d, *J*=1.5 Hz, 1 H), 6.88 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.47 (br. s., 2 H), 4.02 (s, 2 H), 3.47 (br. s., 1 H), 3.21 (s, 3 H), 2.92 (t, *J*=5.9 Hz, 2 H), 2.85 (quin, *J*=6.9 Hz, 1 H), 2.22 (s, 3 H), 1.95 - 2.06 (m, 9 H), 1.79 - 1.95 (m, 4 H), 1.16 - 1.22 (m, 6 H); MS (ESI+) *m/z* 536.2 $(M+H)^+$.
17-AT		(*S*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3,3-dimethylpiperidin-4-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90 (s, 3 H) 0.93 (s, 3 H) 1.18 (d, *J*=6.8 Hz, 6 H) 1.52 - 1.65 (m, 1 H) 1.70 - 1.78 (m, 1 H) 2.01 (s, 3 H) 2.21 (s, 3 H) 2.74 (d, *J*=12.9 Hz, 1 H) 2.83 (dt, *J*=13.6, 6.8 Hz, 1 H) 2.90 - 3.05 (m, 3 H) 3.26 - 3.36 (m, 3 H) 3.42 (d, *J*=13.1 Hz, 1 H) 3.61 - 3.70 (m, 1 H) 4.06 (s, 2 H) 4.63 (d, *J*=4.8 Hz, 1 H) 6.86 (dd, *J*=7.6, 1.3 Hz, 1 H) 6.96 (s, 1 H) 7.07 - 7.15 (m, 3 H) 7.19 (dd, *J*=7.1, 1.0 Hz, 1 H) 7.40 (dd, *J*=8.0, 0.9 Hz, 1 H) 10.89 (br. s., 1 H); MS (ESI+) *m/z* 524.4 $(M+H)^+$.

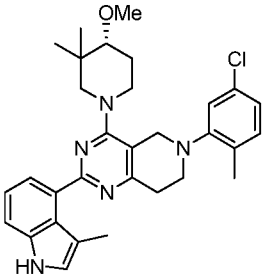
17-AU		(*S*)-4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylmorpholine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.25 (d, *J*=7.6 Hz, 6 H) 1.28 (d, *J*=6.3 Hz, 3 H) 2.11 (s, 3 H) 2.28 (s, 3 H) 2.89 (dt, *J*=13.8, 6.9 Hz, 1 H) 3.08 - 3.24 (m, 2 H) 3.29 - 3.43 (m, 3 H) 3.45 - 3.55 (m, 2 H) 3.57 - 3.71 (m, 2 H) 3.78 (dd, *J*=11.2, 2.7 Hz, 1 H) 3.83 - 3.90 (m, 1 H) 3.92 - 4.10 (m, 2 H) 6.91 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.98 (d, *J*=1.5 Hz, 1 H) 7.07 (s, 1 H) 7.14 (d, *J*=7.8 Hz, 1 H) 7.22 (t, *J*=7.8 Hz, 1 H) 7.36 (d, *J*=7.3 Hz, 1 H) 7.45 (d, *J*=7.8 Hz, 1 H) 8.21 (br. s., 1 H); MS (ESI+) *m/z* 496.3 $(M+H)^+$.
17-AV		(*S*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.26 (d, *J*=7.1 Hz, 6 H) 1.55 - 1.60 (m, 1 H) 1.67 - 1.94 (m, 3 H) 2.10 (s, 3 H) 2.26 (s, 3 H) 2.90 (spt, *J*=7.0 Hz, 1 H) 3.08 - 3.16 (m, 2 H) 3.23 - 3.62 (m, 5 H) 3.76 (dd, *J*=13.4, 4.3 Hz, 1 H) 3.86 - 3.94 (m, 1 H) 3.97 - 4.05 (m, 2 H) 6.92 (dd, *J*=7.7, 1.6 Hz, 1 H) 7.01 (d, *J*=1.5 Hz, 1 H) 7.08 (s, 1 H) 7.13 (d, *J*=7.8 Hz, 1 H) 7.17 - 7.27 (m, 1 H) 7.34 (d, *J*=7.3 Hz, 1 H) 7.48 (d, *J*=8.3 Hz, 1 H) 8.43 (s, 1 H); MS (ESI+) *m/z* 496.5 $(M+H)^+$.
17-AW		(*R*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.25 (d, *J*=6.8 Hz, 6 H) 1.54 - 1.59 (m, 1 H) 1.66 - 1.93 (m, 3 H) 2.11 (s, 3 H) 2.27 (s, 3 H) 2.89 (dt, *J*=13.7, 6.9 Hz, 1 H) 3.03 - 3.22 (m, 2 H) 3.24 - 3.57 (m, 5 H) 3.75 (dd, *J*=13.5, 4.4 Hz, 1 H) 3.85 - 3.94 (m, 1 H) 4.01 (s, 2 H) 6.91 (dd, *J*=7.7, 1.6 Hz, 1 H) 7.00 (d, *J*=1.5 Hz, 1 H) 7.1 (s, 1 H) 7.14 (d, *J*=7.8 Hz, 1 H) 7.18 - 7.26 (m, 1 H) 7.33 (d, *J*=7.3 Hz, 1 H) 7.46 (d, *J*=8.1 Hz, 1 H) 8.29 (br. s., 1 H); MS (ESI+) *m/z* 496.5 $(M+H)^+$.

17-AX		6-(5-isopropyl-2-methylphenyl)-4-((3*R*,4*R*)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 0.97 (d, *J*=6.6 Hz, 3 H) 1.19 (d, *J*=6.8 Hz, 6 H) 1.33 - 1.44 (m, 1 H) 1.65 - 1.73 (m, 1 H) 2.02 (s, 3 H) 2.08 - 2.15 (m, 1 H) 2.21 (s, 3 H) 2.76 (dd, *J*=13.1, 9.9 Hz, 1 H) 2.84 (dt, *J*=13.8, 6.9 Hz, 1 H) 2.92 - 3.05 (m, 4 H) 3.28 (s, 3 H) 3.30 - 3.37 (m, 2 H) 3.70 (d, *J*=12.6 Hz, 1 H) 3.80 (d, *J*=13.4 Hz, 1 H) 3.94 - 4.11 (m, 2 H) 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H) 6.98 (s, 1 H) 7.07 - 7.16 (m, 3 H) 7.17 - 7.23 (m, 1 H) 7.41 (dd, *J*=8.1, 1.0 Hz, 1 H) 10.88 (s, 1 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.
17-AY		6-(5-isopropyl-2-methylphenyl)-4-((*3S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 0.97 (d, *J*=6.6 Hz, 3 H) 1.19 (d, *J*=6.8 Hz, 6 H) 1.31 - 1.45 (m, 1 H) 1.63 - 1.74 (m, 1 H) 2.02 (s, 3 H) 2.07 - 2.15 (m, 1 H) 2.21 (s, 3 H) 2.76 (dd, *J*=13.1, 9.9 Hz, 1 H) 2.84 (dt, *J*=13.8, 6.9 Hz, 1 H) 2.91 - 3.06 (m, 4 H) 3.27 (s, 3 H) 3.30 - 3.39 (m, 2 H) 3.70 (d, *J*=11.4 Hz, 1 H) 3.80 (d, *J*=12.4 Hz, 1 H) 3.94 - 4.12 (m, 2 H) 6.87 (d, *J*=7.8 Hz, 1 H) 6.98 (s, 1 H) 7.05 - 7.16 (m, 3 H) 7.20 (dd, *J*=7.1, 0.8 Hz, 1 H) 7.41 (dd, *J*=8.1, 0.8 Hz, 1 H) 10.89 (br. s., 1 H); MS (ESI+) *m/z* 524.4 $(M+H)^+$.
17-AZ		(*R*)-(1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)pyrrolidin-2-yl)methanol. ^{1}H (400 MHz, CD_2Cl_2) δ ppm 1.26 (d, *J*=6.8 Hz, 6 H) 1.70 - 1.81 (m, 1 H) 1.84 - 1.94 (m, 1 H) 1.97 - 2.11 (m, 2 H) 2.12 (d, *J*=1.0 Hz, 3 H) 2.29 (s, 3 H) 2.81 - 2.97 (m, 1 H) 3.05 - 3.17 (m, 1 H) 3.18 - 3.29 (m, 2 H) 3.33 - 3.44 (m, 1 H) 3.58 - 3.73 (m, 2 H) 3.76 - 3.87 (m, 2 H) 4.07 - 4.17 (m, 1 H) 4.23 - 4.33 (m, 1 H) 4.54 - 4.67 (m, 1 H) 6.93 (dd, *J*=7.7, 1.64 Hz, 1 H) 7.01 (d, *J*=1.8 Hz, 1 H) 7.07 (s, 1 H) 7.15 (d, *J*=7.8 Hz, 1 H) 7.22 (t, *J*=7.7 Hz, 1 H) 7.34 (d, *J*=7.3 Hz, 1 H) 7.47 (d, *J*=7.8 Hz, 1 H) 8.42 (br. s., 1 H); MS

		(ESI+) *m/z* 496.1 $(M+H)^+$.
17-BA		(*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H (400 MHz, CD_2Cl_2) δ ppm 1.19 - 1.29 (m, 9 H) 1.50 - 1.89 (m, 6 H) 2.11 (s, 3 H) 2.28 (s, 3 H) 2.89 (spt, *J*=6.9 Hz, 1 H) 3.07 - 3.17 (m, 2 H) 3.24 (ddd, *J*=13.5, 10.7, 3.2 Hz, 1 H) 3.32 - 3.41 (m, 2 H) 3.53 - 3.63 (m, 1 H) 3.93 - 4.10 (m, 2 H) 4.11 - 4.21 (m, 1 H) 6.90 (dd, *J*=7.71, 1.6 Hz, 1 H) 6.98 (d, *J*=1.5 Hz, 1 H) 7.04 (d, *J*=1.1 Hz, 1 H) 7.13 (d, *J*=7.8 Hz, 1 H) 7.17 - 7.24 (m, 1 H) 7.34 (d, *J*=6.6 Hz, 1 H) 7.42 (dd, *J*=8.1, 1.0 Hz, 1 H) 8.22 (br. s., 1 H); MS (ESI+) *m/z* 494.4 $(M+H)^+$.
17-BB		(*S*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H (400 MHz, CD_2Cl_2) δ ppm 1.19 - 1.31 (m, 9 H) 1.47 - 1.88 (m, 6 H) 2.11 (s, 3 H) 2.28 (s, 3 H) 2.83 - 2.96 (m, 1 H) 3.09 - 3.17 (m, 2 H) 3.24 (ddd, *J*=13.5, 10.7, 3.2 Hz, 1 H) 3.32 - 3.41 (m, 2 H) 3.53 - 3.63 (m, 1 H) 3.93 - 4.10 (m, 2 H) 4.12 - 4.20 (m, 1 H) 6.90 (dd, *J*=7.6, 1.8 Hz, 1 H) 6.98 (d, *J*=1.5 Hz, 1 H) 7.03 - 7.07 (m, 1 H) 7.13 (d, *J*=7.6 Hz, 1 H) 7.18 - 7.25 (m, 1 H) 7.34 (d, *J*=7.3 Hz, 1 H) 7.43 (dd, *J*=8.1, 0.8 Hz, 1 H) 8.20 (br. s., 1 H); MS (ESI+) *m/z* 494.1 $(M+H)^+$.
17-BC		6-(5-isopropyl-2-methylphenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.27 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.35 (d, *J*=7.1 Hz, 1 H), 7.18 - 7.23 (m, 1 H), 7.15 (d, *J*=7.8 Hz, 1 H), 7.05 - 7.07 (m, 1 H), 7.00 (d, *J*=1.5 Hz, 1 H), 6.93 (dd, *J*=7.8, 1.8 Hz, 1 H), 4.26 (d, *J*=8.8 Hz, 2 H), 4.03 - 4.09 (m, 4 H), 3.29 (t, *J*=5.6 Hz, 2 H), 3.24 (s, 3 H), 3.06 - 3.16 (m, 2 H), 2.89 (spt, *J*=6.8 Hz, 1 H), 2.31 (s, 3 H), 2.11 (d, *J*=0.8 Hz, 3 H), 1.51 (s, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 496.1 $(M+H)^+$.

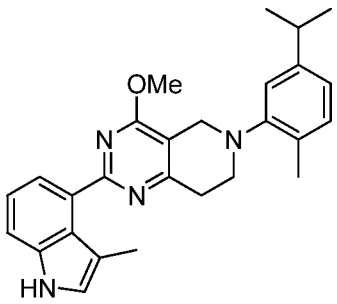
17-BD		1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylazetidin-3-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.89 (br. s., 1 H), 7.40 (br. s., 1 H), 7.18 (d, *J*=6.6 Hz, 1 H), 7.06 - 7.20 (m, 3 H), 7.02 (s, 1 H), 6.89 (d, *J*=7.3 Hz, 1 H), 3.97 - 4.13 (m, 5 H), 3.18 - 3.25 (m, 2 H), 2.81 - 2.92 (m, 3 H), 2.24 (s, 3 H), 2.03 (s, 3 H), 1.42 (s, 3 H), 1.20 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 482.1 $(M+H)^+$.
17-BE		6-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-oxa-6-azaspiro[3.3]heptanes. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.45 - 7.56 (m, 2 H), 7.21 (app. t, *J*=7.8 Hz, 1 H), 7.17 (d, *J*=7.6 Hz, 1 H), 7.11 (s, 1 H), 6.94 - 7.01 (m, 2 H), 4.79 (s, 4 H), 4.53 (br. s., 2 H), 4.09 (s, 2 H), 3.46 (br. s., 1 H), 3.28 (t, *J*=8.8 Hz, 2 H), 2.86 - 2.96 (m, 1 H), 2.30 (s, 3 H), 2.14 (s, 3 H), 1.27 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 494.1 $(M+H)^+$.
17-BF		6-(5-isopropyl-2-methylphenyl)-4-(3-methoxyazetidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.32 (br. s., 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.36 (d, *J*=6.8 Hz, 1 H), 7.18 - 7.21 (m, 1 H), 7.05 (d, *J*=0.5 Hz, 1 H), 6.99 (d, *J*=1.5 Hz, 1 H), 6.93 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.46 (br. s., 2 H), 4.25 - 4.32 (m, 1 H), 4.18 (br. s., 2 H), 4.06 (s, 2 H), 3.26 - 3.32 (m, 5 H), 3.12 (br. s., 2 H), 2.88 (spt, *J*=6.3 Hz, 1 H), 2.31 (s, 3 H), 2.11 (s, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 482.1 $(M+H)^+$.
17-BG		1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.19 (br. s., 1 H), 7.41 (dd, *J*=7.1, 1.0 Hz, 1 H), 7.31 (d, *J*=6.8 Hz, 1 H), 7.17 - 7.21 (m, 1 H), 7.15 (d, *J*=7.6 Hz, 1 H), 7.04 (d, *J*=1.0 Hz, 1 H), 7.00 (d, *J*=1.8 Hz, 1 H), 6.92 (dd, *J*=7.6, 1.8 Hz, 1 H), 4.26 (app. t, *J*=7.6 Hz, 2 H), 4.13 (br. s., 2 H), 4.05 (s, 2 H), 3.29 (t, *J*=5.6 Hz, 2 H), 3.19 (br. s., 1 H),

		3.03 (br. s., 2 H), 2.89 (spt, *J*=7.1 Hz, 1 H), 2.31 (s, 3 H), 2.18 (br. s., 6 H), 2.10 (s, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 495.2 $(M+H)^+$.
17-BH		(3-*endo*)-8-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.28 (br. s, 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.34 (d, *J*=7.6 Hz, 1 H), 7.22 - 7.18 (m, 1 H), 7.14 (d, *J*=7.6 Hz, 1 H), 7.04 (d, *J*=1.0 Hz, 1 H), 7.00 (d, *J*=1.5 Hz, 1 H), 6.92 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.61 (br. s., 2 H), 4.11 (br. s., 1 H), 4.03 (s, 2 H), 3.34 (t, *J*=5.8 Hz, 2 H), 3.15 (br. s., 2 H), 2.89 (spt, *J*=7.1 Hz, 1 H), 2.29 (s, 3 H), 2.20 - 2.27 (m, 4 H), 2.10 (s, 3 H), 1.95 - 2.03 (m, 1 H), 1.79 (d, *J*=14.4 Hz, 2 H), 1.25 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 522.2 $(M+H)^+$.
17-BI		(*S*)-2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.58 (s, 1 H), 7.05 - 7.18 (m, 3 H), 6.97 (d, *J*=1.8 Hz, 1 H), 6.89 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.00 (s, 2 H), 3.69 (d, *J*=10.6 Hz, 1 H), 3.27 - 3.42 (m, 6 H), 3.01 - 3.15 (m, 3 H), 2.91 - 2.99 (m, 1 H), 2.79 - 2.91 (m, 2 H), 2.49 (s, 3 H), 2.36 (s, 3 H), 2.27 (s, 4 H), 1.89 - 2.07 (m, 1 H), 1.60 - 1.78 (m, 1 H), 1.25 (d, *J*=6.8 Hz, 7 H), 1.00 (s, 3 H), 0.96 (s, 3 H); MS (ESI+) *m/z* 513.3 $(M+H)^+$.
17-BJ		(*S*)-6-(5-chloro-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_3CN) δ ppm 9.13 (br. s., 1 H) 7.45 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.22 - 7.26 (m, 1 H) 7.14 - 7.22 (m, 3 H) 7.01 - 7.09 (m, 2 H) 3.98 - 4.10 (m, 2 H) 3.64 - 3.75 (m, 1 H) 3.33 - 3.40 (m, 3 H) 3.32 (s, 3 H) 3.01 - 3.12 (m, 3 H) 2.98 (dd, *J*=9.09, 4.04 Hz, 1 H) 2.86 (d, *J*=12.88 Hz, 1 H) 2.27 (s, 3 H) 2.02 (d, *J*=1.01 Hz, 3 H) 1.99 (dd, *J*=5.43, 3.92 Hz, 1 H) 1.65 (dddd, *J*=13.14, 9.60, 9.47, 3.92 Hz, 1 H) 0.98 (s, 3 H) 0.92 (s, 3 H);

		MS (ESI+) *m/z* 530.3 $(M+H)^+$.
17-BK		(*R*)-6-(5-chloro-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.89 (s, 1 H) 7.41 (dd, *J*=8.1, 1.01 Hz, 1 H) 7.23 (d, *J*=8.1 Hz, 1 H) 7.20 (dd, *J*=7.3, 1.01 Hz, 1 H) 7.08 - 7.16 (m, 3 H) 7.06 (dd, *J*=8.1, 2.0 Hz, 1 H) 3.96 - 4.14 (m, 2 H) 3.66 (d, *J*=13.1 Hz, 1 H) 3.32 - 3.40 (m, 3 H) 3.28 (s, 3 H) 2.94 - 3.09 (m, 4 H) 2.83 (d, *J*=12.9 Hz, 1 H) 2.23 (s, 3 H) 1.90 - 2.04 (m, 4 H) 1.50 - 1.64 (m, 1 H) 0.97 (s, 3 H) 0.89 (s, 3 H); MS (ESI+) *m/z* 530.3 $(M+H)^+$.

Example 18

6-(5-Isopropyl-2-methylphenyl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

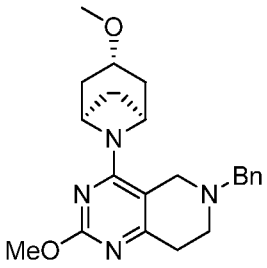


To a solution of 4-chloro-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, prepared as described in **Example 17** (110 mg, 0.188 mmol) in methanol (5 mL) was added 25% sodium methoxide in methanol (40.6 mg, 0.188 mmol). The reaction was stirred for ca. 40 minutes at room temperature at which time the mixture was diluted with EtOAc and water. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was added to a microwave vial, and diluted with EtOH (2 mL) and charged with KOH (ca. 100 mg, 1.75 mmol) and 28% ammonium hydroxide in water (1 mL, 7.25 mmol). The vial was sealed and heated via microwave irradiation at 100 °C for 45 minutes. The reaction mixture was cooled to room temperature and diluted with dichloromethane and brine. The layers were separated and the aqueous layer was extracted two additional times with dichloromethane. The

organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting residue waspurified by silica gel flash chromatography (0-100% ethyl acetate/heptanes) and then further purified by reverse phase HPLC (20-100% MeCN/0.1%NH_4OH in water to afford 6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.16 (br. s., 1 H) 7.37 - 7.46 (m, 1 H) 7.27 - 7.38 (m, 1 H) 7.11 - 7.21 (m, 1 H) 7.07 (d, *J*=7.6 Hz, 1 H) 6.98 - 7.05 (m, 1 H) 6.96 (s, 1 H) 6.76 - 6.90 (m, 1 H) 4.00 (s, 3 H) 3.34 (s, 1 H) 3.17 - 3.28 (m, 1 H) 2.90 - 3.17 (m, 1 H) 2.76 - 2.90 (m, 1 H) 2.24 (s, 2 H) 2.05 (s, 2 H) 1.09 - 1.28 (m, 6 H); MS (ESI+) *m/z* 427.25 $(M+H)^+$.

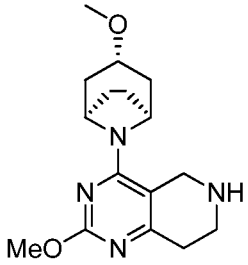
Example 19

19-A. 6-Benzyl-2-methoxy-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



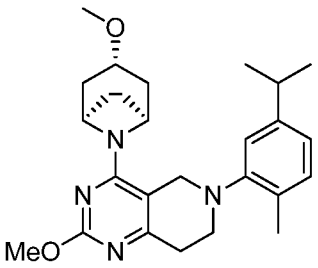
To a microwave vial containing 6-benzyl-2-chloro-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.6 g, 4.0 mmol), prepared in a similar manner to that described in **Example 21** below, was added a 0.5 M solution of NaOMe in THF (40 mL, 20.0 mmol). The vial was sealed and heated in a microwave reactor at 130 °C for 30 min. The reaction mixture was cooled and concentrated. The residue was diluted with DCM and washed with sat aq NH_4Cl solution. The aqueous layer was extracted with DCM (2x). The combined organics were dried (Na_2SO_4), filtered, and concentrated to provide 6-benzyl-2-methoxy-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, which was used in the next step without further purification. MS (ESI+) *m/z* 395.3 $(M+H)^+$.

19-B. 2-Methoxy-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



A mixture of 6-benzyl-2-methoxy-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (crude, 4 mmol), 20% $Pd(OH)_2$ on carbon (wet) (2.25 g, 3.2 mmol) in THF (40 mL), water (10 mL) and acetic acid (0.69 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered through Celite® and the solid were washed with DCM. The combined filtrate was washed with sat aq $NaHCO_3$ solution. Layers were separated and the aqueous layer was extracted with DCM. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (0-10% MeOH (10% NH_4OH)/DCM) to provide 2-methoxy-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 305.0 $(M+H)^+$.

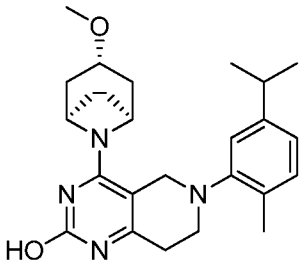
19-C. 6-(5-Isopropyl-2-methylphenyl)-2-methoxy-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



A mixture of 2-methoxy-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.88 g, 2.89 mmol), 5-isopropyl-2-methylphenyl trifluoromethanesulfonate (1.22 g, 4.34 mmol), chloro(2-dicyclohexylphosphino-2'-4'-6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II)–methyl-*t*-butylether adduct (CAS# 1028206-56-5, 0.21g, 0.30 mmol), and Cs_2CO_3 (1.88 g, 5.78 mmol) in THF (3 mL) was heated in a microwave reactor at 140 °C for 2 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (0-50% EtOAc/heptane) to provide 6-(5-isopropyl-2-methylphenyl)-2-methoxy-4-((3-

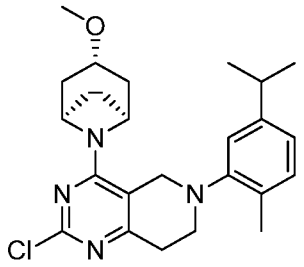
endo)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 437.1 $(M+H)^+$.

19-D. 6-(5-Isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-ol.



A mixture of 6-(5-isopropyl-2-methylphenyl)-2-methoxy-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.9 g, 2.06 mmol), and KOTMS (2.65g , 20.6 mmol) in 1,4-dioxane (20 mL) was heated in a sealed tube at 140 °C for 24 h. The reaction mixture was diluted with DCM and quenched with sat aq NH_4Cl. The aqueous layer was extracted with DCM. The combined organics were washed with brine, dried (Na_2SO_4),filtered, and concentrated to provide 6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-ol, which was used in the next step without further purification. MS (ESI+) *m/z* 423.0 $(M+H)^+$.

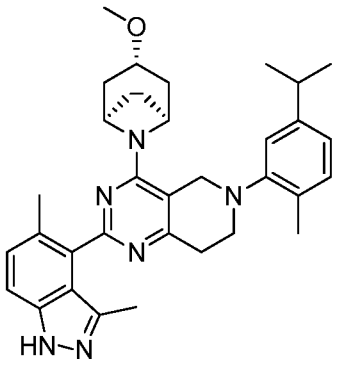
19-E. 2-Chloro-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-ol (crude, 2.06 mmol) in DCE was added Vilsmeier reagent (1.3 g, 10.3 mmol) and the reaction mixture was heated at 40 °C for 18 h. The reaction mixture was washed with water and the aqueous layer was extracted with DCM (2x). The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc/heptane) to provide 2-chloro-6-(5-isopropyl-2-methylphenyl)-4-((3-

endo)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 441.0 $(M+H)^+$.

19-F. 2-(3,5-Dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

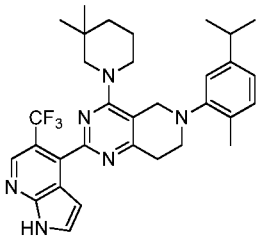
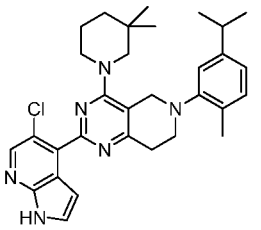
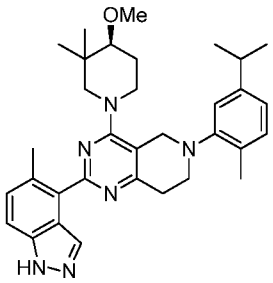


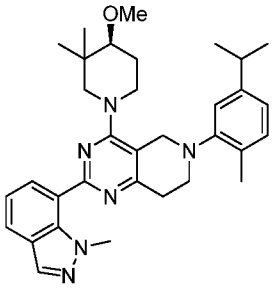
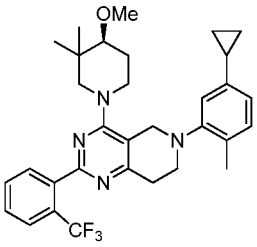
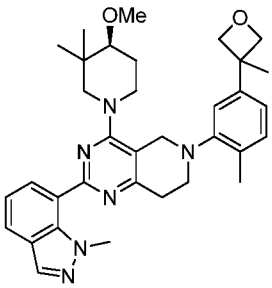
A mixture of 2-chloro-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (26 mg, 0.06 mmol), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indazole (25 mg, 0.06 mmol), $Pd(PPh_3)_4$ (7.0 mg, 0.006 mmol), and Na_2CO_3 (2 M, 0.09 mL, 0.18 mmol) in DME (2 mL) was heated in a microwave reactor at 140 °C for 30 min. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (20-100% EtOAc/heptane) to provide 2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, which was used in the next step without further purification. MS (ESI+) *m/z* 705.0 $(M+H)^+$.

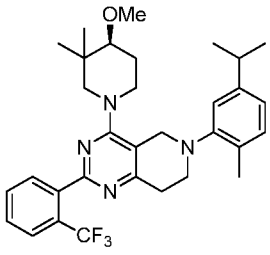
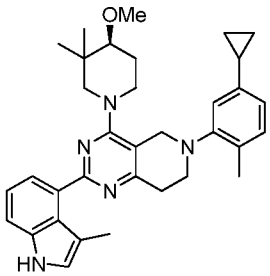
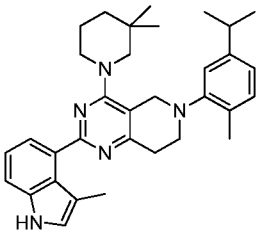
A suspension of 2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (from previous step, theoretically 0.06 mmol) and K_2CO_3 (82 mg, 0.6 mmol) in MeOH (5 mL) was heated at 50 °C for 1 h. The reaction mixture was filtered and washed with MeOH. The filtrate was concentrated and the residue was purified by HPLC (CH_3CN-water with 0.1% NH4OH 10-100%) to provide 2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^1H NMR (400 MHz, CD_2Cl_2) δ ppm 9.83 (br. s., 1 H) 7.35 (d, *J*=8.60 Hz, 1 H) 7.25 (d, *J*=8.60 Hz, 1 H) 7.15 (d, *J*=7.83 Hz, 1 H) 7.00 (d, *J*=1.77 Hz, 1 H) 6.92 (dd, *J*=7.71, 1.64 Hz, 1 H) 4.47 (br. s., 2 H) 4.05 (s, 2 H) 3.46 (t, *J*=4.80 Hz, 1 H) 3.36 (t, *J*=5.94 Hz, 2 H) 3.25 (s, 3 H) 3.01 - 3.10 (m, 2 H) 2.89 (spt, *J*=6.95 Hz, 1 H) 2.30 (s, 3 H) 2.29 (s,

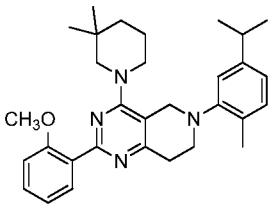
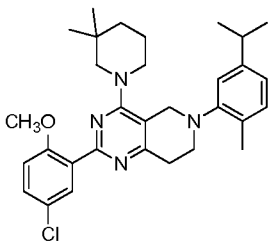
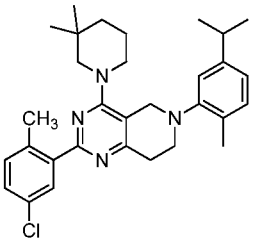
3 H) 2.02 - 2.14 (m, 4 H) 2.00 (s, 3 H) 1.87 - 1.96 (m, 4 H) 1.26 (d, *J*=6.82 Hz, 6 H); MS (ESI+) *m/z* 551.1 $(M+H)^+$.

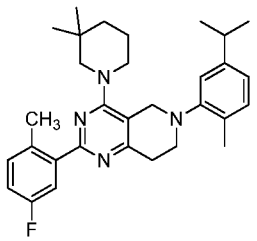
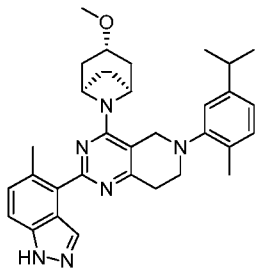
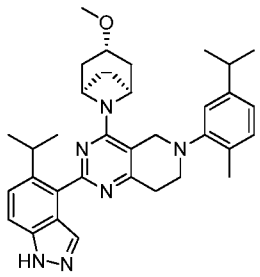
The following compounds were prepared in a similar manner.

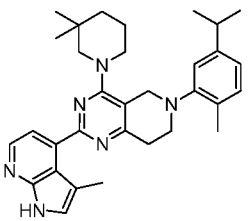
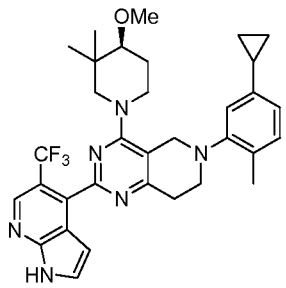
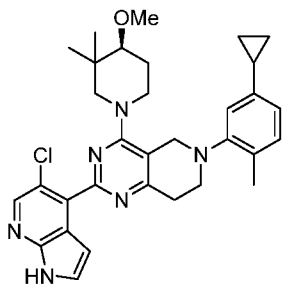
	Structure	Chemical Name&Analytical Data
19-G		4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.22 (br.s., 1 H), 8.63 (s, 1 H), 7.11 (d, *J*=7.6 Hz, 1 H), 6.94 (s, 1 H), 6.87 (d, *J*=7.6 Hz, 1 H), 6.44 (d, *J*=3.3 Hz, 1 H), 4.09 (s, 2 H), 3.38 - 3.32 (m, 2 H), 3.10 (s, 2 H), 2.95 (t, *J*=5.9 Hz, 2 H), 2.83 (td, *J*=7.0, 14.0 Hz, 1 H), 2.23 (s, 3 H), 1.69 - 1.58 (m, 2 H), 1.44 - 1.34 (m, 2 H), 1.18 (d, *J*=7.1 Hz, 6 H), 0.94 (s, 6 H); MS (ESI+) *m/z* 563.3 $(M+H)^+$.
19-H		2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.94 (br. s., 1 H), 8.30 (s, 1 H), 7.50 - 7.60 (m, 1 H), 7.11 (d, *J*=7.8 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 6.41 (d, *J*=5.3 Hz, 1 H), 4.08 (s, 2 H), 3.32 - 3.38 (m, 4 H), 3.11 (s, 2 H), 2.98 (t, *J*=5.8 Hz, 2 H), 2.84 (dt, *J*=13.7, 6.9 Hz, 1 H), 2.22 (s, 3 H), 1.65 (m, 2 H), 1.40 (t, *J*=5.7 Hz, 2 H), 1.19 (d, *J*=7.1 Hz, 6 H), 0.96 (s, 6 H); MS (ESI+) *m/z* 529.2 $(M+H)^+$.
19-I		(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_3CN) δ ppm 8.00 (s, 1 H), 7.67 (d, *J*=13.4 Hz, 1 H), 7.38 (d, *J*=8.6 Hz, 1 H), 7.20 - 7.20 (m, 1 H), 7.15 (d, *J*=7.8 Hz, 1 H), 7.07 (d, *J*=1.8 Hz, 1 H), 6.95 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.09 (s, 2 H), 3.91 - 3.99 (m, 1 H), 3.70 (d, *J*=12.6 Hz, 1 H), 3.48 - 3.57 (m, 1 H), 3.25 - 3.40 (m, 6 H), 3.14 (t, *J*=5.8 Hz, 2 H), 3.07 (dd, *J*=8.0, 3.7 Hz, 1 H), 2.91 (dt, *J*=13.6, 6.8 Hz, 1 H), 2.53 (s, 3

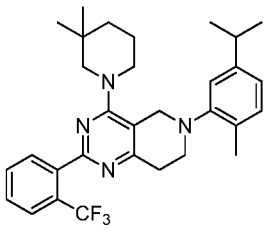
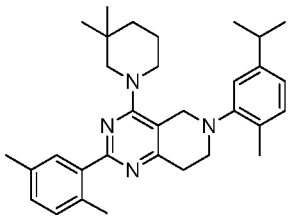
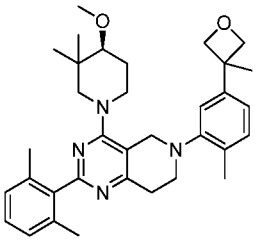
		H), 2.50 (s, 3 H), 1.64 - 1.75 (m, 1 H), 1.25 (d, *J*=6.8 Hz, 6 H), 0.98 (s, 3 H), 0.91 (s, 3 H); MS (ESI+) *m/z* 539.2 $(M+H)^+$.
19-J		(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(1-methyl-1H-indazol-7-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.17 (s, 1 H), 7.87 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.69 (dd, *J*=7.1, 1.01Hz, 1 H), 7.23 (dd, *J*=8.0, 7.2 Hz, 1 H), 7.11 (d, *J*=8.1 Hz, 1 H), 7.00 (d, *J*=1.3 Hz, 1 H), 6.87 (dd, *J*=7.7, 1.4 Hz, 1 H), 4.07 (s, 2 H), 3.90 (s, 3 H), 3.71 (d, *J*=13.4 Hz, 1 H), 3.42 (d, *J*=12.9 Hz, 1 H), 3.29 (s, 3 H), 3.10 (t, *J*=10.4 Hz, 1 H), 2.97 - 3.04 (m, 3 H), 2.80 - 2.92 (m, 2 H), 2.21 (s, 3 H), 1.93 - 2.02 (m, 1 H), 1.51 - 1.63 (m, 1 H), 1.19 (dd, *J*=7.0, 0.6 Hz, 6 H), 0.99 (s, 3 H), 0.93 (s, 3 H); MS (ESI+) *m/z* 539.2 $(M+H)^+$.
19-K		(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.70 - 7.81 (m, 2 H), 7.64 (t, *J*=7.3 Hz, 1 H), 7.50 - 7.59 (m, 1 H), 7.08 (d, *J*=7.8 Hz, 1 H), 6.83 (d, *J*=1.8 Hz, 1 H), 6.72 (dd, *J*=7.6, 1.8 Hz, 1 H), 3.97 (s, 2 H), 3.71 (d, *J*=12.9 Hz, 1 H), 3.29 - 3.41 (m, 6 H), 3.06 (br. s., 1 H), 2.94 (dd, *J*=8.7, 3.9 Hz, 1 H), 2.85 (d, *J*=11.9 Hz, 1 H), 2.25 (s, 3 H), 1.95 (ddt, *J*=13.3, 6.1, 3.6 Hz, 1 H), 1.87 (tt, *J*=8.5, 5.1 Hz, 1 H), 1.62 - 1.73 (m, 1 H), 0.97 (s, 3 H), 0.93 - 0.97 (m, 2 H), 0.93 (s, 3 H), 0.63 - 0.68 (m, 2 H); MS (ESI+) *m/z* 551.4 $(M+H)^+$.
19-L		(*S*)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(1-methyl-1H-indazol-7-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 8.17 (s, 1 H), 7.87 (dd, *J*=8.0, 1.1 Hz, 1 H), 7.69 (dd, *J*=7.1, 1.0 Hz, 1 H), 7.23 (dd, *J*=8.0, 7.2 Hz, 1 H), 7.19 (d, *J*=8.1 Hz, 1 H), 6.98 (d, *J*=1.8 Hz, 1 H), 6.87 (dd, *J*=7.8, 1.8 Hz, 1 H), 4.79 (dd, *J*=5.6, 1.8 Hz, 2 H), 4.52 (dd, *J*=5.6, 1.0 Hz, 2 H), 4.09 (s, 2 H), 3.91 (s, 3 H), 3.70 (d, *J*=13.4

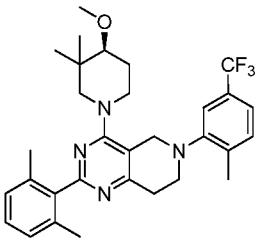
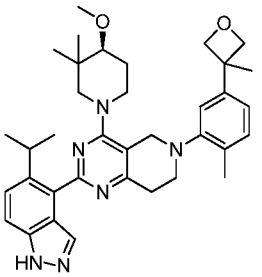
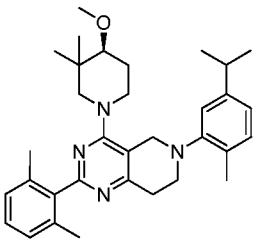
		Hz, 1 H), 3.41 (d, *J*=13.4 Hz, 1 H), 3.35 - 3.37 (m, 1 H), 3.29 (s, 3 H), 3.05 - 3.14 (m, 1 H), 2.97 - 3.04 (m, 3 H), 2.88 (d, *J*=13.1 Hz, 1 H), 2.24 (s, 3 H), 1.93 - 2.03 (m, 1 H), 1.62 (s, 3 H), 1.50 - 1.60 (m, 1 H), 0.99 (s, 3 H), 0.92 (s, 3 H); MS (ESI+) *m/z* 567.0 $(M+H)^+$.
19-M		(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.71 - 7.80 (m, 2 H), 7.64 (t, *J*=7.5 Hz, 1 H), 7.55 (t, *J*=1.0 Hz, 1 H), 7.13 (d, *J*=7.8 Hz, 1 H), 6.96 (d, *J*=1.5 Hz, 1 H), 6.90 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.01 (s, 2 H), 3.70 (d, *J*=12.9 Hz, 1 H), 3.30 - 3.41 (m, 6 H), 3.06 (br. s., 2 H), 2.94 (dd, *J*=8.8, 3.8 Hz, 1 H), 2.81 - 2.90 (m, 2 H), 2.26 (s, 3 H), 1.91 - 2.01 (m, 1 H), 1.61 - 1.73 (m, 1 H), 1.48 - 1.52 (m, 1 H), 1.24 (d, *J*=7.1 Hz, 6 H), 0.98 (s, 3 H), 0.94 (s, 3 H); MS (ESI+) *m/z* 553.4 $(M+H)^+$.
19-N		(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.22 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.34 (d, *J*=7.1 Hz, 1 H), 7.21 (t, *J*=7.7 Hz, 1 H), 7.01 - 7.13 (m, 2 H), 6.84 (s, 1 H), 6.72 (d, *J*=7.8 Hz, 1 H), 4.01 (s, 2 H), 3.71 (br. s., 1 H), 3.43 (d, *J*=11.4 Hz, 1 H), 3.28 - 3.37 (m, 5 H), 3.13 (br. s., 3 H), 2.95 (dd, *J*=8.7, 3.9 Hz, 2 H), 2.26 (s, 3 H), 209 (s, 3 H), 1.98 (dd, *J*=12.8, 9.2 Hz, 1 H), 1.81 - 1.92 (m, 1 H), 1.63 - 1.74 (m, 1 H), 1.00 (s, 3 H), 0.96 (br. s., 3 H), 0.91 - 0.95 (m, 2 H), 0.62 - 0.69 (m, 2 H); MS (ESI+) *m/z* 536.0 $(M+H)^+$.
19-O		4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (br. s., 1 H), 7.44 (dd, *J*=13.0, 7.7 Hz, 2 H), 7.22 - 7.27 (m, 1 H), 7.19 (d, *J*=7.6 Hz, 1 H), 7.02 (d, *J*=18.9

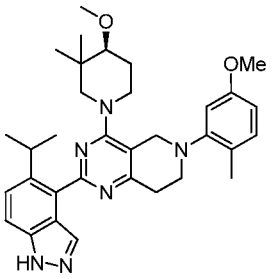
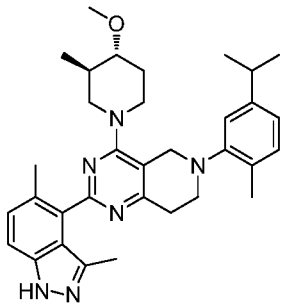
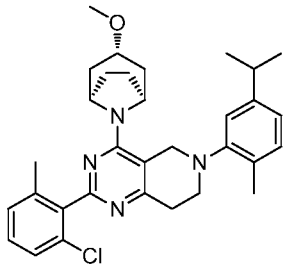
		Hz, 2 H), 6.94 (d, *J*=7.6 Hz, 1 H), 4.12 (s, 2 H), 3.42 (t, *J*=6.1 Hz, 2 H), 3.31 - 3.38 (m, 2 H), 3.12 - 3.19 (m, 4 H), 2.92 (dt, *J*=13.8, 6.8 Hz, 1 H), 2.34 (s, 3 H), 2.17 (s, 3 H), 1.70 - 1.79 (m, 2 H), 1.45 (t, *J*=6.1 Hz, 2 H), 1.30 (d, *J*=6.8 Hz, 6 H), 1.04 (s, 6 H); MS (ESI+) *m/z* 508.4 $(M+H)^+$.
19-P		4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.47 (dd, *J*=7.6, 1.8 Hz, 1 H) 7.36 - 7.43 (m, 1 H) 7.11 (s, 1 H) 7.09 (s, 1 H) 6.98 - 7.04 (m, 2 H) 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H) 3.99 (s, 2 H) 3.76 (s, 3 H) 3.22 - 3.30 (m, 4 H) 3.04 (s, 2 H) 2.93 (t, 2 H) 2.85 (quin, *J*=6.9 Hz, 1 H) 2.20 (s, 3 H) 1.60 - 1.68 (m, 2 H) 1.38 (t, *J*=5.9 Hz, 2 H) 1.20 (d, *J*=7.1 Hz, 6 H) 0.96 (s, 6 H); MS (ESI+) *m/z* 485.1 $(M+H)^+$.
19-Q		2-(5-chloro-2-methoxyphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.49 (d, *J*=2.8 Hz, 1 H) 7.45 (dd, *J*=9.2, 2.8 Hz, 1 H) 7.14 (d, *J*=8.8 Hz, 1 H) 7.10 (d, *J*=7.8 Hz, 1 H) 7.01 (d, *J*=1.3 Hz, 1 H) 6.87 (dd, *J*=7.7, 1.6 Hz, 1 H) 3.98 - 4.02 (m, 2 H) 3.77 (s, 3 H) 3.24 - 3.29 (m, 4 H) 3.04 - 3.08 (m, 2 H) 2.94 (t, *J*=5.8 Hz, 2 H) 2.85 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.20 (s, 3 H) 1.59 - 1.68 (m, 2 H) 1.39 (t, *J*=5.8 Hz, 2 H) 1.20 (d, 6 H) 0.95 (s, 6 H); MS (ESI+) *m/z* 519.1 $(M+H)^+$.
19-R		2-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.80 (d, *J*=2.3 Hz, 1 H) 7.39 - 7.42 (m, 1 H) 7.38 (d, *J*=2.5 Hz, 1 H) 7.32 (d, *J*=8.4 Hz, 1 H) 7.10 (d, *J*=7.8 Hz, 1 H) 6.99 (d, *J*=1.5 Hz, 1 H) 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H) 4.02 (s, 2 H) 3.26 - 3.31 (m, 4 H) 3.05 - 3.08 (m, 2 H) 2.98 (t, *J*=5.8 Hz, 2 H) 2.84 (dq, *J*=7.1, 6.9 Hz, 1 H) 2.51 - 2.53 (m, 2 H) 2.20 (s, 3 H) 1.62 - 1.70 (m, 2 H) 1.40 (t, *J*=5.9 Hz, 2 H) 1.18 (d, 6 H) 0.96 (s, 6 H); MS (ESI+) *m/z* 503.1 $(M+H)^+$.

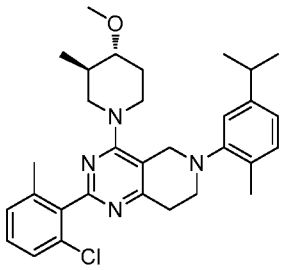
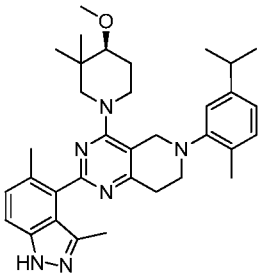
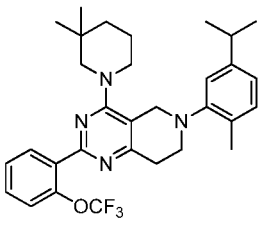
19-S		4-(3,3-dimethylpiperidin-1-yl)-2-(5-fluoro-2-methylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.57 (dd, *J*=10.2, 2.9 Hz, 1 H) 7.32 (dd, *J*=8.5, 5.9 Hz, 1 H) 7.18 (td, *J*=8.4, 2.9 Hz, 1 H) 7.10 (d, *J*=7.8 Hz, 1 H) 7.00 (d, *J*=1.3 Hz, 1 H) 6.86 (dd, *J*=7.6, 1.5 Hz, 1 H) 4.02 (s, 2 H) 3.33 (s, 3 H) 3.26 - 3.32 (m, 4 H) 3.05 - 3.10 (m, 2 H) 2.97 (t, *J*=5.8 Hz, 2 H) 2.84 (spt, *J*=6.8 Hz, 1 H) 2.20 (s, 3 H) 1.61 - 1.71 (m, 2 H) 1.40 (t, *J*=5.8 Hz, 2 H) 1.19 (d, *J*=6.8 Hz, 6 H) 0.96 (s, 6 H); MS (ESI+) *m/z* 487.1 $(M+H)^+$.
19-T		6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.21 (br. s., 1 H) 7.49 (d, J=8.3 Hz, 1 H) 7.30 - 7.43 (m, 2 H) 7.20 (d, J=8.3 Hz, 1 H) 7.07 (d, J=1.5 Hz, 1 H) 6.97 (dd, J=7.7, 1.6 Hz, 1 H) 4.59 (br. s., 2 H) 4.09 (s, 2 H) 3.53 (t, J=4.8 Hz, 1 H) 3.40 (t, J=5.8 Hz, 2 H) 3.32 (s, 3 H) 3.11 - 3.26 (m, 1 H) 2.96 (dt, J=13.9, 7.0 Hz, 1 H) 2.66 (s, 3 H) 2.35 (s, 3 H) 2.08 - 2.25 (m, 4 H) 1.93 - 2.06 (m, 4 H) 1.31 (d, J=6.8 Hz, 6 H); MS (ESI+) *m/z* 537.0 $(M+H)^+$.
19-U		2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 10.24 (br. s., 1 H) 8.05 (s, 1 H) 7.51 - 7.56 (m, 2 H) 7.20 (d, J=7.8 Hz, 1 H) 7.08 (d, J=1.8 Hz, 1 H) 6.97 (dd, J=7.8, 1.8 Hz, 1 H) 4.56 (br. s., 2 H) 4.09 (s, 2 H) 3.68 (quin, J=6.9 Hz, 1 H) 3.52 (t, J=4.8 Hz, 1 H) 3.41 (t, J=5.9 Hz, 2 H) 3.31 (s, 3 H) 3.14 (t, J=5.9 Hz, 2 H) 2.96 (quin, J=6.9 Hz, 1 H) 2.36 (s, 3 H) 2.07 - 2.23 (m, 4 H) 1.92 - 2.04 (m, 4 H) 1.31 (d, J=7.2 Hz, 6 H) 1.33 (d, J=7.2 Hz, 6 H); MS (ESI+) *m/z* 565.1 $(M+H)^+$.

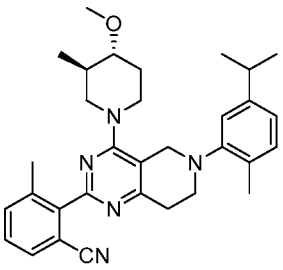
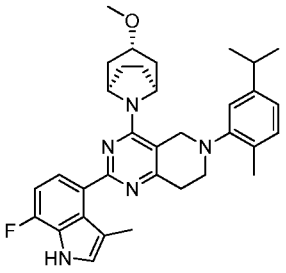
19-V		4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.53 (br s, 1 H), 8.35 (d, *J* = 4.80 Hz, 1 H), 7.41 (d, *J* = 4.80 Hz, 1 H), 7.16 (d, *J* = 7.83 Hz, 1 H), 7.11 – 7.12 (m, 1 H), 6.96 (d, *J* = 1.77 Hz, 1 H), 6.92 (dd, *J* = 1.77, 7.58 Hz, 1 H), 4.07 (s, 2 H), 3.39 (app t, *J* = 6.03 Hz, 2 H), 3.34 (br t, *J* = 5.43 Hz, 2 H), 3.12 – 3.14 (m , 4 H), 2.84 – 2.95 (m, 1 H), 2.30 (s, 3 H), 2.21 (d, *J* = 1.01 Hz, 3 H), 1.69 – 1.75 (m, 2 H), 1.44 (t, *J* = 6.06 Hz, 2 H), 1.26 (d, *J* = 7.07 Hz, 6 H), 1.01 (s, 6 H); MS (ESI+) *m/z* 509.28 $(M+H)^+$.
19-W		(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.68 (s, 1 H), 7.44 (dd, *J*=3.5, 2.3 Hz, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.85 (d, *J*=1.5 Hz, 1 H), 6.74 (dd, *J*=7.7, 1.6 Hz, 1 H), 6.58 (dd, *J*=3.5, 1.8 Hz, 1 H), 4.02 (s, 2 H), 3.70 - 3.76 (m, 1 H), 3.43 (d, *J*=14.1 Hz, 1 H), 3.34 - 3.38 (m, 2 H), 3.33 (s, 3 H), 3.13 (br. s., 3 H), 2.95 (dd, *J*=8.5, 3.9 Hz, 2 H), 2.27 (s, 3 H), 1.91 - 2.00 (m, 1 H), 1.83 - 1.91 (m, 1 H), 1.63 - 1.74 (m, 1 H), 0.98 (s, 3 H), 0.94 - 0.97 (m, 2 H), 0.93 (s, 3 H), 0.63 - 0.70 (m, 2 H); MS (ESI+) *m/z* 590.9 $(M+H)^+$.
19-X		(*S*)-2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.35 (s, 1 H), 7.39 (br. s., 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.86 (d, *J*=1.5 Hz, 1 H), 6.74 (dd, *J*=7.8, 1.5 Hz, 1 H), 6.56 (br. s., 1 H), 4.00 (s, 2 H), 3.73 - 3.83 (m, *J*=8.3 Hz, 1 H), 3.42 - 3.54 (m, 1 H), 3.33 - 3.36 (m, 6 H), 3.12 - 3.26 (m, 2 H), 2.92 - 3.03 (m, 2 H), 2.26 (s, 3 H), 1.93 - 2.02 (m, 1 H), 1.84 - 1.93 (m, 1 H), 1.66 - 1.77 (m, 1 H), 0.99 (s, 3 H), 0.95 - 0.98 (m, 2 H), 0.94 (s, 3 H), 0.64 - 0.69 (m, 2 H); MS (ESI+) *m/z* 556.9 $(M+H)^+$.

19-Y		2-(2,5-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.83 (d, *J*=7.8 Hz, 1 H), 7.71 - 7.78 (m, 2 H), 7.61 - 7.70 (m, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.96 (s, 1 H), 6.86 (d, *J*=9.1 Hz, 1 H), 4.04 (s, 2 H), 3.24 - 3.34 (m, 4 H), 3.08 (s, 2 H), 2.93 (app t, *J*=5.9 Hz, 2 H), 2.77 - 2.88 (m, 1 H), 2.20 (s, 3 H), 1.58 - 1.70 (m, 2 H), 1.34 - 1.43 (m, 2 H), 1.18 (d, *J*=7.1 Hz, 6 H), 0.94 (s, 6 H); MS (ESI+) *m/z* 523.3 $(M+H)^+$.
19-Z		2-(2,5-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 (s, 6 H) 1.23 (d, *J*=7.07 Hz, 6 H) 1.47 (m, *J*=5.80, 5.80 Hz, 2 H) 1.68 - 1.79 (m, 2 H) 2.26 (s, 3 H) 2.35 (s, 3 H) 2.40 (s, 3 H) 2.79 - 2.91 (m, 1 H) 3.01 (m, *J*=5.80, 5.80 Hz, 2 H) 3.12 - 3.19 (m, 2 H) 3.34 - 3.42 (m, 4 H) 4.02 (s, 2 H) 6.88 (d, *J*=7.58 Hz, 1 H) 6.97 (s, 1 H) 7.05 - 7.19 (m, 3 H) 7.39 (s, 1 H); MS (ESI+) *m/z* 483.3 $(M+H)^+$.
19-AA		(*S*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.15 - 7.22 (m, 2 H), 7.07 (d, *J*=7.6 Hz, 2 H), 6.89 (d, *J*=2.0 Hz, 1 H), 6.86 (dd, *J*=7.8, 1.8 Hz, 1 H), 4.91 (d, *J*=5.6 Hz, 2 H), 4.58 (d, *J*=5.6 Hz, 2 H), 4.03 (s, 2 H), 3.62 – 3.71 (m, 1 H), 3.30 - 3.39 (m, 6 H), 3.01 - 3.13 (m, 3 H), 2.94 (dd, *J*=8.8, 3.8 Hz, 1 H), 2.84 (d, *J*=12.6 Hz, 1 H), 2.30 (s, 3 H), 2.11 (s, 6 H), 1.91 - 1.99 (m, 1 H), 1.69 (s, 3 H), 1.62 - 1.68 (m, 1 H), 0.99 (s, 3 H), 0.94 (s, 3 H); MS (ESI+) *m/z* 541.1 $(M+H)^+$.

19-AB		(*S*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.35 (d, *J*=7.8 Hz, 1 H), 7.28 - 7.31 (m, 2 H), 7.19 - 7.24 (m, 1 H), 7.10 (d, *J*=7.6 Hz, 2 H), 4.03 (s, 2 H), 3.72 (br. s., 1 H), 3.38 (t, *J*=5.8 Hz, 2 H), 3.33 (s, 3 H), 3.16 (br. s., 2 H), 2.96 (dd, *J*=8.3, 3.8 Hz, 1 H), 2.38 (s, 3 H), 2.14 (br. s, 6 H), 1.91 - 2.01 (m, 1 H), 1.63 - 1.75 (m, 1 H), 0.97 (s, 3 H), 0.92 (s, 3 H); MS (ESI+) *m/z* 539.0 $(M+H)^+$.
19-AC		(*S*)-2-(5-isopropyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.97 (br. s, 1 H), 7.52 (d, *J*=8.3 Hz, 1 H), 7.47 (d, *J*=8.8 Hz, 1 H), 7.22 (d, *J*=8.1 Hz, 1 H), 6.94 (d, *J*=1.5 Hz, 1 H), 6.89 (d, *J*=7.6 Hz, 1 H), 4.92 (d, *J*=5.6 Hz, 2 H), 4.60 (d, *J*=5.6 Hz, 2 H), 4.06 (s, 2 H), 3.71 (br. s., 1 H), 3.35 - 3.43 (m, 3 H), 3.33 (s, 3 H), 3.14 (br. s., 2 H), 2.95 (dd, *J*=8.3, 3.3 Hz, 1 H), 2.32 (s, 3 H), 1.93 - 2.01 (m, 1 H), 1.71 (s, 3 H), 1.64 - 1.70 (m, 1 H), 1.30 (d, *J*=6.6 Hz, 6 H), 0.99 (s, 3 H), 0.96 (s, 3 H); MS (ESI+) *m/z* 595.0 $(M+H)^+$.
19-AD		(*S*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.16 - 7.22 (m, 1 H), 7.13 (d, *J*=7.6 Hz, 1 H), 7.08 (d, *J*=7.6 Hz, 2 H), 6.95 (d, *J*=1.8 Hz, 1 H), 6.89 (dd, *J*=7.8, 1.5 Hz, 1 H), 4.03 (s, 2 H), 3.69 (br. s., 1 H), 3.30 - 3.39 (m, 6 H), 3.04 (br. s., 3 H), 2.94 (dd, *J*=4.8, 3.8 Hz, 1 H), 2.87 (spt, *J*=6.8 Hz, 1 H), 2.28 (s, 3 H), 2.12 (s, 6 H), 1.91 - 1.99 (m, 1 H), 1.62 - 1.72 (m, 1 H), 1.24 (d, *J*=7.1 Hz, 6 H), 0.99 (s, 3 H), 0.94 (s, 3 H); MS (ESI+) *m/z* 513.3 $(M+H)^+$.

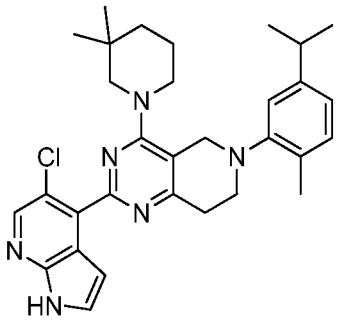
19-AE		(*S*)-2-(5-isopropyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.74 (br s., 1 H), 7.37 (br. s., 2 H) 7.15 (d, *J*=7.8 Hz, 1 H), 6.72 (d, *J*=2.5 Hz, 1 H), 6.63 (d, *J*=7.8 Hz, 1 H), 4.03 (s, 2 H), 3.80 (s, 3 H), 3.31 - 3.38 (m, 6 H), 3.00 (br. s., 1 H), 2.26 (s, 3 H), 1.90 - 2.02 (m, 1 H), 1.73 (br. s., 1 H), 1.32 (br. s, 6 H), 0.96 (s, 3 H), 0.92 (s, 3 H); MS (ESI+) *m/z* 555.0 $(M+H)^+$.
19-AF		2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((*3R,4R*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H) 7.39 (d, *J*=8.6 Hz, 1 H) 7.21 (d, *J*=8.6 Hz, 1 H) 7.11 (d, *J*=8.1 Hz, 1 H) 6.94 (d, *J*=1.3 Hz, 1 H) 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H) 3.96 - 4.16 (m, 2 H) 3.62 - 3.84 (m, 2 H) 3.30 - 3.40 (m, 2 H) 3.26 (s, 3 H) 2.89 - 3.06 (m, 4 H) 2.73 - 2.87 (m, 2 H) 2.21 (s, 3 H) 2.19 (s, 3 H) 2.04 - 2.13 (m, 1 H) 1.87 (s, 3 H) 1.60 - 1.72 (m, 1 H) 1.29 - 1.42 (m, 1 H) 1.18 (d, *J*=7.1 Hz, 6 H) 0.94 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 539.4 $(M+H)^+$.
19-AG		2-(2-chloro-6-methylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.22 - 7.37 (m, 3 H) 7.11 (d, *J*=7.8 Hz, 1 H) 6.99 (d, *J*=1.3 Hz, 1 H) 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H) 4.35 - 4.44 (m, 2 H) 3.98 - 4.05 (m, 2 H) 3.42 - 3.47 (m, 1 H) 3.29 (t, *J*=5.9 Hz, 2 H) 3.20 (s, 3 H) 2.79 - 2.92 (m, 3 H) 2.22 (s, 3 H) 2.08 (s, 3 H) 1.79 - 2.03 (m, 8 H) 1.18 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 531.3 $(M+H)^+$.

19-AH		2-(2-chloro-6-methylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((*3R,4R*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.23 - 7.38 (m, 3 H) 7.10 (d, *J*=8.1 Hz, 1 H) 6.93 (d, *J*=1.5 Hz, 1 H) 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H) 3.93 - 4.11 (m, 2 H) 3.62 - 3.81 (m, 2 H) 3.29 - 3.35 (m, 1 H) 3.26 (s, 3 H) 2.94 - 3.06 (m, 2 H) 2.90 (t, *J*=5.8 Hz, 2 H) 2.73 - 2.87 (m, 2 H) 2.20 (s, 3 H) 2.08 (s, 3 H) 1.59 - 1.71 (m, 1 H) 1.30 - 1.42 (m, 1 H) 1.17 - 1.20 (m, 1 H) 1.17 (d, *J*=6.8 Hz, 6 H) 0.95 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 519.4 $(M+H)^+$.
19-AI		(*S*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD2Cl2) δ ppm 7.30 (d, *J*=8.6 Hz, 1 H), 7.17 (d, *J*=8.6 Hz, 1 H), 7.08 (d, *J*=7.6 Hz, 1 H), 6.75 - 6.92 (m, 2 H), 3.98 (s, 2 H), 3.76 (br. s., 1 H), 3.32 (br. s., 3 H), 3.21 - 3.26 (m, 3 H), 2.91 (br. s., 1 H), 2.78 (spt, *J*=6.8 Hz, 1 H), 2.31 (br. s., 2 H), 2.19 (br. s, 3 H), 2.01 (br. s., 3 H), 1.88 (m, *J*=3.5 Hz, 1 H), 1.58 - 1.69 (m, 1 H), 1.17 (d, *J*=6.8 Hz, 6 H), 0.89 (s, 3 H) 0.84 (s, 3 H); MS (ESI+) m/z 553.1 $(M+H)^+$.
19-AJ		4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethoxy)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (s, 6 H) 1.18 (d, *J*=6.82 Hz, 6 H) 1.40 (app t, *J*=5.94 Hz, 2 H) 1.65 (br. s., 2 H) 2.75 - 2.88 (m, 1 H) 2.94 (t, *J*=5.94 Hz, 2 H) 3.10 (s, 2 H) 4.03 (s, 2 H) 6.86 (dd, *J*=7.71, 1.39 Hz, 1 H) 6.96 (d, *J*=1.26 Hz, 1 H) 7.10 (d, *J*=7.83 Hz, 1 H) 7.45 (d, *J*=8.08 Hz, 1 H) 7.48 - 7.54 (m, 1 H) 7.55 - 7.63 (m, 1 H) 7.95 (dd, *J*=7.58, 1.77 Hz, 1 H); MS (ESI+) *m/z* 539.3 $(M+H)^+$.

19-AK		2-(6-(5-isopropyl-2-methylphenyl)-4-((3*R*,4*R*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)-3-methylbenzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.75 (d, *J*=7.6 Hz, 1 H) 7.64 (d, *J*=7.3 Hz, 1 H) 7.52 (t, *J*=7.7 Hz, 1 H) 7.10 (d, *J*=8.1 Hz, 1 H) 6.98 (d, *J*=1.5 Hz, 1 H) 6.87 (dd, *J*=7.8, 1.5 Hz, 1 H) 3.92 - 4.15 (m, 2 H) 3.70 - 3.90 (m, 2 H) 3.28 - 3.32 (m, 2 H) 3.27 (s, 3 H) 3.02 - 3.12 (m, 1 H) 2.92 - 3.02 (m, 3 H) 2.75 - 2.89 (m, 2 H) 2.32 (s, 3 H) 2.20 (s, 3 H) 2.06 - 2.16 (m, 1 H) 1.61 - 1.74 (m, 1 H) 1.37 (d, *J*=10.9 Hz, 1 H) 1.18 (d, *J*=6.8 Hz, 6 H) 0.96 (d, *J*=6.6 Hz, 3 H). MS (ESI+) *m/z* 510.3 $(M+H)^+$.
19-AL		2-(7-fluoro-3-methyl-1H-indol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.40 (br. s., 1 H) 7.37 (dd, *J*=8.1, 4.8 Hz, 1 H) 7.19 (d, *J*=7.8 Hz, 1 H) 7.11 (s, 1 H) 7.05 (s, 1 H) 6.92 - 7.01 (m, 2 H) 4.56 (br. s., 2 H) 4.07 (s, 2 H) 3.52 (t, *J*=4.7 Hz, 1 H) 3.39 (t, *J*=6.0 Hz, 2 H) 3.32 (s, 3 H) 3.10 (t, *J*=5.8 Hz, 2 H) 2.94 (dt, *J*=13.6, 6.8 Hz, 1 H) 2.34 (s, 3 H) 2.09 - 2.24 (m, 7 H) 1.92 - 2.06 (m, 4 H) 1.31 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 554.5 $(M+H)^+$.

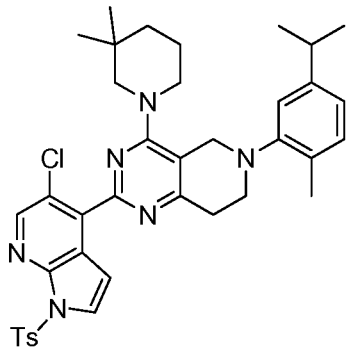
Example 20

20-A. 2-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



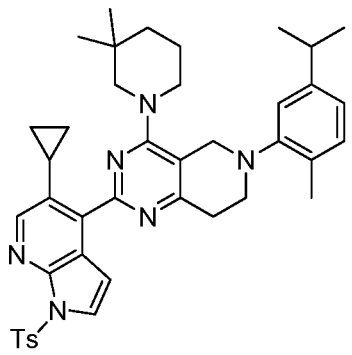
The title compound was prepared in a similar manner to that described in **Example 19**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.94 (br. s., 1 H), 8.30 (s, 1 H), 7.50 - 7.60 (m, 1 H), 7.11 (d, *J*=7.8 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 6.41 (d, *J*=5.3 Hz, 1 H), 4.08 (s, 2 H), 3.32 - 3.38 (m, 4 H), 3.11 (s, 2 H), 2.98 (t, *J*=5.8 Hz, 2 H), 2.84 (dt, *J*=13.7, 6.9 Hz, 1 H), 2.22 (s, 3 H), 1.65 (m, 2 H), 1.40 (t, *J*=5.7 Hz, 2 H), 1.19 (d, *J*=7.1 Hz, 6 H), 0.96 (s, 6 H); MS (ESI+) *m/z* 529.2 $(M+H)^+$.

20-B. 2-(5-Chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



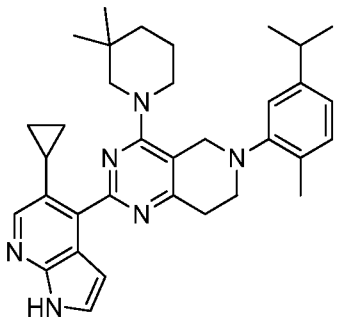
To a solution of 2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (213 mg, 0.403 mmol) in THF (2.4 mL) was added NaH 60% in oil (32 mg, 0.80 mmol) at 0°C. After 15 min, *p*-toluenesulfonylchloride (81 mg, 0.42 mmol) was added and the mixture was allowed to warmed to rt After 16h, water was added and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified via FCC (0-20% EtOAc/heptane) to give the title compound. MS (ESI+) *m/z* 683.2 $(M+H)^+$.

20-C. 2-(5-Cyclopropyl-1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



To a mixture of 2-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (135 mg, 0.198 mmol) in toluene (2 mL) and water (0.1 mL) was added potassium cyclopropyltrifluoroborate (58 mg, 0.39 mmol), tricyclohexylphosphine (11 mg, 0.04 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol) and Cs_2CO_3 (193 mg, 0.593 mmol). The reaction mixture was heated at 100°C for 16 h. Then the reaction mixture was filtered and the residue was purified via FCC (0-30% EtOAc/heptane) to give the title compound. MS (ESI+) *m/z* 689.4 $(M+H)^+$.

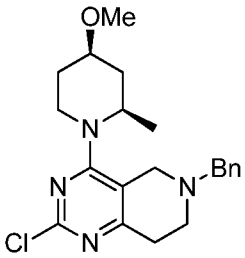
20-D. 2-(5- Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 2-(5-cyclopropyl-1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (50 mg, 0.073 mmol) in EtOH (1.9 mL) was added KOH (24 mg, 0.44 mmol) and 28% aq NH_4OH (303 µL, 7.26 mmol). The mixture was heated at 100 °C for 45 min in a microwave reactor. A saturated solution of aq NH_4Cl was added and the aqueous phase was extracted with EtOAc (3x). The combined phases were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The reaction mixture was then filtered and the residue was purified via FCC (20-60% EtOAc/heptane) to give the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.53 (br. s., 1 H), 8.00 (s, 1H), 7.38 - 7.43 (m, 1 H), 7.11 (d, J=7.8 Hz, 1 H), 6.97 (d, J=1.3 Hz, 1 H), 6.86 (dd, J=7.7, 1.4 Hz, 1 H), 6.38 (dd, J=3.4, 1.9 Hz, 1 H), 4.09 (s, 2 H), 3.34 (t, J=5.9 Hz, 2 H), 3.08 (s, 2 H), 2.98 (t, J=5.8 Hz, 2 H), 2.83 (dt, J=13.6, 6.8 Hz, 1 H), 2.34 - 2.41 (m, 1 H), 2.23 (s, 3H), 1.65 (dt, J=10.6, 5.5 Hz, 2 H), 1.40 (t, J=5.9 Hz, 2 H), 1.18 (d, J=6.8 Hz, 6 H), 0.97 (s, 6 H), 0.73 - 0.82 (m, 2 H), 0.55 - 0.63 (m, 2 H); MS (ESI+) *m/z* 535.4 $(M+H)^+$.

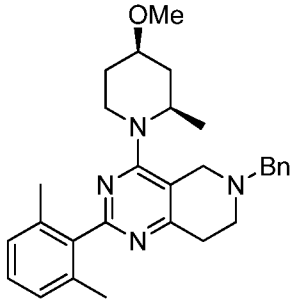
Example 21

21-A. 6-Benzyl-2-chloro-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 6-benzyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (3.31 g, 11.2 mmol) in DMA (13 mL) was added (2*R*,4*R*)-4-methoxy-2-methylpiperidine hydrochoride (1.33 g, 8.03 mmol) and DIPEA (7.0 mL, 40 mmol). The mixture was then heated at 80 °C for 20 h. At that point water was added and the aqueous phase was extracted with a solution of EtOAc/n-heptane (4:1). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduce pressure. The residue was purified via FCC (15-30% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 - 7.39 (m, 4 H), 7.32 (d, *J*=4.3 Hz, 1 H), 3.92 - 4.02 (m, 1 H), 3.75 - 3.82 (m, 1 H), 3.61 - 3.69 (m, 1 H), 3.54 (t, *J*=3.9 Hz, 1 H), 3.36 - 3.42 (m, 6 H), 2.89 - 2.96 (m, 2 H), 2.73 - 2.89 (m, 2 H), 1.75 – 1.83 (m, 4 H), 1.32 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 387.2 $(M+H)^+$.

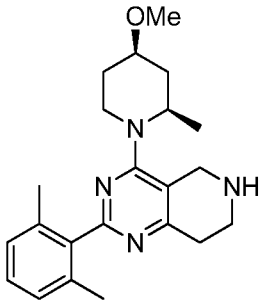
21-B. 6-Benzyl-2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 6-Benzyl-2-chloro-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (775 mg, 2.00 mmol) in DME (7 mL) was added 2,6-dimethylphenylboronic acid (601 mg, 4.01 mmol), $Pd(Ph_3P)_4$ (231 mg, 0.200 mmol) and a 2M solution of sodium carbonate (3.0 mL, 6.0 mmol). The reaction was heated at 130 °C in a microwave reactor for 1 h 15 min. The reaction was filtered and concentrated under reduced pressure. The residue was purified via FCC (0-30% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 - 7.44 (m, 4 H), 7.30 - 7.33 (m, 1 H), 7.12 - 7.19 (m, 1 H), 7.03 - 7.09 (m, 2 H), 3.80 - 3.87 (m, 1 H), 3.73 - 3.77

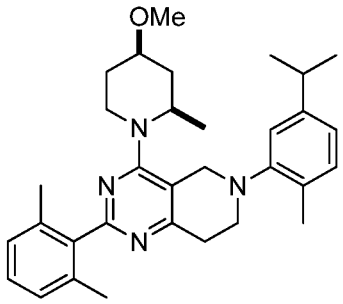
(m, 1 H), 3.62 - 3.72 (m, 2 H), 3.39 - 3.51 (m, 2 H), 3.36 (s, 3 H), 3.21 - 3.31 (m, 1 H), 3.04 - 3.14 (m, 1 H), 2.95 - 3.02 (m, 2 H), 2.84 - 2.93 (m, 1 H), 2.75 - 2.84 (m, 1 H), 2.11 (s, 6 H), 1.83 - 1.97 (m, 2 H), 1.63 - 1.71 (m, 1 H), 1.60 (dd, *J*=13.4, 6.6 Hz, 1 H), 1.17 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 457.3 $(M+H)^+$.

21-C. 2-(2,6-Dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 6-benzyl-2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (549 mg, 1.20 mmol) in THF (9 mL) and water (2 mL) was added acetic acid (206 µL, 3.61 mmol) and $Pd(OH)_2$ (253mg, 0.361 mmol). Hydrogen was bubbled through the solution for 15 min. After 1h, a saturated solution of sodium bicarbonate was added and the solution was filtered over Celite®, washed with a solution of DCM/MeOH (4:1). The aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduce pressure to obtain the title compound. MS (ESI+) *m/z* 367.3 $(M+H)^+$.

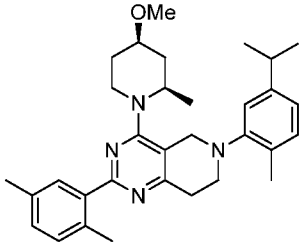
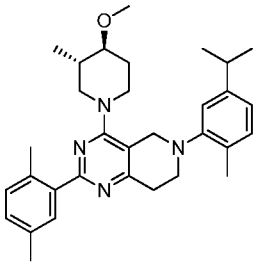
21-D. 2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

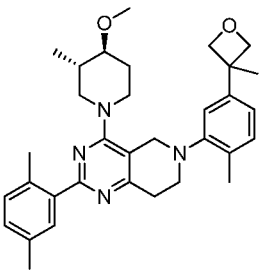
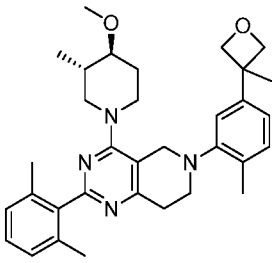
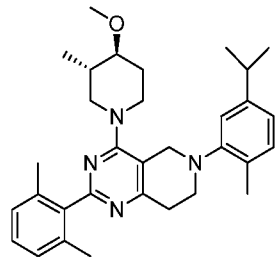


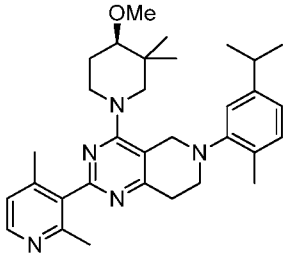
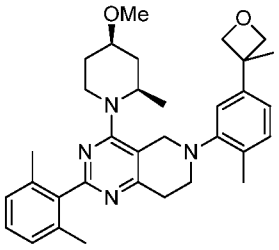
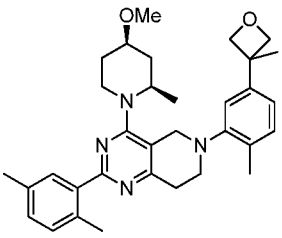
To a solution of 2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (45 mg, 0.12 mmol) in dioxane (455 µL) was added 5-isopropyl-2-methylphenyl trifluoromethanesulfonate (52 mg, 0.18 mmol), Cs_2CO_3 (80 mg, 0.25 mmol) and Chloro(2-

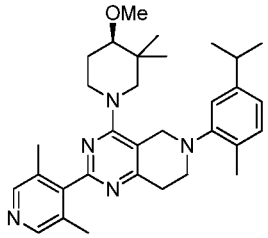
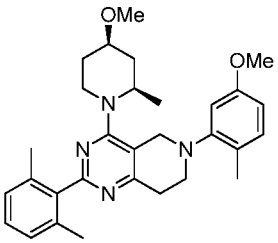
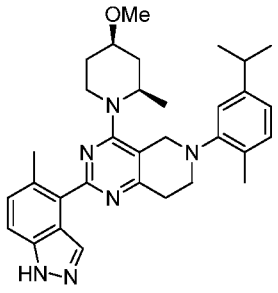
dicyclohexylphosphino-2'-4'-6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II)–methyl-*t*-butylether adduct (14 mg, 0.020 mmol). Reaction was purged with argon and was heated at 90ºC for 16 h. The mixture was diluted with EtOAc and filtered. The residue was purified via FCC (0-30% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.15 - 7.22 (m, 1 H), 7.05 - 7.13 (m, 3 H), 6.91 (s, 1 H), 6.86 (dd, *J*=7.7, 1.4 Hz, 1 H), 4.05 - 4.15 (m, 1 H), 3.92 - 4.01 (m, 1 H), 3.71 - 3.82 (m, 1 H), 3.39 - 3.49 (m, 1 H), 3.31 - 3.36 (m, 2 H), 3.25 (s, 3 H), 3.06 - 3.16 (m, 1 H), 2.91 (t, *J*=5.7 Hz, 2 H), 2.82 (quin, *J*=6.8 Hz, 1 H), 2.22 (s, 3 H), 2.03 (s, 6 H), 1.86 (dt, *J*=13.0, 3.9 Hz, 2 H), 1.54 - 1.67 (m, 2 H), 1.21 - 1.30 (m, 2 H), 1.14 - 1.20 (m, 9 H); MS (ESI+) *m/z* 499.3 $(M+H)^+$.

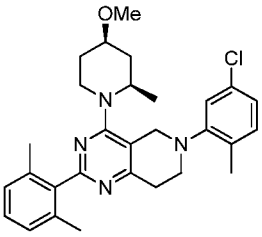
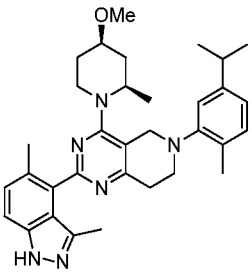
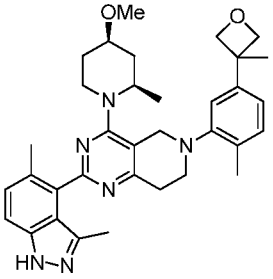
The following compounds were prepared in a similar manner. For the compounds containing an indazole or indole group the synthesis was carried out with the corresponding N-tosyl protected intermediates described in the other examples herein and the removal of the tosyl protecting group at the last step was done described in other examples herein.

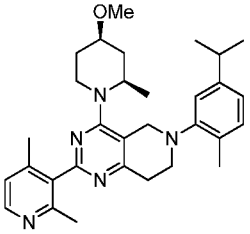
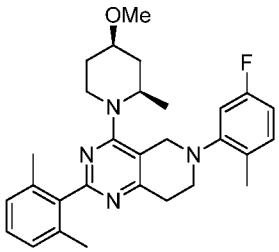
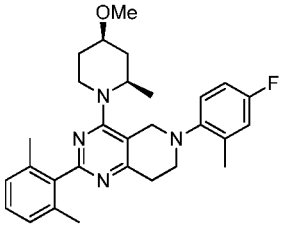
	Structure	Chemical Name&Analytical Data
21-E		2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 7.58 (s, 1 H), 7.13 - 7.16 (m, 2 H), 7.08 - 7.13 (m, 1 H), 6.97 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.01 - 4.09 (m, 1 H), 3.87 - 3.96 (m, 1 H), 3.79 - 3.87 (m, 1 H), 3.43 - 3.50 (m, 1 H), 3.27 (s, 3 H), 3.13 - 3.21 (m, 1 H), 2.98 (t, *J*=5.8 Hz, 2 H), 2.80 - 2.94 (m, 1 H), 2.46 (s, 3 H), 2.32 (s, 3 H), 2.20 (s, 3 H), 1.80 - 1.96 (m, 2 H), 1.52 - 1.71 (m, 2 H), 1.28 (d, *J*=6.8 Hz, 3 H), 1.15 - 1.25 (m, 9 H); MS (ESI+) *m/z* 499.4 $(M+H)^+$.
21-F		2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 0.97 (d, *J*=6.6 Hz, 3 H) 1.19 (d, *J*=6.8 Hz, 6 H) 1.30 - 1.43 (m, 1 H) 1.63 - 1.75 (m, 1 H) 2.05 - 2.15 (m, 1 H) 2.19 (s, 3 H) 2.32 (s, 3 H) 2.47 (s, 3 H) 2.75 (dd, *J*=13.1, 9.9 Hz, 1 H) 2.85 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.92 - 3.09 (m, 4 H) 3.22 - 3.38 (m, 2 H), 3.27 (s, 3 H) 3.64 - 3.73 (m, 1 H) 3.78 (m, 1 H) 3.88 - 4.09 (m, 2 H) 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H) 6.99 (d, *J*=1.3

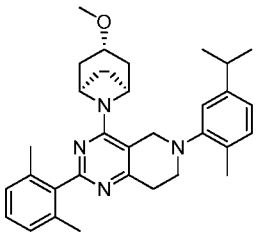
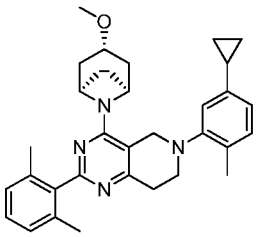
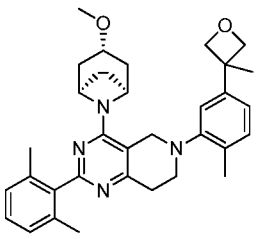
		Hz, 1 H) 7.06 - 7.19 (m, 3 H) 7.58 (s, 1 H); MS (ESI+) *m/z* 499.5 $(M+H)^+$.
21-G		2-(2,5-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 0.97 (d, *J*=6.6 Hz, 3 H) 1.31 - 1.43 (m, 1 H) 1.61 (s, 3 H) 1.65 - 1.75 (m, 1 H) 2.07 - 2.15 (m, 1 H) 2.22 (s, 3 H) 2.32 (s, 3 H) 2.46 (s, 3 H) 2.75 (dd, *J*=13.1, 9.9 Hz, 1 H) 2.93 - 3.08 (m, 4 H) 3.28 (s, 3 H) 3.29 - 3.40 (m, 2 H) 3.64 - 3.84 (m, 2 H) 3.90 - 4.11 (m, 2 H) 4.52 (d, *J*=5.6 Hz, 2 H) 4.78 (d, *J*=5.6 Hz, 2 H) 6.87 (dd, *J*=7.8, 1.8 Hz, 1 H) 6.96 (d, *J*=1.8 Hz, 1 H) 7.07 - 7.23 (m, 3 H) 7.58 (s, 1 H); MS (ESI+) *m/z* 527.4 $(M+H)^+$.
21-H		2-(2,6-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (d, *J*=6.82 Hz, 3 H) 1.31 - 1.42 (m, 1 H) 1.60 (s, 3 H) 1.62 - 1.72 (m, 1 H) 2.05 (s, 6 H) 2.06 - 2.12 (m, 1 H) 2.24 (s, 3 H) 2.74 (dd, *J*=13.4, 9.9 Hz, 1 H) 2.87 - 2.93 (m, 2 H) 2.94 - 3.03 (m, 2 H) 3.27 (s, 3 H) 3.35 (dq, *J*=12.2, 6.4 Hz, 2 H) 3.60 - 3.67 (m, 1 H) 3.73 (d, *J*=13.9 Hz, 1 H) 3.95 - 4.03 (m, 1 H) 4.06 - 4.14 (m, 1 H) 4.50 (d, *J*=5.6 Hz, 2 H) 4.76 (d, *J*=5.6 Hz, 2 H) 6.83 - 6.92 (m, 2 H) 7.05 - 7.11 (m, 2 H) 7.13 - 7.20 (m, 2 H); MS (ESI+) *m/z* 527.3 $(M+H)^+$.
21-I		2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (d, *J*=6.57 Hz, 3 H) 1.17 (d, *J*=6.8 Hz, 6 H) 1.30 - 1.41 (m, 1 H) 1.61 - 1.70 (m, 1 H) 2.05 (s, 6 H) 2.08 - 2.13 (m, 1 H) 2.21 (s, 3 H) 2.75 (dd, *J*=13.6, 10.0 Hz, 1 H) 2.82 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.90 (t, *J*=6.1 Hz, 2 H) 2.94 -

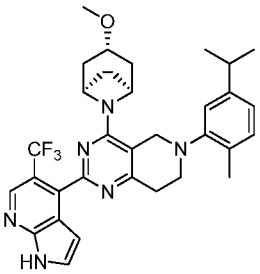
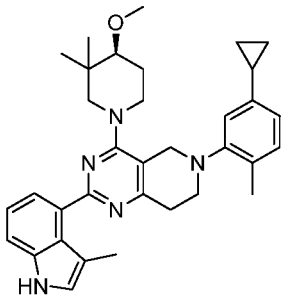
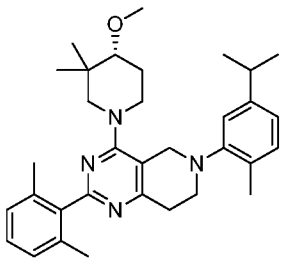
		3.04 (m, 2 H) 3.27 (s, 3 H) 3.31 - 3.37 (m, 2 H) 3.60 - 3.69 (m, 1 H) 3.71 - 3.78 (m, 1 H) 3.95 - 4.02 (m, 1 H) 4.03 - 4.11 (m, 1 H) 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H) 6.92 (d, *J*=1.5 Hz, 1 H) 7.04 - 7.12 (m, 3 H) 7.14 - 7.22 (m, 1 H). MS (ESI+) *m/z* 499.1 $(M+H)^+$.
21-J		(*R*)-2-(2,4-dimethylpyridin-3-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.32 (d, *J*=5.1 Hz, 1 H), 7.14 (d, *J*=5.1 Hz, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.92 (s, 1 H), 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H), 3.99 - 4.14 (m, 2 H), 3.65 (dt, *J*=10.2, 5.1 Hz, 1 H), 3.32 - 3.40 (m, 3 H), 3.28 (s, 3 H), 3.00 - 3.10 (m, 1 H), 2.98 (dd, *J*=9.1, 4.0 Hz, 1 H), 2.91 (t, *J*=5.8 Hz, 2 H), 2.74 - 2.88 (m, 2 H), 2.25 (s, 3 H), 2.21 (s, 3 H), 2.09 (s, 3H), 1.88 - 2.00 (m, 1 H), 1.47 - 1.62 (m, 1 H), 1.17 (d, *J*=7.1 Hz, 6 H), 0.96 (s, 3 H), 0.88 (s, 3 H); MS (ESI+) *m/z* 514.4 $(M+H)^+$.
21-K		2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.22 (m, 2 H), 7.03 - 7.11 (m, 2 H), 6.82 - 6.90 (m, 2 H), 4.76 (dd, *J*=5.6, 2.8 Hz, 2 H), 4.50 (dd, *J*=5.6, 1.8 Hz, 2 H), 4.08 - 4.17 (m, 1 H), 3.92 - 4.01 (m, 1 H), 3.72 - 3.81 (m, 1 H), 3.41 - 3.49 (m, 1 H), 3.33 - 3.39 (m, 2 H), 3.25 (s, 3 H), 3.06 - 3.18 (m, 1 H), 2.91 (t, *J*=5.6 Hz, 2 H), 2.25 (s, 3 H), 2.03 (s, 6 H), 1.79 - 1.91 (m, 2 H), 1.55 - 1.68 (m, 5 H), 1.24 (d, *J*=6.8 Hz, 1 H), 1.19 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 527.4 $(M+H)^+$.
21-L		2-(2,5-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 7.58 (d, *J*=0.5 Hz, 1 H), 7.09 - 7.20 (m, 3 H), 6.95 (d, *J*=1.8 Hz, 1 H), 6.87 (dd, *J*=7.8, 1.8 Hz, 1 H), 4.78 (dd, *J*=5.6, 2.8 Hz, 2 H), 4.52 (dd, *J*=5.6, 1.8 Hz, 2 H), 4.08 (d, *J*=14.9 Hz, 1 H), 3.91 (d, *J*=14.4 Hz, 1 H), 3.79 -

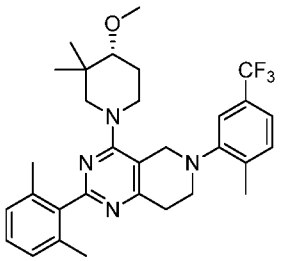
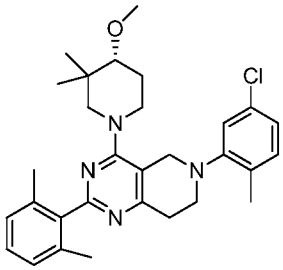
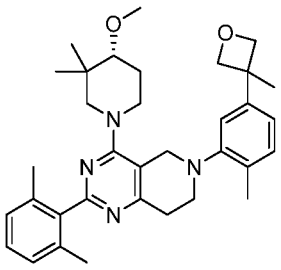
		3.88 (m, 1 H), 3.42 - 3.50 (m, 1 H), 3.32 - 3.35 (m, 2 H), 3.27 (s, 3 H), 3.13 - 3.23 (m, 1 H), 2.98 (t, *J*=5.9 Hz, 2 H), 2.47 (s, 3 H), 2.32 (s, 3 H), 2.23 (s, 3 H), 1.83 - 1.93 (m, 2 H), 1.55 - 1.70 (m, 6 H), 1.22 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 527.4 $(M+H)^+$.
21-M		(*R*)-2-(3,5-dimethylpyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.34 (s, 2 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.92 (d, *J*=1.5 Hz, 1 H), 6.86 (dd, *J*=7.7, 1.4 Hz, 1 H), 3.95 - 4.14 (m, 2 H), 3.56 - 3.76 (m, 1 H), 3.32 - 3.39 (m, 3 H), 3.28 (s, 3 H), 3.05 (ddd, *J*=13.3, 10.1, 3.2 Hz, 1 H), 2.98 (dd, *J*=9.0, 3.9 Hz, 1 H), 2.91 (t, *J*=5.7 Hz, 2 H), 2.77 - 2.88 (m, 2 H), 2.21 (s, 3 H), 2.08 (s, 6 H), 1.89 - 1.97 (m, 1 H), 1.47 - 1.61 (m, 1 H), 1.17 (d, *J*=6.8 Hz, 6 H), 0.96 (s, 3 H), 0.88 (s, 3 H); MS (ESI+) *m/z* 514.3 $(M+H)^+$.
21-N		2-(2,6-dimethylphenyl)-6-(5-methoxy-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.15 - 7.22 (m, 1 H), 7.06 - 7.14 (m, 3 H), 6.68 (d, *J*=2.5 Hz, 1 H), 6.60 (dd, *J*=8.2, 2.4 Hz, 1 H), 4.02 - 4.11 (m, 1 H), 3.88 - 3.96 (m, 1 H), 3.74 - 3.79 (m, 2 H), 3.72 (s, 3 H), 3.40 - 3.48 (m, 1 H), 3.25 (s, 3 H), 3.06 - 3.16 (m, 1 H), 2.96 (t, *J*=5.8 Hz, 2 H), 2.18 (s, 3 H), 2.03 (s, 6 H), 1.80 - 1.90 (m, 2 H), 1.54 - 1.67 (m, 2 H), 1.24 (d, *J*=7.1 Hz, 1 H), 1.16 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 487.3 $(M+H)^+$.
21-O		6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.97 (s, 1 H), 8.08 (s, 1 H), 7.50 (d, *J*=8.3 Hz, 1 H), 7.28 (d, *J*=8.6 Hz, 1 H), 7.12 (d, *J*=7.8 Hz, 1 H), 6.99 (s, 1 H), 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.06 - 4.16 (m, 1 H), 3.92 - 4.00 (m, 1 H), 3.82 - 3.92 (m, 1 H), 3.44 - 3.53 (m, 1 H), 3.32 - 3.39 (m, 2 H), 3.27 (s, 3 H), 3.00 - 3.06 (m, 2 H),

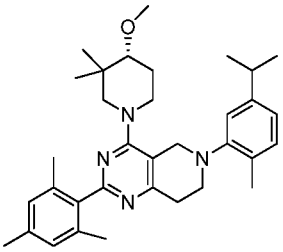
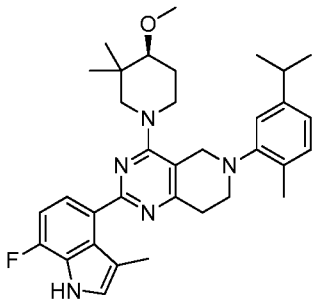
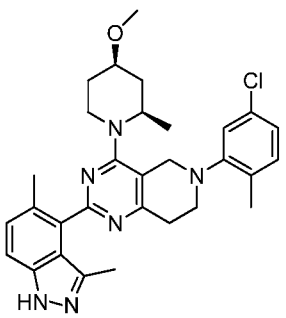
		2.85 (quin, *J*=6.9 Hz, 1 H), 2.55 (s, 3 H), 2.23 (s, 3 H), 1.83 - 1.94 (m, 2 H), 1.59 - 1.72 (m, 2 H), 1.23 (d, *J*=6.6 Hz, 4 H), 1.19 (d, *J*=7.1 Hz, 7 H); MS (ESI+) *m/z* 525.1 $(M+H)^+$.
21-P		6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 (d, *J*=8.3 Hz, 1 H), 7.15 - 7.21 (m, 1 H), 7.13 (d, *J*=2.0 Hz, 1 H), 7.02 - 7.11 (m, 3 H), 4.05 - 4.13 (m, 1 H), 3.93 - 4.01 (m, 1 H), 3.71 - 3.79 (m, 1 H), 3.39 - 3.47 (m, 1 H), 3.25 (s, 3 H), 3.05 - 3.15 (m, 1 H), 2.96 (t, *J*=5.8 Hz, 2 H), 2.24 (s, 3 H), 2.03 (s, 6 H), 1.78 - 1.93 (m, 2 H), 1.51 - 1.67 (m, 2 H), 1.16 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 491.0 $(M+H)^+$.
21-Q		(+)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1 H), 7.40 (d, *J*=8.6 Hz, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=7.8 Hz, 1 H), 6.92 (s, 1 H), 6.87 (d, *J*=7.8 Hz, 1 H), 4.07 - 4.19 (m, 1 H), 3.97 - 4.06 (m, 1 H), 3.70 - 3.86 (m, 1 H), 3.41 - 3.52 (m, 1 H), 3.34 - 3.40 (m, 2 H), 3.25 (s, 3 H), 3.10 - 3.21 (m, 1 H), 2.94 (t, *J*=5.7 Hz, 2 H), 2.82 (quin, *J*=6.9 Hz, 1 H), 2.23 (s, 3 H), 2.17 (s, 3 H), 1.76 - 1.91 (m, 5 H), 1.53 - 1.70 (m, 2 H), 1.09 - 1.27 (m, 10 H); MS (ESI+) *m/z* 539.4 $(M+H)^+$; $[\alpha]^{25}_D$ +0.85 (c 1.0, MeOH). .
21-R		2-(3,5-dimethyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.20 (dd, *J*=10.7, 8.2 Hz, 2 H), 6.81 - 6.94 (m, 2 H), 4.78 (dd, *J*=5.6, 2.5 Hz, 2 H), 4.51 (d, *J*=5.6 Hz, 2 H), 4.08 - 4.21 (m, 1 H), 3.96 - 4.08 (m, 1 H), 3.71 - 3.85 (m, 1 H), 3.42 - 3.51 (m, 1 H), 3.39 (t, *J*=6.1 Hz, 2 H), 3.24 (s, 3 H),

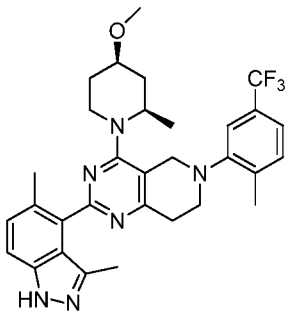
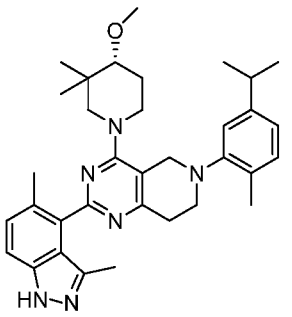
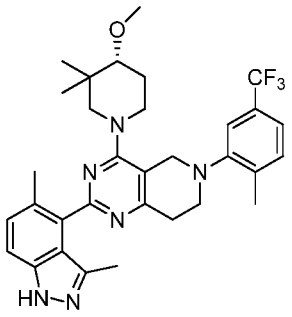
		3.12 - 3.22 (m, 1 H), 2.95 (t, *J*=5.4 Hz, 2 H), 2.43 - 2.47 (m, 1 H), 2.25 (s, 3 H), 2.17 (s, 3 H), 1.78 - 1.90 (m, 5 H), 1.54 - 1.67 (m, 5 H), 1.20 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 567.3 $(M+H)^+$.
21-S		2-(2,4-dimethylpyridin-3-yl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (d, *J*=4.8 Hz, 1 H), 7.15 (d, *J*=5.3 Hz, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.92 (s, 1 H), 6.86 (d, *J*=7.8 Hz, 1 H), 4.05 - 4.17 (m, 1 H), 3.95 (d, *J*=14.9 Hz, 1 H), 3.76 - 3.87 (m, 1 H), 3.42 - 3.51 (m, *J*=3.5 Hz, 1 H), 3.32 - 3.37 (m, 2 H), 3.13 - 3.23 (m, 1 H), 2.93 (t, *J*=5.7 Hz, 2 H), 2.83 (dt, *J*=13.7, 6.9 Hz, 1 H), 2.18 - 2.29 (m, 7 H), 2.08 (s, 3 H), 1.77 - 1.90 (m, 2 H), 1.55 - 1.71 (m, 3 H), 1.19 - 1.24 (m, 4 H), 1.17 (d, *J*=6.8 Hz, 7 H); MS (ESI+) *m/z* 500.3 $(M+H)^+$.
21-T		2-(2,6-dimethylphenyl)-6-(5-fluoro-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.20 - 7.27 (m, 1 H), 7.18 (d, *J*=8.1 Hz, 1 H), 7.05 - 7.12 (m, 2 H), 6.98 (dd, *J*=11.4, 2.5 Hz, 1 H), 6.83 (td, *J*=8.3, 2.5 Hz, 1 H), 4.03 - 4.12 (m, 1 H), 3.90 - 4.00 (m, 1 H), 3.71 - 3.81 (m, 1 H), 3.39 - 3.48 (m, 1 H), 3.25 (s, 3 H), 3.05 - 3.16 (m, 1 H), 2.98 (t, *J*=5.7 Hz, 2 H), 2.42-2.46 (m, 1 H), 2.23 (s, 3 H), 2.03 (s, 6 H), 1.78 - 1.93 (m, 2 H), 1.50 - 1.72 (m, 3 H), 1.20 - 1.31 (m, 1 H), 1.16 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 475.3 $(M+H)^+$.
21-U		2-(2,6-dimethylphenyl)-6-(4-fluoro-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.20 - 7.25 (m, 1 H), 7.16 - 7.19 (m, 1 H), 7.06 - 7.11 (m, 2 H), 7.03 (td, *J*=8.6, 3.0 Hz, 1 H), 3.97 - 4.06 (m, 1 H), 3.87 - 3.94 (m, 1 H), 3.74 (dt, *J*=6.8, 5.5 Hz, 1 H), 3.38 - 3.46 (m, 1 H), 3.24 (s, 4 H), 3.04 - 3.13 (m, 1 H), 2.98 (t, *J*=5.9 Hz, 1 H), 2.42 - 2.46 (m, 1 H), 2.27 (s, 2 H), 2.03 (s,

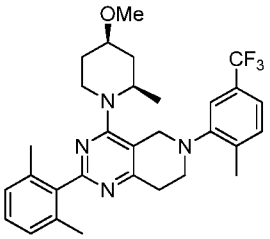
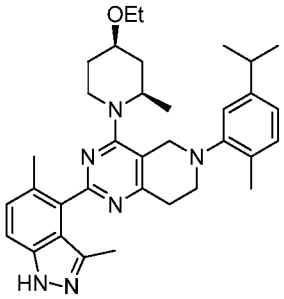
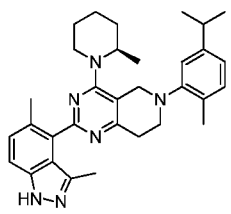
		3 H), 1.78 - 1.91 (m, 1 H), 1.52 - 1.66 (m, 1 H), 1.22 - 1.26 (m, 0 H), 1.14 (d, *J*=6.3 Hz, 2 H); MS (ESI+) *m/z* 475.3 $(M+H)^+$.
21-V		2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.15 - 7.21 (m, 1 H) 7.05 - 7.14 (m, 3 H) 6.99 (d, J=1.8 Hz, 1 H) 6.89 (dd, J=7.7, 1.6 Hz, 1 H) 4.52 (br. s., 2 H) 4.03 (s, 2 H) 3.48 (t, J=4.4 Hz, 1 H) 3.35 (t, J=5.9 Hz, 2 H) 3.28 (s, 3 H) 2.93 (t, J=5.9 Hz, 2 H) 2.85 (ddd, J=13.8, 7.1, 7.0 Hz, 1 H) 2.27 (s, 3 H) 2.10 (s, 6 H) 2.02 - 2.19 (m, 4 H) 1.87 - 2.01 (m, 4 H) 1.23 (d, J=7.1 Hz, 6 H); MS (ESI+) *m/z* 511.4 $(M+H)^+$.
21-W		6-(5-cyclopropyl-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.15 - 7.21 (m, 1 H) 7.04 - 7.11 (m, 3 H) 6.86 (d, *J*=1.8 Hz, 1 H) 6.72 (dd, *J*=7.6, 1.8 Hz, 1 H) 4.52 (br. s., 2 H) 4.01 (s, 2 H) 3.49 (t, *J*=4.3 Hz, 1 H) 3.31 - 3.36 (m, 2 H) 3.28 (s, 3 H) 2.93 (t, *J*=5.8 Hz, 2 H) 2.26 (s, 3 H) 2.10 (s, 6 H) 2.02 - 2.19 (m, 4 H) 1.82 - 2.00 (m, 5 H) 0.91 (dt, *J*=10.6, 4.2 Hz, 2 H) 0.61 (dd, *J*=5.1, 2.1 Hz, 2 H); MS (ESI+) *m/z* 509.1 $(M+H)^+$.
21-X		2-(2,6-dimethylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 (d, J=7.8 Hz, 1 H) 7.16 - 7.22 (m, 1 H) 7.1 - 7.14 (m, 2 H) 6.98 (d, J=1.8 Hz, 1 H) 6.92 - 6.96 (m, 1 H) 5.00 (d, J=5.6 Hz, 2 H) 4.68 (d, J=5.6 Hz, 2 H) 4.49 (br. s., 2 H) 4.05 (s, 2 H) 3.48 - 3.55 (m, 1 H) 3.40 (t, J=5.8 Hz, 2 H) 3.31 (s, 3 H) 3.05 - 3.14 (m, 2 H) 2.38 (s, 3 H) 2.20 (s, 6 H) 2.03 - 2.17 (m, 4 H) 1.89 - 2.02 (m, 4 H) 1.77 (s, 3 H); MS (ESI+) *m/z* 540.0 $(M+H)^+$.

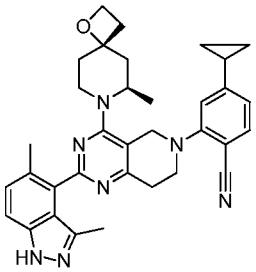
21-Y		6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.67 (s, 1 H) 7.44 (d, J=3.8 Hz, 1 H) 7.14 (d, J=8.3 Hz, 1 H) 7.00 (d, J=1.8 Hz, 1 H) 6.92 (dd, J=7.8, 1.8 Hz, 1 H) 6.57 (d, J=3.5 Hz, 1 H) 4.49 (br. s., 2 H) 4.04 (s, 2 H) 3.46 (t, J=4.8 Hz, 1 H) 3.35 (t, J=6.0 Hz, 2 H) 3.25 (s, 3 H) 3.06 (t, J=6.0 Hz, 2 H) 2.90 (ddd, J=13.8, 7.1, 7.0 Hz, 1 H) 2.30 (s, 3 H) 2.00 - 2.16 (m, 4 H) 1.83 - 1.96 (m, 4 H) 1.26 (d, J=6.8 Hz, 6 H); MS (ESI+) *m/z* 591.0 $(M+H)^+$.
21-Z		(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine . ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.22 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.34 (d, *J*=7.1 Hz, 1 H), 7.19 - 7.23 (m, 1 H), 7.01 - 7.13 (m, 2 H), 6.84 (s, 1 H), 6.72 (d, *J*=7.8 Hz, 1 H), 4.01 (s, 2 H), 3.71 (br. s., 1 H), 3.38 - 3.43 (m, 1 H), 3.34 (br. s., 5 H), 3.13 (br. s., 3 H), 2.95 (dd, *J*=8.7, 3.9 Hz, 2 H), 2.26 (s, 3 H), 2.09 (s, 3 H), 1.92 – 2.01 (m, 1 H), 1.81 - 1.92 (m, 1 H), 1.63 - 1.74 (m, 1 H), 1.00 (s, 3 H), 0.96 (br. s., 3 H), 0.91 - 0.95 (m, 2 H), 0.62 - 0.69 (m, 2 H); MS (ESI+) *m/z* 536.0 $(M+H)^+$.
21-AA		(*R*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.15 - 7.20 (m, 1 H) 7.06 - 7.12 (m, 3 H) 6.91 (d, *J*=1.52 Hz, 1 H) 6.85 (dd, *J*=7.83, 1.52 Hz, 1 H) 4.06 (d, *J*=6.06 Hz, 2 H) 3.62 (br. s., 1 H) 3.31 - 3.36 (m, 3 H) 2.95 - 3.07 (m, 2 H) 2.86 - 2.92 (m, 2 H) 2.78 - 2.86 (m, 2 H) 2.21 (s, 3 H) 2.04 (s, 6 H) 1.89 - 1.98 (m, 1 H) 1.49 - 1.62 (m, 1 H) 1.17 (d, *J*=7.07 Hz, 6 H) 0.96 (s, 3 H) 0.88 (s, 3 H); MS (ESI+) *m/z* 513.4 $(M+H)^+$.

21-AB		(*R*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.43 (d, *J*=7.83 Hz, 1 H) 7.29 - 7.35 (m, 2 H) 7.15 - 7.20 (m, 1 H) 7.05 - 7.10 (m, 2 H) 4.13 (q, *J*=14.65 Hz, 2 H) 3.64 (d, *J*=12.63 Hz, 1 H) 3.40 (t, *J*=6.44 Hz, 2 H) 3.33 (dd, *J*=13.14, 1.26 Hz, 1 H) 3.28 (s, 3 H) 2.99 - 3.08 (m, 1 H) 2.97 (dd, *J*=8.97, 3.92 Hz, 1 H) 2.88 - 2.95 (m, 2 H) 2.84 (d, *J*=12.88 Hz, 1 H) 2.34 (s, 3 H) 2.04 (s, 6 H) 1.89 - 1.96 (m, 1 H) 1.49 - 1.60 (m, 1 H) 0.95 (s, 3 H) 0.86 (s, 3 H); MS (ESI+) *m/z* 539.3 $(M+H)^+$.
21-AC		(*R*)-6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.23 (d, *J*=8.59 Hz, 1 H) 7.13 - 7.20 (m, 2 H) 7.04 - 7.10 (m, 3 H) 4.03 - 4.11 (m, 1 H) 3.95 - 4.03 (m, 1 H) 3.67 (d, *J*=14.15 Hz, 1 H) 3.34 (d, *J*=9.60 Hz, 2 H) 2.90 - 3.09 (m, 4 H) 2.85 (d, *J*=13.14 Hz, 1 H) 2.53 - 2.58 (m, 1 H) 2.23 (s, 3 H) 2.04 (s, 6 H) 1.88 - 1.96 (m, 1 H) 1.49 - 1.61 (m, 1 H) 0.94 (s, 3 H) 0.84 (s, 3 H); MS (ESI+) *m/z* 505.3 $(M+H)^+$.
21-AD		(*R*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.14 - 7.23 (m, 2 H) 7.08 (d, *J*=7.58 Hz, 2 H) 6.84 - 6.92 (m, 2 H) 4.90 (d, *J*=5.56 Hz, 2 H) 4.58 (d, *J*=5.56 Hz, 2 H) 4.04 (s, 2 H) 3.67 (d, *J*=15.92 Hz, 1 H) 3.29 - 3.40 (m, 6 H) 3.05 (br. s., 3 H) 2.94 (dd, *J*=8.84, 3.79 Hz, 1 H) 2.84 (d, *J*=14.40 Hz, 1 H) 2.31 (s, 3 H) 2.12 (s, 6 H) 1.90 - 2.01 (m, 1 H) 1.61 - 1.73 (m, 4 H) 0.97 (d, *J*=16.93 Hz, 6 H); MS (ESI+) *m/z* 541.3 $(M+H)^+$.

21-AE		(*R*)-6-(5-isopropyl-2-methylphenyl)-2-mesityl-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.09 (d, *J*=7.83 Hz, 1 H) 6.91 (s, 1 H) 6.89 (s, 2 H) 6.85 (dd, *J*=7.71, 1.39 Hz, 1 H) 3.99 - 4.11 (m, 2 H) 3.58 - 3.68 (m, 1 H) 3.33 (d, *J*=6.06 Hz, 3 H) 3.28 (s, 3 H) 2.95 - 3.06 (m, 2 H) 2.86 - 2.91 (m, 2 H) 2.77 - 2.85 (m, 2 H) 2.27 (s, 3 H) 2.21 (s, 3 H) 2.02 (s, 6 H) 1.93 (dd, *J*=13.14, 3.79 Hz, 1 H) 1.49 - 1.61 (m, 1 H) 1.16 (d, *J*=6.82 Hz, 6 H) 0.96 (s, 3 H) 0.88 (s, 3 H). MS (ESI+) *m/z* 527.4 $(M+H)^+$.
21-AF		(*S*)-2-(7-fluoro-3-methyl-1H-indol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.25 (br. s., 1 H) 7.22 (dd, J=8.1, 4.8 Hz, 1 H) 7.03 (d, J=7.8 Hz, 1 H) 6.98 (d, J=1.0 Hz, 1 H) 6.88 (d, J=1.5 Hz, 1 H) 6.76 - 6.86 (m, 2 H) 3.95 (s, 2 H) 3.50 - 3.67 (m, 1 H) 3.19 - 3.36 (m, 6 H) 2.94 - 3.06 (m, 3 H) 2.69 - 2.91 (m, 3 H) 2.18 (s, 3 H) 2.03 (s, 3 H) 1.82 - 1.95 (m, 1 H) 1.51 - 1.68 (m, 1 H) 1.16 (d, J=6.8 Hz, 6 H) 0.92 (s, 3 H) 0.89 (s, 3 H); MS (ESI+) m/z 556.4 $(M+H)^+$.
21-AG		6-(5-chloro-2-methylphenyl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.23 (t, *J*=8.1 Hz, 2 H), 7.10 (d, *J*=2.0 Hz, 1 H), 7.06 (dd, *J*=8.1, 1.8 Hz, 1 H), 4.07 - 4.17 (m, 1 H), 3.99 - 4.07 (m, 1 H), 3.74 - 3.84 (m, 1 H), 3.42 - 3.49 (m, 1 H), 3.34 - 3.39 (m, 2 H), 3.25 (s, 3 H), 3.11 - 3.21 (m, 1 H), 2.96 (t, *J*=5.9 Hz, 2 H), 2.25 (s, 3 H), 2.17 (s, 3 H), 1.86 - 1.90 (m, 1 H), 1.84 (s, 3 H), 1.56 - 1.69 (m, 2 H), 1.24 (br. s., 1 H), 1.18 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 531.2 $(M+H)^+$.

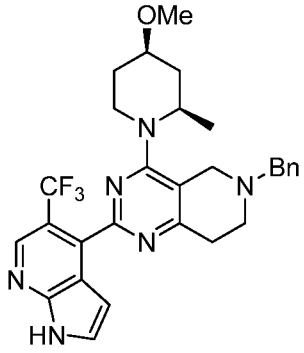
21-AH		2-(3,5-dimethyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1 H), 7.45 (d, *J*=7.8 Hz, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.34 (d, *J*=8.3 Hz, 1 H), 7.28 (s, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 4.16 - 4.24 (m, 1 H), 4.06 - 4.15 (m, 1 H), 3.75 - 3.82 (m, 1 H), 3.44 (t, *J*=5.7 Hz, 2 H), 3.25 (s, 3 H), 3.11 - 3.20 (m, 1 H), 2.95 (t, *J*=6.3 Hz, 2 H), 2.44 - 2.47 (m, 1 H), 2.36 (s, 3 H), 2.17 (s, 3 H), 1.86 - 1.90 (m, 2 H), 1.83 (s, 3 H), 1.56 - 1.66 (m, 2 H), 1.24 (d, *J*=3.0 Hz, 1 H), 1.19 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 565.3 $(M+H)^+$.
21-AI		(*R*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 12.57 (s, 1 H) 7.39 (d, *J*=8.34 Hz, 1 H) 7.21 (d, *J*=8.84 Hz, 1 H) 7.11 (d, *J*=7.83 Hz, 1 H) 6.93 (s, 1 H) 6.84 - 6.89 (m, 1 H) 4.02 - 4.17 (m, 2 H) 3.65 (d, *J*=13.14 Hz, 1 H) 3.33 - 3.41 (m, 3 H) 3.27 (s, 3 H) 3.00 - 3.13 (m, 1 H) 2.98 (dd, *J*=8.97, 3.92 Hz, 1 H) 2.89 - 2.95 (m, 2 H) 2.77 - 2.87 (m, 2 H) 2.22 (s, 3 H) 2.19 (s, 3 H) 1.89 - 1.97 (m, 1 H) 1.87 (s, 3 H) 1.49 - 1.61 (m, 1 H) 1.18 (d, *J*=6.82 Hz, 6 H) 0.96 (s, 3 H) 0.89 (s, 3 H); MS (ESI+) *m/z* 553.3 $(M+H)^+$.
21-AJ		(*R*)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 12.57 (s, 1 H) 7.44 (d, *J*=8.08 Hz, 1 H) 7.39 (d, *J*=8.34 Hz, 1 H) 7.27 - 7.36 (m, 2 H) 7.21 (d, *J*=8.59 Hz, 1 H) 4.10 - 4.25 (m, 2 H) 3.62 - 3.70 (m, 1 H) 3.44 (t, *J*=6.19 Hz, 2 H) 3.36 (d, *J*=13.64 Hz, 1 H) 3.27 (s, 3 H) 3.01 - 3.10 (m, 1 H) 2.98 (dd, *J*=9.09, 3.79 Hz, 1 H) 2.93 (t, *J*=6.32 Hz, 2 H) 2.85 (d, *J*=13.14 Hz, 1 H) 2.35 (s, 3 H) 2.18 (s, 3 H) 1.93 (dd, *J*=13.64, 4.04 Hz, 1 H) 1.85 (s, 3 H) 1.49 - 1.61 (m, 1 H) 0.95 (s, 3 H) 0.87 (s, 3 H);

		MS (ESI+) *m/z* 579.3 $(M+H)^+$.
21-AK		2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.44 (d, *J*=7.8 Hz, 1 H), 7.34 (d, *J*=8.6 Hz, 1 H), 7.29 (s, 1 H), 7.15 - 7.22 (m, 1 H), 7.05 - 7.12 (m, 2 H), 4.11 - 4.21 (m, 1 H), 4.00 - 4.09 (m, 1 H), 3.71 - 3.81 (m, 1 H), 3.42 - 3.48 (m, 1 H), 3.40 (t, *J*=6.1 Hz, 2 H), 3.25 (s, 3 H), 3.11 (ddd, *J*=13.8, 6.6, 4.3 Hz, 1 H), 2.94 (t, *J*=5.9 Hz, 2 H), 2.35 (s, 3 H), 2.03 (s, 6 H), 1.80 - 1.91 (m, 2 H), 1.54 - 1.67 (m, 2 H), 1.18 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 525.2 $(M+H)^+$.
21-AL		2-(3,5-dimethyl-1H-indazol-4-yl)-4-((2R,4R)-4-ethoxy-2-methylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=7.6 Hz, 1 H), 6.92 (s, 1 H), 6.87 (dd, *J*=7.7, 1.4 Hz, 1 H), 4.08 - 4.18 (m, 1 H), 3.96 - 4.05 (m, 1 H), 3.74 - 3.84 (m, 1 H), 3.55 (t, *J*=5.7 Hz, 1 H), 3.40 - 3.49 (m, 2 H), 3.34 - 3.40 (m, 3 H), 3.11 - 3.21 (m, 1 H), 2.94 (t, *J*=5.7 Hz, 2 H), 2.82 (dt, *J*=13.6, 6.8 Hz, 1 H), 2.23 (s, 3 H), 2.17 (s, 3 H), 1.77 - 1.90 (m, 5 H), 1.55 - 1.66 (m, 2 H), 1.15 - 1.23 (m, 9 H), 1.10 (t, *J*=6.9 Hz, 3 H); MS (ESI+) *m/z* 553.5 $(M+H)^+$.
21-AM		(*R*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=8.1 Hz, 1 H), 6.93 (d, *J*=1.5 Hz, 1 H), 6.86 (dd, *J*=7.6, 1.5 Hz, 1 H), 3.88 - 4.17 (m, 3 H), 3.43 - 3.57 (m, 1 H), 3.11 - 3.24 (m, 1 H), 2.89 - 3.00 (m, 2 H), 2.77 - 2.88 (m, 1 H), 2.22 (s, 3 H), 2.17 (br. s., 3 H), 1.84 - 1.90 (m,

		3 H), 1.59 - 1.75 (m, 3 H), 1.52 (d, *J*=4.8 Hz, 3 H), 1.13 - 1.21 (m, 9 H); MS (ESI+) *m/z* 509.4 $(M+H)^+$.
21-AN		4-Cyclopropyl-2-(2-(3,5-dimethyl-1H-indazol-4-yl)-4-((4S,6R)-6-methyl-1-oxa-7-azaspiro[3.5]nonan-7-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)benzonitrile. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.76 (br. s., 1H), 7.40 (d, *J* = 7.83 Hz, 1H), 7.28 (d, *J* = 8.34 Hz, 1H), 7.17 (d, *J* = 8.84 Hz, 1H), 6.54 - 6.67 (m, 2H), 4.36 - 4.50 (m, 2H), 4.31 (d, *J* = 15.16 Hz, 1H), 4.20 (d, *J* = 15.16 Hz, 1H), 3.91 - 4.02 (m, 1H), 3.71 - 3.81 (m, 1H), 3.61 - 3.71 (m, 1H), 3.44 (td, *J* = 4.71, 13.83 Hz, 1H), 3.12 (ddd, *J* = 3.03, 10.04, 13.45 Hz, 1H), 2.98 - 3.05 (m, 2H), 2.45 - 2.57 (m, 1H), 2.34 - 2.45 (m, 1H), 2.15 (s, 3H), 1.97 - 2.08 (m, 1H), 1.86 - 1.94 (m, 2H), 1.84 (s, 3H), 1.76 - 1.83 (m, 2H), 1.11 (d, *J* = 6.82 Hz, 3H), 0.94 - 1.02 (m, 2H), 0.61 - 0.68 (m, 2H). MS (ESI+) *m/z* 560.3 $(M+H)^+$.

Example 22

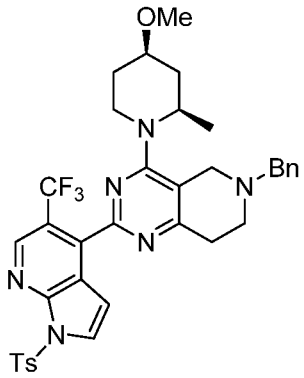
22-A. 6-Benzyl-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



The product was prepared as in a similar manner as described in **Example 21-b** by using 6-benzyl-2-chloro-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (190 mg, 0.491 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine (460 mg, 0.982 mmol) $Pd(PPh_3)_4$ (57 mg, 0.049 mmol) and

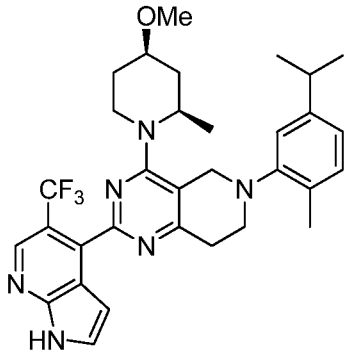
a 2 M solution of $NaHCO_3$ (737 µL, 1.47 mmol). The residue was purified via FCC (0 to 5% MeOH/DCM (1% NH_4OH)) to give the title compound. MS (ESI+) *m/z* 537.0 $(M+H)^+$.

22-B. 6-Benzyl-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(1-tosyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 6-benzyl-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (214 mg, 0.399 mmol) in THF (4 mL) was added NaH 60% in oil (32 mg, 0.80 mmol) at 0°C. After 20 min, p-toluenesulfonyl chloride (91 mg, 0.48 mmol) was added and the reaction was allowed to warm to room temperature. After 2 h, the reaction was quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified via FCC (0-70% EtOAc/heptane) to give the title compound. MS (ESI+) *m/z* 691.1 $(M+H)^+$.

22-C. 6-(5-Isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

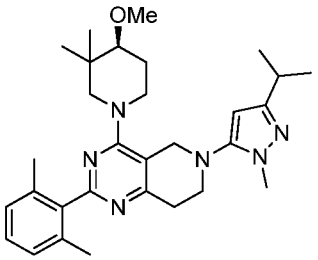


To a solution of 6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(1-tosyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (25

mg, 0.034 mmol), prepared as described in **Examples 21-c** and **21-d**, in EtOH (898 µL) was added KOH (17.2 mg, 0.307 mmol) and NH_4OH (202 µL, 5.12 mmol). The reaction was heated at 100 °C for 40 min in a microwave reactor. The reaction was then concentrated and the residue was disolved in EtOAc and a saturated solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with EtOAc (2x). The organic phases were combined, washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified via FCC (0-60% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.24 (br. s., 1 H), 8.64 (s, 1 H), 7.65 - 7.70 (m, 1 H), 7.11 (d, *J*=7.8 Hz, 1 H), 6.94 (s, 1 H), 6.87 (dd, *J*=7.7, 1.6 Hz, 1 H), 6.41 (dd, *J*=3.5, 1.8 Hz, 1 H), 4.13 (d, *J*=15.4 Hz, 1 H), 3.94 - 4.03 (m, 1 H), 3.86 - 3.94 (m, 1 H), 3.44 - 3.50 (m, 1 H), 3.33 - 3.38 (m, 2 H), 3.25 (s, 3 H), 2.92 - 3.01 (m, 2 H), 2.84 (dt, *J*=13.7, 6.9 Hz, 1 H), 2.43 - 2.47 (m, 1 H), 2.23 (s, 3 H), 1.75 - 1.89 (m, 2 H), 1.61 - 1.72 (m, 2 H), 1.22 (d, *J*=6.8 Hz, 4 H), 1.18 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 579.1 $(M+H)^+$.

Example 23

23-A. (*S*)-2-(2,6-Dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

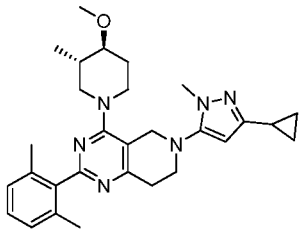
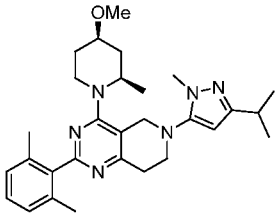


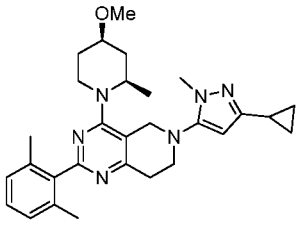
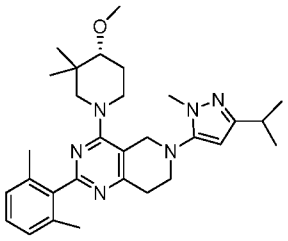
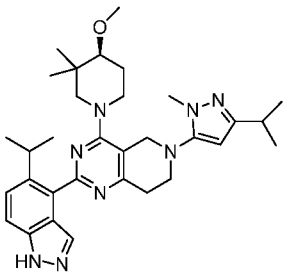
In a microwave reaction vial (*S*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (115 mg, 0.302 mmol), prepared by a method similar to that described by **Examples 21-c** and **21-d**, was combined with methyl isobutyryl acetate (65 mg, 0.45 mmol), toluene (2 mL) and DMAP (7 mg, 0.060 mmol). The vial was heated in a microwave reactor at 150°C for 30 min. The reaction mixture was then diluted with DCM and water. The layers were separated and the aqueous phase was extracted twice with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash column chromatography (0-100% 10:1 EtOAc:MeOH/heptanes) to provide (*S*)-1-(2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylpentane-1,3-dione. MS (ESI+) *m/z* 493.0 $(M+H)^+$

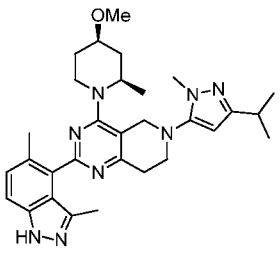
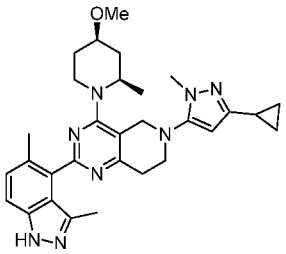
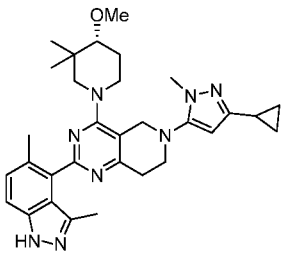
To a solution of Lawesson's Reagent (61 mg, 0.15 mmol) in THF (1 mL) was added pyridine (0.050 mL) followed by methyl hydrazine (9.9 µl, 0.19 mmol). The reaction mixture was stirred for 35 minutes at

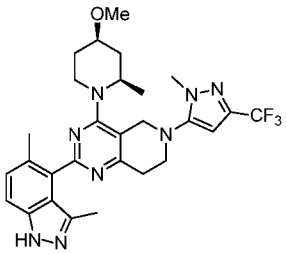
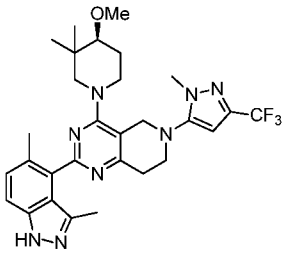
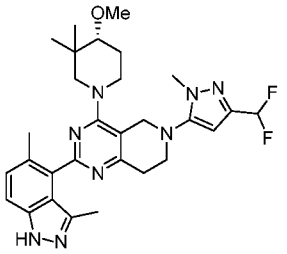
room temperature. A solution of (*S*)-1-(2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylpentane-1,3-dione (62 mg, 0.13 mmol) in THF (1 mL) was added and the reaction was immediately sealed and heated by microwave irradiation for 12 minutes at 125°C. The reaction mixture was concentrated and the resulting residue was purified by flash column chromatography on silica gel (0-5% 10:1 MeOH:NH_4OH/ DCM to provide (*S*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.20 (br. s., 1 H), 7.09 (d, *J*=7.1 Hz, 2 H), 5.66 (s, 1 H), 3.98 (d, *J*=2.3 Hz, 2 H), 3.68 - 3.76 (m, 1 H), 3.66 (s, 3 H), 3.34 (s, 3 H), 3.31 (t, *J*=6.1 Hz, 2 H), 3.07 (br. s., 1 H), 2.93 - 3.00 (m, 1 H), 2.84 (spt, *J*=6.6 Hz, 1 H), 2.13 (br. s., 6 H), 1.92 - 2.00 (m, 1 H), 1.64 - 1.74 (m, 1 H), 1.21 (d, *J*=7.1 Hz, 6 H), 0.96 (s, 3 H), 0.90 (s, 3 H); MS (ESI+) *m/z* 503.2 $(M+H)^+$.

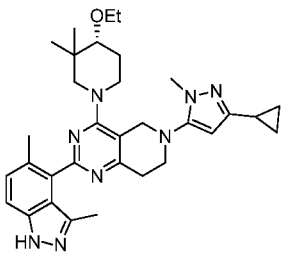
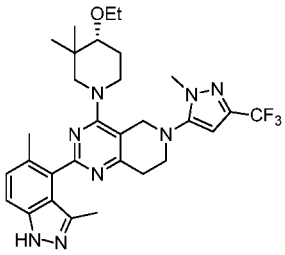
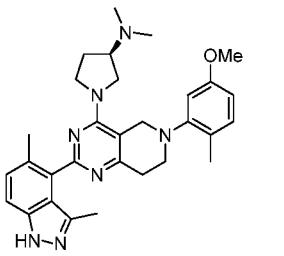
The following compounds were prepared in a similar manner. For the compounds containing an indazole or indole group the synthesis was carried out with the corresponding N-tosyl protected intermediates described in the other examples herein and the removal of the tosyl protecting group at the last step was done described in other examples herein.

	Structure	Chemical Name&Analytical Data
23-B		6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine . ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.51 - 0.63 (m, 2 H) 0.74 - 0.83 (m, 2 H) 0.93 (d, *J*=6.6 Hz, 3 H) 1.29 - 1.42 (m, 1 H) 1.58 - 1.69 (m, 1 H) 1.70 - 1.81 (m, 1 H) 2.01 - 2.10 (m, 1 H) 2.04 (s, 6 H) 2.74 (dd, *J*=13.4, 9.9 Hz, 1 H) 2.88 - 3.06 (m, 4 H) 3.25 - 3.29 (m, 2 H) 3.27 (s, 3 H) 3.56 (s, 3 H) 3.58 - 3.65 (m, 1 H) 3.72 (d, *J*=12.6 Hz, 1 H) 3.96 (s, 2 H) 5.59 (s, 1 H) 7.03 - 7.11 (m, 2 H) 7.12 - 7.22 (m, 1 H); MS (ESI+) *m/z* 487.1 $(M+H)^+$.
23-C		2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.23 (m, 1 H), 7.04 - 7.11 (m, 2 H), 5.68 (s, 1 H), 4.00 - 4.12 (m, 1 H), 3.89 - 4.00 (m, 1 H), 3.67 - 3.77 (m, 1 H), 3.60 (s, 3 H), 3.37 - 3.48 (m, 1 H), 3.25 (s, 3 H), 3.02 - 3.13 (m, 1 H), 2.95 (t, *J*=5.8 Hz, 2 H), 2.76 (dt, *J*=13.8,

		6.9 Hz, 1 H), 2.02 (s, 5 H), 1.78 - 1.91 (m, 2 H), 1.52 - 1.70 (m, 2 H), 1.11 - 1.19 ppm (m, 9 H); MS (ESI+) *m/z* 489.3 $(M+H)^+$.
23-D		6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.23 (m, 1 H), 7.03 - 7.12 (m, 2 H), 5.59 (s, 1 H), 3.98 - 4.08 (m, 1 H), 3.86 - 3.96 (m, 1 H), 3.68 - 3.80 (m, 1 H), 3.57 (s, 3 H), 3.39 - 3.49 (m, 1 H), 3.25 (s, 4 H), 3.02 - 3.13 (m, 1 H), 2.90 - 2.99 (m, 2 H), 2.02 (s, 6 H), 1.80 - 1.92 (m, 2 H), 1.71 - 1.80 (m, 1 H), 1.52 - 1.68 (m, 2 H), 1.15 (d, *J*=6.6 Hz, 3 H), 0.73 - 0.83 (m, 2 H), 0.53 - 0.61 (m, 2 H); MS (ESI+) *m/z* 487.3 $(M+H)^+$.
23-E		(*R*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine; ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.14 - 7.23 (m, 1 H) 7.07 (d, *J*=7.58 Hz, 2 H) 5.65 (s, 1 H) 3.93 - 4.04 (m, 2 H) 3.70 (d, *J*=8.34 Hz, 1 H) 3.66 (s, 3 H) 3.28 - 3.37 (m, 6 H) 3.12 (br. s., 1 H) 3.04 (br. s., 2 H) 2.95 (dd, *J*=8.59, 3.79 Hz, 1 H) 2.85 (dq, *J*=13.86, 6.92 Hz, 2 H) 2.11 (s, 6 H) 1.92 - 2.01 (m, 1 H) 1.63 - 1.75 (m, 1 H) 1.22 (s, 3 H) 1.20 (s, 3 H) 0.97 (s, 3 H) 0.91 (s, 3 H); MS (ESI+) *m/z* 503.4 $(M+H)^+$.
23-F		(*S*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.95 (br. s., 1 H), 7.53 (d, *J*=8.8 Hz, 1 H), 7.47 (d, *J*=8.8 Hz, 1 H), 5.73 (s, 1 H), 4.02 (s, 2 H), 3.68 (m, 4 H), 3.42 (s, 2 H), 3.31 - 3.37 (m, 5 H), 3.14 (br. s., 2 H), 2.96 (dd, *J*=8.2, 3.4 Hz, 1 H), 2.86 (spt, *J*=6.8 Hz, 1 H), 1.93 - 2.02 (m, 1 H), 1.65 - 1.76 (m, 1 H), 1.29 (d, *J*=6.8 Hz, 6 H), 1.23 (d, *J*=6.8 Hz, 6 H), 0.98 (s, 3 H), 0.94 (s, 3 H); MS (ESI+) *m/z* 557.1 $(M+H)^+$.

23-G		2-(3,5-dimethyl-1H-indazol-4-yl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.22 (d, *J*=8.3 Hz, 1 H), 5.63 (s, 1 H), 4.07 - 4.14 (m, 1 H), 3.97 - 4.05 (m, 1 H), 3.75 (q, *J*=6.0 Hz, 1 H), 3.61 (s, 3 H), 3.41 - 3.48 (m, 1 H), 3.33 - 3.38 (m, 2 H), 3.25 (s, 3 H), 3.08 - 3.18 (m, 1 H), 2.95 (t, *J*=5.7 Hz, 2 H), 2.76 (dt, *J*=13.8, 6.9 Hz, 1 H), 2.16 (s, 3 H), 1.81 - 1.89 (m, 5 H), 1.54 - 1.71 (m, 2 H), 1.12 - 1.19 (m, 9 H); MS (ESI+) *m/z* 529.4 $(M+H)^+$.
23-H		6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.58 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 5.55 (s, 1 H), 4.04 - 4.15 (m, 1 H), 3.92 - 4.04 (m, 1 H), 3.70 - 3.81 (m, 2 H), 3.58 (s, 3 H), 3.41 - 3.50 (m, 2 H), 3.25 (s, 3 H), 3.07 - 3.20 (m, 1 H), 2.95 (t, *J*=5.8 Hz, 2 H), 2.16 (s, 3 H), 1.85 (s, 6 H), 1.70 - 1.79 (m, 1 H), 1.55 - 1.70 (m, 2 H), 1.17 (d, *J*=6.6 Hz, 3 H), 0.73 - 0.85 (m, 2 H), 0.50 - 0.64 (m, 2 H); MS (ESI+) *m/z* 527.4 $(M+H)^+$.
23-I		(*R*)-6-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.57 (s, 1 H) 7.38 (d, *J*=8.59 Hz, 1 H) 7.21 (d, *J*=8.59 Hz, 1 H) 5.52 (s, 1 H) 4.07 - 4.14 (m, 1 H) 3.96 - 4.03 (m, 1 H) 3.67 (d, *J*=12.38 Hz, 1 H) 3.57 (s, 3 H) 3.33 (br. s., 2 H) 3.27 (s, 3 H) 3.01 - 3.11 (m, 1 H) 2.98 (dd, *J*=8.97, 3.92 Hz, 1 H) 2.92 (t, *J*=6.06 Hz, 2 H) 2.86 (d, *J*=13.14 Hz, 1 H) 2.55 (br. s., 1 H) 2.18 (s, 3 H) 1.94 (d, *J*=3.28 Hz, 1 H) 1.87 (s, 3 H) 1.70 - 1.80 (m, 1 H) 1.49 - 1.62 (m, 1 H) 0.94 (s, 3 H) 0.84 (s, 3 H) 0.76 - 0.82 (m, 2 H) 0.53 - 0.58 (m, 2 H); MS (ESI+) *m/z* 541.3 $(M+H)^+$.

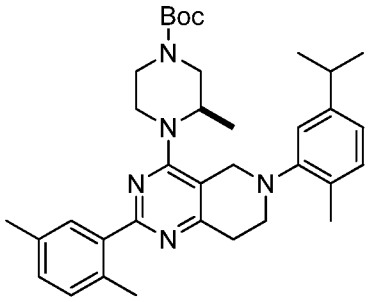
23-J		2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.61 (s, 1 H), 7.40 (d, *J*=8.6 Hz, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 6.35 (s, 1 H), 4.13 - 4.26 (m, 1 H), 4.02 - 4.14 (m, 1 H), 3.73 - 3.89 (m, 4 H), 3.37 - 3.51 (m, 2 H), 3.25 (s, 3 H), 3.14 - 3.19 (m, , 1 H), 2.98 - 3.00 (m, 2 H), 2.89 (s, 1 H), 2.73 (s, 1 H), 2.16 (s, 3 H), 1.75 - 1.92 (m, 5 H), 1.52 - 1.75 (m, 2 H), 1.18 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 555.5 $(M+H)^+$.
23-K		(*S*)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. 1H NMR (400 MHz, DICHLOROMETHANE- d_6) δ ppm 7.36 - 7.42 (m, 1 H), 7.24 - 7.29 (m, 1 H), 6.12 (s, 1 H), 4.02 - 4.13 (m, 2 H), 3.81 (s, 3 H), 3.67 - 3.76 (m, 1 H), 3.37 - 3.44 (m, 2 H), 3.33 (s, 4 H), 3.02 - 3.23 (br. m, 3 H), 2.87 - 3.01 (m, 2 H), 2.29 (s, 3 H), 1.91 - 2.04 (m, 5 H), 1.63 - 1.76 (m, 1 H), 0.97 (s, 3 H), 0.91 (s, 3 H); MS (ESI+) *m/z* 569.4 $(M+H)^+$.
23-L		(*R*)-6-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 6.85 (t, *J*=54.8 Hz, 1 H), 6.11 (s, 1 H), 4.21 (d, *J*=14.9 Hz, 1 H), 4.08 (d, *J*=14.9 Hz, 1 H), 3.73 (s, 3 H), 3.66 - 3.71 (m, 1 H), 3.37 - 3.44 (m, 2 H), 3.27 (s, 3 H), 3.02 - 3.10 (m, 1 H), 2.92 - 3.01 (m, 3 H), 2.87 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.88 - 1.96 (m, 1 H), 1.86 (s, 3 H), 1.50 - 1.62 (m, 1 H), 0.94 (s, 3 H), 0.83 (s, 3 H); MS (ESI+) *m/z* 551.5 $(M+H)^+$.

23-M		(*R*)-6-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 5.52 (s, 1 H), 4.08 (s, 1 H), 4.00 (s, 1 H), 3.64 - 3.74 (m, 1 H), 3.59 - 3.64 (m, 1 H), 3.57 (s, 3 H), 3.00 - 3.11 (m, 2 H), 2.92 (t, *J*=5.8 Hz, 2 H), 2.85 (d, *J*=13.1 Hz, 1 H), 2.17(s, 3 H), 1.82 - 1.92 (m, 4 H), 1.74 (tt, *J*=8.4, 5.0 Hz, 1 H), 1.51 - 1.56 (m, 1 H), 1.09 (t, *J*=6.9 Hz, 3 H), 0.93 (s, 3 H), 0.84 (s, 3 H), 0.75 - 0.81 (m, 2 H), 0.49 - 0.60 (m, 2 H); MS (ESI+) *m/z* 555.5 $(M+H)^+$.
23-N		(*R*)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. 1H NMR (400 MHz, DMSO-d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 6.31 (s, 1 H), 4.15 - 4.32 (m, 1 H), 4.01 - 4.14 (m, 1 H), 3.78 (s, 3 H), 3.70 (d, *J*=13.1 Hz, 1 H), 3.54 - 3.65 (m, 1 H), 3.42 (app q, *J*=6.1 Hz, 2 H), 3.38 (t, *J*=4.0 Hz, 1 H), 3.01 - 3.13 (m, 2 H), 2.96 (br. s., 2 H), 2.88 (d, *J*=13.1 Hz, 1 H), 2.12 - 2.23 (m, 3 H), 1.85 (s, 4 H), 1.47 - 1.66 (m, 1 H), 1.03 - 1.17 (m, 3 H), 0.93 (s, 3 H), 0.75 - 0.87 (m, 3 H); MS(ESI+) *m/z* 583.4 $(M+H)^+$.
23-O		(*R*)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.55 (s, 1 H), 7.36 (d, *J*=8.3 Hz, 1 H), 7.19 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=8.6 Hz, 1 H), 6.68 (d, *J*=2.5 Hz, 1 H), 6.60 (dd, *J*=8.3, 2.5 Hz, 1 H), 4.39 (d, *J*=14.7 Hz, 1 H), 4.18 (d, *J*=14.7 Hz, 1 H), 3.83 (dd, *J*=10.2, 6.7 Hz, 1 H), 3.73 - 3.79 (m, 1 H), 3.72 (s, 3 H), 3.59 - 3.68 (m, 1 H), 3.38 (dd, *J*=10.0, 8.5 Hz, 1 H), 3.26 - 3.29 (m, 1 H), 3.13 - 3.22 (m, 1 H), 2.76 - 2.97 (m, 2 H), 2.62 - 2.66 (m, 1 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 2.15 (s, 6 H), 2.00 - 2.09 (m, 1 H), 1.91 (s, 3 H), 1.64 - 1.76 (m, 1

		H); MS (ESI+) *m/z* 512.3 $(M+H)^+$.

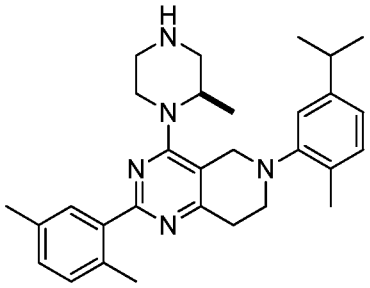
Example 24

24-A. (*R*)-*tert*-Butyl 4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate.



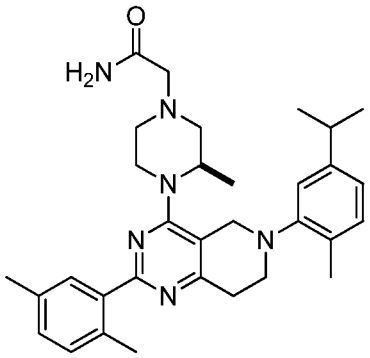
The title compound was prepared in a similar manner to that described in **Example 21**. MS (ESI+) *m/z* 570.4 $(M+H)^+$.

24-B. (*R*)-2-(2,5-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



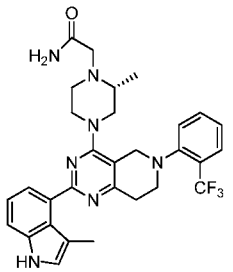
(*R*)-*tert*-Butyl 4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate (60 mg, 0.105 mmol) in DCM (1 mL) was treated with TFA (1 mL, 13.0 mmol) at rt for 15 min. The mixture was then concentrated to provide (*R*)-2-(2,5-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, which was taken on without need further purification. MS (ESI+) *m/z* 470.4 $(M+H)^+$.

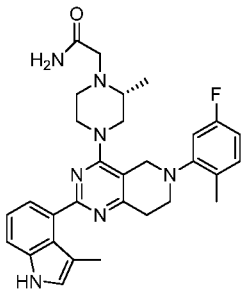
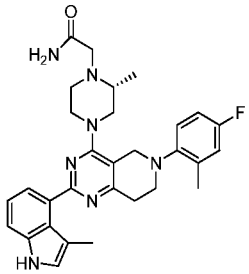
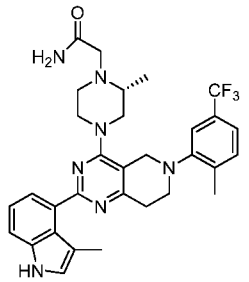
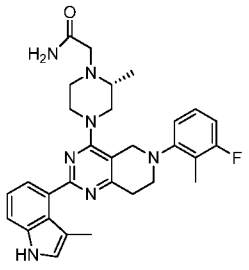
24-C. (*R*)-2-(4-(2-(2,5-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide.

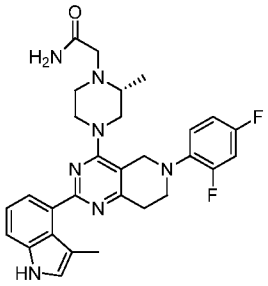
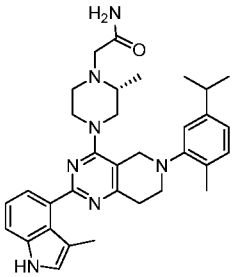
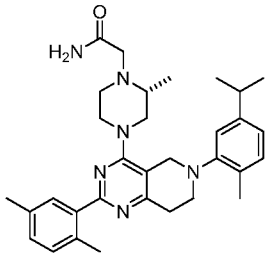


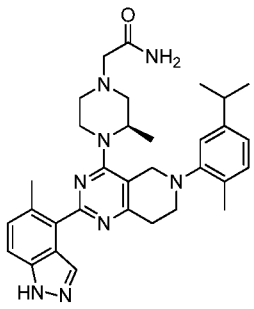
A mixture of (*R*)-2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (43 mg, 0.053 mmol), 2-bromoacetamide (14.6 mg, 0.106 mmol) and DIEA (0.074 mL, 0.424 mmol) in DCM (2 mL) was stirred at rt for 16 h. The reaction was then diluted with EtOAc, and washed successively with sat aq $NaHCO_3$, and brine. The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by HPLC (C18, 15-85% acetonitrile in H_2O with 0.1% NH_4OH) to provide (*R*)-2-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6, at 120 °C) δ ppm 7.58 (s, 1 H) 7.08 - 7.18 (m, 5 H) 6.99 (d, *J*=1.64 Hz, 1 H) 6.87 (dd, *J*=7.71, 1.64 Hz, 1 H) 4.01 - 4.09 (m, 1 H) 3.89 - 4.01 (m, 2 H) 3.48 - 3.58 (m, 1 H) 3.37 - 3.47 (m, 1 H) 2.97 (t, *J*=5.87 Hz, 2 H) 2.81 - 2.90 (m, 3 H) 2.78 (d, *J*=10.36 Hz, 1 H) 2.61 (dd, *J*=11.62, 1.77 Hz, 1 H) 2.47 (s, 3 H) 2.40 (dd, *J*=11.31, 3.35 Hz, 1 H) 2.23 - 2.34 (m, 4 H) 2.20 (s, 3 H) 1.28 (d, *J*=6.44 Hz, 3 H) 1.19 (dd, *J*=6.95, 1.52 Hz, 6 H); MS (ESI+) *m/z* 527.4 $(M+H)^+$.

The following compounds were prepared in a similar manner.

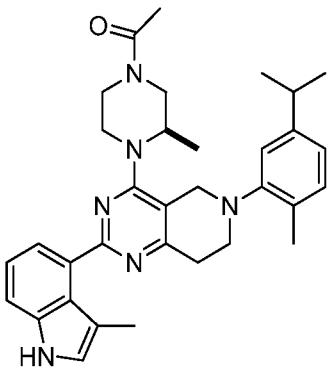
	Structure	Chemical Name & Analytical Data
24-D		(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-(trifluoromethyl)phenyl)-5,6,7,8 tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.93 (br. s., 1 H) 7.68 - 7.82 (m, 3 H) 7.37 - 7.48 (m, 2 H) 7.19 - 7.30 (m, 2 H) 7.05 - 7.18 (m, 3 H) 4.04 (s, 2 H) 3.59 (t, *J*=8.84 Hz, 2 H) 3.05 - 3.24 (m, 3 H) 2.97 (t, *J*=5.56 Hz, 2 H) 2.88 (dd, *J*=12.63, 8.84 Hz, 1 H) 2.72 - 2.82 (m, 2 H) 2.52 - 2.64 (m, 2 H) 2.40 - 2.47 (m, 1 H) 2.02 (s, 3 H) 0.98 (d, *J*=6.06 Hz, 3 H); MS (ESI+) *m/z* 564.4 $(M+H)^+$.

24-E		(*R*)-2-(4-(6-(5-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.92 (d, *J*=1.77 Hz, 1 H) 7.41 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.19 - 7.30 (m, 3 H) 7.08 - 7.16 (m, 3 H) 7.02 (dd, *J*=11.24, 2.65 Hz, 1 H) 6.83 (td, *J*=8.34, 2.53 Hz, 1 H) 4.01 (s, 2 H) 3.62 (t, *J*=11.62 Hz, 2 H) 3.27 - 3.30 (m, 2 H) 3.21 (t, *J*=10.11 Hz, 2 H) 3.13 (d, *J*=16.17 Hz, 1 H) 2.89 - 3.02 (m, 3 H) 2.77 - 2.85 (m, 2 H) 2.59 - 2.65 (m, 1 H) 2.22 (s, 3 H) 2.02 (s, 3 H) 1.02 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 528.4 $(M+H)^+$.
24-F		(*R*)-2-(4-(6-(4-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.93 (br. s., 1 H) 7.42 (d, *J*=7.83 Hz, 1 H) 7.19 - 7.31 (m, 3 H) 7.00 - 7.18 (m, 5 H) 3.97 (br. s., 2 H) 3.61 (br. s., 2 H) 3.17 - 3.29 (m, 4 H) 3.13 (d, *J*=16.42 Hz, 1 H) 2.99 (br. s., 3 H) 2.80 (d, *J*=14.15 Hz, 2 H) 2.60 (d, *J*=1.77 Hz, 1 H) 2.27 (s, 3 H) 2.03 (s, 3 H) 1.02 (br. s., 3 H); MS (ESI+) *m/z* 528.4 $(M+H)^+$.
24-G		(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.93 (br. s., 1 H) 7.31 - 7.50 (m, 4 H) 7.28 (br. s., 1 H) 7.21 (d, *J*=7.07 Hz, 1 H) 7.06 - 7.18 (m, 3 H) 4.02 - 4.17 (m, 2 H) 3.61 (t, *J*=11.37 Hz, 2 H) 3.17 - 3.30 (m, 3 H) 3.11 (d, *J*=16.17 Hz, 1 H) 2.88 - 3.04 (m, 3 H) 2.81 (d, *J*=15.92 Hz, 2 H) 2.60 - 2.70 (m, 1 H) 2.42 - 2.47 (m, 1 H) 2.34 (s, 3 H) 2.02 (s, 3 H) 1.03 (d, *J*=6.06 Hz, 3 H); MS (ESI+) *m/z* 578.4 $(M+H)^+$.
24-H		(*R*)-2-(4-(6-(3-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (d, *J*=2.02 Hz, 1 H) 7.39 - 7.44 (m, 1 H) 7.19 - 7.28 (m, 3 H) 7.07 - 7.17 (m, 3 H) 7.02 (d, *J*=8.08 Hz, 1 H) 6.90 (t, *J*=8.84 Hz, 1 H) 4.04 (s, 2 H) 3.58 - 3.66 (m, 2 H) 3.33 - 3.36 (m, 1 H) 3.28 (s, 2 H) 3.17 - 3.25 (m, 1 H) 3.13 (d, *J*=16.17 Hz, 1 H)

		2.97 - 3.03 (m, 2 H) 2.92 (dd, *J*=12.76, 8.72 Hz, 1 H) 2.77 - 2.86 (m, 2 H) 2.58 - 2.66 (m, 1 H) 2.16 (d, *J*=2.27 Hz, 3 H) 2.03 (s, 3 H) 1.02 (d, *J*=6.06 Hz, 3 H); MS (ESI+) *m/z* 528.4 $(M+H)^+$.
24-I		(*R*)-2-(4-(6-(2,4-difluorophenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (s, 1 H) 7.41 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.01 - 7.30 (m, 8 H) 4.13 (s, 2 H) 3.61 (t, *J*=11.62 Hz, 2 H) 3.47 (t, *J*=6.19 Hz, 2 H) 3.36 (br. s., 1 H) 3.18 - 3.25 (m, 1 H) 3.14 (d, *J*=16.17 Hz, 1 H) 2.89 - 2.99 (m, 3 H) 2.78 - 2.85 (m, 2 H) 2.65 (br. s., 1 H) 2.00 (s, 3 H) 1.03 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 532.4 $(M+H)^+$.
24-J		(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.30 (br. s., 1 H) 7.46 (d, *J*=7.83 Hz, 1 H) 7.35 - 7.42 (m, 1 H) 7.22 (t, *J*=7.71 Hz, 1 H) 7.15 (d, *J*=7.58 Hz, 1 H) 7.08 (s, 1 H) 6.98 (d, *J*=1.52 Hz, 1 H) 6.92 (dd, *J*=7.58, 1.52 Hz, 1 H) 5.36 (d, *J*=7.07 Hz, 2 H) 3.97 - 4.08 (m, 2 H) 3.79 (br. s., 2 H) 3.37 (t, *J*=5.43 Hz, 3 H) 3.21 (br. s., 2 H) 3.03 - 3.15 (m, 1 H) 2.81 - 3.03 (m, 3 H) 2.72 (br. s., 1 H) 2.60 (br. s., 1 H) 2.28 (s, 3 H) 2.11 (s, 3 H) 1.25 (m, 7 H) 1.14 (d, *J*=9.35 Hz, 3 H); MS (ESI+) *m/z* 552.4 $(M+H)^+$.
24-K		(*R*)-2-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, CD_3CN) δ ppm 7.59 (s, 1 H) 7.10 - 7.19 (m, 3 H) 7.03 (d, *J*=1.77 Hz, 2 H) 6.91 (dd, *J*=7.71, 1.64 Hz, 1 H) 5.77 (br. s., 1 H) 3.93 - 4.04 (m, 2 H) 3.64 (dd, *J*=12.63, 2.53 Hz, 2 H) 3.23 - 3.37 (m, 3 H) 3.20 (d, *J*=16.67 Hz, 1 H) 3.02 (t, *J*=6.06 Hz, 2 H) 2.92 - 2.99 (m, 1 H) 2.83 - 2.91 (m, 2 H) 2.78 (d, *J*=16.67 Hz, 1 H) 2.61 - 2.69 (m, 1 H) 2.45 - 2.54 (m, 4 H) 2.35 (s, 3 H) 2.24 (s, 3 H) 1.22 (d, *J*=6.82 Hz, 6 H) 1.07 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 527.4

		$(M+H)^+$.
24-L		(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.09 (s, 1 H) 7.50 (d, *J*=8.34 Hz, 1 H) 7.28 (d, *J*=8.59 Hz, 1 H) 7.10 - 7.18 (m, 2 H) 6.99 (s, 1 H) 6.88 (d, *J*=7.58 Hz, 1 H) 4.07 - 4.15 (m, 1 H) 3.96 - 4.05 (m, 2 H) 3.52 - 3.60 (m, 1 H) 3.45 (t, *J*=11.12 Hz, 1 H) 3.32 - 3.37 (m, 2 H) 3.02 (t, *J*=5.31 Hz, 2 H) 2.75 - 2.91 (m, 4 H) 2.63 (d, *J*=10.36 Hz, 1 H) 2.55 (s, 3 H) 2.38 - 2.46 (m, 1 H) 2.24 - 2.31 (m, 1 H) 2.23 (s, 3 H) 1.31 (d, *J*=6.57 Hz, 3 H) 1.19 (dd, *J*=6.95, 1.64 Hz, 6 H); MS (ESI+) *m/z* 553.4 $(M+H)^+$.

Example 25 25-A. (*R*)-1-(4-(6-(5-Isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone.



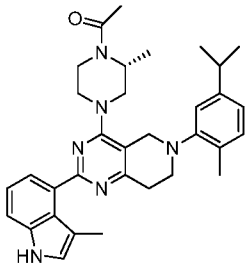
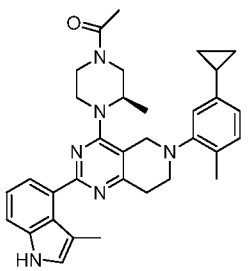
To a solution of (*R*)-tert-butyl 4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate (143 mg, 0.191 mmol), prepared as described in **Example 17**, in DCM (3 mL), was added TFA (2 mL) and the solution was stirred at rt for 30 min. The reaction was concentrated to give the TFA salt of (*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(2-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 649.4 $(M+H)^+$.

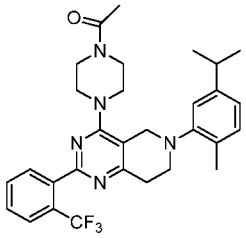
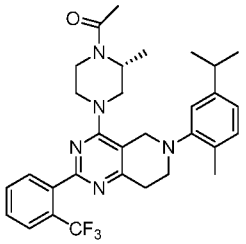
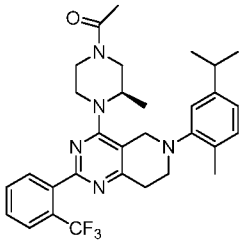
The TFA salt of (*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(2-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (62 mg, 0.095 mmol) was dissolved in DCM (5 mL) and acetic anhydride (0.014 mL, 0.143 mmol) and DIEA (0.133 mL, 0.764 mmol) were added. The reaction was stirred at rt for 45 min and diluted with EtOAc, and washed successively with

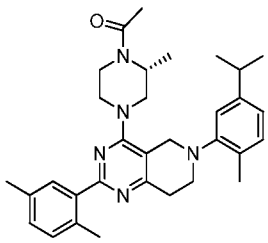
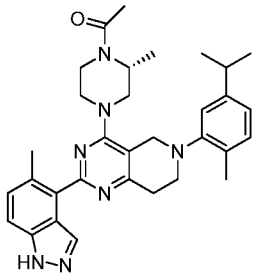
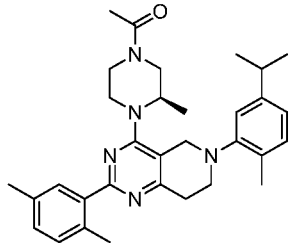
sat $NaHCO_3$ and brine. The organic layer was then dried over Na_2SO_4 and filtered. After concentration, the resulting residue was purified by FCC (60-90% EtOAc/heptane) to provide (*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone. MS (ESI+) *m/z* 691.4 $(M+H)^+$.

(*R*)-1-(4-(6-(5-Isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone was dissolved in EtOH (2 mL), then NH_4OH (0.54 mL, 13.7 mmol) was added followed by KOH (46 mg, 0.821 mmol). The mixture was heated in a microwave reactor at 100 °C for 1 h. The reaction was then diluted with EtOAc and washed with brine. After concentration, the resulting residue was purified by HPLC (C18, 15-85% acetonitrile in H_2O with 0.1% NH_4OH) to provide (*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, CD_3CN) δ ppm 9.15 (br. s., 1 H) 7.46 (d, *J*=8.08 Hz, 1 H) 7.26 (d, *J*=7.33 Hz, 1 H) 7.16 (dd, *J*=16.29, 7.96 Hz, 2 H) 7.06 (d, *J*=13.64 Hz, 2 H) 6.91 (dd, *J*=7.58, 1.52 Hz, 1 H) 3.98 - 4.16 (m, 4 H) 3.46 - 3.67 (m, 2 H) 3.26 - 3.46 (m, 4 H) 2.84 - 3.13 (m, 4 H) 2.26 (s, 3 H) 2.00 - 2.06 (m, 6 H) 1.23 (d, *J*=6.82 Hz, 6 H) 1.11 - 1.21 (m, 3 H); MS (ESI+) *m/z* 537.4 $(M+H)^+$.

The following compounds were prepared in a similar manner.

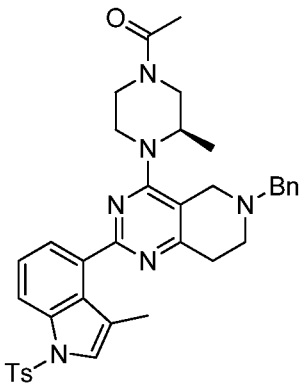
	Structure	Chemical Name & Analytical Data
25-B		(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.91 (s, 1 H) 7.40 - 7.43 (m, 1 H) 7.24 (d, *J*=6.57 Hz, 1 H) 7.09 - 7.16 (m, 3 H) 7.03 (br. s., 1 H) 6.87 (dd, *J*=7.71, 1.39 Hz, 1 H) 4.24 - 4.70 (m, 1 H) 4.03 - 4.22 (m, 2 H) 3.70 - 3.86 (m, 3 H) 3.33 - 3.49 (m, 2 H) 3.04 - 3.17 (m, 1 H) 2.78 - 3.04 (m, 5 H) 2.23 (s, 3 H) 1.96 - 2.05 (m, 6 H) 1.31 (d, *J*=7.07 Hz, 1 H) 1.20 (m 8 H); MS (ESI+) *m/z* 537.4 $(M+H)^+$.
25-C		(*R*)-1-(4-(6-(5-cyclopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (s, 1 H) 7.41 (dd, *J*=7.96, 1.14 Hz, 1 H) 7.22 (d, *J*=6.57 Hz, 1 H) 7.05 - 7.16 (m, 3 H) 6.86 (d, *J*=1.52 Hz, 1 H) 6.69 (dd, *J*=7.83, 1.52 Hz, 1 H) 3.98 - 4.22 (m, 4 H) 3.70 - 3.83 (m, 1 H) 3.45 - 3.70 (m, 2 H) 3.32 - 3.43 (m, 2 H) 3.20 - 3.27 (m, 1 H) 2.88 - 3.07 (m, 3 H) 2.20 (s, 3 H) 1.98 - 2.06 (m, 6 H) 1.83 -

		1.93 (m, 1 H) 1.06 - 1.20 (m, 3 H) 0.88 - 0.95 (m, 2 H) 0.59 - 0.65 (m, 2 H); MS (ESI+) *m/z* 535.4 $(M+H)^+$.
25-D		1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.84 (d, *J*=7.83 Hz, 1 H) 7.73 - 7.79 (m, 2 H) 7.64 - 7.70 (m, 1 H) 7.10 (d, *J*=7.83 Hz, 1 H) 7.00 (d, *J*=1.26 Hz, 1 H) 6.88 (dd, *J*=7.58, 1.52 Hz, 1 H) 4.01 (s, 2 H) 3.54 (dd, *J*=6.32, 3.28 Hz, 4 H) 3.42 - 3.48 (m, 2 H) 3.38 (d, *J*=6.06 Hz, 2 H) 2.97 (t, *J*=5.81 Hz, 2 H) 2.85 (dt, *J*=13.83, 6.85 Hz, 1 H) 2.20 (s, 3 H) 2.01 (s, 3 H) 1.19 (d, *J*=6.82 Hz, 6 H); MS (ESI+) *m/z* 538.1 $(M+H)^+$.
25-E		(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.79 (d, *J*=7.58 Hz, 2 H) 7.67 (t, *J*=7.45 Hz, 1 H) 7.59 (t, *J*=7.58 Hz, 1 H) 7.14 (d, *J*=7.58 Hz, 1 H) 6.97 (s, 1 H) 6.92 (dd, *J*=7.83, 1.52 Hz, 1 H) 3.93 - 4.15 (m, 3 H) 3.59 - 3.82 (m, 2 H) 3.43 - 3.59 (m, 1 H) 3.25 - 3.43 (m, 3 H) 3.16 (br. s., 2 H) 2.97 - 3.11 (m, 1 H) 2.84 - 2.97 (m, 1 H) 2.28 (s, 3 H) 2.06 (d, *J*=8.84 Hz, 3 H) 1.20 - 1.35 (m, 10 H); MS (ESI+) *m/z* 552.2 $(M+H)^+$.
25-F		(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.84 (d, *J*=7.83 Hz, 1 H) 7.72 - 7.79 (m, 2 H) 7.64 - 7.71 (m, 1 H) 7.10 (d, *J*=7.83 Hz, 1 H) 6.98 (s, 1 H) 6.87 (dd, *J*=7.71, 1.39 Hz, 1 H) 3.94 - 4.18 (m, 4 H) 3.52 - 3.70 (m, 2 H) 3.43 (dd, *J*=13.14, 3.79 Hz, 1 H) 3.37 (br. s., 1 H) 3.17 - 3.27 (m, 1 H) 2.90 - 3.03 (m, 3 H) 2.78 - 2.90 (m, 2 H) 2.20 (s, 3 H) 1.96 - 2.07 (m, 3 H) 1.05 - 1.22 (m, 9 H); MS (ESI+) *m/z* 552.3 $(M+H)^+$.

25-G		(*R*)-1-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, DMSO-d_6, at 100 °C) δ ppm 7.63 (s, 1 H) 7.09 - 7.17 (m, 3 H) 7.00 (s, 1 H) 6.87 (d, *J*=8.08 Hz, 1 H) 4.46 (br. s., 1 H) 3.94 - 4.15 (m, 3 H) 3.83 (d, *J*=12.76 Hz, 1 H) 3.70 (d, *J*=13.64 Hz, 1 H) 3.24 - 3.43 (m, 3 H) 3.18 (dd, *J*=13.20, 3.47 Hz, 1 H) 3.04 (d, *J*=1.77 Hz, 1 H) 2.79 - 2.92 (m, 2 H) 2.34 (s, 3 H) 2.24 (s, 3 H) 2.02 (s, 3 H) 1.16 - 1.31 (m, 9 H); MS (ESI+) *m/z* 512.4 $(M+H)^+$.
25-H		(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.02 (br. s., 1 H) 8.13 (s, 1 H) 7.52 (d, *J*=7.07 Hz, 1 H) 7.30 (d, *J*=8.34 Hz, 1 H) 6.99 - 7.21 (m, 2 H) 6.88 (d, *J*=7.58 Hz, 1 H) 4.17 (d, *J*=14.91 Hz, 3 H) 3.85 (br. s., 1 H) 3.77 (d, *J*=12.13 Hz, 2 H) 3.39 - 3.53 (m, 1 H) 3.27 (br. s., 2 H) 3.12 (br. s., 1 H) 3.05 (br. s., 2 H) 2.93 - 3.02 (m, 1 H) 2.87 (dt, *J*=13.64, 6.82 Hz, 1 H) 2.55 (s, 3 H) 2.24 (s, 3 H) 2.03 (d, *J*=17.68 Hz, 3 H) 1.31 (d, *J*=5.31 Hz, 1 H) 1.09 - 1.26 (m, 8 H); MS (ESI+) *m/z* 538.4 $(M+H)^+$.
25-I		(*R*)-1-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone^{1}H NMR (400 MHz, DMSO-d_6, at 120 °C) δ ppm 7.62 (s, 1 H) 7.09 - 7.17 (m, 3 H) 6.98 (d, *J*=1.89 Hz, 1 H) 6.88 (dd, *J*=7.64, 1.83 Hz, 1 H) 4.00 - 4.21 (m, 3 H) 3.93 (br. s., 1 H) 3.76 (br. s., 1 H) 3.51 - 3.59 (m, 1 H) 3.32 - 3.42 (m, 4 H) 3.24 (br. s., 1 H) 3.01 (t, *J*=6.19 Hz, 2 H) 2.85 - 2.95 (m, 4 H) 2.34 (s, 3 H) 2.25 (s, 3 H) 2.03 (s, 3 H) 1.22 (d, *J*=6.95 Hz, 6 H) 1.17 (d, *J*=6.44 Hz, 3 H); MS (ESI+) *m/z* 512.4 $(M+H)^+$.

Example 26

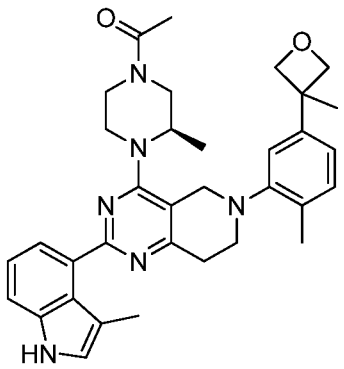
26-A. (*R*)-1-(4-(6-Benzyl-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone.



A mixture of 6-benzyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.655 g, 1.89 mmol), (*R*)-1-(3-methylpiperazin-1-yl)ethanone 2,2,2-trifluoroacetate (1 g, 2.84 mmol) and DIEA (2.65 mL, 15.2 mmol) in i-PrOH (25 mL) was heated to 80 °C for 48 h. The reaction mixture was then diluted with EtOAc, and washed successively with sat aq $NaHCO_3$ and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated. The resulting residue was diluted with DCM and filtered to remove solid. The filtrate was concentrated and purified by FCC (0-5% MeOH in DCM) to provide (*R*)-1-(4-(6-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone. MS (ESI+) *m/z* 400.3 $(M+H)^+$.

A mixture of (*R*)-1-(4-(6-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone (0.27 g, 0.675 mmol), 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indole (0.305 g, 0.743 mmol) and 2 M aq Na_2CO_3 (1.1 mL, 2.19 mmol) in DME (3 mL) was degassed by sparging with argon. $Pd(PPh_3P)_4$ (0.117 g, 0.101 mmol) was then added and the mixture was heated in a microwave reactor at 140 °C for 1.5 h. The reaction was filtered and diluted with EtOAc, washed successively with sat aq Na_2CO_3 and, brine, and then dried over Na_2SO_4. After concentration the residue was purified by FCC (5-70% EtOAc/heptane) to provide (*R*)-1-(4-(6-benzyl-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone. MS (ESI+) *m/z* 649.3 $(M+H)^+$.

26-B. (*R*)-1-(3-Methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone.



A mixture of (*R*)-1-(4-(6-benzyl-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone (0.35 g, 0.539 mmol), acetic acid (0.154 mL, 2.70 mmol), THF (9 mL) and H_2O (3 mL) was degassed via vacuum and recharged with nitrogen gas (2 x). Then 20 mol% $Pd(OH)_2$/carbon (0.114 g, 0.162 mmol) was added and the mixture was degassed via vacuum and placed under an atmosphere of hydrogen. The mixture was stirred at rt under H_2 atmosphere via balloon for 2 h and then filtered. The solution was then diluted with EtOAc and washed with sat aq $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to provide (*R*)-1-(3-methyl-4-(2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone, which was used without the need for further purification. MS (ESI+) *m/z* 559.3 $(M+H)^+$.

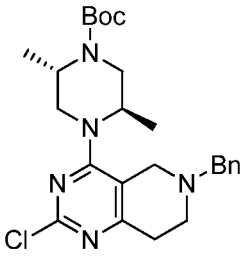
A mixture of (*R*)-1-(3-methyl-4-(2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone (0.155 g, 0.278 mmol), 2-methyl-5-(3-methyloxetan-3-yl)phenyl trifluoromethanesulfonate (0.086 g, 0.278 mmol) prepared as described in **Example 13**, cesium carbonate (0.272 g, 0.834 mmol) and chloro(2-dicyclohexylphosphino-2'-4'-6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II)–methyl-*t*-butylether adduct (CAS#1028276-56-5) (0.031 g, 0.042 mmol) in THF (4 mL) was heated in a microwave reactor at 140 °C for 3 h. The reaction was then filtered and concentrated, the resulting residue was purified by FCC (60-100% EtOAc/DCM) to provide (*R*)-1-(3-methyl-4-(2-(3-methyl-1-tosyl-1H-indol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone. MS (ESI+) *m/z* 719.3 $(M+H)^+$.

A mixture of (*R*)-1-(3-methyl-4-(2-(3-methyl-1-tosyl-1H-indol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone (0.104 g, 0.145 mmol), 30% ammonium hydroxide (0.854 mL, 21.70 mmol) and KOH (0.073 g, 1.302 mmol) in EtOH (4 mL) was heated in a microwave reactor at 100 °C for 30 min. The mixture was concentrated and partially purified by FCC (0-6% MeOH in DCM). Further purification with HPLC (C18, 15-85% CH_3CN in H_2O

with 0.1% NH_4OH) provided (*R*)-1-(3-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone. ^1H NMR (400 MHz, DMSO-d_6 at 120 °C) δ ppm 10.50 (br. s., 1 H) 7.42 (d, *J*=8.08 Hz, 1 H) 7.25 (d, *J*=7.20 Hz, 1 H) 7.19 (d, *J*=7.83 Hz, 1 H) 7.07 - 7.15 (m, 2 H) 6.97 (s, 1 H) 6.90 (d, *J*=7.96 Hz, 1 H) 4.79 (d, *J*=5.43 Hz, 2 H) 4.53 (d, *J*=5.05 Hz, 2 H) 4.05 - 4.19 (m, 3 H) 3.91 (br. s., 1 H) 3.75 (br. s., 1 H) 3.56 (d, *J*=13.26 Hz, 1 H) 3.22 - 3.48 (m, 5 H) 3.00 (t, *J*=5.62 Hz, 2 H) 2.29 (s, 3 H) 2.07 (s, 3 H) 1.99 - 2.04 (m, 3 H) 1.65 (s, 3 H) 1.17 (d, *J*=6.44 Hz, 3 H); MS (ESI+) *m/z* 565. 4 $(M+H)^+$.

Example 27

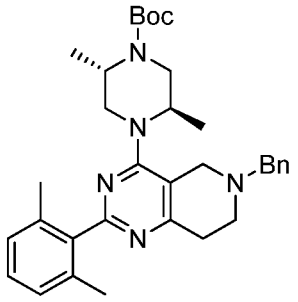
27-A. *Racemic tert*-Butyl 4-(6-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate.



A mixture of 6-benzyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (2.0 g, 6.80 mmol), (*trans*)-2,5-dimethylpiperazine dihydrochloride (7.63 g, 40.8 mmol), DIEA (15.4 mL, 88 mmol) and iPrOH (180 mL) was heated at 80 °C for 3.5 days. At that time the reaction was diluted with diethyl ether and the solid was removed by filtration. The filtrate was then washed with brine and the organic layer was dried (Na_2SO_4), filtered and concentrated to provide crude *racemic* 6-benzyl-2-chloro-4-(*trans*)-2,5-dimethylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, which was then carried to the next step without further purification. MS (ESI+) *m/z* 372.2 $(M+H)^+$

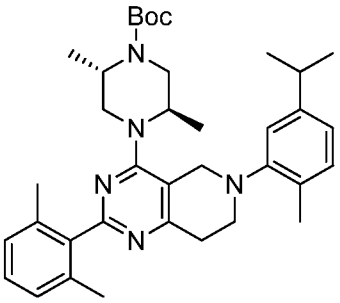
A solution of *racemic* 6-benzyl-2-chloro-4-(*trans*)-2,5-dimethylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (2.53 g, 6.80 mmol), Boc_2O (2.26 g, 10.2 mmol), DIEA (3.6 mL, 20.4 mmol) and DCM (30 mL) was stirred at rt for 30 min. At that point the reaction was diluted with DCM and washed with sat aq $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was then purified by FCC (10-50% EtOAc/heptane) to give *racemic* tert-butyl 4-(6-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate. MS (ESI+) *m/z* 472.2 $(M+H)^+$.

27-B. *Racemic tert*-Butyl 4-(6-benzyl-2-(2,6-dimethylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate.



To a solution of *racemic* tert-butyl 4-(6-benzyl-2-chloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate (0.54 g, 1.14 mmol) in DME (9 mL) was added 2,6-dimethylphenylboronic acid (0.257 g, 1.72 mmol), $Pd(Ph_3P)_4$ (0.198 g, 0.172 mmol) and a 2 M aq solution of sodium carbonate (1.9 mL). The reaction was heated at 140 °C in a microwave reactor for 1.75 h. The reaction was filtered and diluted with EtOAc and brine. The organic layer was separated and then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by FCC (55-80% EtOAc/heptane) to give the title compound. MS (ESI+) *m/z* 542.5 $(M+H)^+$.

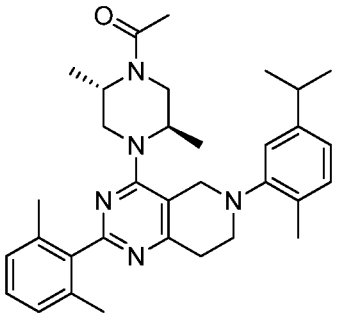
27-C. *Racemic tert*-Butyl 4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate.



To a solution of *racemic* tert-butyl 4-(6-benzyl-2-(2,6-dimethylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate (0.43 g, 0.794 mmol) in THF (9 mL) and water (3 mL) was added acetic acid (227 μL, 3.97 mmol) and 20% $Pd(OH)_2$ on carbon (50% wet) (0.167 g, 0.238 mmol). The flask was evacuated and purged with hydrogen gas and then placed under a hydrogen atmosphere. After stirring at rt for 1 h the mixture was filtered over Celite®, and the Celite® pad was washed with EtOAc. The filtrate was washed with sat aq $NaHCO_3$ and then the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain *racemic tert*-butyl 4-(2-(2,6-dimethylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate. MS (ESI+) *m/z* 452.3 $(M+H)^+$.

To a solution of *racemic* tert-butyl 4-(2-(2,6-dimethylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate (0.187 g, 0.414 mmol) in THF (4 mL) was added 5-isopropyl-2-methylphenyl trifluoromethanesulfonate (0.175 g, 0.620 mmol) prepared as described in **Example 15**, Cs_2CO_3 (0.404 g, 1.24 mmol) and chloro(2-dicyclohexylphosphino-2'-4'-6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II)–methyl-*t*-butylether adduct (0.046 mg, 0.062 mmol). The reaction was purged with argon and was heated at 130 °C for 3 h in a microwave reactor. The mixture was then concentrated and the residue was purified via FCC (10-35% EtOAc/heptane) to give *racemic* tert-butyl 4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate. MS (ESI+) *m/z* 584.4 $(M+H)^+$.

27-D.*Racemic* 1-(4-(2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)ethanone.



To a solution of *racemic* tert-butyl 4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazine-1-carboxylate (0.227 g, 0.389 mmol) and DCM (3 mL) at rt was added TFA (1 mL). After 25 min an additional 0.5 mL aliquot of TFA was added. After 1 h more the reaction was concentrated under reduced pressure to give 2-(2,6-dimethylphenyl)-4-((*trans*)-2,5-dimethylpiperazin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine as a TFA salt. MS (ESI+) *m/z* 484.4 $(M+H)^+$

To a solution of the TFA salt of 2-(2,6-dimethylphenyl)-4-((*trans*)-2,5-dimethylpiperazin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine TFA salt (0.113 g, 0.233 mmol), DIEA (0.33 mL, 1.87 mmol) and DCM (5 mL) was added Ac_2O (0.044 mL, 0.467 mmol). The reaction was stirred at rt for 1 h before being diluted with EtOAc. The solution was washed with sat aq $NaHCO_3$ and then brine before the organic layers were separated and then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by FCC (35-45% EtOAc/heptane) to give *racemic*- 1-(4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-

(*trans*)-2,5-dimethylpiperazin-1-yl)ethanone. ^{1}H NMR (400 MHz, DMSO-d_6, at 100 °C) δ ppm 7.14 - 7.19 (m, 1 H) 7.05 - 7.12 (m, 3 H) 6.91 (d, *J*=1.39 Hz, 1 H) 6.86 (dd, *J*=7.71, 1.52 Hz, 1 H) 4.29 (dt, *J*=6.22, 3.27 Hz, 1 H) 4.12 - 4.18 (m, 1 H) 4.00 - 4.07 (m, 1 H) 3.50 - 3.58 (m, 1 H) 3.41 - 3.47 (m, 1 H) 3.39 (t, *J*=6.19 Hz, 2 H) 2.93 (br. s., 4 H) 2.84 (dt, *J*=13.80, 6.93 Hz, 1 H) 2.52 (br. s., 1 H) 2.25 (s, 3 H) 2.08 (s, 6 H) 2.01 (s, 3 H) 1.19 (dd, *J*=6.95, 2.40 Hz, 6 H) 1.10 - 1.17 (m, 6 H); MS (ESI+) *m/z* 526.4 $(M+H)^+$.

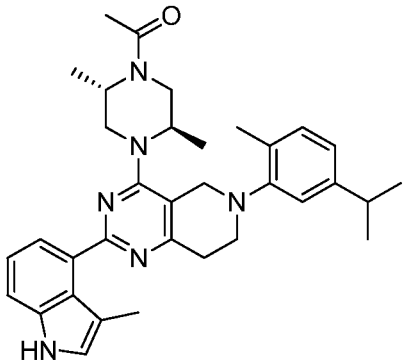
The *racemic*- 1-(4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)ethanone was then separated by chiral HPLC (WhelkO column; 40% EtOH/heptanes; 1.2 mL/min to give the following two compounds:

27-E.Enantiomer-1: R_t 9.78 min, (WhelkO1 20 X 250 mm column, 50% EtOH in heptane). ^{1}H NMR (400 MHz, DMSO-d_6, at 120 °) δ ppm 7.14 - 7.19 (m, 1 H) 7.05 - 7.12 (m, 3 H) 6.92 (d, *J*=1.52 Hz, 1 H) 6.87 (dd, *J*=7.77, 1.58 Hz, 1 H) 4.40 (br. s., 1 H) 4.27 - 4.34 (m, 1 H) 4.10 - 4.19 (m, 1 H) 4.01 - 4.10 (m, 1 H) 3.52 - 3.58 (m, 1 H) 3.37 - 3.48 (m, 4 H) 2.94 (t, *J*=6.25 Hz, 2 H) 2.86 - 2.89 (m, 1 H) 2.82 (br. s., 1 H) 2.25 (s, 3 H) 2.09 (s, 6 H) 2.01 (s, 3 H) 1.20 (dd, *J*=6.95, 2.02 Hz, 6 H) 1.15 (dd, *J*=12.82, 6.63 Hz, 6 H); MS (ESI+) *m/z* 526.4 $(M+H)^+$

27-F. Enantiomer-2: R_t 14.69 min, (WhelkO1 20 X 250 mm column, 50% EtOH in heptane). ^{1}H NMR (400 MHz, DMSO-d_6, 120 °C) δ ppm 7.14 - 7.19 (m, 1 H) 7.05 - 7.12 (m, 3 H) 6.92 (s, 1 H) 6.87 (dd, *J*=7.77, 1.45 Hz, 1 H) 4.34 - 4.49 (m, 1 H) 4.30 (dt, *J*=6.76, 3.44 Hz, 1 H) 4.10 - 4.19 (m, 1 H) 4.01 - 4.10 (m, 1 H) 3.52 - 3.58 (m, 1 H) 3.37 - 3.48 (m, 4 H) 2.94 (t, *J*=6.13 Hz, 2 H) 2.81 - 2.84 (m, 2 H) 2.26 (s, 3 H) 2.09 (s, 6 H) 2.01 (s, 3 H) 1.20 (dd, *J*=6.88, 1.96 Hz, 6 H) 1.15 (dd, *J*=12.82, 6.63 Hz, 6 H); MS (ESI+) *m/z* 526.4 $(M+H)^+$

The following compound was prepared in a similar manner.

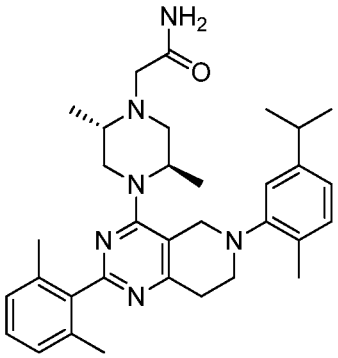
27-G.*Racemic* 1-((*trans*)-4-(6-(5-Isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,5-dimethylpiperazin-1-yl)ethanone



^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ ppm 10.58 (br. s., 1 H) 7.41 (d, *J*=8.21 Hz, 1 H) 7.23 - 7.25 (m, 1 H) 7.08 - 7.13 (m, 3 H) 6.97 (s, 1 H) 6.87 (dd, *J*=8.08, 1.26 Hz, 1 H) 4.33 (d, *J*=4.67 Hz, 1 H) 4.09 - 4.17 (m, 1 H) 4.00 - 4.09 (m, 1 H) 3.54 (br. s., 2 H) 3.39 (t, *J*=6.51 Hz, 2 H) 2.97 - 3.02 (m, 5 H) 2.81 - 2.90 (m, 1 H) 2.25 (s, 3 H) 1.99 - 2.08 (m, 6 H) 1.14 - 1.23 (m, 12 H). MS (ESI+) *m/z* 551.4 $(M+H)^+$.

Example 28

28-A.*Racemic*- 2-(-4-(2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)acetamide.



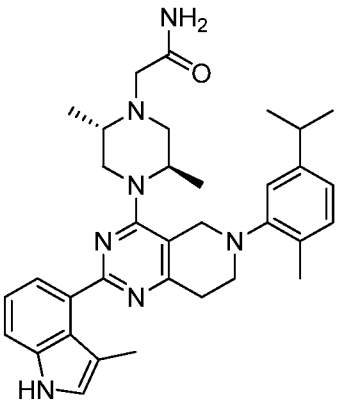
The title compound was prepared in a similar manner to those described in **Examples 24** and **28** above. MS (ESI+) *m/z* 541.3 $(M+H)^+$. *Racemic*- 2-(-4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)acetamide was then separated by chiral HPLC (Cel-LUX2 column; 30% EtOH/heptanes; 1.2 mL/min) to give the two corresponding enantiomers:

28-B.Enantiomer-1: R_t 11.83 min, (Cel-LUX2 20 X 250 mm column, 30% EtOH in heptane). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.21 (m, 2 H) 7.10 (t, *J*=7.83 Hz, 4 H) 6.83 - 6.91 (m, 2 H) 4.01 - 4.13 (m, 2 H) 3.88 (br. s., 1 H) 3.32 - 3.42 (m, 3 H) 2.95 - 3.02 (m, 1 H) 2.91 (d, *J*=9.09 Hz, 4 H) 2.83 (dt, *J*=12.88, 6.19 Hz, 3 H) 2.24 - 2.30 (m, 1 H) 2.22 (s, 3 H) 2.03 (s, 6 H) 1.16 (dd, *J*=6.82, 3.28 Hz, 6 H) 1.11 (d, *J*=6.32 Hz, 3 H) 0.96 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 541.4 $(M+H)^+$.

28-C. Enantiomer-2: R_t 16.10 min, (Cel-LUX2 20 X 250 mm column, 30% EtOH in heptane). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.15 - 7.21 (m, 2 H) 7.10 (t, *J*=7.83 Hz, 4 H) 6.84 - 6.90 (m, 2 H) 4.01 - 4.12 (m, 2 H) 3.88 (br. s., 1 H) 3.33 - 3.42 (m, 3 H) 2.95 - 3.01 (m, 1 H) 2.91 (d, *J*=9.09 Hz, 4 H) 2.79 - 2.86 (m, 3 H) 2.27 (dd, *J*=11.37, 5.81 Hz, 1 H) 2.22 (s, 3 H) 2.03 (s, 6 H) 1.16 (dd, *J*=6.82, 3.28 Hz, 6 H) 1.11 (d, *J*=6.32 Hz, 3 H) 0.96 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 541.4 $(M+H)^+$.

The following compound was prepared in a similar manner.

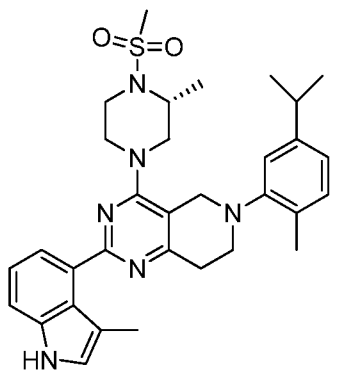
28-D.*Racemic*- 2-(4-(6-(5-Isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)acetamide.



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (s, 1 H) 7.42 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.20 - 7.23 (m, 1 H) 7.10 - 7.19 (m, 5 H) 6.94 (d, *J*=1.52 Hz, 1 H) 6.87 (dd, *J*=7.83, 1.52 Hz, 1 H) 3.99 - 4.12 (m, 2 H) 3.89 - 3.97 (m, 1 H) 3.34 - 3.44 (m, 3 H) 3.00 - 3.10 (m, 1 H) 2.89 - 3.00 (m, 4 H) 2.79 - 2.88 (m, 3 H) 2.28 (dd, *J*=11.75, 5.68 Hz, 1 H) 2.22 (s, 3 H) 2.03 (s, 3 H) 1.18 (dd, *J*=6.82, 3.03 Hz, 6 H) 1.14 (d, *J*=6.32 Hz, 3 H) 0.98 (d, *J*=6.32 Hz, 3 H). MS (ESI+) *m/z* 566.4 $(M+H)^+$.

Example 29

(*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(methylsulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

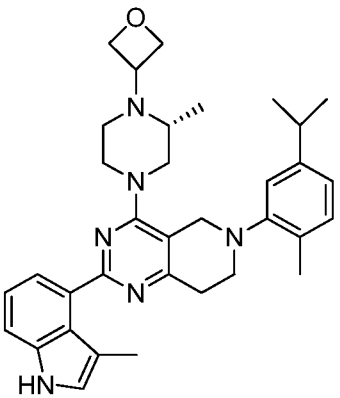


A mixture of (*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (52 mg, 0.080 mmol), prepared in a manner similar to that described in **Example 25,** methanesulfonyl chloride (0.01 mL, 0.096 mmol) and DIEA (0.042 mL, 0.240 mmol) in DCM (3 mL) was stirred at rt for 30 min. The reaction mixture was diluted with EtOAc, washed successively with sat $NaHCO_3$, and brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified via FCC (5-50% EtOAc/heptane) to provide (*R*)-6-(5-

isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-(methylsulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 727.4 $(M+H)^+$.

To a solution of (*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-(methylsulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (40 mg, 0.055 mmol) in MeOH (4 mL), NH_4OH (0.325 mL, 8.25 mmol) and KOH (27.8 mg, 0.495 mmol) was added. The mixture was heated in a microwave reactor 100 °C for 1 h. The mixture was then filtered and concentrated. The resulting residue was purified via FCC (0-45% EtOAc/heptane) to provide (*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(methylsulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.91 (d, *J*=2.02 Hz, 1 H) 7.40 - 7.43 (m, 1 H) 7.24 (dd, *J*=7.33, 1.01 Hz, 1 H) 7.09 - 7.16 (m, 3 H) 7.02 (d, *J*=1.26 Hz, 1 H) 6.87 (dd, *J*=7.83, 1.26 Hz, 1 H) 4.03 - 4.16 (m, 3 H) 3.70 - 3.84 (m, 2 H) 3.56 (d, *J*=12.88 Hz, 1 H) 3.33 - 3.42 (m, 2 H) 3.23 - 3.28 (m, 1 H) 3.14 (dd, *J*=12.88, 3.54 Hz, 1 H) 2.92 - 3.06 (m, 6 H) 2.79 - 2.90 (m, 1 H) 2.22 (s, 3 H) 2.03 (s, 3 H) 1.32 (d, *J*=6.82 Hz, 3 H) 1.19 (dd, *J*=6.95, 1.89 Hz, 6 H); MS (ESI+) *m/z* 573.4 $(M+H)^+$.

Example 30 30-A. (*R*)-6-(5-Isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



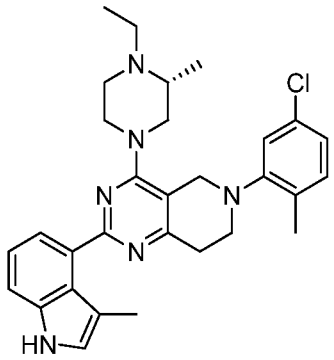
A mixture of (*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (53 mg, 0.082 mmol), oxetan-3-one (17.6 mg, 0.245 mmol) and $Na(AcO)_3BH$ (51.9 mg, 0.245 mmol) in DCM (3 mL) was stirred at rt for 3 h. At that point starting material remained so additional oxetan-3-one (17.7 mg, 0.245 mmol) and $Na(AcO)_3BH$ (51.9 mg, 0.245 mmol) were added and the reaction stirred for 16 h. The mixture was then diluted with EtOAc, washed with sat $NaHCO_3$ and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC (5-65% EtOAc/heptane) to provide (*R*)-6-(5-

isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 705.5 $(M+H)^+$.

The crude product was then dissolved product in MeOH (4 mL). NH_4OH (0.50 mL, 12.8 mmol) and KOH (43.0 mg, 0.766 mmol) were added. The mixture was then heated in a microwave reactor at 100 °C for 45 min before being filtered and concentrated. The residue was then and purified by FCC (0-45% EtOAc/heptane) to provide (*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (d, *J*=1.52 Hz, 1 H) 7.41 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.22 (dd, *J*=7.33, 1.01 Hz, 1 H) 7.09 - 7.16 (m, 3 H) 6.98 (d, *J*=1.26 Hz, 1 H) 6.87 (dd, *J*=7.71, 1.39 Hz, 1 H) 4.45 - 4.56 (m, 4 H) 3.96 - 4.07 (m, 2 H) 3.71 (quin, *J*=6.88 Hz, 1 H) 3.42 - 3.57 (m, 2 H) 3.36 (s, 1 H) 3.20 - 3.27 (m, 1 H) 3.00 - 3.10 (m, 1 H) 2.96 (t, *J*=5.81 Hz, 2 H) 2.79 - 2.88 (m, 1 H) 2.67 - 2.73 (m, 1 H) 2.55 (d, *J*=3.79 Hz, 1 H) 2.43 - 2.48 (m, 1 H) 2.16 - 2.25 (m, 4 H) 2.03 (s, 3 H) 1.18 (d, *J*=6.82 Hz, 6 H) 0.90 (d, *J*=6.32 Hz, 3 H; MS (ESI+) *m/z* 551.4 $(M+H)^+$.

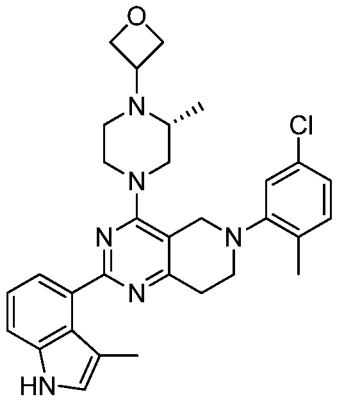
The following compounds were prepared in a similar manner.

30-B. (*R*)-6-(5-Chloro-2-methylphenyl)-4-(4-ethyl-3-methylpiperazin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (s, 1 H) 7.41 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.17 - 7.25 (m, 3 H) 7.04 - 7.16 (m, 3 H) 4.03 (s, 2 H) 3.58 - 3.66 (m, 1 H) 3.55 (d, *J*=12.63 Hz, 1 H) 3.31 - 3.36 (m, 3 H) 3.12 - 3.22 (m, 1 H) 2.87 - 3.02 (m, 3 H) 2.77 - 2.86 (m, 1 H) 2.68 - 2.77 (m, 1 H) 2.31 - 2.36 (m, 2 H) 2.23 (s, 3 H) 2.02 (s, 3 H) 1.02 (d, *J*=6.32 Hz, 3 H) 0.96 (t, *J*=7.20 Hz, 3 H); MS (ESI+) *m/z* 515.3/517.4 $(M+H)^+$.

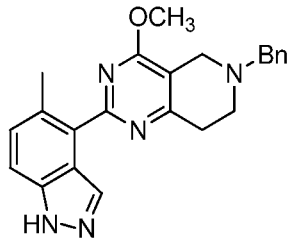
30-C. (*R*)-6-(5-Chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.90 (s, 1 H) 7.39 - 7.42 (m, 1 H) 7.17 - 7.25 (m, 3 H) 7.04 - 7.16 (m, 3 H) 4.44 - 4.57 (m, 4 H) 4.02 (s, 2 H) 3.71 (t, *J*=6.95 Hz, 1 H) 3.52 - 3.58 (m, 1 H) 3.47 (dd, *J*=12.00, 1.39 Hz, 1 H) 3.31 - 3.36 (m, 1 H) 3.21 - 3.27 (m, 1 H) 2.95 - 3.08 (m, 3 H) 2.67 - 2.70 (m, 1 H) 2.45 (dd, *J*=3.54, 1.52 Hz, 1 H) 2.14 - 2.26 (m, 5 H) 2.03 (d, *J*=0.76 Hz, 3 H) 0.88 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 543.3/545.3 $(M+H)^+$.

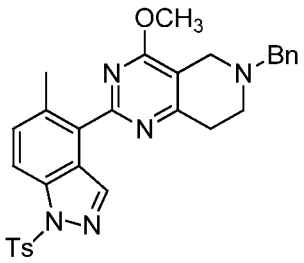
Example 31

31-A. 6-Benzyl-4-methoxy-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



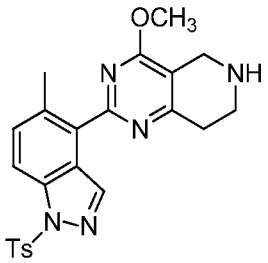
A mixture of 6-benzyl-2-chloro-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.09 g, 3.75 mmol), (5-methyl-1H-indazol-4-yl)boronic acid (600 mg, 3.41 mmol), $Pd(PPh_3)_4$ (197 mg, 0.170 mmol), and Na_2CO_3 (2 M, 5.97 mL, 11.9 mmol) in DME (11 mL) was heated in a microwave reactor at 140 °C for 1.5 h. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (20-100% EtOAc/heptane) to provide 6-benzyl-4-methoxy-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 386.2 $(M+H)^+$.

31-B. 6-benzyl-4-methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



6-Benzyl-4-methoxy-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (2.00 g, 5.19 mmol) was added to a suspension of NaH (60% dispersion in mineral oil, 415 mg, 10.4 mmol) in THF (50 mL) at 0 °C. After 20 min, TsCl (1.19 g, 6.23 mmol) was added. The reaction mixture was stirred for 20 min and sat aq NH_4Cl solution was added to quench excess base. The resulting mixture was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc/heptane) to provide 6-benzyl-4-methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 540.2 $(M+H)^+$.

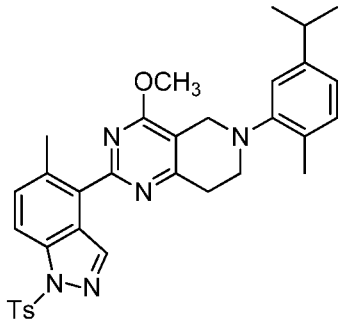
31-C. 4-Methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



A mixture of 6-benzyl-4-methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.85 g, 3.43 mmol) and $Pd(OH)_2$ on carbon (wet) (10%, 0.722 g, 1.03 mmol) in water (7.5 mL) and acetic acid (0.59 mL) was stirred under 1 atm of hydrogen at room temperature for 2.5 h. The reaction mixture was filtered through Celite® and the solids were washed with EtOAc. The combined filtrates were washed with saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (0-10% MeOH (10% NH_4OH)/DCM) to provide 4-methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 450.1 $(M+H)^+$.

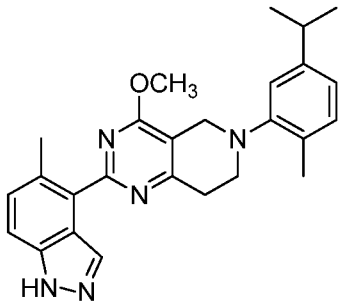
31-D. 6-(5-Isopropyl-2-methylphenyl)-4-methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-

tetrahydropyrido[4,3-d]pyrimidine.



A mixture of 4-methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (250 mg, 0.556 mmol), 5-isopropyl-2-methylphenyl trifluoromethanesulfonate (235 mg, 0.834 mmol), X-Phos (53.0 mg, 0.111 mmol), $Pd_2(dba)_3$ (50.9 mg, 0.056 mmol), and Cs_2CO_3 (362 mg, 1.11 mmol) in THF (3 mL) was heated in a microwave reactor at 140 °C for 60 min. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (0-50% EtOAc/heptane) to provide 6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 582.1 $(M+H)^+$.

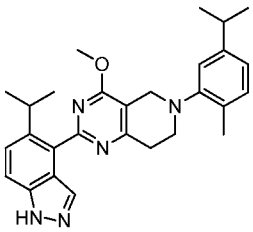
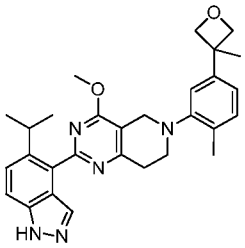
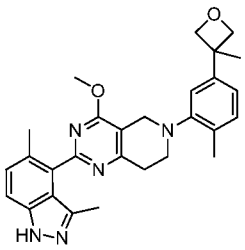
31-E. 6-(5-Isopropyl-2-methylphenyl)-4-methoxy-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

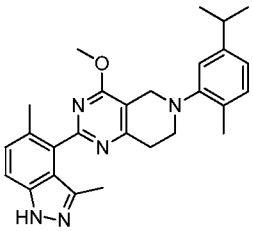


A mixture of 6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(5-methyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (200 mg, 0.344 mmol), KOH (80 mg, 1.43 mmol) and concentrated aq NH_4OH solution (4 mL) in MeOH (8 mL) was heated in a microwave reactor at 80 °C for 30 min. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3x). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc/heptanes) to provide 6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine as a

white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.31 (s, 1 H) 7.52 (d, *J*=8.34 Hz, 1 H) 7.40 (d, *J*=8.59 Hz, 1 H) 7.21 (d, *J*=7.83 Hz, 1 H) 7.11 (d, *J*=1.52 Hz, 1 H) 6.97 (dd, *J*=7.71, 1.64 Hz, 1 H) 4.04 - 4.20 (m, 5 H) 3.37 (t, *J*=5.68 Hz, 2 H) 3.19 (t, *J*=5.56 Hz, 2 H) 2.88 - 3.01 (m, 1 H) 2.70 (s, 3 H) 2.37 (s, 3 H) 1.31 (d, *J*=6.82 Hz, 6 H); MS (ESI+) *m/z* 428.1 $(M+H)^+$.

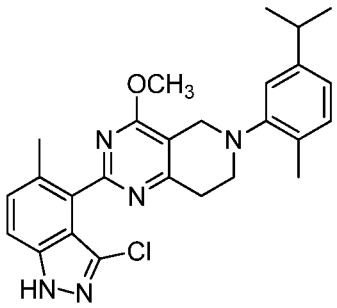
The following compounds were prepared in a similar manner.

	Structure	Chemical Name&Analytical Data
31-F		2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.94 (s, 1 H) 7.40-7.46 (m, 2 H) 7.06 (d, J=8.1 Hz, 1 H) 6.97 (d, J=1.5 Hz, 1 H) 6.83 (dd, J=7.6, 1.8 Hz, 1 H) 3.99 (s, 2 H) 3.94 (s, 3 H) 3.48 (quin, J=6.9 Hz, 1 H) 3.23 (t, J=5.68 Hz, 2 H) 3.04 (t, J=5.68 Hz, 2 H) 2.81 (quin, J=6.9 Hz, 1 H) 2.24 (s, 3 H) 1.22 (d, J=6.8 Hz, 6 H) 1.17 (d, J=7.1 Hz, 6 H); MS (ESI+) *m/z* 456.1 $(M+H)^+$.
31-G		2-(5-isopropyl-1H-indazol-4-yl)-4-methoxy-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (br. s., 1 H) 7.44 - 7.70 (m, 2 H) 7.27 (d, J=8.3 Hz, 1 H) 7.08 (d, J=1.8 Hz, 1 H) 6.94 (dd, J=7.7, 1.9 Hz, 1 H) 5.04 (d, J=5.6 Hz, 2 H) 4.70 (d, J=5.8 Hz, 2 H) 4.15 (s, 2 H) 4.09 (s, 3 H) 3.60 (quin, J=6.9 Hz, 1 H) 3.39 (t, J=5.7 Hz, 2 H) 3.23 (t, J=5.3 Hz, 2 H) 2.42 (s, 3 H) 1.80 (s, 3 H) 1.37 (d, J=6.8 Hz, 6 H); MS (ESI+) *m/z* 484.0 $(M+H)^+$.
31-H		2-(3,5-dimethyl-1H-indazol-4-yl)-4-methoxy-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. 1H NMR (400 MHz, CD_2Cl_2) δ ppm 9.88 (br. s., 1 H) 7.45 (d, J=8.3 Hz, 1 H) 7.33 (d, J=8.3 Hz, 1 H) 7.27 (d, J=7.8 Hz, 1 H) 7.06 (d, J=1.8 Hz, 1 H) 6.93 (dd, J=7.7, 1.9 Hz, 1 H) 4.99 (d, J=5.3 Hz, 2 H) 4.66 (d, J=5.3 Hz, 2 H) 4.15

		(s, 2 H) 4.05 (s, 3 H) 3.38 (t, J=5.7 Hz, 2 H) 3.14 (t, J=5.7 Hz, 2 H) 2.40 (s, 3 H) 2.34 (s, 3 H) 2.05 (s, 3 H) 1.77 (s, 3 H); MS (ESI+) m/z 470.3 $(M+H)^+$.
31-I		2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. 1H NMR (400 MHz, CD_2Cl_2) δ ppm 7.39 - 7.48 (m, 1 H) 7.29 - 7.37 (m, 1 H) 7.21 (d, J=7.8 Hz, 1 H) 7.10 (d, J=1.5 Hz, 1 H) 6.97 (dd, J=7.6, 1.8 Hz, 1 H) 4.15 (s, 2 H) 4.05 (s, 3 H) 3.37 (t, J=5.7 Hz, 2 H) 3.13 (t, J=5.6 Hz, 2 H) 2.87 - 3.02 (m, 1 H) 2.38 (s, 3 H) 2.35 (s, 3 H) 2.08 (s, 3 H) 1.31 (d, J=7.1 Hz, 6 H); MS (ESI+) m/z 442.3 $(M+H)^+$.

Example 32

32-A. 2-(3-Chloro-5-methyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8 tetrahydropyrido[4,3-d]pyrimidine.

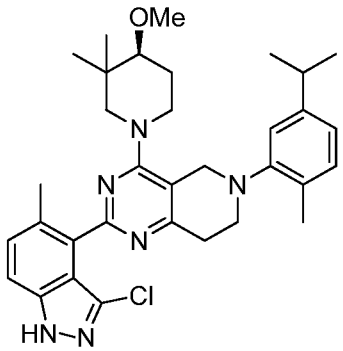


Elite® bleach (5.25% sodium hypochlorite) was added dropwise to a solution of 6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (40 mg, 0.094 mmol) in EtOH (4 mL) at 0 °C. The reaction was monitored by LC-MS. After all the starting material was consumed, the reaction mixture was directly loaded onto reverse phase HPLC and purified (CH_3CN-water 0-100%) to provide 2-(3-chloro-5-methyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^1H NMR (400 MHz, CD_3CN) δ ppm 11.23 (br. s., 1 H) 7.55 (d, *J*=8.59 Hz, 1 H) 7.41 (d, *J*=8.59 Hz, 1 H) 7.18 (d, *J*=7.58 Hz, 1 H) 7.10 (d, *J*=2.02 Hz, 1 H) 6.95 (dd, *J*=7.71, 1.89 Hz, 1 H) 4.11(s, 2 H) 3.97 (s, 3 H) 3.32 (t, *J*=5.68 Hz, 2 H) 3.01 - 3.06

(m, 2 H) 2.92 (ddd, *J*=13.83, 6.88, 6.82 Hz, 1 H) 2.33 (s, 3 H) 2.31 (s, 3 H) 1.26 (d, *J*=6.82 Hz, 6 H); MS (ESI+) *m/z* 462.1 $(M+H)^+$.

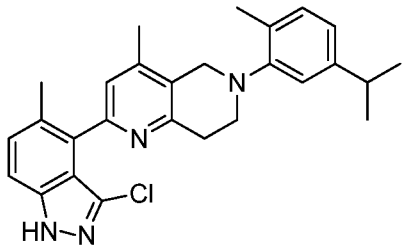
The following compounds were prepared in a similar manner.

32-B. (*S*)-2-(3-Chloro-5-methyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



^{1}H NMR (400 MHz, CD_3CN) δ ppm 7.50 (d, *J*=8.6 Hz, 1 H), 7.36 (d, *J*=8.6 Hz, 1 H), 7.13 (d, *J*=7.8 Hz, 1 H), 7.01 (d, *J*=1.5 Hz, 1 H), 6.90 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.02 - 4.14 (m, 2 H), 3.65 - 3.70 (m, 1 H), 3.33 - 3.40 (m, 3 H), 3.30 (s, 3 H), 3.05 (ddd, *J*=13.1, 10.0, 3.2 Hz, 1 H), 2.95 – 2.99 (m, 3 H), 2.82 - 2.91 (m, 2 H), 2.25 (s, 6 H), 1.57 – 1.66 (m, 1 H), 1.23 (d, *J*=6.6 Hz, 6 H), 0.97 (s, 3 H), 0.91 (s, 3 H); MS (ESI+) *m/z* 573.0 $(M+H)^+$.

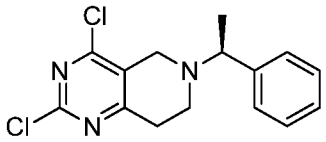
32-C. 2-(3-Chloro-5-methyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine.



^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 10.32 (br. s., 1 H) 7.38 (s, 2 H) 7.21 (d, *J*=7.58 Hz, 1 H) 7.08 - 7.13 (m, 2 H) 6.97 (dd, *J*=7.58, 1.77 Hz, 1 H) 4.21 (s, 2 H) 3.37 - 3.42 (m, 2 H) 3.20 - 3.26 (m, 2 H) 2.95 (dt, *J*=13.83, 6.85 Hz, 1 H) 2.40 (s, 3 H) 2.35 (s, 3 H) 2.30 (s, 3 H) 1.31 (d, *J*=6.82 Hz, 6 H); MS (ESI+) *m/z* 445.0 $(M+H)^+$.

Example 33

33-A. (*S*)-2,4-Dichloro-6-(1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



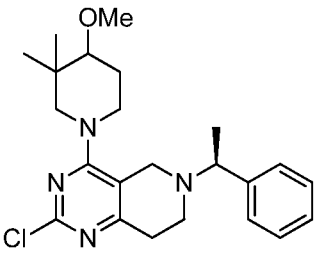
A mixture of ceric ammoniumnitrate (22.6 g, 41.3 mmol), (*S*)-phenyl-ethylamine (25 g, 207 mmol), and THF (100 mL) was cooled to 10 °C and then ethylacrylate (51.6 g, 516 mmol) was added dropwise. The reaction mixture was then brought to rt and then warmed to 60 °C and heated for 15 h. The mixture was diluted with water and EtOAc and the organic layer was then separated, dried (Na_2SO_4), filtered and concentrated. The residue was purified by FCC (30% EtOAc/hexanes) to give (*S*)-diethyl 3,3'-((1-phenylethyl)azanediyl)dipropanoate. MS (ESI+) *m/z* 322 $(M+H)^+$.

A suspension of NaH (2.24 g, 93.4 mmol) in THF (20 mL) was cooled to 0 °C and as solution of (*S*)-diethyl 3,3'-((1-phenylethyl)azanediyl)dipropanoate (15 g, 46.7 mmol) in THF was then added dropwise. The reaction mixture was allowed to warm to rt and then warmed to 60 °C and heated for 3 h. The mixture was diluted with water and EtOAc and the organic layer was then separated, dried (Na_2SO_4), filtered and concentrated. The residue was purified by FCC (5-7% EtOAc/hexanes) to give (*S*)-ethyl 4-oxo-1-((*S*)-1-phenylethyl)piperidine-3-carboxylate.

A combination of urea (0.37 g, 15.6 mmol), sodium methoxide (1.47 g, 27.2 mmol) and MeOH (50mL) was cooled to 0 °C and then a solution of (*S*)-ethyl 4-oxo-1-((*S*)-1-phenylethyl)piperidine-3-carboxylate (9.0 g, 7.8 mmol) in THF was added. The reaction mixture was allowed to warm to rt and then warmed to 60 °C and heated for 3 h. The mixture was diluted with water and EtOAc and the organic layer was then separated, dried (Na_2SO_4), filtered and concentrated. The residue was purified by FCC (8-10% MeOH/CH_2Cl_2) to give (*S*)-6-(1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diol.

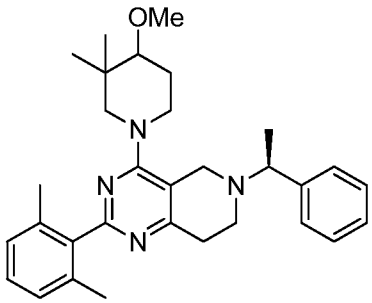
A combination of $POCl_3$ (10 mL) and DIEA (2.0 mL) was cooled to 0 °C and then (*S*)-6-(1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diol (2.0 g, 7.38) in THF was added The reaction mixture was allowed to warm to rt and then warmed to 60 °C and heated for 3 h. The mixture was diluted with water and EtOAc and the organic layer was then separated, dried (Na_2SO_4), filtered and concentrated. The residue was purified by FCC (10% EtOAc/hexanes) to give (*S*)-2,4-dichloro-6-(1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 310 (M+2).

33-B. (±)-2-Chloro-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-((*S*)-1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



A mixture of *racemic* 4-methoxy-3,3-dimethylpiperidine (0.30 g, 1.95 mmol), (*S*)-2,4-dichloro-6-(1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.40 g, 1.30 mmol), DIEA (0.50 g, 3.90 mmol), and isopropanol (10 mL) was heated at 60 °C for 24 h. The mixture was diluted with water and EtOAc and the organic layer was then separated, dried (Na_2SO_4), filtered and concentrated. The residue was taken to the next step without further purification. MS (ESI+) *m/z* 415.2 $(M+H)^+$.

33-C. (±)-2-(2,6-Dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-((*S*)-1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

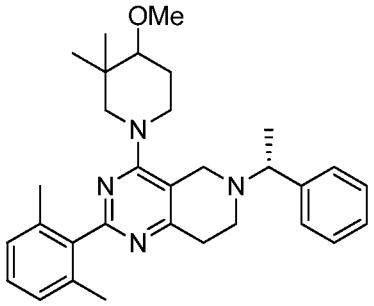


A mixture of 2,6-dimethylphenyl boronic acid (0.081 g, 0.54 mmol), (±)-2-chloro-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-((*S*)-1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.15 g, 0.36 mmol), $Pd(PPh_3P)_4$ (0.041 g, 0.036 mmol), sat aq Na_2CO_3 (2.0 mL), and DMF (5 mL) was placed under a nitrogen atmosphere and heated to 120 °C in a microwave reactor for 0.5 h. The mixture was diluted with water and EtOAc and the organic layer was then separated, dried (Na_2SO_4), filtered and concentrated. The residue was then purified by semi-prep HPLC (Column: ZORBAX, XDB, C-18; A: 10 mM NH_4OAc in water; B: MeCN; Flow Rate: 20 mL/min; Gradient: 0.0 min, 70.0% MeCN, 2.0 min, 80.0% MeCN, 6.0 min, 90.0% MeCN). After lyophilization, the mixture was dissolved in DCM and washed with water to remove NH_4OAc, dried over Na_2SO_4 and solvents were removed under reduced pressure. MS (ESI+) *m/z* 485.3 $(M+H)^+$.

The following compounds were prepared in a similar manner.

33-B. (±)-2-(2,6-Dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-((*R*)-1-

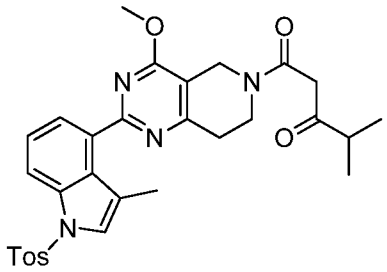
phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



MS (ESI+) *m/z* 485.4 $(M+H)^+$.

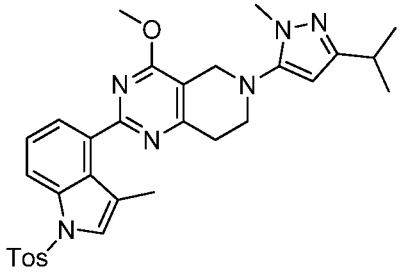
Example 34

34-A. 1-(4-Methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylpentane-1,3-dione.



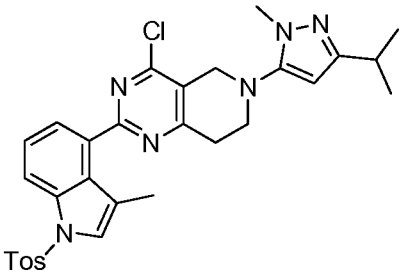
To a solution of 4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, prepared as described in **Example 17**, (300 mg, 0.67 mmol) in toluene (3 mL), in a 2-5 mL microwave vial, was added methyl 4-methyl-3-oxopentanoate (0.28 mL, 2 mmol) followed by DMAP (25 mg, 0.2 mmol). The reaction vessel was then sealed and heated via microwave irradiation at 150 °C for 35 min. The reaction mixture was then cooled to room temperature and diluted with dichloromethane and water. The layers were separated and the organic layer was dried by passing through a phase separator and then concentrated. The resulting residue was purified via silica gel flash chromatography (45-90% ethyl acetate/heptanes) to furnish 1-(4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylpentane-1,3-dione. MS (ESI+) *m/z* 561.3 $(M+H)^+$.

34-B . 6-(3-Isopropyl-1-methyl-1H-pyrazol-5-yl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 1-(4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylpentane-1,3-dione (350 mg, 0.624 mmol) in THF (3.3 mL), in a 2-5 mL microwave vial, was added Lawesson's reagent (278 mg, 0.687 mmol) and methyl hydrazine (0.049 mL, 0.94 mmol). The vessel was immediately sealed and heated via microwave irradiation at 120 °C for 10 minutes. The reaction was then cooled to room temperature and diluted with dichloromethane and water. The layers were separated and the aqueous layer was extracted two additional times with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified via silica gel flash chromatography (45-67% ethyl acetate / heptanes) to provide 6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 571.4 $(M+H)^+$.

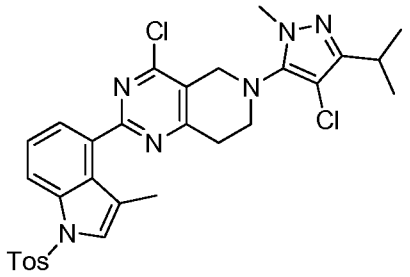
34-C. 4-Chloro-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



Ethanol (1.8 mL) was added to 6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (195 mg, 0.342 mmol) followed by 12 N aqueous hydrochloric acid (1.8 mL, 21.8 mmol). The mixture was then heated to 87 °C for ca. 15 hours. The mixture was then cooled to room temperature, diluted with dichloromethane, and slowly neutralized with saturated aqueous sodium bicarbonate. The resulting layers were separated and the aqueous layers were extracted an additional time with dichloromethane. The organic layers were combined and dried by passing through a phase separator and then concentrated. The resulting residue was diluted with 1,2-dichloroethane (3.5 mL) and place at 0 °C. Then N-chloromethylene-N,N-dimethyl ammonium chloride

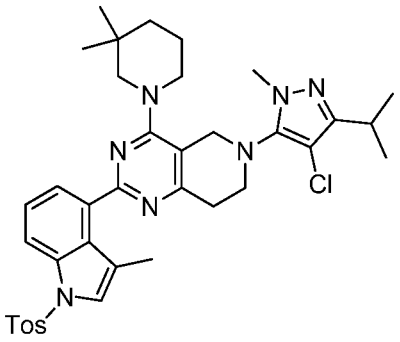
(Vilsmeier reagent) (85 mg, 067 mmol) was added. The resulting mixture was then heated to 35 °C. After 5 minutes at 35 °C the mixture was diluted with dichloromethane, and slowly neutralized with saturated aqueous sodium bicarbonate. The resulting layers were separated and the aqueous layers were extracted an additional time with dichloromethane. The organic layers were combined and dried over Na_2SO_4, filtered and concentrated to furnish 4-chloro-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine without the need for further purification. MS (ESI+) *m/z* 575.3 $(M+H)^+$.

34-D. 4-Chloro-6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



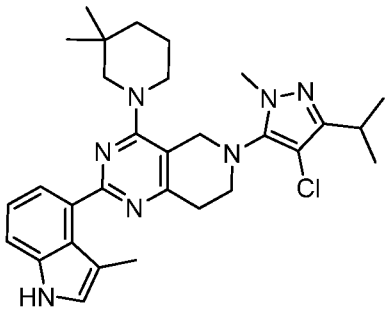
To a solution of 4-chloro-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (90 mg, 0.156 mmol) in MeCN (2.0 mL) at 0 °C was added N-chlorosuccinimide (21 mg, 0.156 mmol). The reaction was permitted to stir for 2.5 h at 0 °C, and then was diluted with diethyl ether and saturated aqueous sodium bicarbonate. The layers were separated and the organic layer was washed once with brine, dried over $MgSO_4$, filtered and concentrated to furnish 4-chloro-6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine without the need for further purification. MS (ESI+) *m/z* 609.2 $(M+H)^+$.

34-E. 6-(4-Chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



Isopropanol (2.2 mL) was added to 4-chloro-6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (85 mg, 0.139 mmol) in a microwave vial. Then diisopropylethylamine (0.1 mL, 0.573 mmol) was added followed by the HCl salt of 3,3-dimethylpiperidine (25 mg, 0.167 mmol). The vessel was sealed and heated via microwave irradiation at 120 °C for 2.5 h then cooled to room temperature and diluted with dichloromethane and brine. The layers were separated and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified via silica gel flash chromatography (25-55% ethyl acetate / heptanes) to provide 6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 686.4 $(M+H)^+$.

34-F. 6-(4-Chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.



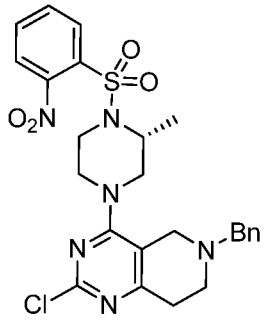
Ethanol (1.8 mL) was added to 6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (74 mg, 0.108 mmol) in a microwave vial. Next, KOH (61 mg, 1.08 mmol) was added followed by 28% aqueous ammonium hydroxide (0.6 mL, 4.35 mmol). The vessel was sealed and heated via microwave irradiation at 100 °C for 75 minutes. The reaction mixture was cooled to room temperature and diluted with dichloromethane and water. The layers were separated and the organic layer was dried by passing through a phase separator. The eluent was concentrated and the resulting residue was purified by reverse

phase HPLC (20-55% MeCN/Water(0.1% TFA)). The eluent from the HPLC was neutralized with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic extract was dried by passing through a phase separator and concentrating to provide 6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.

^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 0.97 (s, 6 H) 1.26 (d, *J*=7.1 Hz, 6 H) 1.39 - 1.46 (m, 2 H) 1.66 - 1.77 (m, 2 H) 2.09 (s, 3 H) 2.99 (dt, *J*=13. 9, 7.0 Hz, 1 H) 3.04 - 3.12 (m, 4 H) 3.25 - 3.34 (m, 2 H) 3.53 - 3.59 (m, 2 H) 3.63 (s, 3 H) 4.30 (s, 2 H) 7.04 (br. s., 1 H) 7.20 (t, *J*=7.7 Hz, 1 H) 7.32 (d, *J*=6.3 Hz, 1 H) 7.41 (d, 1 H) 8.22 (br. s., 1 H); MS (ESI+) *m/z* 532.4 $(M+H)^+$.

Example 35

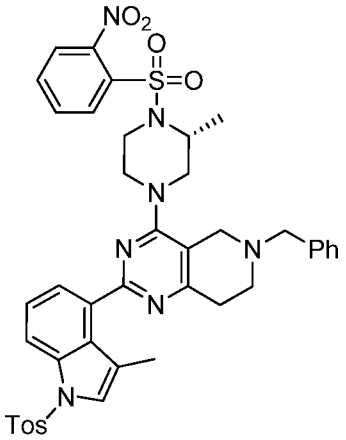
35-A. (*R*)-6-Benzyl-2-chloro-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



Isopropanol (80 mL) was added to 6-benzyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (CAS# 778574-06-4 2.5 g, 8.50 mmol) followed by triethylamine (3.55 mL, 25.5 mmol) and (*R*)-2-methylpiperazine (1.28 g, 12.8 mmol). The mixture was heated at 50 °C for 6.5 hours and then cooled to room temperature and diluted with dichloromethane and water. The layers were separated and the aqueous layer was extracted one additional time with dichloromethane. The organic layers were combined dried over Na_2SO_4, filtered, and concentrated. A portion of the resulting residue (1.3g) was then dissolved in dichloromethane (25 mL) and charged with triethylamine (1.2 mL, 8.7 mmol). The mixture was placed at 0 °C and then 2-nitrobenzene-1-sulfonyl chloride (0.97 g, 4.4 mmol) was added. The mixture was stirred at 0 °C for 30 minutes then warmed to room temperature and stirred an additional 1 hour. The mixture was then quenched with saturated aqueous sodium bicarbonate and stirred for 1 hour. The mixture was then further diluted with dichloromethane and saturated aqueous sodium bicarbonate and the layers separated. The aqueous layer was extracted one additional time with dichloromethane. The organic layers were combined dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (50-85% ethyl acetate/heptanes) to

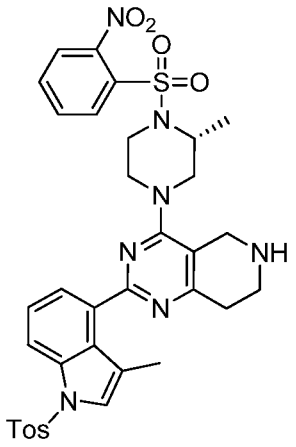
afford: (*R*)-6-benzyl-2-chloro-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 686.4 $(M+H)^+$.

35-B. (*R*)-6-Benzyl-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



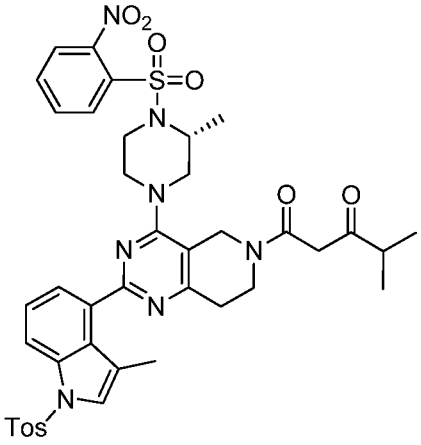
1,2-Dimethoxyethane (6.75 mL) was added to a 20 mL microwave vial containing a mixture of (*R*)-6-benzyl-2-chloro-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.1 g, 2.03 mmol) and 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indole (0.92 g, 2.23 mmol). Then 2M aqueous Na_2CO_3 was added and the reaction mixture was degassed via three argon/vacuum cycles, then charged with $Pd(Ph_3P)_4$ (0.234 g, 0.203 mmol). The vial was sealed and heated via microwave irradiation at 140 °C for 90 minutes. The mixture was then cooled to room temperature and diluted with Et_2O and water. The layers were separated and the aqueous layer was extracted two additional times with dichloromethane. The organic layers were combined dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography [55-75% ethyl acetate(containing 2%EtOH)/heptanes] to afford (*R*)-6-benzyl-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 792.5 $(M+H)^+$.

35-C. (*R*)-2-(3-Methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



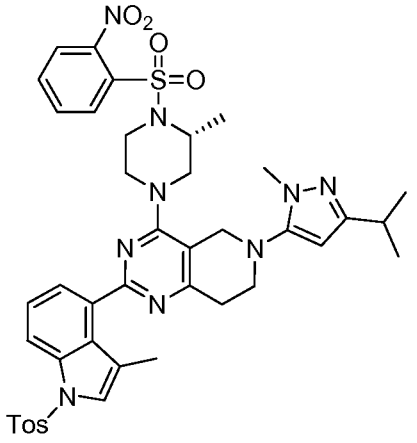
To a solution of (*R*)-6-benzyl-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.17 g, 1.47 mmol) in MeCN (15 mL) was added 1-chloroethyl carbonochloridate (0.18 mL, 1.62 mmol), and the mixture was stirred for 15 minutes at which time the mixture was concentrated *in vacuo*. The resulting residue was dissolved in a 2:1 mixture of dichloromethane:methanol (15 mL) and heated at 40 °C for 1 hour and then placed at room temperature for ca. 15 h. The mixture was then diluted with dichloromethane and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted two additional times with dichloromethane. The organic layers were combined dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (3-12% MeOH/DCM) to provide (*R*)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 702.3 $(M+H)^+$.

35-D. (*R*)-4-Methyl-1-(2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)pentane-1,3-dione.



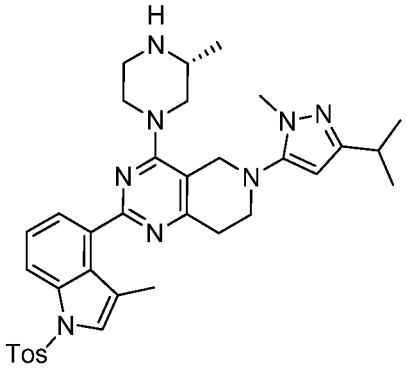
The title compound was prepared from (*R*)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine following the procedure described in **Example 34**. MS (ESI+) *m/z* 814.3 $(M+H)^+$.

35-E. (*R*)-6-(3-Isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



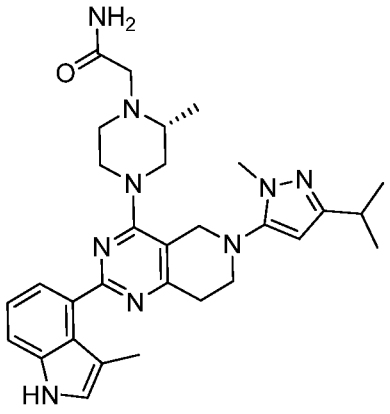
The title compound was prepared from (*R*)-4-methyl-1-(2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)pentane-1,3-dione following the procedure described in **Example 34**. MS (ESI+) *m/z* 824.4 $(M+H)^+$.

35-F. (*R*)-6-(3-Isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of (*R*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (105 mg, 0.127 mmol) in DMF (3 mL) was added DBU (0.1 mL, 0.64 mmol) followed by 2-mercaptoacetic acid (0.018 mL, 0.255 mmol). The mixture was stirred for 3 hours and then diluted with water and dichloromethane. The layers were separated and the aqueous layer was extracted three additional times with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified via silica gel flash chromatography [4-25% (2 M NH_3 in MeOH)/DCM] to provide (*R*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 639.4 $(M+H)^+$.

35-G. (*R*)-2-(4-(6-(3-Isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide.

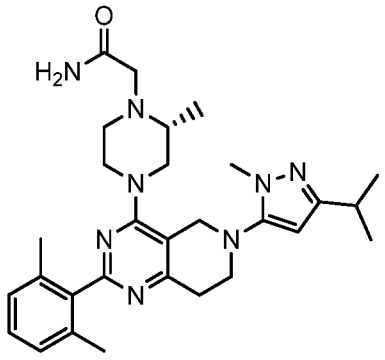


To a solution of (*R*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (78 mg, 0.122 mmol) in MeCN (2 mL) was added diisopropylethylamine (0.064 mL, 0.37 mmol) followed by 2-bromoacetamide (20 mg, 0.146 mmol). The mixture was heated to 55 °C and stirred for 105 minutes, then cooled to room temperature

and quenched with saturated aqueous NH_4Cl. The mixture was diluted with dichloromethane and saturated aqueous sodium bicarbonate and the layers were separated. The aqueous layer was extracted two additional times with dichoromethane and the organic layers were then combined, dried over Na_2SO_4, filtered and concentrated. The resulting residue was then dissolved in ethanol (2.1 mL) and placed in a microwave vial. The vial was charged with KOH (69 mg, 1.24 mmol) and 28% aqueous ammonium hydroxide (0.7 mL, 5.1 mmol), sealed and heated via microwave irradiation at 100 °C for 70 minutes. The mixture was then cooled to room temperature, diluted with dichloromethane and water and then neutralized with 1M aqueous $NaHSO_4$. The resulting layers were separated and the organic layer was dried by passing through a phase separator. The eluent was concentrated and purified by reverse phase HPLC [10-55% MeCN/(0.1% NH_4OH)water] to furnish (*R*)-2-(4-(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (d, *J*=6.3 Hz, 3 H) 1.16 (d, *J*=6.8 Hz, 6 H) 2.02 (s, 3 H) 2.59 - 2.66 (m, 1 H) 2.72 - 2.85 (m, 3 H) 2.89 - 3.00 (m, 3 H) 3.13 (d, *J*=16.2 Hz, 1 H) 3.20 - 3.26 (m, 1 H) 3.27 - 3.30 (m, 3 H) 3.56 - 3.64 (m, 5 H) 4.01 (s, 2 H) 5.73 (s, 1 H) 7.08 - 7.13 (m, 2 H) 7.13 - 7.16 (m, 1 H) 7.18 - 7.22 (m, 1 H) 7.26 (d, *J*=2.8 Hz, 1 H) 7.41 (dd, *J*=8.1, 1.0 Hz, 1 H) 10.90 (s, 1 H); MS (ESI+) *m/z* 542.4 $(M+H)^+$.

Example 36

(*R*)-2-(4-(2-(2,6-Dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide.

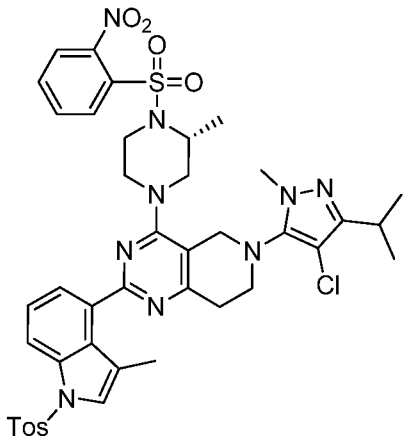


MeCN (2 mL) was added to 4-chloro-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, prepared as described in **Example 16**, (110 mg, 0.278 mmol) in a microwave vial. The vial was then charged with diisopropylethylamine (0.24 mL, 1.38 mmol) and (*R*)-2-methylpiperazine (56 mg, 0.556 mmol). The vial was sealed and heated via microwave irradiation at 100 °C for 45 minutes. The mixture was cooled to room temperature and then charged with 2-bromoacetamide (115 mg, 0.833 mmol), re-sealed and heated via microwave irradiation at 100 °C for 10

minutes. The reaction was then cooled to room temperature and adsorbed *in vacuo* onto silica and loaded onto a silica gel flash chromatography column for purification [0-10% (10% NH_4OH)MeOH/DCM]. The material was then further purified by additional silica gel flash chromatography {0-35% [10% MeOH (containing 1% NH_4OH)/EtOAc]/DCM} to furnish (*R*)-2-(4-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.27 (br. s., 1 H) 7.17 (d, *J*=7.58 Hz, 1 H) 7.13 (br. s., 1 H) 7.08 (d, *J*=7.58 Hz, 2 H) 5.72 (s, 1 H) 3.98 (s, 2 H) 3.59 (s, 3 H) 3.51 - 3.58 (m, 2 H) 3.25 - 3.32 (m, 3 H) 3.16 - 3.24 (m, 1 H) 3.11 (d, *J*=16.17 Hz, 1 H) 2.94 (br. s., 3 H) 2.71 - 2.85 (m, 3 H) 2.56 - 2.65 (m, 1 H) 2.05 (s, 6 H) 1.11 - 1.19 (m, 6 H) 1.00 (d, *J*=6.06 Hz, 3 H); MS (ESI+) *m/z* 517.34 $(M+H)^+$.

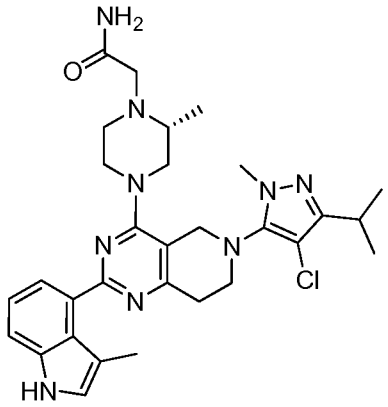
Example 37

37-A. (*R*)-6-(4-Chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



The title compound was prepared from (*R*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine following the procedure described in **Example 34**. MS (ESI+) *m/z* 858.4 $(M+H)^+$.

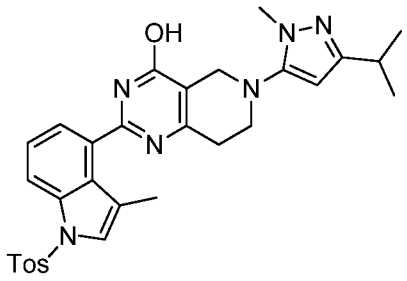
37-B. (*R*)-2-(4-(6-(4-Chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide.



The title compound was prepared from (*R*)-6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine by following the procedures described in **Examples 35**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 (d, *J*=6.3 Hz, 3 H) 1.20 (d, *J*=6.8 Hz, 6 H) 2.03 (s, 3 H) 2.58 - 2.65 (m, 1 H) 2.76 - 3.00 (m, 6 H) 3.10 - 3.23 (m, 2 H) 3.27 - 3.30 (m, 1 H) 3.52 (t, *J*=6.1 Hz, 2 H) 3.55 - 3.64 (m, 5 H) 4.21 - 4.34 (m, 2 H) 7.07 - 7.13 (m, 2 H) 7.13 - 7.16 (m, 1 H) 7.21 (dd, *J*=7.3, 1.0 Hz, 1 H) 7.23 - 7.27 (m, 1 H) 7.41 (dd, *J*=8.0, 0.9 Hz, 1 H) 10.90 (s, 1 H); MS (ESI+) *m/z* 576.5 $(M+H)^+$.

EXAMPLE 38

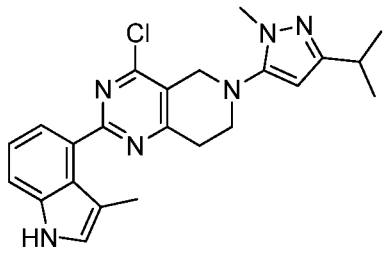
38-A. 6-(3-Isopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-ol.



To a solution of 6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-methoxy-2-(3-methyl-1-tosyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (1.8 g, 3.15 mmol), prepared as described in **Example 16**, in ethanol (10 mL) in a 150 mL sealed tube, was added concentrated hydrochloride (10 mL). After the tube was sealed, the reaction was stirred and heated to 85 °C for 18 h. The reaction mixture wascooled to 0°C and poured into ice water. Solid $NaHCO_3$ was added to neutralize the reaction mixture, then the mixture was extracted with DCM twice and the combined organic layers were dried over Na_2SO_4. The resulting residue was purified via silica gel FCC (0-100% EtOAc/heptane) to provide 6-(3-isopropyl-1-

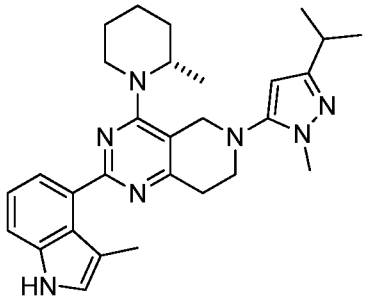
methyl-1*H*-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-ol. MS (ESI+) *m/z* 557.2 $(M+H)^+$.

38-B. 4-Chloro-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3-methyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.



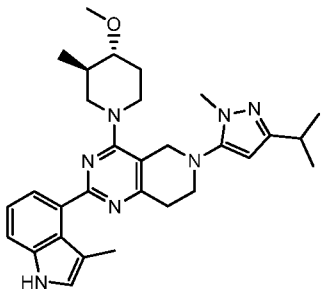
To a solution of 6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-ol (550 mg, 0.988 mmol) in methanol (5 mL) in a microwave vial, was added potassium hydroxide (554 mg, 9.88 mmol) and then 28% ammonium hydroxide (1 mL, 0.988 mmol). The reaction was heated at 80 °C via microwave irradiation for 45 min. The reaction mixture was poured into iced water, then 4 N aq HCl was added to acidify the reaction mixture to pH=1, then $NaHCO_3$ solid was added to neutralize reaction mixture to pH=7-8. The mixture was extracted twice with a solution of 5% trifluoroethanol in DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was dissolved in dichloroethane (3 mL), and the reaction flask was charged with phosphorus oxychloride (3.67 mL, 39.5 mmol). The reaction flask was capped and then heated to 80°C for 1 h. The reaction mixture was cooled to r.t. and poured into ice water and diluted with acetone (10 mL). The reaction mixture was stirred for 30 min to provide a clear solution. At that point, $NaHCO_3$ solid was added to neutralize the reaction, and the mixture was extracted twice with DCM. The resulting residue was purified via silica gel FCC (0-100% EtOAc/heptane) to provide 4-chloro-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3-methyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. MS (ESI+) *m/z* 421.2 $(M+H)^+$.

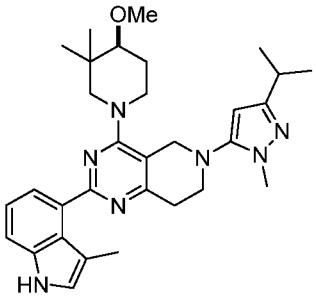
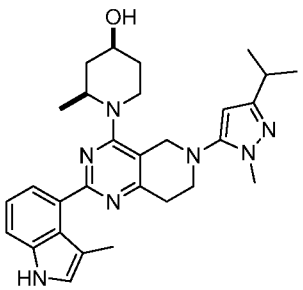
38-C. (*S*)-6-(3-Isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 4-chloro-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3-methyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine (50 mg, 0.123 mmol) in *N,N*-dimethylacetamide (1.5 mL), was added diisopropylethylamine (0.15 mL, 0.86 mmol) and (*S*)-2-methylpiperidine (37 mg, 0.37 mmol). The reaction was stirred and heated to 125 °C for 24 h. After cooling, the mixture was directly purified via HPLC ((0.1% ammonium hydroxide in acetonitrile)/water=35%-100%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.23 (br. s., 1 H), 7.42 (d, *J*=8.1 Hz, 1 H), 7.33 (d, *J*=8.1 Hz, 1 H), 7.16 - 7.26 (m, 1 H), 7.04 (s, 1 H), 5.69 (s, 1 H), 4.06 - 4.16 (m, 1 H), 3.90 - 4.06 (m, 2 H), 3.67 (s, 3 H), 3.53 (d, *J*=13.4 Hz, 1 H), 3.29 - 3.40 (m, 2 H), 3.16 - 3.29 (m, 1 H), 3.10 (d, *J*=4.5 Hz, 2 H), 2.85 (dt, *J*=13.8, 6.9 Hz, 1 H), 2.10 (s, 3 H), 1.74 - 1.91 (m, 2 H), 1.65 - 1.74 (m, 2 H), 1.48 - 1.65 (m, 2 H), 1.22 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 484.4 $(M+H)^+$.

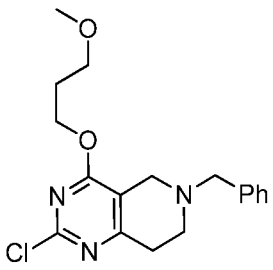
The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data
38-D		(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-((3*R*,4*R*)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.22 (br. s., 1 H), 7.43 (d, *J*=7.8 Hz, 1 H), 7.34 (d, *J*=7.3 Hz, 1 H), 7.16 - 7.24 (m, 1 H), 7.05 (s, 1 H), 5.68 (s, 1 H), 4.01 (s, 2 H), 3.84 (d, *J*=13.4 Hz, 1 H), 3.73 (d, *J*=14.4 Hz, 1 H), 3.66 (s, 3 H), 3.35 (s, 3 H), 3.31 - 3.35 (m, 2 H), 3.10 (t, *J*=4.9 Hz, 2 H), 2.98 - 3.07 (m, 1 H), 2.94 (td, *J*=9.2, 4.3 Hz, 1 H), 2.81 - 2.89 (m, 1 H), 2.76 (dd, *J*=12.9, 10.4 Hz, 1 H), 2.10 - 2.19 (m, 1 H), 2.09 (s, 3 H), 1.71 - 1.84 (m, 1 H), 1.45 - 1.60 (m, 1 H), 1.22 (d, *J*=6.8 Hz, 6 H), 1.01 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 514.4 $(M+H)^+$.

38-E		(*S*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.28 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.35 (d, *J*=7.1 Hz, 1 H), 7.15 - 7.25 (m, 1 H), 7.06 (s, 1 H), 5.67 (s, 1 H), 4.03 (s, 2 H), 3.73 (d, *J*=11.6 Hz, 1 H), 3.66 (s, 3 H), 3.42 (d, *J*=11.4 Hz, 1 H), 3.35 (s, 3 H), 3.31 - 3.35 (m, 2 H), 3.04 - 3.27 (m, 3 H), 2.97 (dd, *J*=8.5, 3.9 Hz, 2 H), 2.78 - 2.91 (m, 1 H), 2.09 (s, 3 H), 1.91 - 2.04 (m, 1 H), 1.65 - 1.78 (m, 1 H), 1.21 (d, *J*=6.8 Hz, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H); MS (ESI+) *m/z* 528.4 $(M+H)^+$.
38-F		(±)-1-(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-4-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.25 (br. s., 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.34 (d, *J*=8.1 Hz, 1 H), 7.21 (t, *J*=7.7 Hz, 1 H), 7.06 (s, 1 H), 5.70 (s, 1 H), 4.17 (d, *J*=15.2 Hz, 1 H), 3.96 (d, *J*=15.4 Hz, 1 H), 3.84 - 3.93 (m, 1 H), 3.70 - 3.77 (m, 1 H), 3.68 (s, 3 H), 3.32 - 3.40 (m, 1 H), 3.22 - 3.32 (m, 1 H), 3.06 - 3.13 (m, 2 H), 2.95 - 3.05 (m, 2 H), 2.80 - 2.90 (m, 1 H), 2.51 (br. s., 1 H), 2.09 (s, 3 H), 1.90 - 2.06 (m, 2 H), 1.56 - 1.70 (m, 1 H), 1.42 - 1.55 (m, 1 H), 1.22 (d, *J*=7.1 Hz, 6 H), 1.18 (d, *J*=6.1 Hz, 3 H); MS (ESI+) *m/z* 500.3 $(M+H)^+$.

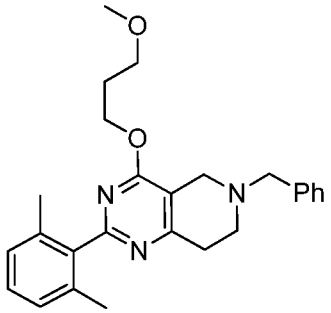
Example 39

39-A. 6-Benzyl-2-chloro-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



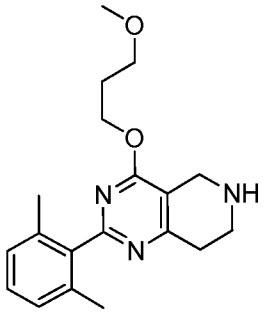
To a solution of 3-methoxypropan-1-ol (0.500 mL, 5.23 mmol) in *t*-butanol (5 mL) was added a 60% dispersion of NaH in oil (70 mg, 1.75 mmol). The resulting suspension was permitted to stir for 30 minutes at which time the reaction was placed at 0 °C and charged with 6-benzyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (CAS# 778574-06-4, 300 mg, 1.02 mmol) as a solution in THF (1.5 mL). After 20 minutes the mixture was quenched with saturated aqueous NH_4Cl, and diluted with ethyl acetate and water. The layers were then separated and the organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified via silica gel flash chromatography to provide 6-benzyl-2-chloro-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 348.1 $(M+H)^+$.

39-B. 6-Benzyl-2-(2,6-dimethylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



The title compound was prepared from provide 6-benzyl-2-chloro-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine following the procedure described in **Example 16.** MS (ESI+) *m/z* 418.1 $(M+H)^+$.

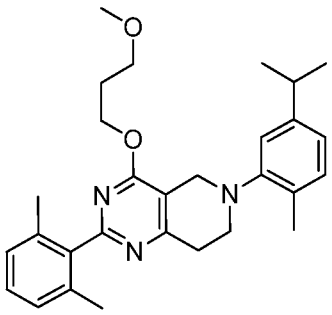
39-C. 2-(2,6-Dimethylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 6-benzyl-2-(2,6-dimethylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (170 mg, 0.41 mmol) in THF (3.5 mL) was added water (0.5 mL) and acetic acid (0.070 mL, 1.22 mmol). The reaction mixture was placed under argon and then charged with 20 mol%

$Pd(OH)_2/C$ (50% wet, 114 mg, 0.081 mmol). The atmosphere was then replaced with hydrogen gas via a balloon and was permitted to stir for 5 hours. The mixture was then neutralized with saturated aqueous sodium bicarbonate, diluted with dichloromethane and filtered through a pad of Celite®. The eluent was further diluted with dichloromethane and saturated aqueous sodium bicarbonate and the layers were separated. The aqueous layer was extracted two additional times with dichloromethane. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography [7-20% (2 M NH_3 in MeOH)/DCM] to furnish 2-(2,6-dimethylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 328.3 $(M+H)^+$.

39-D. 2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine.

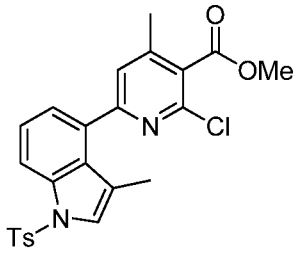


To 5-isopropyl-2-methylphenyl trifluoromethanesulfonate, prepared as described in **Example 15** (153 mg, 0.541 mmol) in a microwave vial was added a solution of 2-(2,6-dimethylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine in THF (4 mL). Next, Cs_2CO_3 (235 mg, 0.721 mmol) was added and the reaction mixture was degassed via a series of argon/vacuum cycles. The reaction mixture was then charged with chloro(2-dicyclohxylphosphino-2',4',6',-triisopropyl-1,1'-biphenyl)-[2-(2-aminoethyl)phenyl)]-palladium(II) (CAS# 1028206-56-5, 26.6 mg, 0.036 mmol). The vessel was then sealed and heated via microwave irradiation at 140 °C for 90 minutes. The reaction was then cooled to room temperature and diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted once with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (5-50% ethyl acetate/heptanes) to provide 2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. ^1H NMR (400 MHz, CD_2Cl_2) δ ppm 1.25 (d, *J*=7.1 Hz, 6 H) 2.08 (quin, *J*=6.3 Hz, 2 H) 2.28 (s, 6 H) 2.49 (s, 3 H) 2.92 (dt, *J*=13.8, 6.9 Hz, 1 H) 3.28 (s, 3 H) 3.49 (t, *J*=5.9 Hz, 2 H) 3.58 (t, *J*=5.7 Hz, 2 H) 3.81 (t, *J*=5.6 Hz, 2 H) 4.37 (s, 2 H) 4.71 (t,

J=6.4 Hz, 2 H) 7.12 (dd, *J*=7.7, 1.4 Hz, 1 H) 7.17 (s, 1 H) 7.20 - 7.27 (m, 3 H) 7.36 - 7.41 (m, 1 H); MS (ESI+) *m/z* 460.4 $(M+H)^+$.

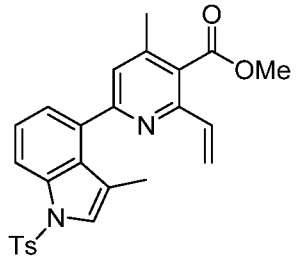
Example 40

40-A. Methyl 2-chloro-4-methyl-6-(3-methyl-1-tosyl-1H-indol-4-yl)nicotinate.



A mixture of methyl 2,6-dichloro-4-methylnicotinate (0.250 g, 1.14 mmol), 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indole (**Example 6**) (0.514 g, 1.25 mmol), $Pd(Ph_3P)_4$ (0.131 g, 0.114 mmol), and CsF (0.345 g, 2.27 mmol), in DMF (5 mL) was heated at 110 °C for 6 h. At that time the vessel was removed from the oil bath and allowed to cool to rt. The mixture was diluted with brine (50 mL) and EtOAc (50 mL). The layers were mixed and then separated. The aqueous layer was further extracted with EtOAc (50 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was then purified via FCC (0-10% EtOAc/heptane) to give the title compound. MS ESI *m/z* 469.0 & 470.9 $(M+H)^+$.

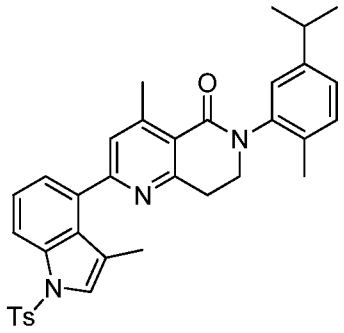
40-B. Methyl 4-methyl-6-(3-methyl-1-tosyl-1H-indol-4-yl)-2-vinylnicotinate.



A solution of methyl 2-chloro-4-methyl-6-(3-methyl-1-tosyl-1H-indol-4-yl)nicotinate (0.348 g, 0.742 mmol) in DMF (5 mL) was sparged with argon for 10 min before *trans*-$Pd(PPh_3)_2Cl_2$ (0.052 g, 0.074 mmol), tri-n-butyl(vinyl)tin (0.353 g, 1.11 mmol), and BHT (0.016 g, 0.074 mmol) were added. The resulting suspension was sparged with argon for 5 min and the vessel was sealed and heated at 60 °C. After 24 h the reaction was allowed to cool to rt and 50% KF on Celite® was added. The resulting slurry was then filtered over Celite® eluting with EtOAc. The organic was then washed with 10% KF in water

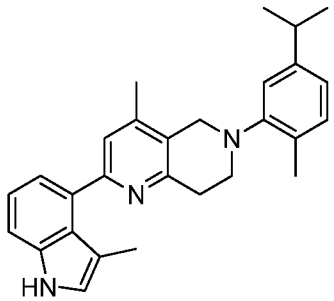
and then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by FCC (5-40% EtOAc/heptane) to give the title compound. MS ESI *m/z* 461.1 $(M+H)^+$.

40-C. 6-(5-Isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1-tosyl-1H-indol-4-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one.



A solution of methyl 4-methyl-6-(3-methyl-1-tosyl-1H-indol-4-yl)-2-vinylnicotinate (0.19 g, 0.413 mmol), and 5-isopropyl-2-methylaniline (0.074 g, 0.495 mmol) in AcOH (5 mL) was heated to 110 °C for 18 h. At that point, the reaction was concentrated under reduced pressure. The residue was then taken up in DCM (25 mL) and washed with 1 M aq NaOH (25 mL). The aqueous layer was further extracted with DCM (2 x 25 mL) and the combined organic layers were then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by FCC (20-65% EtOAc/heptane) to give the title compound. MS ESI *m/z* 578.3 $(M+H)^+$.

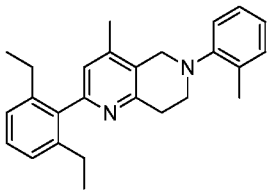
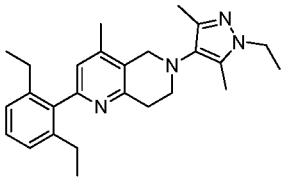
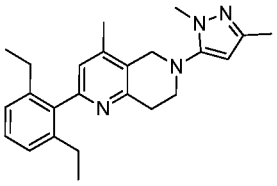
40-D. 6-(5-Isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine.

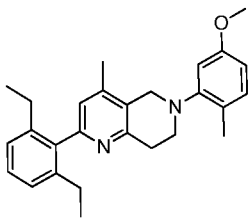
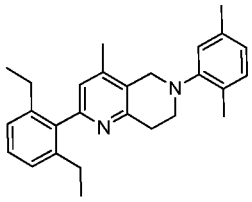
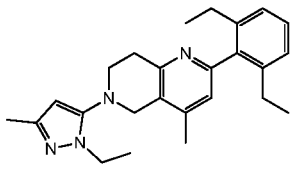
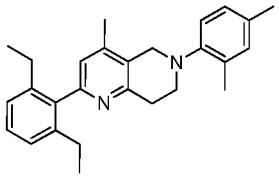


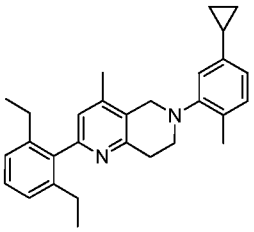
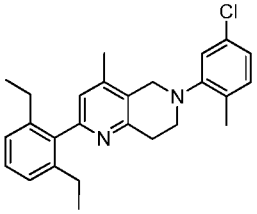
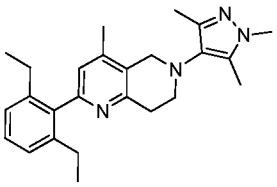
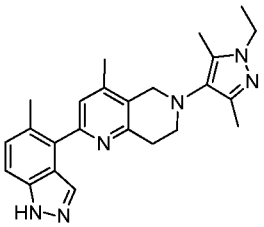
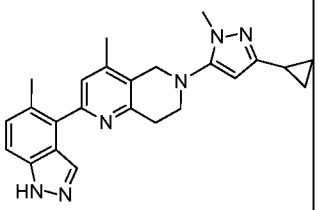
To a solution of 6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1-tosyl-1H-indol-4-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (0.156 g, 0.270 mmol) in THF (5 mL) at rt was added $LiAlH_4$ (5.40 mL, 1 M in THF). The reaction mixture was left to stir at rt until conversion was deemed complete as judged by LCMS. The reaction was quenched with water and then 1 M aq NaOH. The mixture was then extracted with DCM. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue

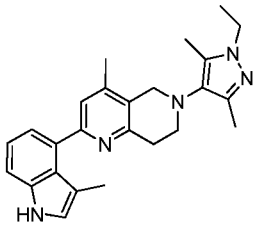
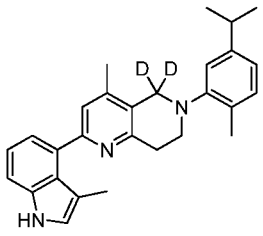
was then purified by FCC (10-60% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.88 (br. s., 1 H), 7.38 (d, *J*=8.1 Hz, 1 H), 7.21 (s, 1 H), 7.05 - 7.17 (m, 4 H), 6.96 (d, *J*=6.3 Hz, 1 H), 6.90 (d, *J*=8.8 Hz, 1 H), 4.10 (s, 2 H), 3.21 - 3.37 (m, 2 H), 3.01 - 3.09 (m, 2 H), 2.81 - 2.92 (m, 1 H), 2.30 (s, 3 H), 2.28 (s, 3 H), 1.89 (s, 3 H), 1.21 (d, *J*=7.1 Hz, 6 H); MS ESI *m/z* 410.4 $(M+H)^+$.

For the preparation of deuterated compounds $LiAlD_4$ was used in a similar method in place of $LiAlH_4$. The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data MS (ESI) *m/z* $(M+H)^+$
40-E		2-(2,6-diethylphenyl)-4-methyl-6-(o-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39 – 7.41 (m, 1 H), 7.25 – 7.29 (m, 3 H), 7.18 – 7.21 (m, 3 H), 7.09 – 7.13 (m, 1 H), 4.18 (s, 2 H), 3.56 (br t, *J* = 5.68 Hz, 2 H), 3.34 (br t, *J* = 5.68 Hz, 2 H), 2.52 – 2.41 (m, 5 H), 2.37 (s, 3 H), 2.18 – 2.28 (m, 2 H), 1.11 (t, *J* = 7.58 Hz, 6 H); MS (ESI+) *m/z* 371.17 $(M+H)^+$.
40-G		2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. 2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.31 (m, 1 H) 7.12 (d, *J*=7.58 Hz, 2 H) 6.96 (s, 1 H) 4.06 (s, 2 H) 3.93 (q, *J*=7.16 Hz, 2 H) 3.29 (obs , 2 H,) 2.93 (t, *J*=5.56 Hz, 2 H) 2.25 (q, *J*=7.41 Hz, 4 H) 2.19 (s, 6 H) 2.16 (s, 3 H) 1.26 (t, *J*=7.20 Hz, 3 H) 0.98 (t, *J*=7.45 Hz, 6 H); MS (ESI+) *m/z* 403.3 $(M+H)^+$.
40-H		2-(2,6-diethylphenyl)-6-(1,3-dimethyl-1H-pyrazol-5-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.12 (d, *J*=7.58 Hz, 2 H) 7.00 (s, 1 H) 5.81 (s, 1 H) 4.08 (s, 2 H) 3.63 (s, 3 H) 3.23 (t, *J*=5.81 Hz, 2 H) 3.03 (t, *J*=5.68 Hz, 2 H) 2.22 - 2.28 (m, 7 H) 2.10 (s, 3 H) 0.98 (t, *J*=7.45 Hz, 6 H); MS (ESI+) *m/z* 375.4 $(M+H)^+$.

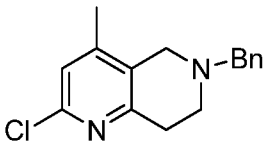
40-I		2-(2,6-diethylphenyl)-6-(5-methoxy-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.25 - 7.29 (m, 1 H) 7.13 (d, *J*=7.58 Hz, 3 H) 6.99 (s, 1 H) 6.80 (d, *J*=2.53 Hz, 1 H) 6.61 (dd, *J*=8.34, 2.53 Hz, 1 H) 4.09 (s, 2 H) 3.74 (s, 3 H) 3.23 (t, *J*=5.68 Hz, 2 H) 3.01 (t, *J*=5.56 Hz, 2 H) 2.22 - 2.30 (m, 10 H) 0.99 (t, *J*=7.58 Hz, 6 H); MS (ESI+) *m/z* 401.3 $(M+H)^+$.
40-J		2-(2,6-diethylphenyl)-6-(2,5-dimethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.25 - 7.30 (m, 1 H) 7.05 - 7.15 (m, 4 H) 6.99 (s, 1 H) 6.83 (d, *J*=7.58 Hz, 1 H) 4.09 (s, 2 H) 3.21 (t, *J*=5.68 Hz, 2 H) 3.02 (t, *J*=5.43 Hz, 2 H) 2.23 - 2.31 (m, 13 H) 0.99 (t, *J*=7.58 Hz, 6 H); MS (ESI+) *m/z* 385.4 $(M+H)^+$.
40-K		2-(2,6-diethylphenyl)-6-(1-ethyl-3-methyl-1H-pyrazol-5-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.12 (d, *J*=7.58 Hz, 2 H) 7.00 (s, 1 H) 5.83 (s, 1 H) 4.07 (s, 2 H) 3.96 (q, *J*=7.33 Hz, 2 H) 3.21 (t, *J*=5.68 Hz, 2 H) 3.02 (t, *J*=5.81 Hz, 2 H) 2.19 - 2.29 (m, 7 H) 2.12 (s, 3 H) 1.33 (t, *J*=7.20 Hz, 3 H) 0.98 (t, *J*=7.45 Hz, 6 H); MS (ESI+) *m/z* 389.4 $(M+H)^+$.
40-L		2-(2,6-diethylphenyl)-6-(2,4-dimethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.10 - 7.19 (m, 3 H) 6.97 - 7.07 (m, 3 H) 4.05 (s, 2 H) 3.19 (t, *J*=5.68 Hz, 2 H) 3.01 (t, *J*=5.56 Hz, 2 H) 2.22 - 2.31 (m, 13 H) 0.99 (t, *J*=7.58 Hz, 6 H); MS (ESI+) *m/z* 385.4 $(M+H)^+$.

40-M		6-(5-cyclopropyl-2-methylphenyl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.25 - 7.30 (m, 1 H) 7.07 - 7.16 (m, 3 H) 6.96 - 7.01 (m, 2 H) 6.69 (dd, *J*=7.71, 1.64 Hz, 1 H) 4.10 (s, 2 H) 3.23 (t, *J*=5.68 Hz, 2 H) 2.99 (t, *J*=5.56 Hz, 2 H) 2.22 - 2.31 (m, 10 H) 1.89 (tt, *J*=8.37, 5.02 Hz, 1 H) 0.99 (t, *J*=7.58 Hz, 6 H) 0.87 - 0.94 (m, 2 H) 0.60 - 0.66 (m, 2 H); MS (ESI+) *m/z* 411.4 $(M+H)^+$.
40-N		6-(5-chloro-2-methylphenyl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.23 - 7.30 (m, 3 H) 7.13 (d, *J*=7.58 Hz, 2 H) 7.07 (dd, *J*=8.08, 2.27 Hz, 1 H) 7.00 (s, 1 H) 4.14 (s, 2 H) 3.24 (t, *J*=5.81 Hz, 2 H) 3.03 (t, *J*=5.56 Hz, 2 H) 2.23 - 2.31 (m, 10 H) 0.99 (t, *J*=7.45 Hz, 6 H); MS (ESI+) *m/z* 405.2 $(M+H)^+$.
40-O		2-(2,6-diethylphenyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.29 (m, 1 H) 7.12 (d, *J*=7.58 Hz, 2 H) 6.96 (s, 1 H) 4.06 (s, 2 H) 3.60 (s, 3 H) 3.29 (s, 2 H) 2.93 (t, *J*=5.56 Hz, 2 H) 2.25 (q, *J*=7.58 Hz, 4 H) 2.19 (d, *J*=4.29 Hz, 6 H) 2.14 (s, 3 H) 0.98 (t, *J*=7.58 Hz, 6 H); MS (ESI+) *m/z* 389.4 $(M+H)^+$.
40-P		6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.97 (br. s., 1 H) 7.76 (s, 1 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.28 (d, *J*=8.59 Hz, 1 H) 7.23 (s, 1 H) 4.08 (s, 2 H) 3.94 (q, *J*=7.07 Hz, 2 H) 3.33 - 3.36 (m, 2 H) 3.02 (t, *J*=5.43 Hz, 2 H) 2.36 (s, 3 H) 2.24 (s, 3 H) 2.20 (s, 3 H) 2.18 (s, 3 H) 1.27 (t, *J*=7.20 Hz, 3 H); MS (ESI+) *m/z* 401.3 $(M+H)^+$.
40-Q		6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.99 (s, 1 H) 7.76 (s, 1 H) 7.47 (d, *J*=8.34 Hz, 1 H) 7.25 - 7.31 (m, 2 H) 5.76 (s, 1 H) 4.09 (s,

		2 H) 3.62 (s, 3 H) 3.25 (t, *J*=5.81 Hz, 2 H) 3.10 (t, *J*=5.56 Hz, 2 H) 2.36 (s, 3 H) 2.29 (s, 3 H) 1.74 - 1.83 (m, 1 H) 0.77 - 0.84 (m, 2 H) 0.59 - 0.65 (m, 2 H); MS (ESI+) *m/z* 399.3 $(M+H)^+$.
40-R		6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.88 (br. s., 1 H) 7.38 (d, *J*=8.08 Hz, 1 H) 7.18 (s, 1 H) 7.08 - 7.13 (m, 2 H) 6.92 - 6.96 (m, 1 H) 4.06 (s, 2 H) 3.93 (q, *J*=7.07 Hz, 2 H) 3.31 - 3.35 (m, 2 H) 2.98 (t, *J*=5.31 Hz, 2 H) 2.22 (s, 3 H) 2.19 (s, 3 H) 2.16 (s, 3 H) 1.89 (s, 3 H) 1.27 (t, *J*=7.33 Hz, 3 H); MS (ESI+) *m/z* 400.4 $(M+H)^+$.
40-S		^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.89 (br. s., 1 H), 7.38 (d, *J*=7.8 Hz, 1 H), 7.21 (s, 1 H), 7.12 (t, *J*=6.9 Hz, 2 H), 7.08 (s, 2 H), 6.96 (d, *J*=7.1 Hz, 1 H), 6.89 (d, *J*=7.6 Hz, 1 H), 3.26 (t, *J*=5.6 Hz, 2 H), 3.04 (t, *J*=5.4 Hz, 2 H), 2.86 (dt, *J*=13.8, 6.9 Hz, 1 H), 2.30 (s, 3 H), 2.27 (s, 3 H), 1.89 (s, 3 H), 1.21 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 412.3 $(M+H)^+$.

Example 41

41-A. 6-Benzyl-2-chloro-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine.

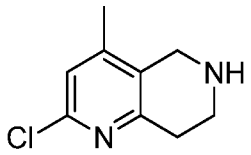


A mixture of 1-benzyl-4-piperidone (19.6 mL, 106 mmol), acetoacetamide (11.7 g, 116 mmol) in Eaton's reagent (40 mL) was allowed to stir at 110 °C. After stirring for 18 h, the reaction mixture was cooled to rt, and then slowly poured into stirred aq $NaHCO_3$ (150 g of NaHCO3 in 1000 mL of water. The mixture was diluted with DCM (1000 mL) and H_2O (50 mL), and the two phases were separated. The products were extracted once with DCM (500 mL) from the aqueous layer. The combined organic layer was washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The brown residue was triturated with acetone (200 mL). The precipitated solid was collected on a funnel, washed with acetone (100 mL), and dried under reduced pressure to give 6-benzyl-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ol. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.71 (br s, 1 H), 7.26 – 7.35 (m, 5

H), 6.22 (s, 1 H), 3.71 (s, 2 H), 3.34 (s, 2 H), 2.70 – 2.73 (m, 2 H), 2.77 – 2.79 (m, 2 H), 2.03 (s, 3 H); MS (ESI+) *m/z* 255.42 $(M+H)^+$.

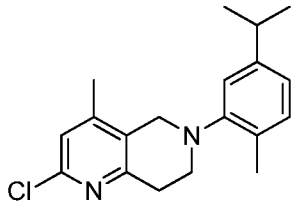
A solution of 6-benzyl-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ol (13.6 g, 53.5 mmol), benzyltriethylammonium chloride (24.4 g, 107 mmol) and $POCl_3$ (100 mL, 1069 mmol) was allowed to stir at 105 °C. After stirring for 18 h, the mixture was cooled to rt, and diluted with EtOAc (100 mL). The precipitate was collected on a funnel, washed with EtOAc (200 mL), and then dried under reduced pressure to give benzyl-2-chloro-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine as a dihydrochloride salt. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.02 (br s, 1 H), 7.71 – 7.73 9m, 2 H), 7.48 – 7.49 (m, 3 H), 7.34 (s, 1 H), 4.21 – 4.57 (m, 4 H), 3.60 – 3.62 (m, 1 H), 3.28 – 3.37 (m, 2 H), 3.02 – 3.05 (m, 1 H), 2.19 (s, 3 H); MS (ESI+) *m/z* 273.33 $(M+H)^+$.

41-B. 2-Chloro-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride.



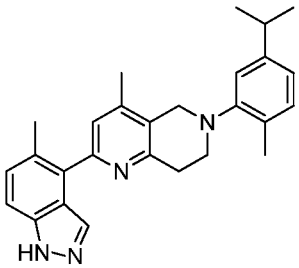
To a suspension of crude benzyl-2-chloro-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine dihydrochloride (8.00 g, 23.1 mmol) in DCM (100 mL), 2 M Na_2CO_3aq (50 mL) was added. The mixture was stirred for 20 min, and then diluted with brine. The products were extracted twice with DCM, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give crude (6.14 g). A solution of the residue and ACECl (5.05 mL, 46.3 mmol) in DCE (100 mL) was allowed to stir at 70 °C for 1.5 h under nitrogen. MeOH (50 mL) was added and the mixture was stirred at the same temperature for 1 h. The mixture was cooled to rt and concentrated. The residue was triturated with MeOH (10 mL) and EtOAc (400 mL), and the white solid was collected on a funnel, washed with EtOAc (200 mL), and dried under reduced pressure to give 2-chloro-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (4.54 g): ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (br s, 2 H), 7.33 (s, 1 H), 4.21 – 4.24 (app t, 2 H), 3.41 – 3.43 (m, 2 H), 3.05 (t, J = 6.57 Hz, 2 H), 2.24 (s, 3 H); MS (ESI+) *m/z* 183.44 $(M+H)^+$.

41-C. 2-Chloro-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine.



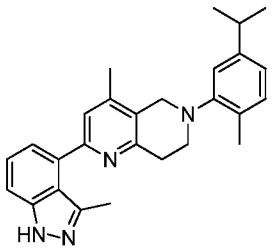
To a suspension of 2-chloro-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (4.03 g, 18.39 mmol) in DCM (100 mL), 2 M aq Na_2CO_3 (100 mL) was added. After stirring for 30 min, the mixture was diluted with brine (200 mL). The products were extracted twice with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. A suspension of the residue (3.25 g), 5-isopropyl-2-methylphenyl trifluoromethanesulfonate (11.42 g, 40.5 mmol), $Pd_2(dba)_3.CHCl_3$ adduct (0.762 g, 0.736 mmol), *rac*-BINAP (0.945 g, 1.471 mmol) and Cs_2CO_3 (17.98 g, 55.2 mmol) in toluene (17 mL) and *t*-butanol (3 mL) was allowed to stir at 90 °C for 23 h under argon. The reaction was cooled to rt, and diluted with EtOAc and brine. The products were extracted three times with EtOAc. The combined organic layer was dried over Na_2SO_4, and filtered. The filtrate was added to 60 g of silica gel and then concentrated. The residue was washed with EtOAc on a funnel, and then the filtrate was concentrated. The residue was purified by flash column chromatography on 330 g of silica gel (with 25 g pre-column; eluent: heptane/EtOAc = 100:0 to 80:20) to give the desired product along with 18 mol% of Carvacrol (2.97 g). The mixture was purified by flash column chromatography on 55 g of NH-modified silica gel (with 20 g of aminopropyl-modified silca gel as pre-column; eluent: heptane/EtOAc = 100:0 to 90:10) to give 2-chloro-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (2.50 g) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.16 (d, J = 7.83 Hz, 1 H), 6.99 – 7.00 (m, 2 H), 6.92 – 6.95 (m, 1 H), 3.98 (s, 2 H), 3.28 (t, J = 5.81 Hz, 2 H), 3.12 (br t, J = 5.68 Hz, 2 H), 2.84 – 2.94 (m, 1 H), 2.29 (s, 3 H), 2.20 (s, 3 H), 1.26 (d, J = 6.82 Hz, 6 H); MS (ESI+) *m/z* 315.34 $(M+H)^+$.

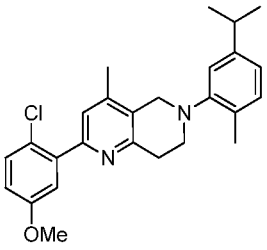
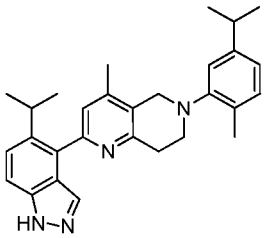
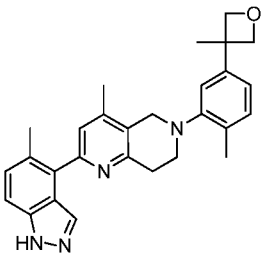
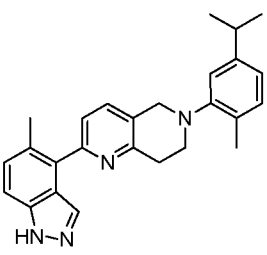
41-D. 6-(5-Isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine.

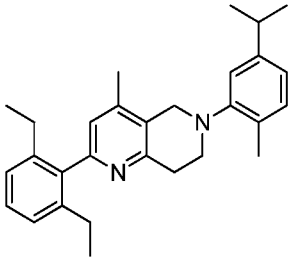
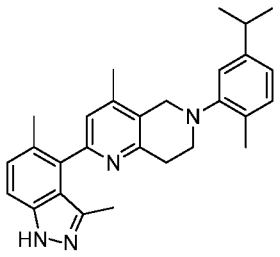


A mixture of 2-chloro-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (2.50 g, 7.94 mmol), 5-methyl-1H-indazol-4-ylboronic acid (1.817 g, 10.32 mmol), $Pd(PPh_3)_4$ (0.918 g, 0.794 mmol) and K_3PO_4 (3.37 g, 15.88 mmol) in 1,4-dioxane (30 mL) and H_2O (3 mL) was heated at 130 °C for 1 h under nitrogen in a microwave reactor. The mixture was concentrated and diluted with EtOAc and brine. The products were extracted twice with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified twice by flash column chromatography on 120 g of silica gel (with 25 g of silica gel pre-column; eluent: heptane/EtOAc = 75:25 to 30:70) to give a yellow solid. The yellow solid was suspended with 25 g of aminopropyl-modified silica gel in DCM, and the suspension was concentrated. The residue was loaded on 55 g of NH-silica gel and purified by flash column chromatography (eluent: heptane/EtOAc = 75:25 to 25:75) to give the desired product (2.50 g). The product was triturated in CH_3CN/H_2O, collected on a funnel and dried under reduced pressure to give 6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (2.23 g) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.03 (br s, 1 H), 7.90 (d, J = 0.67 Hz, 1 H), 7.40 (dd, J = 0.67, 8.50 Hz, 1 H), 7.32 (d, J = 8.50 Hz, 1 H), 7.19 (d, J = 7.75 Hz, 1 H), 7.16 (s, 1 H), 7.08 (d, J = 1.60 Hz, 1 H), 6.94 – 6.97 (dd, J = 1.60, 7.75 Hz, 1 H), 4.14 (s, 2 H), 3.38 (br t, J = 5.68 Hz, 2 H), 3.26 (br t, J = 5.69 Hz, 2 H), 2.87 – 2.98 (m, 1 H), 2.44 (s, 3 H), 2.37 (s, 3 H), 2.31 (s, 3 H), 1.29 (d, J = 6.82 Hz, 6 H); MS (ESI+) *m/z* 411.33 $(M+H)^+$.

The following compounds were prepared in a similar manner.

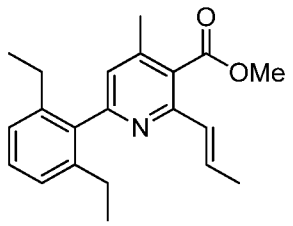
	Structure	Chemical Name & Analytical Data MS (ESI) *m/z* $(M+H)^+$
41-E		6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. TFA salt ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32 – 7.42 (m, 4 H), 7.22 (d, J = 7.83 Hz, 1 H), 7.06 (d, J = 1.77 Hz, 1 H), 7.00 – 7.02 (m, 1 H), 4.19 (s, 2 H), 3.66 (app t, 2 H), 3.41 (br t, J = 5.68 Hz, 2 H), 2.88 – 2.98 (m, 1 H), 2.49 (s, 3 H), 2.35 (s, 3 H), 2.22 (s, 3 H), 1.29 (d, J = 6.82 Hz, 6 H); MS (ESI+) *m/z* 411.26 $(M+H)^+$.

41-F		2-(2-chloro-5-methoxyphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35 (d, *J* = 8.84 Hz, 1 H), 7.28 (s, 1 H), 7.18 (d, *J* = 7.83 Hz, 1 H), 7.10 (d, *J* = 3.28 Hz, 1 H), 7.05 (d, *J* = 1.77 Hz, 1 H), 6.94 (dd, *J* = 1.77, 7.83 Hz, 1 H), 6.86 (dd, *J* = 3.28, 8.84 Hz, 1 H), 4.09 (s, 2 H), 3.83 (s, 3 H), 3.34 (br t, *J* = 5.68 Hz, 2 H), 3.24 (br t, *J* = 5.68 Hz, 2 H), 2.89 – 2.97 (m, 1 H), 2.34 (s, 3 H), 2.28 (s, 3 H), 1.28 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 421.30 $(M+H)^+$.
41-G		2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79 (s, 1 H), 7.45 – 7.50 (m, 2 H), 7.20 (d, *J* = 7.75 Hz, 1 H), 7.11 (s, 1 H), 7.08 (d, *J* = 1.60 Hz, 1 H), 6.96 (dd, *J* = 1.60, 7.75 Hz, 1 H), 4.15 (s, 2 H), 3.38 (br t, *J* = 5.68 Hz, 2 H), 3.18 – 3.26 (m, 3 H), 2.88 – 2.98 (m, 1 H), 2.38 (s, 3 H), 2.31 (s, 3 H), 1.29 (d, *J* = 6.82 Hz, 6 H), 1.26 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 439.3 $(M+H)^+$.
41-H		4-methyl-2-(5-methyl-1H-indazol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.01 (br s, 1 H), 7.78 (app t, 1 H), 7.47 (dd, *J* = 1.01, 8.51 Hz, 1 H), 7.29 (d, *J* = 8.51 Hz, 1 H), 7.27 (s, 1 H), 7.21 (d, *J* = 7.83 Hz, 1 H), 7.08 (d, *J* = 1.94 Hz, 1 H), 6.89 (dd, *J* = 1.94, 7.83 Hz, 1 H), 4.83 (d, *J* = 5.56 Hz, 2 H), 4.55 (d, *J* = 5.56 Hz, 2 H), 4.13 (s, 2 H), 3.30 (br t, *J* = 5.81 Hz, 2 H), 3.10 (br t, *J* = 5.56 Hz, 2 H), 2.37 (s, 3 H), 2.32 (s, 3 H), 2.31 (s, 3 H), 1.65 (s, 3 H); MS (ESI+) *m/z* 439.44 $(M+H)^+$.
41-I		6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.98 (br s, 1 H), 7.91 (d, *J* = 1.26 Hz, 1 H), 7.53 (d, *J* = 7.83 Hz, 1 H), 7.42 (dd, *J* = 1.01, 8.59 Hz, 1 H), 7.30 – 7.34 (m, 2 H), 7.18 (d, *J* = 7.66 Hz, 1 H), 7.03 (d, *J* = 1.94 Hz, 1 H), 6.94 (dd, *J* = 1.94, 7.66 Hz, 1 H), 4.24 (s, 2 H), 3.39 (br t, *J* = 5.94 Hz, 2 H), 3.27 (br t, *J* = 5.68 Hz, 2 H), 2.86 – 2.96 (m, 1 H),

		2.44 (s, 3 H), 2.37 (s, 3 H), 1.28 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 397.3 $(M+H)^+$.
41-J		2-(2,6-diethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.31 (m, 1 H) 7.10 - 7.16 (m, 3 H) 7.07 (d, *J*=1.52 Hz, 1 H) 7.00 (s, 1 H) 6.89 (dd, *J*=7.58, 1.52 Hz, 1 H) 4.11 (s, 2 H) 3.21 - 3.28 (m, 2 H) 2.99 (app t, *J*=5.56 Hz, 2 H) 2.86 (spt, *J*=6.86 Hz, 1 H) 2.27 (s, 6 H) 2.22 - 2.31 (obs m, 4 H) 1.20 (d, *J*=6.82 Hz, 6 H) 0.99 (t, *J*=7.45 Hz, 6 H) MS (ESI+) *m/z* 413.3 $(M+H)^+$.
41-K		2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.55 (br. s., 1 H) 7.38 (d, *J*=8.34 Hz, 1 H) 7.23 (d, *J*=8.34 Hz, 1 H) 7.08 - 7.17 (m, 3 H) 6.90 (d, *J*=7.83 Hz, 1 H) 4.14 (s, 2 H) 3.25 - 3.30 (m, 2 H) 3.00 - 3.07 (m, 2 H) 2.82 - 2.90 (m, 1 H) 2.31 (s, 3 H) 2.28 (s, 3 H) 2.16 (s, 3 H) 1.78 (s, 3 H) 1.21 (d, *J*=6.82 Hz, 6 H); MS (ESI+) *m/z* 426.4 $(M+H)^+$.

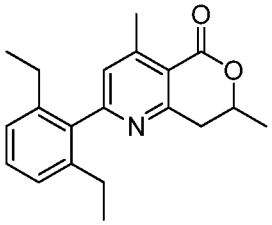
Example 42

42-A. (*E*)-Methyl 6-(2,6-diethylphenyl)-4-methyl-2-(prop-1-en-1-yl)nicotinate.



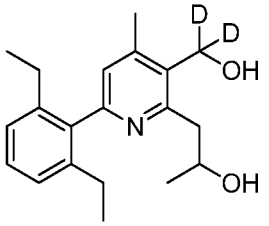
The title compound was prepared by similar method to that described in **Example 41** using (*E*)-prop-1-en-1-ylboronic acid. MS (ESI+) *m/z* 324.3 $(M+H)^+$.

42-B. 2-(2,6-Diethylphenyl)-4,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridin-5-one.



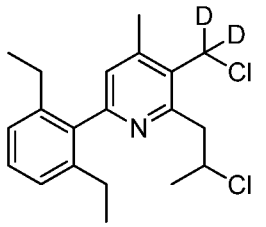
A mixture of (E)-methyl 6-(2,6-diethylphenyl)-4-methyl-2-(prop-1-enyl)nicotinate (150 mg, 0.464 mmol), H_2O (0.17 mL, 9.28 mmol) and TFA (2.9 mL, 37.1 mmol) was heated in a microwave reactor at 160 °C for 30 min. Starting materal was observed. Additional TFA (0.5 mL) and H_2O (0.05mL) were added and heating continued at 160°C for 45 min and then at 140°C for 2 h. The reaction was then poured into sat $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and then dried over Na_2SO_4 and concentrated. The residue was then purified with FCC (0-50% EtOAc/heptane) to provide 2-(2,6-diethylphenyl)-4,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridin-5-one. MS (ESI+) *m/z* 310.3 $(M+H)^+$.

42-C. 1-(6-(2,6-Diethylphenyl)-3-(hydroxy($^2H_2$)methyl)-4-methylpyridin-2-yl)propan-2-ol.



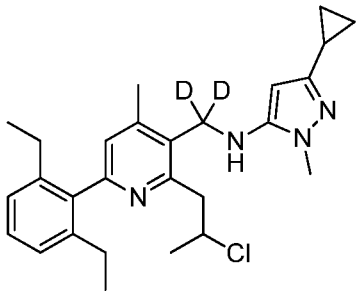
A mixture of 2-(2,6-diethylphenyl)-4,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridin-5-one (118 mg, 0.381 mmol), sodium borodeuteride (63.9 mg, 1.53 mmol) in THF/EtOH (2:1) (6 mL) was heated to 60 °C for 3 h. The reaction was diluted with EtOAc and filtered. The filtrate was concentrated and purified with FCC (5-60% EtOAc/heptane) to provide 1-(6-(2,6-diethylphenyl)-3-(hydroxyl($^2H_2$)methyl)-4-methylpyridin-2-yl)propan-2-ol. MS (ESI+) *m/z* 316.4 $(M+H)^+$.

42- D. 3-(Chloro($^2H_2$)methyl)-2-(2-chloropropyl)-6-(2,6-diethylphenyl)-4-methylpyridine.



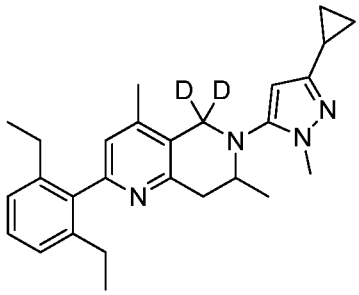
A mixture of 1-(6-(2,6-diethylphenyl)-3-(hydroxy($^2H_2$)methyl)-4-methylpyridin-2-yl)propan-2-ol (99 mg, 0.314 mmol) and $SOCl_2$ (0.14 mL, 1.88 mmol) in DCM (5 mL) was stirred at rt for 3 h. The reaction was poured into sat aq $NaHCO_3$ carefully and diluted with EtOAc. The layers were mixed and then separated. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The residue, following concentration, provided crude 3-(chloro($^2H_2$)methyl)-2-(2-chloropropyl)-6-(2,6-diethylphenyl)-4-methylpyridine. MS (ESI+) *m/z* 352.2 $(M+H)^+$.

42-E. N-((2-(2-Chloropropyl)-6-(2,6-diethylphenyl)-4-methylpyridin-3-yl)($^2H_2$)methyl)-3-cyclopropyl-1-methyl-1H-pyrazol-5-amine.



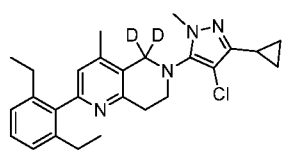
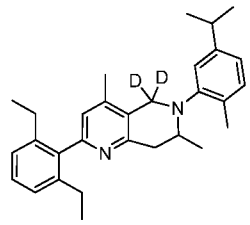
A mixture of 3-(chloro($^2H_2$)methyl)-2-(2-chloropropyl)-6-(2,6-diethylphenyl)-4-methylpyridine (29.6 mg, 0.084 mmol), 3-cyclopropyl-1-methyl-1H-pyrazol-5-amine (57.6 mg, 0.420 mmol), NaI (37.8 mg, 0.252 mmol) and DIEA (0.044 mL, 0.252 mmol) in THF (3 mL) was stirred at rt for 1 h. Then the reaction mixture was heated to 60 °C for 4 h. The reaction was then diluted with EtOAc, washed with sat aq $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC (5-100% EtOAc/heptane followed by 0-10% MeOH/DCM) to provide N-((2-(2-chloropropyl)-6-(2,6-diethylphenyl)-4-methylpyridin-3-yl)($^2H_2$)methyl)-3-cyclopropyl-1-methyl-1H-pyrazol-5-amine. MS (ESI+) *m/z* 453.3 $(M+H)^+$.

42-F. 6-(3-Cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-diethylphenyl)-4,7-dimethyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine.



To a solution of N-((2-(2-chloropropyl)-6-(2,6-diethylphenyl)-4-methylpyridin-3-yl)($^2H_2$)methyl)-3-cyclopropyl-1-methyl-1H-pyrazol-5-amine (14.2 mg, 0.031 mmol) in acetonitrile (2 mL), DIEA (0.016 mL, 0.094 mmol) was added followed by NaI (9.4 mg, 0.063 mmol). The mixture was heated in a microwave reactor at 160 °C for 30 min. At that point the reaction was diluted with EtOAc and washed with sat aq $NaHCO_3$ and then brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated. The residue was then purified with FCC (5-50% EtOAc/heptane) to provide *racemic* 6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-diethylphenyl)-4,7-dimethyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.23 - 7.32 (m, 1 H) 7.13 (d, *J*=7.58 Hz, 2 H) 6.91 (s, 1 H) 5.67 (s, 1 H) 3.68 (s, 3 H) 3.41 - 3.53 (m, 1 H) 3.15 - 3.29 (m, 1 H) 2.87 (dd, *J*=17.05, 6.44 Hz, 1 H) 2.33 (q, *J*=7.49 Hz, 4 H) 2.22 (s, 3 H) 1.84 (tt, *J*=8.46, 5.05 Hz, 1 H) 1.01 - 1.08 (m, 9 H) 0.82 - 0.89 (m, 2 H) 0.63 - 0.69 (m, 2 H). MS (ESI+) *m/z* 417.4 $(M+H)^+$. Two enantimers were obtained by chiral separation (OD 4.6 X 250 mm column, 5% EtOH in heptane). **42-G enanatiomer 1:** R_t 9.26 min, MS (ESI+) *m/z* 417.3 $(M+H)^+$; **42-H enanatiomer 1:** R_t 12.62 min, MS (ESI+) *m/z* 417.3 $(M+H)^+$.

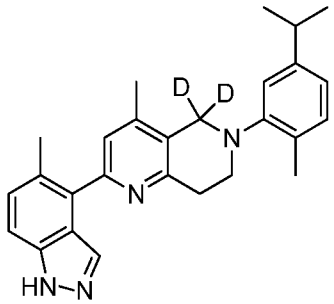
The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data
42-I		6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.45 (t, *J*=7.71 Hz, 1 H) 7.37 (s, 1 H) 7.23 (d, *J*=7.83 Hz, 2 H) 3.67 (s, 3 H) 3.53 - 3.60 (m, 2 H) 3.48 (t, *J*=5.56 Hz, 2 H) 2.37 - 2.50 (m, 5 H) 2.18 - 2.31 (m, 2 H) 1.79 - 1.91 (m, *J*=8.15, 8.15, 5.43, 5.31 Hz, 1 H) 1.10 (t, *J*=7.45 Hz, 6 H) 0.84 - 0.93 (m, 4 H). MS (ESI+) *m/z* 437.3 $(M+H)^+$.
42-J		**43-J** *racemic* -2-(2,6-diethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4,7-dimethyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.09 - 7.17 (m, 4 H) 6.99 (s, 1 H) 6.91 (dd, *J*=7.71, 1.64 Hz, 1 H) 3.53 - 3.60 (m, 1 H) 3.13 (dd, *J*=16.93, 4.80 Hz, 1 H) 2.85 (dt, *J*=13.71, 6.92 Hz, 1 H) 2.67 - 2.75 (m, 1 H) 2.22 - 2.32 (m, 10 H) 1.16 - 1.23 (m, 6 H) 0.93 - 1.03 (m, 9 H); MS (ESI+) *m/z* 429.4 $(M+H)^+$. **43-K** ent-1 R_t 5.38 min, (OD 4.6 X 250 mm column, 5% EtOH in heptane). MS (ESI+) *m/z* 429.4 $(M+H)^+$

		43-L ent-2 R_t 6.50 min, OD 4.6 X 250 mm column, 5% EtOH in heptane). MS (ESI+) *m/z* 429.4 (M+H)

Example 43

43-A. . 6-(5-Isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine.



A solution of 2-Chloro-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (3.10 g, 12.7 mmol), Boc_2O (3.06 g, 14.0 mmol) and DIPEA (3.34 mL, 19.1 mmol) in DCM (30 mL) was allowed to stir at rt for 45 min. The mixture was diluted with 5% aqueous citric acid and DCM. The organic layer was separated in a separatory funnel, and concentrated. The residue was purified by flash column chromatography on 80 g of silica gel (with 25g silica gel pre-column; eluent: heptane/EtOAc = 100:0 to 50:50) to give *tert*-butyl 2-chloro-4-methyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.02 (s, 1 H), 4.47 (s, 2 H), 3.71 (t, *J* = 5.81 Hz, 2 H), 2.95 (br t, *J* = 5.68 Hz, 2 H), 2.23 (s, 3 H), 1.50 (s, 9 H); MS (ESI+) *m/z* 283.30 $(M+H)^+$.

To a suspension of ruthenium trichloride (0.141 g, 0.681 mmol) and NaIO4 (8.32 g, 38.9 mmol) in H_2O (30 mL) at 0 °C, a solution of *tert*-butyl 2-chloro-4-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (2.75 g, 9.73 mmol) in EtOAc (30 mL) was added. After stirring for 5 min., the reaction mixture was warmed up to rt and stirred. After stirring for 21.5 h, the mixture was diluted with EtOAc and brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. The crude was purified by flash column chromatography on 80 g of silica gel (with 25g pre-column of silica gel; eluent: heptane/EtOAc = 100:0 to 70:30) to give *tert*-butyl 2-chloro-4-methyl-5-oxo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (2.10 g) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.15 (s, 1 H), 3.98 (t, *J* = 6.32 Hz, 2 H), 3.13 (t, *J* = 6.32 Hz, 2 H), 2.70 (s, 3 H), 1.58 (s, 9 H).

A solution of *tert*-butyl 2-chloro-4-methyl-5-oxo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (2.08 g, 7.01 mmol) and borane-d_3-THF complex solution (21.0 mL, 21.0 mmol) was allowed to stir at 60 °C for 17 h under nitrogen. The reaction mixture was cooled to rt, and quenched with MeOH (2 mL). The

mixture was diluted with saturated aqueous NH_4Cl, brine and EtOAc. The products were extracted twice with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give *tert*-butyl 2-chloro-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine-6-carboxylate along with an impurity as colorless oil (94% deuterium incorporation). The obtained material was used without further purification: MS (ESI+) *m/z* 285.30 $(M+H)^+$.

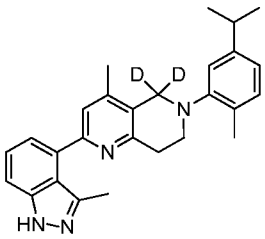
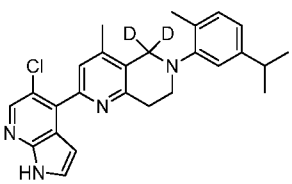
To a solution of give *tert*-butyl 2-chloro-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine-6-carboxylate (1.59 g, 5.58 mmol) in EtOAc (8 mL), 4 M HCl in 1,4-dioxane (6.98 mL, 27.9 mmol) was added and a white solid precipitated. After stirring for 1 h, additional 4 M HCl in 1,4-dioxane (6.98 mL, 27.9 mmol) was added. After stirring for further 1 h, MeOH (10 mL) was added to the reaction mixture, followed by the addition of EtOAc (400 mL). The precipitated solid was collected on a funnel, washed with EtOAc (100 mL), and dried under reduced pressure to give the desired product as a hydrochloride salt (1.29 g). The solid was neutralized with 2 M Na_2CO_3aq (10 mL) in DCM (10 mL). The mixture was allowed to stir for 1 h. The mixture was diluted with brine and DCM. The organic layer was separated and concentrated to give 2-chloro-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine (93%D): ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.96 (s, 1 H), 3.17 (t, *J* = 5.94 Hz, 2 H), 2.91 (t, *J* = 5.94 Hz, 2 H), 2.17 (s, 3 H).

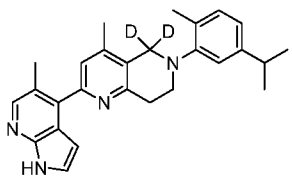
A suspension of 2-chloro-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine (0.92 g, 4.98 mmol), 5-isopropyl-2-methylphenyl trifluoromethanesulfonate (4.22 g, 14.95 mmol), $Pd_2(dba)_3.CHCl_3$ adduct (0.206 g, 0.199 mmol), *rac*-BINAP (0.248 g, 0.399 mmol) and Cs_2CO_3 (4.87 g, 14.95 mmol) in toluene (4 mL) and *tert*-Butanol (0.7 mL) was allowed to stir at 90 °C for 17 h under nitrogen. The reaction mixture was cooled to rt and diluted with EtOAc and brine. The products were extracted three times with EtOAc. The organic layer was dried over Na_2SO_4, and filtered. The residue was purified by flash column chromatography on 80 g of silica gel (with 15 g pre-column of silica gel; eluent: heptane/EtOAc = 100:0 to 80:20), followed by flash column chromatography on 20 g of NH-modified silica gel (with 15 g pre-column of NH-modified silica gel; eluent: heptane/EtOAc = 100:0 to 90:10) to give 2-chloro-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine (94%D) as a pale orange solid: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.16 (d, *J* = 7.83 Hz, 1 H), 6.99 – 7.00 (m, 2 H), 6.92 – 6.95 (m, 1 H), 3.28 (t, *J* = 5.81 Hz, 2 H), 3.12 (t, *J* = 5.81 Hz, 2 H), 2.84 – 2.94 (m, 1 H), 2.29 (s, 3 H), 2.20 (s, 3 H), 1.26 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 317.40 $(M+H)^+$.

A mixture of 2-chloro-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine (120 mg, 0.379 mmol), 5-methyl-1*H*-indazol-4-ylboronic acid (87 mg, 0.492 mmol), $Pd(PPh_3)_4$ (43.8 mg, 0.038 mmol) and K_3PO_4 (161 mg, 0.757 mmol) in 1,4-dioxane (1.3 mL) and H_2O (0.13 mL) at 130 °C for 1 h under nitrogen in a microwave reactor. The mixture was concentrated and diluted with EtOAc and brine. The products were extracted twice with EtOAc, and the combined organic

layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified twice by flash column chromatography on 12 g of silica gel (eluent: heptane/EtOAc = 75:25 to 30:70), followed by flash column chromatography on 12 g of NH-modified silica gel (eluent: heptane/EtOAc = 75:25 to 25:75) to give 6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.06 (br s, 1 H), 7.90 (d, *J* = 1.01 Hz, 1 H), 7.37 – 7.40 (m, 1 H), 7.31 (d, *J* = 8.59 Hz, 1H), 7.19 (d, *J* = 7.66 Hz, 1H), 7.16 (s, 1 H), 7.07 (d, *J* = 1.85 Hz, 1 H), 6.95 (dd, *J* = 1.85, 7.66 Hz, 1 H), 3.37 (br t, *J* = 5.81 Hz, 2 H), 3.26 (br t, *J* = 5.81 Hz, 2 H), 2.87 – 2.97 (m, 1 H), 2.44 (s, 3 H), 2.37 (s, 3 H), 2.31 (s, 3 H), 1.28 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 413.27 $(M+H)^+$.

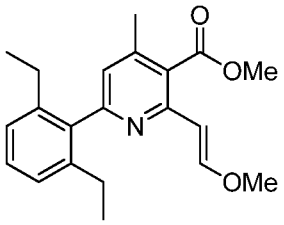
The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data MS (ESI) *m/z* $(M+H)^+$
43-B		6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.78 (br s, 1 H), 7.51 (d, *J* = 7.83 Hz, 1 H), 7.35 – 7.39 (m, 1 H), 7.34 (s, 1 H), 7.10 – 7.15 (m, 2 H), 7.09 (d, *J* = 1.94 Hz, 1 H), 6.90 (dd, *J* = 1.94, 7.58 Hz, 1 H), 3.27 (br t, *J* = 5.68 Hz, 2 H), 3.07 (br t, *J* = 5.68 Hz, 2 H), 2.82 – 2.92 (m, 1 H), 2.32 (s, 3 H), 2.27 (s, 3 H), 2.23 (s, 3 H), 1.21 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 413.4 $(M+H)^+$.
43-C		2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.95 (br s, 1 H), 8.32 (s, 1 H), 7.55 (d, *J* = 3.54 Hz, 1 H), 7.35 (s, 1 H), 7.14 (d, *J* = 7.66 Hz, 1H), 7.10 (d, *J* = 1.60 Hz, 1H), 6.89 (dd, *J* = 1.60, 7.66 Hz, 1 H), 6.30 (d, *J* = 3.54 Hz, 1H), 3.27 (br t, *J* = 5.68 Hz, 2 H), 3.09 (br t, *J* = 5.68 Hz, 2 H), 2.83 – 2.93 (m, 1 H), 2.32 (s, 3 H), 2.28 (s, 3 H), 1.22 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 433.13 $(M+H)^+$.

43-D		6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.55 (br s, 1 H), 8.15 (s, 1 H), 7.40 – 7.41 (m, 1 H), 7.27 (m, 1 H), 7.14 (d, *J* = 7.83 Hz, 1 H), 7.10 – 7.10 (m, 1 H), 6.89 – 6.91 (m, 1 H), 6.22 – 6.23 (m, 1 H), 3.27 (br t, J = 5.81 Hz, 2 H), 3.08 (br t, *J* = 5.68 Hz, 2 H), 2.84 – 2.91 (m, 1 H), 2.33 (s, 3 H), 2.32 (s, 3 H), 2.28 (s, 3 H), 1.22 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z* 413.3 $(M+H)^+$.

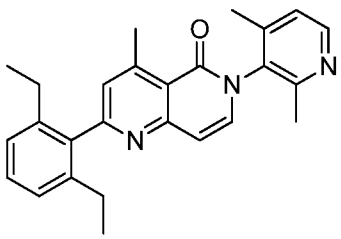
Example 44

44-A. (E)-Methyl 6-(2,6-diethylphenyl)-2-(2-methoxyvinyl)-4-methylnicotinate.



The title compound was prepared with in a similar manner to that described in **Example 41.** MS (ESI+) *m/z* 354.4 $(M+H)^+$.

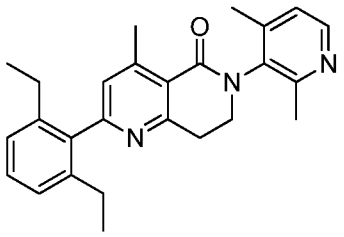
44-B. 2-(2,6-Diethylphenyl)-6-(2,4-dimethylpyridin-3-yl)-4-methyl-1,6-naphthyridin-5(6H)-one.



To a solution of (*E*)-methyl 6-(2,6-diethylphenyl)-2-(2-methoxyvinyl)-4-methylnicotinate (82 mg, 0.23 mmol) in toluene (2.8 mL) and acetic acid (1.9 mL) was added 2,4-dimethylpyridin-3-amine (425 mg, 3.48 mmol). Reaction was heated at 115 °C for 6 h. The mixture was concentrated under reduce pressure. The residue was purified via FCC (40-80% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.43 (d, *J*=4.8 Hz, 1 H), 7.58 (d, *J*=7.6 Hz, 1 H), 7.31 - 7.36 (m, 3 H), 7.19 (d,

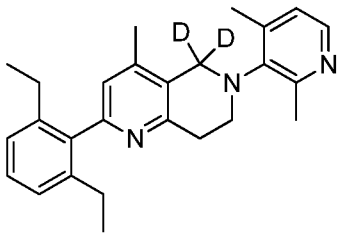
J=7.6 Hz, 2 H), 6.78 (d, *J*=7.6 Hz, 1 H), 2.84 (s, 3 H), 2.24 - 2.35 (m, 7 H), 2.11 (s, 3 H), 1.02 (t, *J*=7.6 Hz, 6 H); MS (ESI+) *m/z* 398.3 $(M+H)^+$.

44-C. 2-(2,6-Diethylphenyl)-6-(2,4-dimethylpyridin-3-yl)-4-methyl-7,8-dihydro-1,6-naphthyridin-5(6H)-one.



To a solution of 2-(2,6-diethylphenyl)-6-(2,4-dimethylpyridin-3-yl)-4-methyl-1,6-naphthyridin-5(6H)-one (44 mg, 0.11 mmol) and ammonium formate (70 mg, 1.1 mmol) was added Pd/C (118 mg, 5%). Reaction was sealed and was heated at 80 °C for 2 h. Reaction was filtered. The residue was purified via FCC (40-80% EtOAc/heptane) to give the title compound. MS (ESI+) *m/z* 400.4 $(M+H)^+$.

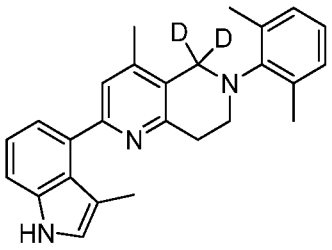
44-D. 2-(2,6-Diethylphenyl)-6-(2,4-dimethylpyridin-3-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine.



To 2-(2,6-diethylphenyl)-6-(2,4-dimethylpyridin-3-yl)-4-methyl-7,8-dihydro-1,6-naphthyridin-5(6H)-one (32 mg, 0.08 mmol) was added a 1M solution of lithium aluminum deuteride (1.60 mL). After 16 h, solution was cooled down to 0 °C and sodium sulfate hydrate was added slowly. The mixture was filtered and concentrated under reduced pressure. The residue was purified via FCC (0-70% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.13 (d, 1 H), 7.24 - 7.30 (m, 1 H), 7.13 (d, *J*=7.6 Hz, 2 H), 7.06 - 7.11 (m, 1 H), 6.96 - 7.01 (m, 1 H), 3.41 (t, *J*=5.6 Hz, 2 H), 2.99 (t, *J*=5.4 Hz, 2 H), 2.34 (s, 3 H), 2.27 (q, *J*=7.6 Hz, 4 H), 2.21 (s, 3 H), 1.00 (t, 6 H); MS (ESI+) *m/z* 388.3 $(M+H)^+$.

The following compounds were prepared in a similar manner.

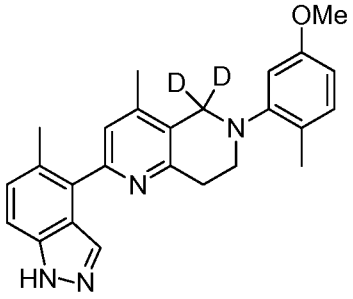
44-B. 6-(2,6-dimethylphenyl)-4-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-(5,5-$^2H_2$)tetrahydro-1,6-naphthyridine.



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.88 (br. s., 1 H), 7.38 (dd, *J*=7.9, 0.9 Hz, 1 H), 7.20 (s, 1 H), 7.12 (s, 1 H), 7.10 (d, *J*=8.1 Hz, 1 H), 7.03 - 7.08 (m, 2 H), 6.99 - 7.03 (m, 1 H), 6.94 - 6.99 (m, 1 H), 3.44 (t, *J*=5.6 Hz, 2 H), 3.02 (t, *J*=5.4 Hz, 2 H), 2.31 (s, 6 H), 2.23 (s, 3 H), 1.90 (s, 3 H); MS (ESI+) *m/z* 384.3 $(M+H)^+$.

Example 45

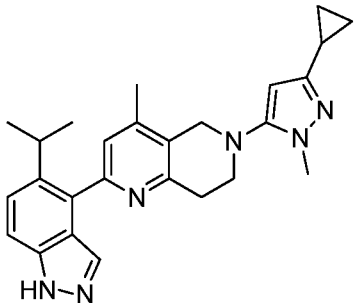
6-(5-Methoxy-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine.



To a solution of 6-(5-methoxy-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (48 mg, 0.085 mmol), prepared as in **Example 40,** in THF (170 µL) was added a 1M solution of lithium aluminum deuteride (424 µL). After 2.5 h, solution was cooled down to 0°C and sodium sulfate hydrate was added slowly. The mixture was filtered and concentrated under reduce pressure. The residue was purified via FCC (50-80% EtOAc/heptane) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.99 (s, 1 H), 7.77 (s, 1 H), 7.47 (d, *J*=8.6 Hz, 1 H), 7.20 - 7.35 (m, 2 H), 7.14 (d, *J*=8.3 Hz, 1 H), 6.80 (d, *J*=2.5 Hz, 1 H), 6.62 (dd, *J*=8.2, 2.7 Hz, 1 H), 3.75 (s, 3 H), 3.21 - 3.29 (m, 2 H), 3.09 (t, *J*=5.8 Hz, 2 H), 2.37 (s, 3 H), 2.32 (s, 3 H), 2.25 (s, 3 H); MS (ESI+) *m/z* 401.3 $(M+H)^+$.

Example 46

46-A. 6-(3-Cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine.



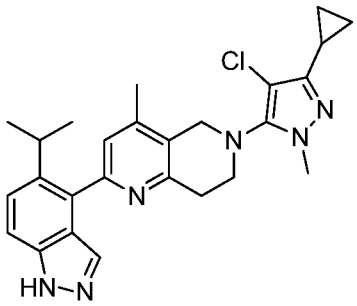
Microwave was used to irradiated a suspension of 2-chloro-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (1.00 g, 4.56 mmol), methyl 3-cyclopropyl-3-oxopropanoate (1.298 g, 9.13 mmol), 4-pyrrolidinopyridine (0.068 g, 0.456 mmol) and DIPEA (1.20 mL, 6.85 mmol) in toluene (10 mL) at 150 °C for 45 min. The mixture was cooled to rt and diluted with 1 M HClaq (10 mL) and EtOAc. The products were extracted twice with EtOAc. The combined organic layer was washed with a mixed solution of 1M HClaq/brine (1mL/2 mL), dried over Na_2SO_4, filtered, and concentrated to give crude. The residue was purified by flash column chromatography on 12 g of silica gel (eluent: DCM/EtOAc = 90:10 to 0:100) to give crude 1-(2-chloro-4-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-3-cyclopropylpropane-1,3-dione (0.70 g): MS (ESI+) *m/z* 293.31 $(M+H)^+$. The obtained material was used without futher purification.

Microwave was used to irradiated a solution of crude give crude 1-(2-chloro-4-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-3-cyclopropylpropane-1,3-dione (0.70 g), pyridine (1.5 mL, 19.1 mmol), Lawesson's reagent (1.064 g, 2.63 mmol) and methyl hydrazine (0.151 mL, 2.87 mmol) in THF (9 mL) at 120 °C for 20 min. The mixture was diluted with EtOAc and brine. The organic layer was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on 80 g of silica gel (eluent: heptane/EtOAc = 80:20 to 0:100) to give 2-chloro-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (110 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.02 (s, 1 H), 5.56 (s, 1 H), 3.96 (s, 2 H), 3.69 (s, 3 H), 3.08 – 3.23 (m, 4 H), 2.19 (s, 3 H), 1.83 – 1.90 (m, 1 H), 0.86 – 0.91 (m, 2 H), 0.68 – 0.72 (m, 2 H); MS (ESI+) *m/z* 303.28 $(M+H)^+$.

Microwave was used to irradiated a solution of 2-chloro-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (30 mg, 0.099 mmol), crude 5-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (38.2 mg, 0.119 mmol), $Pd(PPh_3)_4$ (11.45 mg, 9.91 μmol) and K_3PO_4 (42.1 mg, 0.198 mmol) in 1,4-dioxane (0.5 mL) and H_2O (0.05 mL) at 130 °C for 1 h under nitrogen. Additional $Pd(PPh_3)_4$ (22.90 mg, 0.020 mmol) was added to the mixture. Microwave was irradiated to the mixture at 130 °C for further 2 h under nitrogen. The mixture was diluted with brine and

EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated.The residue was purified by flash column chromatography on 12 g of silica gel (eluent: DCM/MeOH = 100:0 to 10:1) to give 6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.98 (br s, 1 H), 7.76 (d, *J* = 0.76 Hz, 1 H), 7.45 – 7.51 (m, 2 H), 7.12 (s, 1 H), 5.65 (s, 1 H), 4.11 (s, 2 H), 3.75 (s, 3 H), 3.30 – 3.33 (app t, 2 H), 3.15 – 3.24 (m, 3 H), 2.30 (s, 3 H), 1.87 – 1.94 (m, 1 H), 1.25 (d, *J* = 7.07 Hz, 6 H), 0.89 – 0.94 (m, 2 H), 0.72 – 0.76 (m, 2 H); MS (ESI+) *m/z* 427.33 $(M+H)^+$.

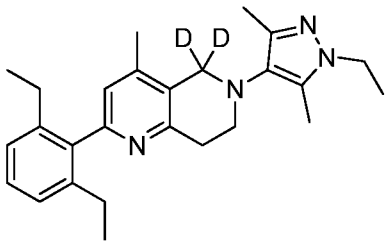
46-B. 6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine.



To a solution of 6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (20 mg, 0.047 mmol) in THF (0.5 mL), NCS (6.26 mg, 0.047 mmol) was added at rt. After stirring for 2.5 h, the reaction mixture was diluted with H_2O and DCM. The organic layer was separated and concentrated. The residue was purified by flash column chromatography on 12 g of NH-modified silica gel (eluent: DCM/MeOH = 100:0 to 10:1) to give the desired product along with a small amount of pinacol (10 mg). The crude was purified by HPLC (C18, H_2O (0.1%NH_4OH)/CH_3CN) to give 6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (2.6 mg) as a pink solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.02 (br s, 1 H), 7.77 (s, 1 H), 7.46 – 7.51 (m, 2 H), 7.13 (s, 1 H), 4.36 (s, 2 H), 3.72 (s, 3 H), 3.58 (t, *J* = 5.81 Hz, 2 H), 3.16 – 3.23 (m, 3 H), 2.28 (s, 3 H), 1.85 – 1.92 (m, 1 H), 1.26 (d, *J* = 6.82 Hz, 6 H), 0.93 (s, 2 H), 0.90 – 0.92 (m, 2 H); MS (ESI+) *m/z* 461.14 $(M+H)^+$.

Example 47

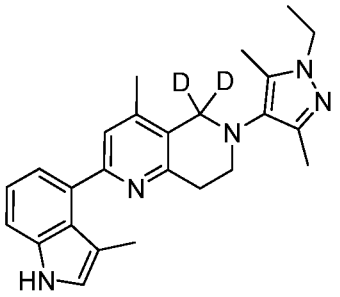
47-A. 2-(2,6-Diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine.



A mixture of 2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-7,8-dihydro-1,6-naphthyridin-5(6H)-one (88 mg, 0.211 mmol), prepared with similar method to that described in **Example 41**, and 1M lithium aluminun deuteride (2.11 mL, 2.11 mmol) was stirred at rt for 1 h. The reaction was then quenched with $Na_2SO_4 \cdot 10H_2O$ and then diluted with THF and filtered. The filtrate was concentrated and the resulting residue was purified by HLPC (XB C18 15-85% acetonitrile in H_2O with 0.1% NH_4OH) to provide 2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.12 (d, *J*=7.83 Hz, 2 H) 6.96 (s, 1 H) 3.93 (q, *J*=7.07 Hz, 2 H) 3.29 (d, *J*=5.56 Hz, 2 H) 2.93 (t, *J*=5.56 Hz, 2 H) 2.25 (q, *J*=7.49 Hz, 4 H) 2.17 (d, *J*=13.89 Hz, 9 H) 1.26 (t, *J*=7.20 Hz, 3 H) 0.98 (t, *J*=7.58 Hz, 6 H). MS (ESI+) *m/z* 405.3 $(M+H)^+$.

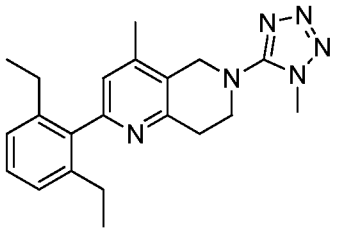
The following compounds were prepared in a similar manner.

47-B. 6-(1-Ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine.



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.88 (br. s., 1 H) 7.38 (d, *J*=7.33 Hz, 1 H) 7.18 (s, 1 H) 7.07 - 7.14 (m, 2 H) 6.94 (d, *J*=6.32 Hz, 1 H) 3.93 (q, *J*=7.33 Hz, 2 H) 3.33 (br. s., 1 H) 3.28 (s, 1 H) 2.98 (t, *J*=5.68 Hz, 2 H) 2.12 - 2.25 (m, 9 H) 1.89 (s, 3 H) 1.27 (t, *J*=7.20 Hz, 3 H); MS (ESI+) *m/z* 402.3 $(M+H)^+$.

Example 48 2-(2,6-Diethylphenyl)-4-methyl-6-(1-methyl-1H-tetrazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine.



A solution of methyl 6-(2,6-diethylphenyl)-4-methyl-2-vinylnicotinate (0.50 g, 1.62 mmol) and ammonium acetate (1.25 g, 16.2 mmol) in AcOH (9 mL) was allowed to stir at 120 °C in a sealed tube. After stirring for 14 h, the reaction mixture was cooled to rt, and concentrated. The residue was partitioned between DCM and aq 2 M Na_2CO_3, and extracted with DCM. The separated organic layer was concentrated. The residue was purified by flash column chromatography on 40 g of silica gel (eluent: DCM/EtOAc = 80:20 to 0:100) to give 2-(2,6-diethylphenyl)-4-methyl-7,8-dihydro-1,6-naphthyridin-5(6*H*)-one. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 (t, *J* = 7.75 Hz, 1 H), 7.14 (d, *J* = 7.75 Hz, 1 H), 7.06 (s, 1 H), 6.01 (br s, 1 H), 3.58 – 3.62 (m, 2 H), 3.20 (t, *J* = 6.57 Hz, 2 H), 2.76 (s, 3 H), 2.31 – 2.37 (m, 4 H), 1.06 (t, *J* = 7.58 Hz, 2 H); MS (ESI+) *m/z* 295.32 $(M+H)^+$.

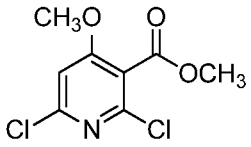
In a flask where 2-(2,6-diethylphenyl)-4-methyl-7,8-dihydro-1,6-naphthyridin-5(6H)-one (299 mg, 1.016 mmol) was placed, LAH in THF (5.0 mL, 5.08 mmol) was added. After stirring for 45 min, additional LAH in THF (5.0 mL, 5.08 mmol) was added. After stirring for further 2.5 h, the reaction mixture was diluted with H_2O and then with aq 1 M NaOH. The products were extracted with DCM. The separated organic solution was concentrated to give crude. The crude was dissolved in 1.25 M HCl/MeOH (3 mL), and stirred for 5 min. The solution was concentrated to give crude as yellow oil. The crude was dissolved in isopropyl acetate, and concentrated to give the desired product as its hydrochloride salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 -7.27 (m, 1 H), 7.13 (d, *J* = 7.83 Hz, 1 H), 6.96 (s, 1 H), 4.27 (s, 2 H), 3.50 (br t, *J* = 6.06 Hz 2 H), 3.25 (br t, *J* = 6.06 Hz, 2 H), 2.30 – 2.35 (m, 4 H), 2.27 (s, 3 H), 1.05 (t, *J* = 7.58 Hz, 2 H); MS (ESI+) *m/z* 281.35 $(M+H)^+$.

To a solution of 2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine dihydrochloride (21.7 mg, 0.061 mmol) in THF (0.5 mL), 1.6 M *n*-BuLi in hexanes (0.119 mL, 0.190 mmol) was added at –78 °C under nitrogen. After stirring for 10 min. at the same temperature, 1-methyl-5-(methylsulfonyl)-1*H*-tetrazole (24.90 mg, 0.154 mmol) was added. The mixture was warmed up to rt and stirred for 19 h. The mixture was diluted with brine and EtOAc. The products were extracted with EtOAc, and the organic layer was concentrated. The crude was purified by RP-HPLC (X-Bridge Phenyl®, H_2O (0.1%NH_4OH)/CH_3CN), then the fractions including the desired product were lyophilized to give the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 – 7.30 (m, 2 H), 7.14 (d, *J* = 7.58 Hz, 1 H), 6.98

(s, 1 H), 4.58 (s, 2 H), 4.01 (s, 3 H), 3.68 (t, J = 5.94 Hz, 2 H), 3.25 (br t, J = 5.94 Hz, 2 H), 2.30 – 2.37 (m, 7 H), 1.06 (t, J = 7.58 Hz, 6 H); MS (ESI+) *m/z* 363.27 $(M+H)^+$.

Example 49

49-A. Methyl 2,6-dichloro-4-methoxynicotinate.

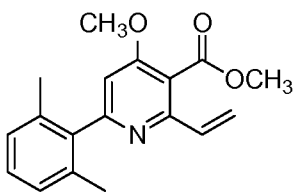


To a solution of methyl 2,4,6-trichloronicotinate [(5.04 g, 20.96 mmol), prepared as described in WO2010/31589] in methanol (52 mL) was added the sodium methoxide (25 wt % in methanol, 5.04 mL, 22.0 mmol) at room temperature. The cloudy white mixture was stirred for 17 h, then partitioned between EtOAc and water. The layers were separated and the aqueous layer was further extracted with EtOAc (2x). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by FCC (0-20% EtOAc:heptane) to provide methyl 2,6-dichloro-4-methoxynicotinate. MS (ESI+) *m/z* 236.1 $(M+H)^+$.

Methyl 2,6-dichloro-4-methoxynicotinate was also prepared using the alternative method described below:

A 1.0 M solution of TMPMgCl·LiCl in THF and toluene [(15.6 mL, 15.6 mmol) was added to 2,6-dichloro-4-methoxypyridine (2.32 g, 13.0 mmol), prepared as described in WO2007/21710] and the clear orange-brown reaction mixture stirred at room temperature. After 20 min, the resulting Grignard solution was added dropwise to a solution of methyl chloroformate (3.08 mL, 39.1 mmol) in toluene (52 mL). After stirring for 15 min, the reaction mixture was partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, then dried over sodium sulfate, filtered, and concentrated. The residue was purified by FCC (0-25% EtOAc:heptanes) to provide methyl 2,6-dichloro-4-methoxynicotinate.

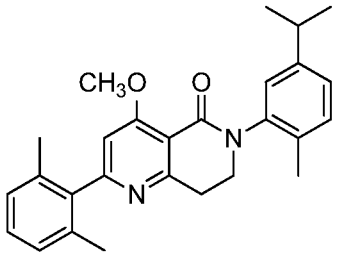
49-B. Methyl 6-(2,6-dimethylphenyl)-4-methoxy-2-vinylnicotinate.



A mixture of methyl 2,6-dichloro-4-methoxynicotinate (2.3 g, 9.74 mmol), 2,6-dimethylphenylboronic acid (1.75 g, 11.7 mmol), $Pd(PPh_3)_4$ (1.13 g, 0.974 mmol), and 2.0 M aqueous sodium carbonate solution (14.6 mL, 29.2 mmol) in DMF (97 mL) was degassed by evacuation and backfilling with nitrogen (5 cycles). The reaction mixture was then heated to 110 °C and stirred at that temperature. After 16.5 h, 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (4.17 mL, 24.36 mmol) was added to the reaction mixture, followed by $Pd(PPh_3)_4$ (500 mg, 0.417 mmol) and 2.0 M aqueous sodium carbonate solution (7 mL, 13.98 mmol). The resulting mixture was further stirred at 110 °C.

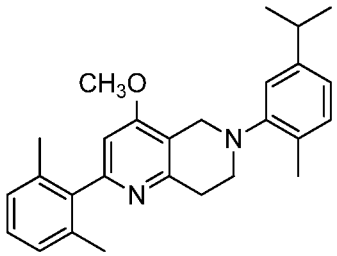
After 4.5 h, the reaction mixture was hot filtered, rinsing with EtOAc, and the filtrate was concentrated on the rotovap to remove a portion of the DMF. The residual concentrate was partitioned between EtOAc and water with brine. The aqueous layer was extracted with EtOAc (2x), and the combined organic layers were washed with brine (3x), then dried over sodium sulfate, filtered, and concentrated. The residue was purified by FCC (0-25% EtOAc/heptane) to provide methyl 6-(2,6-dimethylphenyl)-4-methoxy-2-vinylnicotinate. MS (ESI+) *m/z* 298.2 $(M+H)^+$.

49-C. 2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-7,8-dihydro-1,6-naphthyridin-5(6H)-one.



A solution of 6-(2,6-dimethylphenyl)-4-methoxy-2-vinylnicotinate (1.77 g, 5.95 mmol) and 5-isopropyl-2-methylaniline (4.44 g, 29.8 mmol) in toluene (26.5 mL) and acetic acid (13.2 mL) was heated to 110 °C and stirred at that temperature. After 12 h, the reaction mixture was removed from the heat and concentrated on the rotovap to remove the bulk of the solvent. The residue was partitioned between EtOAc and aqueous 1 N sodium hydroxide solution with added brine. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, then dried over sodium sulfate, filtered, and concentrated. The residue was purified by FCC (0-15% EtOAc/DCM) to provide 2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-7,8-dihydro-1,6-naphthyridin-5(6H)-one. The product contained some 5-isopropyl-2-methylaniline and was used in the next step without further purification. MS (ESI+) *m/z* 415.2 $(M+H)^+$.

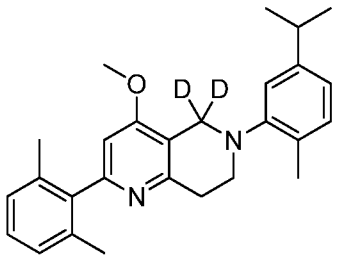
49-D. 2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy 5,6,7,8-tetrahydro-1,6-naphthyridine.



A 1.0 M solution of lithium aluminum hydride in THF (405 μL, 0.405 mmol) was added to a vessel containing 2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-7,8-dihydro-1,6-naphthyridin-5(6H)-one (42 mg, 0.101 mmol). The reaction mixture, which bubbled and turned clear orange, was stirred at room temperature. After 1 h, the reaction mixture was diluted with 1 mL of THF and cooled to 0 °C with an ice bath. 150 μL of a 9:1 THF/H_2O mixture was added dropwise, followed by the slow addition of 100 μL of 1 N aqueous NaOH. After stirring for 5 min, the ice bath was removed and 100 μL of H_2O and 1 mL of THF were added in sequence. The mixture was stirred for 10 min, then 150 mg of magnesium sulfate were added and the flask was stirred and shaken gently. The mixture was then filtered over Celite® and the filter cake washed with EtOAc. The filtrate was concentrated and the residue purified by FCC (0-20% EtOAc/heptane) to provide 2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.19 (dd, *J*=8.4, 6.8 Hz, 1 H) 7.09 - 7.14 (m, 3 H) 7.03 (d, *J*=1.5 Hz, 1 H) 6.89 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.81 (s, 1 H) 4.00 - 4.03 (m, 2 H) 3.86 (s, 3 H) 3.22 (t, *J*=5.7 Hz, 2 H) 2.97 (t, *J*=5.6 Hz, 2 H) 2.86 (spt, *J*=6.8 Hz, 1 H) 2.25 (s, 3 H) 2.03 (s, 6 H) 1.19 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 401.3 $(M+H)^+$.

The following compounds were prepared in a similar manner.

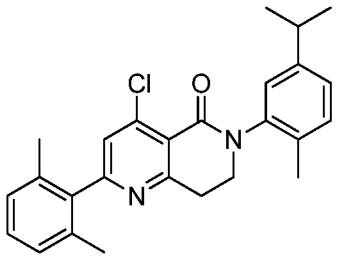
49-E. 2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy 5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine.



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.16 - 7.22 (m, 1 H) 7.08 - 7.14 (m, 3 H) 7.02 (d, *J*=1.8 Hz, 1 H) 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.81 (s, 1 H) 3.86 (s, 3 H) 3.21 (t, *J*=5.7 Hz, 2 H) 2.96 (t, *J*=5.7 Hz, 2 H)

2.85 (spt, *J*=6.9 Hz, 1 H) 2.24 (s, 3 H) 2.03 (s, 6 H) 1.19 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 403.3 $(M+H)^+$.

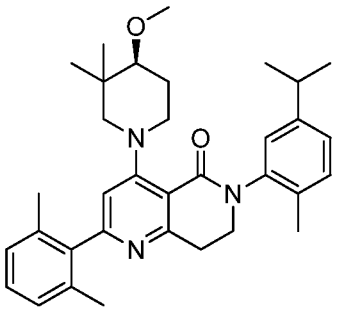
Example 50 50-A. 4-Chloro-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one.



To a solution of 2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-7,8-dihydro-1,6-naphthyridin-5(6H)-one (1.49 g, 3.59 mmol) in dioxane (23.96 mL) was added potassium trimethylsilanolate (2.306 g, 17.97 mmol) as a solid in one portion. The 75-mL pressure vessel was sealed and the reaction mixture heated to 140 °C for 3 h. The reaction mixture was allowed to cool to room temperature before opening the vessel. The reaction mixture was then poured into water and DCM and the aqueous pH adjusted to pH 7 with 1 N HCl. The aqueous layers was further extracted with DCM (2x) and the combined organic layers washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude 2-(2,6-dimethylphenyl)-4-hydroxy-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one was used directly in the next step without further purification.

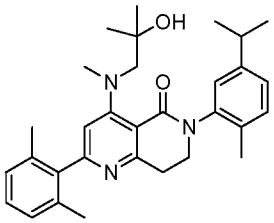
To a solution of crude 2-(2,6-dimethylphenyl)-4-hydroxy-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (1.4 g, 3.50 mmol) in DCM (35.0 mL) was added Vilsmeier's reagent (0.895 g, 6.99 mmol) as a solid in one portion and the reaction mixture stirred at room temperature. After 2 h 500 mg of Vilsmeier's reagent was added and stirring continued. After 35 min an additional portion of 200 mg of Vilsmeier's reagent was added and stirring continued. After 15 min the reaction mixture was diluted with DCM and poured into saturated aqueous sodium bicarbonate solution containing 1 N NaOH. The layers were separated and the aqueous layer was extracted with DCM (2x). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by FCC (0-20% EtOAc/heptane) to provide 4-chloro-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one. MS (ESI+) *m/z* 419.2 $(M+H)^+$.

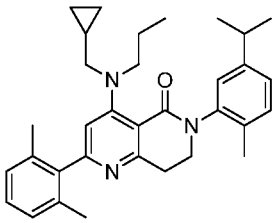
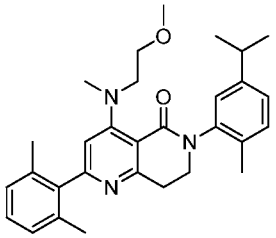
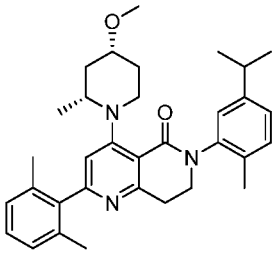
50-B. (*S*)-2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one.



A 10-mL reaction flask containing an orange solution of 4-chloro-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (100 mg, 0.239 mmol), (*S*)-4-methoxy-3,3-dimethylpiperidine HCl salt (129 mg, 0.716 mmol), and DIEA (208 µL, 1.193 mmol) in DMA (1.2 mL) was placed in a sand bath preheated to 110 °C and stirred at that temperature. After 4 h the reaction mixture was allowed to cool to room temperature, then diluted with DCM and poured into mixture of saturated aqueous sodium bicarbonate solution and brine. The aqueous layer was extracted with DCM (3x), and the combined organic layers were washed with brine, then dried over sodium sulfate, filtered, and concentrated. The residue was purified by FCC (0-100% EtOAc/heptane) to provide (*S*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.07 - 7.25 (m, 6 H) 6.73 (s, 1 H) 3.80 - 3.96 (m, 1 H) 3.63 - 3.79 (m, 1 H) 3.27 (s, 3 H) 3.09 - 3.24 (m, 2 H) 2.93 - 3.07 (m, 3 H) 2.79 - 2.92 (m, 2 H) 2.18 - 2.22 (m, 3 H) 2.06 (s, 6 H) 1.79 - 1.94 (m, 1 H) 1.48 - 1.65 (m, 1 H) 1.21 (d, *J*=6.8 Hz, 6 H) 1.14 - 1.19 (m, 1 H) 0.90 (s, 3 H) 0.83 (s, 1 H)* 0.78 (s, 2 H)*; MS (ESI+) *m/z* 526.3 $(M+H)^+$. (*indicates one methyl group appearing as two peaks due to restricted rotation).

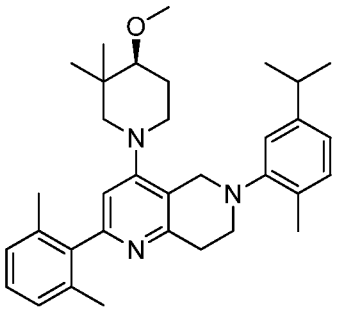
The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data
50-C		2-(2,6-dimethylphenyl)-4-((2-hydroxy-2-methylpropyl)(methyl)amino)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.05 - 7.26 (m, 6 H) 6.91 (s, 1 H) 4.32 (s, 1 H) 3.86 - 4.00 (m, 1 H) 3.63 - 3.75 (m, 2 H) 3.17 - 3.29 (m, 2 H) 3.03 (s, 3 H) 2.94 - 3.02 (m, 1 H) 2.88 (quin, *J*=6.9 Hz, 1 H) 2.19 (s, 3 H) 2.04 (s, 6 H) 1.21 (d, *J*=6.8 Hz, 6 H) 1.04 (s, 6 H); MS (ESI+) *m/z* 486.3 $(M+H)^+$.

50-D		4-((cyclopropylmethyl)(propyl)amino)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one. 1H NMR (400 MHz, DMSO-d_6) δ ppm 7.06 - 7.26 (m, 6 H) 6.68 (s, 1 H) 3.82 - 3.93 (m, 1 H) 3.63 - 3.73 (m, 1 H) 3.35 - 3.51 (m, 2 H) 3.07 - 3.31 (m, 3 H) 2.93 - 3.04 (m, 1 H) 2.87 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.20 (s, 3 H) 2.06 (s, 6 H) 1.49 - 1.59 (m, 2 H) 1.21 (d, *J*=6.8 Hz, 6 H) 1.01 - 1.08 (m, 1 H) 0.82 (t, *J*=7.3 Hz, 3 H) 0.43 - 0.50 (m, 2 H) 0.10 - 0.16 (m, 2 H); MS (ESI+) *m/z* 496.3 $(M+H)^+$.
50-E		2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2-methoxyethyl)(methyl)amino)-7,8-dihydro-1,6-naphthyridin-5(6H)-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.07 - 7.24 (m, 6 H) 6.67 (s, 1 H) 3.83 - 3.93 (m, 1 H) 3.67 - 3.77 (m, 1 H) 3.53 - 3.56 (m, 2 H) 3.47 - 3.53 (m, 2 H) 3.23 (dd, *J*=9.5, 4.2 Hz, 1 H) 3.20 (s, 3 H) 2.95 - 3.05 (m, 1 H) 2.93 (s, 3 H) 2.87 (dt, *J*=13.9, 6.9 Hz, 1 H) 2.18 (s, 3 H) 2.06 (s, 6 H) 1.20 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 472.3 $(M+H)^+$.
50-F		2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.08 - 7.24 (m, 6 H) 6.69 (s, 0.5 H)* 6.64 (s, 0.5 H)* 3.87 - 3.99 (m, 2 H) 3.65 - 3.85 (m, 1 H) 3.52 (qd, 1 H) 3.35 - 3.44 (m, 1 H) 3.24 (d, *J*=1.8 Hz, 3 H) 3.11 - 3.22 (m, 1 H) 2.94 - 3.10 (m, 1 H) 2.88 (quin, *J*=6.9 Hz, 1 H) 2.18 (d, *J*=4.3 Hz, 3 H) 2.06 (s, 6 H) 1.65 - 1.96 (m, 4 H) 1.25 (d, *J*=6.8 Hz, 2 H)* 1.21 (d, *J*=7.1 Hz, 6 H) 1.18 (d, *J*=6.8 Hz, 1 H)*, * indicates additional peaks due to restricted rotation; MS (ESI+) *m/z* 512.3 $(M+H)^+$.

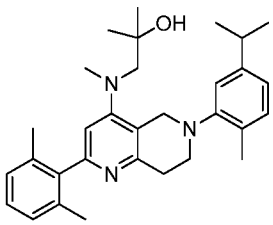
Example 51

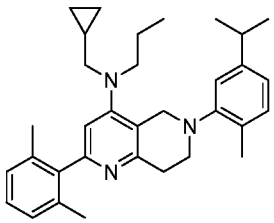
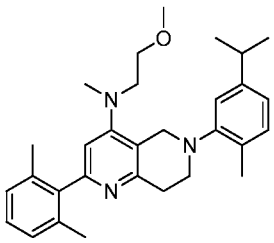
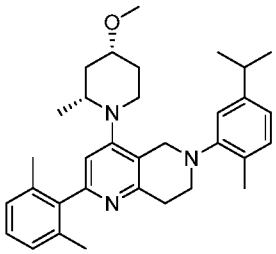
51-A. (*S*)-2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine.



A 1.0 M solution of lithium aluminum hydride in THF (23.0 mL, 3.00 mmol) was added to a vessel containing (*S*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (63 mg, 0.120 mmol). The reaction flask was then capped and the pink reaction mixture was heated to 55 °C and stirred at that temperature. After 1.5 h the oil bath was removed, the reaction mixture was diluted with 6 mL of THF, and the reaction flask cooled to 0 °C. Then 0.9 mL of a 9:1 THF/H_2O mixture was added dropwise, followed by 3 mL of THF, and 0.3 mL of 2 N NaOH was slowly added. After stirring for 5 min, the ice bath was removed and 600 µL of H_2O and 6 mL of THF were added. The mixture was stirred for 10 min, then 900 mg of magnesium sulfate were added and the mixture further stirred. The mixture was then filtered over Celite® and the filter cake washed with EtOAc. The filtrate was concentrated and the residue was purified by FCC (0-50% EtOAc/heptanes) to provide (*S*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.19 (m, 1 H) 7.06 - 7.12 (m, 3 H) 6.94 (d, *J*=1.5 Hz, 1 H) 6.83 (dd, *J*=7.8, 1.5 Hz, 1 H) 6.68 (s, 1 H) 4.10 - 4.22 (m, 2 H) 3.28 (s, 3 H) 3.07 - 3.18 (m, 1 H) 2.73 - 3.04 (m, 6 H) 2.23 (s, 3 H) 2.00 (s, 6 H) 1.91 - 2.03 (m, 2 H) 1.58 (d, *J*=9.3 Hz, 1 H) 1.20 - 1.28 (m, 1 H) 1.16 (d, *J*=6.8 Hz, 6 H) 1.01 (d, *J*=10.4 Hz, 6 H); MS (ESI+) *m/z* 512.4 $(M+H)^+$.

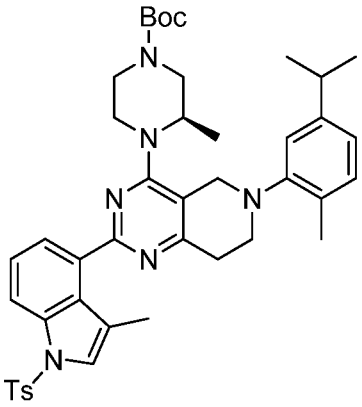
The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data MS (ESI) *m/z* $(M+H)^+$
51-B		1-((2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)(methyl)amino)-2-methylpropan-2-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.13 - 7.19 (m, 1 H) 7.06 - 7.12 (m, 3 H) 6.92 (d, *J*=1.5 Hz, 1 H) 6.86 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.75 (s, 1 H) 4.37 (s, 1 H) 4.05 - 4.10 (m, 2 H) 3.11 (s, 2 H) 2.91 (s, 3 H) 2.89 - 2.96 (m, 2 H) 2.80 (dt, *J*=13.6, 6.8 Hz, 0 H) 2.23 (s, 3 H) 2.01 (s, 6 H) 1.16 (d, *J*=6.8 Hz,

		6 H) 1.06 (s, 6 H); MS (ESI+) *m/z* 472.3 $(M+H)^+$.
51-C		N-(cyclopropylmethyl)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-N-propyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.22 (m, 1 H) 7.07 - 7.12 (m, 3 H) 6.90 (d, *J*=1.5 Hz, 1 H) 6.85 (dd, *J*=7.6, 1.5 Hz, 1 H) 6.79 (s, 1 H) 4.03 - 4.09 (m, 2 H) 3.14 (t, *J*=7.1 Hz, 2 H) 2.89 - 2.98 (m, 4 H) 2.80 (dt, *J*=13.8, 6.9 Hz, 1 H) 2.23 (s, 3 H) 2.01 (s, 6 H) 1.45 (m, 2 H) 1.15 (d, *J*=6.8 Hz, 6 H) 0.87 - 0.94 (m, 1 H) 0.83 (t, *J*=7.3 Hz, 3 H) 0.35 - 0.42 (m, 2 H) 0.04 - 0.10 (m, 2 H); MS (ESI+) *m/z* 482.3 $(M+H)^+$.
51-D		2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-N-(2-methoxyethyl)-N-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.13 - 7.19 (m, 1 H) 7.06 - 7.12 (m, 3 H) 6.95 (d, *J*=1.5 Hz, 1 H) 6.85 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.68 (s, 1 H) 4.04 - 4.08 (m, 2 H) 3.52 (t, *J*=5.6 Hz, 2 H) 3.29 (t, *J*=6.2 Hz, 2 H) 3.20 (s, 3 H) 3.19 - 3.24 (m, 2 H) 2.96 (t, *J*=5.9 Hz, 2 H) 2.75 - 2.88 (m, 4 H) 2.23 (s, 3 H) 2.02 (s, 6 H) 1.18 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 458.3 $(M+H)^+$.
51-E		2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.15 - 7.21 (m, 1 H) 7.08 - 7.13 (m, 3 H) 6.90 - 6.94 (m, 2 H) 6.86 (dd, *J*=7.7, 1.6 Hz, 1 H) 4.23 (d, *J*=15.7 Hz, 1 H) 4.02 (d, *J*=15.7 Hz, 1 H) 3.34 - 3.42 (m, 1 H) 3.26 - 3.30 (m, 2 H) 3.25 (s, 3 H) 3.15 - 3.22 (m, 1 H) 2.89 - 3.09 (m, 3 H) 2.82 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.24 (s, 3 H) 2.00 (s, 6 H) 1.97 - 2.11 (m, 2 H) 1.34 - 1.44 (m, 1 H) 1.19 - 1.25 (m, 1 H) 1.17 (d, *J*=6.8, Hz, 3 H)* 1.15 (d, *J*=6.8, Hz, 3 H)* 0.91 (d, 3 H), * indicates additional peaks due to restricted rotation; MS (ESI+) *m/z* 498.4 $(M+H)^+$.

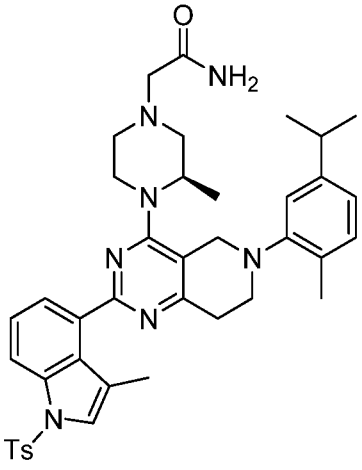
Example 52

52-A. (*R*)-*tert*-Butyl 4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate



A mixture of 4-chloro-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (**Example 17-E**) (0.274 g, 0.468 mmol), (*R*)-*tert*-butyl 3-methylpiperazine-1-carboxylate (0.375 g, 1.87 mmol) and DIEA (0.33 mL, 1.87 mmol) in N,N-dimethylacetamide (3 mL) was heated at 125 °C for 15 h. Reaction mixture was diluted with EtOAc, washed with sat aq $NaHCO_3$ and brine. The organic layer was then dried over Na_2SO_4, concentrated, purified via FCC (0-40% EtOAc/heptane) to provide the title compound . MS (ESI+) *m/z* 749.4 $(M+H)^+$.

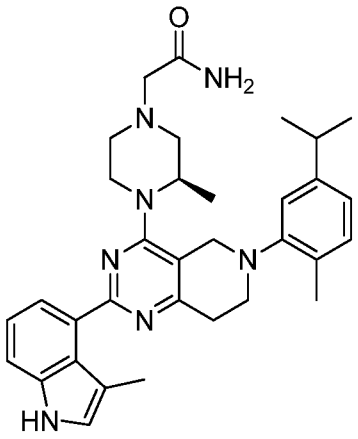
52-B. (*R*)-2-(4-(6-(5-Isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide



A solution of (*R*)-*tert*-butyl 4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazine-1-carboxylate (0.143 g, 0.191 mmol), TFA (2 mL) and DCM (3 mL) was stirred at rt for 30 min before being concentrated. To the resulting residue in DCM (3 mL) were added DIEA (0.133 mL, 0.764 mmol), 2-bromoacetamide (0.040 g, 0.287 mmol) and sodium iodide (0.043 g, 0.287 mmol). The mixture was stirred at rt for 20 h and then diluted

with EtOAc. The mixture was washed with sat aq $NaHCO_3$ and then brine. The organic layer was then dried over Na_2SO_4. After concentration, the residue was purified via FCC (60-90% EtOAc/heptane) to provide the title compound. MS (ESI+) *m/z* 706.4 $(M+H)^+$.

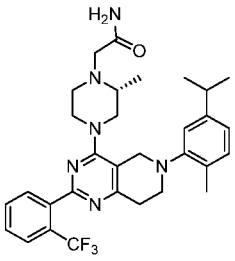
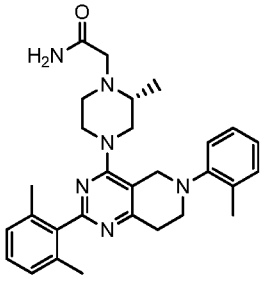
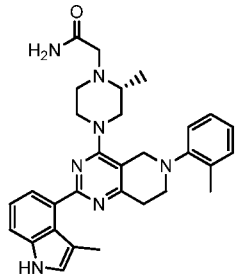
52-C. (*R*)-2-(4-(6-(5-Isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide.

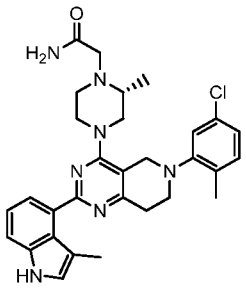
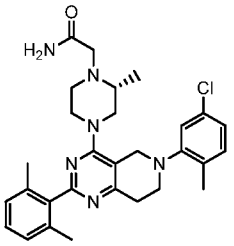
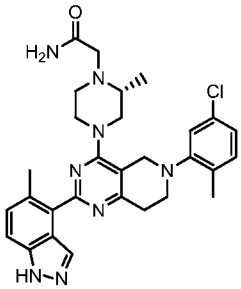


A mixture of (*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide (0.075 mg, 0.106 mmol), 30% ammonium hydroxide (0.63 mL 15.94 mmol) and potassium hydroxide (0.054 g, 0.956 mmol) in ethanol (3 mL) was heated in a microwave reactor at 100 °C for 1 h. The reaction mixture was concentrated and then filtered before being purified via HPLC (RP C18, 15-85% CH_3CN in H_2O with 0.1% NH_4OH to provide the title compound. ^1H NMR (400 MHz, CD_3CN) δ ppm 9.16 (br. s., 1 H) 7.45 (d, *J*=8.08 Hz, 1 H) 7.25 (dd, *J*=7.20, 1.14 Hz, 1 H) 7.15 (dd, *J*=15.28, 7.71 Hz, 2 H) 7.01 - 7.09 (m, 2 H) 6.82 - 6.94 (m, 2 H) 5.80 (br. s., 1 H) 3.94 - 4.13 (m, 3 H) 3.51 - 3.60 (m, 1 H) 3.41 - 3.50 (m, 1 H) 3.28 - 3.41 (m, 2 H) 2.95 - 3.12 (m, 2 H) 2.82 - 2.95 (m, 3 H) 2.78 (d, *J*=10.86 Hz, 1 H) 2.57 - 2.66 (m, 1 H) 2.47 - 2.56 (m, 1 H) 2.37 (td, *J*=10.74, 3.03 Hz, 1 H) 2.26 (s, 3 H) 2.05 (s, 3 H) 1.30 (d, *J*=6.82 Hz, 3 H) 1.23 (dd, *J*=6.82, 1.01 Hz, 6 H); MS (ESI+) *m/z* 552.4 $(M+H)^+$.

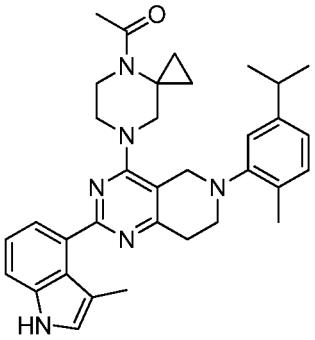
The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data MS (ESI) *m/z* $(M+H)^+$

52-D		(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.75 - 7.80 (m, 2 H) 7.65 (t, *J*=7.45 Hz, 1 H) 7.56 (t, *J*=7.71 Hz, 1 H) 7.14 (d, *J*=7.58 Hz, 1 H) 7.06 (br. s., 1 H) 6.96 (d, *J*=1.52 Hz, 1 H) 6.91 (dd, *J*=7.71, 1.64 Hz, 1 H) 3.92 - 4.04 (m, 2 H) 3.67 (d, *J*=12.38 Hz, 2 H) 3.21 - 3.40 (m, 4 H) 3.08 (t, *J*=5.81 Hz, 2 H) 2.77 - 2.98 (m, 4 H) 2.60 - 2.74 (m, 1 H) 2.47 - 2.60 (m, 1 H) 2.27 (s, 3 H) 1.24 (d, *J*=6.82 Hz, 6 H) 1.09 (d, *J* 5.81 Hz, 3 H); MS (ESI+) *m/z* 567.4 $(M+H)^+$.
52-E		(*R*)-2-(4-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.27 (m, 4 H), 7.05 - 7.12 (m, 2 H), 6.97 - 7.04 (m, 1 H), 3.98 (s, 2 H), 3.57 (t, *J*=12.4 Hz, 2 H), 3.24 - 3.29 (m, 2 H), 3.15 - 3.23 (m, 1 H), 3.11 (app. d, *J*=16.2 Hz, 1 H), 2.96 (t, *J*=5.7 Hz, 2 H), 2.90 (dd, *J*=12.8, 8.7 Hz, 1 H), 2.81 (s, 1 H), 2.75 - 2.79 (m, 1 H), 2.59 (t, *J*=6.1 Hz, 1 H), 2.43 - 2.48 (m, 1 H), 2.26 (s, 3 H), 2.06 (s, 6 H), 1.00 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 485.2 $(M+H)^+$.
52-F		(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.23 (br. s., 1 H), 7.44 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.35 (dd, *J*=7.2, 0.9 Hz, 1 H), 7.19 - 7.25 (m, 3 H), 7.11 - 7.15 (m, 1 H), 7.05 - 7.08 (m, 1 H), 7.03 (dd, *J*=7.3, 1.3 Hz, 1 H), 4.01 (s, 2 H), 3.68 (d, *J*=12.1 Hz, 2 H), 3.23 - 3.39 (m, 4 H), 3.13 (t, *J*=5.7 Hz, 2 H), 2.89 - 3.02 (m, 2 H), 2.84 (app. d, *J*=16.9 Hz, 1 H), 2.64 - 2.73 (m, 1 H), 2.59 (t, *J*=9.9 Hz, 1 H), 2.33 (s, 3 H), 2.10 (d, *J*=1.0 Hz, 3 H), 1.11 (d, *J*=6.1 Hz, 3 H); MS (ESI+) *m/z* 510.3 $(M+H)^+$.

52-G		(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.25 (br. s., 1 H), 7.44 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.35 (dd, *J*=7.3, 1.0 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.17 (dd, *J*=8.1, 0.5 Hz, 1 H), 7.10 (d, *J*=2.3 Hz, 1 H), 7.05 - 7.07 (m, 1 H), 7.03 (dd, *J*=8.1, 2.0 Hz, 1 H), 3.98 (s, 2 H), 3.66 (app. d, *J*=11.9 Hz, 2 H), 3.24 - 3.38 (m, 4 H), 3.14 (t, *J*=5.9 Hz, 2 H), 2.90 - 3.03 (m, 2 H), 2.85 (app. d, *J*=16.9 Hz, 1 H), 2.64 - 2.75 (m, 1 H), 2.60 (t, *J*=9.9 Hz, 1 H), 2.29 (s, 3 H), 2.10 (d, *J*=0.8 Hz, 3 H), 1.11 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 544.3 $(M+H)^+$.
52-H		(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.26 (d, *J*=2.8 Hz, 1 H), 7.23 (d, *J*=8.3 Hz, 1 H), 7.15 - 7.20 (m, 2 H), 7.12 (d, *J*=2.8 Hz, 1 H), 7.09 (s, 1 H), 7.07 (m, *J*=1.8 Hz, 1 H), 7.05 (d, *J*=2.0 Hz, 1 H), 4.01 (br. s., 2 H), 3.53 - 3.62 (m, 2 H), 3.31 (br. s, 2 H), 3.26 - 3.29 (m, 1 H), 3.17 - 3.25 (m, 1 H), 3.11 (app. d, *J*=16.2 Hz, 1 H), 2.88 - 2.99 (m, 3 H), 2.76 – 2.82 (m, 2 H), 2.57 - 2.65 (m, 1 H), 2.23 (s, 3 H), 2.05 (s, 6 H), 1.01 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 519.2 $(M+H)^+$.
52-I		(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.13 (s, 1 H), 7.50 (d, *J*=7.8 Hz, 1 H), 7.22 - 7.31 (m, 3 H), 7.11 - 7.15 (m, 1 H), 7.08 (dd, *J*=7.8, 1.8 Hz, 1 H), 3.97 - 4.08 (m, 2 H), 3.60 - 3.68 (m, 2 H), 3.13 (app. d, *J*=16.2 Hz, 1 H), 3.06 (t, *J*=5.7 Hz, 1 H), 2.92 - 3.00 (m, 1 H), 2.77 - 2.86 (m, 2 H), 2.54 - 2.57 (m, 3 H), 2.23 - 2.26 (m, 3 H), 1.03 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 545.2 $(M+H)^+$.

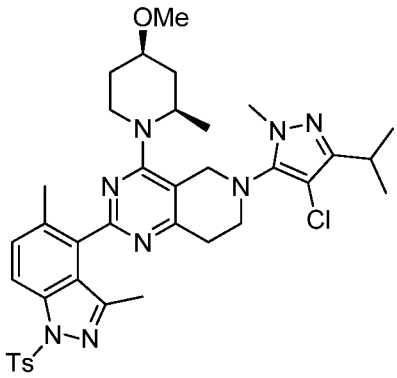
Example 53 **1-(7-(6-(5-Isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4,7-diazaspiro[2.5]octan-4-yl)ethanone.**



Prepared in a similar manner to that described in **Example 52** using 4,7-diazaspiro[2.5]octane dihydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.89 (s, 1 H) 7.41 (dd, *J*=7.83, 1.01 Hz, 1 H) 7.21 (dd, *J*=7.33, 1.01 Hz, 1 H) 7.07 - 7.16 (m, 3 H) 6.99 (d, *J*=1.26 Hz, 1 H) 6.87 (dd, *J*=7.71, 1.39 Hz, 1 H) 4.01 (s, 2 H) 3.61 - 3.83 (m, 2 H) 3.36 - 3.52 (m, 2 H) 3.32 (br. s., 4 H) 2.97 (t, *J*=5.81 Hz, 2 H) 2.85 (quin, *J*=6.82 Hz, 1 H) 2.21 (s, 3 H) 2.12 (s, 3 H) 2.01 (s, 3 H) 1.20 (d, *J*=7.07 Hz, 6 H) 0.94 - 1.09 (m, 4 H); MS (ESI+) *m/z* 549.4 $(M+H)^+$.

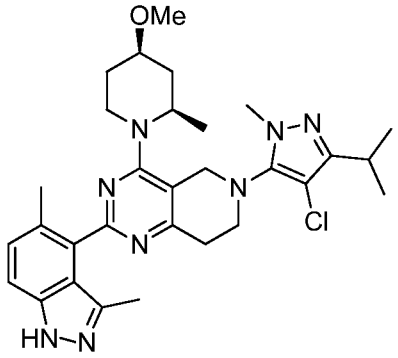
Example 54

54-A. 6-(4-Chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



The title compound was prepared in a similar manner to that described in **Example 34-D** using 2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 717.3 $(M+H)^+$.

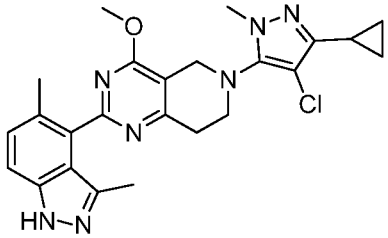
54-B. 6-(4-Chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



The title compound was prepared in a similar manner to that described in **Example 19-F** using 6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1 H), 7.40 (d, *J*=8.6 Hz, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 4.23 - 4.39 (m, 2 H), 3.62 (s, 3 H), 3.46 - 3.58 (m, 1 H), 3.38 - 3.46 (m, 1 H), 3.02 - 3.12 (m, 1 H), 2.92 - 2.99 (m, 4 H), 2.84 - 2.92 (m, 1 H), 2.16 (s, 3 H), 1.96 (s, 1 H), 1.89 (br. s., 1 H), 1.85 (s, 6 H), 1.49 - 1.67 (m, 3 H), 1.20 (d, *J*=6.8 Hz, 6 H), 1.14 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 563.3 $(M+H)^+$.

The following compound was prepared in a similar manner.

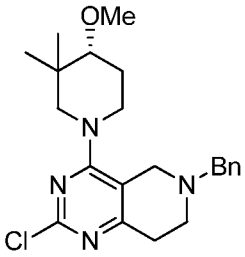
54-B. 6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.85 (br. s., 1 H) 7.39 - 7.52 (m, 1 H) 7.33 (d, *J*=8.3 Hz, 1 H) 4.33 (s, 2 H) 4.04 (s, 3 H) 3.70 (s, 3 H) 3.59 (t, *J*=5.8 Hz, 2 H) 3.08 (t, *J*=5.7 Hz, 2 H) 2.33 (s, 3 H) 2.059 (s, 3 H) 1.89 (quin, *J*=6.8 Hz, 1H) 0.83 - 0.97 (m, 4 H); MS (ESI+) *m/z* 464.2 $(M+H)^+$.

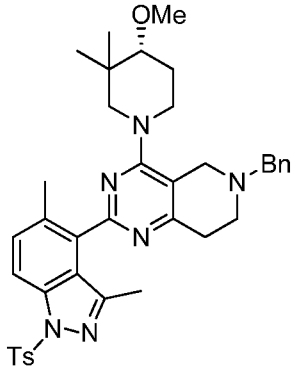
Example 55

55-A. (*R*)-6-Benzyl-2-chloro-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



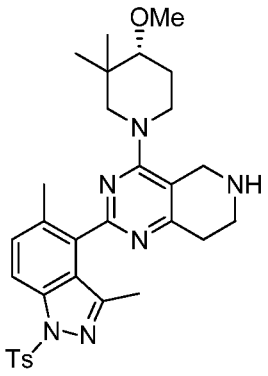
To a solution of 6-benzyl-2,4-dichloro-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (5.55 g, 18.8 mmol) in iPrOH (170 mL) was added (*R*)-4-methoxy-3,3-dimethylpiperidin-1-ium chloride, **Example 7-D** (3.08 g, 17.1 mmol) and TEA (7.2 mL, 51.4 mmol). The reaction mixture was then heated overnight at 50 °C. At that point the solvent was removed in vacuo and the residue was purified via FCC (0-50% EtOAc/heptane) to give the title compound. MS (ESI+) *m/z* 401.3 $(M+H)^+$.

55-B. (*R*)-6-Benzyl-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



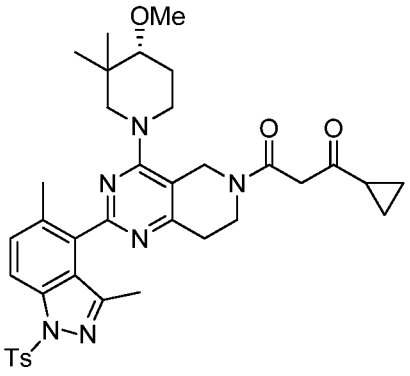
To a solution of (*R*)-6-benzyl-2-chloro-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (5.04 g, 12.6 mmol) in 1,4-dioxane (100 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-indazole, **Example 3**, (6.16 g, 12.6 mmol), $Pd(Ph_3P)_4$ (2.18 g, 1.89 mmol) and a 2 M solution of sodium carbonate (18.9 mL, 37.7 mmol). The reaction mixture was heated at 100 °C under a nitrogen atmosphere for 16 h. The reaction mixture was then allowed to cool to rt and was diluted with EtOAc and water. The layers were mixed and then separated. The organic layer was washed with water and then brine. The separated organic layer was then dried over sodium sulfate, filtered and concentrated. The residue was then purified via FCC (0-70% EtOAc/heptane) to give the title compound. MS (ESI+) *m/z* 665.6 $(M+H)^+$.

55-C. (*R*)-2-(3,5-Dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of (*R*)-6-benzyl-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (3.0 g, 4.51 mmol) in THF (24 mL) and water (6 mL) was added acetic acid (1.30 mL, 22.6 mmol). The solution was warmed to 40 °C and $Pd(OH)_2$ 20% on carbon (0.792 mg, 1.13 mmol) was added. The mixture was then stirred under a hydrogen atmosphere for 2.25 h. The mixture was then allowed to cool to rt and was filtered over Celite®, washing with EtOAc and MeOH. The filtrate was then basified with aqueous 1 N NaOH and extracted with EtOAc (3 x). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduce pressure. The residue was then purified via FCC (0-15% MeOH/DCM; with 10% NH_4OH in DCM) to obtain the title compound. MS (ESI+) *m/z* 575.5 $(M+H)^+$.

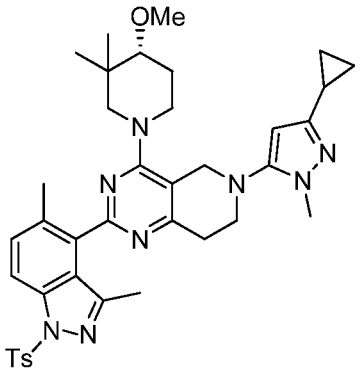
55-D. (*R*)-1-Cyclopropyl-3-(2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5*H*)-yl)propane-1,3-dione.



A solution of (*R*)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.200 g, 0.35 mmol), 4-DMAP (0.013 g, 0.10 mmol) and methyl 3-cyclopropyl-3-oxopropanoate (0.13 mL, 1.04 mmol) in toluene (3 mL) was heated at 150 °C in a microwave reactor for 35 min. The reaction was then diluted with EtOAc and water. The aqueous phase was extracted further with EtOAc (3x) and the combined organic layers were dried over anhydrous

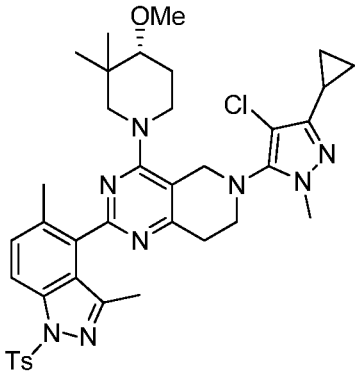
sodium sulfate, filtered, and concentrated under reduce pressure. The residue was then purified via FCC (0-10% MeOH/DCM) to obtain the title compound. MS (ESI+) *m/z* 685.6 $(M+H)^+$.

55-E. (*R*)-6-(3-Cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



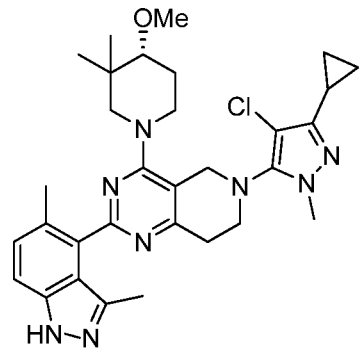
A microwave vial was charged with (*R*)-1-cyclopropyl-3-(2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5*H*)-yl)propane-1,3-dione (0.563 g, 0.82 mmol) and THF (5 mL) and placed under a nitrogen atmosphere. Methyl hydrazine (87 µL, 1.64 mmol), pyridine (0.25 mL) and Lawesson's reagent (0.366 g, 0.90 mmol) were then added in sequence. The vessel was sealed and heated at 125 °C in a microwave reactor for 12 min. At that point the reaction mixture was concentrated and the residue was purified via FCC (0-10% MeOH/DCM; 10% NH_4OH in DCM) to obtain the title compound. ^1H NMR (400 MHz, DMSO-*d6*) δ ppm 8.56 - 8.61 (m, 1 H), 8.05 (d, *J*=8.6 Hz, 1 H), 7.79 (d, *J*=8.3 Hz, 2 H), 7.56 (d, *J*=8.8 Hz, 1 H), 7.38 (d, *J*=8.6 Hz, 2 H), 5.52 (s, 1 H), 4.08 (d, *J*=13.4 Hz, 1 H), 3.96 (d, *J*=15.4 Hz, 1 H), 3.61 - 3.69 (m, 1 H), 3.55 (s, 3 H), 3.28 - 3.31 (m, 2 H), 3.26 (s, 3 H), 3.04 (t, *J*=10.2 Hz, 1 H), 2.94 - 2.99 (m, 1 H), 2.82 - 2.92 (m, 2 H), 2.33 (s, 3 H), 2.19 (s, 3 H), 1.86 - 1.94 (m, 1 H), 1.83 (s, 3 H), 1.67 - 1.78 (m, 1 H), 1.45 - 1.58 (m, 1 H), 0.91 (s, 3 H), 0.74 - 0.83 (m, 5H), 0.50 - 0.58 (m, 2 H); MS (ESI+) *m/z* 695.6 $(M+H)^+$.

55-F. (*R*)-6-(4-Chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of (*R*)-6-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.062 g, 0.089 mmol) in DCM (2 mL) under an atmosphere of nitrogen was added N-chlorosuccinimide (0.012 g, 0.089 mmol). The mixture was left to stir for 1 h at rt. The reaction mixture was then directly purified by FCC (40-75% EtOAc/heptanes) to give the title compound. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 8.08 (d, *J*=8.3 Hz, 1 H), 7.79 (d, *J*=8.3 Hz, 2 H), 7.45 (d, *J*=8.8 Hz, 1 H), 7.25 (d, *J*=8.3 Hz, 2 H), 4.32 (d, *J*=14.7 Hz, 1 H), 4.22 (d, *J*=14.4 Hz, 1 H), 3.67 (d, *J*=11.6 Hz, 1 H), 3.58 (s, 3 H), 3.52 (dq, *J*=12.8, 6.3 Hz, 2 H), 3.28 - 3.36 (m, 4 H), 3.09 (br. s., 1 H), 2.99 (br. s., 2 H), 2.92 (dd, *J*=8.6, 3.8 Hz, 1 H), 2.86 (d, *J*=11.6 Hz, 1 H), 2.72 (s, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H), 1.88 - 1.96 (m, 4 H), 1.78 - 1.88 (m, 1 H), 1.52 - 1.69 (m, 3 H), 0.94 (s, 3 H), 0.81 - 0.90 (m, 8 H); MS (ESI+) *m/z* 729.4 $(M+H)^+$.

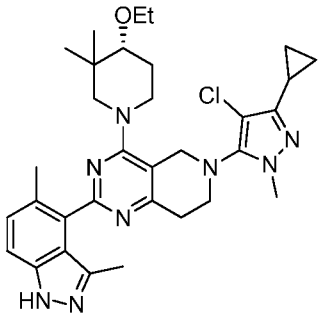
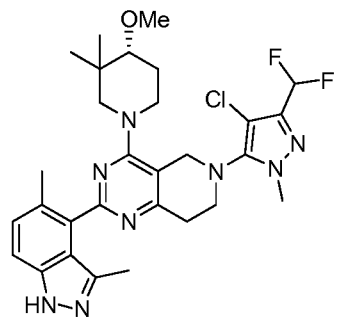
55-G. (*R*)-6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

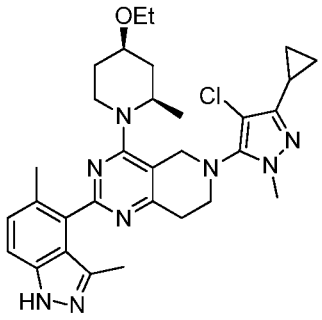
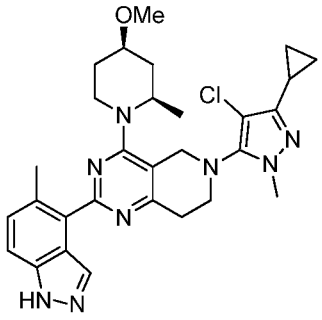
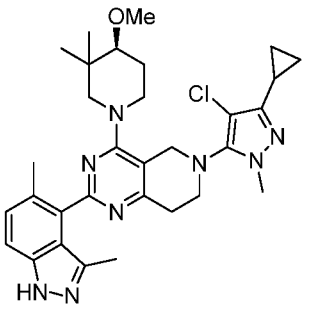


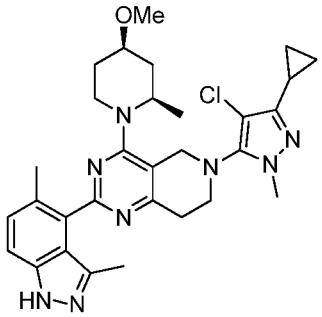
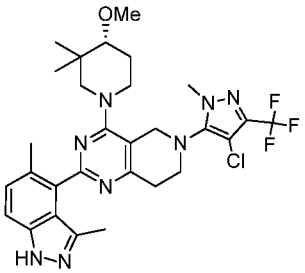
To a solution of (*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.050 g, 0.068 mmol) in MeOH (3 mL) was added K_2CO_3 (0.057 g, 0.410 mmol). The mixture was heated at 55

°C under a nitrogen atmosphere for 2 h. At that point the mixture was diluted with EtOAc and washed with sat aq NH_4Cl and then brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by FCC (0-10% MeOH/DCM) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.8 Hz, 1 H), 4.39 (d, *J*=14.9 Hz, 1 H), 4.25 (d, *J*=14.7 Hz, 1 H), 3.62 - 3.78 (m, 1 H), 3.56 (s, 3 H), 3.46 - 3.55 (m, 2 H), 3.30 (d, *J*=3.5 Hz, 1 H), 3.26 (s, 3 H), 2.99 - 3.08 (m, 1 H), 2.97 (dd, *J*=9.1, 4.0 Hz, 1 H), 2.92 (app. t, *J*=5.9 Hz, 2 H), 2.85 (d, *J*=12.9 Hz, 1 H), 2.18 (s, 3 H), 1.85 - 1.96 (m, 4 H), 1.74 - 1.82 (m, 1 H), 1.49 – 1.60 (m, 1 H), 0.92 (s, 3 H), (overlapped m, 2 H), 0.81 (s, 3H), 0.72 - 0.77 (m, 2 H); MS (ESI+) *m/z* 575.5 $(M+H)^+$.

The following compounds were prepared in a similar manner.

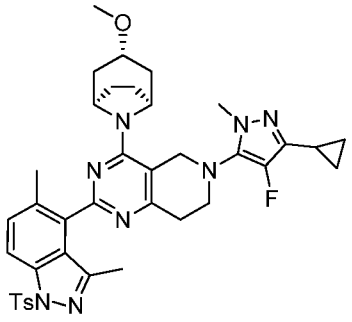
	Structure	Chemical Name & Analytical Data
55-H		(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.08 - 7.30 (m, 1 H), 4.33 - 4.48 (m, 1 H), 4.16 - 4.31 (m, 1 H), 3.64 - 3.75 (m, 1 H), 3.58 - 3.63 (m, 1 H), 3.54 - 3.57 (m, 3 H), 3.46 - 3.54 (m, 2 H), 2.99 - 3.10 (m, 2 H), 2.92 (t, *J*=5.8 Hz, 2 H), 2.84 (d, *J*=13.1 Hz, 1 H), 2.15 - 2.22 (m, 3 H), 1.83 - 1.91 (m, 4 H), 1.74 - 1.82 (m, 1 H), 1.50 - 1.63 (m, 1 H), 1.09 (t, *J*=6.9 Hz, 3 H), 0.90 - 0.94 (m, 3 H), 0.82 - 0.88 (m, 5 H), 0.71 - 0.77 (m, 2 H); MS(ESI+) *m/z* 590.4 $(M+H)^+$
55-I		(*R*)-6-(4-chloro-3-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.8 Hz, 1 H), 6.93 (t, *J*=53.1 Hz, 1 H), 4.45 (d, *J*=14.7 Hz, 1 H), 4.31 (d, *J*=14.9 Hz, 1 H), 3.71 (s, 3 H), 3.64 - 3.69 (m, 1 H), 3.53 - 3.62 (m, 2 H), 3.26 (s, 3 H), 3.00 - 3.09 (m, 1 H), 2.91 - 3.00 (m, 3 H), 2.85 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.85 - 1.97 (m, 4 H), 1.50 - 1.63 (m, 1 H), 0.92 (s, 3 H), 0.83 (s, 3 H); MS (ESI+)

		m/z 585.5 $(M+H)^+$.
55-J		6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-ethoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 12.61 (s, 1 H) 7.40 (d, *J*=8.34 Hz, 1 H) 7.22 (d, *J*=8.59 Hz, 1 H) 4.31 - 4.38 (m, 1 H) 4.23 - 4.31 (m, 1 H) 3.65 - 3.78 (m, 1 H) 3.58 (s, 3 H) 3.48 - 3.56 (m, 3 H) 3.39 - 3.48 (m, 2 H) 3.24 - 3.29 (m, 1 H) 3.03 - 3.15 (m, 1 H) 2.93 (t, *J*=5.81 Hz, 2 H) 2.16 (s, 3 H) 1.82 - 1.92 (m, 5 H) 1.78 (tt, *J*=8.34, 5.05 Hz, 1 H) 1.50 - 1.65 (m, 2 H) 1.15 (d, *J*=6.32 Hz, 3 H) 1.10 (t, *J*=6.95 Hz, 3 H) 0.82 - 0.88 (m, 2 H) 0.71 - 0.77 (m, 2 H); MS (ESI+) *m/z* 575.4 $(M+H)^+$.
55-K		6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-methyl-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 13.00 (s, 1 H), 8.06 - 8.10 (m, 1 H), 7.51 (dd, *J*=8.5, 0.6 Hz, 1 H), 7.29 (d, *J*=8.6 Hz, 1 H), 4.20 - 4.41 (m, 2 H), 3.72 - 3.87 (m, 1 H), 3.58 (s, 3 H), 3.49 - 3.56 (m, 2 H), 3.42 - 3.49 (m, 1 H), 3.26 (s, 3 H), 3.11 - 3.19 (m, 1 H), 3.03 (app. t, *J*=5.7 Hz, 2 H), 2.54 (s, 3 H), 1.84 - 1.97 (m, 2 H), 1.79 (tt, *J*=8.3, 5.1 Hz, 1 H), 1.56 - 1.71 (m, 2 H), 1.19 (d, *J*=6.6 Hz, 3 H), 0.82 - 0.89 (m, 2 H), 0.72 - 0.77 (m, 2 H); MS (ESI+) *m/z* 547.5 $(M+H)^+$.
55-L		(*S*)-6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, Acetone-*d*6) δ ppm 11.71 (br. s., 1 H), 7.42 (d, *J*=8.3 Hz, 1 H), 7.23 (d, *J*=8.6 Hz, 1 H), 4.48 (d, *J*=14.9 Hz, 1 H), 4.39 (d, *J*=14.9 Hz, 1 H), 3.72 - 3.81 (m, 1 H), 3.53 - 3.67 (m, 5 H), 3.41 (dd, *J*=13.1, 1.8 Hz, 1 H), 3.32 (s, 3 H), 3.10 - 3.19 (m, 1 H), 2.98 - 3.07 (m, 3 H), 2.92 (d, *J*=12.9 Hz, 1 H), 2.78 - 2.81 (m, 2 H), 2.26 (s, 3 H), 1.96 - 1.98 (m, 3 H), 1.79 - 1.88 (m, 1 H), 1.62 - 1.73 (m, 1 H), 0.98

		(s, 3 H), 0.92 (s, 3 H), 0.71 - 0.90 (m, 5 H); MS (ESI+) *m/z* 575.4 $(M+H)^+$.
55-M		6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 4.21 - 4.41 (m, 2H), 3.65 - 3.76 (m, 1H), 3.58 (s, 3H), 3.47 - 3.56 (m, 2H), 3.37 - 3.45 (m, 1H), 3.20 - 3.26 (m, 3H), 3.02 - 3.14 (m, 1H), 2.94 (t, *J* = 6.1 Hz, 2H), 2.16 (s, 3H), 1.83 - 1.92 (m, 5H), 1.73 - 1.82 (m, 1H), 1.51 - 1.66 (m, 2H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.81 - 0.90 (m, 2H), 0.70 - 0.78 (m, 2H); MS(ESI+) *m/z* 561.3 $(M+H)^+$.
55-N		(*R*)-6-(4-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.1 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 4.47 (d, *J*=15.2 Hz, 1 H), 4.33 (d, *J*=14.9 Hz, 1 H), 3.76 (s, 3 H), 3.63 - 3.72 (m, 1 H), 3.57 - 3.63 (m, 2 H), 3.26 (s, 3 H), 3.00 - 3.09 (m, 1 H), 2.91 - 3.00 (m, 3 H), 2.86 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.90 - 1.96 (m, 1 H), 1.88 (s, 3 H), 1.51 - 1.62 (m, 1 H), 0.92 (s, 3 H), 0.83 (s, 3 H); MS (ESI+) *m/z* 603.5 $(M+H)^+$.

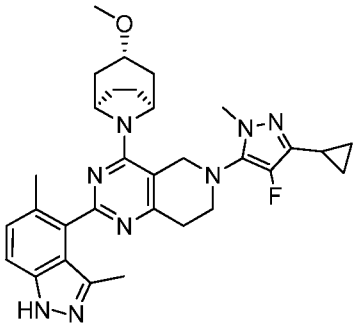
Example 56

56-A. 6-(3-Cyclopropyl-4-fluoro-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



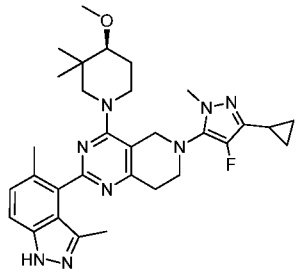
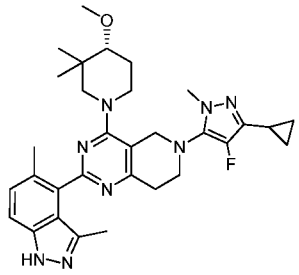
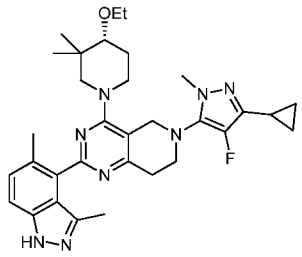
To a solution of 6-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (45 mg, 0.13 mmol), prepared in a similar method as described in **Example 55-E**, in acetonitrile (1 mL) was added Selectfluor® (88 mg, 0.13 mmol), and the reaction mixture was stirred at rt overnight. The reaction mixture was concentrated and the residue purified by silica gel flash chromatography (0-100% ethyl acetate/heptanes) to afford 6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI+) *m/z* 711.7 $(M+H)^+$.

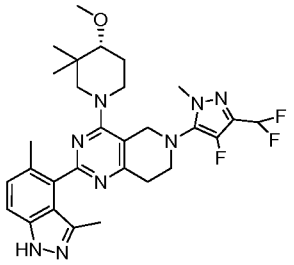
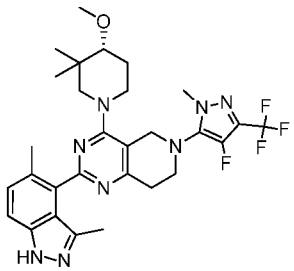
56-B. 6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine was prepared in a similar method as described in **Example 55-G**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.57 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 4.37 (br. s., 2 H), 4.21 (s, 2 H), 3.55 (s, 3 H), 3.40 - 3.46 (m, 4 H), 3.20 (s, 3 H), 2.89 (t, *J*=5.8 Hz, 2 H), 2.18 (s, 3 H), 1.93 - 2.04 (m, 4 H), 1.82 - 1.88 (m, 6 H), 1.74 - 1.81 (m, 1 H), 0.80 - 0.87 (m, 2 H), 0.70 - 0.75 (m, 2 H); MS (ESI+) *m/z* 557.6 $(M+H)^+$.

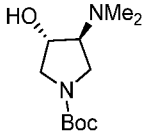
The following compounds were prepared with similar method.

	Structure	Chemical Name & Analytical Data
56-C		*(S)*-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (br. s., 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.3 Hz, 1 H), 4.29 (d, *J*=13.4 Hz, 1 H), 4.17 (d, *J*=14.1 Hz, 1 H), 3.64 - 3.74 (m, 1 H), 3.54 (s, 3 H), 3.42 - 3.50 (m, 2 H), 3.27 (s, 3 H), 2.95 - 3.10 (m, 2 H), 2.89 - 2.96 (m, 2 H), 2.80 - 2.89 (m, 1 H), 2.58 - 2.63 (m, 1 H), 2.18 (s, 3 H), 1.83 - 1.96 (m, 4 H), 1.71 - 1.81 (m, 1 H), 1.49 - 1.60 (m, 1 H), 0.92 (s, 3 H), 0.78 - 0.87 (m, 5 H), 0.66 - 0.75 (m, 2 H); MS (ESI+) *m/z* 559.4 $(M+H)^+$.
56-D		*(R)*-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 4.29 (d, *J*=14.9 Hz, 1 H), 4.16 (d, *J*=15.2 Hz, 1 H), 3.64 - 3.72 (m, 1 H), 3.53 (s, 3 H), 3.46 (t, *J*=6.2 Hz, 2 H), 3.27 (s, 3 H), 3.00 - 3.08 (m, 1 H), 2.97 (dd, *J*=9.0, 3.9 Hz, 1 H), 2.91 (app. t, *J*=6.1 Hz, 2 H), 2.84 (d, *J*=12.9 Hz, 1 H), 2.18 (s, 3 H), 1.88 - 1.95 (m, 1 H), 1.87 (s, 3 H), 1.72 - 1.81 (m, 1 H), 1.49 - 1.60 (m, 1 H), 0.92 (s, 3 H), 0.80 - 0.86 (m, 5 H), 0.68 - 0.74 (m, 2 H); MS (ESI+) *m/z* 559.5 $(M+H)^+$.
56-E		*(R)*-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. 1H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 4.22 - 4.34 (m, 1 H), 4.10 - 4.20 (m, 1 H), 3.65 - 3.75 (m, 1 H), 3.55 - 3.64 (m, 1 H), 3.53 (s, 3 H), 3.46 (t, *J*=6.1 Hz, 2 H), 2.99 - 3.10 (m, 2 H), 2.88 - 2.95 (m, 2 H), 2.84 (d, *J*=12.9 Hz, 1 H), 2.18 (s, 3 H),

		2.00 (s, 1 H), 1.87 (s, 4 H), 1.72 - 1.81 (m, 1 H), 1.55 (d, *J*=10.1 Hz, 1 H), 1.23 (s, 1 H), 1.09 (t, *J*=6.9 Hz, 3 H), 0.91 (s, 3 H), 0.79 - 0.87 (m, 5 H), 0.67 - 0.74 (m, 2 H); MS(ESI+) *m/z* 573.5 $(M+H)^+$.
56-F		(*R*)-6-(3-(difluoromethyl)-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.1 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 6.95 (t, *J*=53.3 Hz, 1 H), 4.36 (d, *J*=14.7 Hz, 1 H), 4.23 (d, *J*=15.2 Hz, 1 H), 3.63 - 3.75 (m, 4 H), 3.53 (t, *J*=6.2 Hz, 2 H), 3.27 (s, 3 H), 3.01 - 3.10 (m, 1 H), 2.90 - 3.00 (m, 3 H), 2.86 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.88 - 1.96 (m, 1 H), 1.87 (s, 3 H), 1.50 - 1.61 (m, 1 H), 0.92 (s, 3 H), 0.82 (s, 3 H); MS (ESI+) m/z 569.6 $(M+H)^+$.
56-G		(*R*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(4-fluoro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.8 Hz, 1 H), 4.40 (d, *J*=15.2 Hz, 1 H), 4.25 (d, *J*=15.2 Hz, 1 H), 3.75 (s, 3 H), 3.65 - 3.72 (m, 1 H), 3.55 (t, *J*=6.3 Hz, 2 H), 3.27 (s, 3 H), 3.01 - 3.10 (m, 1 H), 2.91 - 3.00 (m, 3 H), 2.86 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.88 - 1.95 (m, 1 H), 1.86 (s, 3 H), 1.50 - 1.62 (m, 1 H), 0.92 (s, 3 H), 0.82 (s, 3 H); MS (ESI+) *m/z* 587.5 $(M+H)^+$.

Example 57

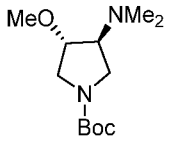
57-A. *Racemic* (*trans*)-*tert*-butyl 3-(dimethylamino)-4-hydroxypyrrolidine-1-carboxylate.



To a solution of *racemic (trans)*-4-(dimethylamino)pyrrolidin-3-ol dihydrochloride (0.87 g, 4.28 mmol) in DCM (10 mL) was added triethylamine (2.39 mL, 17.1 mmol) and di-*tert*-butyl dicarbonate (0.99 mL,

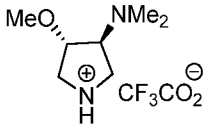
4.28 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with water and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide *racemic (trans)-tert*-butyl 3-(dimethylamino)-4-hydroxypyrrolidine-1-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.09 (d, *J*=4.8 Hz, 1 H), 4.09 (br. s., 1 H), 3.42 (m, 2 H), 3.08 - 3.18 (m, 1 H), 2.95 - 3.04 (m, 1 H), 2.17 (s, 6 H), 1.39 (s, 9 H).

57-B. *Racemic (trans)-tert*-butyl-3-(dimethylamino)-4-methoxypyrrolidine-1-carboxylate.



To a solution of *racemic (trans)-tert*-butyl 3-(dimethylamino)-4-hydroxypyrrolidine-1-carboxylate (0.96 g, 4.17 mmol) in THF (40 mL) at 0 °C was added NaH (0.25 g, 6.25 mmol, 60% dispersion in mineral oil), and the reaction mixture was stirred at 0 °C for 10 min. Then, iodomethane (0.29 mL, 4.6 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with sat aq NH_4Cl and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide *racemic-(trans)-tert*-butyl-3-(dimethylamino)-4-methoxypyrrolidine-1-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.84 (br. s., 1 H), 3.46 - 3.54 (m, 1 H), 3.25 (s, 3 H), 3.12 - 3.22 (obs m, 3 H), 2.72 (br. s., 1 H), 2.16 (s, 6 H), 1.39 (s, 9 H).

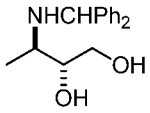
57-C. *Racemic (trans)*-3-(dimethylamino)-4-methoxypyrrolidin-1-ium 2,2,2-trifluoroacetate.



To a solution of *racemic (trans)-tert*-butyl-3-(dimethylamino)-4-methoxypyrrolidine-1-carboxylate (0.68 g, 2.8 mmol) in DCM (4.0 mL) was added TFA (2.1 mL, 28 mmol), and the reaction mixture was stirred at room temperature for 18 h. Then, the reaction mixture was concentrated under reduced pressure to provide *racemic* (*trans*)-3-(dimethylamino)-4-methoxypyrrolidin-1-ium 2,2,2-trifluoroacetate. ^{1}H NMR (400 MHz, DEUTERIUM OXIDE) δ ppm 4.42 - 4.48 (m, 1 H), 3.96 - 4.05 (m, 2 H), 3.60 (d, *J*=5.4 Hz, 2 H), 3.48 - 3.55 (m, 1 H), 3.39 (s, 3 H), 2.97 (s, 6 H).

Example 58

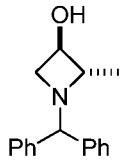
58-A. *Racemic*-(2*R,3*R**)-3-(benzhydrylamino)butane-1,2-diol.**



To a stirred suspension of (*E*)-but-2-en-1-ol (825 µL, 9.32 mmol) in DCM (23 mL) was added m-CPBA (2.19 g, 9.79 mmol) at 0°C. The reaction was allowed to warm to room temperature and was stirred for 16 h. Then the reaction mixture was cooled down to 0°C and the solution was filtered and the solid was rinsed with cold DCM. The filtrate was concnetrated and carried over to the next step.

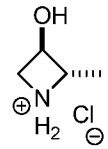
To a solution of 3-(methyloxiran-2-yl)methanol (0.826 g, 9.38 mmol) in DCM was added α-aminodiphenylmethane (1.50 mL, 8.44 mmol) and titanium(IV) isopropoxide (5.5 mL, 18.7 mmol), and the reaction mixture was heated at 60°C for 16 h. A saturated aqueous solution of Rochelle's salt was added to the mixture followed by a solution of 3 N NaOH. The reaction miture was stirred overnight. The aqueous phase was then extracted with DCM (3 x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via FCC (30-60% EtOAc/heptanes) to give the title compound. MS (ESI+) *m/z* 272.4 $(M+H)^+$.

58-B. *Racemic*-(*trans*)-1-benzhydryl-2-methylazetidin-3-ol.



Preparation of *racemic*-(*trans*)-1-benzhydryl-2-methylazetidin-3-ol was done as described in *Tetrahedron Letters*, 1991, *32*, 6935-6938; in this instance the starting material used was racemic. ^{1}H NMR (400MHz ,$CDCl_3$) δ ppm 7.47 - 7.38 (m, 5 H), 7.35 - 7.24 (m, 5 H), 4.36 (s, 1 H), 3.95 (quin, *J* = 6.4 Hz, 1 H), 3.69 (ddd, *J* = 1.0, 6.4, 7.7 Hz, 1 H), 3.03 (quin, *J* = 6.1 Hz, 1 H), 2.61 -2.54 (m, 1 H), 1.79 - 1.71 (m, 1 H), 0.77 (d, *J* = 6.3 Hz, 3 H).

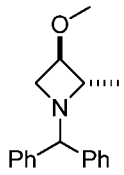
58-C. *Racemic*-(*trans*)-3-hydroxy-2-methylazetidin-1-ium chloride.



To a solution of r*acemic*-(*trans*)-1-benzhydryl-2-methylazetidin-3-ol (0.137 g, 0.541 mmol) in MeOH (5.41 mL) was added 10% Pd/C (57 mg, 0.027 mmol) and 4 M HCl in dioxane (406 µL, 1.62 mmol). H_2 was bubbled through the solution for 15 min, and the reaction mixture was stirred overnight. The mixture was filtered through a pad of Celite® and rinsed with DCM. The filtrate was concentrated to give the title compound.

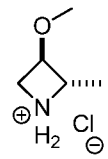
Example 59

59-A. *Racemic*-(*trans*)-1-benzhydryl-3-methoxy-2-methylazetidine.



To a solution of r*acemic*-(*trans*)-1-benzhydryl-2-methylazetidin-3-ol (0.198 g, 0.782 mmol) in THF (16 mL) was added iodomethane (98 µL, 1.6 mmol) and sodium hydride (0.035 g, 0.86 mmol, 60% in mineral oil). After 1.5 h, water was added and the mixture was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via FCC (0-15% EtOAc/n-heptanes) to give the title compound. MS (ESI+) *m/z* 268.2 $(M+H)^+$.

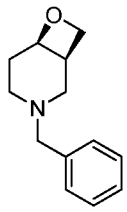
59-B. *Racemic*-(*trans*)-3-methoxy-2-methylazetidin-1-ium chloride.



Preparation of r*acemic*-(*trans*)-3-methoxy-2-methylazetidin-1-ium chloride was done as described in **Example 58-C**.

Example 60

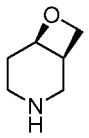
60-A. *Racemic* (*cis*)-3-benzyl-7-oxa-3-azabicyclo[4.2.0]octane.



Step 1: To a solution of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride salt (5.2 g, 17.5 mmol) in EtOH (80 mL) was added $NaBH_4$ (5.29 g, 140 mmol). The reaction mixture was stirred at room temperature for 4 h, then filtered through celite and concentrated under reduced pressure. The residue was dissolved in DCM, washed with water, dried over Na_2SO_4, filtered and concentrated to afford a mixture of *cis* and *trans* diastereomers of 1-benzyl-3-(hydroxymethyl)piperidin-4-ol, which was used for the next step without further purification.

Step 2: To a solution of above crude *cis* and *trans* mixture of 1-benzyl-3-(hydroxymethyl)piperidin-4-ol (2.69 g, 12.16 mmol) in DCM (60 mL) was added DIPEA (3.39 mL, 24.31 mmol) and MsCl (0.947 mL, 12.2 mmol) dropwise at 0 °C. The reaction mixture was further stirred for 1.5 h at 0-5 °C and then quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to afford a mixture of mono- and bi-mesylated compounds. The crude was then dissolved in THF (250 mL) and added NaH (1.05 g, 43.8 mmol, 60% in mineral oil) portionwise at room temperature. After being stirred for 40 min at room temperature, the reaction mixture was then heated to 65 °C for 4.5 h. The reaction mixture was cooled to room temperature, then quenched with water and concentrated in vacuo. The residue was dissolved in EtOAc, washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (0-100% EtOAc/heptanes) to provide *racemic* (*cis*)-3-benzyl-7-oxa-3-azabicyclo[4.2.0]octane as a colorless oil. ^1H NMR (400 MHz, CD_2Cl_2) δ ppm 7.32 - 7.41 (m, 5H), 4.97 (ddd, J = 3.03, 4.42, 6.19 Hz, 1H), 4.68 (t, J = 5.68 Hz, 1H), 4.07 - 4.13 (m, 1H), 3.53 - 3.60 (m, 2H), 2.90 - 2.98 (m, 1H), 2.82 - 2.90 (m, 1H), 2.52 - 2.59 (m, 2H), 2.49 (dd, J = 6.32, 11.37 Hz, 1H), 1.83 - 1.87 (m, 2H).

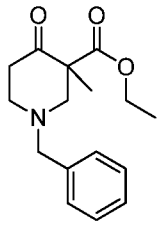
60-B. *Racemic* (*cis*)-7-oxa-3-azabicyclo[4.2.0]octane.



To a solution of *racemic* (*cis*)-3-benzyl-7-oxa-3-azabicyclo[4.2.0]octane (440 mg, 2.165 mmol) and HOAc (200 µL, 3.49 mmol) in MeOH (40 mL) was added Pd/C (5%, 461 mg, 0.216 mmol) at room temperature under nitrogen atmosphere. The vessel was evacuated and backfilled with hydrogen 3 times and then left to stir under hydrogen atmosphere for 3 h. The mixture was then filtered through celite and the celite was washed with MeOH and EtOAc. The filtrates were combined and concentrated under reduced pressure (bath temperature < 30 °C) to provide *racemic* (*cis*)-7-oxa-3-azabicyclo[4.2.0]octane as an acetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 5.11 (td, *J* = 3.32, 6.76 Hz, 1H), 4.84 (t, *J* = 6.57 Hz, 1H), 4.24 (dd, *J* = 3.92, 6.44 Hz, 1H), 3.46 (dd, *J* = 6.95, 13.52 Hz, 1H), 3.33 - 3.40 (m, 1H), 3.04 - 3.14 (m, 3H), 1.95 - 2.02 (m, 2H).

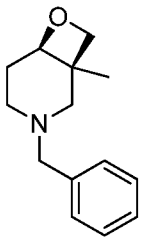
Example 61

61-A. Ethyl 1-benzyl-3-methyl-4-oxopiperidine-3-carboxylate.



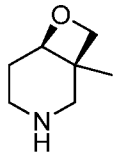
To a suspension of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride (20 g, 67.2 mmol) in THF (130 mL)/DMF (130 mL) was added KOH (powder, 7.64 g, 136 mmol) at room temperature. The reaction mixture was stirred for 5-10 min, then added iodomethane (4.62 mL, 73.9 mmol) dropwise. The reaction mixture was further stirred for 3 h at room temperature and then quenched with water. The aqueous phase was extracted with diethyl ether twice. The organic phases were combined and washed with water, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (0-20% EtOAc/heptanes) to provide ethyl 1-benzyl-3-methyl-4-oxopiperidine-3-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.15 - 7.45 (m, 5H), 4.00 - 4.21 (m, 2H), 3.66 (d, *J* = 13.39 Hz, 1H), 3.47 (d, *J* = 13.39 Hz, 1H), 3.30 (dd, *J* = 2.78, 11.62 Hz, 1H), 2.96 - 3.08 (m, 1H), 2.77 (ddd, *J* = 6.69, 11.68, 14.46 Hz, 1H), 2.36 - 2.45 (m, 1H), 2.27 - 2.35 (m, 1H), 2.14 (d, *J* = 11.37 Hz, 1H), 1.15 (t, *J* = 7.07 Hz, 3H), 1.09 (s, 3H).

61-B. *Racemic* (*cis*)-3-benzyl-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane.



The above compound was synthesized in a similar manner as **Example 60-A** to provide *racemic (cis)*-3-benzyl-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane. ^{1}H NMR (400 MHz, CDCl2) δ ppm 7.17 - 7.47 (m, 5H), 4.49 - 4.65 (m, 1H), 4.27 (d, *J* = 5.05 Hz, 1H), 4.12 (d, *J* = 5.05 Hz, 1H), 3.57 (br. s., 2H), 2.47 - 2.62 (m, 4H), 1.73 - 1.95 (m, 2H), 1.17 (s, 3H).

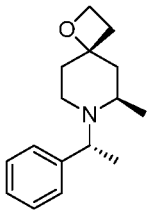
61-C. *Racemic (cis)*-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane.



The above compound was synthesized in a similar manner as **Example 60-B** to provide *racemic (cis)*-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane as an acetic acid salt. ^{1}H NMR (400 MHz, CD3OD) δ ppm 4.74 (t, *J* = 2.91 Hz, 1H), 4.44 (d, *J* = 6.32 Hz, 1H), 4.39 (d, *J* = 6.57 Hz, 1H), 3.32 - 3.39 (m, 1H), 3.18 - 3.29 (m, 2H), 3.10 (d, *J* = 13.39 Hz, 1H), 1.95 - 2.10 (m, 2H), 1.28 (s, 3H).

Example 62

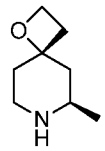
62-A. (4*S*,6*R*)-6-Methyl-7-((*R*)-1-phenylethyl)-1-oxa-7-azaspiro[3.5]nonane.



To a solution of trimethylsulfoxonium iodide (10.1 g, 46.0 mmol) in t-BuOH (anhydrous, 10 mL) was added tBuOK (1M in t-BuOH, 36.8 mL, 36.8 mmol) and the resulting mixture was stirred at 60 °C for 1 h. Then a solution of (*R*)-2-methyl-1-((*R*)-1-phenylethyl)piperidin-4-one (2 g, 9.20 mmol) in t-BuOH (6 mL) was added slowly. The reaction mixture was heated at 60 °C for 72 h, then cooled to room

temperature and poured into water. The aqueous phase was extracted with EtOAc (2x). The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (0-30% EtOAc/heptanes) to provide the desired isomer (4*S*,6*R*)-6-methyl-7-((*R*)-1-phenylethyl)-1-oxa-7-azaspiro[3.5]nonane as a colorless oil (0.67 g, 30%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.48 (d, *J* = 7.83 Hz, 2H), 7.34 (t, *J* = 7.58 Hz, 2H), 7.24 (t, *J* = 6.82 Hz, 1H), 4.39 - 4.51 (m, 2H), 4.25 (q, *J* = 6.74 Hz, 1H), 2.78 - 3.01 (m, 1H), 2.30 - 2.45 (m, 3H), 2.21 - 2.30 (m, 1H), 2.13 (td, *J* = 2.56, 13.07 Hz, 1H), 1.85 - 1.95 (m, 1H), 1.44 - 1.62 (m, 2H), 1.28 (d, *J* = 6.82 Hz, 3H), 1.20 (d, *J* = 6.32 Hz, 3H).

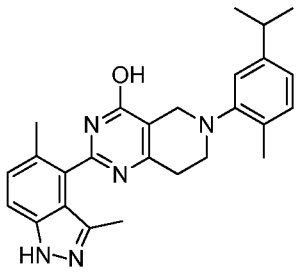
62-B. (4*S*,6*R*)-6-Methyl-1-oxa-7-azaspiro[3.5]nonane.



The above compound was synthesized in a similar manner as **Example 60-B** to provide (4*S*,6*R*)-6-methyl-1-oxa-7-azaspiro[3.5]nonane as an acetic acid salt. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 4.53 (t, *J* = 7.83 Hz, 2H), 3.19 - 3.30 (m, 2H), 3.01 (dt, *J* = 3.03, 13.14 Hz, 1H), 2.45 (dt, *J* = 1.26, 7.83 Hz, 2H), 2.15 - 2.28 (m, 2H), 1.93 (dt, *J* = 4.80, 13.77 Hz, 1H), 1.77 (dd, *J* = 12.51, 13.77 Hz, 1H), 1.34 (d, *J* = 6.57 Hz, 3H).

Example 63

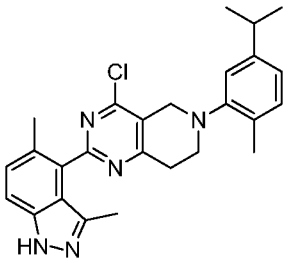
63-A. 2-(3,5-Dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ol.

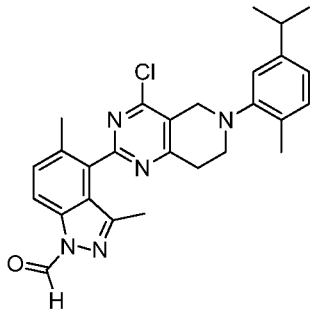


Ethanol (12 mL) was added to 2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (2.07 g, 3.47 mmol), followed by 12 N aqueous hydrochloric acid (12 mL). The mixture was then heated at 85 °C for 18 h. The mixture was cooled to room temperature, diluted with dichloromethane and slowly neutralized with saturated aqueous sodium

bicarbonate. The resulting layers were separated and the aqueous layers were extracted with dichloromethane. The organic layers were combined. The combined organics were dried and concentrated. The residue was purified by FCC (0-100% EtOAc/heptane) to provide 2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ol. MS (ESI^+) *m/z* 428.3 $(M+H)^+$.

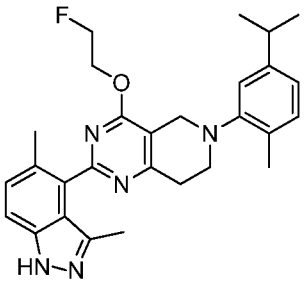
63-B. 4-Chloro-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine and 63-C. 4-(4-Chloro-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)-3,5-dimethyl-1H-indazole-1-carbaldehyde.





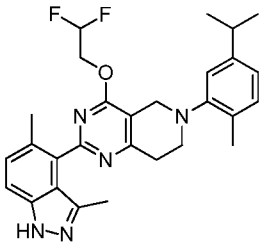
To a suspension of 2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ol (1.3 g, 3.04 mmol) in DCE (50 mL) was added Vilsmeier reagent (1.95 g, 15.2 mmol). The mixture was heated at 50 °C for 2 h. LC-MS showed reaction complete. The reaction mixture was poured into water, and the layers were separated. The aqueous layer was extracted with DCM. The organics were combined and concentrated. The residue was purified by FCC (0-100% EtOAc/heptane) to provide 4-chloro-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine MS (ESI^+) m/z 446.3 $(M+H)^+$ and 4-(4-chloro-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)-3,5-dimethyl-1H-indazole-1-carbaldehyde MS (ESI^+) m/z 474.3 $(M+H)^+$.

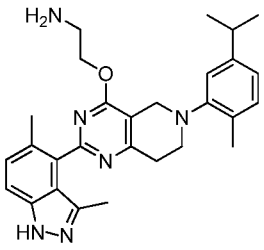
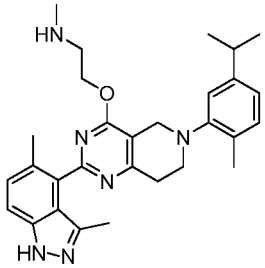
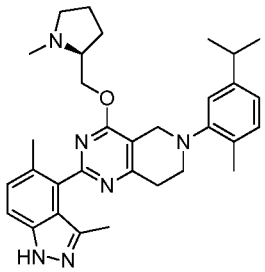
63-D. 2-(3,5-Dimethyl-1H-indazol-4-yl)-4-(2-fluoroethoxy)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

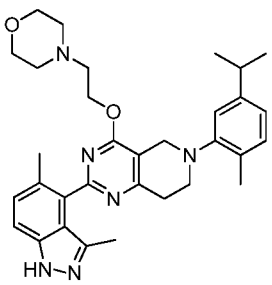
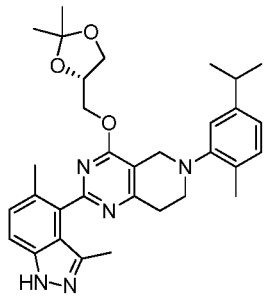


To a solution of 4-(4-chloro-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)-3,5-dimethyl-1H-indazole-1-carbaldehyde (30 mg, 0.063 mmol) in THF (3 mL) was added 2-fluoroethanol (16.2 mg, 0.25 mmol) and NaH (15.1 mg, 0.63 mmol, 60% in mineral oil). The mixture was stirred at room temperature for 4 h. LC-MS showed reaction complete. The reaction mixture was concentrated and the residue was partitioned between saturated aqueous NH_4Cl solution and DCM. The layers were separated and the aqueous layer was extracted further with DCM. The organics were combined and concentrated. The residue was purified by FCC (0-100% EtOAc/heptane) to provide 2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-fluoroethoxy)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.47 (d, J = 8.59 Hz, 1H), 7.34 (s, 1H), 7.15 (d, J = 7.71 Hz, 1H), 7.06 (d, J = 1.39 Hz, 1H), 6.92 (dd, J = 1.52, 7.71 Hz, 1H), 4.71 - 4.81 (m, 2H), 4.67 (s, 2H), 4.13 (s, 2H), 3.33 - 3.39 (m, 2H), 3.05 (t, J = 5.56 Hz, 2H), 2.88 (td, J = 6.93, 13.80 Hz, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 1.98 (s, 3H), 1.25 (d, J = 6.82 Hz, 6H) ; MS (ESI$^+$) m/z 474.4 $(M+H)^+$.

The following compounds were prepared in a similar manner.

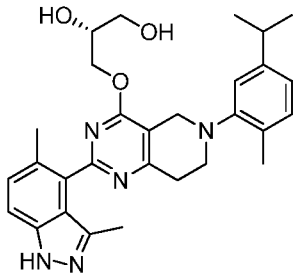
	Structure	Chemical Name & Analytical Data
63-E		4-(2,2-difluoroethoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.47 (d, J = 8.59 Hz, 1H), 7.33 (d, J = 8.59 Hz, 1H), 7.14 (d, J = 7.71 Hz, 1H), 7.06 (d, J = 1.52 Hz, 1H), 6.92 (dd, J = 1.52, 7.71 Hz, 1H), 6.03 - 6.38 (m, 1H), 4.71 (dt, J = 3.66, 14.21 Hz, 2H), 4.14 (s, 2H), 3.36 (t, J = 5.68 Hz, 2H), 3.07 (t, J = 5.62 Hz, 2H), 2.88 (td, J = 6.93, 13.80 Hz, 1H), 2.32 (s, 1H), 2.28 (s, 3H), 1.98 (s, 3H), 1.25 (d, J = 6.82 Hz, 6H); MS (ESI$^+$) m/z 492.5 $(M+H)^+$.

63-F		2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)ethanamine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.46 (d, J = 8.59 Hz, 1H), 7.32 (d, J = 8.84 Hz, 1H), 7.14 (d, J = 7.83 Hz, 1H), 7.08 (d, J = 1.64 Hz, 1H), 6.92 (dd, J = 1.71, 7.77 Hz, 1H), 4.44 - 4.52 (m, 2H), 4.16 (s, 2H), 3.33 - 3.37 (m, 2H), 2.99 - 3.09 (m, 4H), 2.88 (td, J = 6.90, 13.86 Hz, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 1.99 (s, 3H), 1.25 (d, J = 6.95 Hz, 6H); MS (ESI$^+$) *m/z* 471.5 $(M+H)^+$.
63-G		2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-N-methylethanamine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.46 (d, J = 8.59 Hz, 1H), 7.32 (d, J = 8.59 Hz, 1H), 7.14 (d, J = 7.96 Hz, 1H), 7.08 (d, J = 1.64 Hz, 1H), 6.92 (dd, J = 1.64, 7.71 Hz, 1H), 4.52 - 4.59 (m, 2H), 4.15 (s, 2H), 3.32 - 3.37 (m, 2H), 3.04 (t, J = 5.62 Hz, 2H), 2.93 - 2.99 (m, 2H), 2.88 (td, J = 6.90, 13.86 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 1.98 (s, 3H), 1.25 (d, J = 6.95 Hz, 6H); MS (ESI$^+$) *m/z* 485.6 $(M+H)^+$.
63-H		(*S*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.46 (d, J = 8.46 Hz, 1H), 7.32 (d, J = 8.59 Hz, 1H), 7.14 (d, J = 7.96 Hz, 1H), 7.05 (d, J = 1.52 Hz, 1H), 6.91 (dd, J = 1.71, 7.77 Hz, 1H), 4.47 - 4.55 (m, 1H), 4.40 (dd, J = 6.32, 11.24 Hz, 1H), 4.07 - 4.20 (m, 2H), 3.33 - 3.39 (m, 2H), 3.00 - 3.09 (m, 3H), 2.87 (td, J = 6.93, 13.80 Hz, 1H), 2.76 (dtd, J = 4.55, 6.62, 8.61 Hz, 1H), 2.44 (s, 3H), 2.29 - 2.38 (m, 4H), 2.27 (s, 3H), 2.00 - 2.10 (m, 1H), 1.99 (s, 3H), 1.73 - 1.83 (m, 2H), 1.62 - 1.73 (m, 1H), 1.20 - 1.28 (m, 6H); MS (ESI$^+$) m/z 525.5 $(M+H)^+$.

63-I		4-(2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)ethyl)morpholine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.46 (d, J = 8.46 Hz, 1H), 7.32 (d, J = 8.59 Hz, 1H), 7.14 (d, J = 7.83 Hz, 1H), 7.05 (d, J = 1.64 Hz, 1H), 6.92 (dd, J = 1.71, 7.77 Hz, 1H), 4.62 (t, J = 5.56 Hz, 2H), 4.12 (s, 2H), 3.60 - 3.68 (m, 4H), 3.35 (t, J = 5.68 Hz, 2H), 3.04 (t, J = 5.62 Hz, 2H), 2.83 - 2.93 (m, 1H), 2.81 (t, J = 5.62 Hz, 2H), 2.50 - 2.59 (m, 4H), 2.32 (s, 3H), 2.27 (s, 3H), 1.99 (s, 3H), 1.25 (d, J = 6.95 Hz, 6H); MS (ESI$^+$) m/z 541.5 $(M+H)^+$.
63-J		(*S*)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI$^+$) m/z 542.5 $(M+H)^+$.

Example 64

(*R*)-3-((2-(3,5-Dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)propane-1,2-diol.

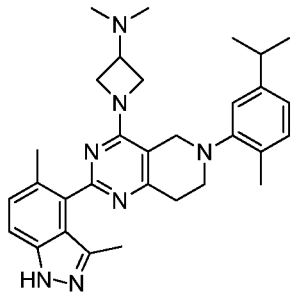


A solution of (*S*)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (20 mg, 0.037 mmol) in TFA (0.9 mL) and H_2O (0.1 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated and the residue was partitioned between DCM and saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with DCM. The organics were combined and concentrated. The

residue was purified by reverse phase HPLC (C18, 10-100% acetonitrile in H_2O with 0.1% NH_4OH) to give (*R*)-3-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)propane-1,2-diol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.33 (d, J = 8.46 Hz, 1H), 7.21 (d, J = 8.59 Hz, 1H), 7.08 (d, J = 7.96 Hz, 1H), 6.97 (d, J = 1.52 Hz, 1H), 6.86 (dd, J = 1.71, 7.77 Hz, 1H), 4.36 - 4.47 (m, 2H), 4.06 (s, 2H), 3.88 - 3.95 (m, 1H), 3.53 - 3.60 (m, 1H), 3.46 - 3.52 (m, 1H), 3.26 (t, J = 5.68 Hz, 2H), 3.02 - 3.10 (m, 2H), 2.76 - 2.86 (m, 1H), 2.26 (s, 3H), 2.20 (s, 3H), 1.92 (s, 3H), 1.17 (d, J = 6.95 Hz, 6H); MS (ESI^+) m/z 502.5 $(M+H)^+$.

Example 65

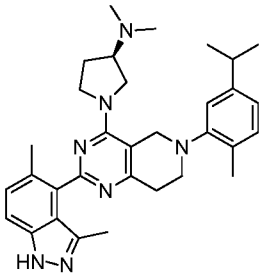
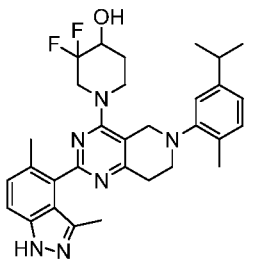
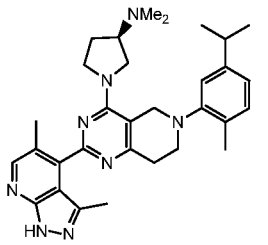
65-A. 1-(2-(3,5-Dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine.

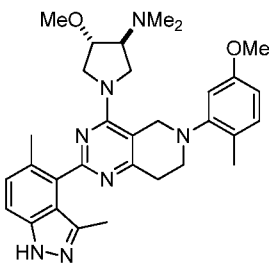
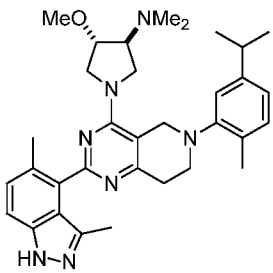


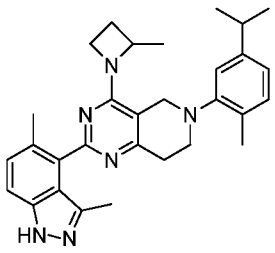
A solution of 4-chloro-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (30 mg, 0.07 mmol), N,N-dimethylazetidin-3-amine bistrifluoroacetate salt (20.0 mg, 0.2 mmol) and DIEA (0.06 mL, 0.35 mmol) in DMA (1.5 mL) was heated to 180 °C for 3 min in a microwave reactor. The reaction mixture was filtered through a 0.45 μM PTFE filter and the filtrate was purified by reverse phase HPLC (C18, 10-100% acetonitrile-H_2O with 0.1% NH_4OH) to afford 1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.43 (d, J = 8.46 Hz, 1H), 7.30 (d, J = 8.59 Hz, 1H), 7.13 (d, J = 7.83 Hz, 1H), 7.04 (d, J = 1.39 Hz, 1H), 6.91 (dd, J = 1.52, 7.71 Hz, 1H), 4.36 (t, J = 8.21 Hz, 2H), 4.08 - 4.20 (m, 4H), 3.32 - 3.38 (m, 2H), 3.18 - 3.27 (m, 1H), 2.79 - 2.97 (m, 3H), 2.31 (s, 3H), 2.27 (s, 3H), 2.18 (s, 6H), 2.04 (s, 3H), 1.24 (d, J = 6.95 Hz, 6H); MS (ESI^+) *m/z* 510.5 $(M+H)^+$.

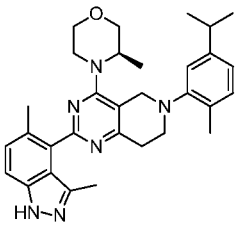
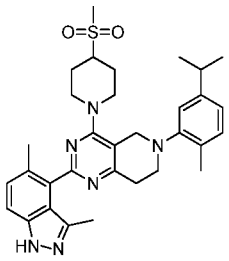
The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data

65-B		(*R*)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.42 (d, J = 8.46 Hz, 1H), 7.30 (d, J = 8.72 Hz, 1H), 7.13 (d, J = 7.96 Hz, 1H), 7.04 (d, J = 1.52 Hz, 1H), 6.90 (dd, J = 1.58, 7.77 Hz, 1H), 4.36 - 4.45 (m, 1H), 4.24 (d, J = 14.6 Hz, 1H), 3.88 - 4.01 (m, 2H), 3.76 (dt, J = 6.57, 10.55 Hz, 1H), 3.54 (dd, J = 8.59, 10.61 Hz, 1H), 3.41-3.25 (m, 2H overlap with solvent), 2.96 - 3.08 (m, 1H), 2.78 - 2.95 (m, 3H), 2.29 (m, 12H), 2.15 - 2.26 (m, 1H), 2.03 (s, 3H), 1.83 (quin, J = 10.26 Hz, 1H), 1.24 (d, J = 6.95 Hz, 6H); MS (ESI$^+$) *m/z* 524.5 (M+H)$^+$.
65-C		1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3,3-difluoropiperidin-4-ol. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 7.39 (d, *J*=8.3 Hz, 1 H), 7.27 (d, *J*=8.6 Hz, 1 H), 7.14 (d, *J*=7.8 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.92 (dd, *J*=7.7, 1.6 Hz, 1 H), 3.93 - 4.13 (m, 3 H), 3.71 - 3.91 (m, 1 H), 3.49 - 3.68 (m, 2 H), 3.40 (td, *J*=6.1, 1.5 Hz, 3 H), 3.12 (t, *J*=5.7 Hz, 2 H), 2.89 (spt, *J*=6.8 Hz, 1 H), 2.28 (s, 6 H), 2.04 - 2.19 (m, 1 H), 1.98 (s, 3 H), 1.86 - 1.96 (m, 1 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) m/z 547.5 (M+H)+.
65-D		(*R*)-1-(2-(3,5-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.14 (s, 1 H), 8.41 (s, 1 H), 7.12 (d, *J*=7.8 Hz, 1 H), 7.01 (d, *J*=1.5 Hz, 1 H), 6.88 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.43 (d, *J*=15.2 Hz, 1 H), 4.20 (d, *J*=14.9 Hz, 1 H), 3.89 (dd, *J*=10.4, 7.1 Hz, 1 H), 3.74 - 3.82 (m, 1 H), 3.58 - 3.69 (m, 1 H), 3.38 - 3.45 (m, 1 H), 3.13 - 3.23 (m, 1 H), 2.90 - 3.00 (m, 1 H), 2.79 - 2.88 (m, 2 H), 2.28 (s, 3 H), 2.23 (s, 3 H), 2.16 (s, 6 H), 2.05 - 2.09 (m, 1 H), 2.04 (s, 3 H), 1.64 - 1.76 (m, 1 H), 1.19 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 525.3 (M+H)$^+$.

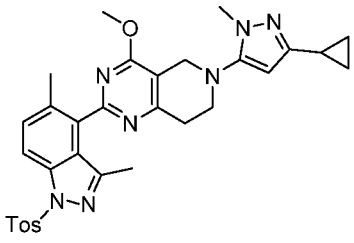
65-E **65-F**		The *racemic* (*trans)*-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine was separated by chiral HPLC (AD-H column; 20%IPA (5mM NH_4OH) in CO_2; 75g/min) to give the following two compounds: **Enantiomer-1 (65-E)**: $[\alpha]_D^{20}$ −6.8; R_t 5.4 min, (AD-H 20 X 250 mm column; 20%IPA (5mM NH_4OH) in CO_2; 75g/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=8.8 Hz, 1 H), 6.71 (d, *J*=2.5 Hz, 1 H), 6.60 (dd, *J*=8.2, 2.7 Hz, 1 H), 4.31 (d, *J*=14.9 Hz, 1 H), 4.25 (d, *J*=14.7 Hz, 1 H), 3.89 - 3.96 (m, 2 H), 3.71 - 3.78 (m, 4 H), 3.54 - 3.65 (m, 2 H), 3.23 - 3.29 (m, 5 H), 2.84 - 2.90 (m, 2 H), 2.75 - 2.82 (m, 1 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 2.19 (s, 6 H), 1.90 (s, 3 H); MS (ESI+) *m/z* 542.3 $(M+H)^+$. **Enantiomer-2 (65-F)**: $[\alpha]_D^{20}$ +4.6; R_t 6.8 min, (AD-H 20 X 250 mm column; 20%IPA (5mM NH_4OH) in CO_2; 75g/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=8.3 Hz, 1 H), 6.71 (d, *J*=2.5 Hz, 1 H), 6.60 (dd, *J*=8.2, 2.7 Hz, 1 H), 4.31 (d, *J*=14.7 Hz, 1 H), 4.25 (d, *J*=14.7 Hz, 1 H), 3.90 - 3.95 (m, 2 H), 3.71 - 3.79 (m, 4 H), 3.54 - 3.63 (m, 2 H), 3.23 - 3.28 (m, 5 H), 2.87 (t, *J*=5.8 Hz, 2 H), 2.76 - 2.81 (m, 1 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 2.19 (s, 6 H), 1.90 (s, 3 H); MS (ESI+) *m/z* 542.3 $(M+H)^+$.
65-G **65-H**		The *racemic* (*trans)*-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine was separated by chiral HPLC (AD-H column; 20%IPA (5mM NH_4OH) in CO_2; 80g/min) to give the following two compounds: **Enantiomer-1 (65-G)**: $[\alpha]_D^{20}$ +8.0; R_t 3.5 min, (AD-H column 20 X 250 mm column; 20%IPA (5mM NH_4OH) in CO_2; 80g/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 7.12 (d, *J*=8.1 Hz, 1 H), 6.99 - 7.02 (m, 1 H), 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.29 (s, 2 H), 3.89 - 3.96 (m, 2 H), 3.73 - 3.81 (m, 1 H), 3.53 - 3.64 (m, 2 H), 3.26 -

		3.28 (m, 4H), 2.77 - 2.91 (m, 2 H), 2.23 (s, 3 H), 2.22 (s, 3 H), 2.19 (s, 6 H), 1.91 (s, 3 H), 1.19 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 554.4 $(M+H)^+$. **Enantiomer-2 (65-H)**: $[\alpha]_D^{20}$ −10.5; R_t 4.5 min (AD-H column 20 X 250 mm column; 20%IPA (5mM NH_4OH) in CO_2; 80g/min). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.57 (br. s, 1 H), 7.38 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 7.12 (d, *J*=7.8 Hz, 1 H), 7.01 (br. s, 1 H), 6.89 (d, *J*=7.8 Hz, 1 H), 4.29 (br. s., 2 H), 3.92 (br. s., 2 H), 3.71 - 3.82 (m, 1 H), 3.58 (br. s., 2 H), 3.25 - 3.30 (m, 4 H), 2.78 - 2.93 (m, 4 H), 2.23 (s, 3 H), 2.22 (s, 3 H), 2.19 (br. s., 6 H), 1.91 (s, 3 H), 1.19 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 554.4 $(M+H)^+$.
65-I **65-J**		The *racemic* 2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine was separated by chiral HPLC (IB column; 40%IPA (10mM NH4OH) in CO2; 75g/min) to give the following two compounds: **Enantiomer-1** (**65-I**): R_t 2.1 min, (IB column 20 X 250 mm column; 40%IPA (10mM NH_4OH) in CO_2; 75g/min). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.6 Hz, 1 H), 7.20 (d, *J*=8.3 Hz, 1 H), 7.12 (d, *J*=7.8 Hz, 1 H), 6.99 (s, 1 H), 6.88 (dd, *J*=7.8, 1.5 Hz, 1 H), 4.47 - 4.59 (m, 1 H), 4.25 - 4.33 (m, 1 H), 4.12 - 4.25 (m, 2 H), 3.95 (d, *J*=15.2 Hz, 1 H), 3.24 - 3.29 (m, 1 H), 3.15 - 3.23 (m, 1 H), 2.74 - 2.92 (m, 3 H), 2.35 - 2.43 (obs m, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 1.91 (s, 3 H), 1.87 - 1.98 (obs m, 1 H), 1.34 (d, *J*=6.1 Hz, 3 H), 1.20 (d, *J*=1.0 Hz, 3 H), 1.18 (d, *J*=0.8 Hz, 3 H) ; MS (ESI+) *m/z* 481.4 $(M+H)^+$. **Enantiomer-2** (**65-J**): R_t 2.5 min (IB column 20 X 250 mm column; 40%IPA (10mM NH_4OH) in CO_2; 75g/min). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 7.12 (d, *J*=8.1 Hz, 1 H), 6.99 (s, 1 H), 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.47 - 4.61 (m, 1 H), 4.25 - 4.34 (m, 1 H), 4.11 - 4.25 (m, 2 H), 3.95 (d, *J*=15.4 Hz, 1 H), 3.24 - 3.29 (m, 1 H), 3.15 - 3.24 (m, 1 H), 2.76 - 2.91 (m, 3 H), 2.36 - 2.43 (obs m, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 1.91 (s, 3 H), 1.87 - 1.98 (obs m, 1 H), 1.34 (d, *J*=6.1 Hz, 3 H), 1.20 (d, *J*=1.0 Hz, 3

		H), 1.18 (d, *J*=1.0 Hz, 3 H) ; MS (ESI+) *m/z* 481.4 $(M+H)^+$.
65-K		(*R*)-4-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.22 (d, *J*=8.8 Hz, 1 H), 7.11 (d, *J*=8.1 Hz, 1 H), 6.95 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.04 (s, 2 H), 3.86 - 3.97 (m, 1 H), 3.80 (d, *J*=11.1 Hz, 1 H), 3.62 - 3.71 (m, 1 H), 3.48 - 3.61 (m, 2 H), 3.35 - 3.41 (m, , 4 H), 2.95 (t, *J*=5.8 Hz, 2 H), 2.76 - 2.89 (m, 1 H), 2.22 (s, 3 H), 2.18(s, 3 H), 1.88 (s, 3 H), 1.17 - 1.19 (m, 9 H); MS (ESI+) *m/z* 511.5 (M+H); MS (ESI+) *m/z* 511.5 $(M+H)^+$.
65-L		2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-(methylsulfonyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.6 (s, 1H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.22 (d, *J*=8.8 Hz, 1 H), 7.11 (d, *J*=8.1 Hz, 1 H), 6.96 (d, *J*=1.5 Hz, 1 H), 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.05 (s, 2 H), 3.99 (d, *J*=13.4 Hz, 2 H), 3.37 (t, *J*=5.9 Hz, 2 H), 2.98 - 3.05 (m, 2H), 2.92 (s, 3 H), 2.79 - 2.88 (m, 1 H), 2.78 (s, 2 H), 2.20 (d, *J*=9.3 Hz, 6 H), 2.06 (d, *J*=12.1 Hz, 2 H), 1.87 (s, 3 H), 1.67 (qd, *J*=12.4, 3.7 Hz, 2 H), 1.19 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 573.3 $(M+H)^+$.

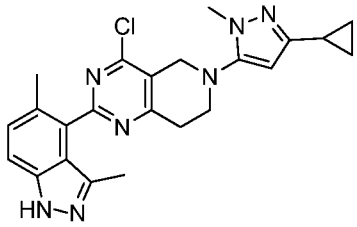
Example 66

66-A. 6-(3-Cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



This compound was prepared in a similar manner as described in **Example 34-B**. MS (ESI^+) *m/z* 584.4 $(M+H)^+$.

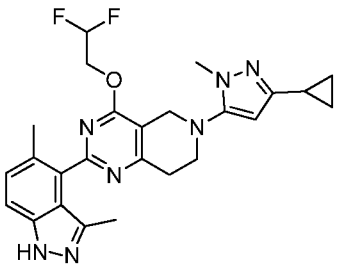
66-B. 4-Chloro-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



This compound was prepared in a similar manner as described in **Example 63** from 6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI^+) *m/z* 434.3 $(M+H)^+$.

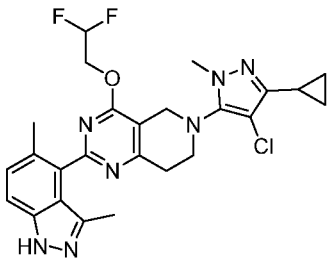
Example 67

67-A. 6-(3-Cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-(2,2-difluoroethoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



Title compound was prepared in a similar manner as described in **Example 63-D** from 4-chloro-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI^+) *m/z* 480.3 $(M+H)^+$.

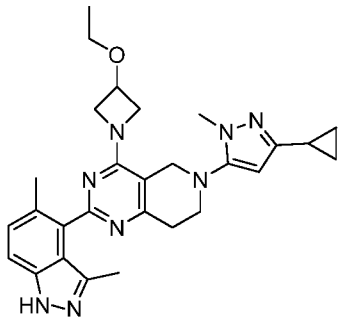
67-B. 6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-(2,2-difluoroethoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



Title compound was prepared in a similar manner as described in **Example 68-B** from 6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-(2,2-difluoroethoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.47 (d, J = 8.59 Hz, 1H), 7.33 (d, J = 8.72 Hz, 1H), 6.02 - 6.36 (m, 1H), 4.69 (dt, J = 3.66, 14.21 Hz, 2H), 4.38 (s, 2H), 3.68 (s, 3H), 3.59 (t, J = 5.68 Hz, 2H), 3.03 (t, J = 5.68 Hz, 2H), 2.26 (s, 3H), 1.97 (s, 3H), 1.80 - 1.91 (m, 1H), 0.80 - 0.94 (m, 4H); MS (ESI$^+$) m/z 514.4 $(M+H)^+$.

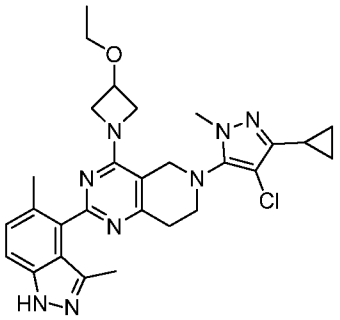
Example 68

68-A. 6-(3-Cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(3-ethoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



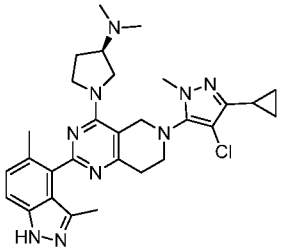
This compound was prepared in a similar manner as described in **Example 65-A** from 4-chloro-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI$^+$) *m/z* 499.5 $(M+H)^+$.

68-B. 6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(3-ethoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



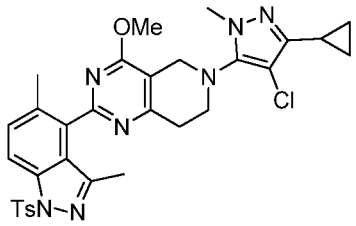
To a solution of 6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(3-ethoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (30 mg, 0.060 mmol) in DCM (2 mL) was added N-chlorosuccinimide (9.64 mg, 0.072 mmol) at room temperature. The mixture was stirred for 30 min then concentrated. The residue was purified by reverse phase HPLC (C18, 10-100% acetonitrile-H_2O with 0.1% NH_4OH) to give 6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(3-ethoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.43 (d, J = 8.46 Hz, 1H), 7.30 (d, J = 8.59 Hz, 1H), 4.49 (dd, J = 6.63, 9.41 Hz, 2H), 4.35 - 4.45 (m, 3H), 4.14 (dd, J = 4.04, 10.36 Hz, 2H), 3.66 (s, 3H), 3.46 - 3.55 (m, 4H), 2.89 (t, J = 5.68 Hz, 2H), 2.27 (s, 3H), 2.04 (s, 3H), 1.81-1.88 (m, 1H), 1.19 (t, J = 7.01 Hz, 3H), 0.76 - 0.93 (m, 4H); MS (ESI$^+$) *m/z* 533.4 $(M+H)^+$.

The following compounds were prepared in a similar manner.

	Structure	Chemical Name & Analytical Data
68-C		(*R*)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine. ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ ppm 7.42 (d, J = 8.59 Hz, 1H), 7.29 (d, J = 8.59 Hz, 1H), 4.42 (d, J = 14.91 Hz, 1H), 3.86 - 3.98 (m, 2H), 3.75 (dt, J = 6.69, 10.55 Hz, 1H), 3.65 (s, 3H), 3.43 - 3.64 (m, 4H), 2.94 - 3.06 (m, 1H), 2.78 - 2.94 (m, 2H), 2.30 (s, 6H), 2.27 (s, 3H), 2.16 - 2.25 (m, 1H), 2.04 (s, 3H), 1.77 - 1.91 (m, 2H), 0.78 - 0.92 (m, 4H); MS (ESI$^+$) *m/z* 546.5 $(M+H)^+$.

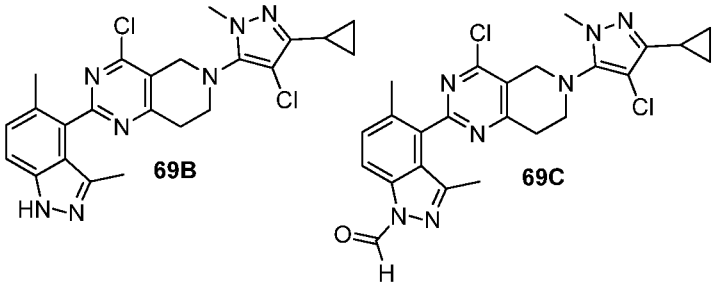
Example 69

69-A. 6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of 6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (7.0 g, 11.99 mmol) in DCM (120 mL) was added N-chlorosuccinimide (1.76 g, 13.19 mmol) at room temperature, and the reaction mixture was stirred overnight. The mixture was then concentrated and the residue was directly purified by FCC (20-100% EtOAc/heptane) to provide 6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI^+) *m/z* 619.9 $(M+H)^+$.

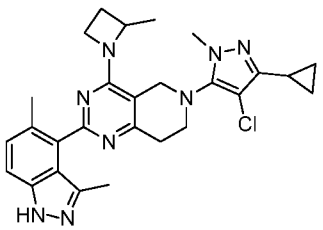
69-B. 4-Chloro-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine and **65-C. 4-(4-Chloro-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)-3,5-dimethyl-1H-indazole-1-carbaldehyde.**

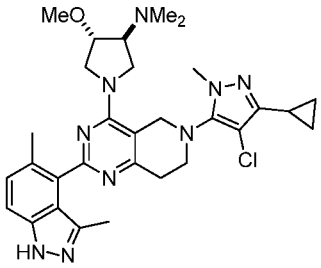
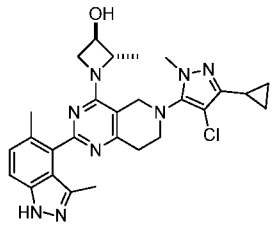


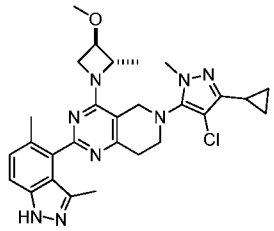
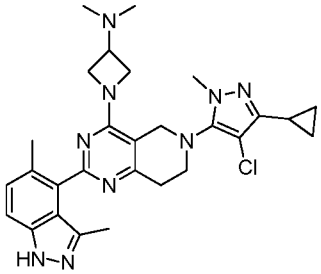
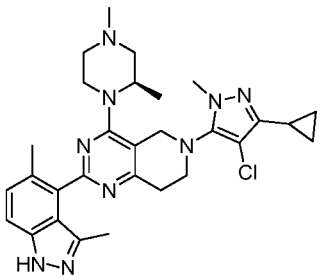
To a solution of 6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (5.4 g, 8.74 mmol) in EtOH (50 mL) was added concentrated HCl (21.2 mL, 699 mmol) at room temperature, and the reaction mixture was then heated to 100 °C for 24 h. The mixture was then cooled to room temperature and 200 mL of water was added. Then, solid NaOH was added until the pH of the solution reached pH 10. EtOAc was added to the reaction mixture and the resulting layers were separated and the aqueous layers were extracted with EtOAc (3x). The organic layers were combined and the combined organics were dried (Na_2SO_4), filtered and concentrated to a light yellow solid and used without further purification. The yellow solid (2.47 g, 5.49 mmol) was dissolved in DMF (55 mL) and Vilsmeier reagent (3.51 g, 27.4 mmol) was added to the

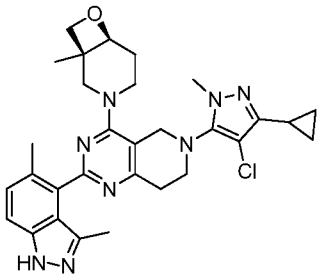
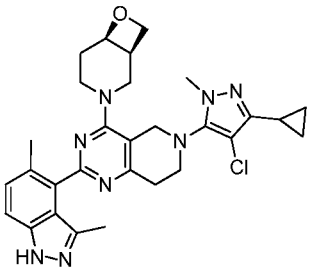
mixture at room temperature , and the reaction mixture was stirred for 15 min. Then, the reaction mixture was poured into water, and Et_2O added. The layers were separated and the aqueous layer was extracted with Et_2O. The organics were combined and washed with 5% aqueous LiCl. The organics were then dried (Na_2SO_4), filtered and concentrated to a yellow oil. The residue was purified by FCC (20-100% EtOAc/heptane) to provide 4-chloro-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine *and* 4-(4-chloro-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)-3,5-dimethyl-1H-indazole-1-carbaldehyde, MS (ESI^+) m/z 468.1 $(M+H)^+$ and MS (ESI^+) m/z 496.1 $(M+H)^+$, respectively.

The following compounds were prepared from 4-chloro-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine or 4-(4-chloro-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)-3,5-dimethyl-1H-indazole-1-carbaldehyde in a similar manner to **Example 65-A**.

69-D 69-E		The *racemic* 6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine was separated by chiral HPLC (LUX-2 column; 30% EtOH/heptanes; 1.0 mL/min) to give the following two compounds: **Enantiomer-1 (69-D)**: R_t 11.52 min, (LUX-2 4.6 X 250 mm column, 30% EtOH in heptane). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.54 (s, 1 H), 7.36 (d, *J*=8.5 Hz, 1 H), 7.19 (d, *J*=8.8 Hz, 1 H), 4.49 - 4.58 (m, 1 H), 4.45 (d, *J*=15.4 Hz, 1 H), 4.22 - 4.31 (m, 1 H), 4.09 - 4.22 (m, 2 H), 3.60 (s, 3 H), 3.43 - 3.52 (m, 1 H), 2.74 - 2.91 (m, 2 H), 2.34 - 2.44 (m, 1 H), 2.19 (s, 3 H), 1.92 (s, 3 H), 1.85 - 1.90 (m, 1 H), 1.74 - 1.83 (m, 1 H), 1.33 (d, *J*=6.2 Hz, 3 H), 0.82 - 0.90 (m, 2 H), 0.72 - 0.78 (m, 2 H); MS (ESI+) *m/z* 503.3 $(M+H)^+$. **Enantiomer-2 (69-E)**: R_t 15.86 min, (LUX-2 4.6 X 250 mm column, 30% EtOH in heptane). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.53 (s, 1 H), 7.36 (d, *J*=8.5 Hz, 1 H), 7.19 (d, *J*=8.6 Hz, 1 H), 4.49 - 4.57 (m, 1 H), 4.45 (d, *J*=15.0 Hz, 1 H), 4.23 - 4.30 (m, 1 H), 4.10 - 4.22 (m, 2 H), 3.60 (s, 3 H), 3.43 - 3.52 (m, 1 H), 3.34 - 3.41 (m, 1 H), 2.75 - 2.90 (m, 2 H), 2.35 - 2.44 (m, 1 H), 2.19

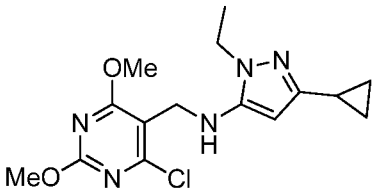
		(s, 3 H), 1.92 (s, 3 H), 1.84 - 1.90 (m, 1 H), 1.74 - 1.82 (m, 1 H), 1.33 (d, *J*=6.1 Hz, 3 H), 0.81 - 0.88 (m, 2 H), 0.72 - 0.78 (m, 2 H); MS (ESI+) *m/z* 503.3 $(M+H)^+$
69-F 69-G		The *racemic* (*trans)*-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine was separated by chiral HPLC (WhelkOD-H column; 15% EtOH (DEA)/heptanes; 1.0 mL/min) to give the following two compounds: **Enantiomer-1 (69-F)**: R_t 10.05 min, (WhelkOD-H 4.6 X 250 mm column, 15% EtOH (DEA) in heptane). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.8 Hz, 1 H), 4.49 - 4.61 (m, 2 H), 3.87 - 3.94 (m, 2 H), 3.69 - 3.76 (m, 1 H), 3.52 - 3.63 (m, 5 H), 3.41 - 3.49 (m, 2 H), 3.26 (s, 3 H), 2.86 (t, *J*=5.4 Hz, 2 H), 2.74 - 2.81 (m, 1 H), 2.20 (s, 3 H), 2.18 (s, 6 H), 1.92 (s, 3 H), 1.74 - 1.83 (m, 1 H), 0.82 - 0.88 (m, 2 H), 0.73 - 0.78 (m, 2 H); MS (ESI+) *m/z* 576.3 $(M+H)^+$. **Enantiomer-2 (69-G)**: R_t 14.69 min, (WhelkOD-H 4.6 X 250 mm column, 15% EtOH (DEA) in heptane). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 4.48 - 4.59 (m, 2 H), 3.87 - 3.94 (m, 2 H), 3.69 - 3.76 (m, 1 H), 3.53 - 3.63 (m, 5 H), 3.42 - 3.48 (m, 2 H), 3.26 (s, 3 H), 2.83 - 2.90 (m, 2 H), 2.74 - 2.81 (m, 1 H), 2.20 (s, 3 H), 2.18 (s, 6 H), 1.92 (s, 3 H), 1.73 - 1.83 (m, 1 H), 0.81 - 0.89 (m, 1 H), 0.70 - 0.78 (m, 1 H); MS (ESI+) *m/z* 576.3 $(M+H)^+$.
69-H		*racemic (trans)*-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylazetidin-3-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.57 (s, 1 H), 7.38 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 5.64 (d, *J*=6.3 Hz, 1 H), 4.51 - 4.39 (m, 2 H), 4.20 - 3.99 (m, 3 H), 3.84 (dd, *J*=5.3, 8.1 Hz, 1 H), 3.60 (s, 3 H), 3.53 - 3.42 (m, 1 H), 3.41 - 3.35 (m, 1 H), 2.92 - 2.74 (m, 2 H), 2.19 (s, 3 H), 1.91 (s, 3 H),

		1.83 - 1.73 (m, 1 H), 1.29 (d, *J*=6.3 Hz, 3 H), 0.89 - 0.81 (m, 2 H), 0.78 - 0.71 (m, 2 H); MS (ESI+) *m/z* 519.1 $(M+H)^+$.
69-I		*racemic* 6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((*trans)*-3-methoxy-2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.57 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 4.52 - 4.41 (m, 2 H), 4.31 - 4.22 (m, 1 H), 4.10 (d, *J*=15.2 Hz, 1 H), 3.96 (dd, *J*=4.7, 8.5 Hz, 1 H), 3.84 (td, *J*=4.5, 6.2 Hz, 1 H), 3.60 (s, 3 H), 3.53 - 3.44 (m, 1 H), 3.43 - 3.36 (m, 1 H), 3.23 - 3.18 (s, 3 H), 2.92 - 2.75 (m, 2 H), 2.19 (s, 3 H), 1.90 (s, 3 H), 1.75-1.82 (m, 1 H), 1.34 (d, *J*=6.3 Hz, 3 H), 0.89 - 0.82 (m, 2 H), 0.78 - 0.71 (m, 2 H); MS (ESI+) *m/z* 533.1 (M+H).
69-J		1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H) 7.37 (d, *J*=8.59 Hz, 1 H) 7.19 (d, *J*=8.59 Hz, 1 H) 4.33 (s, 2 H) 4.18 (t, *J*=7.96 Hz, 2 H) 3.98 (dd, *J*=8.84, 5.31 Hz, 2 H) 3.60 (s, 3 H) 3.40 - 3.49 (m, 2 H) 3.00 - 3.13 (m, 1 H) 2.81 (t, *J*=5.43 Hz, 2 H) 2.19 (s, 3 H) 2.05 (s, 6 H) 1.92 (s, 3 H) 1.78 (tt, *J*=8.34, 5.05 Hz, 1 H) 0.82 - 0.90 (m, 2 H) 0.72 - 0.79 (m, 2 H), MH (ESI+) *m/z* 532.5 $(M+H)^+$.
69-K		(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2,4-dimethylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.34 Hz, 1 H), 7.21 (d, *J*=8.59 Hz, 1 H), 4.27 - 4.36 (m, 1 H), 4.17 - 4.27 (m, 1 H), 3.95 (d, *J*=6.32 Hz, 1 H), 3.57 (s, 3 H), 3.45 - 3.55 (m, 2 H), 3.39 - 3.44 (m, 1 H), 3.21 - 3.30 (m, 2 H), 2.93 (t, *J*=5.94 Hz, 2 H), 2.18 - 2.25 (m, 2 H), 2.17 (s, 3 H), 2.14 (s, 3 H), 2.02 - 2.09 (m, 1 H), 1.89 (s, 3 H), 1.73 - 1.82 (m, 1 H), 1.18 (d, *J*=6.57 Hz, 3 H), 0.82 - 0.88 (m, 2 H), 0.72 - 0.77 (m, 2 H); MS (ESI+) m/z 546.5 (M+H).

69-L		*racemic* (1*S**,6*S**)-3-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane. ^{1}H NMR (400 MHz, CD_3CN) δ ppm 10.72 (br. S., 1 H), 7.40 (d, *J*=8.34 Hz, 1 H), 7.24 (d, *J*=8.59 Hz, 1 H), 4.59 (t, *J*=3.16 Hz, 1 H), 4.55 (d, *J*=14.91 Hz, 1 H), 4.44 (d, *J*=6.06 Hz, 1 H), 4.28 (d, *J*=14.91 Hz, 1 H), 4.23 (d, *J*=5.81 Hz, 1 H), 3.92 (td, *J*=11.81, 4.42 Hz, 1 H), 3.65 (d, *J*=13.64 Hz, 1 H), 3.57 - 3.63 (m, 4 H), 3.57 (s, 3 H), 3.45 - 3.53 (m, 2 H), 3.30 (d, *J*=13.39 Hz, 1 H), 2.89 - 3.06 (m, 2 H), 2.24 (s, 3 H),1.98 - 2.06 (m, 1 H), 1.80 - 1.87 (m, 2 H), 1.21 (s, 3 H), 0.83 - 0.89 (m, 2 H), 0.75 - 0.80 (m, 2 H). MS (ESI+) *m/z* 559.5 $(M+H)^+$.
69-M		*racemic* (*cis*)-3-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-7-oxa-3-azabicyclo[4.2.0]octane. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.48 (br. s, 1H), 7.26 (d, *J* = 8.59 Hz, 1H), 7.16 (d, *J* = 9.09 Hz, 1H), 4.93 - 5.00 (m, 1H), 4.63 (dd, *J* = 6.32, 7.58 Hz, 1H), 4.47 (d, *J* = 14.65 Hz, 1H), 4.35 (t, *J* = 5.68 Hz, 1H), 4.14 (d, *J* = 14.65 Hz, 1H), 3.91 - 4.01 (m, 1H), 3.54 - 3.71 (m, 3H), 3.52 (s, 3H), 3.47 - 3.51 (m, 1H), 3.35 - 3.44 (m, 1H), 3.07 - 3.17 (m, 1H), 2.85 - 3.07 (m, 2H), 2.20 (s, 3H), 1.92 (s, 3H), 1.86 - 1.91 (m, 2H), 1.75 (tt, *J* = 5.34, 8.18 Hz, 1H), 0.73 - 0.80 (m, 4H); MS (ESI+) *m/z* 545.3 $(M+H)^+$.

Example 70

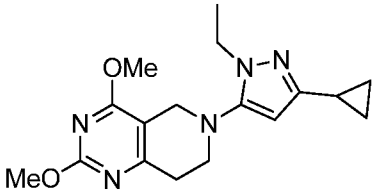
70-A. N-((4-Chloro-2,6-dimethoxypyrimidin-5-yl)methyl)-3-cyclopropyl-1-ethyl-1H-pyrazol-5-amine.



To a precooled (–78 °C) solution of 4-chloro-2,6-dimethoxypyrimidine (7.0 g, 40.1 mmol) in THF (125 mL) under a nitrogen atmosphere was added *n*-BuLi (17.6 mL, 44.1 mmol, 2.5 M in heptane). The resulting solution was maintained at –78 °C for 0.5 h before DMF (7.45 mL, 96 mmol) was added. The resulting solution was stirred at –78 °C for 20 min and then removed from the dry ice bath and allowed to stir for 30 min. At that point the solution was returned to the dry ice bath and stirred for 20 min before being quenched by the slow addition of 30 mL of 6 N HCl. The flask was removed from the dry ice bath and allowed to warm to rt where it was left stirring for 2 h. The mixture was partially concentrated under reduced pressure and then was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted further with EtOAc (2 x 300 mL) and the combined organic layers were then dried over sodium sulfate, filtered and concentrated. After drying on high vacuum the product 4-chloro-2,6-dimethoxypyrimidine-5-carbaldehyde was taken to the next step without further purification. MS (ESI^+) m/z 202.9 $(M+H)^+$.

A solution of 4-chloro-2,6-dimethoxypyrimidine-5-carbaldehyde (2.4 g, 11.8 mmol), and 3-cyclopropyl-1-ethyl-1H-pyrazol-5-amine (2.15 g, 14.2 mmol) in THF was heated at 50 °C for 3 h. The flask was then removed from the heating bath and cooled in an ice bath and EtOH (13 mL) was added followed by $NaBH_4$ (0.896 g, 23.7 mmol). The resulting mixture was left to gradually warm to rt and stir for 18 h. The excess $NaBH_4$ was quenched slowly with saturated aqueous NH_4Cl and diluted with EtOAc. The aqueous layer was further extracted with EtOAc (2 x 250 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was then purified via FCC (20-75% EtOAc/heptane) to give the title compound N-((4-chloro-2,6-dimethoxypyrimidin-5-yl)methyl)-3-cyclopropyl-1-ethyl-1H-pyrazol-5-amine. MS (ESI^+) m/z 338.0 $(M+H)^+$.

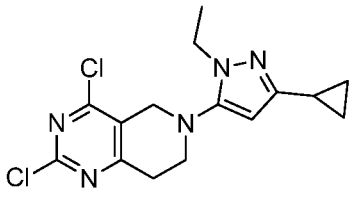
70-B. 6-(3-Cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2,4-dimethoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



To a solution of N-((4-chloro-2,6-dimethoxypyrimidin-5-yl)methyl)-3-cyclopropyl-1-ethyl-1H-pyrazol-5-amine (2.42 g, 7.16 mmol) in DME (50 mL) and water (15 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.5 mL, 14.3 mmol), $Pd(Ph_3P)_4$ (0.828 g, 0.716 mmol) and sodium carbonate (2.47 g, 23.3 mmol). The mixture was sparged with argon for 15 min and then heated at reflux for 18 h. The mixture was then absorbed onto silica gel and dried under reduced pressure. After dry loading, the product was purified by FCC (10-75% EtOAc/heptane) to give 3-cyclopropyl-N-((2,4-dimethoxy-6-vinylpyrimidin-5-yl)methyl)-1-ethyl-1H-pyrazol-5-amine. MS (ESI^+) m/z 330.1 $(M+H)^+$.

3-Cyclopropyl-N-((2,4-dimethoxy-6-vinylpyrimidin-5-yl)methyl)-1-ethyl-1H-pyrazol-5-amine (2.10 g, 6.38 mmol) was taken up in AcOH (40 mL) and heated at 100 °C for 5h. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (150 mL) and washed with saturated aqueous $NaHCO_3$ (150 mL). The aqueous layer was further extracted with EtOAc (3 x 150 mL) and the combined organic layers were then dried over sodium sulfate, filtered and concentrated. The residue was then purified by FCC (40-80% EtOAc/heptane) to give the title compound 6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2,4-dimethoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI^+) m/z 330.2 $(M+H)^+$.

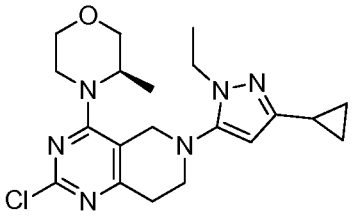
70-C. 2,4-Dichloro-6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



A solution of 6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2,4-dimethoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.20 g, 3.64 mmol) in 12 N HCl (15 mL) and EtOH (15 mL) was heated at reflux for 8 h. The solvent was then removed under reduced pressure and the product 6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diol taken to the next step without further purification. MS (ESI^+) m/z 302.1 $(M+H)^+$.

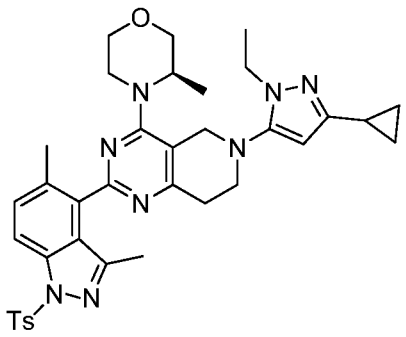
To 6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diol (1.10 g, 3.64 mmol) was added $POCl_3$ (11.4 mL) and this mixture was heated to reflux. After 3.5 h the excess $POCl_3$ was removed by distillation. The residue was cooled to 0 °C and added slowly to a solution of MeOH (50 mL) and Et_3N (12 mL). The solution was stirred at rt for 15 min and evaporated. The residue was dissolved in DCM and washed with a solution of saturated aqueous $NaHCO_3$. The aqueous layer was further extracted with DCM (2x). The combined organic layers were dried with sodium sulfate, filtered and concentrated. The residue was purified by FCC (0-50% EtOAc/heptane) to provide the title compound 2,4-dichloro-6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine. MS (ESI^+) m/z 338.0 $(M+H)^+$.

70-D. (*R*)-4-(2-Chloro-6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine.



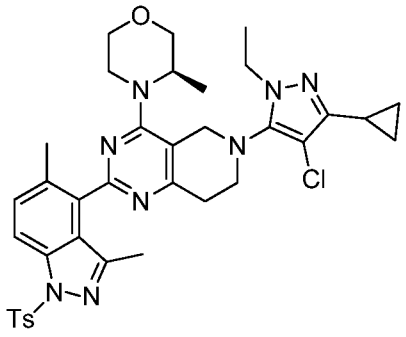
To a solution of 2,4-dichloro-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.110 g, 0.325 mmol) in DMA (2.2 mL) was added (*R*)-3-methylmorpholine (49.3 mg, 0.488 mmol) and DIPEA (284 µL, 1.63 mmol). The mixture was heated at 110 °C for 2 h. Water was added and the aqueous phase was extracted with EtOAc (3x). The organic phases were combined, washed with brine (3x), dried with sodium sulfate, filtered and concentrated under reduce pressure. Purification by FCC (0-60% EtOAc/heptane) provided the title compound (*R*)-4-(2-chloro-6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine. MS (ESI^+) m/z 403.1 $(M+H)^+$.

70-E. (*R*)-4-(6-(3-Cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine.



To a solution of (*R*)-4-(2-chloro-6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine (0.116 g, 0.288 mmol) in DME (1.4 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indazole (0.129 g, 0.302 mmol), $Pd(Ph_3P)_4$ (0.033 g, 0.029 mmol) and aqueous Na_2CO_3 (0.43 mL, 2 M). The mixture was sparged with argon and heated in a microwave reactor at 130°C for 1 h 20 min. The mixture was filtered and concentrated under reduced pressure. Purification by FCC (40-100% EtOAc/heptane) provided the title compound (*R*)-4-(6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine. MS (ESI^+) m/z 667.2 $(M+H)^+$.

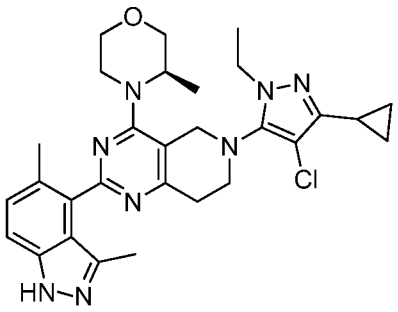
70-F. (*R*)-4-(6-(4-Chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine.



To a solution of (*R*)-4-(6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine (0.075 g, 0.112 mmol) in DCM (2.2 mL) was added NCS (0.016 g, 0.124 mmol). After 1 h the solvent was removed under reduced pressure and the residue purified directly by FCC (20-80% EtOAc/heptanes) to provide the title compound (*R*)-4-(6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-

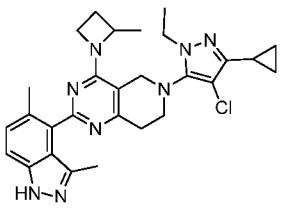
indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine. MS (ESI^+) m/z 701.1 $(M+H)^+$.

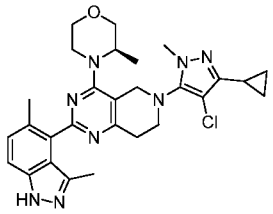
70-G. (*R*)-4-(6-(4-Chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine.

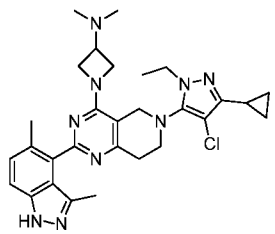


To a solution of (*R*)-4-(6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine (0.081 g, 0.116 mmol) in MeOH (3 mL) was added K_2CO_3 (0.080 g, 0.578 mmol). The mixture was was heated at 55 °C for 1 h 30 min. The methanol was removed under reduced pressure and the residue was taken up in water and the aqueous phase was neutralized to pH=6 (with 3 N HCl) and then extracted with EtOAc (3x). The combined organic phases were washed with brine, dried with sodium sulfate, filtered and concentrated under reduce pressure. Purification by FCC (0-4% MeOH/DCM) provided the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 4.33 (d, J = 14.9 Hz, 1H), 4.18 (d, J = 15.0 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 3.87 – 3.82 (m, 1H), 3.81 – 3.74 (m, 1H), 3.67 (dd, J = 11.2, 2.9 Hz, 1H), 3.63 – 3.42 (m, 4H), 3.39 – 3.31 (m, 1H), 3.00 – 2.93 (m, 2H), 2.18 (s, 3H), 1.88 (s, 3H), 1.84 – 1.73 (m, 1H), 1.29 – 1.21 (m, 3H), 1.14 (d, J = 6.6 Hz, 3H), 0.89 – 0.81 (m, 4H), 0.80 – 0.73 (m, 1H); MS (ESI+) *m/z* 547.2 $(M+H)^+$.

The following compounds were prepared in a similar manner.

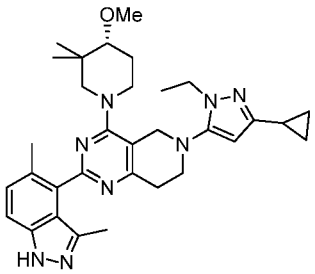
	Structure	Chemical Name & Analytical Data
70-H **70-I**		The *racemic* 6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine was separated by SFC MS-100; mobile phase: 5-55% MeOH + 5 mM NH_4OH in CO_2, 5 ml/min; column: CelLUX2, 5 μm, 4.6 x 100 mm) to provide the corresponding enantiomers. **Enantiomer-1 (70-H):** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.54 (s, 1 H) 7.36 (d, J=8.46 Hz, 1

		H) 7.19 (d, *J*=8.59 Hz, 1 H) 4.48 - 4.56 (m, 1 H) 4.45 (d, *J*=15.41 Hz, 1 H) 4.22 - 4.28 (m, 1 H) 4.17 (q, *J*=7.58 Hz, 1 H) 4.09 (d, *J*=15.41 Hz, 1 H) 3.91 - 3.98 (m, 2 H) 3.42 - 3.52 (m, 1 H) 3.36 (d, *J*=7.20 Hz, 1 H) 2.75 - 2.92 (m, 2 H) 2.35 - 2.41 (m, 1 H) 2.19 (s, 3 H) 1.92 (s, 3 H) 1.84 - 1.90 (m, 1 H) 1.80 (tt, *J*=8.32, 5.07 Hz, 1 H) 1.33 (d, *J*=6.06 Hz, 3 H) 1.26 (t, *J*=7.20 Hz, 3 H) 0.83 - 0.88 (m, 2 H) 0.74 - 0.79 (m, 2 H); MS (ESI^+) *m/z* 517.5 $(M+H)^+$; 98.6%ee (R_t 3.67 min, instrument: SFC MS-100; mobile phase: 5-55% MeOH + 5 mM NH_4OH in CO_2, 5 ml/min; column: CelLUX2, 5 μm, 4.6 x 100 mm) **Enantiomer-2 (70-I):** ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.54 (s, 1 H) 7.36 (d, *J*=8.46 Hz, 1 H) 7.19 (d, *J*=8.46 Hz, 1 H) 4.42 - 4.55 (m, 2 H) 4.22 - 4.29 (m, 1 H) 4.16 (q, *J*=7.87 Hz, 1 H) 4.09 (d, *J*=15.16 Hz, 1 H) 3.90 - 3.99 (m, 2 H) 3.43 - 3.51 (m, 1 H) 3.33 - 3.39 (m, 1 H) 2.74 - 2.92 (m, 2 H) 2.35 - 2.43 (m, 1 H) 2.19 (s, 3 H) 1.92 (s, 3 H) 1.85 - 1.90 (m, 1 H) 1.74 - 1.85 (m, 1 H) 1.33 (d, *J*=6.19 Hz, 3 H) 1.26 (t, *J*=7.20 Hz, 3 H) 0.82 - 0.90 (m, 2 H) 0.73 - 0.80 (m, 2 H); MS (ESI^+) *m/z* 517.4 $(M+H)^+$; 98%ee (R_t 3.97 min, instrument: SFC MS-100; mobile phase: 5-55% MeOH + 5 mM NH_4OH in CO_2, 5 ml/min; column: CelLUX2, 5 μm, 4.6 x 100 mm)
70-J		(*R*)-4-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.61 (br. s., 1 H), 7.46 - 7.33 (m, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 4.42 - 4.29 (m, 1 H), 4.29 - 4.13 (m, 1 H), 3.85 (br. s., 1 H), 3.79 (d, *J*=11.1 Hz, 1 H), 3.72 - 3.64 (m, 1 H), 3.62 - 3.52 (m, 6 H), 3.53 - 3.46 (m, 2 H), 2.95 (br. s., 2 H), 2.18 (s, 3 H), 1.89 (s, 3 H), 1.83 - 1.69 (m, 1 H), 1.15 (d, *J*=6.3 Hz, 3 H), 0.90 - 0.81 (m, 2 H), 0.78 - 0.67 (m, 2 H); MS (ESI+) *m/z* 533.2 $(M+H)^+$.

70-K		1-(6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.19 (d, *J*=8.6 Hz, 1 H), 4.32 (s, 2 H), 4.18 (t, *J*=8.0 Hz, 2 H), 4.03 - 3.88 (m, 4 H), 3.42 (t, *J*=5.6 Hz, 2 H), 3.13 - 2.98 (m, 1 H), 2.82 (t, *J*=5.4 Hz, 2 H), 2.19 (s, 3 H), 2.11 - 2.00 (m, 6 H), 1.92 (s, 3 H), 1.80 (tt, *J*=5.1, 8.3 Hz, 1 H), 1.27 (t, *J*=7.2 Hz, 3 H), 0.91 - 0.81 (m, 2 H), 0.81 - 0.70 (m, 2 H); MS (ESI+) *m/z* 546.2 $(M+H)^+$.

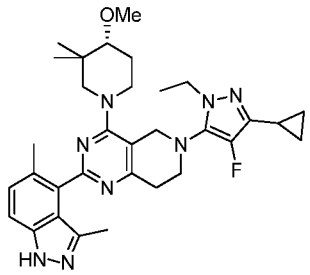
Example 71

71-A. (*R*)-6-(3-Cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



(*R*)-6-(3-Cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, prepared in a similar method as described in **Example 70-E**, was treated in a similar method as described in **Example 70-G**. The residue was purified by FCC (3-6% MeOH/DCM) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 5.54 (s, 1 H), 4.16 - 4.04 (m, 1 H), 4.00 - 3.94 (m, 1 H), 3.89 (q, *J*=7.1 Hz, 2 H), 3.66 (d, *J*=13.6 Hz, 1 H), 3.27 (s, 3 H), 3.11 - 2.76 (m, 5 H), 2.18 (s, 3 H), 1.91 (dd, *J*=4.5, 9.1 Hz, 1 H), 1.87 (s, 3 H), 1.77 (tt, *J*=5.0, 8.4 Hz, 1 H), 1.54 (q, *J*=9.3 Hz, 1 H), 1.30 (t, *J*=7.2 Hz, 3 H), 0.93 (s, 3 H), 0.83 (s, 3 H), 0.82 - 0.77 (m, 2 H), 0.59 - 0.52 (m, 2 H); MS(ESI+) *m/z* 555.2 $(M+H)^+$.

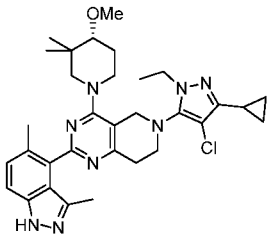
71-B. (*R*)-6-(3-Cyclopropyl-1-ethyl-4-fluoro-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



(*R*)-6-(3-Cyclopropyl-1-ethyl-4-fluoro-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine was prepared in a similar method as described in **Example 56-A**. The residue was purified by FCC (3-6% MeOH/DCM) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 4.32 - 4.20 (m, 1 H), 4.19 - 4.07 (m, 1 H), 3.85 (q, *J*=7.1 Hz, 2 H), 3.67 (d, *J*=13.9 Hz, 1 H), 3.54 - 3.39 (m, 2 H), 3.28 (br. s., 3 H), 3.11 - 2.89 (m, 3 H), 2.84 (d, *J*=13.1 Hz, 1 H), 2.63 - 2.54 (m, 1 H), 2.23 - 2.13 (m, 3 H), 1.96 - 1.84 (m, 1 H), 1.83 - 1.72 (m, 1 H), 1.53 (d, *J*=9.6 Hz, 1 H), 1.25 (t, *J*=7.2 Hz, 3 H), 0.91 (s, 3 H), 0.87 – 0.82 (m, 2H), 0.82 (s, 3H), 0.76 - 0.68 (m, 2 H); MS (ESI+) *m/z* 573.5 $(M+H)^+$.

Example 72

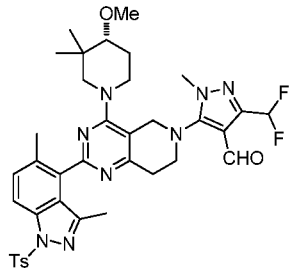
(*R*)-6-(4-Chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



The title compound was prepared from (*R*)-6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine by removal of the tosyl protecting group as in **Example 70-G** followed by chlorination of the pyrazole in a similar manner as described in **Example 70-F**. The residue was purified by FCC (2-6% MeOH/DCM) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.8 Hz, 1 H), 4.44 - 4.30 (m, 1 H), 4.21 (d, *J*=14.7 Hz, 1 H), 3.89 (q, *J*=7.1 Hz, 2 H), 3.67 (d, *J*=12.9 Hz, 1 H), 3.58 - 3.40 (m, 2 H), 3.28 (br. s., 3 H), 3.13 - 2.78 (m, 5 H), 2.18 (s, 3 H), 1.89-1.93 (obs m. 1 H), 1.87 (s, 3 H), 1.76-1.83 (m, 1 H), , 1.48-1.58 (m, 1 H), 1.23 (t, *J*=7.2 Hz, 3 H), 0.91 (s, 3 H), 0.89 - 0.83 (m, 2 H), 0.82 (s, 3 H), 0.80 - 0.71 (m, 2 H); MS (ESI+) *m/z* 589.2 (M+H).

Example 73

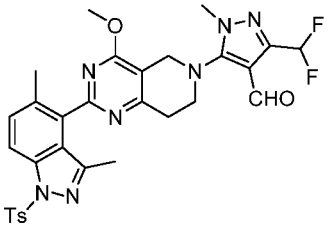
73-A. (*R*)-3-(Difluoromethyl)-5-(2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbaldehyde.



A mixture of (*R*)-2-(3,5-dimethyl-1-tosyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (320 mg, 0.557 mmol), 5-chloro-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carbaldehyde (217 mg, 1.114 mmol) and cesium fluoride (169 mg, 1.114 mmol) in DMA (2.2 mL) was heated at 140 °C for 1.5 h. The reaction mixture was then partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (2x). The combined organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by FCC (EtOAc-heptane 10-100%) to provide (*R*)-3-(difluoromethyl)-5-(2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbaldehyde. MS (ESI+) *m/z* 733.4 $(M+H)^+$.

The following compound was prepared in a similar manner.

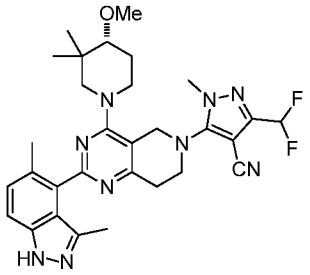
73-B. 3-(Difluoromethyl)-5-(2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-methoxy-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbaldehyde



MS (ESI+) *m/z* 622.2 $(H+H)^+$.

Example 74

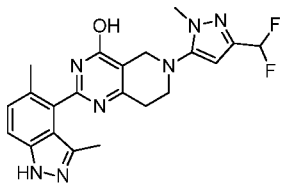
74-A. (*R*)-3-(Difluoromethyl)-5-(2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbonitrile.



A vessel was charged with (*R*)-3-(difluoromethyl)-5-(2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbaldehyde (54 mg, 0.074 mmol), hydroxylamine hydrochloride (77 mg, 1.105 mmol), and DMSO (491 μL). The vessel was capped and placed in a sand bath preheated to 100 °C and the reaction mixture was stirred at that temperature. After 2 h the mixture was diluted with methanol and transferred to a round-bottomed flask. Potassium carbonate was added, and the mixture stirred for 2 h at 60 °C, then allowed to cool to room temperature. The mixture was then filtered through Celite and concentrated, redissolved in methanol, filtered through a syringe filter, and purified by HPLC (15-100% CH_3CN in water with 0.1% NH_4OH) to provide (*R*)-3-(difluoromethyl)-5-(2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbonitrile. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.44 (d, *J*=8.6 Hz, 1 H), 7.31 (d, *J*=8.6 Hz, 1 H), 6.54 - 6.92 (m, 1 H), 4.64 (d, *J*=14.8 Hz, 1 H), 4.53 (d, *J*=14.8 Hz, 1 H), 3.85 - 3.95 (m, 1 H), 3.80 (s, 3 H), 3.67 - 3.75 (m, 2 H), 3.52 (dd, *J*=13.4, 1.3 Hz, 1 H), 3.37 (s, 3 H), 3.01 - 3.10 (m, 4 H), 2.26 (s, 3 H), 2.01 (s, 3 H), 1.97 - 2.06 (m, 1 H), 1.67 - 1.79 (m, 1 H), 1.01 (s, 3 H), 0.93 (s, 3 H); MS (ESI+) *m/z* 576.4 $(M+H)^+$.

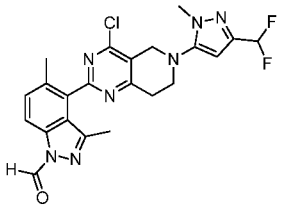
Example 75

75-A. 6-(3-(Difluoromethyl)-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ol.



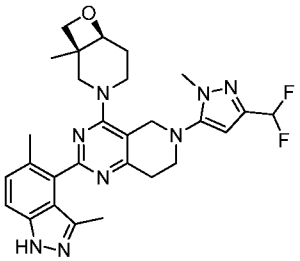
To a solution of 3-(difluoromethyl)-5-(2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-methoxy-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbaldehyde (0.8 g, 1.287 mmol) in ethanol (10.7 mL) was added concentrated HCl (2.1 mL). The microwave vessel was sealed and the mixture was irradiated at 125 °C for 1 h 20 min. The reaction mixture was then cooled to 0 °C and poured into ice water. Solid sodium bicarbonate was slowly added to neutralize the reaction mixture to pH=7, then the crude product was extracted with DCM (3x) and the combined organic layers were dried over sodium sulfate to provide 6-(3-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ol, MS (ESI+) *m/z* 426.4 $(M+H)^+$.

75-B. 4-(4-Chloro-6-(3-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)-3,5-dimethyl-1H-indazole-1-carbaldehyde.



This compound was prepared in a similar manner to **Example 69-C**. MS (ESI+) *m/z* 472.1 $(M+H)^+$.

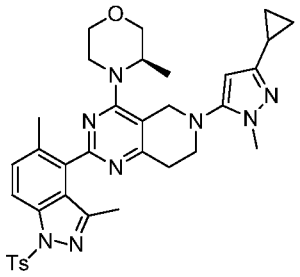
75-C. *Racemic* (1*S,6*S**)-3-(6-(3-(Difluoromethyl)-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane.**



This compound was prepared in a similar manner to **Example 65-A**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1 H), 7.38 (d, *J*=8.59 Hz, 1 H), 7.20 (d, *J*=8.84 Hz, 1 H) ,6.85 (t, *J*=55.00 Hz, 1 H), 6.17 (s, 1 H), 4.57 (t, *J*=3.03 Hz, 1 H), 4.30 - 4.39 (m, 2 H), 4.14 - 4.22 (m, 2 H) , 3.92 (td, *J*=12.00, 4.29 Hz, 1 H), 3.73 (s, 3 H), 3.67 (d, *J*=13.39 Hz, 1 H), 3.49 - 3.57 (m, 1 H), 3.38 - 3.46 (m, 1 H), 3.29 - 3.36 (m, 2 H), 2.86 - 3.05 (m, 2 H), 2.19 (s, 3 H), 1.96 - 2.07 (m, 1 H), 1.89 (s, 3 H), 1.85 - 1.92 (m, 1 H), 1.20 (s, 3 H); MS (ESI+) *m/z* 535.2 $(M+H)^+$.

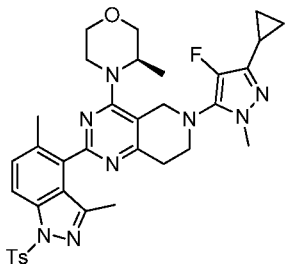
Example 76

76-A. (*R*)-4-(6-(3-Cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine.



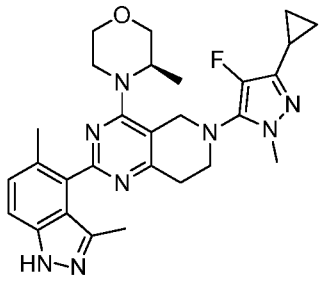
The title compound was prepared from (*R*)-4-(2-chloro-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine in a similar manner to **Example 70-E**. MS (ESI+) *m/z* 653.4 $(M+H)^+$.

76-B. (*R*)-4-(6-(3-Cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine.



The title compound was prepared from (*R*)-4-(6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine as described in **Example 56-A**. MS (ESI+) *m/z* 671.2 $(M+H)^+$.

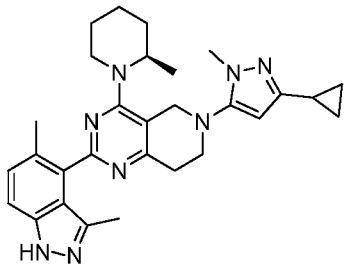
76-C. (*R*)-4-(6-(3-Cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine.



The title compound was prepared from (*R*)-4-(6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine as described in **Example 55-G**. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.70 (br. s., 1H), 7.29 (d, *J* = 8.59 Hz, 1H), 7.18 (d, *J* = 8.34 Hz, 1H), 4.08 (td, *J* = 13.89, 15.41 Hz, 2H), 3.71 - 3.82 (m, 2H), 3.67 (dd, *J* = 2.91, 11.24 Hz, 1H), 3.52 - 3.60 (m, 2H), 3.51 (s, 3H), 3.25 - 3.47 (m, 4H), 2.87 - 3.12 (m, 2H), 2.15 (br. s., 3H), 1.87 (br. s., 3H), 1.72 (tt, *J* = 5.40, 8.24 Hz, 1H), 1.15 (d, *J* = 6.57 Hz, 3H), 0.63 - 0.85 (m, 4H). MS (ESI+) *m/z* 517.3 $(M+H)^+$.

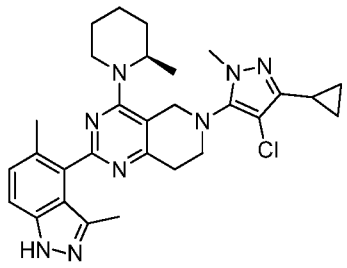
Example 77

77-A. (*R*)-6-(3-Cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.



(*R*)-6-(3-Cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1-tosyl-1H-indazol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, prepared in a similar method as described in **Example 55-E**, was treated in a similar method as described in Example **55-G**. The residue was purified by FCC (1-7% MeOH/DCM) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.45 - 7.31 (m, 1 H), 7.21 (d, *J* =8.8 Hz, 1 H), 5.55 (s, 1 H), 4.10 - 3.88 (m, 3 H), 3.57 (s, 3 H), 3.51 - 3.40 (m, 1 H), 3.14 (t, *J* =11.2 Hz, 1 H), 2.93 (t, *J* =5.9 Hz, 2 H), 2.17 (s, 3 H), 1.87 (s, 3 H), 1.80 - 1.45 (m, 8 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 0.84 - 0.73 (m, 2 H), 0.61 - 0.50 (m, 2 H)); MS(ESI+) *m/z* 497.3 (M+H).

77-B. (*R*)-6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

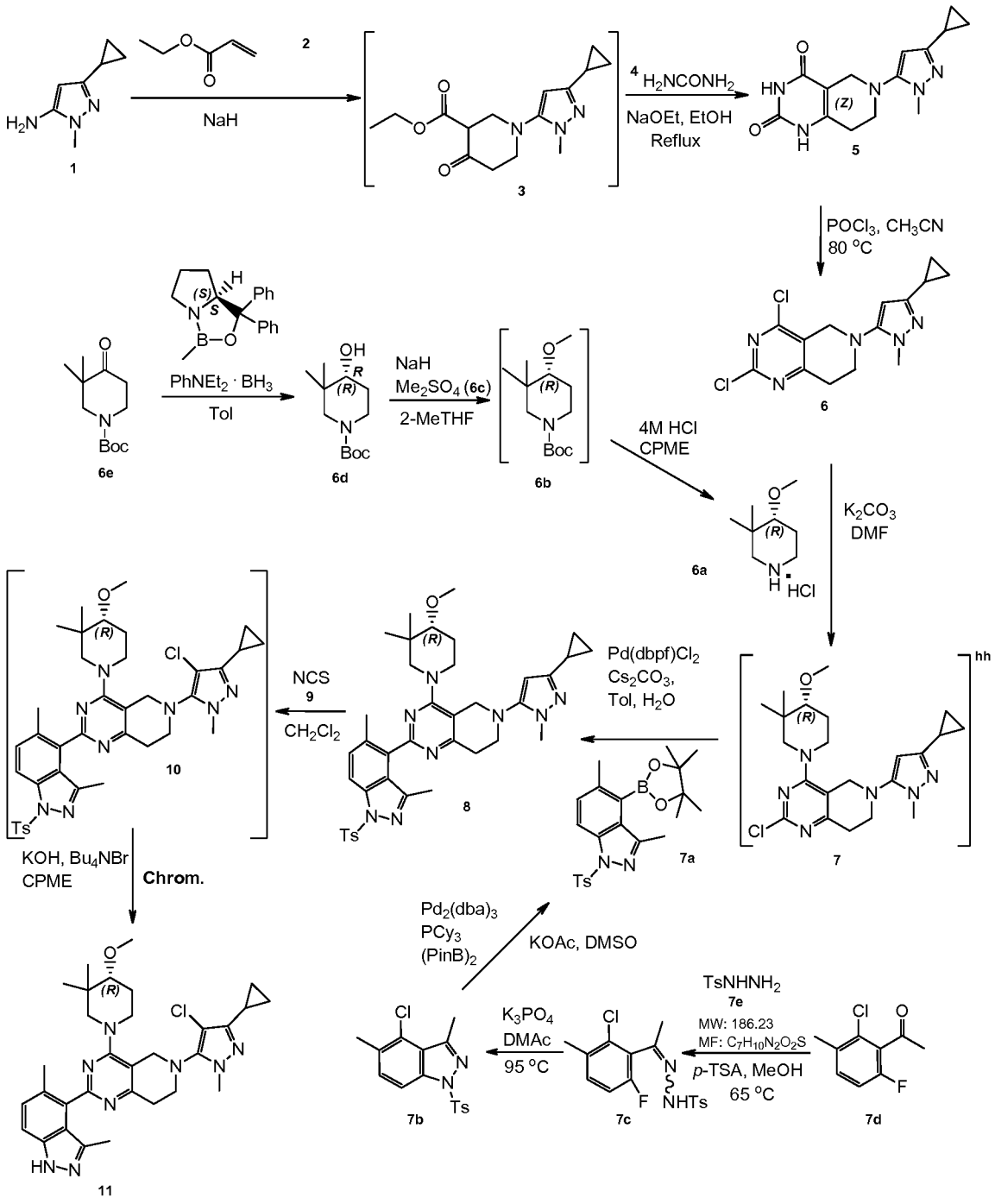


(*R*)-6-(4-Chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine was prepared in a similar method as described in **Example 55-F**. The residue was purified by FCC (1-7% MeOH/DCM) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 4.38 - 4.16 (m, 2 H), 3.99 (d, *J*=6.6 Hz, 1 H), 3.57 (s, 3 H), 3.54 - 3.49 (m, 2 H), 3.45 - 3.37 (m, 1 H), 3.14 (t, *J*=10.7 Hz, 1 H), 2.93 (t, *J*=5.8 Hz, 2 H), 2.17 (s, 3 H), 1.89 (s, 3 H), 1.83 - 1.74 (m, 1 H), 1.44-1.73 (m, 6 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 0.88 - 0.82 (m, 2 H), 0.78 - 0.72 (m, 2 H); MS (ESI+) *m/z* 531.3 (M+H).

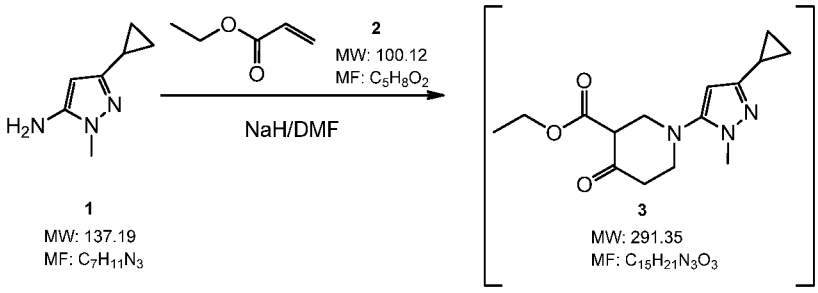
Example 78

Alternate synthesis of Example 55-G

General Synthetic Scheme:

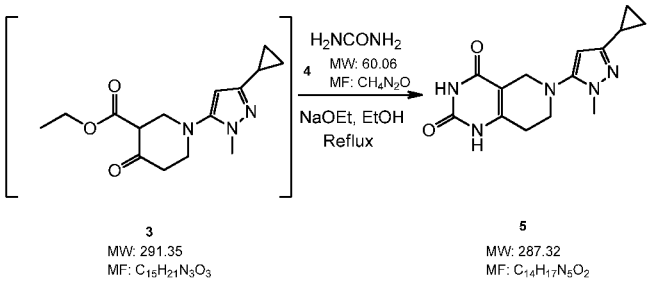

NaH
NaOEt, EtOH
Reflux
POCl3, CH3CN
80 °C
PhNEt2 · BH3
Tol
NaH
Me2SO4 (6c)
2-MeTHF
4M HCl
CPME
K2CO3
DMF
Pd(dbpf)Cl2
Cs2CO3,
Tol, H2O
NCS
9
CH2Cl2
KOH, Bu4NBr
CPME
Chrom.
Pd2(dba)3
PCy3
(PinB)2
KOAc, DMSO
TsNHNH2
7e
MW: 186.23
MF: C7H10N2O2S
p-TSA, MeOH
65 °C
K3PO4
DMAc
95 °C
Boc
Ts
NHTs

Step 1 + 2 → [3]



Into a nitrogen-purged 22 L 4-necked RBF, 500 g of 5-aminopyrazol **1** , 3500 mL of DMF was added and cooled to 2 °C. 160 g of 60 % NaH in mineral oil (1.1 eq) was added in portions. The reaction was stirred at 0-5 °C for 60 min and a suspension formed. 870 mL of ethylacrylate (2.2 eq) at 5-20 °C was added to the reaction over 20 minutes. The reaction was stirred at 0-20 °C for 1.5 h followed by addition of 260 g of HOAc, 5000 mL of EtOAc, 5000 mL 5% Na2CO3 solution, and 5000 mL of water. Two layers formed, were separated and the aqueous layer was extracted twice with 2000 mL of EtOAc. All of the EtOAc layers were combined and held at room temperature overnight. The combined EtOAc layers were passed through a silica gel pad and washed with 1500 mL EtOAc. The filtrate and wash were combined, concentrated to minimal volume as a brown oily residue and purged with nitrogen at room temperature overnight. 1268 g of thick oil product was obtained with HPLC purity (254 nm): 35.08 %. Yield: 119.7 % (no purity correction).

Step [3] + 4 → 5

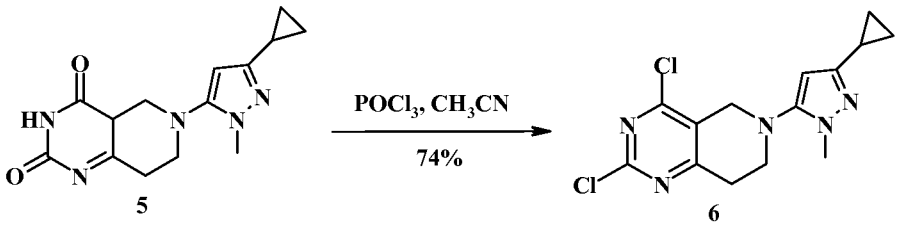


Into a 22 L 4-necked RBF 498 g of urea **4**, 1268 g of crude ketoester **3**, 5000 mL of absolute EtOH and 3800 g of 21 % NaOEt/EtOH solution was added. The mixture was heated to 80 °C and stirred at 80 °C for 30 h. The mixture was then allowed to cool to room temperature and stirred overnight. The mixture was then cooled to 0-5 °C and 733 g of HOAc was added via addition funnel over 40 min at 0-10 °C. The mixture was then split into 4 equal parts. Each part was concentrated at 50 °C/30 mbar to a thick slurry. To each part 1000 mL of water and 500 mL DCM was added. The four parts were recombined

and the pH of the aqueous layer was adjusted to 8.8 by adding 50 % NaOH solution. Solids formed and 2.0 L of water and 1.0 L of DCM were added. The whole batch was filtered and washed with 500 mL EtOAc. The filtered material was dried at 55 °C/30 mbar over the weekend. 65.3 g of beige solid was obtained. HPLC purity (254 nm): 95.58 %. ^{1}H NMR (DMSO-d6): consistent with the molecular structure. LC-MS: ES+ 288.0.

The filtrate was filtered again, washed with water and the aqueous layer was discarded. 3.0 g of beige solid was isolate on the filter. The DCM filtrate and EtOAc wash was concentrated under vacuum, and the residue was dissolved in 1.2 L of 2.0 M HCl solution. 1.0 L TBME was added and the pH was adjusted to 8.8 by adding 200 g of 50% NaOH solution. The mixture was allowed to stir for 60 minutes at 38 °C and then filtered. The pH of the aqueous layer was adjusted to 3.0 by adding concentrated HCl solution. The pH was adjusted to -0.24 with concentrated HCl solution and 500 mL TBME was added. The layers were separated and the aqueous layer was washed with 1.0 L TBME. The pH was adjusted to 7.5 with 50% NaOH solution and held at room temperature overnight. The aqueous layer (pH 7.0-7.5) was then extracted three times with 1.0 L of 2-Me THF. The aqueous layer was discarded and the 2-Me THF layers were combined and then concentrated at 40 °C/30 mbar. The 2-Me THF is azeotropically removed with iPOAc. Bottom is thick, supernatant has negligible amount of product. Decant the supernatant and rinse the residue with iPOAc. Discard the iPOAc supernatant. Into the residue, add 500 mL THF. Heat, a suspension is formed. Add 500 mL iPOAc. Concentrate to 800 mL. Cool to rt and stir at rt for overnight. Filter, wash with iPOAc. Dry at 65 °C/30 mbar overnight. 58.0 g of beige solid was obtained. HPLC (254 nm): 95.1 %. ^{1}H NMR (DMSO-d6): consistent with the molecular structure. Combined yield from amine **1** (two crops): 12.6 %.

Step 5 → 6



5

MW: 287.32
MF: $C_{14}H_{17}N_5O_2$

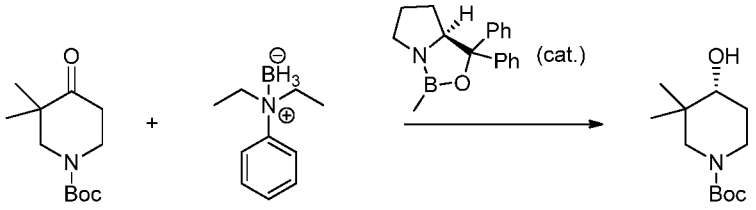
6

MW: 324.22
MF: $C_{14}H_{15}Cl_2N_5$

$POCl_3$ (176 mL) was slowly added to a suspension of **5** (200 g, 97.7% purity) and MeCN (1.05 L) in a 5-L flask at 77 to 80 °C over 30 min (slightly exothermic reaction, HCl gas evolution). The contents were gently refluxed at 80-81 °C for 16 h to obtain an orange-brown suspension and then PSC was checked (by HPLC, < 2% S.M.). H_2O (600 mL) was added slowly into flask at 5-10 °C over 30 min

(exothermic reaction) and then the contents were stirred at 5-10 °C for 2 h. i-PrOAc (3.47 L) was added into pot over 2 min, and a solution of Na_2CO_3 (504 g) in H_2O (6.2 L) was then added slowly into the mixture at 5-10 °C over 1 h (CO_2 gas evolution). The mixture was maintained at 10 to 20 °C overnight (final pH 5.5-6.0). The bottom aqueous layer was discarded. The top organic layer was washed once with H_2O (1.2 L) and once with saturated NaCl solution (1.2 L), dried over anhydrous $MgSO_4$, filtered, and then concentrated (55 °C, 35 mbar) to a thick suspension. TBME (800 mL) was added into flask and the suspension was heated at 45 °C for 30 min and heptanes (800 mL) were then added. The contents were cooled to 15 °C over 30 min and then the solids were filtered (fast filtration). The filter cake was dried in a vacuum oven (55-60 °C, 35 mbar) for 16 h to give **6** (164 g) as a yellow solid. HPLC Purity (254 nm) of **6**: 99.53% ^{1}H NMR Analysis ($CDCl_3$): Consistent with the structure. Theoretical Yield = [(200x0.977)/287.32]x324.22 = 220.6 g. Actual Yield = (164x0.9953)/220.6= 74.0%

Step 6e → 6d

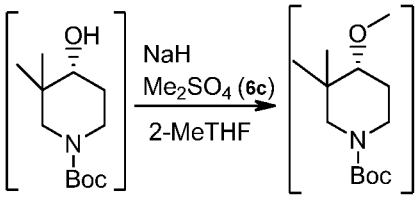


Into a nitrogen-purged 4-necked 12 L RBF 38.9 g of S-Me CBS catalyst 2.35 L of anhydrous toluene and 471 g of BH_3.diethylaniline (DEAB) complex was added. A solution of 649.2 g of ketone in 3.90 L of anhydrous toluene was prepared in a 5 L RBF by stirring at rt. The mixture in the 12 L RBF was heated to 35 °C and the ketone solution was added at 35-42 °C in 55 min. The mixture was stirred for 30 minutes at 40-30 °C. The clear mixture is cooled to 10-15 °C and 4.06 L of 1.0 M HCl solution was added over 10 minutes while controlling temp at 15-25 °C. The mixture is stirred for 30 minutes at 20 °C for 30 min. The layers are separated and the organic phase is washed with 4.0 L of 1.0 M HCl solution, 2.0 L 1.0 N NaHCO3 solution and twice with 2.0 L of water. The combined organic layers were concentrated at 50 °C / 30 mbar to yield 657 g of an oily product. Into the 657 g of crude oily product 1.0 L of heptane was added at 50 °C. The mixture was cooled to 0-10 °C, seeded and stirred at 0-10 °C for 1 h. The mixture was filtered and washed with 500 mL cold heptane. The isolated solids were dried at 35 °C/30 mbar over the weekend. 542.1 g of white solid was obtained. HPLC purity (210 nm): 94.7 %.

Chiral HPLC (205 nm): 99.8 % ee. 1H NMR (DMSO-d6): clean and consistent with the molecular structure. ML Chiral HPLC (205 nm): 90.8 % ee.

The mother liquor was concentrated to remove all volatiles at 50 °C/30 mbar. 350 g of heptane was added and the mixture was cooled to 0-5 °C, seeded and stirred at 0-5 °C for 2 h. The mixture was filtered and the solids were washed with cold heptane. The collected solids were dried at 35 °C/30 mbar overnight. 39.8 g of white solid was obtained. HPLC purity (210 nm): 96.4 %. Chiral HPLC (205 nm): 98.8 % ee. 1H NMR (DMSO-d6): clean and consistent with the molecular structure.
Discard the ML Chiral HPLC (205 nm): 73.6 % ee. Overall yield: 90.4%

Step 6d + 6c → [6b]

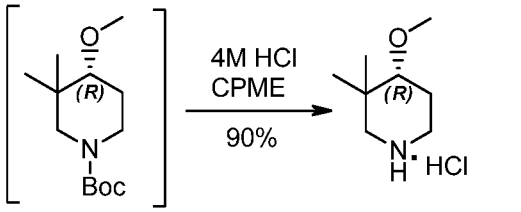


6d
MW: 229.32
MF: $C_{12}H_{23}NO_3$

6b
MW: 241.33
MF: $C_{13}H_{23}NO_3$

To a 12 L nitrogen purged RBF was added 572 g of chiral alcohol **6d** and 4900 mL of 2-Me THF. The mixture was cooled to 0-10 °C and 199.5 g of 60 % NaH in mineral oil was added in portions. The mixture was stirred at 0-10 °C for 30 minutes and 566.3 g of Me2SO4 was added in portions at 0-10 °C. 5.3 mL of water was added and the suspension was stirred at 5-20 °C for 16 hours. The mixture was cooled to 0-5 °C and 570 mL of water and 1140 mL 20% K2CO3 solution were added dropwise. Stir at rt for 2 h. Upon standing the layers were separated and the organic layer was washed twice with 1100 mL 20 % NaCl solution and once with 1000 mL water. The organic layer was concentrated at 50 °C/30 mbar yielding 858.7 g of an oily residue. Overall yield: 121 %.

Step [6b] → 6a

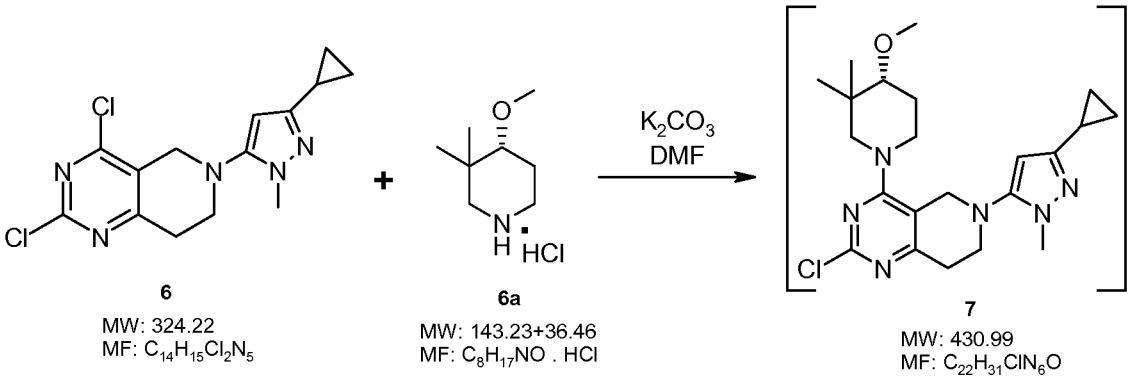


6b
MW: 241.33
MF: $C_{13}H_{23}NO_3$

6a
MW: 141.21 + 36.46
MF: $C_8H_{15}NO$. HCl

To a 12 L nitrogen purged RBF was added 848.7 g of crude Boc-amine **6b** and 800 mL CPME. At room temperature 2.66 L 4.0 M HCl/CPME was added and the mixture was allowed to stir at room temperature for 18 hours. 4000 mL of heptane was added and the mixture was allowed to stir at room temperature for 2 hours. The mixture was filtered and washed with 1000 mL heptanes. The isolated solid was dried at 35 °C/30 mbar over the weekend. 514.6 g of white solid **6a** was obtained. Yield: 82.1 %.
^{1}H NMR (D_2O): consistent with the molecular structure.

Step 6 + 6a → [7]



6
MW: 324.22
MF: $C_{14}H_{15}Cl_2N_5$

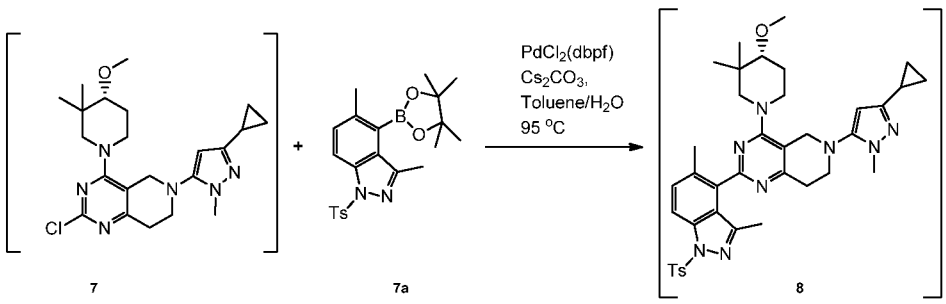
6a
MW: 143.23+36.46
MF: $C_8H_{17}NO$. HCl

7
MW: 430.99
MF: $C_{22}H_{31}ClN_6O$

A 12-L 4-necked RBF, was charged with **6** (404.4 g, 1.247 mol), **6a** (261.9 g, 1.457 mol) and DMF (2.5 L) at room temperature. Stirred at room temperature to give a slurry. Cooled to 0-5 °C. Added K_2CO_3 (518.6 g, 3.752 mol) portion wise in 30 minutes while maintaining the temperature at 0-5 °C. Stirred the resulting good slurry at 0-5 °C for 6 hours. Slowly warmed to room temperature. After 8 hours (from finishing addition of K_2CO_3), stop stirring and let it stand over night. Stirred at room temperature and added MTBE (3.0 L) to a slurry. Added H_2O (3.0 L), exothermic (Tmax ~31 °C). A bi-phasic solution with small amount of solids. Transferred the reaction mixture to a 22-L flask with bottom valve. Rinsed the 12-L RBF with MTBE (4.09 L) and H_2O (2.67 L), and transferred into the 22-L flask. Stirred at RT for ~1 h. Let it settle. Still small amount of solids between the layers. Added MTBE (0.79

L, total 7.88 L) and H_2O (0.63 L, total 6.30 L). Still some solids did not dissolve (solids soluble in H_2O). Separated the aqueous layer. The rag layer with some solids was kept with organic layer. Washed the organic layer with H_2O (250 mL) to dissolve the solids. Removed the aqueous layer. Extracted the 250 mL aqueous layer with MTBE (1.0 L). Saved the MTBE layer and discarded the aqueous layer. Extracted the 1st aqueous layer with the 1.0 L MTBE layer and 1.66 L of fresh MTBE (total: 2.66 L). Separated the MTBE layer (HPLC indicated no **7** in the aqueous layer, discarded). The MTBE layer was combined into the 1st organic layer. Extracted with H_2O (1.77 L), followed by 20% brine (1.77 L). Separated the organic layer. Concentrated on rotovapor to a foaming oil residue to afford **7**. Weight: 605 g. Stand on bench at room temperature over night. HPLC: 91.03%, **6**: n.d., regio-isomer of **7**: 6.11% (254 nm). LC-MS (M+1: 431.0, 432.8) confirmed the structure. Added toluene (500 mL). Concentrated on rotovapor to a foaming oil residue. Added toluene (500 mL). Concentrated on rotovapor to a foaming oil residue. Weight: 661.2 g. Used directly in the next step.

Step [7] + 7a → [8]



7
MW: 430.99
MF: $C_{22}H_{31}ClN_6O$

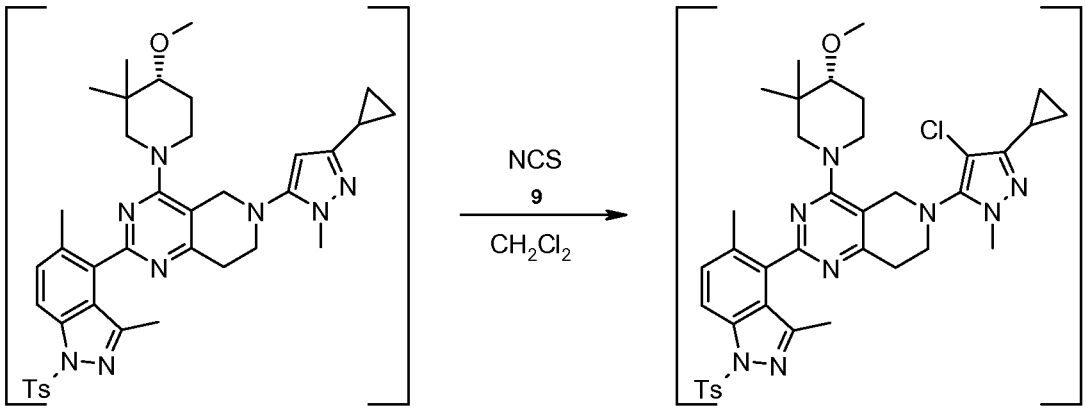
7a
MW: 426.35
MF: $C_{22}H_{27}BN_2O_4S$

8
MW: 694.91
MF: $C_{38}H_{46}N_8O_3S$

A nitrogen purged 12 L 4-necked RBF was charged with 584.1 g of the crude 7/toluene solution, 273.3 g of 7a, 30.8 g of $Pd(dbpf)Cl_2$, and 3.3 L of toluene. Nitrogen was bubbled through the mixture for 30 min and then heated to 60 °C while bubbling with nitrogen was continued. In a 1000_mL Erlenmyer flask 520.8 g of cesium carbonate and 374 mL of water was charged. Nitrogen was bubbled through the solution at 60 °C for 30 minutes. At 60 °C, the cesium carbonate solution was charged to the mixture. The mixture was then refluxed at 93-95 °C for 17.5 h and then cooled. At 30 °C 2.5 L of water was added and 2 dark layers formed. The organic layer was isolated and filtered through a celite bed. The organic layer was extracted with 1.9 L 2.0 M HCl solution twice. The aqueous layers were combined and washed with 1.9 L of toluene. 446 mL of 50 % NaOH solution and 3.9 L EtOAc at 40 °C were added to the aqueous layer and 100 mL 4.0 N NaOH solution was used to adjust pH to 9. The layers were separated and the organic layer was held at room temperature overnight. The organic layer was washed

with 3.9 L 20 % NaCl solution. The organic layer was concentrated yielding 600 g of a residue. The residue was taken up in 1000 mL MTBE at 40 °C and 22 g of pica 120 was added and mixed. The mixture was filtered through a silica gel pad with 1.0 L TBME at room temperature by gravity overnight. The TBME solution was charged to a 22 L RBF and 500 mL 5-6 N HCl in iPA was added and stirred at room temperature for 40 minutes. The mixture was filtered and the filter cake was washed three time with 1.0 L EtOAc. The wet filter cake was transferred to a 22 L RBF using 6.0 L 5 % Na2CO3 solution and 6.0 L EtOAc. The layers were separated and the organic layer was washed with 2.0 L 20% NaCL solution. The organic layer was held at room temperature overnight and then concentrated to dryness at 40°C/30 mbar. The residue was taken up in 1.0 L DCM at 30-40 °C and filtered through a celite bed in a sintered-glass funnel washed with 500 mL DCM and concentrated at 40 °C/30 mbar to dryness. Use another 1000 mL DCM to dissolve the residue and concentrate at 40°C/30 mar again to dryness. 538.1 g of black foaming solid was obtained. ^{1}H NMR ($CDCl_3$): consistent. HPLC (210 nm): 95.8 % product. LC-MS: ES+ 695.2. Overall yield: 95.1 % from dichloropyrimidine (no purity correction).

Step [8] + 9 → [10]



8
MW: 694.91
MF: $C_{38}H_{46}N_8O_3S$

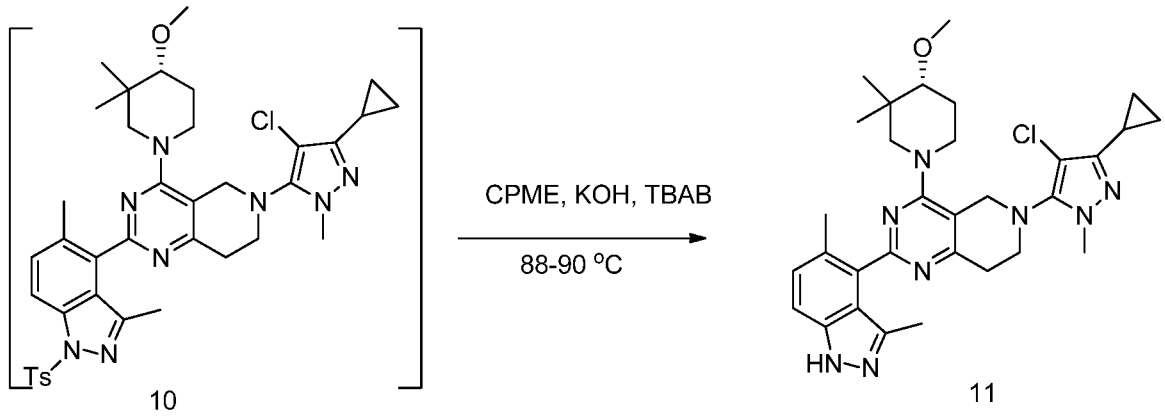
10
MW: 729.35
MF: $C_{38}H_{45}ClN_8O_3S$

8 (534 g, 768.5 mmol) was dissolved in CH_2Cl_2 (2.00 L). A little bit of solids and tiny amount of H_2O was observed. Added 60 g of anhydrous $MgSO_4$. Filtered and rinsed with CH_2Cl_2 (1.0 L) (filtration was slow) and added into the reaction mixture. Charged into a 12-L, 4 necked RBF at RT under N_2. Rinsed with CH_2Cl_2 (0.5 L) and added into the reaction mixture. Charged NCS (102.6 g, 768.5 mmol) at room temperature in 5-10 min (slightly exothermic, Tr from 14 °C to 20 °C). Rinsed with CH_2Cl_2 (0.5 L, total 4.0 L) and added into the reaction mixture (20 °C). A brown solution. Stirred at room temperature

under N_2 overnight.

Added H_2O (2.00 L) and stirred at room temperature for 30-60 min. Let it settle for 2 h. Separated the organic layer and washed it with H_2O (2.00 L). Separated the organic layer and washed it with saturated aqueous $NaHCO_3$ (2.00 L). Separated the organic layer, dried with anhydrous $MgSO_4$ (100 g) and let the mixture stand at room temperature overnight. Filtered off $MgSO_4$ and concentrated the reaction mixture was concentrated on rotovapor under vacuum to dryness to a foaming oil residue (weight: 470 g). Added CPME (350 mL) and concentrated under vacuum to dryness to a foaming oil residue. Repeated two more times to obtain **10** as an foaming oil residue. Weight: 470 g (crude yield: 83%). HPLC: 91.6%, **11**: 1.26%, 7.2 min impurity: 4.67% and several other small impurities (210 nm). LC-MS (M+1: 729.1, 731.1) confirmed the structure.

Step 10 → 11



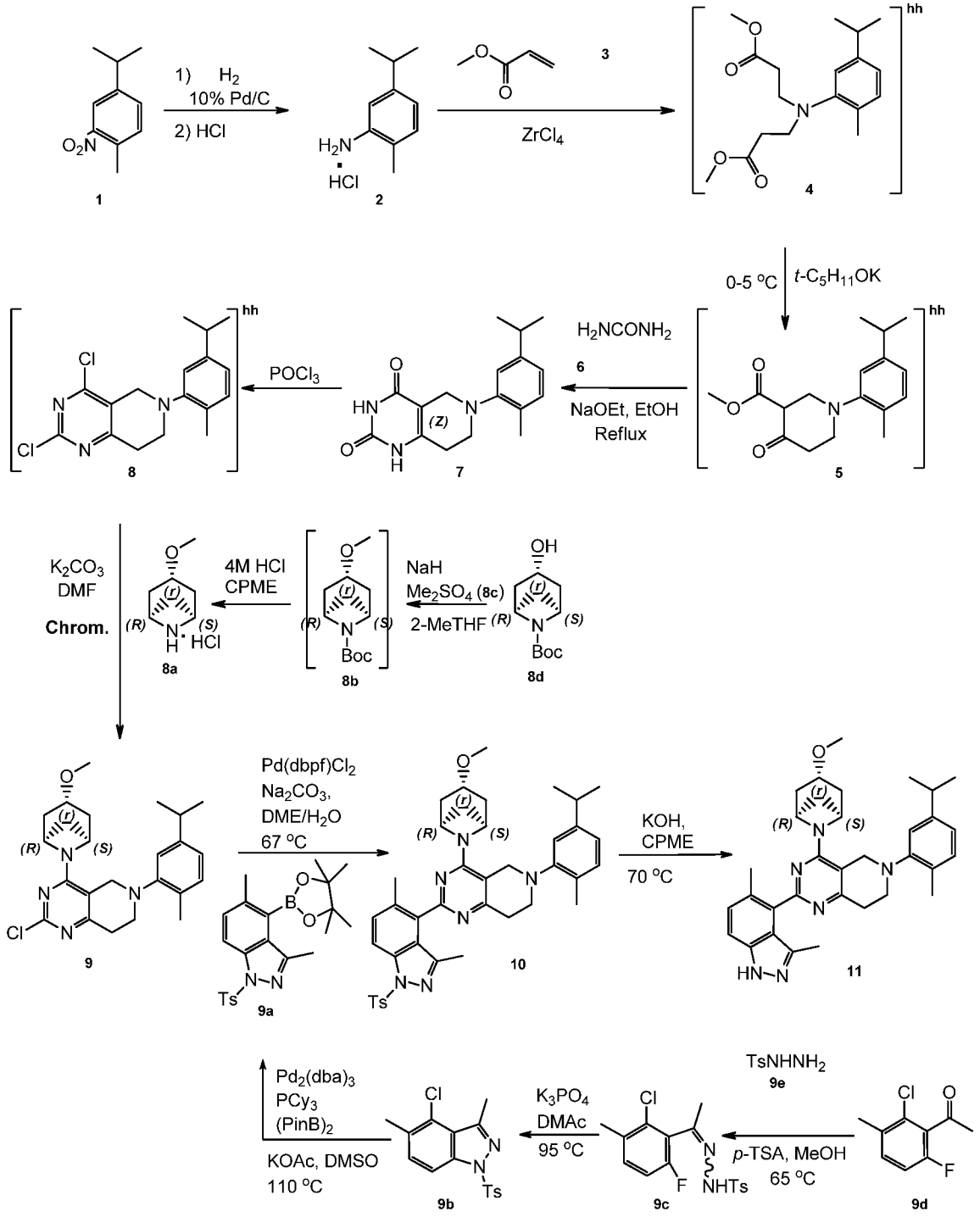
10 11

Charge a 5-L flask with 235 g of crude compound **10**, 2300 mL of CPME, and 36 g of KOH. Heat to 90 oC, add 23.5g of TBAB. Hold at 90.6 °C for 3h. Cool to 20°C, add 600 mL of water, stir for 30 min. Separated two layers. Wash the organic layer with 400 mL of water twice and 500 mL of brine. Concentrate the organic layer to dryness to give 175 g of the desired product in 95% yield. Purified the product via column chromatography. Charge a 5-L flask with 1600 mL of water, then slowly add a solution of 170 g of the product in 400 mL of methanol. Stir at 20° C for 1 h after addition. Filter the solids and washed the wet cake with 20% MeOH in water. Dry at 45 oC for 16 h to give 160 g of the desired product in 94% yield. LC-MS and NMR confirmed the structure. HPLC: 98.6%; residual solvents met specs.

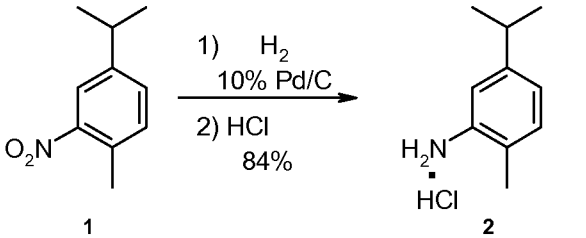
Example 79

Alternate synthesis of Example 19-F

General Synthetic Scheme:



Step 1 → 2



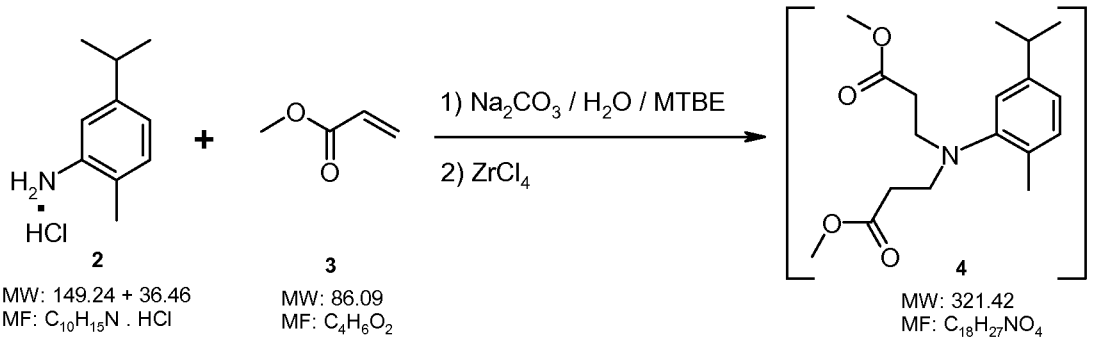
1
MW: 179.22
MF: $C_{10}H_{13}NO_2$

2
MW: 149.24 + 36.46
MF: $C_{10}H_{15}N$. HCl

To a 5-L hydrogenator was charged 10% Pd/C (50% wet, 12.0 g) and purged with N_2 5 times. Charged EtOH (2.0 L), then **1** (426.6 g). Rinsed with EtOH (1.2 L, total 3.2 L) and added into the reaction mixture. Purged with N_2 5 times, then H_2 5 times. Hydrogenated at 15 pisg of H_2, 325 rpm stirring and 25 °C for 6 h. No H_2 uptake after 3.5 h. The reaction mixture was stored in the reactor at RT under N_2 over night. The reaction mixture was filtered through a celite pad. Rinsed the reactor with EtOH (110 g). Rinsed the celite pad with the EtOH rinse, then with fresh EtOH (150 mL). Combined the reaction mixture and rinses to afford a dark blue solution. Concentrated it on rotovapor to dryness to obtain crude **2** free base as a dark blue liquid. Weight: 360 g. HPLC: 81.3% (254 nm). ^1H and ^{13}C-NMR confirmed the structure with some impurities.

Crude **2** free base was added with CPME (150 mL) to give a solution. Concentrated to dryness (weight: 408 g) on rotovapor. The residue was dissolved in CPME (2.0 L) to give a dark blue solution. Added 4M HCl in CPME (650 mL) slowly (1 h). Solids started to form after 200 mL of HCl was added. Rinsed with CPME (850 mL, total 3.55 L, including from residue **2**) and added into the reaction mixture. A good pinkish slurry (T 36 °C). Slowly cooled to room temperature. Stirred at room temperature over night. The solids were filtered through a polypropylene pad and washed with CPME (3.0 L). Dried the solid in the vacuum oven at 40 °C for over weekend (not much change after a few hours) to afford a pink solid. Weight: 374.5 g (wet: 419.6 g), yield: 84.7%. HPLC: 99.0% (254 nm). HPLC: 94.2%, ~1% regio-isomer (210 nm, 254 nm), ~3.8% des-isopropyl **2** (254 nm). NMR and LC-MS (M+1: 150.1) confirmed the structure.

Step 2 + 3 → [4]

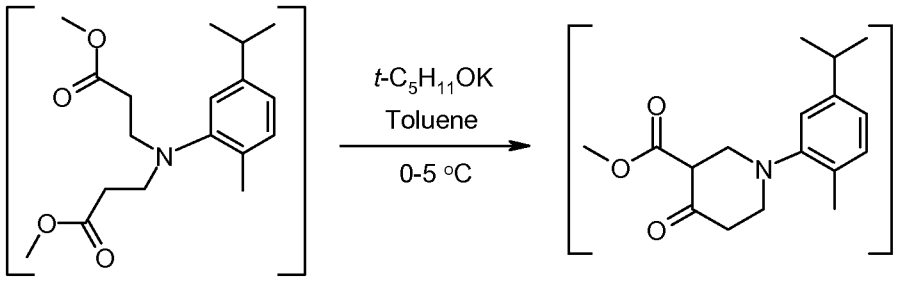


Mix 4.1 L of 10% Na_2CO_3 solution, 370 g of aniline HCl salt (**2**), and 4.0 L TBME at ambient temperature for 30 min. Two clear layers formed. Separate, and wash the organic phase twice with 1.0 L 20 % NaCl solution. HPLC of the organic layer (210 nm): 93.7 % aniline (5.34 m), 5.66 % 2.7 min, 0.6 % 5.2 min. Dry the organic layer with 80 g of anhydrous magnesium sulfate. Filter off the solids, wash with TBME. Concentrate the combined TBME solution at 45 °C/30 mbar to dryness. Purge with nitrogen for 2 h. 295 g of oily aniline free base was obtained. HPLC (210 nm): 94.4 % aniline (5.34 m), 5.2 % 2.7 min, 0.4 % 5.2 min. ^{1}H NMR (DMSO-d_6): consistent with the molecular structure.

Mix the 295 g of aniline free base and 700 g (700 mL) of acrylate (**3**). Cool the batch to 0 – 5 °C with an ice/water bath. Then add through a solid addition funnel 69.1 g of $ZrCl_4$ powder over 2 h at 6 ± 3 °C. Stir at 0 – 5 °C for 30 minutes. Remove the ice bath, allow the batch to warm up to room temperature. Stir at 10 – 20 °C for 3 h. HPLC: 79.3 % product **4** (8.89 min), 1.3 % mono-addition product (7.93 min), 5.6 % 6.71 min, 7.5 % 14.1 min out of total except acrylate.

At ambient temperature, add into the batch 2.0 L toluene and 1.36 L of 10% Na_2CO_3 solution while controlling batch temperature at room temperature. Filter the batch through a celite bed and wash with 300 mL toluene. Separate, and wash the toluene layer with 500 mL 1.0 M $NaHCO_3$ solution (aq pH 10) and wash twice with 500 mL 20% NaCl solution (aq pH 8, 6.5). Dry the organic layer with 50 g of $MgSO_4$. Filter off the solid and wash with toluene. Concentrate the combined toluene filtrate at 45 °C/30 mbar, then at 60 °C/30 mbar to dryness. Purge the product **4** with nitrogen over weekend. 644.9 g of orange liquid was obtained. This oily product **4** was directly used in the next step without further purification. Yield: 100.7% (no purity correction). HPLC purity (210 nm): 81.7 %. Major impurities: 5.0 % 6.7 min, 1.4 % mono-addition product (7.9 min), 0.6 % 9.4 min, 1.2 % 11.0 min, 6.8 % 14.1 min. ^{1}H NMR (DMSO-d_6): consistent with the molecular structure.

Step [4] → [5]

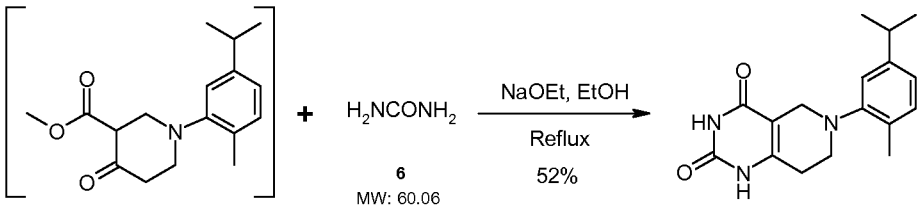


4
MW: 321.42
MF: $C_{18}H_{27}NO_4$

5
MW: 289.38
MF: $C_{17}H_{23}NO_3$

Into a solution of 630.7 g of diester in 6.3 L of toluene pre-cooled to 0~5 °C with an ice/water bath, was added through an addition funnel 2.475 kg of 25% potassium amylate solution in toluene at 0 – 5 °C dropwise over 60 min. The batch became a yellow suspension at the end of addition. Stir the batch at 0 – 5 °C for 30 min. At 0-15 °C, add 294.6 g of HOAc dropwise in 15 min and 5.5 L of 1.0 M $NaHCO_3$ solution. Mix the batch at ambient temperature and separate the aqueous layer. Wash the organic phase twice with 2 L 20% NaCl solution. Dry the organic layer with 100 g of anhydrous $MgSO_4$. Filter off the solid, wash with toluene. Hold the combined toluene solution at ambient temperature overnight. Concentrate the toluene solution at 55 °C/30 mbar to dryness and purge with nitrogen for 2 h. 622.1 g of yellow oil was obtained. This oily product was directly used in the next step without further purification. Yield: 101.8 %. HPLC (210 nm): 41.2 % 11.3 min, 49.6 % 12.5 min (probably keto-enol tautomerization), major impurities: 2.3 % 7.6 min, 0.7 % 15.6 min. ^{1}H NMR (DMSO-d_6): consistent with the molecular structure.

Step [5] + 6 → 7



5
MW: 289.38
MF: $C_{17}H_{23}NO_3$

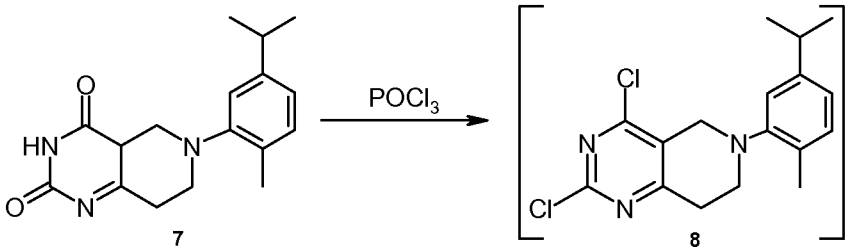
6
MW: 60.06
MF: CH_4N_2O

7
MW: 299.38
MF: $C_{17}H_{21}N_3O_2$

Into a mixture of 271.1 g of urea (**6**) and 622.1 g of ketoester (**5**) in 3.75 L of EtOH (fresh), was added 2.117 kg of 21 % NaOEt/EtOH in portions at 15 °C. Stir and heat the batch to 80°C for 20 h under even agitation. Allow the batch to cool down to ambient temperature over night. Cool the batch to 12 °C

with an ice bath, add 392.3 g of HOAc into the batch slowly at 12 – 16 °C over 20 min. Concentrate the batch in 1.5 L portions at 50 °C/30 mbar to nearly dryness. Stir the solid residue in 6.0 L of water at ambient temperature for 1 h. Filter and wash the cake with 1.0 L of water. Stir the wet filter cake with 1.7 L of *i*-POAc, and heat to reflux. Stir and cool to ambient temperature, and stir over night. Filter the batch and wash the cake with 600 mL of *i*-POAc. Dry the filter cake at 60 °C/30 mbar over night to obtain 335.7 g of **7** as beige powder. Yield: 52.2%. HPLC (210 nm): 95.5 % ^{1}H NMR (DMSO-d_6): consistent with the molecular structure.

Step 7 → [8]



7
MW: 299.38
MF: $C_{17}H_{21}N_3O_2$

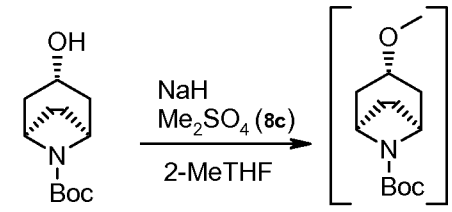
8
MW: 336.27
MF: $C_{17}H_{19}Cl_2N_3$

To a 3-necked, 5-L round-bottomed flask, equipped with a mechanical stirrer, a thermometer, a reflux condenser, a heating mantle, and a nitrogen inlet is charged at ambient temperature, 106g (354mmol) of the starting material, uracil, **7** and 1.0L of toluene. Stir the beige yellow slurry at 23°C for 10min. Add in one portion, 1.040kg (6.78mol) of phosphorous oxychloride. Heat the mixture to an internal temperature at 105°C over 30min. Maintain at this temperature for 6h. The reaction mixture over time will turn into a clear dark solution, which is an indication that the chlorination reaction is complete. HPLC shows no more uracil, **7** is left. The solution is cooled to 23°C and is held overnight.

The excess phosphorous oxychloride is distilled off under vacuum, while maintaining the batch temperature at below 45°C. The remaining $POCl_3$ is azeotropically removed by the addition of two 300mL additions of toluene. Dilute the reaction mixture in 1.0L of toluene. Cool the dark solution to an internal temperature at 15°C. Basify the toluene solution with an aqueous solution of 200g of sodium carbonate in 1.5L of water. Make sure the final pH is 9. Stir the resulting tan suspension at ambient temperature for 1h. Separate layers. Extract the aqueous layer with 500mL of toluene. Wash the combined organic layers with 400mL of brine and 100mL of water. Separate layers. Concentrate the

organic layer to a constant weight of, T: 156g of **8** as a dark oil in >100% yield. HPLC, TLC and ^{1}H-NMR: consistent with the molecular structure.

Step 8d + 8c → [8b]

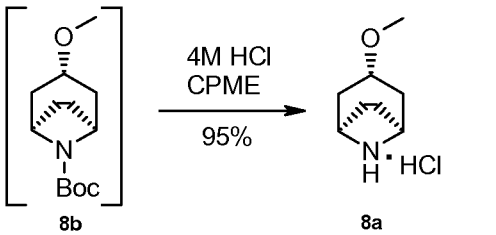


8d
MW: 227.31
MF: $C_{12}H_{21}NO_3$

8b
MW: 241.33
MF: $C_{13}H_{23}NO_3$

N-BOC-Nortropin **8d** (106.5 g) was stirred with 2-MeTHF (450 mL) at RT to give a slurry. Cooled to 12 °C. Added with NaH (60% in mineral oil, 37.48 g) at this temperature and rinsed with 2-MeTHF (50 mL). Some bubbles were observed at beginning, but not much exothermic. Stirred at 10 °C for 30 minutes to obtain a slurry. Added $(CH_3)_2SO_4$ (106.4 g). Rinsed with 2-MeTHF (100 mL, total 600 mL) and added into the reaction mixture to obtain a slurry. Added H_2O (1 mL). Slowly warm to RT (slowly exothermic, temperature rose to ~30 °C, then cooled down). Stirred at RT for over night. Cooled the reaction mixture to ~10 °C. Added H_2O (100 mL). Added 20% K_2CO_3 aqueous solution (200 mL) to give a bi-phasic solution (pH 14). Stirred at RT for 2 hours. Transferred to a separatory funnel. Rinsed with TBME (300 mL) and added into the reaction mixture. Separated the aqueous layer and discarded. The organic layer was extracted with H_2O (300 mL each) twice. The organic layer was concentrated to dryness on rotovapor. Added CPME (100 mL) and concentrated to dryness on rotovapor to obtain **8b** as an oil residue. Weight: 139.3 g. Used directly in the next step without further purification.

Step [8b] → 8a

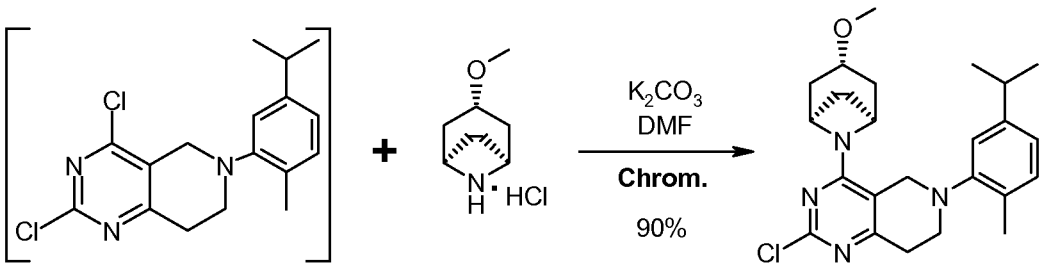


8b
MW: 241.33
MF: $C_{13}H_{23}NO_3$

8a
MW: 141.21 + 36.46
MF: $C_8H_{15}NO$. HCl

8b (139.3 g, from 468.53 mmol of BOC-nortropin) was transferred to a 2-L, 4-necked RBF. Rinsed with CPME (50 mL) and added into the reaction mixture. Cooled to 5-10 °C. Still a solution. Added with 4M HCl in CPME (340 mL) at this temperature. Stirred and slowly warmed to room temperature. Stirred at room temperature over night to obtain a slurry. Added heptanes (400 mL) to obtain a white slurry. Stirred at RT for 2 h. The solids were filtered through a polypropylene pad and washed with heptanes (50 mL) under N_2 flow. Dried the solid in the vacuum oven at 40 °C for over weekend to afford a white solid. Weight: 81.3 g (wet: 84.2 g), yield: 97.6% (from **8d**). NMR (D_2O) confirmed the structure.

Step [8] + 8a → 9



8
MW: 336.27
MF: $C_{17}H_{19}Cl_2N_3$

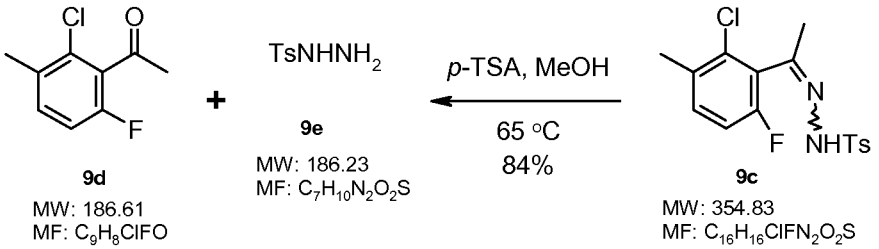
8a
MW: 141.21 + 36.46
MF: $C_8H_{15}NO$. HCl

9
MW: 441.02
MF: $C_{25}H_{33}ClN_4O$

To a 3-necked, 3-L, round-bottomed flask, equipped with a mechanical stirrer, a thermometer, a nitrogen inlet and an addition funnel, and a cooling bath, was charged at 20°C, 105g (760mmol) of potassium carbonate, 66g (372mmol) of HCl salt of **8a** and 5g (35mmol) of free base form of **8a** and 500mL of DMF. Mechanically stir the suspension at 20°C for 10min and cool to an internal temperature at below 5°C over 30min. Add to the cold suspension, a solution of 112g (333mmol) (containing 18% of toluene) of the dichloride, **8** in 300mL of DMF over 15min via an addition funnel. Rinse the funnel twice with 50mL of DMF. Maintain at this temperature for 10h. Warm the reaction mixture gradually to ambient temperature overnight. Cool the reaction mixture to an internal temperature at 15°C. Dilute with 800mL of ethyl acetate. Dilute with 1.02L of water in portions, while maintaining the internal temperature at below 22°C. Stir the orange solution with precipitates at 20°C for 30min. Separate layers. Check the pH of the aqueous layer and ensure it is 10. Wash the dark organic layer with 750mL of water. Wash with 500mL of a 10% citric acid solution. Check the pH to be 2. Finally, wash the organic layer with 400mL of brine. Concentrate down the organic layer at a bath temperature at 45°C to a constant weight of, T: 164g of **9** as a tan oil in >100% yield, which solidifies into a waxy yellow solid upon standing. HPLC indicates no signs of solvent DMF. TLC shows only trace amount of the starting material dichloride, **8**.

The crude product, **9** was passed through a silica gel pad to eliminate the 4% des-isopropyl adduct. Simply, dissolve 182g of crude nortropine adduct, **9** in 50mL of dichloromethane and 200mL of toluene. Load the solution onto a 328g silica gel (60-230mesh) bed. [1.8g of silica to 1g of crude **9**]. Elute with 100% toluene. The desired product, 9 elutes first, leaving all others including the des-isopropyl by-product behind. After combining fractions and concentrating down to constant weight, the yield is 148g of a pale yellow oil, which solidifies over time into a bright light yellow solid of **9**. The purity is ~98% by HPLC at 210nm.

Step 9d + 9e → 9c



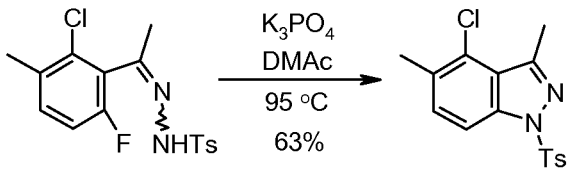
9d
MW: 186.61
MF: C_9H_8ClFO

9e
MW: 186.23
MF: $C_7H_{10}N_2O_2S$

9c
MW: 354.83
MF: $C_{16}H_{16}ClFN_2O_2S$

To a 5-L 4-necked RBF, charged **9d** (498.3 g), **9e** (621.6 g, 1.25 eq), *p*-TSA monohydrate (50.8 g, 0.1 eq) and MeOH (2.5 L) to afford a white slurry. Stirred at room temperature. Warmed the reaction mixture to 65 °C in 45 min. Stirred the reaction mixture at 65 °C for ~8 h. The reaction mixture was cooled down slowly to room temperature and stirred at room temperature overnight to obtain a white slurry. The reaction mixture was further cooled to 5 °C and stirred for 3-4 h. The solids were filtered through a polypropylene pad and washed three times with cold MeOH (333 mL). Dried the solid in the vacuum oven at 50 °C for over night to afford a white solid. Weight: 824 g (wet: 873.6 g), yield: 87%. HPLC (E/Z mixture): 100% (210 nm), 99.61% (254 nm). NMR (E/Z isomer ratio: ~4.6/1.0) and LC-MS (M+1: 354.9, 356.7) confirmed the structure.

Step 9c → 9b



9c
MW: 354.83
MF: $C_{16}H_{16}ClFN_2O_2S$

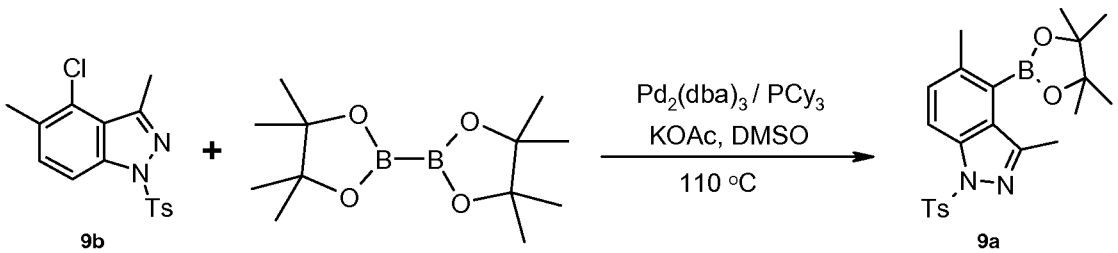
9b
MW: 334.83
MF: $C_{16}H_{15}ClN_2O_2S$

To a 12-L 4-necked RBF, charged **9c** (819 g), K_3PO_4 (979.9 g, 2.0 eq) and DMAc (3.28 L) at room

temperature to afford a white slurry. Warmed the reaction mixture to 95±3 °C in 45 min. Stirred at 95±3 °C for 10 hours. Cooled down slowly to room temperature and stirred at room temperature for over night. Added H_2O (6.56 L) in 1.5 h while maintaining temperature <35 °C with ice bath. Cooled the reaction mixture to 20 °C and stirred for 1 h. The solids were filtered through a polypropylene pad and washed with H_2O (4 L). Dried the solid in the vacuum oven at 50-60 °C for over night to 593 g. Continued drying at 50-60 °C for over weekend to afford a light brown solid. Weight: 583.1 g (wet: 698.4 g), yield: 75.4%. HPLC: 97.0% (254 nm).

To a 5-L 4-necked RBF, charged **9b** (402.0 g) and 2-propanol (4.02 L) to obtain a slurry. Stirred the reaction mixture at RT. Warmed to 82 °C in 45 min. Stirred the reaction mixture at 82 °C for 1 h. Cooled to room temperature. The reaction mixture was cooled down slowly to 5 °C and stirred at this temperature for 1 h. The solids were filtered through a polypropylene pad and washed with cold 2-propanol (1.35 L). Dried the solid in the vacuum oven at 50-60 °C for over night to afford a creamy colored sandy solid. Weight: 339.9 g (wet: 341.7 g), yield: 84.6% (total 63.7%). HPLC: 99.0% (254 nm). NMR and LC-MS (M+1: 334.9, 336.8) confirmed the structure.

Step 9b → 9a



9b
MW: 334.83
MF: $C_{16}H_{15}ClN_2O_2S$

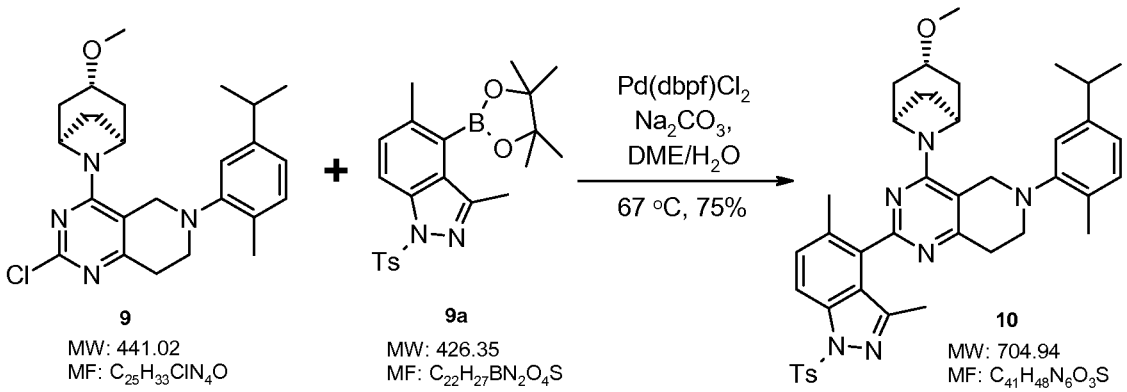
MW: 253.94
MF: $C_{12}H_{24}B_2O_4$

9a
MW: 426.35
MF: $C_{22}H_{27}BN_2O_4S$

Into a nitrogen-purged 5-L 4-necked RBF, add 45.1 g $Pd_2(dba)_3$, 66.4 g of PCy_3, and 1.0 L nitrogen-bubbled DMSO. Stir at room temperature while bubbling nitrogen for 60 min in a 12-L 4-necked RBF with nitrogen for 30 min, then add 660.2 g of tosyl indazole, 1,502 g of pinacol diboron (3.0 eq), 580.6 g of KOAc (3.0 eq), and 5.5 L of DMSO. Bubble nitrogen through and purge the head space of the batch for 10 min, then heat to 70 °C in 60 min while maintaining nitrogen bubbling and purging. At 70 °C, add all preformed catalyst/DMSO thin suspension as prepared above. Heat the batch to 110 °C and stir at 110 °C for 15 h while maintaining nitrogen bubbling and purging. Cool the batch to room temperature and hold over weekend. Heat the batch to 50 °C to make the batch from a thick suspension to a flow-flowing suspension, transfer all contents into a 22-L 4-necked RBF with 5,500 mL 2-MeTHF, 5,000 mL water, and 160 g of celite. Stir the batch at 40-50 °C for 30 min. Separate the organic layer. Back-extract the

aqueous layer with 1.0 L of 2-MeTHF and 1.5 L water. Filter the combined organic layer and aqueous layer containing celite through a celite pad, wash with 2,000 mL of 2-MeTHF. Separate the organic layer. Hold the solution at room temperature overnight. Wash the organic layer with 3.0 L of 20% NaCl solution, and 4.0 L 6% NaCl solution. Divide the organic layer into 3 parts, concentrate each at 40 °C/30 mbar to nearly dryness, add each 600 mL heptane, concentrate at 40 °C/30 mbar to nearly dryness. Add into each 600 mL heptane. Stir at 45 °C to make a free-flowing suspension. Combine into a 12-L RBF, add 5.3 L more heptane. Stir at 45°C for 2 h, cool to room temperature and stir overnight. Filter the batch, wash the cake with 2.0 L of heptane. Dry the wet cake at 55 °C/30 mbar over night. 596.8 g of light pink solid was obtained. Yield: 71.0%. HPLC purity (254 nm): 98.2 %. LC-MS: ES+ 426.9. NMR ($CDCl_3$): consistent with the molecular structure.

Step 9 + 9a → 10



9
MW: 441.02
MF: $C_{25}H_{33}ClN_4O$

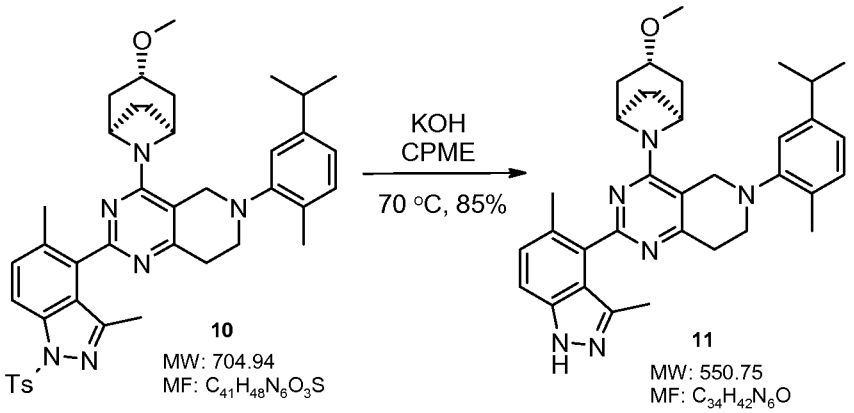
9a
MW: 426.35
MF: $C_{22}H_{27}BN_2O_4S$

10
MW: 704.94
MF: $C_{41}H_{48}N_6O_3S$

To a 3-necked, 2-L round-bottomed flask, equipped with a mechanical stirrer, a reflux condenser, a heating mantle, a thermometer and a nitrogen inlet is charged at 20°C, 40g (90.7mmol) of nortropine adduct, **9**, 46.3g (108.6mmol) of the indazole boronate, **9a** and 600mL of dimethoxyethane to give a clear light brown solution. Stir vigorously at 20°C for 10min to ensure visually that all chunks of solids have dissolved. Add an aqueous solution of 30g (283mmol) of sodium carbonate in 330mL of water. Add 2.0g (3.07mmol) of the Pd catalyst (3.4mol%) and rinse with 50mL of dimethoxyethane. Heat the solution-like mixture to an internal temperature at 67°C quickly in less than 15min. Stir and maintain at this temperature for 2h. Cool to ambient temperature. The reaction mixture, a tan slurry is filtered through a Buchner funnel under house vacuum over a polypropylene pad. Wash the filter cake twice with 100mL of MTBE, twice with 100mL of water and once with 50mL of dimethoxyethane. Dry the filter cake at an oven temperature at 48°C under house vacuum with a slight nitrogen bleed for 20h to obtain T: 61g of the desired crude Suzuki product **10** in ~95% yield.

Dissolve 161g of crude Suzuki product in 650mL of dichloromethane. Wash the clear pale yellow solution twice with 160mL of water and 276g of brine. Pass the organic solution through a short 228g pad of silica gel (60-230mesh). Eluted with 100% dichloromethane and followed by 30% ethyl acetate / dichloromethane. The fractions are combined and concentrated down. Residual dichloromethane is chased off with 400mL of MTBE to obtain 360g of a wet cake. The wet cake of **10** is mechanically stirred in 1.4L of MTBE at an internal temperature at 45°C. The slurry is stirred at ambient temperature overnight and is filtered under house vacuum over a Buchner funnel over a polypropylene pad. Wash the filtered cake with MTBE and air-dried at ambient temperature for 30min. The solids are then dried at an oven temperature at 48°C under house vacuum with a slight nitrogen bleed for 18h to afford: 135g of purified Suzuki product, **10** in ~84% recovery. The purity is >99% by HPLC at 210nm. The structure is consistent by ^{1}H-NMR and LC/MS (MH^+ = 705).

Step 10 → 11



To a 3-necked, 3-L round-bottomed flask, equipped with a mechanical stirrer, a heating mantle, a reflux condenser, and a nitrogen inlet, was charged at 20°C, 100g (142mmol) of **10**, 20g (357mmol) of powderized potassium hydroxide and 1L of cyclopentyl methyl ether. Stir mechanically the slurry at 20°C for 10min. Heat gradually to an internal temperature at 68°C. Stir and maintain at this temperature for 7h. Cool the reaction mixture to 20°C. Stir overnight. Add 500mL of water, 500mL of cyclopentyl methyl ether and 500mL of brine. Separate layers. Wash the organic layer with 500mL of water and 500mL of brine. Separate layers. Dilute the organic layer with 500mL of isopropyl acetate. Wash the organic layer with 700mL of water. Separate layers. Pass the organic layer through a coarse sintered glass funnel under house vacuum over a fiber glass filtered paper. Concentrate the organic layer at a bath temperature at 40°C to constant weight to obtain T: 221g of crude **11** as a gummy oil.

The crude product of **11**, the free base form of the drug substance, LKP581 will have to be solidify out. Initially, solids of **11** can be obtained by scratching it from heptane. However, as much as 2% of solvent retention based on ^{1}H-NMR made this process unacceptable. After much process development efforts and inputs from the crystallization group, a feasible condition is devised, allowing the delivery of the CSP batch of LKP581 as a solid, with the right purity level and yield. Hence, met the AUDD. Simply, dissolve the crude oil of **11** in methanol. Carefully, add it into water. Filter and dry.

Example 80

MTBE solvate of Example 19-F

To 100mg of the amorphous free form of Example 19-F, 100µL of MTBE was added. On stirring a clear solution is formed. The solution was stirred at -20°C and over approx. 60 minutes a precipitate was formed. The resulting solid was collected by filtration and dried at 40°C under vacuum for 72 hours. The solid form is crystalline by XRPD, with a melting point of 102.8°C and a concurrent 4.9% weight loss. The XRPD is shown in Figure 1. The DSC and TGA are shown in Figure 2.

Powder X-Ray Diffraction Peaks of Example 19-F from MTBE

Angle 2θ	d value Å	Relative Intensity %
3.433	25.74	29.9
6.369	13.88	40.3
7.058	12.52	50.3
9.306	9.50	49.6
10.522	8.41	42.5
11.908	7.43	54.2
12.511	7.08	36.7
13.434	6.59	69.3
15.527	5.71	54.8
16.385	5.41	60.6
17.39	5.10	100
18.883	4.70	78.1
20.285	4.38	52.9
22.351	3.98	34.1
23.297	3.82	38.5

Example 81

Me-THF solvate of Example 19-F

To 100mg of the amorphous free form, 100µL (or 200 µL) of Me-THF was added. On stirring a clear solution is formed. The solution was stirred at -20°C and over approx. 2 hours a precipitate was formed. The resulting solid was collected by filtration and dried at 40°C under vacuum for 72 hours.

Material collected and analyzed without drying was found to have a different XRPD pattern than the dried material suggesting a conversion of crystalline forms. Conversion could be followed by XPRD over ~30 minutes under ambient conditions.

The solid form is crystalline by XRPD, with a melting point of 126.8°C and a concurrent 1.5% weight loss. The XRPD is shown in Figure 3 and Figure 5. The DSC and TGA are shown in Figure 4.

Powder X-Ray Diffraction Peaks of Example 19-F initial precipitate from Me-THF

Angle 2θ	d value Å	Relative Intensity %
4.394	20.11	93.1
6.959	12.70	41.8
8.629	10.24	38.1
11.31	7.82	30.8
13.387	6.61	40.3
16.778	5.28	100
17.287	5.12	75.3
17.865	4.96	73.2
18.849	4.70	63.7
19.452	4.56	56.4
22.353	3.97	44.6
22.83	3.89	38
26.312	3.38	26.2

Powder X-Ray Diffraction Peaks of Example 19-F dried material from Me-THF

Angle 2θ	d value Å	Relative Intensity %
5.148	17.16	100
7.37	11.99	40.2
9.908	8.92	29.1

10.807	8.18	20
11.489	7.70	24
13.904	6.36	17.9
14.434	6.13	18.3
15.273	5.80	19.7
15.879	5.58	28.6
17.164	5.16	56.6
19.318	4.59	21.4

Example 82

Toluene solvate of Example 19-F

To 100mg of the amorphous free form, 150µL of toluene was added. On stirring a clear solution is formed. The solution was stirred at -20°C and over approx. 12 hours a precipitate was formed. The resulting solid was collected by filtration and dried at 40°C under vacuum for 72 hours.

The solid form is crystalline by XRPD, with a melting point of 117.4°C and a concurrent 3.2% weight loss. The XRPD is shown in Figure 6. The DSC and TGA are shown in Figure 7.

Powder X-Ray Diffraction Peaks of Example 19-F from toluene

Angle	d value	Relative Intensity
2θ	Å	%
5.134	17.21	35.9
7.431	11.90	35.9
9.97	8.87	35.8
10.975	8.06	37.2
11.562	7.65	33.4
12.209	7.25	26.4
13.632	6.50	28.8
14.448	6.13	46.1
15.032	5.89	32.5
15.865	5.59	37.3
16.974	5.22	100
17.28	5.13	68.2
18.829	4.71	65.6
22.402	3.97	25

23.165	3.84	29.4

Example 83

EtOAc solvate of Example 19-F

To 100mg of the amorphous free form, 150µL of EtOAc was added. On stirring a clear solution is formed. The solution was stirred at -20°C and over approx. 4 hours a precipitate was formed. The resulting solid was collected by filtration and dried at 40°C under vacuum for 72 hours.

The solid form is crystalline by XRPD, with a melting point of 117.4°C and a concurrent 3.2% weight loss. The XRPD is shown in Figure 8. The DSC and TGA are shown in Figure 9.

Powder X-Ray Diffraction Peaks of Example 19-F from EtOAc

Angle 2θ	d value Å	Relative Intensity %
5.188	17.03	64.2
7.43	11.90	70.2
9.171	9.64	18.7
10.048	8.80	42.2
11.07	7.99	61.8
11.555	7.66	66
12.318	7.19	27.1
13.778	6.43	33.8
14.49	6.11	52.1
15.972	5.55	37.9
17.394	5.10	100
19.025	4.66	68.4
23.283	3.82	38.3

Example 84

Example 19-F Hydrochloride Form A

Example 19-F hydrochloride Form A was prepared on a 100mg scale. To the Example 19-F free base material, a solution of 0.1N HCl in IPA was added at a 1:1.1 molar ratio creating a slight excess of HCl. Upon addition of the acid, the solution became transparent after <1min of stirring. The solution was protected from light and allowed to stir at room temperature. Opacity is observed after a few hours but the reaction mixture is allowed to stir for 48hrs. Material was collected by vacuum filtration, rinsed with

IPA, and dried by pulling air through the sample on in vacuum filtration set-up for 1 hour. The yield was approximately 85%.

By elemental analysis and Karl-Fisher, Example 19-F Hydrochloride was determined to be a monochloride salt without a stoichiometric hydrate. It is crystalline and experiences a loss of water at 127°C (broad DSC endotherm) followed by a melt at 190°C. Mass loss is observed in a stepwise manner by TGA: 5.4% wt by 138°C and an additional 2.8% wt by 186°C. The XRPD is shown in Figure 11. The TGA is shown in Figure 12. The non-hermetic DSC is shown in Figure 13. The hermetic DSC is shown in Figure 14.

XRPD peaks of Example 19-F Hydrochloride form A

Angle 2θ	d value Å	Relative Intensity %
4.666	18.94	28.9
6.928	12.76	32.5
7.63	11.59	100
9.394	9.41	55.6
10.875	8.14	21.1
12.252	7.22	21.7
14.263	6.21	26.2
15.378	5.76	41
17.227	5.15	31.1
18.146	4.89	54.6
19.187	4.63	52.4
26.521	3.36	29.8

Example 85

Example 19-F Hydrochloride Form B

Example 19-F Hydrochloride Form B was on a 500mg scale. Its synthesis is similar to that of Form A except that additional drying time is used. To the Example 19-F free base material, a solution of 0.1N HCl in IPA was added at a 1:1.1 molar ratio creating a slight excess of HCl. Upon addition of the acid, the solution became transparent after <1min of stirring. The solution was protected from light and allowed to stir at room temperature. Opacity is observed after a few hours but the reaction mixture is allowed to stir for 48hrs. Material was collected by vacuum filtration, rinsed with IPA, dried by pulling

air through the sample on in vacuum filtration set-up for 1 hour and then placed in a vacuum oven (40°C) for 72hrs. Form B resulted after this period. The yield was approximately 85%.

Aqueous suspensions of Example 19-F Hydrochloride Form A and Example 19-F Hydrochloride Form B were prepared. Form A became amorphous in 24hrs; Form B appears to retain a small amount of Form B crystallinity but becomes significantly amorphous

By ion chromatography, Example 19-F Hydrochloride Form B was determined to be a monochloride salt. It is crystalline and experiences a loss of water at 127°C (broad DSC endotherm) followed by a melt at 199°C. By 167°C, 5.5% wt. is lost by TGA. The XRPD is shown in Figure 15. The TGA is shown in Figure 16. The non-hermetic DSC is shown in Figure 17.

XRPD peaks of Example 19-F Hydrochloride form B

Angle 2θ	d value Å	Relative Intensity %
4.916	17.98	27.1
7.407	11.94	44.1
8.041	11.00	85
8.368	10.57	100
9.681	9.14	41.3
9.983	8.86	39.7
13.252	6.68	30.2
15.006	5.90	45
15.554	5.70	39.2
19.271	4.61	47.2
20.137	4.41	35.4

Example 86

Example 19-F Phosphate Form A

Example 19-F Phosphate Form A was produced on a 25mg scale. Example 19-f free base was dissolved in acetone at 42mg/mL. Next a solution of 0.1M phosphoric acid in acetone was added at a 1:1.5 molar ratio generating an excess of acid. The solution concentration of free base was thus 19.6mg/mL. Some immediate haziness was observed. The solution was allowed to stir over 48hrs at room temperature yielding an opaque suspension. The material was collected by vacuum filtration, washed with acetone and dried in a vacuum oven (40°C) for 24hrs.

Example 19-F Phosphate Form A is crystalline and melts at 128°C. The XRPD is shown in Figure 18. The hermetic DSC is shown in Figure 19.

XRPD peaks of Example 19-F Phosphate form A

Angle 2θ	d value Å	Relative Intensity %
4.73	18.68	100
7.956	11.11	12
9.584	9.23	19
10.644	8.31	15.1
13.588	6.52	13.1
14.548	6.09	15.5
16.287	5.44	25.9
17.266	5.14	21.1
11.835	7.48	14
18.948	4.68	19.1

Example 87

Example 19-F Phosphate Form B

Example 19-F Phosphate Form B was produced on a 25mg scale. Example 19-F free base material was dissolved in acetone at 9.2mg/mL. Next, a solution of 0.1M phosphoric acid in acetone was added at a 1:1.4 molar ratio generating an excess of acid. The solution concentration of the free base was thus 7.45mg/mL. The solution was clear upon addition of the phosphoric acid. The solution was allowed to stir over 72hrs at room temperature yielding an opaque suspension. The material was collected by vacuum filtration, washed with acetone and dried by pulling air through the vacuum filtration apparatus approximately 30 minutes.

By ion chromatography, Example 19-F Phosphate Form B was determined to be a monophosphate salt. It is crystalline and has several endotherms as determined by hermetic DSC: 119°C, 131°C and 164°C. The XRPD is shown in Figure 20. The hermetic DSC is shown in Figure 21.

XRPD peaks of Example 19-F Phosphate form B

Angle 2θ	d value Å	Relative Intensity %
4.428	19.95	100

5.873	15.05	16.4
7.086	12.47	20.8
7.993	11.06	57.6
10.188	8.68	23.1
11.865	7.46	25.8
13.382	6.62	54.8
14.434	6.14	29.6
16.946	5.23	32.1
18.742	4.73	58.7
20.709	4.29	29.3
21.718	4.09	29.1
22.728	3.91	38.7

Example 88

Example 19-F Phosphate Form C

After 2 DVS cycles from 0-85% RH, Example 19-F Phosphate Form B was found to convert to Example 19-F Phosphate Form C.

By elemental analysis and Karl-Fisher, Example 19-F Form C was determined to be a monophosphate salt with a stoichiometric dihydrate. It is crystalline and experiences a loss of water at 70°C (broad DSC endotherm) followed by a melt at 165°C. By 119°C, 1.2% wt. is lost by TGA. The XRPD is shown in Figure 22. The non-hermetic DSC is shown in Figure 23. TGA is shown in Figure 24.

XRPD peaks of Example 19-F Phosphate form C

Angle	d value	Relative Intensity
2θ	Å	%
4.50	19.65	100
7.93	11.15	11.6
8.65	10.22	13.9
10.63	8.32	10.3
12.00	7.38	15.8
13.85	6.39	21.9
15.35	5.77	14
16.06	5.52	15.4
17.65	5.03	18

18.82	4.72	18.7

Example 89.

Solubility of Example 19-F, Example 19-F Hydrochloride Form A, and Example 19-F Phosphate Form C

	24hr Equilibrium Solubility (mg/mL) [pH]		
	Example 19-F	Example 19-F Hydrochloride Form A	Example 19-F Phosphate Form C
Physical Form	Amorphous	Crystalline	Crystalline
pH 1	< 0.0005 [1.32]	0.14 [1.41]	0.83 [1.22]
pH 4.5	< 0.0005 [4.28]	<0.001 [4.54]	0.006 [3.70]
pH 6.8	< 0.0005 [6.62]	<0.001 [6.86]	0.001 [5.83]
SGF	< 0.0005 [1.3]	0.13 [2.20]	0.55 [1.84]
SIF	*	<0.001 [6.60]	0.001 [6.56]
FeSSIF pH 5.5	< 0.0005 [7]	1.01 [5.78]	0.65 [5.22]
FaSSIF pH 6.5	< 0.0005 [6.47]	0.01 [6.58]	0.02 [6.09]
Water	< 0.0005 [6.09]	<0.001 [4.68]	0.04 [3.33]
Capmul MCM	>26.5	24.97	4.21
Corn oil glyceride	>26.1	23.08	13.14
20%HPbCD	0.003	0.03	0.77
PG	3.426	13.89	15.48
PEG300	8.260	10.19	13.89
50% PEG300	0.016	8.01	5.23
10%Solutol	0.078	7.77	8.96
10% Cremophor	*	5.14	8.76
1%Tween80	0.006	0.52	0.71
1%SLS	0.005	0.48	0.53
MEPC5	*	16.45	22.07
MEPC4	*	11.57	25.96

* Data not available

Example 90

Key *in vivo* data demonstrating advanced biopharmaceutical performance

Example 19-F Hydrochloride Form B (30 and 100mpk) and Example 19-F Phosphate Form C (100mpk) have been dosed in a suspension formulation (0.1% Tween80/0.5% MC) at 100mpk in Sprague Dawley Rats. At 30mpk the HCl salt has similar plasma exposure levels to those observed after a microemulsion dose. The exposure at 100mpk was lower from the salt forms compared to the microemulsion. The plasma exposure after a 300mpk dose of the HCl salt is approximately the same as after the 100mpk dose. The date from this experiment is summarized in Figure 25.

The Example 19-F Hydrochloride Form B suspension particle size was d(0.5) and d(0.9) were 4.3μm and 13.8μm respectively. The Example 19-F Phosphate Form C suspension particle size was d(0.5) and d(0.9) were 8.5μm and 37.0μm respectively. After 24hrs, the solids in suspension had become mostly amorphous.

Example 91

Solvate of Example 55-G

To 100mg of free base Example 55-G, 1000μL of 10% EtOAc in heptane was added. On stirring a fine suspension is formed. Suspension was heated to 50°C at 1°C/min and held for 30 minutes at which point it was cooled at 0.5°C/min to 5°C where it was held for 30 minutes. The resulting solid was collected by filtration washed with 1000μL cold heptane and dried at 40°C under vacuum for 72 hours.

This form is crystalline by XRPD with a melting point of 134.8°C and a concurrent weight loss of 4.3%. XRPD is shown in Figure 26. DSC and TGA are shown in Figure 27.

Powder X-Ray Diffraction Peaks of Example 55-G from 10% EtOAc in heptane

Angle 2θ	d value Å	Relative Intensity %
6.805	12.99	13.7
7.752	11.41	18.4
8.75	10.11	17.7
10.211	8.66	19.6
10.909	8.11	14
11.635	7.61	24.6
12.485	7.09	26.9
12.972	6.82	18.6
14.159	6.26	79.2

14.831	5.97	29.2
15.714	5.64	21.8
16.227	5.46	45.3
17.249	5.14	100
17.899	4.96	35
18.411	4.82	35.4
19.351	4.59	28.1
20.094	4.42	31.3
22.443	3.96	21.7
23.089	3.85	49.9
23.813	3.74	30.7
24.303	3.66	22.8
25.326	3.52	25.9
25.809	3.45	30.2
27.193	3.28	24.3
27.973	3.19	25.3
28.863	3.09	20

Example 92

Tri-hydrate of Example 55-G

To 600mg of free base Example 55-G, 7500µL of 50% MeOH in water was added. On stirring a fine suspension is formed which is amorphous in nature. Suspension was heated to 50°C at 1°C/min and held for 30 minutes at which point it was cooled at 0.5°C/min to 5°C where it was held for 30 minutes. The resulting solid was collected by filtration then dried at 40°C under vacuum for 72 hours. Yield was approximately 92%

This form is crystalline by XRPD with a melting point of 123.7°C and a weight loss on heating of 6.6%. Water content is 7.5% by Karl Fischer. The XRPD is shown in Figure 28. The DSC and TGA are shown in Figure 29. The sealed pan DSC is shown in Figure 30.

Powder X-Ray Diffraction Peaks of Figure 55-G from 50% MeOH in water

Angle	d value	Relative Intensity
2θ	Å	%
6.602	13.39	17.9
8.161	10.83	100

9.746	9.08	19.2
12.689	6.98	62.2
13.109	6.75	39.9
13.91	6.37	20.2
14.544	6.09	29.1
16.441	5.39	20.9
16.999	5.22	27.9
17.517	5.06	22.9
19.318	4.59	29.4
21.222	4.19	34.3
22.71	3.92	37.8
23.065	3.86	29.5
24.253	3.67	23.4
25.351	3.51	31.9
27.787	3.21	30.8

Example 93

Sulfate of Example 55-G

To 100mg of free base Example 55-G, 1M equivalent of sulfuric acid and 1000µL of acetone was added. On stirring a clear solution is formed. This solution was heated to 50°C at 1°C/min and held for 30 minutes at which point it was cooled at 0.5°C/min to 5°C where it was held for 30 minutes. The resulting solid was collected by cold filtration then dried at 40°C under vacuum for 72 hours.

This form is weakly crystalline hemisulfate with a melting point of 131.4°C and a concurrent weight loss of 1.8% up to 200°C. XRPD is shown in Figure 31. DSC and TGA are shown in Figure 32.

Powder X-Ray Diffraction Peaks of Example 55-G sulfate

Angle	d value	Relative Intensity
2θ	Å	%
5.227	16.91	100
6.198	14.26	29.4
8.648	10.23	42.1
10.047	8.80	82.2
11.452	7.73	42.6
12.769	6.93	63.4

14.551	6.09	68.4
16.203	5.47	63.1
17.059	5.20	56.1
17.827	4.98	56.1
19.214	4.62	55.9
19.952	4.45	55.1

Example 94

Tosylate of Example 55-G

To 600mg of free base Example 55-G, 1M equivalent of p-toluenesulfonic hydrate acid and 7500µL of acetone was added. On stirring a clear solution is formed. This solution was heated to 50°C at 1°C/min and held for 30 minutes at which point it was cooled at 0.5°C/min to 5°C where it was held for 30 minutes. The resulting solid was collected by filtration then dried at 40°C under vacuum for 72 hours. Yield was approximately 75%.

This form is weakly crystalline 1:1 tosylate salt with a melting point of 143.8°C and a concurrent weight loss of 1.2% up to 200°C. XRPD is shown in Figure 33. DSC and TGA are shown in Figure 34.

Powder X-Ray Diffraction Peaks of Example 55-G tosylate

Angle 2θ	d value Å	Relative Intensity %
4.157	21.25	64.4
6.405	13.80	47.6
8.264	10.70	51.4
9.769	9.05	47.3
12.366	7.16	57.6
13.724	6.45	72.2
14.639	6.05	87.5
16.026	5.53	77.1
18.069	4.91	100
18.889	4.70	82.4

Example 95

Besylate of Example 55-G

To 100mg of free base Example 55-G, 1M equivalent of benzene sulfonic acid and 1000µL of acetone was added. On stirring a clear solution is formed. This solution was heated to 50°C at 1°C/min and held for 30 minutes at which point it was cooled at 0.5°C/min to 5°C where it was held for 30 minutes. The resulting solid collected by filtration and dried at 40°C under vacuum for 72 hours.

This form is crystalline, 1:1 besylate salt acetone solvate with a melting point of 155.7°C. There is a lower temperature endotherm at 85.9°C with a concurrent weight loss of 5.4% which likely corresponds to loss of acetone. XRPD is shown in Figure 35. DSC and TGA are shown in Figure 36.

Powder X-Ray Diffraction Peaks of Example 55-G besylate

Angle 2θ	d value Å	Relative Intensity %
6.799	13.00	22.1
7.624	11.60	14.9
8.215	10.76	26
9.196	9.62	40.7
10.674	8.29	22.8
11.177	7.92	11.3
11.715	7.55	11.3
13.324	6.65	28.5
13.71	6.46	100
14.352	6.17	24.9
14.912	5.94	49.6
15.358	5.77	35
16.169	5.48	54.2
16.706	5.31	21.8
17.16	5.17	27.6
17.465	5.08	52.4
17.737	5.00	33.1
18.952	4.68	14
19.915	4.46	46.3
21.568	4.12	17.1
22.119	4.02	69
22.422	3.97	35.4
23.656	3.76	18

24.45	3.64	76.1
25.535	3.49	17.3
27.668	3.22	19.9
28.393	3.14	32.3
29.209	3.06	18.5
29.832	2.99	18.1
30.595	2.92	18.5
33.143	2.70	17.7

Example 96

MTBE solvate of Example 55-G

To 100mg of free base Example 55-G, 1000µL of 10% MTBE in heptane (or neat MTBE may also be used) was added. On stirring a fine suspension is formed. Suspension was heated to 50°C at 1°C/min and held for 30 minutes at which point it was cooled at 0.5°C/min to 5°C where it was held for 30 minutes. The resulting solid was collected by filtration and dried at 40°C under vacuum for 72 hours.

This form is crystalline with a melting point of 134.2°C with a concurrent weight loss of 6.9% corresponding to loss of MTBE. XRPD is shown in Figure 37. DSC and TGA are shown in Figure 38.

Powder X-Ray Diffraction Peaks of Example 55-G MTBE solvate

Angle 2θ	d value Å	Relative Intensity %
4.074	21.69	13.9
6.728	13.14	22.3
7.659	11.54	36.3
8.627	10.25	26.8
10.148	8.72	27
10.853	8.15	19.4
11.418	7.75	39.3
12.313	7.19	31.9
12.889	6.87	27.3
14.043	6.31	88.8
14.684	6.03	27.6
15.969	5.55	61.2
16.689	5.31	50.7

17.149	5.17	100
17.842	4.97	39.2
18.338	4.84	43.1
19.119	4.64	33.9
19.752	4.49	32
23.113	3.85	37.6
24.397	3.65	22.2
25.187	3.54	22
25.794	3.45	24.9
27.159	3.28	20.3

Example 97

Moisture sorption properties of different crystalline Example 55-G forms compared to the amorphous free form

	amorphous	Di-hydrate	Sulfate	tosylate	Besylate (acetone solvate)	Hydrate
DVS % Weight gain						
40% RH	1.9	-1	3.5	2.2	-3.5	7.1
90% RH	3.3	-0.2 *	9	5.3	-2 *	9.3

Solubility of different crystalline Example 55-G forms compared to the amorphous free form

mg/mL (pH)	amorphous	Di-hydrate	tosylate	Besylate (acetone solvate)	hydrate
pH 1.2	> 10 [1.2]	5.698 (1.59)	1.618 (1.47)	3.161 (1.44)	4.402 (1.7)
pH 4.5	0.01 [4.8]	< 0.0005 (4.46)	< 0.0005 (4.54)	< 0.0005 (4.39)	< 0.0005 (4.54)
pH 6.8	< 0.0005 [6.8]	0.041 (3.82)	0.257 (2.97)	0.075 (3.57)	< 0.0005 (6.63)
SGF	> 10 [1.6]	6.603 (1.33)	2.034 (1.31)	3.179 (1.31)	7.061 (1.4)
FeSSIF (pH 5.5)	1.2 [5.6]	< 0.0005 (4.51)	< 0.0005 (5.1)	< 0.0005 (5.5)	0.001 (5.75)
FaSSIF (pH 6.5)	0.07 [6.9]	0.081 (3.54)	< 0.0005 (5.7)	< 0.0005 (5.98)	< 0.0005 (6.56)
Water	< 0.0005 [6.2]	0.451 (2.64)	0.495 (2.42)	0.457 (2.57)	< 0.0005 (6.12)

Example 98

***in vivo* data**

Example 55-G hydrate was dosed in a suspension formulation (0.1% Tween80/0.5% MC) at 30 and 100mpk to Sprague Dawley Rats. At 30mpk the hydrate has similar plasma exposure levels to those observed after a dose of microemulsion or amorphous form suspension. The exposure at 100mpk was slightly lower from the crystalline hydrate compared to the microemulsion or amorphous suspension.

However the increase in exposure was proportional with dose for the hydrate suggesting the form would be suitable for use in higher dose *in vivo* work. The results of this experiment are summarized in Figure 39.

Example 99

FLIPR Assay

Compounds were tested for their ability to inhibit C5a-mediated calcium mobilization using a stable cell line over expressing the human C5aR & the Gα15 protein on the FLIPR (Fluorescent Imaging Plate Reader) Tetra system. Cells were maintained in culture media containing DMEM (Dulbecco's Modified Eagle Medium) with 4.5 g/L glucose, 10% fetal bovine serum, 100 U/mL, 1x non-essential amino acid, and 250 µg/mL G418 (Geneticin). Prior to testing of compounds, cells were plated at 10,000 cells/well in clear bottom 384-well black plate, and incubated overnight at 37 °C with 5% CO_2. On the day of experiment, culture media was removed, and replaced with assay buffer HBSS (Hanks' Balanced Salt Solution) with 20 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) and 0.1% BSA (bovine serum albumin) BSA containing calcium 5 dye (Molecular Devices) and 2.5 mM probenecid. After 1 hour incubation at 37 °C, 5% CO_2 for 60 min, cells were pre-incubated with compounds for 30 minutes at room temperature, in 1% DMSO (dimethyl sulfoxide). Human C5a at the EC50 (0.1 -0.25 nM) concentration was then added and changes in calcium mobilization were detected using FLIPR.

Example number	FLIPR IC_{50} (nM)
23-I	0.5
17-M	30
29	2
19-F	4
16-I	48
20-D	164
21-AJ	6
21-R	1
24-G	7
17-Y	160
21-AF	4

Example number	FLIPR IC_{50} (nM)
23-H	1
30-A	16
17-T	54
19-AE	4
17-AP	10
17-H	10
22-C	2
21-AH	1
24-I	464
17-AN	31
31-I	9

Example number	FLIPR IC_{50} (nM)
54-B	2
17-AM	2
17-R	10
43-A	56
23-G	2
16-V	338
17-AI	19
21-AG	1
24-D	91
42-K	217
19-AD	2
44-E	38
19-N	29
21-D	0.5
40-L	180
47-B	56
21-AK	5
42-H	58
17-G	4
42-I	14
23-F	5
50-E	790
24-L	6
40-Q	868

Example number	FLIPR IC_{50} (nM)
24-E	75
44-D	131
17-AY	9
16-O	90
17-AQ	16
19-AF	1
17-AJ	94
43-D	802
17-BK	163
46-B	42
46-A	20
19-AI	2
40-S	78
42-L	4
21-Q	1
40-M	11
21-X	308
23-D	8
40-D	132
45	27
19-AC	4
21-M	56
33-C	79
40-P	37

Example number	FLIPR IC_{50} (nM)
19-AB	17
31-H	77
28-D	4
41-F	550
21-S	30
41-E	21
21-E	23
19-AK	31
24-C	31
25-C	5
19-L	746
32-B	2
53	18
17-AS	46
25-F	23
55-I	1
23-K	64
55-G	2
19-Q	112
17-BG	15
17-BE	415
55-L	3
48	198
28-B	3

Example number	FLIPR IC_{50} (nM)
21-P	7
19-AH	4
41-G	3
41-D	49
21-AB	4
21-AE	9
21-AI	1
41-J	22
26-B	20
17-P	13
19-K	65
19-X	47
52-C	1
17-AZ	39
17-AV	12
55-H	4
23-J	8
55-J	5
24-J	8
39-D	74
32-A	6
55-M	1
51-D	197
23-C	40

Example number	FLIPR IC_{50} (nM)
56-C	1
56-B	2
21-N	2
21-K	2
63-E	23
56-F	1
21-AM	1
55-N	6
55-G	4
68-C	16
69-M	8
46-C	25
69-H	4
70-G	9
65-H	4

Example number	FLIPR IC_{50} (nM)
21-AL	1
56-E	2
68-B	2
65-B	2
65-K	2
63-G	31
63-I	32
65-A	1
70-J	12
69-L	1
65-I	1
69-J	67
69-I	4
70-K	20
71-B	2

Example 100

Human Whole Blood CD11b Up-regulation Assay

Whole blood was collected in sodium heparin tubes and the assay started within 2 hours of the blood draw. The blood was incubated with compounds in 1% DMSO (dimethyl sulfoxide) at room temperature for 10 minutes with gentle rocking. 2 nM of human C5a was then added for 15 minutes at room temperature with gentle rocking. Following the C5a incubation period cells were washed once with cold FACS (fluorescence-activated cell sorting) buffer (phosphate buffered saline + 0.5% bovine serum albumin). FITC (fluorescein isothiocyanate) mouse anti-human CD15 and PE-Cy5 (phycoerythrin-cyanine 5) mouse anti-human CD11b antibodies (Becton Dickinson) were gently mixed with the cells and allowed to incubate for 30 minutes on ice protected from the light. Cells were then washed three times with cold FACS buffer. Red blood cells (RBC) were lysed by incubating with BD FACS lysis buffer

(Becton Dickinson) for 10 minutes at room temperature. Cells were pelleted and the lysing procedure was repeated until all RBCs were lysed. The remaining leukocytes were resuspended in BD lysis buffer. Samples were acquired on the LSRII flow cytometer and 10,000 events of the CD15+ granulocyte population were collected. The CD11b median fluorescence intensity of the CD15+ cell population was evaluated using FACSDiva software (Becton Dickinson).

Example number	hCD11b IC_{50} (nM)
23-I	22
19-F	13
29	300
17-AN	423
31-I	18
24-E	385
21-AJ	15
21-R	15
24-G	670
55-G	23
21-AF	28
54-B	19
17-R	42
43-A	178
56-C	6
23-G	25
21-AG	22
24-D	1500
19-AD	26
44-E	188

Example number	hCD11b IC_{50} (nM)
23-H	24
30-A	5785
17-T	451
19-AE	22
17-AP	513
17-H	300
22-C	17
21-AH	6
17-AY	45
55-H	4
16-O	2250
17-AQ	277
19-AF	6
17-BK	40
56-B	45
46-B	224
46-A	1987
19-AI	7
40-S	793
21-Q	7

Example number	hCD11b IC_{50} (nM)
21-D	7
47-B	1420
21-AK	51
17-G	114
42-I	2120
23-F	28
24-L	391
19-AB	26
31-H	72
28-D	58
21-S	180
21-E	422
19-AK	30
25-C	183
32-B	24
17-AS	67
55-L	36
28-B	107
21-N	8
21-K	11
23-C	95
23-J	38
21-AL	19
63-E	29

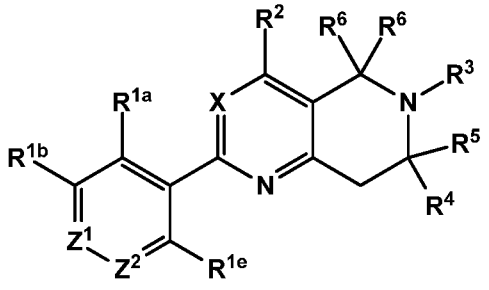
Example number	hCD11b IC_{50} (nM)
40-M	69
23-D	18
40-D	264
45	583
19-AC	50
21-M	181
33-C	238
21-P	26
19-AH	17
41-G	70
41-D	153
21-AB	11
21-AE	93
21-AI	8
41-J	302
26-B	907
23-K	11
17-P	70
52-C	178
24-J	423
32-A	63
55-M	15
65-K	26
63-G	197

Example number	hCD11b IC_{50} (nM)
56-F	11
21-AM	7
55-N	12
55-G	5
68-C	69
69-M	45
76-C	46
69-H	196
70-G	19
68-B	17
71-B	10

Example number	hCD11b IC_{50} (nM)
63-I	60
65-A	30
70-J	39
69-L	54
65-I	19
69-J	112
69-I	25
70-K	37
65-H	56
65-B	16
70-H	41
70-I	38

What is claimed is

1. A compound of formula (I) or a salt thereof:



(I)

wherein

X is N or CH;

Z^1 is N or CR^{1c};

Z^2 is N or CR^{1d}, wherein at least one of Z^1 and Z^2 is not N;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy, cyano or halogen;

R^{1b} is selected from the group consisting of hydrogen, amino, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and mono- and di-C_1-C_4alkylamino;

R^{1c} is hydrogen, halogen or C_1-C_6alkyl;

R^{1d} is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{1e} is selected from hydrogen, halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy and haloC_1-C_6alkoxy, sulfone, C_3-C_7cycloalkyl; or

R^{1a} and R^{1b} taken in combination form a 5 member saturated or unsaturated heterocyclic ring having one or two ring heteroatoms selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 independently selected C_1-C_6alkyl or halogen substituents;

wherein at least one of R^{1a} and R^{1e} is not hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl and $(CH_2)_pNR^{2a}R^{2b}$, wherein each alkyl and alkoxy group is substituted with 0 or 2 substituents selected from the group consisting of hydroxy, halogen, and C_1-C_4alkoxy, amino, mono- and di-C_1-C_4 alkylamino;

p is 0 or 1;

R^{2a} is hydrogen, C_1-C_6alkyl or hydroxyC_1-C_6alkyl;

R^{2b} is hydrogen, C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_4alkyl, wherein each alkyl is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxycarbonyl, or heterocycle wherein the heterocycle is a saturated, unsaturated or aromatic five or six member ring having 1 or 2 ring heteroatoms

selected from N, O or S and is unsubstituted or substituted with 1 or 2 independently selected C_1-C_4alkyl substituents; or

$NR^{2a}R^{2b}$ taken in combination form a 4 to 8 member saturated heterocyclic ring system having 1 or 2 rings and 0 or 1 additional ring heteroatoms selected from N, O or S, the saturated heterocyclic ring system is unsubstituted or substituted with 1-4 substituents independently selected from the group consisting of C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxyC_1-C_4alkyl, hydroxyC_1-C_4alkyl, halogen, amino, mono- and di-C_1-C_4alkylamino, C_1-C_4alkoxycarbonyl, C_1-C_4alkanoyl, $S(O)_2C_1$-C_4alkyl, $CH_2C(O)(C_1$-C_4alkoxy) and $CH_2C(O)NH_2$;

R_3 is selected from the group consisting of substituted phenyl, substituted heteroaryl, and phenylC_1-C_3alkyl, wherein the heteroaryl is selected from pyridyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, and isoxazolyl, and wherein each phenyl or heteroaryl group is substituted with 1, 2 or 3 substituents which are independently selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, C_3-C_6cycloalkyl, and saturated oxacycle having 4, 5, or 6 ring atoms and one ring oxygen, which oxacycle is unsubstituted or substituted with 1 or 2 independently selected C_1-C_4alkyl substituents, and wherein each phenyl or heteroaryl comprises at least one non-hydrogen substituent *ortho* to the point of attachment to the remainder of the compound of formula (I);

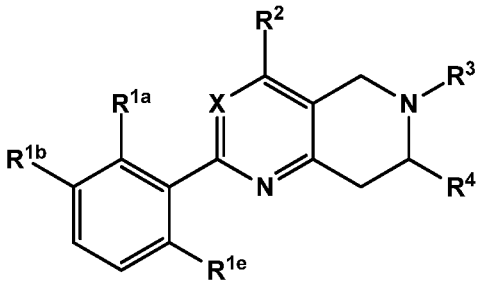
R_4 is hydrogen or C_1-C_4alkyl;

R^5 is hydrogen; or

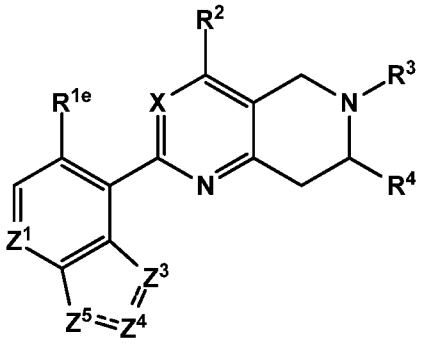
R^4 and R^5 taken in combination are oxo; and

R^6 is hydrogen at each occurrence or CR^6_2, taken in combination, form a divalent carbonyl.

2. A compound of claim 1, which is a compound of formula (II) or formula (III), or a salt thereof:



(II)



(III)

wherein

Z^1 is N or CH;

Z^3 is N(H), N(C_1-C_4alkyl), or C(R^{1f});

Z^4 is N or CH;

Z^5 is N(H), N(C_1-C_4alkyl) or C(R^{1g}), wherein one or two of Z^3, Z^4 and Z^5 is nitrogen;

R^{1f} is hydrogen, C_1-C_4alkyl or halogen; and

R^{1g} is hydrogen or C_1-C_4alkyl.

3. A compound of claim 1 or claim 2, in which R^3 is phenyl or 1H-pyrazolyl, each of which is substituted with 1 or 2 independently selected C_1-C_4alkyl groups and 0, 1 or 2 additional substituents selected from the group consisting of halogen, cyano, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy, cyclopropyl, oxetanyl or 1-methyl-oxetanyl.

4. The compound of claim 2 or claim 3, in which R^{1a} is hydrogen or methyl;

R^{1e} is hydrogen, halogen, cyano, methyl or trifluoromethyl, wherein at least one of R^{1a} and R^{1e} is not hydrogen;

Z^3 is C(R^{1f});

Z^4 is N or CH;

Z^5 is N(H); and

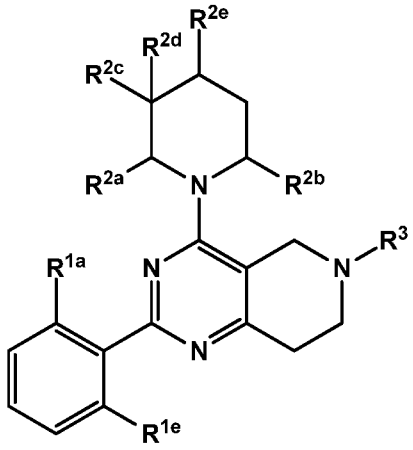
R^{1f} is hydrogen or methyl.

5. The compound of any one of claims 1 to 3, in which R^1 is 2,6-dimethylphenyl, 2,6-diethylphenyl, 3,5-dimethyl-1*H*-indazol-4-yl, 3,5-dimethyl-1*H*-indol-4-yl, 3,5-dimethyl-1*H*-indol-4-yl, 3,5-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl, or 5-trifluoromethyl-3*H*-pyrrolo[2,3-*b*]pyridin-4-yl.

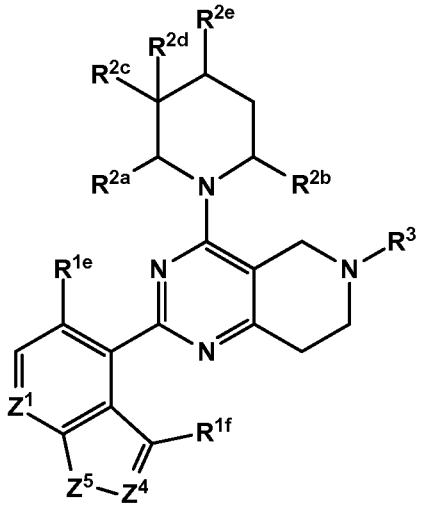
6. The compound of any one of claims 1 to 5, in which R^4 is hydrogen.

7. The compound of any one of claims 1 to 5, in which X is N.

8. A compound of any one of claims 1 to 7, which is a compound of formula (IV) or (V), or a salt thereof:



(IV)



(V)

wherein

R^{2a}, R^{2b}, R^{2c}, and R^{2d} are independently selected from hydrogen and C_1-C_4alkyl; or

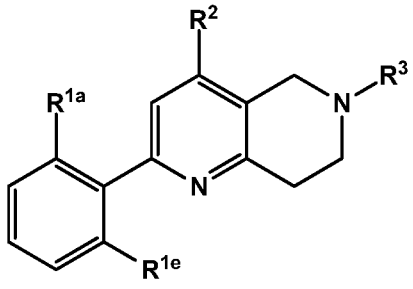
R^{2a} and R^{2b}, taken in combination, form a divalent C_1-C_3alkylene group; and

R^{2e} is hydroxy or C_1-C_4alkoxy.

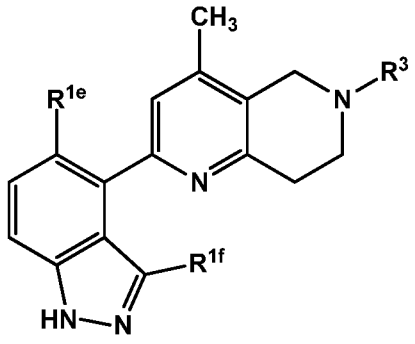
9. The compound of any one of claims 1 to 5, in which X is CH.

10. The compound of any one of claims 1 to 5 or 9, in which R^2 is hydrogen or methyl.

11. A compound of any one of claims 1 to 5, 9 or 10, which is a compound of formula (VI) or (VII), or a salt thereof:



(VI)



(VII)

wherein

in formula (VI), R^{1a} and R^{1e} are methyl or ethyl; or

in formula (VII), R^{1e} and R^{1f} are hydrogen or methyl, wherein at least one R^{1e} or R^{1f} is methyl.

12. A compound of claim 1, or a salt thereof, in which R^6 is deuterium.

13. A compound of claim 1, or a salt thereof, which compound is selected from the group consisting of

racemic 1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-4-ol;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

*racemic*1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-4-ol;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3-methoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(1,3-dimethyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-N-(2-methoxyethyl)-N-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

1-((2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(3-(2-methoxyethyl)-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(tetrahydrofuran-2-yl)-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

N-cyclopentyl-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-*N*-methyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-amine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

*racemic*1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

(*R*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(2-methylpyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-*N*-methyl-*N*-((tetrahydrofuran-2-yl)methyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-amine;

racemic 2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(3-(methoxymethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-(4-(methoxymethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*S*)-1-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.;

1-((2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol;

ethyl 1-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidine-3-carboxylate;

2,2'-((2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)azanediyl)diethanol;

2-(2,6-dimethylphenyl)-N-propyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

methyl 2-((2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)acetate;

(*R*)-2-((6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)amino)-3-methylbutan-1-ol;

4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2R,4S)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*S*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol;

6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2*S*,4*S*)-4-methoxy-2-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-N,N-dimethyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

2-(2,6-dimethylphenyl)-N-(2-methoxyethyl)-N-methyl-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-(4-methoxypiperidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-(3,3-dimethylpyrrolidin-1-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,2-dimethylmorpholine;

4-(azetidin-1-yl)-2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(4-methoxypiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-chloro-2-methylphenyl)-4-(4-methoxypiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-methyl-1-(methyl(2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)amino)propan-2-ol;

1-((6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpropan-2-ol;

6-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,2-dimethylmorpholine;

6-(5-isopropyl-2-methylphenyl)-N,N-dimethyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3,3-dimethylpiperidin-4-ol;

6-(5-isopropyl-2-methylphenyl)-N-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

N-isopropyl-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

4-(azetidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-4-ol;

6-(5-isopropyl-2-methylphenyl)-N-(2-methoxyethyl)-N-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)azetidin-3-ol;

racemic 6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3-fluoroazetidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3,3-dimethylpiperidin-4-ol;

(*S*)-4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylmorpholine;

(*S*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-ol;

(*R*)-1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol;

6-(5-isopropyl-2-methylphenyl)-4-((3*R*,4*R*)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-(1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)pyrrolidin-2-yl)methanol;

(*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*S*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylazetidin-3-ol;

6-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-oxa-6-azaspiro[3.3]heptane;

6-(5-isopropyl-2-methylphenyl)-4-(3-methoxyazetidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

1-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine;

(3-*endo*)-8-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]octan-3-ol;

(*S*)-2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*S*)-6-(5-chloro-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(3-methyl-1-tosyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.;

2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(1-methyl-1H-indazol-7-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(1-methyl-1H-indazol-7-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-chloro-2-methoxyphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-chloro-2-methylphenyl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-2-(5-fluoro-2-methylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5- Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3,3-dimethylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,5-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*R*)-2-(2,4-dimethylpyridin-3-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,5-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(3,5-dimethylpyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(5-methoxy-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3,5-dimethyl-1H-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,4-dimethylpyridin-3-yl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(5-fluoro-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(4-fluoro-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-cyclopropyl-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(2,6-dimethylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(5-cyclopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-((3*S*,4*S*)-4-methoxy-3-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-dimethylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(4-(2-(2,5-Dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(2-(2,6-dimethylphenyl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide;

(*R*)-2-(4-(2-(2,6-dimethylphenyl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(o-tolyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(2,6-dimethylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-chloro-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-(trifluoromethyl)phenyl)-5,6,7,8 tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(4-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(2-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide.;

(*R*)-2-(4-(6-(3-fluoro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(2,4-difluorophenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)acetamide;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-cyclopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone;

1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)ethanone;

(*R*)-1-(4-(2-(2,5-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperazin-1-yl)ethanone;

(*R*)-1-(3-methyl-4-(2-(3-methyl-1H-indol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone;

racemic 1-(4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)ethanone;

racemic 1-((*trans*)-4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2,5-dimethylpiperazin-1-yl)ethanone;

racemic 2-(-4-(2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)acetamide;

racemic 2-(4-(6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-(*trans*)-2,5-dimethylpiperazin-1-yl)acetamide;

(*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(methylsulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-isopropyl-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-;

methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-4-(4-ethyl-3-methylpiperazin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(5-chloro-2-methylphenyl)-2-(3-methyl-1H-indol-4-yl)-4-(3-methyl-4-(oxetan-3-yl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-methoxy-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-; tetrahydropyrido[4,3-d]pyrimidine;

2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(5-isopropyl-1H-indazol-4-yl)-4-methoxy-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3-chloro-5-methyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy-5,6,7,8 tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(3-chloro-5-methyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic 2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-((S)-1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic 2-(2,6-dimethylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-((*R*) 1-phenylethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

(*R*)-4-methyl-1-(2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)pentane-1,3-dione;

(*R*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methyl-4-((2-nitrophenyl)sulfonyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1-tosyl-1H-indol-4-yl)-4-(3-methylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(4-(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(2-(2,6-dimethylphenyl)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*R*)-2-(4-(6-(4-chloro-3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-2-methylpiperazin-1-yl)acetamide;

(*S*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-((3R,4R)-4-methoxy-3-methylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic 1-(6-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-4-ol;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(3-methoxypropoxy)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-4-methyl-6-(o-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(1,3-dimethyl-1H-pyrazol-5-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(5-methoxy-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(2,5-dimethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(1-ethyl-3-methyl-1H-pyrazol-5-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(2,4-dimethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(5-cyclopropyl-2-methylphenyl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(5-chloro-2-methylphenyl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-4-methyl-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-2-(3-methyl-1H-indol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(5-fluoro-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(3-methyl-1H-indol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro($^2H_2$)-1,6-naphthyridine.;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2-chloro-5-methoxyphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(5-isopropyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

4-methyl-2-(5-methyl-1H-indazol-4-yl)-6-(2-methyl-5-(3-methyloxetan-3-yl)phenyl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-diethylphenyl)-4,7-dimethyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(2,6-diethylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4,7-dimethyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(3-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(5-isopropyl-2-methylphenyl)-4-methyl-2-(5-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(2,4-dimethylpyridin-3-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(3-methyl-1H-indol-4-yl)-6-(2,6-dimethylphenyl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine ;

6-(5-methoxy-2-methylphenyl)-4-methyl-2-(5-methyl-1H-indazol-4-yl)-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(5-isopropyl-1H-indazol-4-yl)-4-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-diethylphenyl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(3-methyl-1H-indol-4-yl)-6-(1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)-4-methyl-5,6,7,8-tetrahydro(5,5-$^2H_2$)-1,6-naphthyridine;

2-(2,6-diethylphenyl)-4-methyl-6-(1-methyl-1H-tetrazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy 5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-methoxy 5,6,7,8-tetrahydro(5,5-^{2}-1,6-naphthyridine;

(*S*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

2-(2,6-dimethylphenyl)-4-((2-hydroxy-2-methylpropyl)(methyl)amino)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

4-((cyclopropylmethyl)(propyl)amino)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2-methoxyethyl)(methyl)amino)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one;

(*S*)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

1-((2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-4-yl)(methyl)amino)-2-methylpropan-2-ol;

N-(cyclopropylmethyl)-2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-N-propyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-amine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-N-(2-methoxyethyl)-N-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-amine;

2-(2,6-dimethylphenyl)-6-(5-isopropyl-2-methylphenyl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine;

2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-ethoxy-2-methylpiperidin-1-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(4-chloro-3-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-ethoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-2-(5-methyl-1*H*-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-((2*R*,4*R*)-4-methoxy-2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-2-(3,5-dimethyl-1*H*-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-6-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((3-*endo*)-3-methoxy-8-azabicyclo[3.2.1]octan-8-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(S)-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(R)-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine; and

(R)-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-ethoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(S)-6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic (cis)-3-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane;

(R)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-cyclopropyl-2-(2-(3,5-dimethyl-1H-indazol-4-yl)-4-((4*S*,6*R*)-6-methyl-1-oxa-7-azaspiro[3.5]nonan-7-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)benzonitrile;

(R)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

(R)-6-(4-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(R)-6-(3-(difluoromethyl)-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(R)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(4-fluoro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-fluoroethoxy)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(2,2-difluoroethoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)ethanamine;

2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-N-methylethanamine;

(S)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-((1-methylpyrrolidin-2-yl)methoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

4-(2-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)ethyl)morpholine;

(*R*)-3-((2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)propane-1,2-diol;

1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine;

(*R*)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3,3-difluoropiperidin-4-ol;

(*R*)-1-(2-(3,5-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

(3S,4S)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(3R,4R)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(3R,4R)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(3S,4S)-1-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(*R*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-4-(2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine;

2-(3,5-dimethyl-1H-indazol-4-yl)-6-(5-isopropyl-2-methylphenyl)-4-(4-(methylsulfonyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-4-(2,2-difluoroethoxy)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(3-ethoxyazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

(R)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(S)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(3R,4R)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

(3S,4S)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-4-methoxy-N,N-dimethylpyrrolidin-3-amine;

racemic (trans)-1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-2-methylazetidin-3-ol;

racemic 6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-((*trans)*-3-methoxy-2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

1-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2,4-dimethylpiperazin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

racemic (1*S**,6*S**)- 3-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane;

racemic (*cis*)-3-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-7-oxa-3-azabicyclo[4.2.0]octane;

(*R*)-4-(6-(4-Chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*S*)-6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylazetidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-4-(6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine;

1-(6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine;

(*R*)-6-(3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(3-cyclopropyl-1-ethyl-4-fluoro-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-6-(4-chloro-3-cyclopropyl-1-ethyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine;

(*R*)-3-(difluoromethyl)-5-(2-(3,5-dimethyl-1H-indazol-4-yl)-4-(4-methoxy-3,3-dimethylpiperidin-1-yl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-1-methyl-1H-pyrazole-4-carbonitrile

Racemic (1*S**,6*S**)-3-(6-(3-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-1-methyl-7-oxa-3-azabicyclo[4.2.0]octane;

(*R*)-4-(6-(3-cyclopropyl-4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-3-methylmorpholine;

(R)-6-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine; and

(*R*)-6-(4-chloro-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-(3,5-dimethyl-1H-indazol-4-yl)-4-(2-methylpiperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

14. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and a therapeutically effective amount of a compound of any one of claims 1 to 13.

15. A combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to any one of claims 1 to 13 and a second therapeutically active agent.

16. A method of inhibiting C5a induced anaphalaxis in a subject is provided, the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 13.

17. A method of treating a disorder or a disease in a subject mediated by complement activation, the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 13.

18. The method of claim 17, in which the disease or disorder is selected from the group consisting of age-related macular degeneration, geographic atrophy, diabetic retinopathy, uveitis, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyanagi-Harada syndrome, intermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular cicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, retinal vein occlusion, neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus

erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration, neural regeneration, dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, pulmonary fibrosis, asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, antiphospholipid syndrome, glomerulonephritis and obesity.

19. A method of treating age related macular degeneration comprising administering to a subject in need thereof an effective amount of a composition comprising a compound of any one of claims 1 to 14.

20. A compound according to any one of claims 1 to 13, for use as a medicament.

21. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment of a disorder or disease in a subject mediated by complement activation.

22. Use of a compound according to any one of claims 1 to 13, for the treatment of age-related macular degeneration.

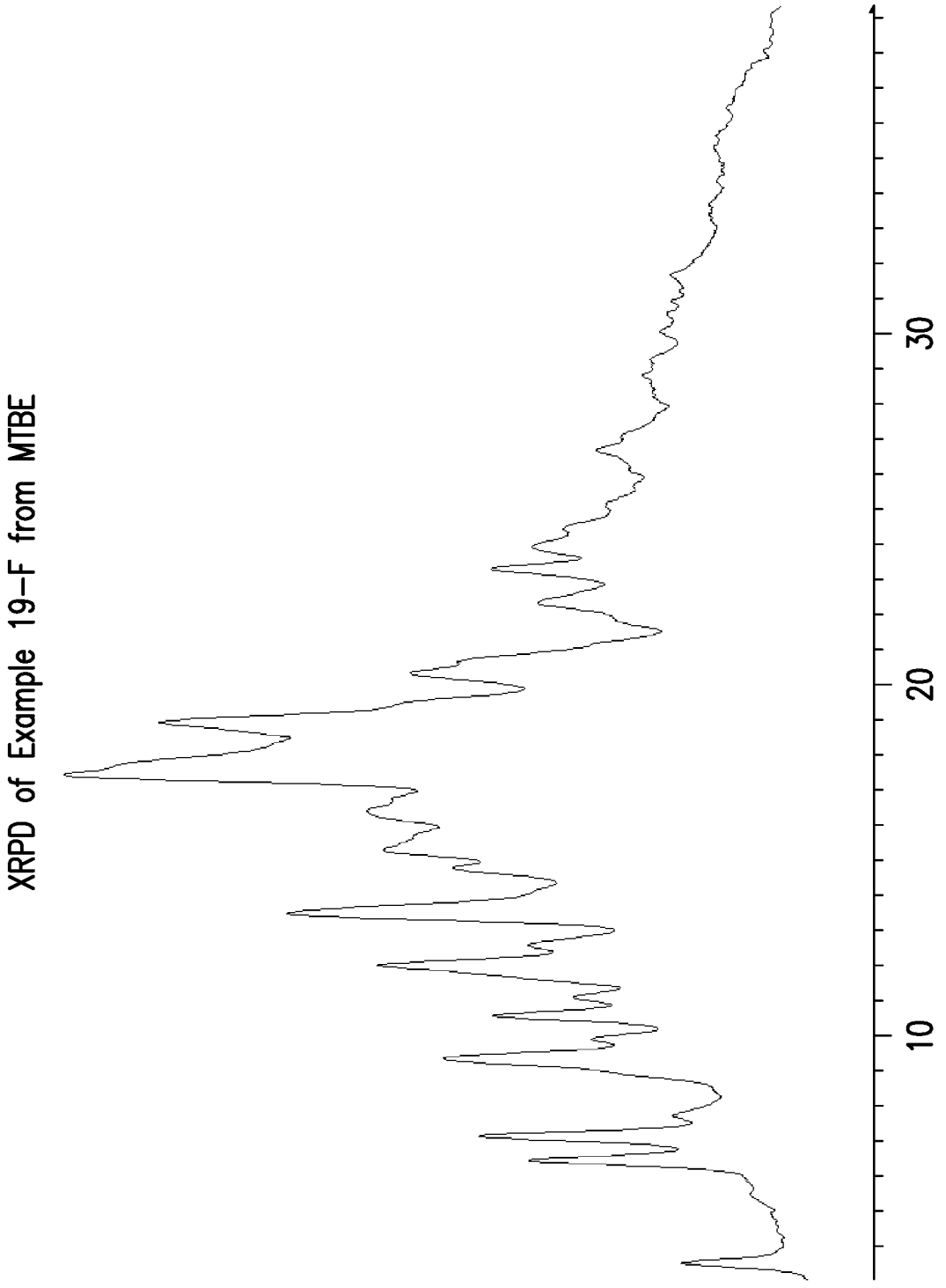


FIG. 1

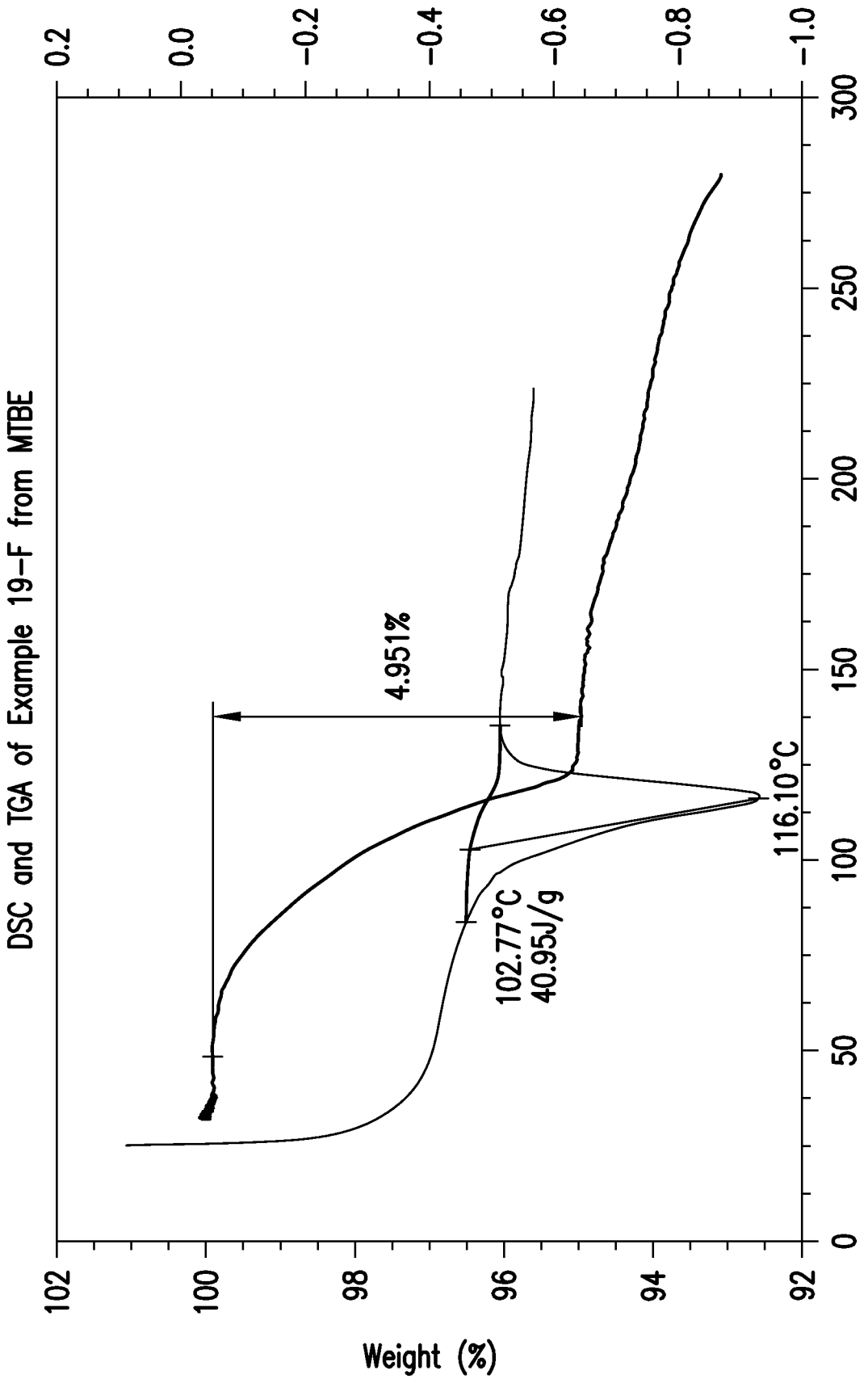

DSC and TGA of Example 19-F from MTBE
Heat Flow (W/g)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
Weight (%)
102
100
98
96
94
92
Temperature (°C)
0
50
100
150
200
250
300
4.951%
116.10°C
102.77°C
40.95J/g

FIG.2

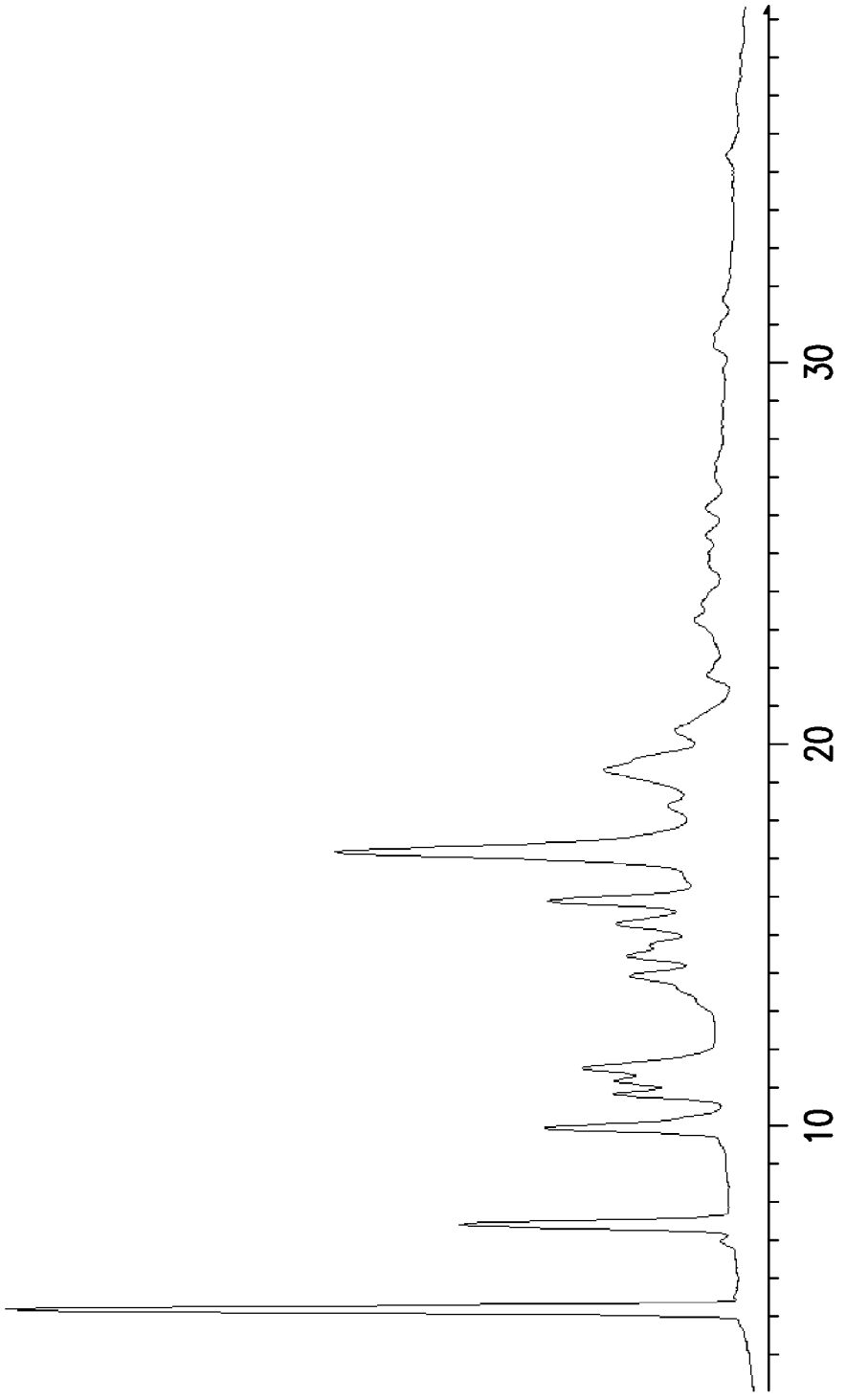


FIG.3

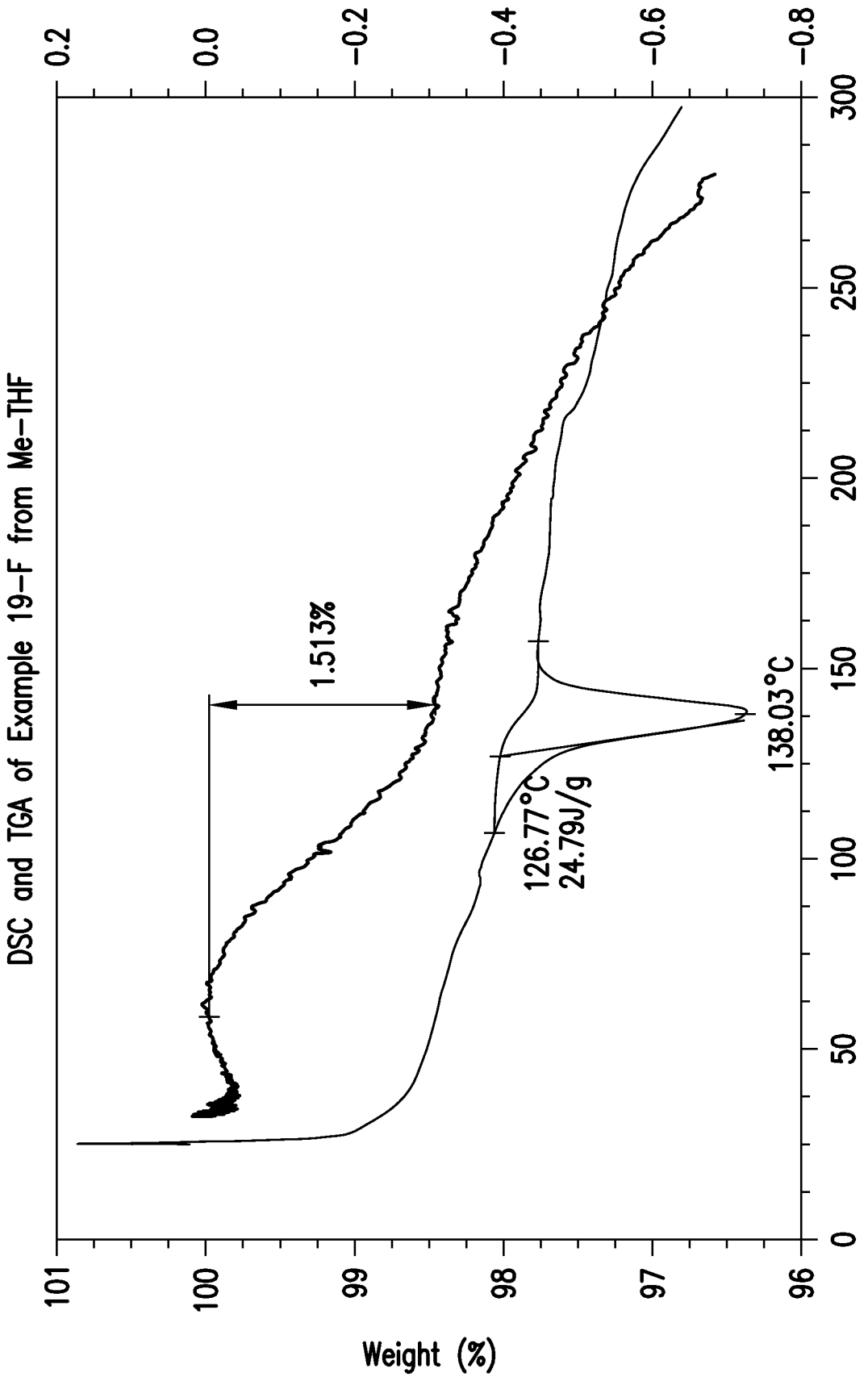

DSC and TGA of Example 19-F from Me-THF
Heat Flow (W/g)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
Weight (%)
101
100
99
98
97
96
Temperature (°C)
0
50
100
150
200
250
300
1.513%
126.77°C
24.79J/g
138.03°C

FIG.4

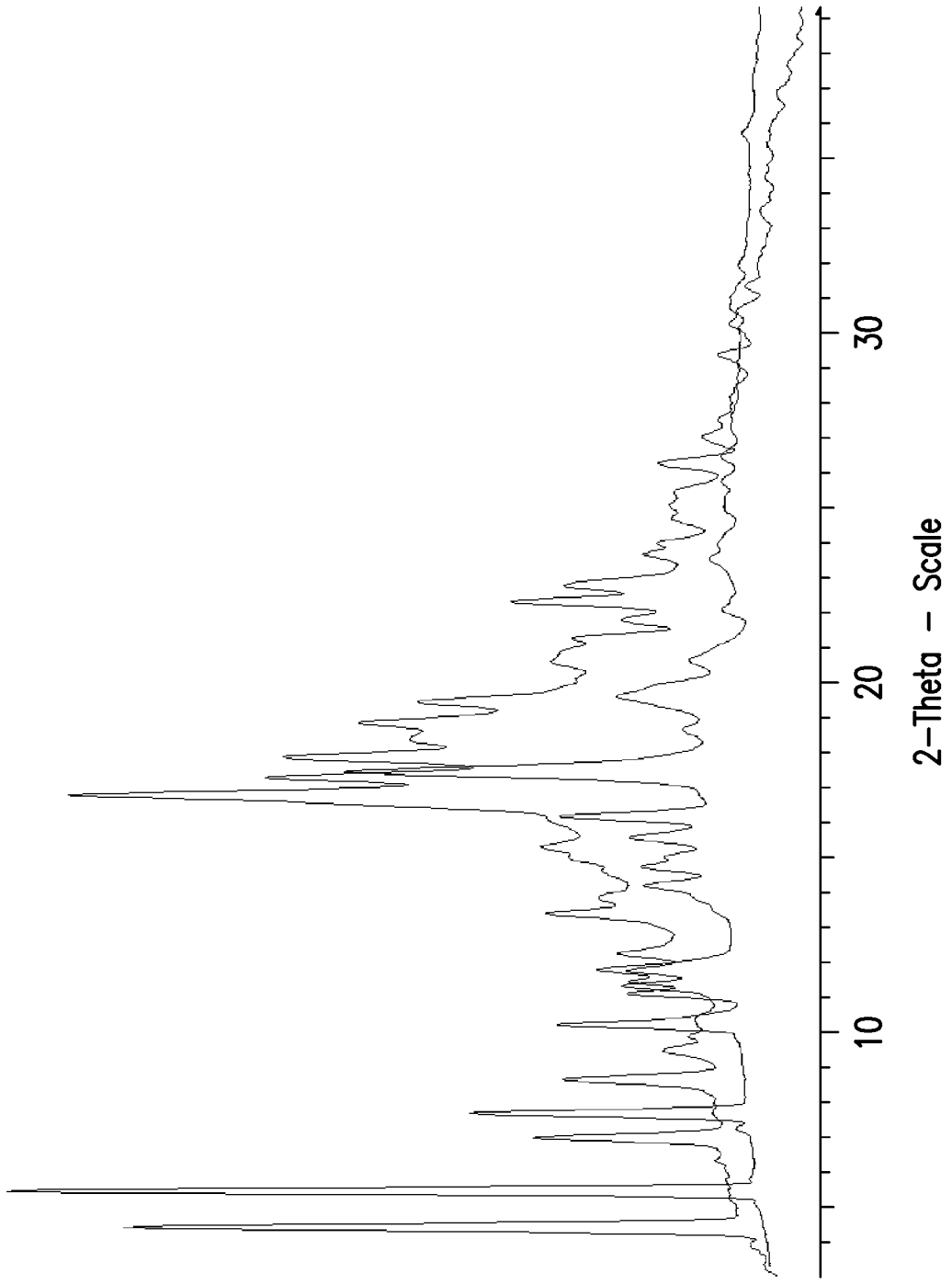

XRPD of Example 19-F of the inital precipitate (upper pattern) and dried material (lower pattern) from Me-THF
10
20
30
2-Theta - Scale

FIG.5

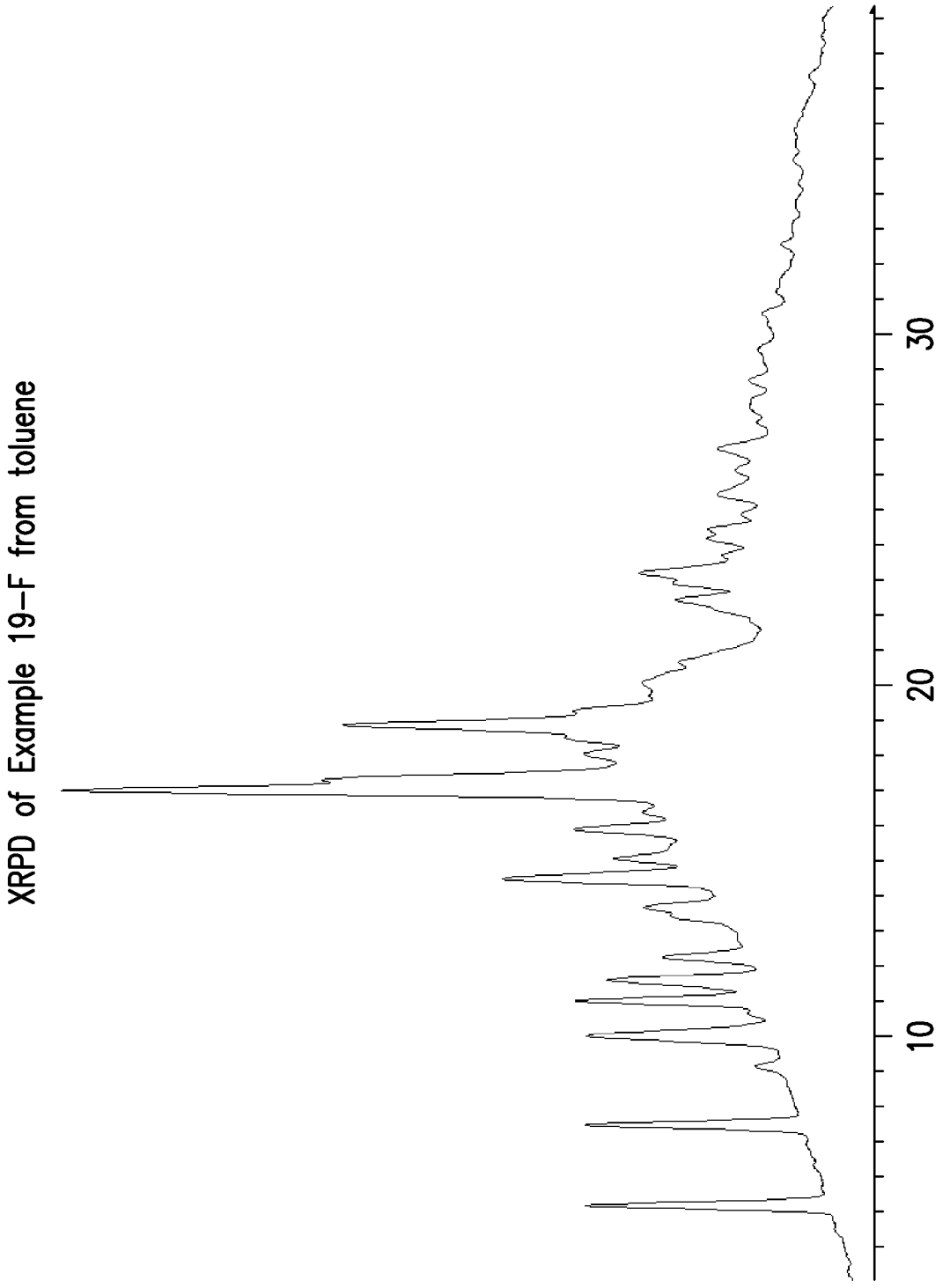


FIG.6

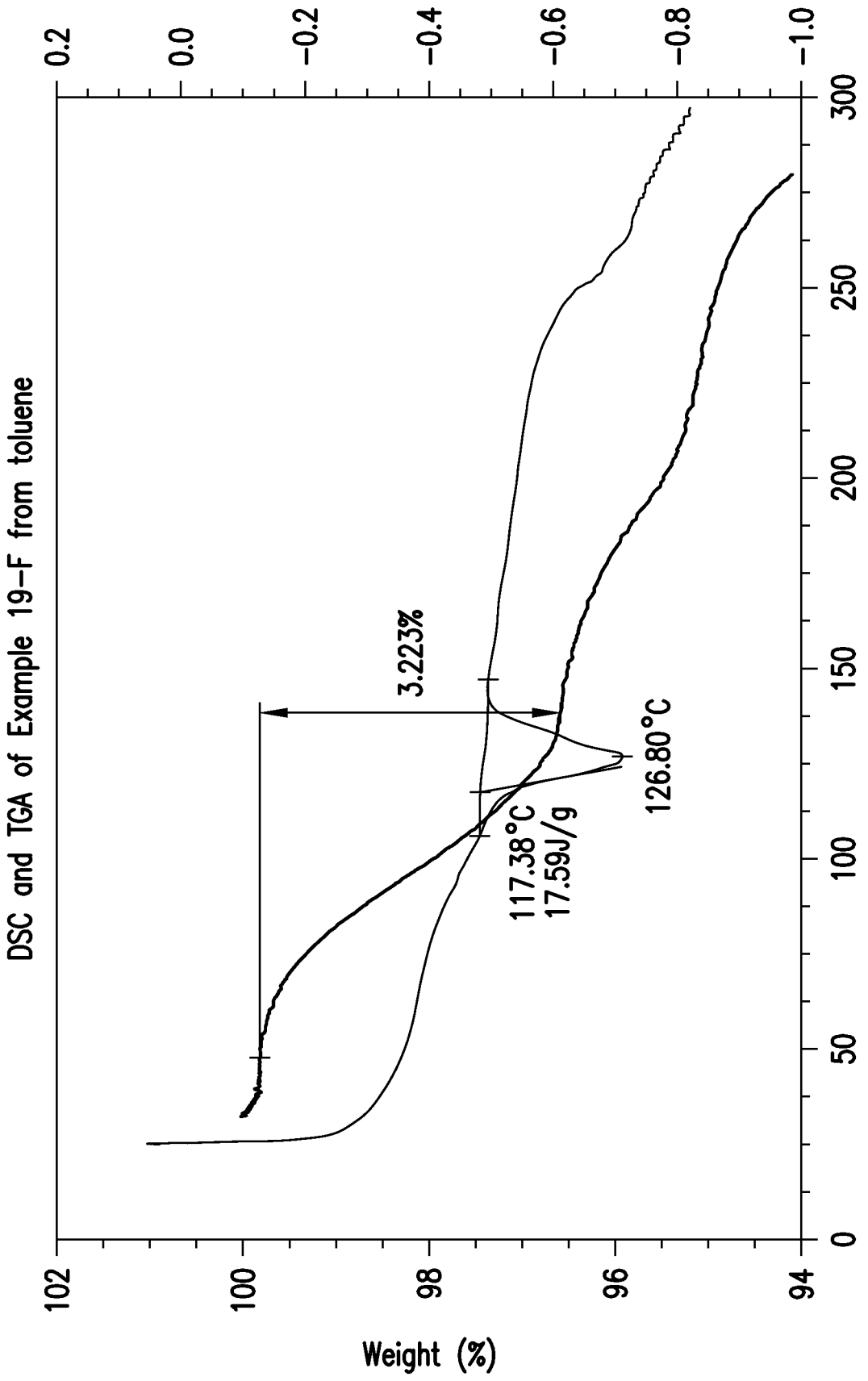

DSC and TGA of Example 19-F from toluene
Heat Flow (W/g)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
Weight (%)
102
100
98
96
94
Temperature (°C)
0
50
100
150
200
250
300
3.223%
117.38°C
17.59J/g
126.80°C

FIG. 7

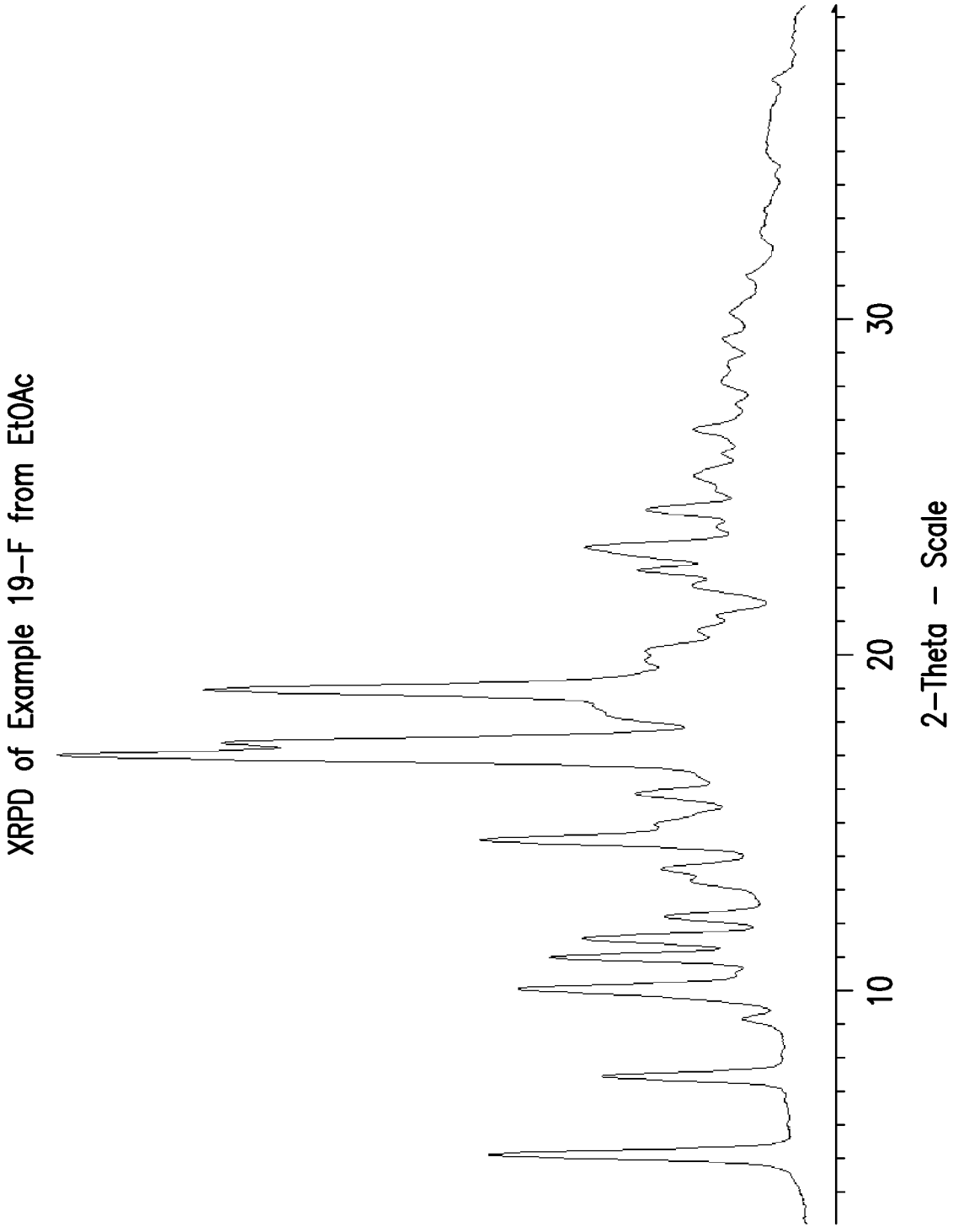


FIG.8

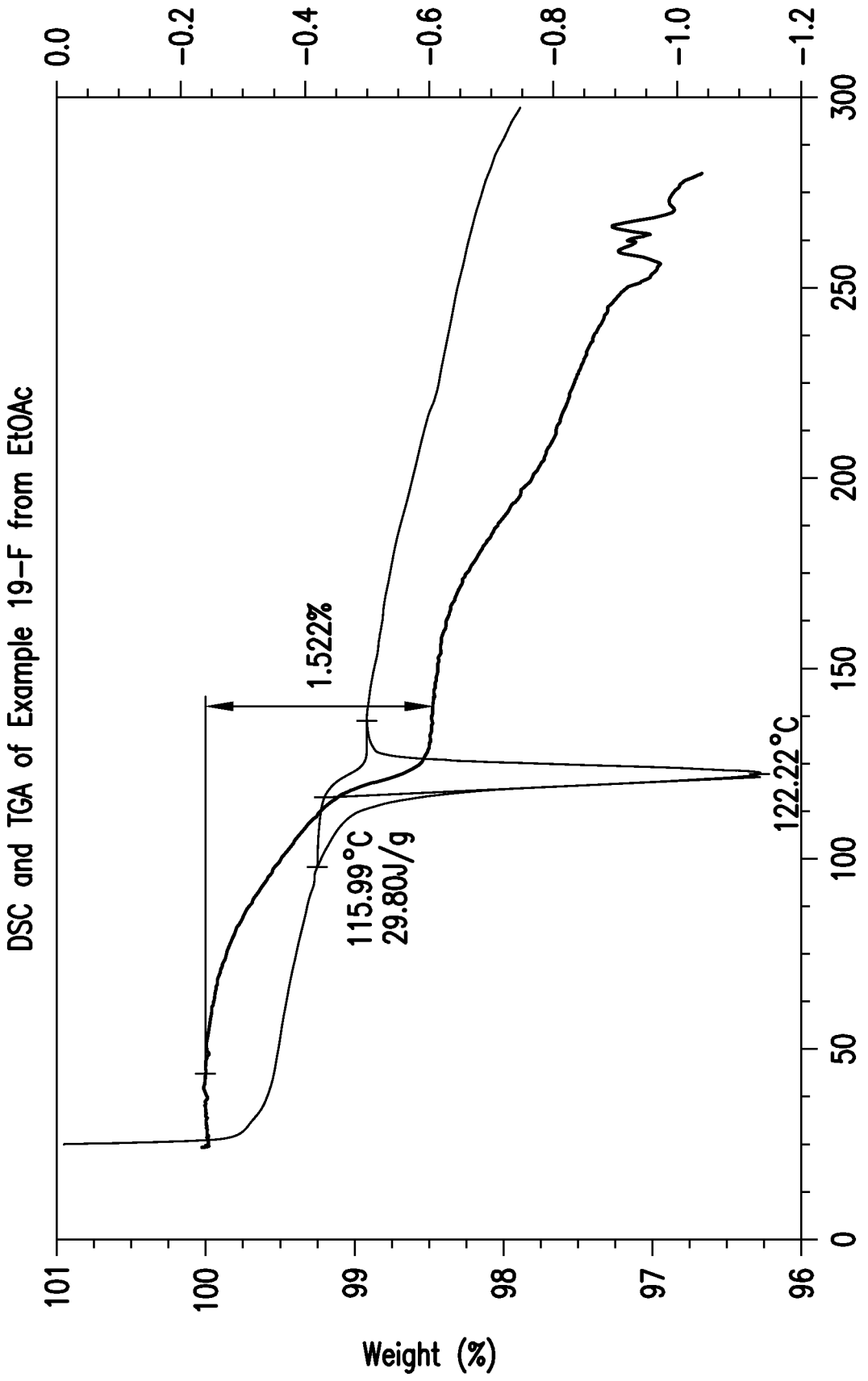

DSC and TGA of Example 19-F from EtOAc
Heat Flow (W/g)
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
300
250
200
150
100
50
0
Temperature (°C)
1.522%
115.99°C
29.80J/g
122.22°C
101
100
99
98
97
96
Weight (%)

FIG.9

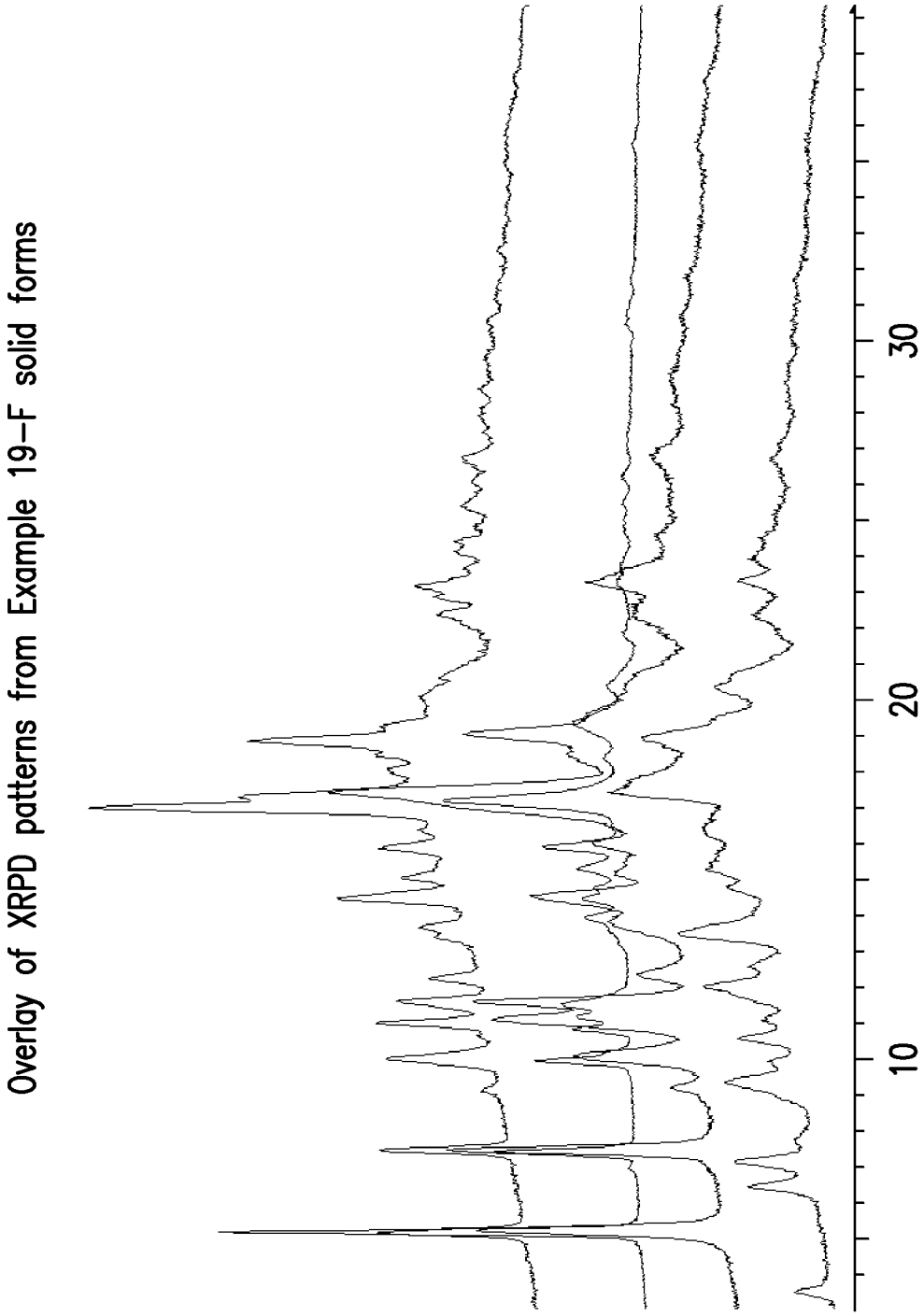

Overlay of XRPD patterns from Example 19-F solid forms
10
20
30
2-Theta - Scale

FIG.10

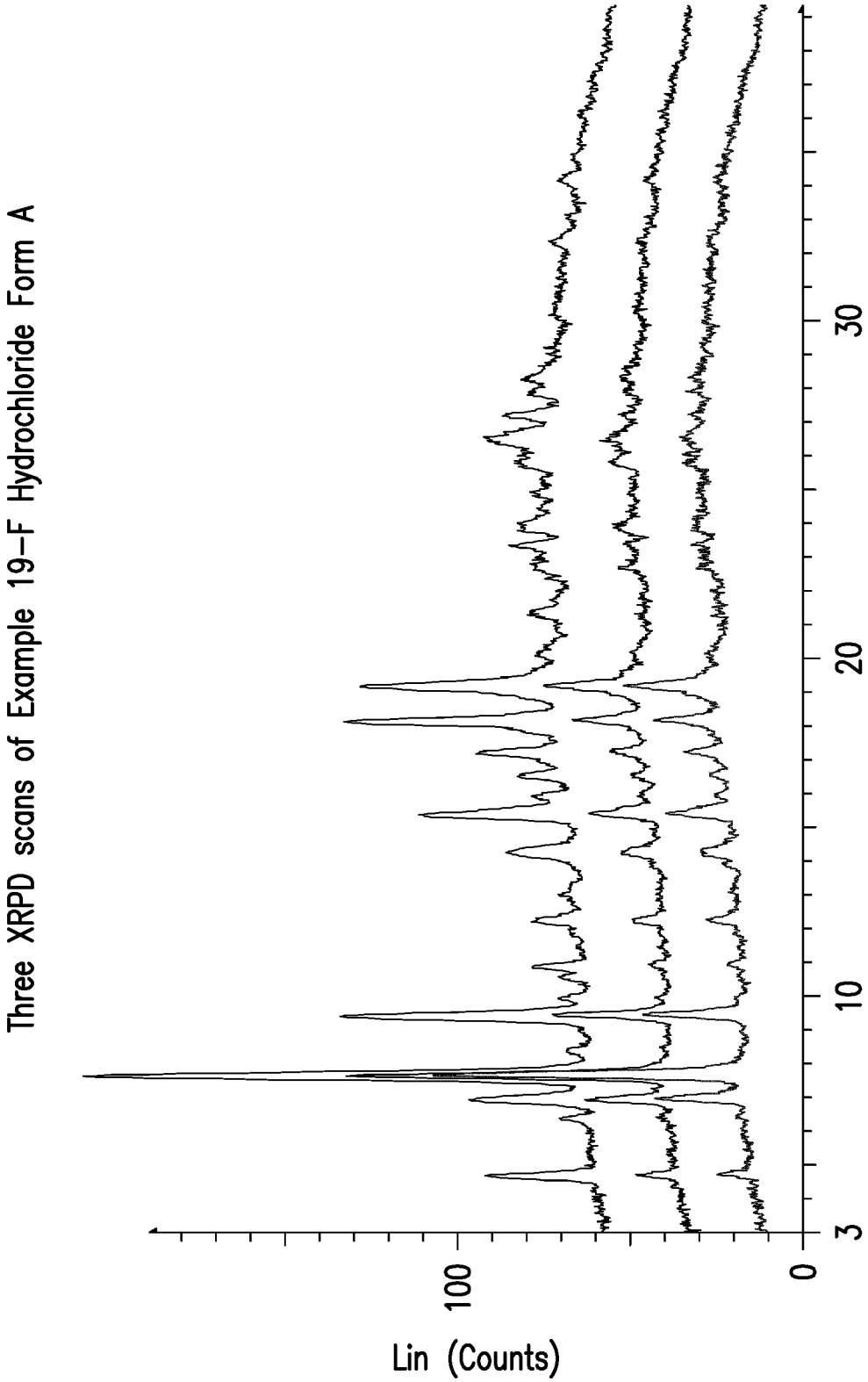

Three XRPD scans of Example 19-F Hydrochloride Form A
Lin (Counts)
0
100
3
10
20
30
2-Theta - Scale

FIG. 11

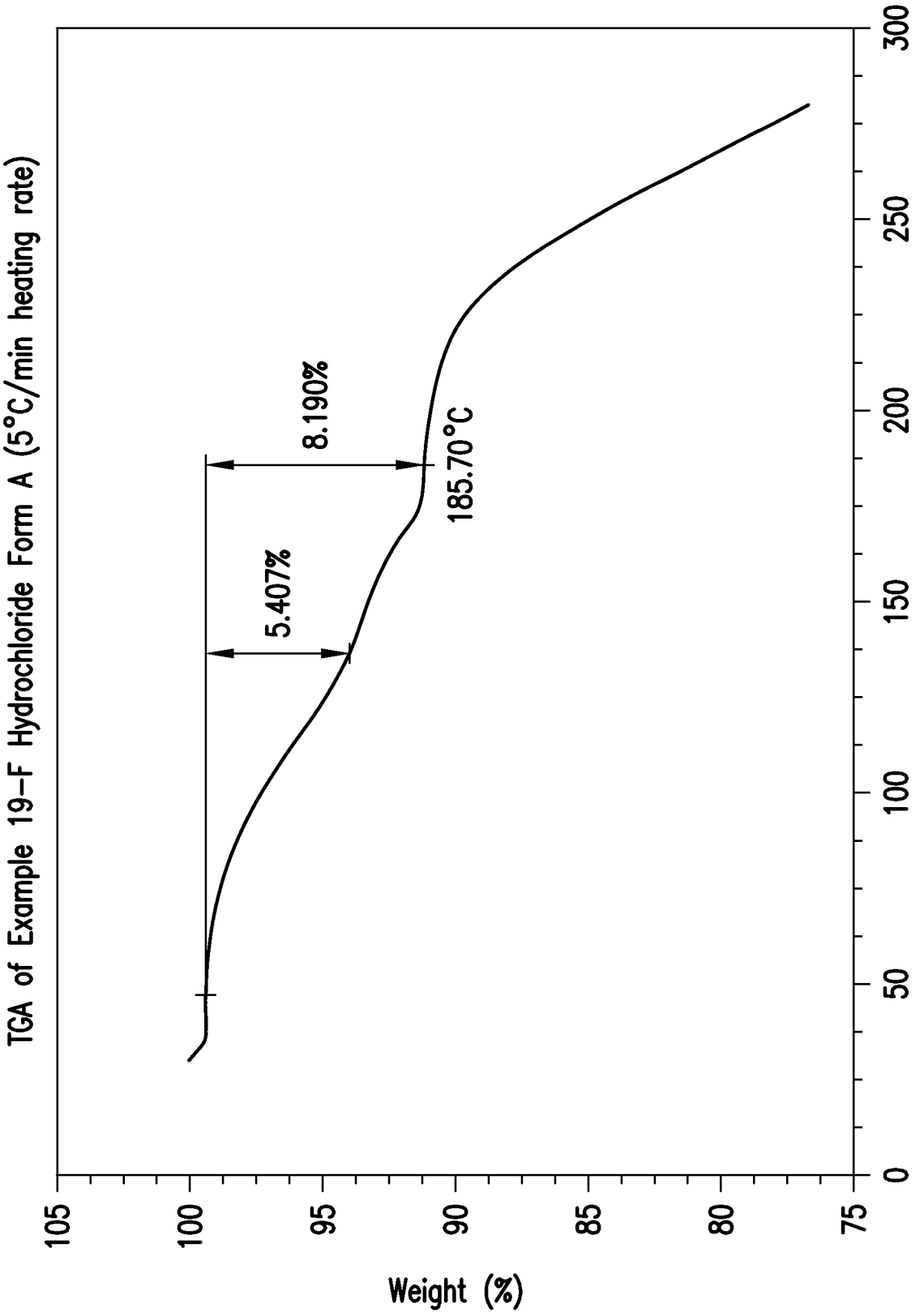

TGA of Example 19-F Hydrochloride Form A (5°C/min heating rate)
Weight (%)
Temperature (°C)
105
100
95
90
85
80
75
0
50
100
150
200
250
300
8.190%
5.407%
185.70°C

FIG. 12

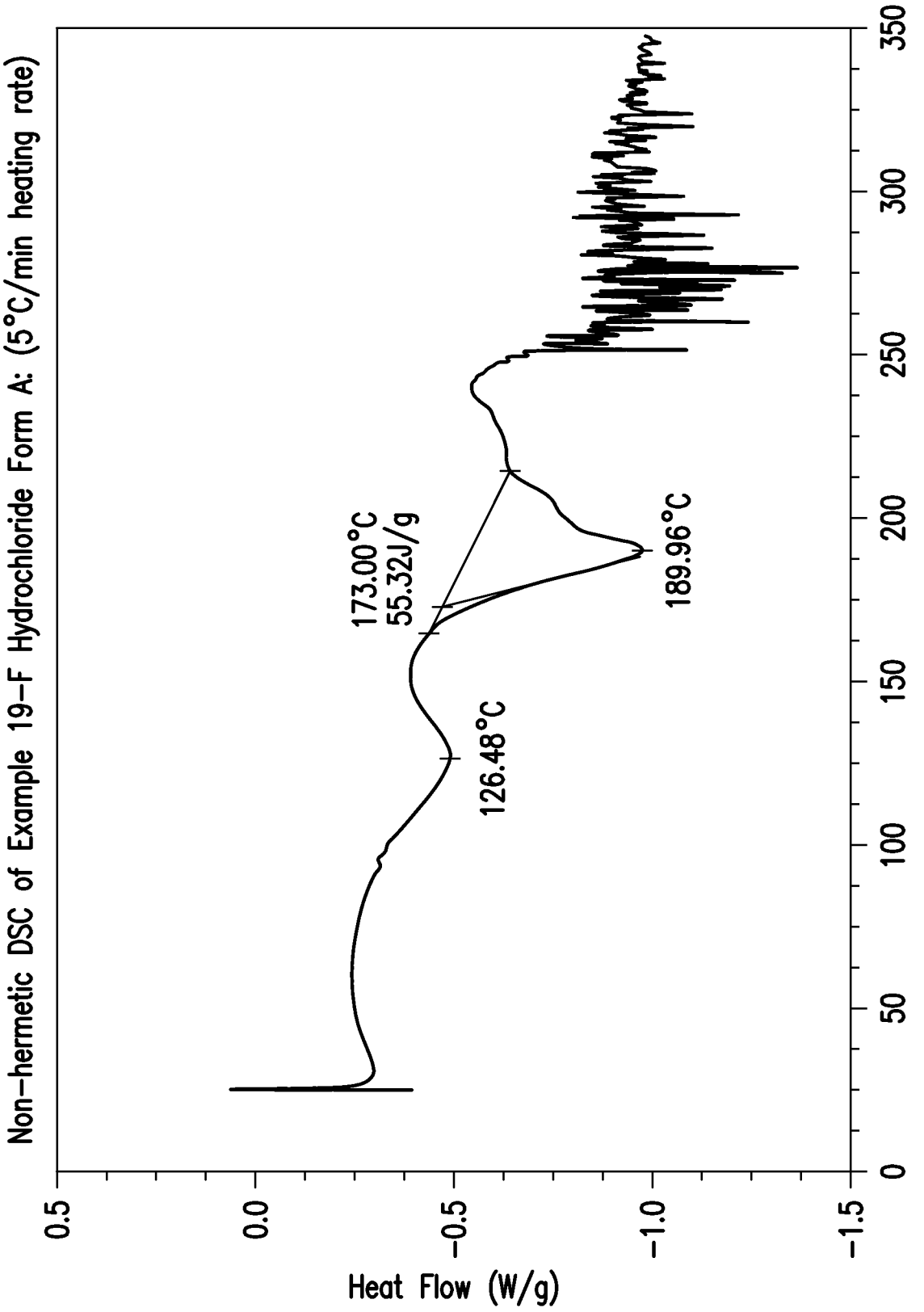

Non-hermetic DSC of Example 19-F Hydrochloride Form A: (5°C/min heating rate)
173.00°C
55.32J/g
126.48°C
189.96°C
Heat Flow (W/g)
0.5
0.0
-0.5
-1.0
-1.5
0
50
100
150
200
250
300
350
Temperature (°C)

FIG. 13

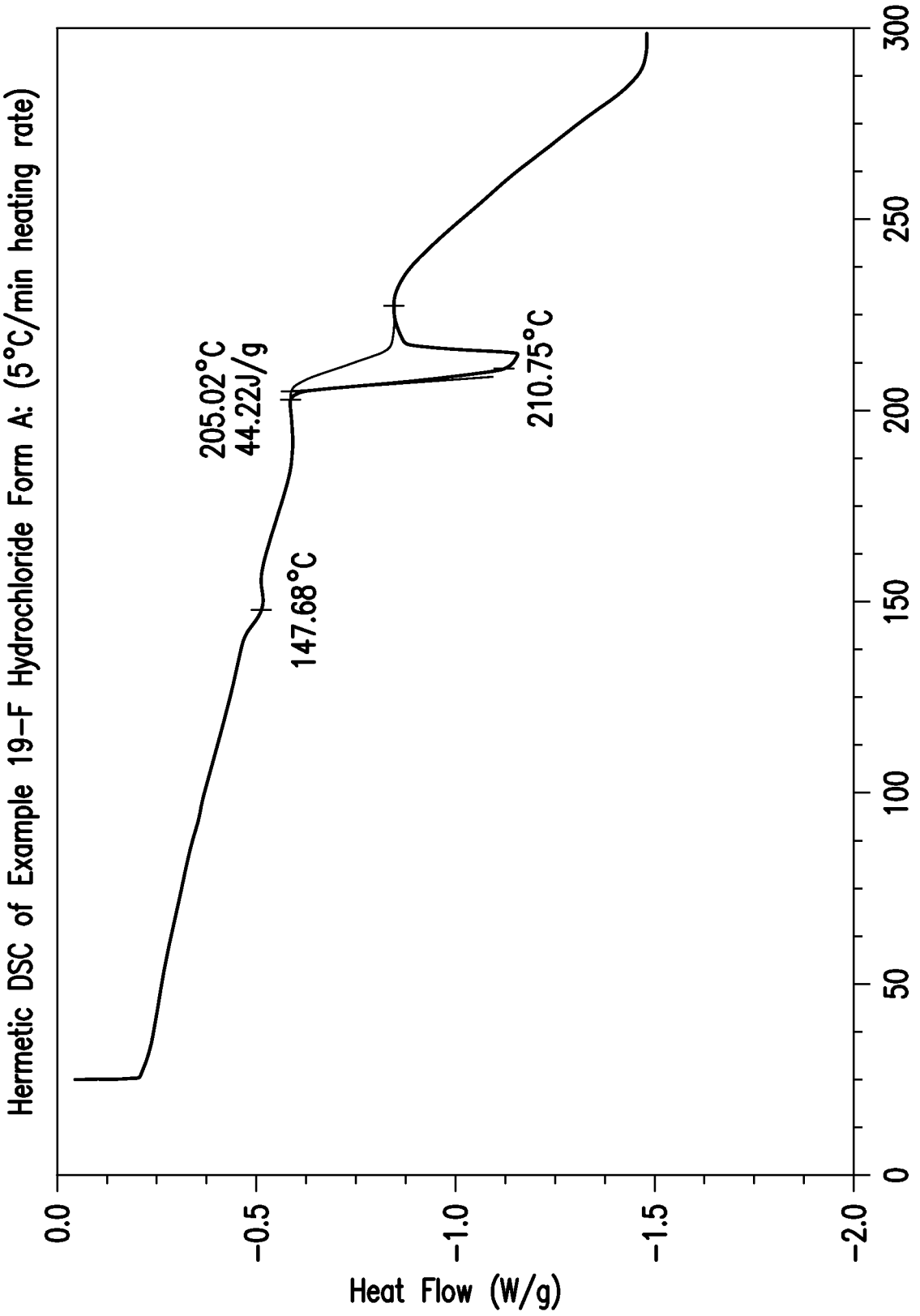

Hermetic DSC of Example 19-F Hydrochloride Form A: (5°C/min heating rate)
205.02°C
44.22J/g
147.68°C
210.75°C
Heat Flow (W/g)
0.0
-0.5
-1.0
-1.5
-2.0
Temperature (°C)
0
50
100
150
200
250
300

FIG. 14

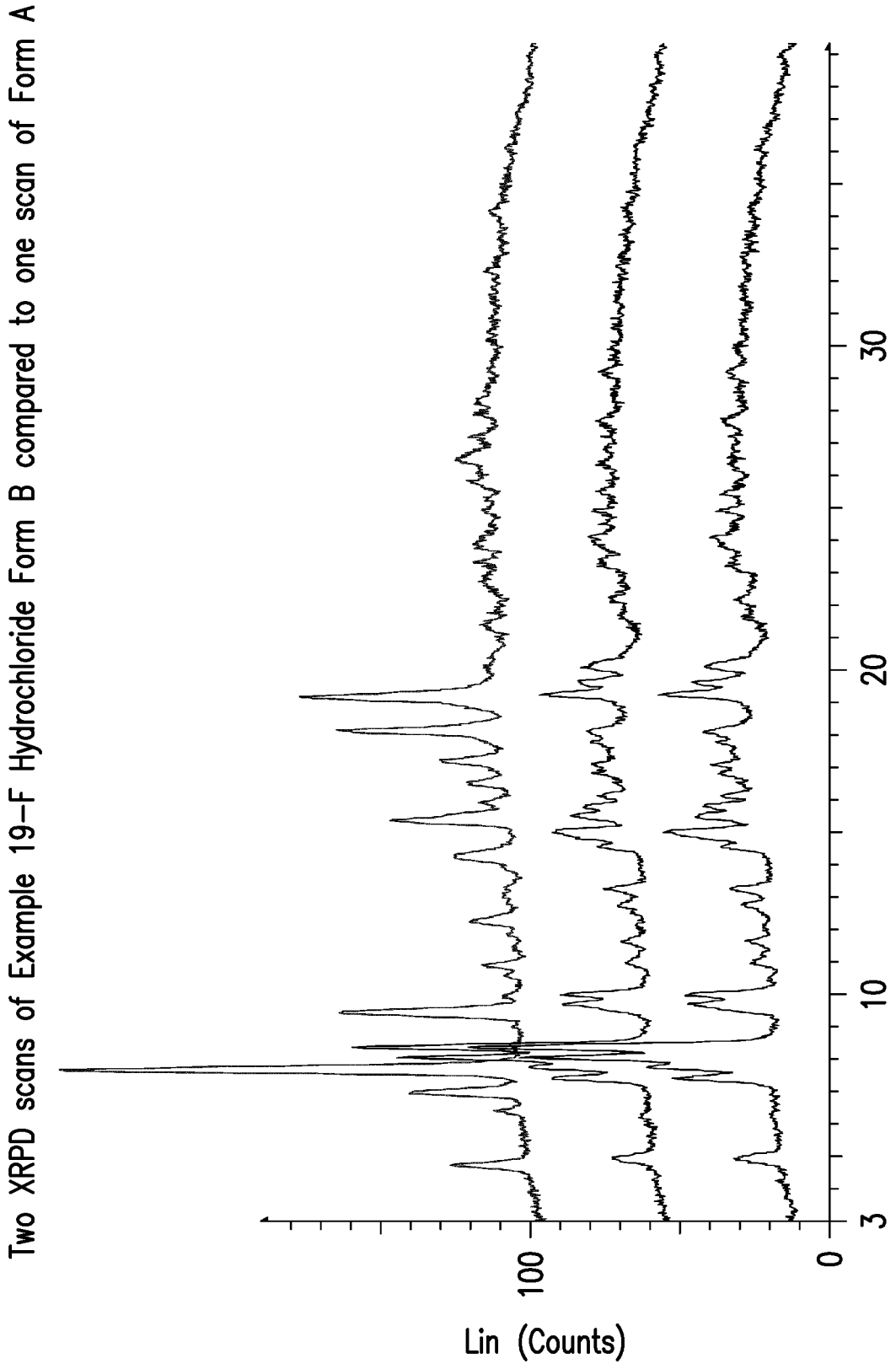

Two XRPD scans of Example 19-F Hydrochloride Form B compared to one scan of Form A
Lin (Counts)
100
0
3
10
20
30
2-Theta - Scale

FIG.15

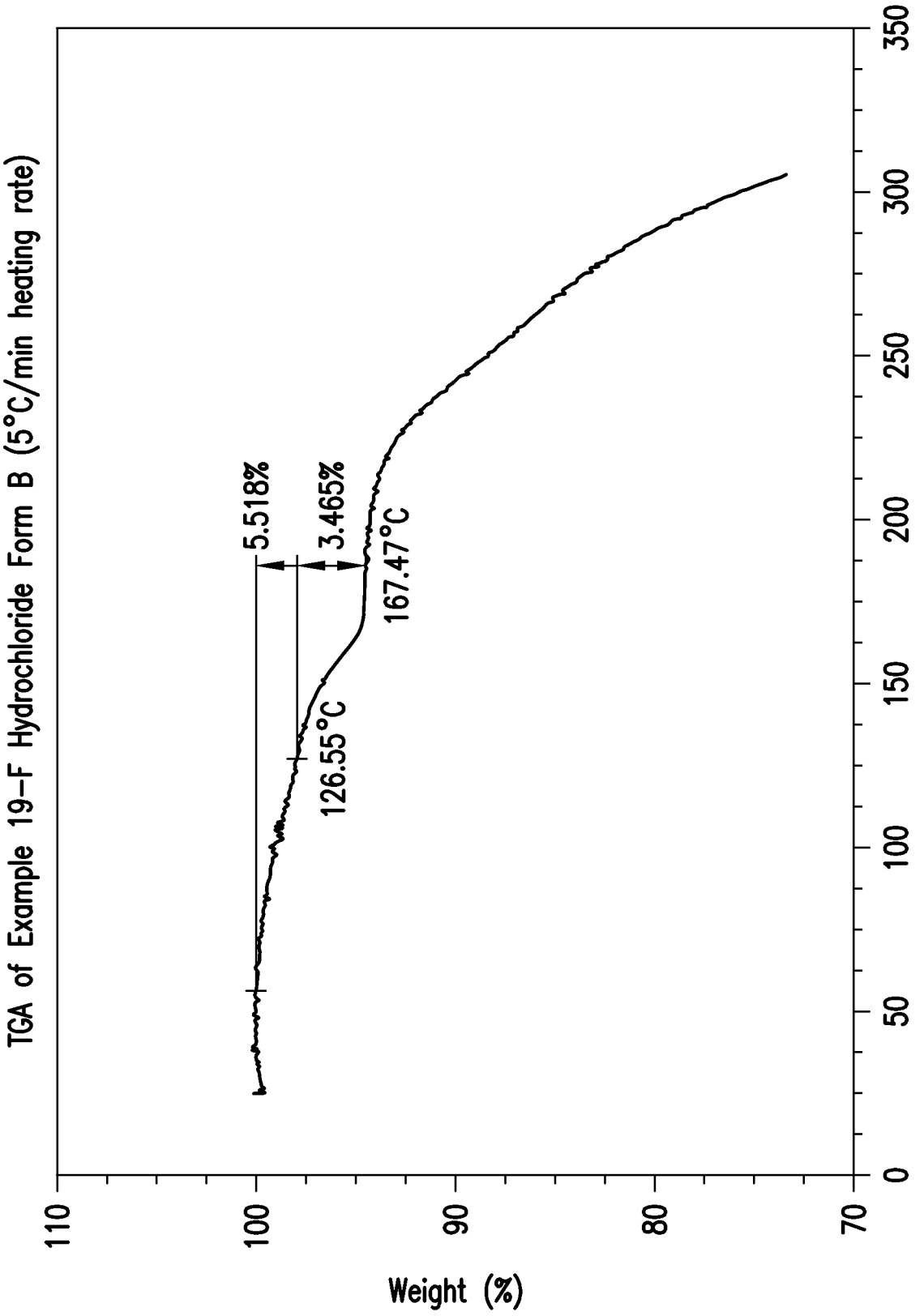

TGA of Example 19-F Hydrochloride Form B (5°C/min heating rate)
5.518%
3.465%
126.55°C
167.47°C
Weight (%)
110
100
90
80
70
Temperature (°C)
0
50
100
150
200
250
300
350

FIG. 16

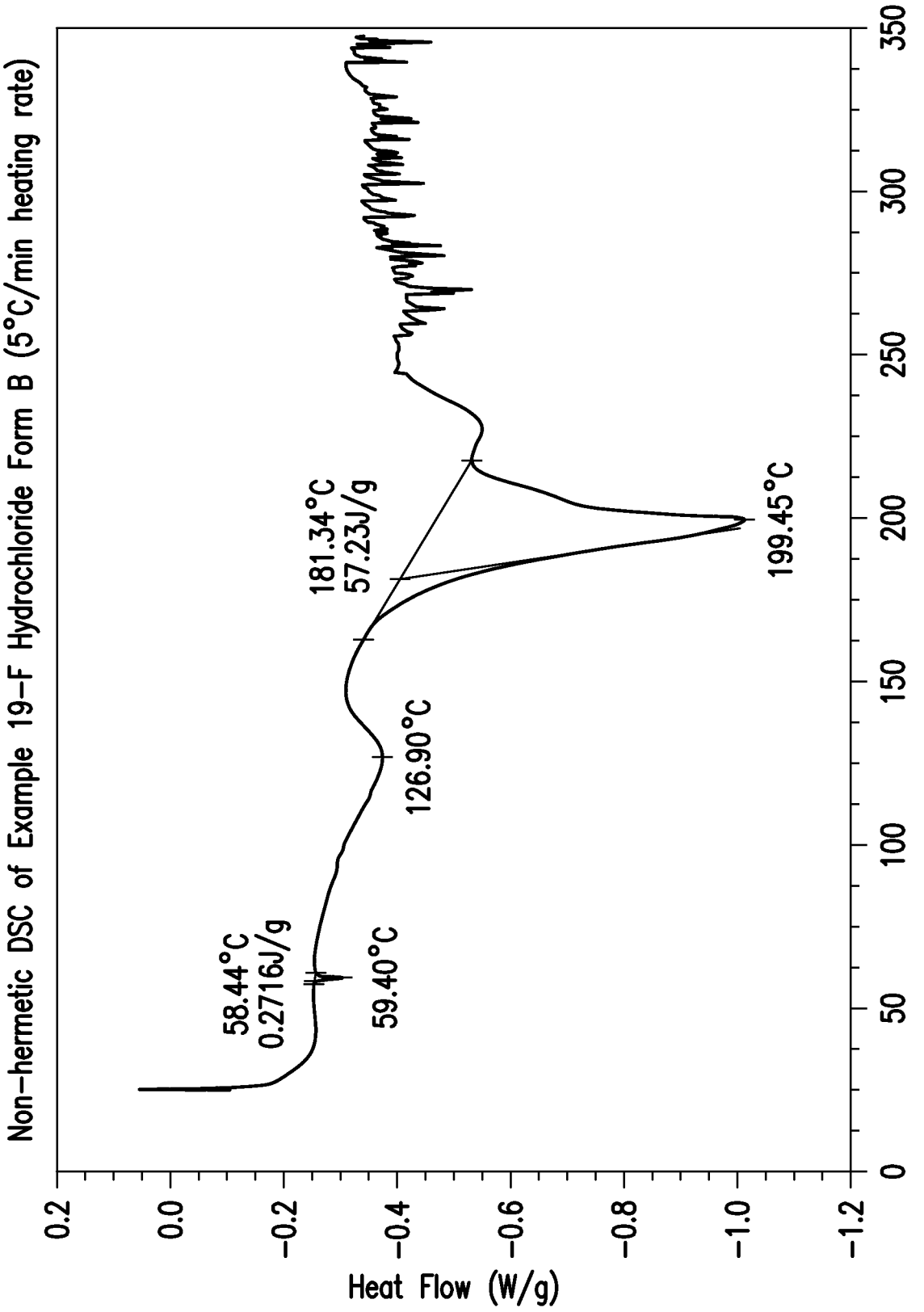

Non-hermetic DSC of Example 19-F Hydrochloride Form B (5°C/min heating rate)
58.44°C
0.2716J/g
59.40°C
126.90°C
181.34°C
57.23J/g
199.45°C
Heat Flow (W/g)
Temperature (°C)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
0
50
100
150
200
250
300
350

FIG. 17

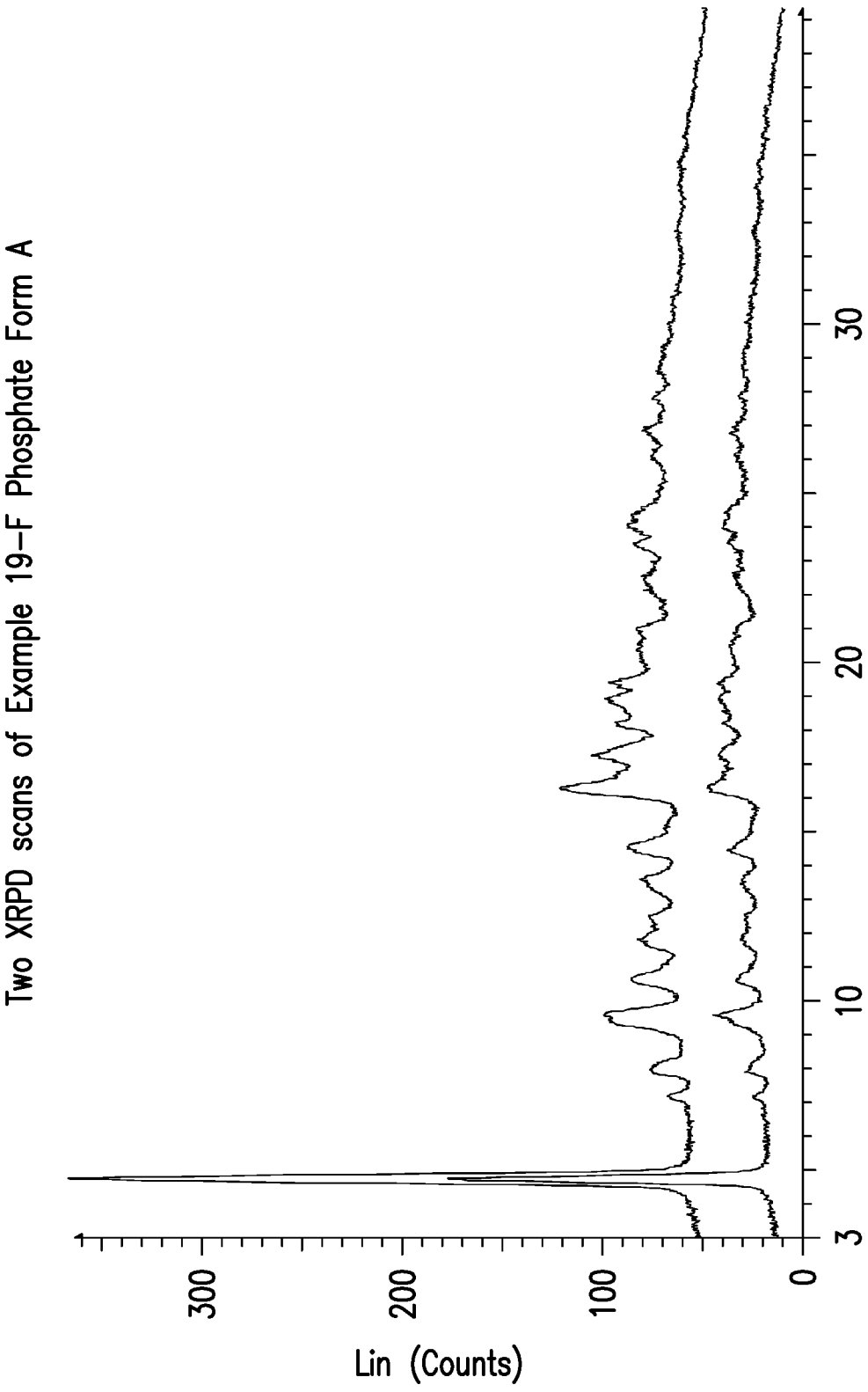

Two XRPD scans of Example 19-F Phosphate Form A
Lin (Counts)
300
200
100
0
3
10
20
30
2-Theta - Scale

FIG.18

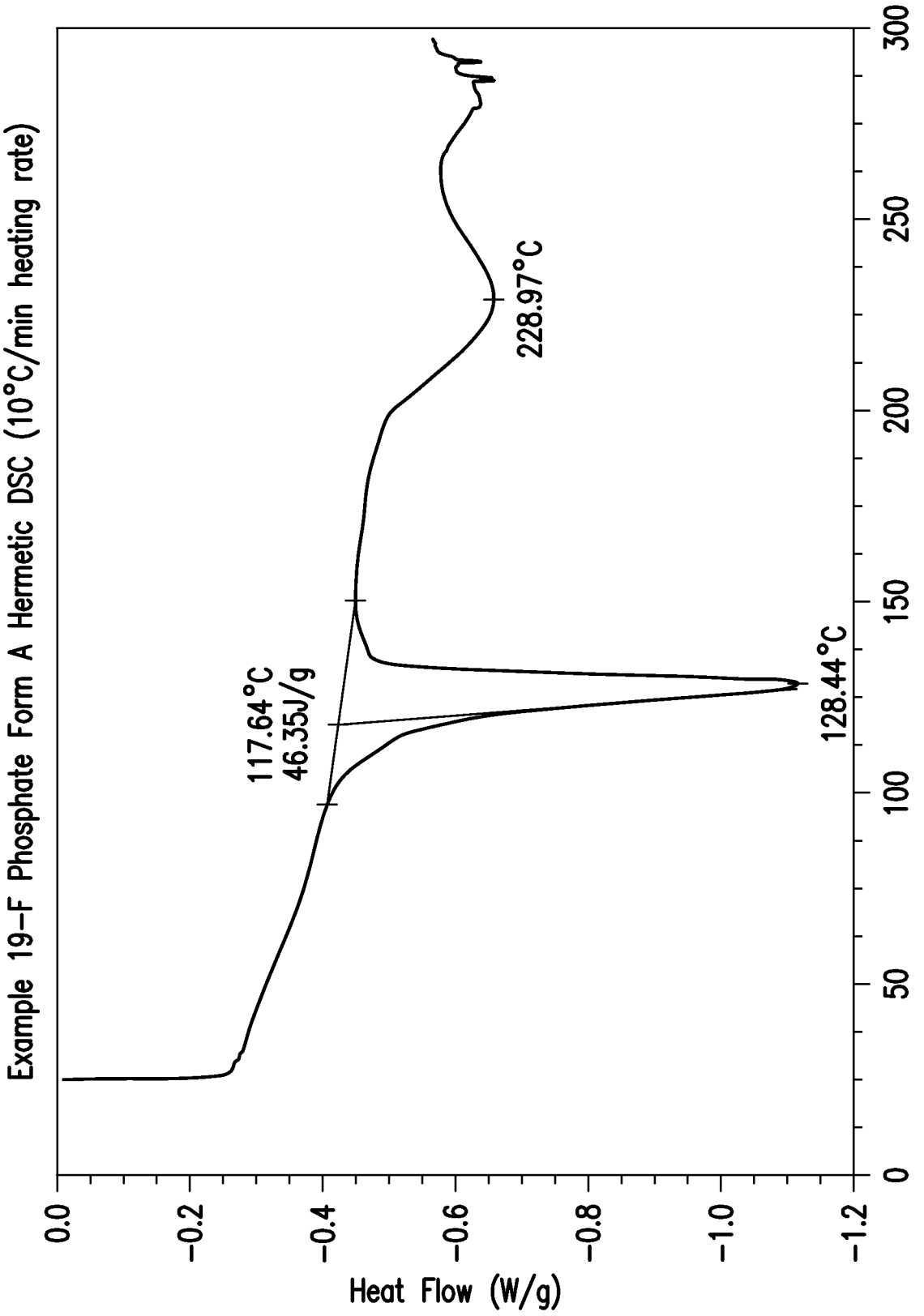

Example 19-F Phosphate Form A Hermetic DSC (10°C/min heating rate)
117.64°C
46.35J/g
228.97°C
128.44°C
Heat Flow (W/g)
Temperature (°C)
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
0
50
100
150
200
250
300

FIG. 19

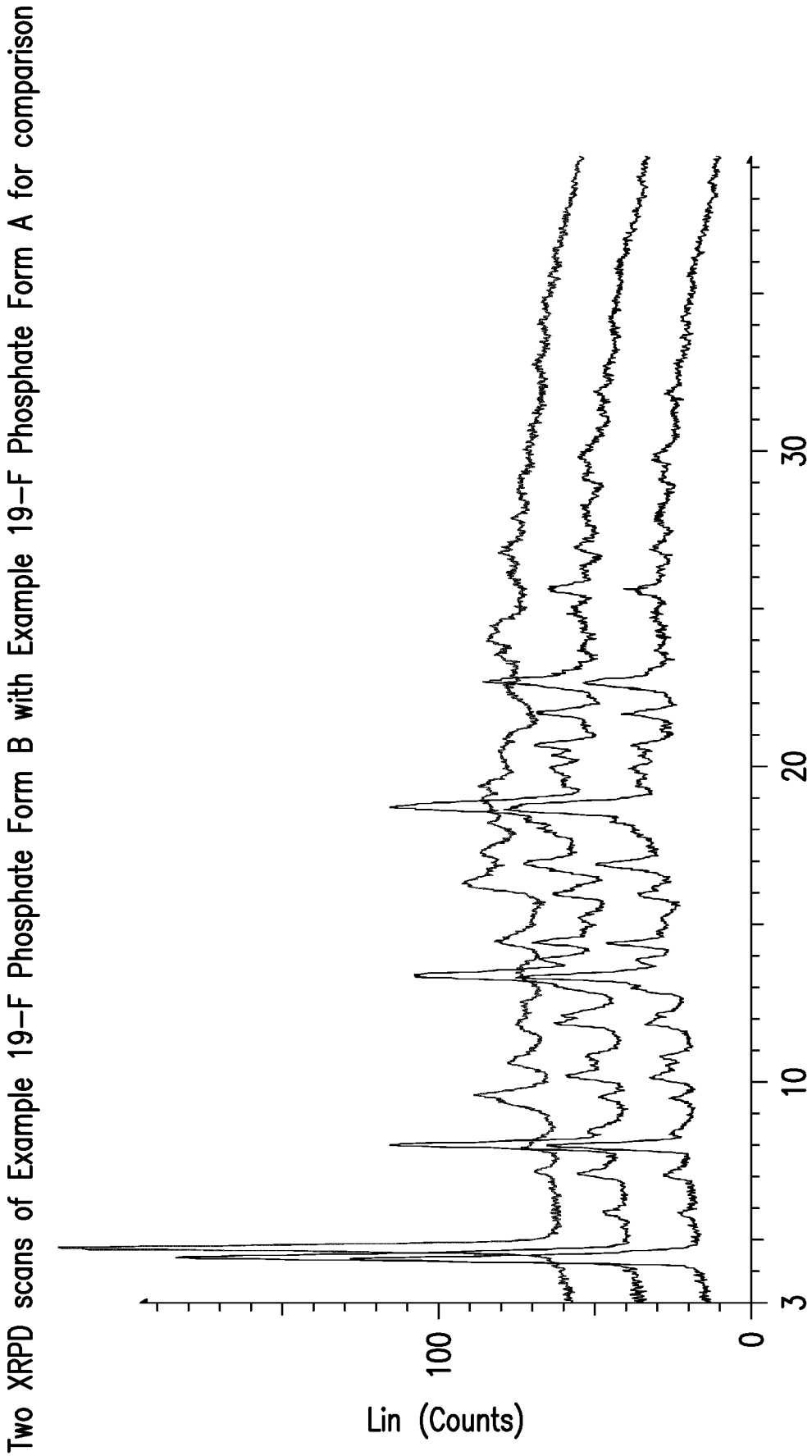

Two XRPD scans of Example 19–F Phosphate Form B with Example 19–F Phosphate Form A for comparison
Lin (Counts)
0
100
3
10
20
30
2–Theta – Scale

FIG.20

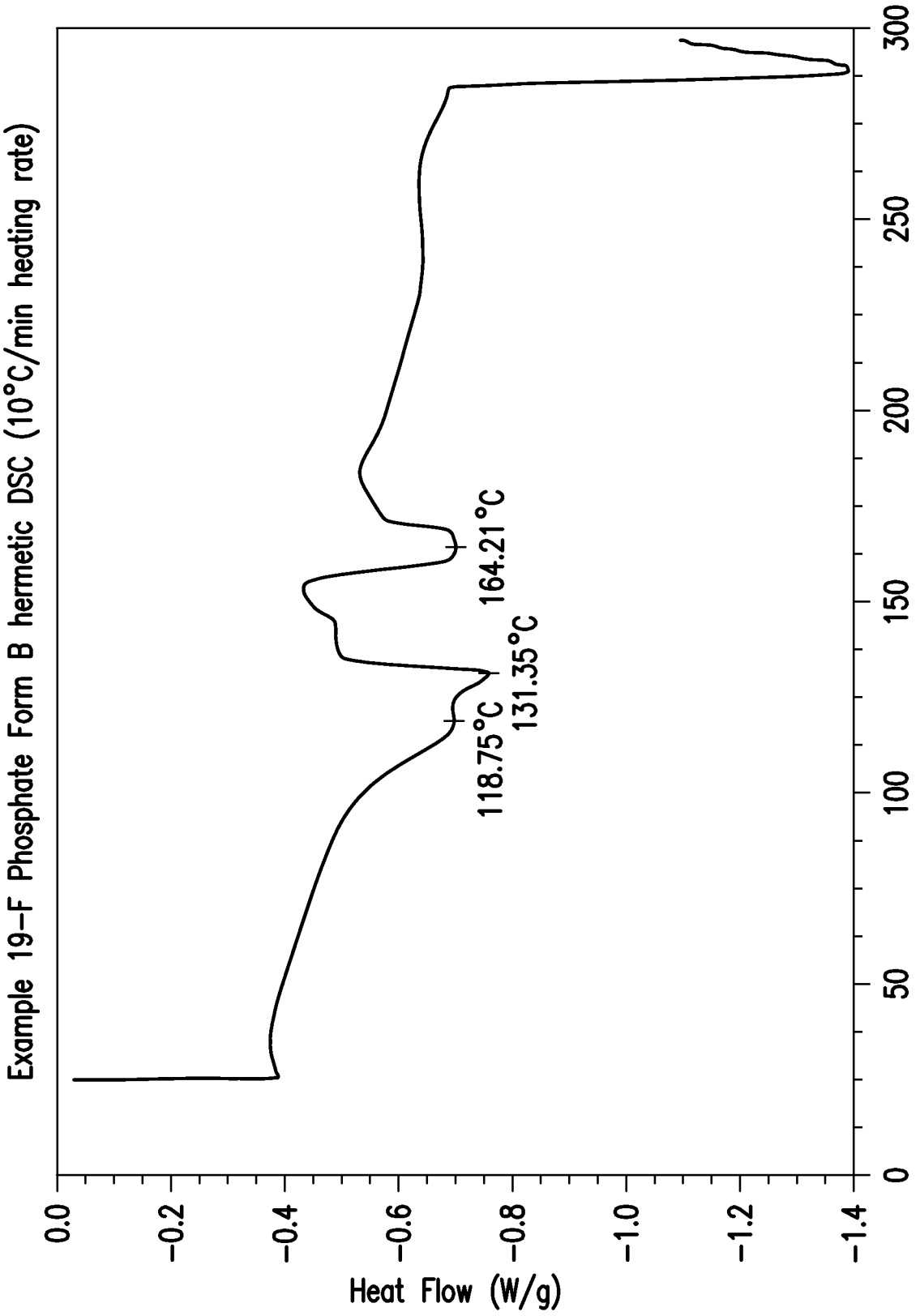

Example 19-F Phosphate Form B hermetic DSC (10°C/min heating rate)
Heat Flow (W/g)
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
Temperature (°C)
0
50
100
150
200
250
300
118.75°C
131.35°C
164.21°C

FIG.21

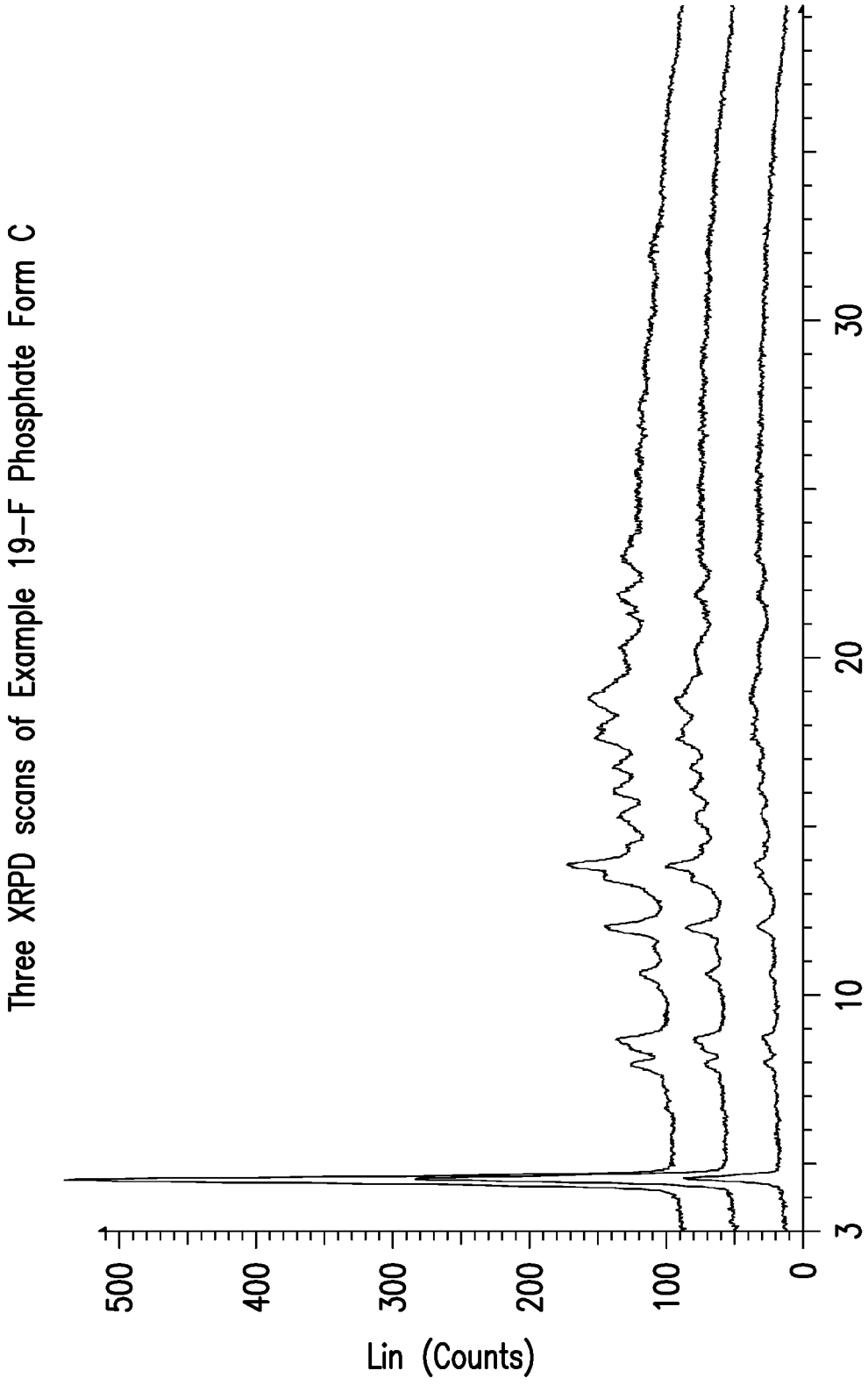

Three XRPD scans of Example 19-F Phosphate Form C
Lin (Counts)
500
400
300
200
100
0
3
10
20
30
2-Theta - Scale

FIG.22

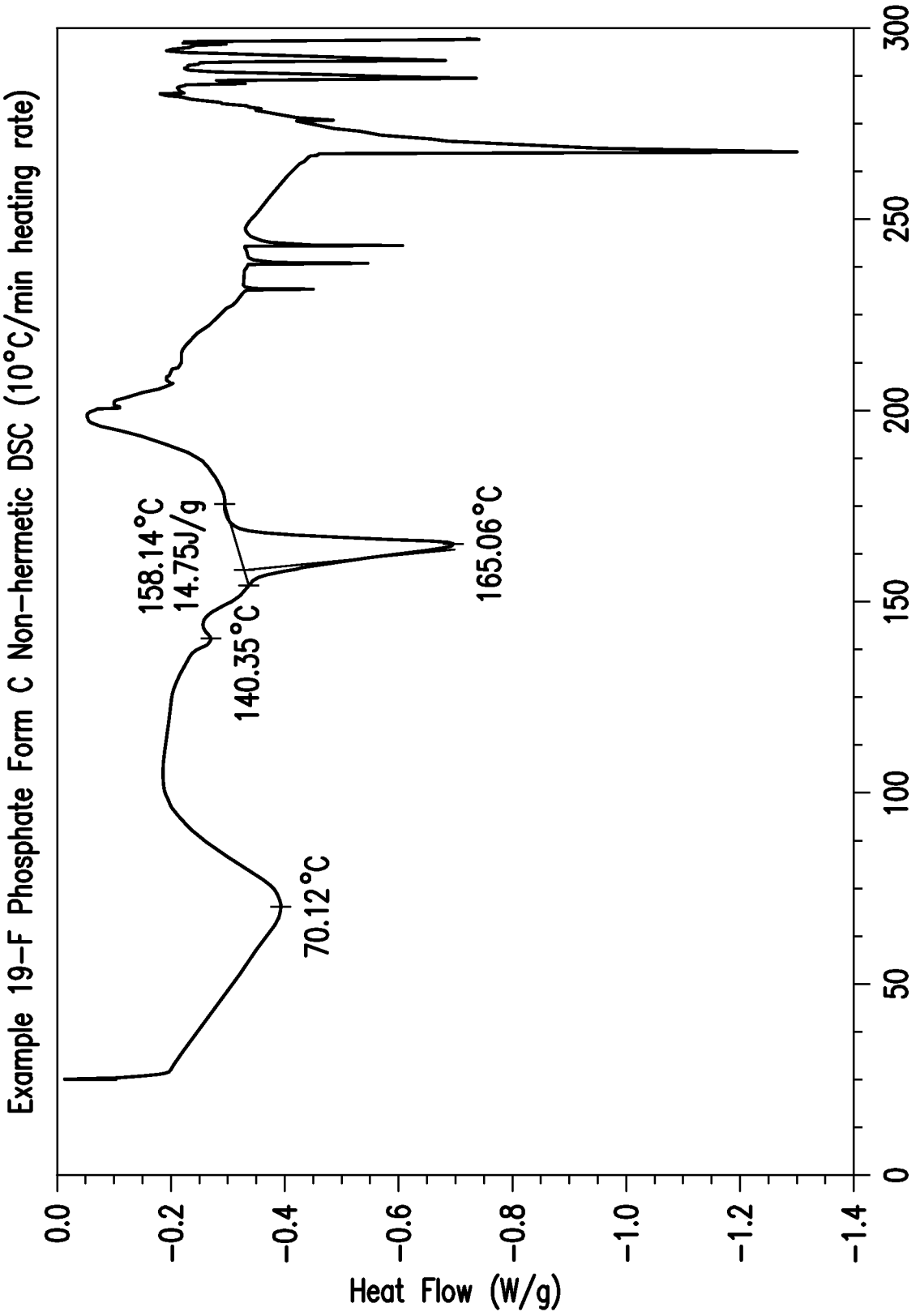

Example 19-F Phosphate Form C Non-hermetic DSC (10°C/min heating rate)
158.14°C
14.75J/g
140.35°C
165.06°C
70.12°C
Heat Flow (W/g)
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
Temperature (°C)
0
50
100
150
200
250
300

FIG.23

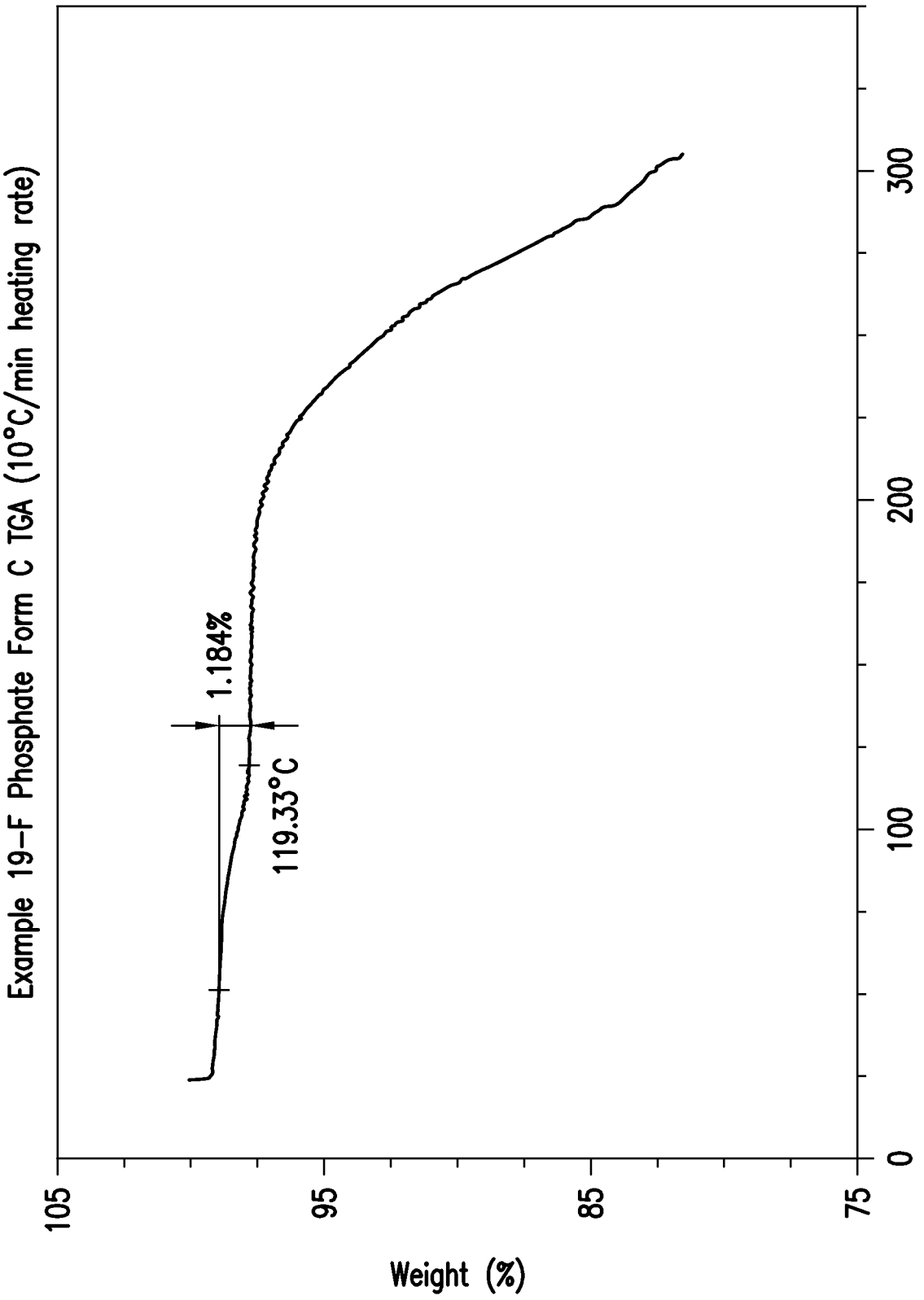

Example 19-F Phosphate Form C TGA (10°C/min heating rate)
1.184%
119.33°C
105
95
85
75
Weight (%)
0
100
200
300
Temperature (°C)

FIG.24

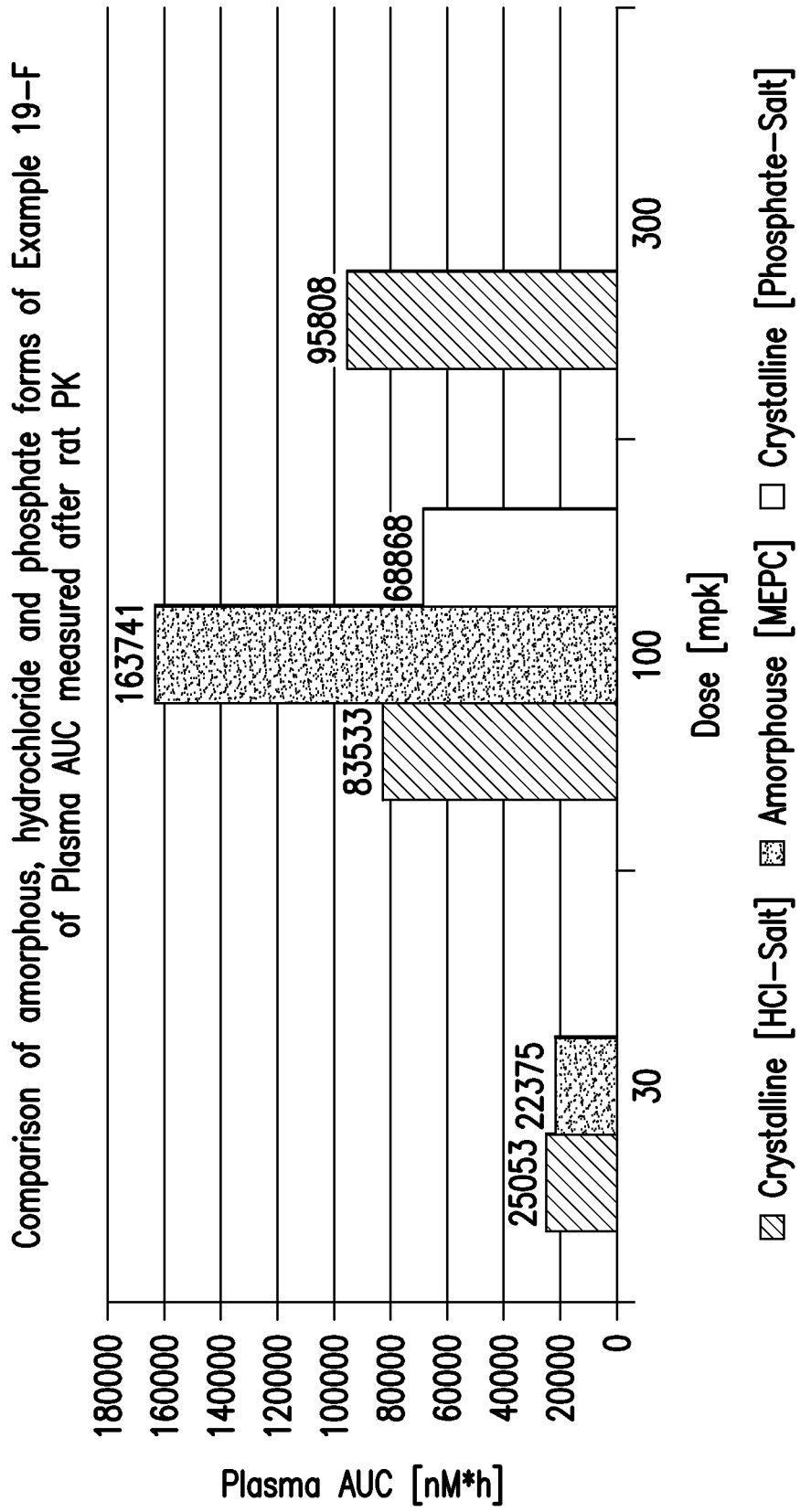

Comparison of amorphous, hydrochloride and phosphate forms of Example 19-F
of Plasma AUC measured after rat PK
Plasma AUC [nM*h]
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
163741
83533
25053
22375
68868
95808
30
100
300
Dose [mpk]
Crystalline [HCl-Salt]
Amorphouse [MEPC]
Crystalline [Phosphate-Salt]

FIG.25

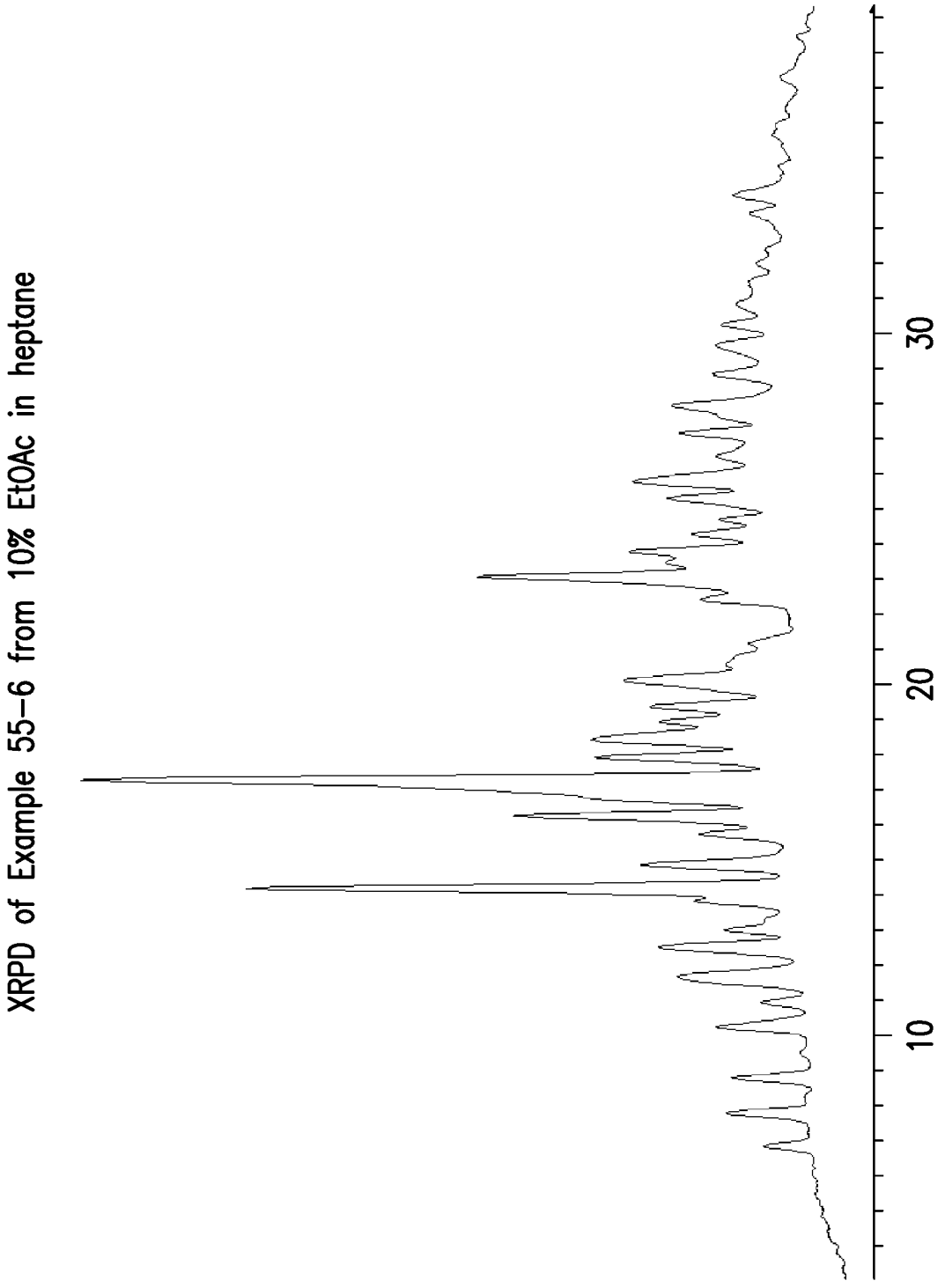

XRPD of Example 55-6 from 10% EtOAc in heptane
10
20
30
2-Theta - Scale

FIG.26

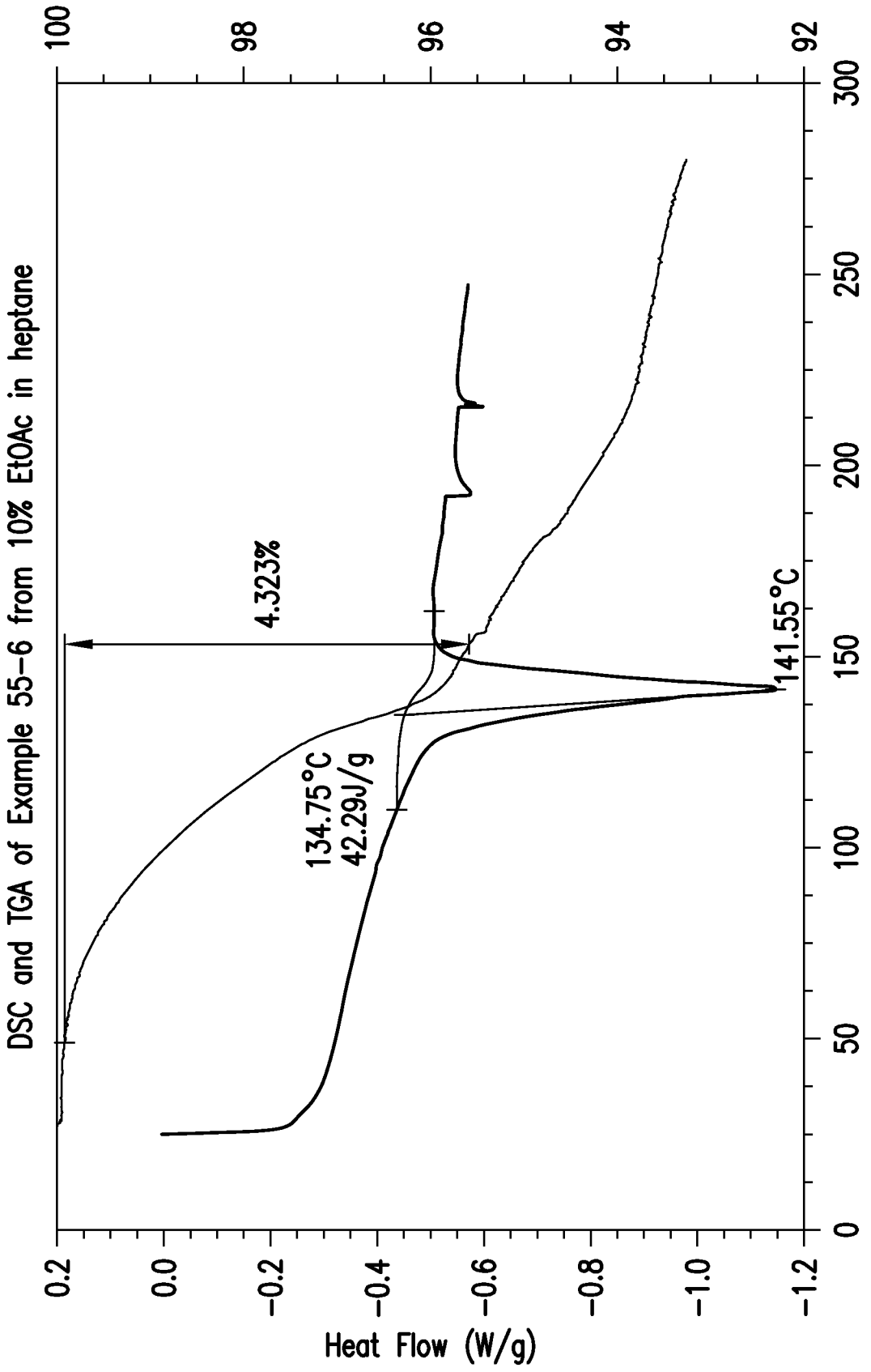

DSC and TGA of Example 55-6 from 10% EtOAc in heptane
Weight (%)
100
98
96
94
92
4.323%
141.55°C
134.75°C
42.29J/g
Heat Flow (W/g)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
Temperature (°C)
0
50
100
150
200
250
300

FIG.27

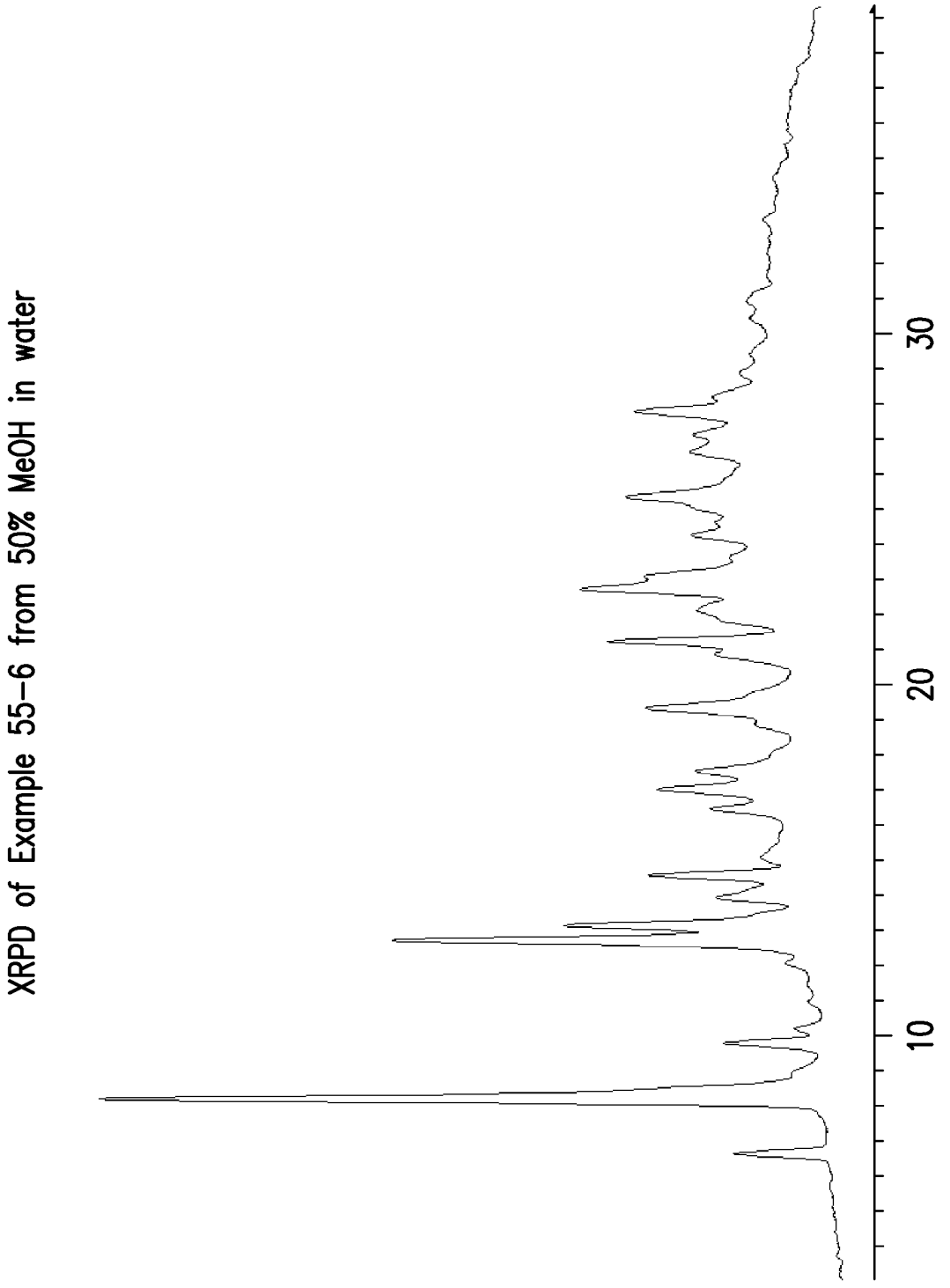

XRPD of Example 55-6 from 50% MeOH in water
10
20
30
2-Theta - Scale

FIG.28

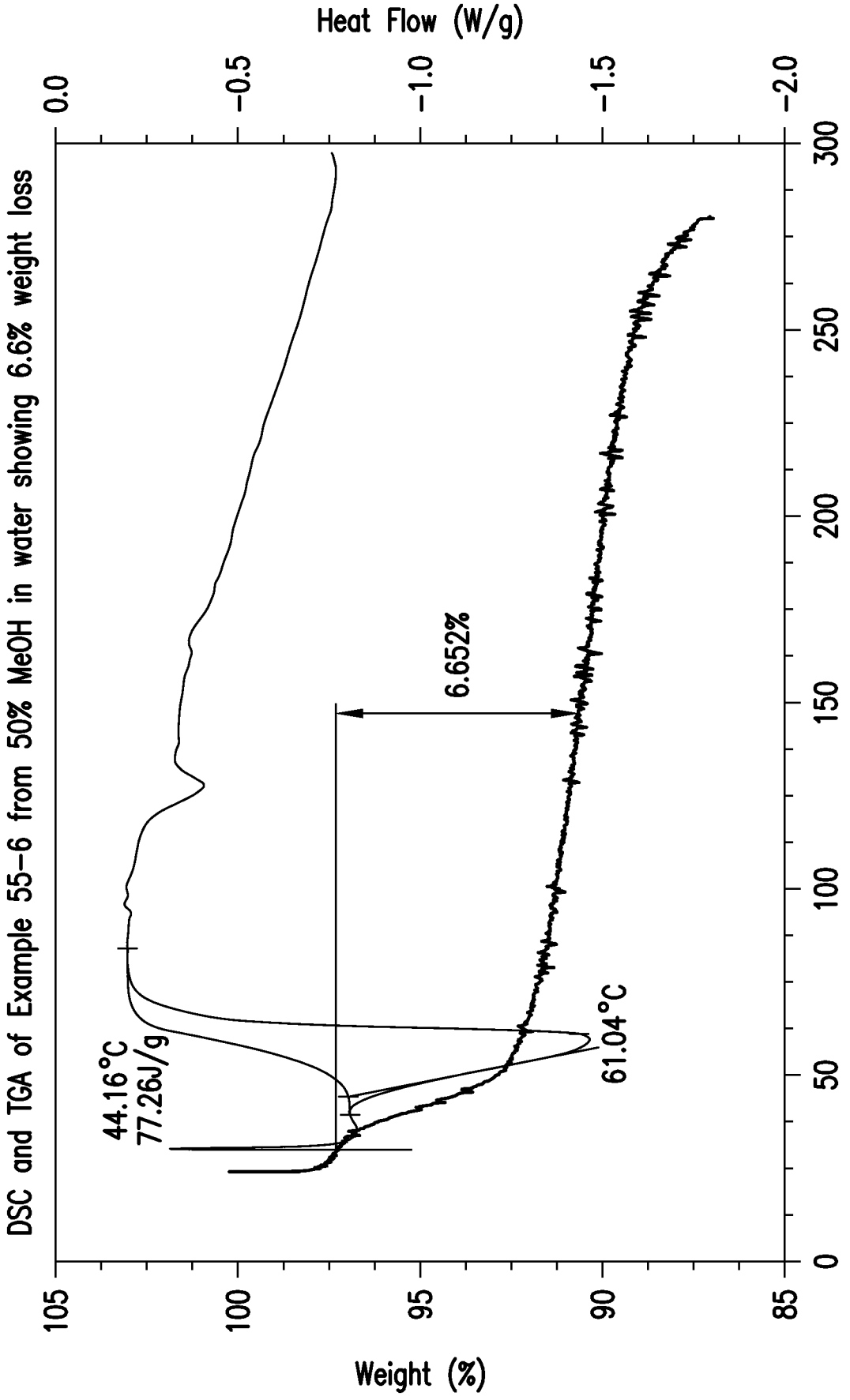

DSC and TGA of Example 55-6 from 50% MeOH in water showing 6.6% weight loss
Heat Flow (W/g)
0.0
-0.5
-1.0
-1.5
-2.0
Weight (%)
105
100
95
90
85
Temperature (°C)
0
50
100
150
200
250
300
6.652%
44.16°C
77.26J/g
61.04°C

FIG.29

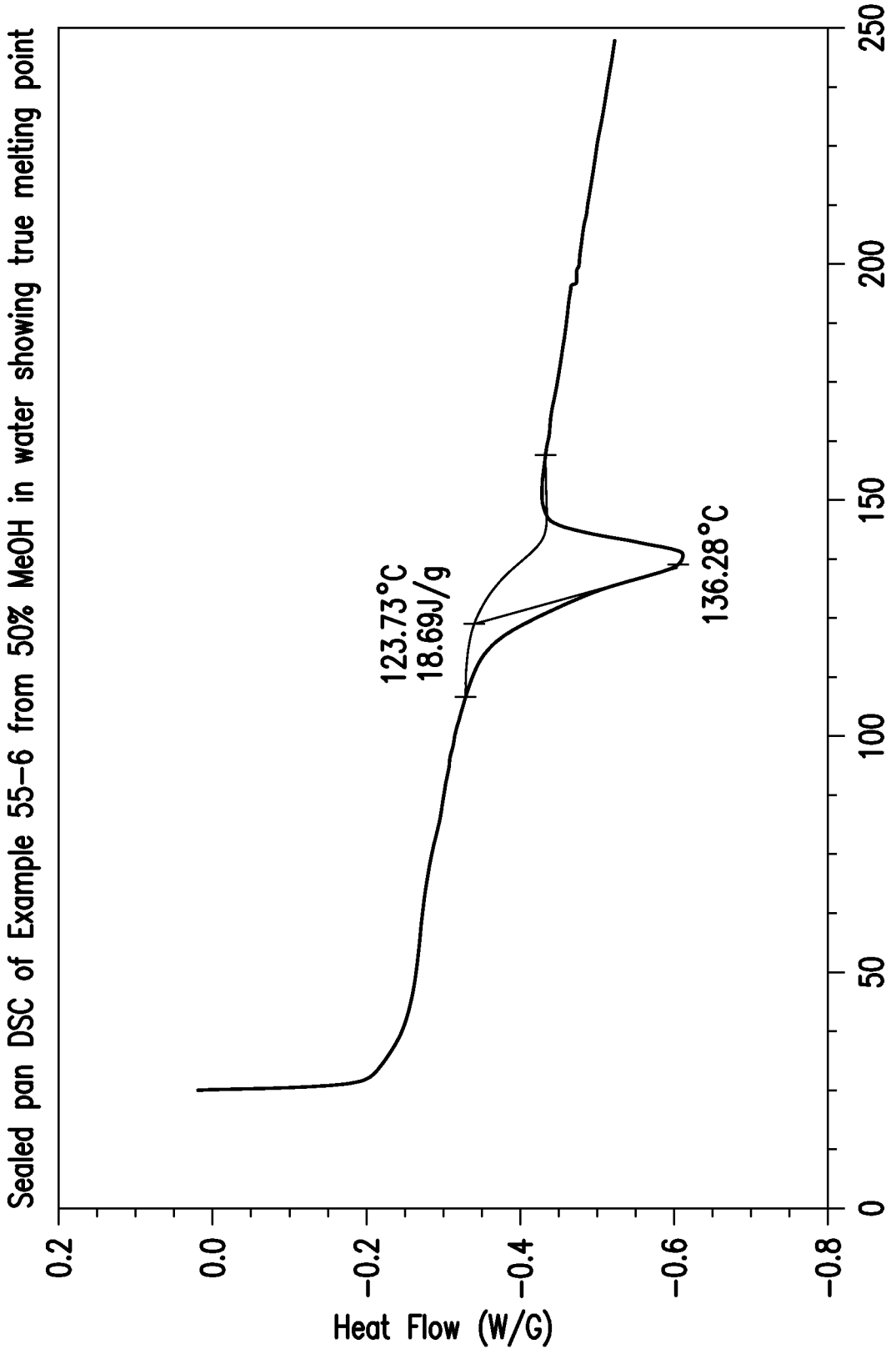

Sealed pan DSC of Example 55-6 from 50% MeOH in water showing true melting point
123.73°C
18.69J/g
136.28°C
Heat Flow (W/G)
Temperature (°C)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
0
50
100
150
200
250

FIG.30

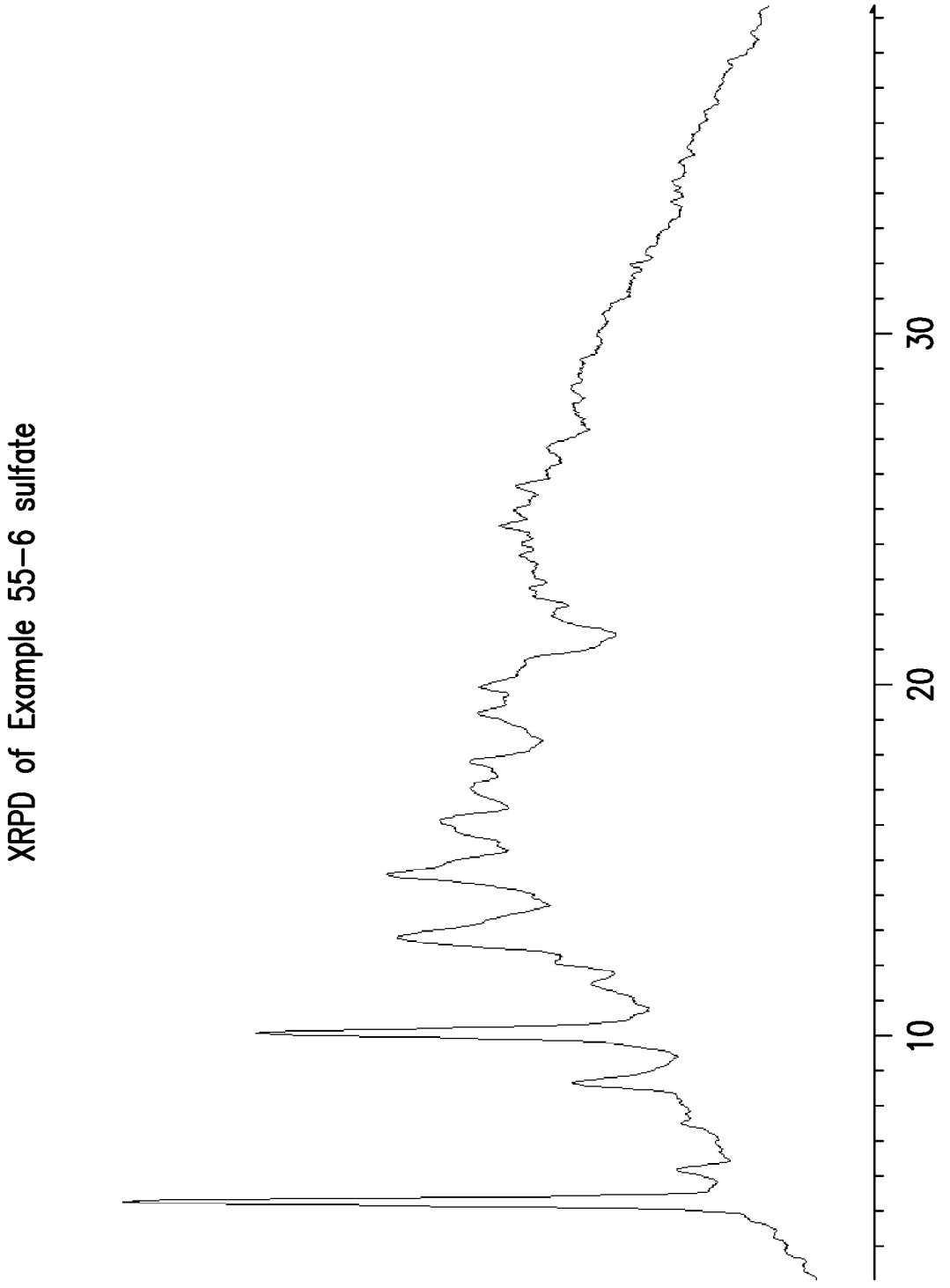


FIG.31

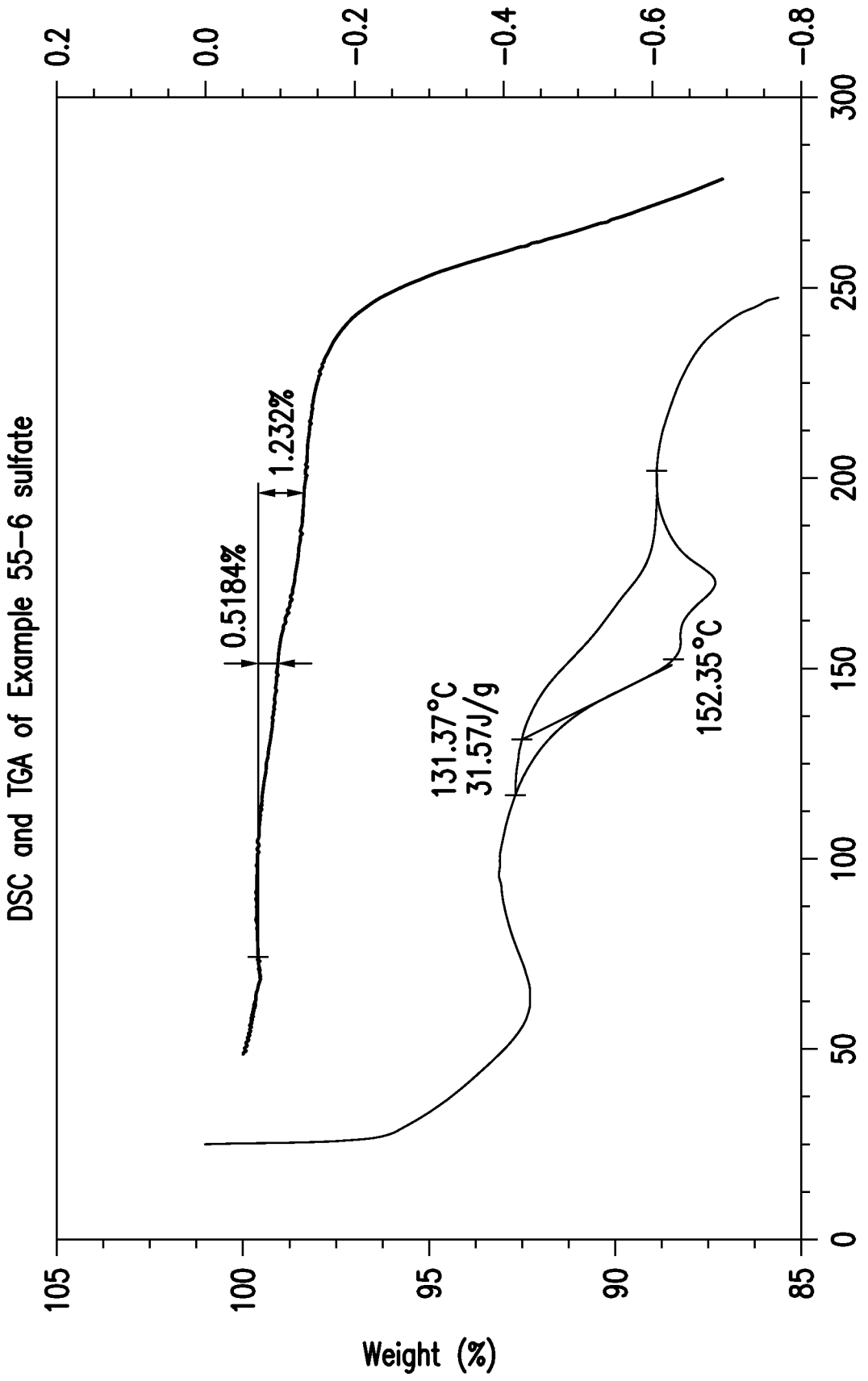

DSC and TGA of Example 55-6 sulfate
Heat Flow (W/g)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
Weight (%)
105
100
95
90
85
Temperature (°C)
0
50
100
150
200
250
300
0.5184%
1.232%
131.37°C
31.57J/g
152.35°C

FIG.32

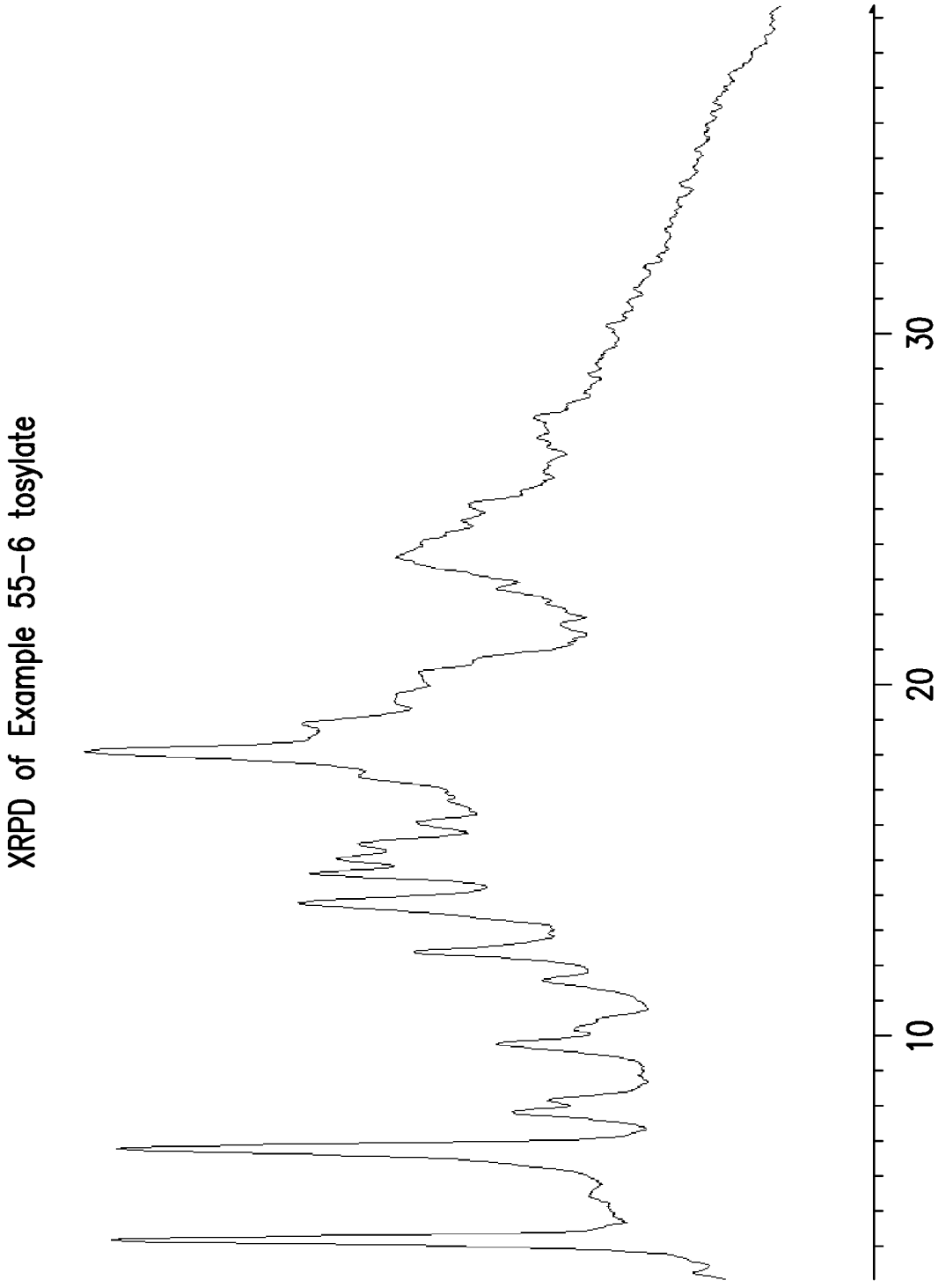


FIG.33

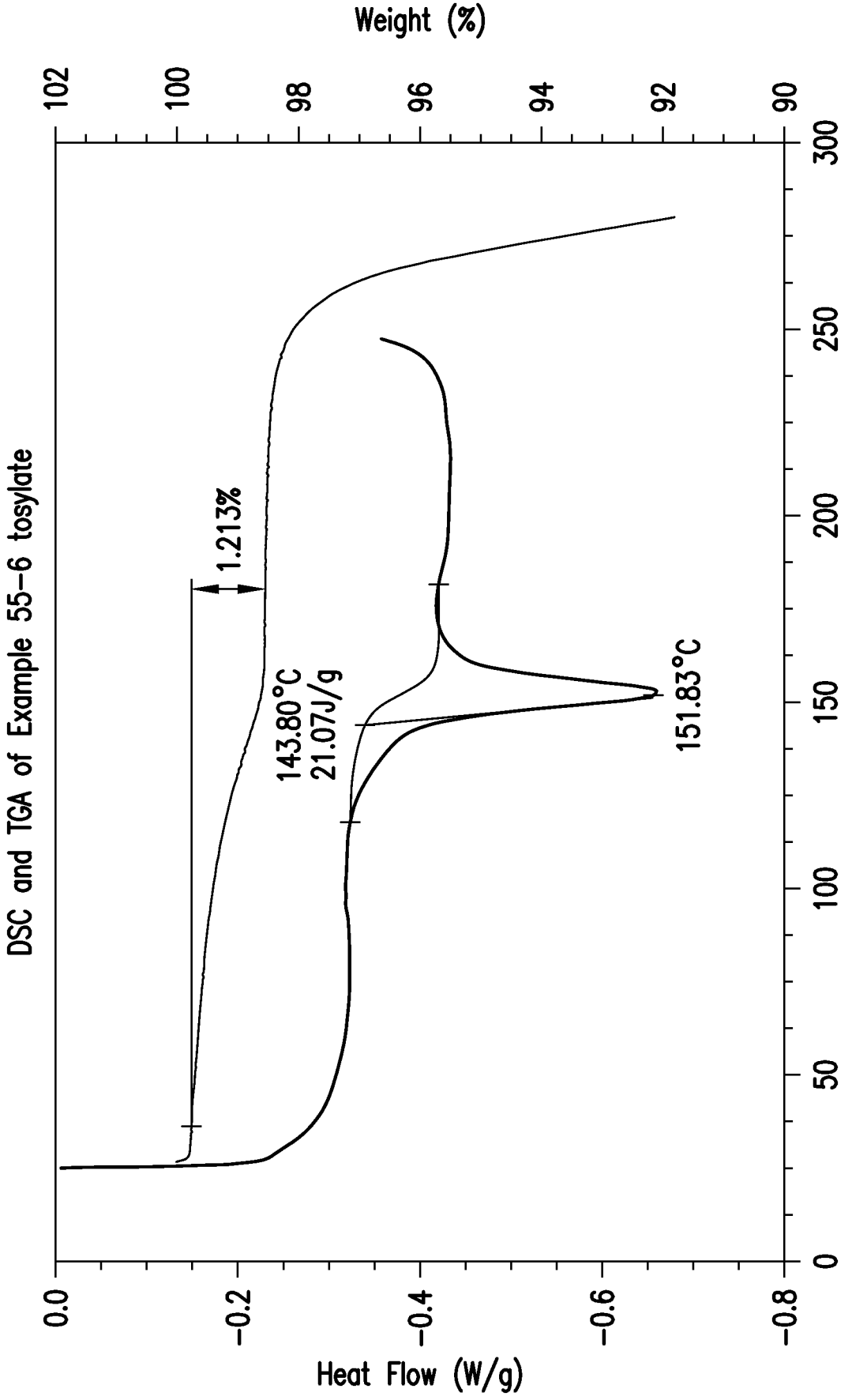

DSC and TGA of Example 55-6 tosylate
Weight (%)
102
100
98
96
94
92
90
1.213%
143.80°C
21.07J/g
151.83°C
300
250
200
150
100
50
0
Temperature (°C)
0.0
-0.2
-0.4
-0.6
-0.8
Heat Flow (W/g)

FIG.34

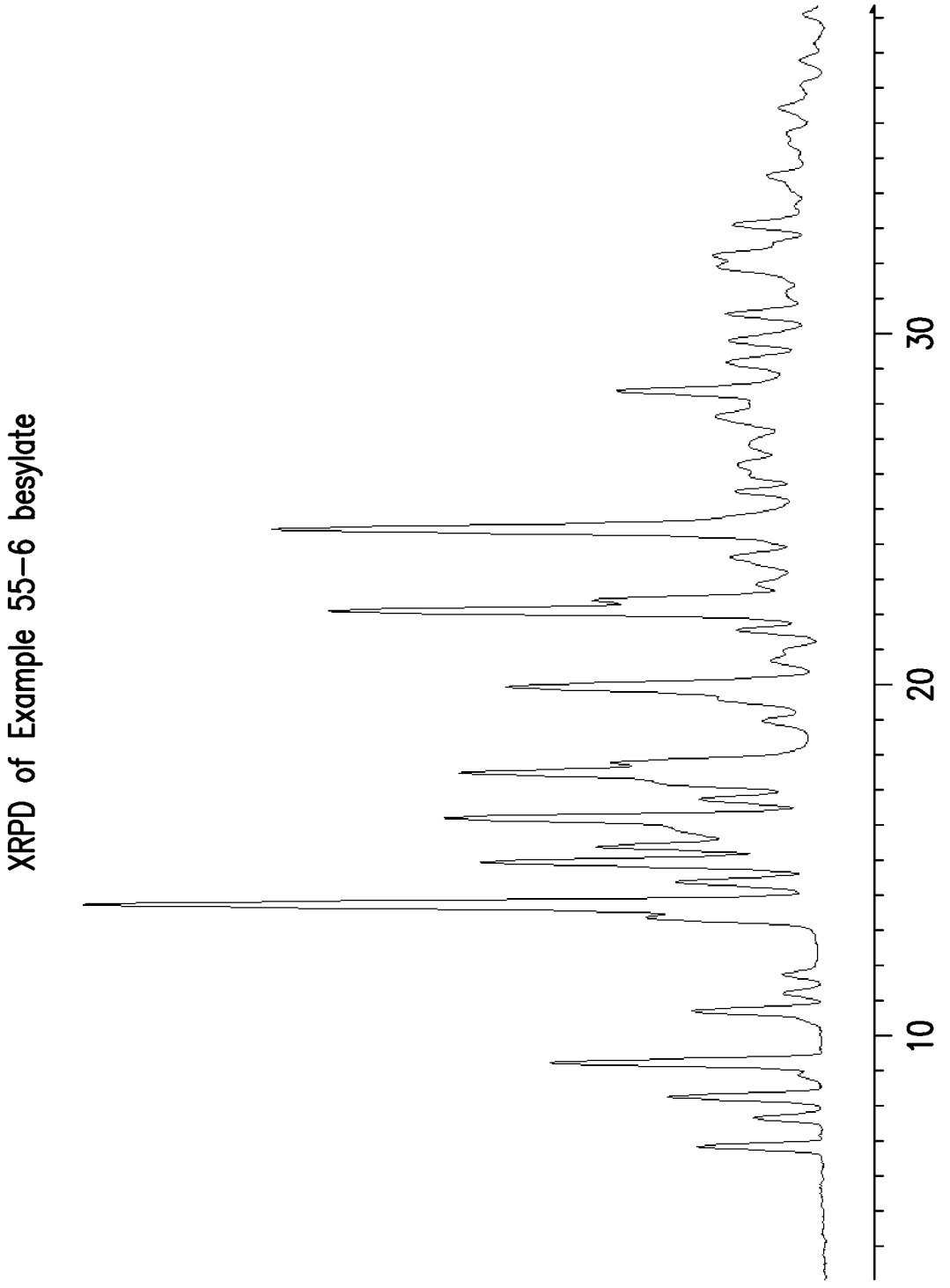


FIG.35

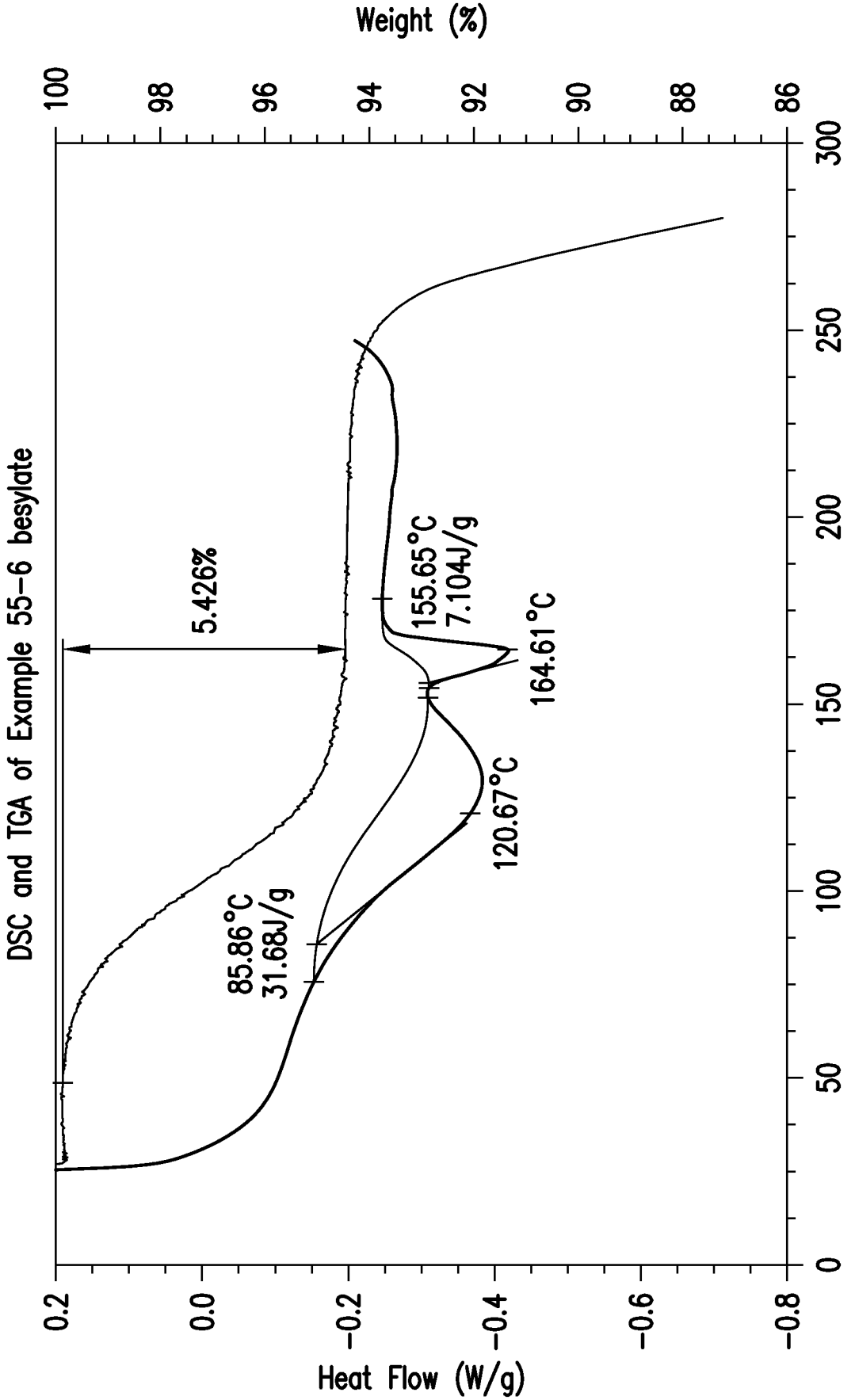

DSC and TGA of Example 55-6 besylate
Weight (%)
100
98
96
94
92
90
88
86
5.426%
155.65°C
7.104J/g
164.61°C
120.67°C
85.86°C
31.68J/g
300
250
200
150
100
50
0
Temperature (°C)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
Heat Flow (W/g)

FIG.36

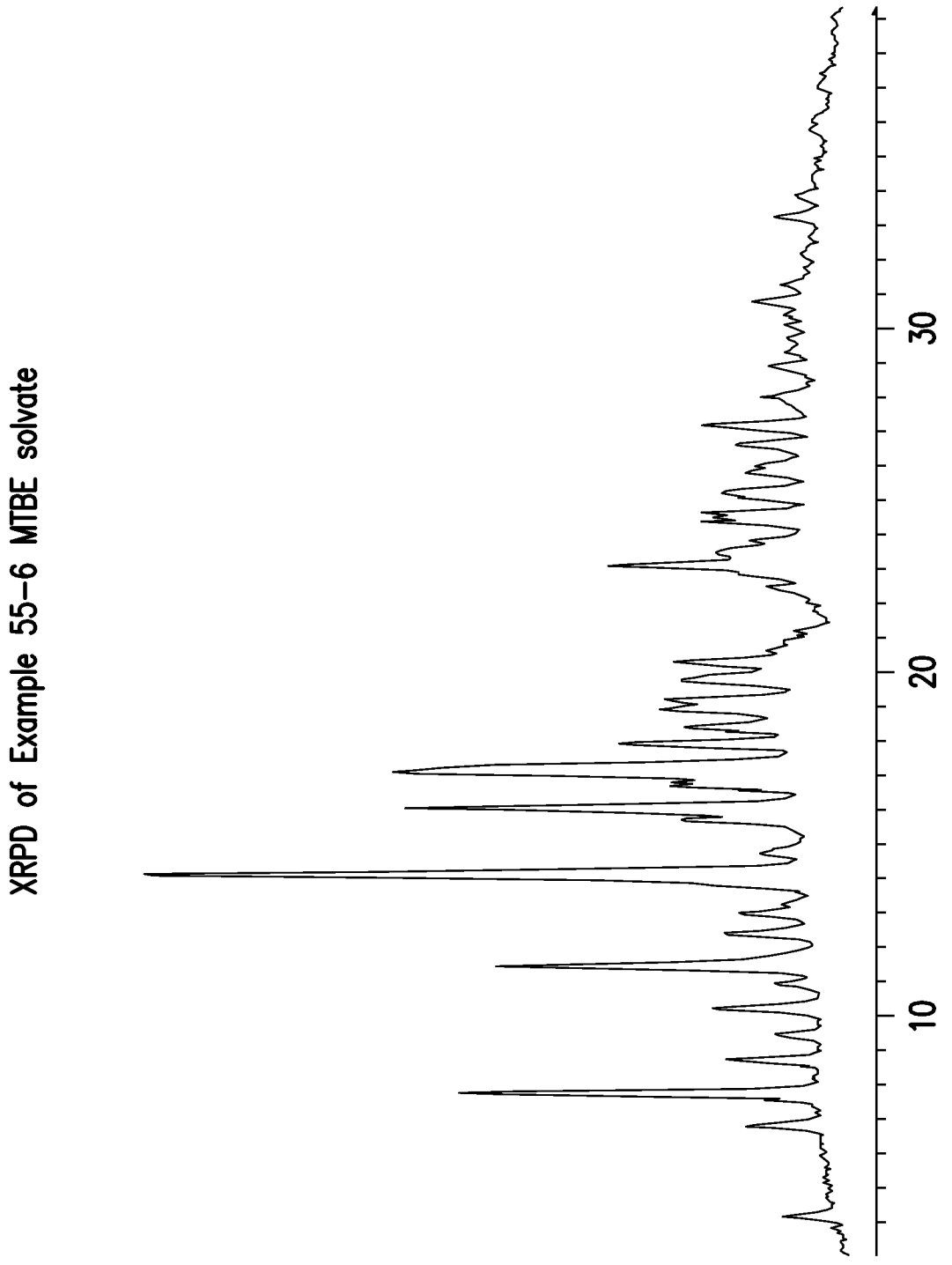


FIG.37

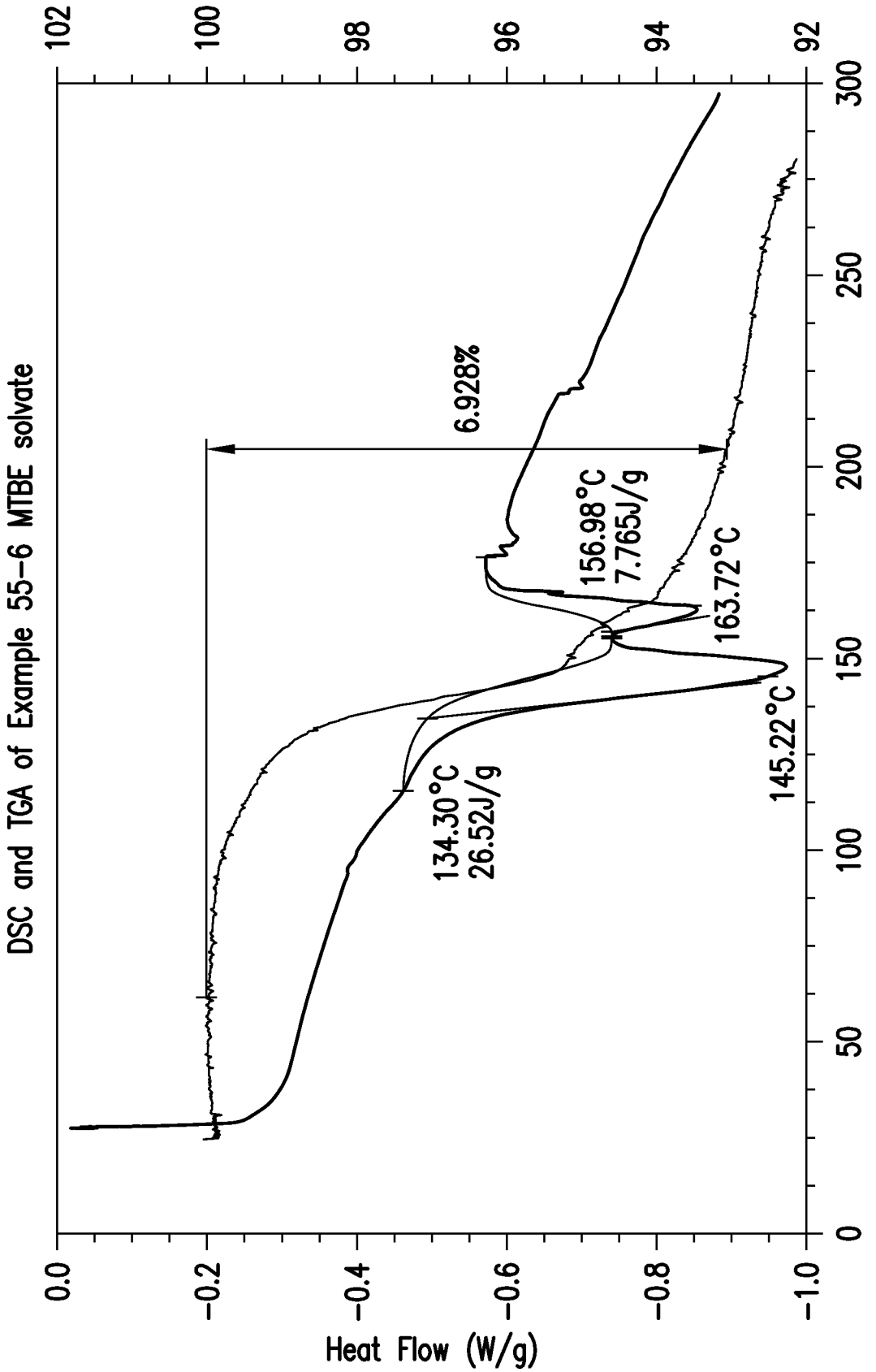

DSC and TGA of Example 55-6 MTBE solvate
Weight (%)
102
100
98
96
94
92
6.928%
156.98°C
7.765J/g
163.72°C
145.22°C
134.30°C
26.52J/g
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
Heat Flow (W/g)
0
50
100
150
200
250
300
Temperature (°C)

FIG.38

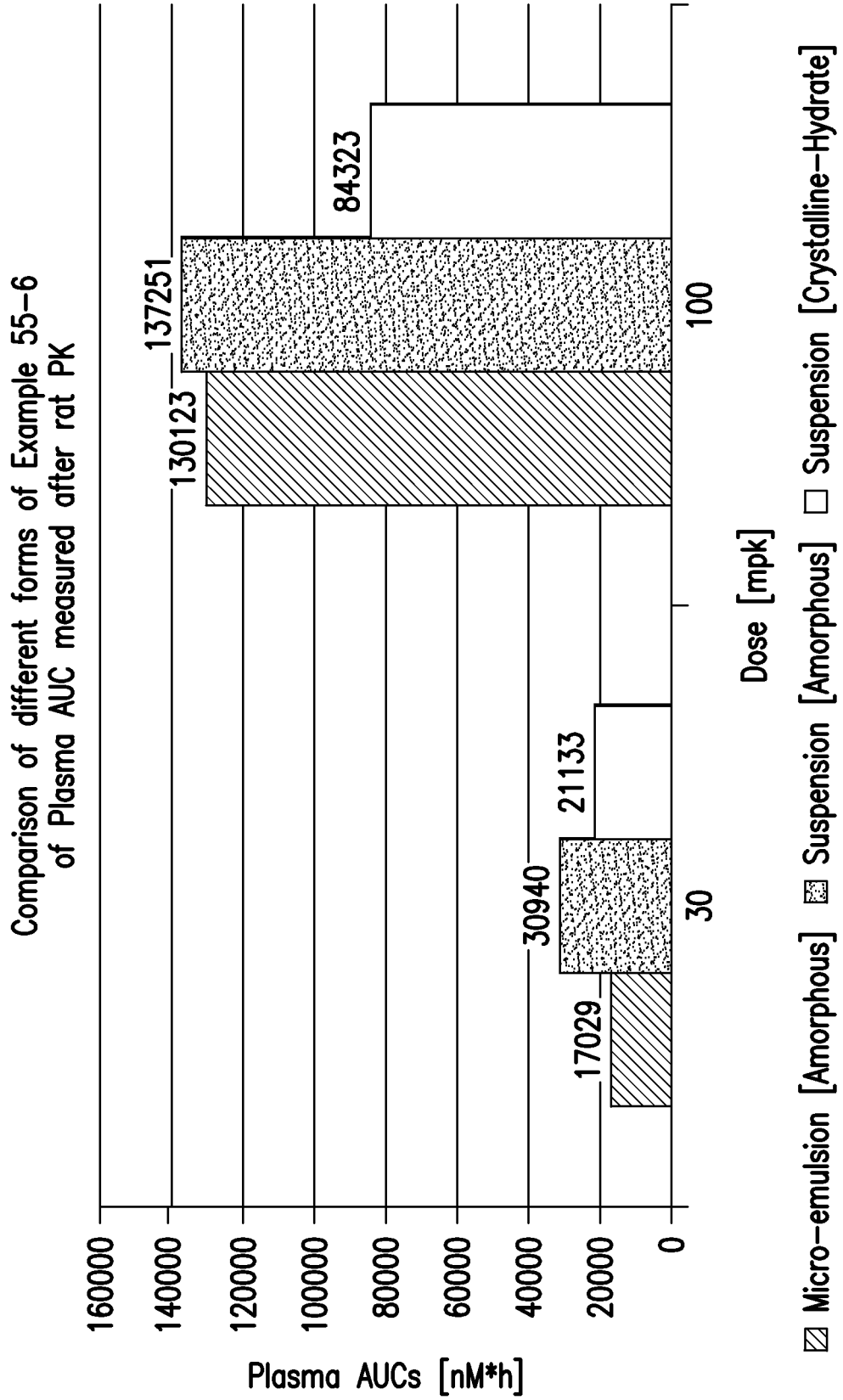

Comparison of different forms of Example 55-6
of Plasma AUC measured after rat PK
Plasma AUCs [nM*h]
160000
140000
120000
100000
80000
60000
40000
20000
0
137251
84323
130123
30940
21133
17029
100
30
Dose [mpk]
Micro-emulsion [Amorphous]
Suspension [Amorphous]
Suspension [Crystalline-Hydrate]

FIG.39

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/047617

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/4375 A61K31/519 A61P27/02 A61P37/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/110416 A2 (NEUROGEN CORP [US]; MAYNARD GEORGE D [US]; GHOSH MANUKA [US]; YUAN JUN) 24 November 2005 (2005-11-24) claims 1,109	1-22
A	WO 2005/014558 A1 (VERTEX PHARMA [US]; WILSON DEAN M [US]; TERMIN ANDREAS P [US]; NEUBERT) 17 February 2005 (2005-02-17) claim 89; table 2; compounds 64,71	1-15
A	WO 2010/014939 A1 (GENENTECH INC [US]; BERGERON PHILIPPE [US]; COHEN FREDERICK [US]; ESTR) 4 February 2010 (2010-02-04) claim 6	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2012	19/09/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gettins, Marc

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/047617

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005110416 A2	24-11-2005	AU 2005244104 A1	24-11-2005
		CA 2563607 A1	24-11-2005
		EP 1745033 A2	24-01-2007
		JP 4906715 B2	28-03-2012
		JP 2007536263 A	13-12-2007
		US 2005277654 A1	15-12-2005
		US 2010022516 A1	28-01-2010
		WO 2005110416 A2	24-11-2005
WO 2005014558 A1	17-02-2005	AR 045445 A1	26-10-2005
		AT 548358 T	15-03-2012
		AU 2004263515 A1	17-02-2005
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		CN 1894222 A	10-01-2007
		EP 1663994 A1	07-06-2006
		JP 4808156 B2	02-11-2011
		JP 2007501258 A	25-01-2007
		JP 2011207914 A	20-10-2011
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		US 2005187217 A1	25-08-2005
		US 2012040935 A1	16-02-2012
		WO 2005014558 A1	17-02-2005
		ZA 200601859 A	26-03-2008
WO 2010014939 A1	04-02-2010	AR 073354 A1	03-11-2010
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		CA 2729045 A1	04-02-2010
		CN 102171194 A	31-08-2011
		CO 6311051 A2	22-08-2011
		EC SP11010796 A	28-02-2011
		EP 2318377 A1	11-05-2011
		JP 2011529920 A	15-12-2011
		MA 32580 B1	01-08-2011
		PE 04032011 A1	04-07-2011
		TW 201018681 A	16-05-2010
		US 2010069357 A1	18-03-2010
		US 2012165313 A1	28-06-2012
		WO 2010014939 A1	04-02-2010

COMPUESTOS DE TETRAHIDROPIRIDO-PIRIDINA Y TETRAHIDROPIRIDO-PIRIMIDINA Y SU USO COMO MODULADORES DE RECEPTORES DE C5A

CAMPO DE LA INVENCIÓN

Esta invención se refiere en general a compuestos de tetrahidropirido-piridina, tetrahidropirido pirimidina y compuestos heterocíclicos relacionados, que actúan como moduladores de receptores de C5A del complemento mamífero, y a composiciones farmacéuticas que comprenden tales moduladores. La presente invención se refiere además al uso de estos moduladores en el tratamiento de una variedad de trastornos inflamatorios y del sistema inmune y como sondas para la localización de los receptores de c5a.

ANTECEDENTES DE LA INVENCIÓN

El sistema del complemento es un componente crucial del sistema inmune innato y comprende un grupo de proteínas que normalmente se presentan en un estado inactivo. Estas proteínas se organizan en tres vías de activación: la clásica, la lectina, y las vías alternativas (V. M. Holers, In Clinical Immunology: Principles and Practice, ed RR Rich, Mosby Pres; 1996, 363-391). Las moléculas de los microorganismos, anticuerpos o componentes celulares pueden activar estas vías resultando en la formación de complejos de proteasa conocidos como la C3-convertasa y la C5-convertasa. La vía clásica es una cascada dependiente de calcio/magnesio, que normalmente se activa mediante la formación de complejos antígeno-anticuerpo. También se puede activar de forma independiente del anticuerpo mediante la fijación de la proteína C reactiva formando complejos con ligandos y por muchos patógenos, incluyendo bacterias gram-negativas. La vía alternativa es una cascada dependiente de magnesio que es activada por el depósito y la activación de C3 en ciertas superficies susceptibles (por ejemplo, los polisacáridos de la pared celular de levaduras y bacterias, y ciertos materiales biopoliméricos).

C5a, un péptido de 74 aminoácidos, se genera en la cascada del complemento por la escisión de la proteína C5 del complemento por la enzima convertasa C5 del complemento. C5a tiene ambos efectos anafilatóxico (ej., broncoconstrictor y espasmogénico vascular) y quimiotáctico. Por lo tanto, es activo en originar tanto las fases vasculares como las celulares de las respuestas inflamatorias. Debido a que es una proteína plasmática y, por tanto, en general casi instantáneamente disponible en un sitio de un estímulo de incitación, es un mediador importante en términos de iniciar la compleja serie de eventos que resultan en aumento y

amplificación de un estímulo inflamatorio inicial. Los efectos anafilatóxicos y quimiotácticos del péptido C5a se creen son mediados a través de su interacción con el receptor de C5a (antígeno CD88), un receptor de membrana acoplado a proteínas G de 52 kD (GPCR). C5a es un potente quimioatrayente de leucocitos polimorfonucleares, que lleva neutrófilos, basófilos, eosinófilos y monocitos a los sitios de inflamación y/o daño celular. C5a es uno de los agentes quimiotácticos más potentes conocidos para una amplia variedad de tipos de células inflamatorias. C5a también prepara los neutrófilos para diversas funciones antibacterianas (ej., fagocitosis). Además, C5a estimula la liberación de mediadores de la inflamación (ej., histaminas, TNF-α, IL-1, IL-6, IL-8, prostaglandinas, y leucotrienos) y la liberación de enzimas lisosomales y otros componentes citotóxicos a partir de los granulocitos. Entre sus otras acciones, C5a también promueve la producción de radicales de oxígeno activados y la contracción del músculo liso.

La degeneración macular es un término clínico que se utiliza para describir una familia de enfermedades que se caracterizan por una pérdida progresiva de la visión central asociada con anormalidades de la membrana de Bruch, la coroides, la retina neural y/o el epitelio pigmentario de la retina. En el centro de la retina se encuentra la mácula lútea, que tiene aproximadamente entre 1/3 a ½ cm de diámetro. La mácula proporciona la visión detallada, particularmente en el centro (la fóvea), debido a que los conos tienen más densidad y debido a la alta proporción de células ganglionares a células fotoreceptoras. Los vasos sanguíneos, las células ganglionares, la capa nuclear interna y las células, y las capas plexiformes están todos desplazados hacia un lado (en lugar de permanecer encima de las células fotoreceptoras), lo que permite a la luz un camino más directo a los conos. Bajo la retina se encuentra la coroides, una parte del tracto uveal y el epitelio pigmentado retiniano (EPR), que se encuentra entre la retina neural y la coroides. Los vasos sanguíneos coroideos proporcionan nutrición a la retina y sus células visuales.

La degeneración macular relacionada con la edad (AMD por su sigla en inglés), la forma más común de degeneración macular, se asocia con la pérdida progresiva de la agudeza visual en la parte central del campo visual, los cambios en la visión del color, y una deficiente o anormal adaptación a la oscuridad y sensibilidad. Dos manifestaciones clínicas principales de AMD se han descrito como la forma seca, o atrófica y la forma neovascular o exudativa. La forma seca se asocia con muerte celular atrófica de la retina central o mácula, necesaria para la visión fina utilizada en actividades como leer, conducir o reconocer rostros. Alrededor del 10-20% de estos pacientes con AMD avanzan hacia la segunda forma de AMD, conocida como AMD neovascular (también conocida como AMD húmeda).

AMD neovascular se caracteriza por el crecimiento anormal de vasos sanguíneos debajo de la mácula y la pérdida vascular, lo que resulta en el desplazamiento de la retina, hemorragia y cicatrización. Esto resulta en un deterioro de la visión durante un período de semanas a años. Los casos de AMD neovascular se originan a partir de AMD seca intermedia o avanzada. La forma neovascular es respondable de un 85% de la ceguera legalmente establecida asociada con AMD. En AMD neovascular, mientras los vasos sanguíneos anormales dejan escapar líquido y sangre, se forma un tejido de cicatrización que destruye la retina central.

Los nuevos vasos sanguíneos en AMD neovascular generalmente se derivan de la coroides y se conocen como neovascularización coroidal (CNV). La patogénesis de nuevos vasos coroideos es poco conocida, pero factores como inflamación, isquemia, y producción local de factores angiogénicos se consideran importantes. Un estudio publicado sugiere que la CNV es causada por la activación del complemento en un modelo murino asistido por láser (Bora PS, J. Immunol 2005;. 174, 491-497).

La evidencia genética humana implica la participación del sistema del complemento, en particular la vía alternativa, en la patogénesis de la Degeneración Macular Relacionada con la Edad (AMD). Se han encontrado asociaciones significativas entre AMD y polimorfismos en el factor del complemento H (CFH) (Edwards, AO, polimorfismo del factor del complemento H y degeneración macular relacionada con la edad. Science. Abril 15 de 2005, 308 (5720) :421-4; Hageman GS. Un haplotipo común en el factor genético regulador del complemento H (HF1/CFH) predispone los individuos a la degeneración macular relacionada con la edad. Proc Natl Acad Sci EE.UU. Mayo 17 de 2005;. 102 (20) :7227-32; Haines JL. La variante del factor del complemento H aumenta el riesgo de degeneración macular relacionada con la edad. Science Abril 15 de 2005, 308 (5720) :419-21;. Klein RJ, polimorfismo del factor del complemento H en degeneración macular relacionada con la edad. Science Abril 15 de 2005, 308 (5720):385-9;.. Lau Li, Asociación del polimorfismo Y402H H en el gen del factor del complemento H y degeneración macular neovascular relacionada con la edad en pacientes chinos. Invest Ophthalmol Vis Sci. 2006 Aug;. 47 (8):3242-6;. Simonelli F, Polimorfismo p.402Y> H en la proteína del factor del complemento H es un factor de riesgo para la degeneración macular relacionada con la edad en una población italiana. Br. J Ophthalmol 2006 Sep;. 90(9):1142-5, y Zareparsi S, Fuerte asociación de la variante Y402H en el factor del complemento H en 1q32 con susceptibilidad a degeneración macular relacionada con la edad. Am J Hum Genet 2005 Jul; 77(1) :149-53), factor del complemento B (CFB) y complemento C2 (Gold B, Variación en el factor B (BF) y genes del componente del complemento 2 (C2), se asocian con la degeneración macular relacionada con la edad. Nat Genet Abril 2006; 38(4) :458-62. y Jakobsdóttir J, C2 and CFB genes inage-related maculopathy and joint action with CFH and LOC387715 genes. PLoS One. Mayo de 2008 21; 3 (5):e2199), y más recientemente

en complemento C3 (Despriet DD, componente del complemento C3 y el riesgo de degeneración macular relacionada con la edad. Ophthalmology. Marzo de 2009; 116(3):474-480 e2,. Maller JB, La variación en el factor del complemento 3 se asocia con un riesgo de degeneración macular relacionada con la edad. Nat Genet Oct. 2007; 39 (10):1200-1 y Park KH, Complement Component 3 (C3) Haplotypes And Risk Of Advanced Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci. 2009 Jul; 50(7):3386-93. Feb. 21 de 2009). En conjunto, las variaciones genéticas en los componentes de vía alternativa CFH, CFB, y C3 pueden predecir el resultado clínico en casi 80% de los casos.

En la actualidad no existe ningún tratamiento médico comprobado para AMD seca y muchos pacientes con AMD neovascular se vuelven legalmente ciegos a pesar del tratamiento actual con agentes anti-VEGF como Lucentis. Por lo tanto, sería deseable proporcionar agentes terapéuticos para el tratamiento o prevención de enfermedades mediadas por complemento, y particularmente para el tratamiento de AMD.

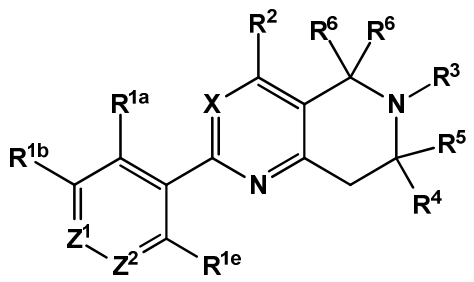
RESUMEN DE LA INVENCIÓN

La presente invención proporciona compuestos que modulan, e inhiben preferiblemente, la activación de receptores de C5a y/o transducción de señales mediadas por el receptor de C5a. Tales moduladores del receptor de C5a son preferiblemente ligandos del receptor de C5a de alta afinidad y actúan como antagonistas (por ejemplo, agonistas inversos) de los receptores del complemento C5a, tales como receptores humanos C5a. Dentro de ciertos aspectos, los moduladores del receptor de C5a proporcionados en este documento son tetrahidropirido-piridinas y tetrahidropirido- pirimidinas.

Diversas realizaciones de la invención se describen en la presente. Se reconocerá que las características especificadas en cada realización se pueden combinar con otras características especificadas para proporcionar realizaciones adicionales.

Dentro de ciertos aspectos, los moduladores del receptor de C5a proporcionados en la presente son compuestos de la Fórmula I y sus sales:

Dentro de ciertos aspectos, los moduladores del receptor de C5a proporcionados en la presente son compuestos de la Fórmula I y sales de los mismos:



(I)

en donde

X es N o CH;

Z^1 es N o CR^{1c};

Z^2 es N o CR^{1d}, en donde al menos uno de Z^1 y Z^2 no es N;

R^{1a} se selecciona del grupo que consta de hidrógeno, C_1- C_6 alquilo, C_1- C_6 alcoxilo, halo C_1 - C_6alquilo, haloC_1 - C_6alcoxilo, ciano o halógeno;

R^{1b} se selecciona del grupo que consta de hidrógeno, amino, hidroxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y mono y di C_1 - C_4alquilamino;

R^{1c} es hidrógeno, halógeno o C_1- C_6alquilo;

R^{1d} se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6alquilo, y C_1- C_6alcoxilo;

R^{1e} se selecciona entre hidrógeno, halógeno, ciano, C_1- C_6alquilo, haloC_1 - C_6alquilo, C_1- C_6alcoxilo y haloC_1 - C_6alcoxilo; o

R^{1a} y R^{1b} tomados en combinación forman un anillo heterocíclico saturado o insaturado de 5 miembros que tiene uno o dos heteroátomos de anillo seleccionados entre N, O o S, dicho anillo heterocíclico es sustituido con 0, 1, o 2 sustituyentes de C_1- C_6 alquilo o halógeno independientemente seleccionados;

en donde al menos uno de R^{1a} y R^{1e} no es hidrógeno;

R^2 se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, C_1 - C_6alcoxilo, C_1- C_6alquiltio, C_3- C_7cicloalquilo, C_3- C_7cicloalquilC_1- C_4alquilo y $(CH_2)_p NR^{2a}R^{2b}$, en donde cada grupo alquilo y alcoxilo está sustituido con 0 ó 1 sustituyente seleccionado del grupo que consta de hidroxilo, halógeno, y C_1- C_4alcoxilo;

p es 0 o 1;

R^{2a} es hidrógeno, C_1- C_6alquilo o hidroxiC_1 - C_6 alquilo;

R^{2b} es hidrógeno, C_1- C_6alquilo, C_3- C_7cicloalquilo o C_3- C_7cicloalquilC_1 - C_4alquilo, en donde cada alquilo es sustituido o no sustituido por hidroxilo, C_1 - C_4alcoxilo, C_1- C_4alcoxicarbonilo, o heterociclo en donde el heterociclo es un saturado, insaturado o un anillo aromático de cinco o seis miembros que tiene 1 o 2 heteroátomos de anillo seleccionados entre N, O o S y es sustituido o no sustituido con 1 ó 2 sustituyentes de C_1- C_4alquilo independientemente seleccionados; o

$NR^{2a}R^{2b}$ tomados en combinación forman un sistema de anillo heterocíclico saturado de 4 a 8 miembros que tiene 1 ó 2 anillos y 0 o 1 heteroátomos de anillo adicional seleccionados entre N, O o S, el sistema de anillo heterocíclico saturado es sustituido o no sustituido por 1- 4 sustituyentes independientemente seleccionados del grupo que consta de C_1- C_4alquilo, hidroxilo, C_1- C_4alcoxilo, C_1- C_4alcoxiC_1 - C_4alquilo, hidroxiC_1 - C_4alquilo, halógeno, amino,

mono y di- C_1- C_4alquilamino, C_1 - C_4alcoxicarbonilo, C_1- C_4alcanoilo, S (O) $_2C_1$- C_4alquilo y CH_2C (O) NH_2;

R^3 se selecciona del grupo que consta de fenilo sustituido, heteroarilo sustituido, y fenilC_1- C_3alquilo, en donde el heteroarilo se selecciona de piridilo, pirazolilo, imidazolilo, tetrazolilo, oxazolilo, y isoxazolilo, y en donde cada grupo fenilo o heteroarilo es sustituido por 1, 2 o 3 sustituyentes los cuales son independientemente seleccionados del grupo que consta de C_1- C_4alquilo, C_1- C_4alcoxilo, halógeno, ciano, haloC_1 - C_4alquilo, haloC_1 - C_4alcoxilo, hidroxiC_1 - C_4alquilo, C_1- C_4alcoxiC_1 - C_4alquilo, C_3- C_6cicloalquilo, y oxaciclo saturado que tiene 4, 5, o 6 átomos de anillo y un oxígeno de anillo, dicho oxaciclo es sustituido o no sustituido con 1 ó 2 sustituyentes de C_1- C_4alquilo independientemente seleccionados, y en donde cada fenilo o heteroarilo comprende al menos un sustituyente orto no- hidrógeno al punto de fijación al resto del compuesto de la fórmula (I);

R^4 es hidrógeno o C_1- C_4alquilo;

R^5 es hidrógeno; o

R^4 y R^5 tomados en combinación son oxo; y

R^6 es hidrógeno en cada ocurrencia o CR^6_2, tomada en combinación, forma un carbonilo divalente.

En otra realización, la invención proporciona una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de acuerdo con la definición de la fórmula (I) o las sub fórmulas del mismo y uno o más vehículos farmacéuticamente aceptables.

En otra realización, la invención proporciona una combinación, en particular una combinación farmacéutica, que comprende una cantidad terapéuticamente efectiva del compuesto de acuerdo con la definición de la fórmula (I) o las sub fórmulas de los mismos y uno o más agentes terapéuticamente activos.

La invención proporciona además métodos para tratar o prevenir enfermedades mediadas por el complemento, el método comprende los pasos de identificación de un paciente con necesidad de terapia de modulación del complemento y la administración de un compuesto de la fórmula (I) o una sub fórmula del mismo. Las enfermedades mediadas por el complemento incluyen enfermedades oftalmológicas (incluyendo la degeneración macular relacionada con la edad y la atrofia geográfica temprana o neovascular), enfermedades autoinmunes (incluyendo artritis, artritis reumatoide), enfermedades respiratorias, enfermedades cardiovasculares.

Otros aspectos de la invención se discuten más adelante.

BREVE DESCRIPCIÓN DE LOS ILUSTRACIONES

La figura 1. ilustra los patrones de difracción de rayos X de polvos del Ejemplo 19- F a partir de MTBE.

La figura 2. ilustra la calorimetría de barrido diferencial (DSC) y el análisis termogravimétrico (TGA) del Ejemplo 19- F a partir de MTBE.

La figura 3. ilustra los patrones de difracción de rayos X de polvos del Ejemplo 19- F a partir de Me- THF.

La figura 4. ilustra la calorimetría de barrido diferencial (DSC) y el análisis termogravimétrico (TGA) del Ejemplo 19- F a partir de Me- THF.

La figura 5. ilustra los patrones de difracción de rayos X de polvos del Ejemplo 19- F del precipitado inicial (patrón superior) y el material secado (patrón inferior) a partir de Me-THF.

La figura 6. ilustra los patrones de difracción de rayos X de polvos del Ejemplo 19- F a partir de tolueno.

La figura 7. ilustra la calorimetría diferencial de barrido (DSC) y el análisis termogravimétrico (TGA) del Ejemplo 19- F a partir de tolueno.

La figura 8. ilustra los patrones de difracción de rayos X de polvos del Ejemplo 19- F a partir de acetato de etilo.

La figura 9. ilustra la calorimetría diferencial de barrido (DSC) y el análisis termogravimétrico (TGA) del Ejemplo 19- F a partir de acetato de etilo.

La figura 10. superposiciones de los patrones de difracción de rayos X de polvos de las formas sólidas del Ejemplo 19- F.

La figura 11. ilustra los patrones de difracción de rayos X de polvos de la forma de clorhidrato A del Ejemplo 19- F.

La figura 12. ilustra el análisis termogravimétrico (TGA) de la forma de clorhidrato A del Ejemplo 19- F (tasa de calentamiento 5 ° C / min).

La figura 13. ilustra la calorimetría diferencial de barrido no hermético (DSC) de la forma de clorhidrato A del Ejemplo 19- F: (tasa de calentamiento 5 ° C / min).

La figura 14. ilustra la calorimetría de barrido diferencial hermético (DSC) de la forma de clorhidrato A del Ejemplo 19- F (tasa de calentamiento 5 ° C / min).

La figura 15. ilustra los patrones de difracción de rayos X de polvos de dos barridos de la forma de clorhidrato B del Ejemplo 19- F en comparación con un barrido de la forma A.

La figura 16. ilustra el análisis termogravimétrico (TGA) de la forma de clorhidrato B del Ejemplo 19- F (tasa de calentamiento 5 ° C / min).

La figura 17. ilustra la calorimetría diferencial de barrido no hermético (DSC) de la forma de clorhidrato B del Ejemplo 19- F (tasa de calentamiento 5 ° C / min).

La figura 18. ilustra los patrones de difracción de rayos X de polvos de la forma de fosfato A del Ejemplo 19- F.

La figura 19. ilustra la calorimetría de barrido diferencial hermético (DSC) de la forma de fosfato A del Ejemplo 19- F (tasa de calentamiento 10 ° C / min).

La figura 20. ilustra los patrones de difracción de rayos X de polvos de la forma de fosfato B del Ejemplo 19- F con la forma de fosfato A del Ejemplo 19- F para comparación.

La figura 21. ilustra la calorimetría de barrido diferencial hermético (DSC) de la forma de fosfato B del Ejemplo 19- F (tasa de calentamiento 10 ° C / min).

La figura 22. ilustra los patrones de difracción de rayos X de polvos de la forma de fosfato C del Ejemplo 19- F.

La figura 23. ilustra la calorimetría diferencial de barrido no hermético (DSC) de la forma de fosfato C del Ejemplo 19- F (tasa de calentamiento 10 ° C / min).

La figura 24. ilustra el análisis termogravimétrico (TGA) de la forma de fosfato C del Ejemplo 19- F (tasa de calentamiento 10 ° C / min).

La figura 25. Comparación de las formas amorfas de hidrocloruro, y fosfato del Ejemplo 19- F de AUC plasmática medida después de PK de rata.

La figura 26. ilustra los patrones de difracción de rayos X de polvos del Ejemplo 55- G a partir de EtOAc al 10% en heptano.

La figura 27. ilustra la calorimetría de barrido diferencial (DSC) y el análisis termogravimétrico (TGA) del Ejemplo 55- G a partir de EtOAc al en heptano.

La figura 28. ilustra los patrones de difracción de rayos X de polvos del Ejemplo 55- G a partir de MeOH al 50% en agua.

La figura 29. ilustra la calorimetría de barrido diferencial (DSC) y el análisis termogravimétrico (TGA) del Ejemplo 55- G a partir de MeOH al 50% en agua mostrando 6,6% de pérdida de peso.

La figura 30. ilustra la calorimetría de barrido diferencial en recipiente sellado (DSC) del Ejemplo 55- G a partir de MeOH al 50% en agua mostrando el verdadero punto de fusión.
La figura 31. ilustra los patrones de difracción de rayos X de polvos de sulfato del Ejemplo 55- G.

La figura 32. ilustra la calorimetría de barrido diferencial (DSC) y el análisis termogravimétrico (TGA) de sulfato del Ejemplo 55- G.

La figura 33. ilustra los patrones de difracción de rayos X de polvos de tosilato del Ejemplo 55- G.

La figura 34. ilustra la calorimetría de barrido diferencial (DSC) y el análisis termogravimétrico (TGA) de tosilato del Ejemplo 55- G.

La figura 35. ilustra los patrones de difracción de rayos X de polvos de besilato del Ejemplo 55- G.

La figura 36. ilustra la calorimetría de barrido diferencial (DSC) y el análisis termogravimétrico (TGA) de besilato del Ejemplo 55- G.

La figura 37. ilustra los patrones de difracción de rayos X de polvos de solvato MTBE del Ejemplo 55- G.

La figura 38. ilustra la calorimetría de barrido diferencial (DSC) y el análisis termogravimétrico (TGA) de solvato MTBE del Ejemplo 55- G.

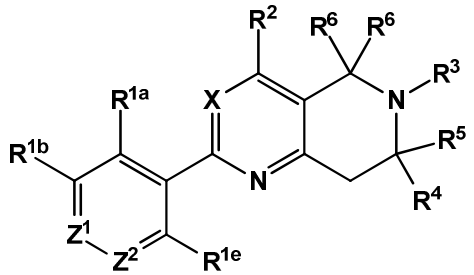
La figura 39. ilustra una comparación de las diferentes formas del Ejemplo 55- G de AUC plasmática medida después de PK de rata.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Como se señaló anteriormente, la presente invención proporciona tetrahidropirido-pirimidinas, tetrahidropiridopiridinas y compuestos heterocíclicos relacionados que modulan la activación de receptores de C5a y / o transducción de señales mediada por el receptor de C5a. Tales compuestos pueden ser utilizados *in vitro* o *in vivo* para modular (preferiblemente inhibir) la actividad del receptor de C5a (algunas veces conocido de aquí en adelante como C5aR) en una variedad de contextos.

En una primera realización, la invención proporciona compuestos de la fórmula I y las sales farmacéuticamente aceptables de los mismos, los cuales modulan el sistema del complemento. Más particularmente, los compuestos de la invención modulan la respuesta mediada por C5a inducida mediante la activación de cualquiera de las vías clásicas, alternativas o de lectina del sistema del complemento.

En una primera realización, se proporcionan compuestos de la fórmula I y sales de los mismos las cuales están representadas por la estructura:



(I)

en donde

X es N o CH;

Z^1 es N o CR^{1c};

Z^2 es N o CR^{1d}, en donde al menos uno de Z^1 y Z^2 no es N;

R^{1a} se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, C_1- C_6alcoxilo, haloC_1 - C_6alquilo, haloC_1 - C_6alcoxilo, ciano o halógeno;

R^{1b} se selecciona del grupo que consta de hidrógeno, amino, hidroxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y mono y di C_1- C_4alquilamino;

R^{1c} es hidrógeno, halógeno o C_1- C_6alquilo;

R^{1d} se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6alquilo, y C_1- C_6alcoxilo;

R^{1e} se selecciona entre hidrógeno, halógeno, ciano, C_1- C_6alquilo, haloC_1 - C_6alquilo, C_1- C_6alcoxilo y haloC_1 - C_6alcoxilo; o

R^{1a} y R^{1b} tomados en combinación forman un anillo heterocíclico saturado o insaturado de 5 miembros que tiene uno o dos heteroátomos de anillo seleccionados entre N, O o S, dicho anillo heterocíclico es sustituido por 0, 1, o 2 sustituyentes de C_1- C_6alquilo o halógeno independientemente seleccionados;

en donde al menos uno de R^{1a} y R^{1e} no es hidrógeno;

R^2 se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, C_1 - C_6alcoxilo, C_1- C_6alquiltio, C_3- C_7cicloalquilo, C_3- C_7cicloalquilC_1- C_4alquilo y $(CH_2)_pNR_{2a}R_{2b}$, en donde cada grupo alquilo y alcoxilo es sustituido por 0 o 1 sustituyente seleccionado del grupo que consta de hidroxilo, halógeno, y C_1- C_4alcoxilo;

p es 0 o 1;

R^{2a} es hidrógeno, C_1- C_6alquilo o hidroxiC_1 - C_6alquilo;

R^{2b} es hidrógeno, C_1- C_6alquilo, C_3- C_7cicloalquilo o C_3- C_7cicloalquilC_1 - C_4alquilo, en donde cada alquilo es sustituido o no sustituido por hidroxilo, C_1 - C_4alcoxilo, C_1- C_4alcoxicarbonilo, o heterociclo en donde el heterociclo es un saturado, insaturado o un anillo aromático de cinco o seis miembros que tiene 1 o 2 heteroátomos de anillo seleccionados entre N, O o S y es sustituido o no sustituido con 1 ó 2 sustituyentes de C_1- C_4 alquilo independientemente seleccionados; o

$NR^{2a}R^{2b}$ tomados en combinación forman un sistema de anillo heterocíclico saturado de 4 a 8 miembros que tiene 1 ó 2 anillos y 0 o 1 heteroátomo de anillo adicional seleccionados entre N, O o S, el sistema de anillo heterocíclico saturado es sustituido o no sustituido por 1- 4 sustituyentes seleccionados independientemente del grupo que consta de C_1- C_4alquilo, hidroxilo, C_1- C_4alcoxilo, C_1- C_4alcoxiC_1 - C_4alquilo, hidroxiC_1 - C_4alquilo, halógeno, amino, mono y di C_1- C_4alquilamino, C_1 - C_4alcoxicarbonilo, C_1- C_4 alcanoilo, S (O) $_2C_1$- C_4alquilo, CH_2C (O) (C_1- C_4 alcoxilo) y CH_2C (O) NH_2;

R^3 se selecciona del grupo que consta de fenilo sustituido, heteroarilo sustituido, y fenilC_1- C_3alquilo, en donde el heteroarilo se selecciona de piridilo, pirazolilo, imidazolilo, tetrazolilo, oxazolilo, y isoxazolilo, y en donde cada grupo fenilo o heteroarilo es sustituido por

1, 2 o 3 sustituyentes los cuales son independientemente seleccionados del grupo que consta de C_1- C_4alquilo, C_1- C_4alcoxilo, halógeno, ciano, haloC_1 - C_4alquilo, haloC_1 - C_4alcoxilo, hidroxiC_1 - C_4alquilo, C_1- C_4alcoxiC_1 - C_4alquilo, C_3- C_6cicloalquilo, y oxaciclo saturado que tiene 4, 5, o 6 átomos de anillo y un oxígeno de anillo, dicho oxaciclo es sustituido o no sustituido por 1 ó 2 sustituyentes de C_1- C_4alquilo independientemente seleccionados, y en donde cada fenilo o heteroarilo comprende al menos un sustituyente *orto* no- hidrógeno al punto de fijación al resto del compuesto de la fórmula (I);

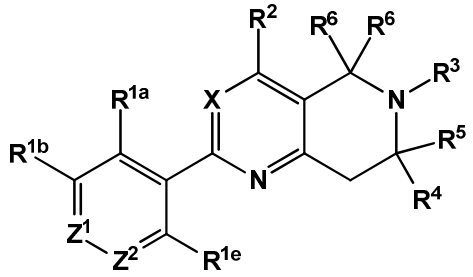
R^4 es hidrógeno o C_1- C_4 alquilo;

R^5 es hidrógeno; o

R^4 y R^5 tomados en combinación son oxo; y

R^6 es hidrógeno en cada ocurrencia o CR^6_2, tomado en combinación, forma un carbonilo divalente.

En otra realización, se proporcionan compuestos de la fórmula I y sales de los mismos, los cuales se representan por la estructura:



(I)

en donde

X es N o CH;

Z^1 es N o CR^{1c};

Z^2 es N o CR^{1d}, en donde al menos uno de Z^1 y Z^2 no es N;

R^{1a} se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, C_1- C_6alcoxilo, haloC_1 - C_6alquilo, haloC_1 - C_6alcoxilo, ciano o halógeno;

R_{1b} se selecciona del grupo que consta de hidrógeno, amino, hidroxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y mono y di C_1- C_4alquilamino;

R^{1c} es hidrógeno, halógeno o C_1- C_6 alquilo;

R^{1d} se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6 alquilo, y C_1- C_6 alcoxilo;

R^{1e} se selecciona entre hidrógeno, halógeno, ciano, C_1- C_6alquilo, haloC_1 - C_6alquilo, C_1- C_6alcoxilo y haloC_1- C_6alcoxilo, sulfona, C_3- C_7cicloalquilo; o

R^{1a} y R^{1b} tomados en combinación forman un anillo heterocíclico saturado o insaturado de 5 miembros que tiene uno o dos heteroátomos de anillo seleccionados entre N, O o S, dicho

anillo heterocíclico es sustituido con 0, 1, o 2 sustituyentes de C_1- C_6alquilo o halógeno independientemente seleccionados;

en donde al menos uno de R^{1a} y R^{1e} no es hidrógeno;

R^2 se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, C_1 - C_6alcoxilo, C_1- C_6alquiltio, C_3- C_7cicloalquilo, C_3- C_7cicloalquilC_1- C_4alquilo y $(CH_2)_pNR^{2a}R^{2b}$, en donde cada grupo alquilo y alcoxilo es sustituido por 0 o 2 sustituyentes seleccionados del grupo que consta de hidroxilo, halógeno, y C_1- C_4alcoxilo, amino, mono y di C_1- C_4alquilamino;

p es 0 o 1;

R^{2a} es hidrógeno, C_1- C_6alquilo o hidroxiC_1 - C_6alquilo;

R^{2b} es hidrógeno, C_1- C_6alquilo, C_3- C_7cicloalquilo o C_3- C_7cicloalquilC_1- C_4alquilo, en donde cada alquilo es sustituido o no sustituido con hidroxilo, C_1 - C_4alcoxilo, C_1- C_4alcoxicarbonilo, o heterociclo en donde el heterociclo es un saturado, insaturado o un anillo aromático de cinco o seis miembros que tiene 1 o 2 heteroátomos de anillo seleccionados entre N, O o S y es sustituido o no sustituido con 1 ó 2 sustituyentes de C_1- C_4alquilo independientemente seleccionados; o

$NR^{2a}R^{2b}$ tomados en combinación forman un sistema de anillo heterocíclico saturado de 4 a 8 miembros que tiene 1 ó 2 anillos y 0 o 1 heteroátomo de anillo adicional seleccionados entre N, O o S, el sistema de anillo heterocíclico saturado es sustituido o no sustituido por 1- 4 sustituyentes seleccionados independientemente del grupo que consta de C_1- C_4alquilo, hidroxilo, C_1- C_4alcoxilo, C_1- C_4alcoxiC_1- C_4alquilo, hidroxiC_1 - C_4alquilo, halógeno, amino, mono y di C_1- C_4alquilamino, C_1 - C_4alcoxicarbonilo, C_1- C_4alcanoilo, S (O) $_2C_1$- C_4alquilo, CH_2C (O) (C_1- C_4alcoxilo) y CH_2C (O) NH_2;

R^3 se selecciona del grupo que consta de fenilo sustituido, heteroarilo sustituido, y fenilC_1- C_3alquilo, en donde el heteroarilo se selecciona de piridilo, pirazolilo, imidazolilo, tetrazolilo, oxazolilo, y isoxazolilo, y en donde cada grupo fenilo o heteroarilo es sustituido por 1, o 2 3 sustituyentes que son independientemente seleccionados del grupo que consta de C_1- C_4alquilo, C_1- C_4alcoxilo, halógeno, haloC_1 - C_4alquilo, haloC_1 - C_4alcoxilo, hidroxiC_1 - C_4alquilo, C_1- C_4alcoxiC_1 - C_4alquilo, C_3- C_6cicloalquilo, y oxaciclo saturado que tiene 4 , 5, o 6 átomos de anillo y un oxígeno de anillo, dicho oxaciclo es sustituido o no sustituido con 1 ó 2 sustituyentes de C_1- C_4alquilo independientemente seleccionados, y en donde cada fenilo o heteroarilo comprende al menos un sustituyente *orto* no- hidrógeno con respecto al punto de unión al resto del compuesto de la fórmula (I);

R^4 es hidrógeno o C_1- C_4alquilo;

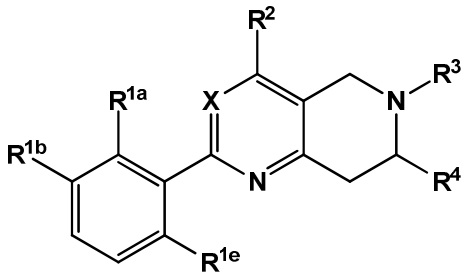
R^5 es hidrógeno; o

R^4 y R^5 tomados en combinación son oxo; y

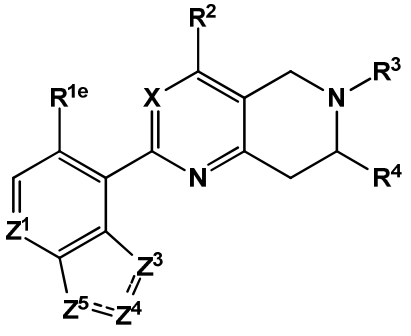
R^6 es hidrógeno en cada ocurrencia o CR^6_2, tomado en combinación, forma un carbonilo divalente.

La expresión "en donde cada fenilo o heteroarilo comprende al menos un sustituyente orto no- hidrógeno al punto de unión al resto del compuesto de la fórmula (I)" significa que el anillo de fenilo o heteroarilo tiene al menos un sustituyente *orto* al anillo de tetrahidropirido-piridina o pirimidina- tetrahidropirido de la fórmula (I).

En una segunda realización, se proporciona un compuesto de la fórmula (I), de realización uno, dicho compuesto es un compuesto de la fórmula (II) o la fórmula (III), o una sal del mismo:



(II)



(III)

en donde

Z^1 es N o CH;

Z^3 es N (H), N (C_1- C_4alquilo), o C (R^{1f});

Z^4 es N o CH;

Z^5 es N (H), N (C_1- C_4alquilo) o C (R^{1g}), en donde uno o dos de Z_3, Z_4 y Z_5 es nitrógeno;

R^{1f} es hidrógeno, C_1- C_4alquilo o halógeno; y

R^{1g} es hidrógeno o C_1- C_4alquilo.

En una tercera realización, se proporciona un compuesto de la realización uno o dos, en el que R^3 es fenilo o 1H- pirazolilo, cada uno de los cuales es sustituido por 1 ó 2 grupos de C_1-C_4alquilo independientemente seleccionados y 0, 1 o 2 sustituyentes adicionales seleccionados del grupo que consta de halógeno, ciano, C_1- C_4alquilo, haloC_1- C_4alquilo, C_1- C_4alcoxilo, ciclopropilo, oxetanilo o 1- metil- oxetanilo. En ciertos compuestos de la tercera realización, R^3 es fenilo o 1H- pirazolilo, cada uno de los cuales es sustituido por 1 ó 2 grupos de C1-C4alquilo independientemente seleccionados y 0 o 1 sustituyente adicional seleccionado del grupo que consta de halógeno, C_1- C_4alquilo, haloC_1 - C_4alquilo, C_1- C_4alcoxilo, ciclopropilo, oxetanilo o 1- metil- oxetanilo.

En una cuarta realización, se proporciona un compuesto de la realización dos o tres, en el que R^{1a} es hidrógeno o metilo;

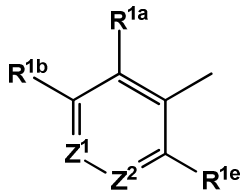
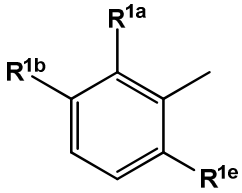
R^{1e} es hidrógeno, metilo o trifluorometilo, en donde al menos uno de R^{1a} y R^{1e} no es hidrógeno;

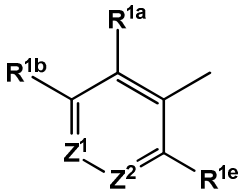
Z^3 es C (R^{1f});

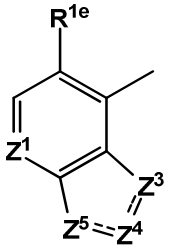
Z^4 es N o CH;

Z^5 es N (H), y

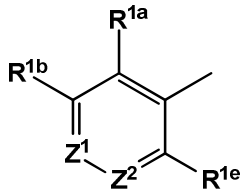
R^{1f} es hidrógeno o metilo.

En una quinta realización, se proporciona un compuesto de cualquiera de las realizaciones de uno a tres, en el que el fragmento  de la fórmula (I) o el fragmento  de la fórmula (II) es 2,6- dimetilfenilo o 2,6 dietilfenilo;

O el fragmento  de la fórmula (I) o el fragmento



de la fórmula (III) es 5- metil- 1H- indazol- 4- ilo, 3- metil- 1H- indol- 4- ilo, 3,5- dimetil- 1H- indazol- 4- ilo, 3,5- dimetil - 1H- indol- 4- ilo, 3,5- dimetil- 1H- indol- 4- ilo, o 3,5- dimetil- 1H- pirazolo [3,4- b] piridin- 4- ilo, 5- trifluorometil- 3H- pirrolo [2,3- b] piridin- 4- ilo.



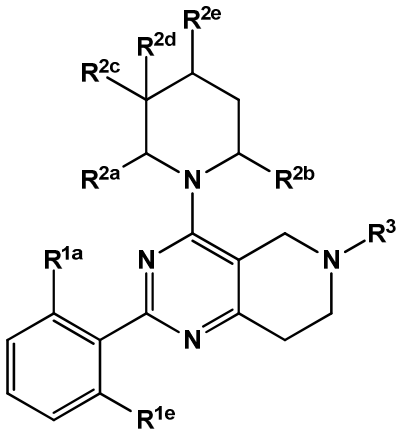
En ciertos aspectos de la quinta realización, el fragmento de la fórmula (I) es 2,6- dimetilfenilo, 2,6- dietilfenil 5- metil- 1H- indazol- 4- ilo, 3- metil- 1H- indol- 4- ilo, 3,5- dimetil- 1H- pirazolo [3,4- b] piridin- 4- ilo o 5- metil- 1H- indazol- 4- ilo.

En una sexta realización, se proporciona un compuesto de cualquiera de las realizaciones uno a cinco, en el que R^4 es hidrógeno.

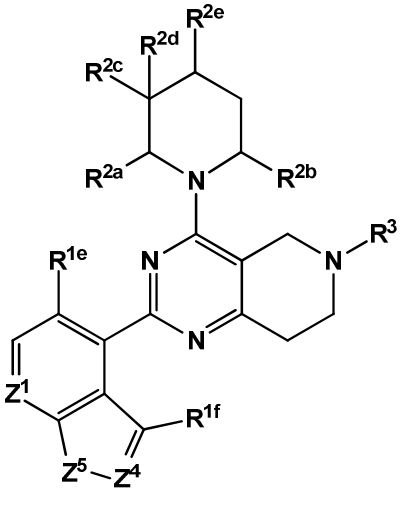
En una séptima realización, se proporciona un compuesto de cualquiera de las realizaciones uno a cinco, en el cual X es N.

En ciertos aspectos, los compuestos de cualquiera de las realizaciones uno a siete incluyen aquellos compuestos en los cuales R^2 es metilo, metoxilo, o metoxi- piperidin- 1- ilo, los cuales son sustituidos adicionalmente con uno o dos grupos de metilo. En ciertos compuestos, R^2 se selecciona entre metilo, metoxilo, 2- metil- 4- metoxi- piperidin- 1- ilo, 3,3- dimetil- 4- metoxi- piperidin- 1- ilo, 2,5- dimetil- 4- metoxi- piperidin- 1- ilo y 2,5,5- trimetil- 4- metoxi- piperidin- 1- ilo.

En una octava realización, se proporciona un compuesto de cualquiera de las realizaciones uno a siete, dicho compuesto es un compuesto de la fórmula (IV) o (V), o una sal del mismo:



(IV)



(V)

en donde

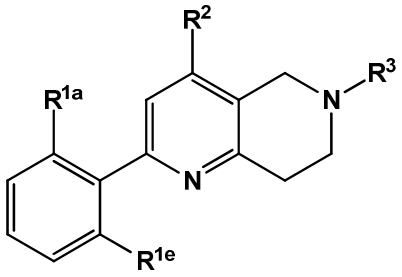
R^{2a}, R^{2b}, R^{2c}, y R^{2d} se seleccionan independientemente de hidrógeno y C_1- C_4alquilo; o R^{2a} y R^{2b}, en combinación, forman un grupo de C_1- C_3alquileno divalente;

R^{2e} es hidroxilo o C_1- C_4alcoxilo.

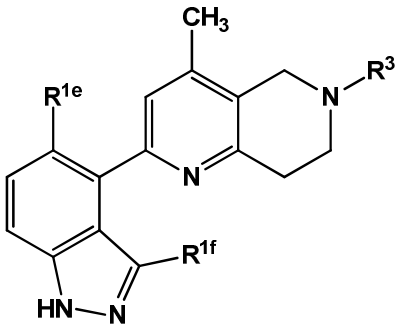
En una novena realización, se proporciona un compuesto de cualquiera de las realizaciones uno a cinco, en la que el X es CH.

En una décima realización, se proporciona un compuesto de cualquiera de las realizaciones uno a cinco o nueve, en la que R^2 es hidrógeno o metilo.

En una undécima realización, se proporciona un compuesto de cualquiera de las realizaciones uno a cinco, nueve o diez, dicho compuesto es un compuesto de la fórmula (VI) o (VII), o una sal del mismo:



(VI)



(VII)

en donde

en la fórmula (VI), R^{1a} y R^{1e} son metilo o etilo; o

en la fórmula (VII), R^{1e} y R^{1f} son hidrógeno o metilo, en donde al menos uno R^{1f} o R^{1e} es metilo.

En una duodécima realización, un compuesto o una sal del mismo, de acuerdo con la fórmula (I), en la cual R^6 es deuterio.

En otra realización, se proporciona compuestos de cualquiera de las realizaciones 9 a 11, en los que R^3 es fenilo o 1H- pirazolilo, cada uno de los cuales es sustituido por 1 ó 2 grupos de C_1- C_4alquilo independientemente seleccionados y 0 o 1 sustituyente adicional seleccionados del grupo que consta de halógeno, C_1- C_4alquilo, haloC_1- C_4alquilo, C_1- C_4alcoxilo, ciclopropilo, oxetanilo o 1- metil- oxetanilo.

En ciertas otras realizaciones de acuerdo con cualquiera de las realizaciones uno a doce R^3 es 2- metil- 5- trifluorofenilo, 2- metil- 5- clorofenilo, 2- metil- 5- isopropil- fenilo, 3- ciclopropil- 1H- pirazol- 5 - ilo, 3- propil- 1H- pirazol- 5- ilo, 4- cloro- 3- ciclopropil- 1H- pirazol- 5- ilo, o 4- cloro- 3- propil- 1H- pirazol- 5- ilo.

En una realización decimotercera, compuestos individuales de acuerdo a la invención son aquellos enumerados en la sección de los Ejemplos a continuación. En ciertos aspectos, el compuesto se selecciona del grupo que consta de:

1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperidin- 4- ol racémico;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina *racémica*;

1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidin- 4- ol *racemico*;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (3- metoxiazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (1,3- dimetil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- N- (2- metoxietil)- N- metil- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

1- ((2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (3- (2- metoxietil)- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (tetrahidrofuran- 2- il)- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

N- ciclopentil- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- *N*- metil- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- amina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol *racémico*;

(*R*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (2- metilpirrolidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- *N*- metil- *N*- ((tetrahidrofuran- 2- il)metil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- amina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (3- (metoximetil)piperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina *racémica*;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (4- (metoximetil)piperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*S*)- 1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.;

1- ((2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol;

1- (2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidina- 3- carboxilato de etilo;

2,2'- ((2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)azanediil)dietanol;

2- (2,6- dimetilfenil)- N- propil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

2- ((2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)acetato de metilo;

(*R*)- 2- ((6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)amino)- 3- metilbutan- 1- ol;

4- (3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2R,4S)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*S*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1*H*- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3- metilpiperidin- 3- ol;

6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2*S*,4*S*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- N,N- dimetil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

2- (2,6- dimetilfenil)- N- (2- metoxietil)- N- metil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- (4- metoxipiperidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpirrolidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,2- dimetilmorfolina;

4- (azetidin- 1- il)- 2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (4- metoxipiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- cloro- 2- metilfenil)- 4- (4- metoxipiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- metil- 1- (metil(2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)amino)propan- 2- ol;

1- ((6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol;

6- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,2- dimetilmorfolina;

6- (5- isopropil- 2- metilfenil)- N,N- dimetil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3,3- dimetilpiperidin- 4- ol;

6- (5- isopropil- 2- metilfenil)- N- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

N- isopropil- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

4- (azetidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidin- 4- ol racémico;

6- (5- isopropil- 2- metilfenil)- N- (2- metoxietil)- N- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)azetidin- 3- ol;

6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémica;

4- (3- fluoroazetidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3,3- dimetilpiperidin- 4- ol;

(*S*)- 4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3- metilmorfolina;

(*S*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol;

(*R*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperidin- 3- ol;

6- (5- isopropil- 2- metilfenil)- 4- ((3*R*,4*R*)- 4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((*3S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- (1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)pirrolidin- 2- il)metanol;

(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- (3- metoxi- 3- metilazetidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilazetidin- 3- ol;

6- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- oxa- 6- azaspiro[3.3]heptano;

6- (5- isopropil- 2- metilfenil)- 4- (3- metoxiazetidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina;

(3- *endo*)- 8- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 8- azabiciclo[3.2.1]octan- 3- ol;

(*S*)- 2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*S*)- 6- (5- cloro- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.;

2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (1- metil- 1H- indazol- 7- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (1- metil- 1H- indazol- 7- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (2- metoxifenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- cloro- 2- metoxifenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 2- (5- fluoro- 2- metilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- isopropil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1*H*- pirrolo[2,3- *b*]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- Ciclopropil- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- Dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,5- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,6- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*R*)- 2- (2,4- dimetilpiridin- 3- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,5- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (3,5- dimetilpiridin- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (5- metoxi- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- cloro- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,4- dimetilpiridin- 3- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (5- fluoro- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (4- fluoro- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- ciclopropil- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (4- (2- (2,5- Dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (2- (2,6- dimetilfenil)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperazin- 1- il)acetamida;

(*R*)- 2- (4- (2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- cloro- 2- metilfenil)- 2- (2,6- dimetilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- cloro- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- (trifluorometil)fenil)- 5,6,7,8 tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (4- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)acetamida.;

(*R*)- 2- (4- (6- (3- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (2,4- difluorofenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- ciclopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona;

1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona;

(*R*)- 1- (3- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona;

1- (4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)etanona racémica;

1- ((*trans*)- 4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,5- dimetilpiperazin- 1- il)etanona racémica;

2- (- 4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)acetamida racémica;

2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)acetamida racémica;

(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (metilsulfonil)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- ; metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 4- (4- etil- 3- metilpiperazin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- metoxi- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- ; tetrahidropirido[4,3- d]pirimidina;

2- (5- isopropil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metoxi- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- isopropil- 1H- indazol- 4- il)- 4- metoxi- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3- cloro- 5- metil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metoxi- 5,6,7,8 tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (3- cloro- 5- metil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- ((*S*)- 1- feniletil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémica;

2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- ((R) 1- feniletil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémica;

6- (4- cloro- 3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*R*)- 4- metil- 1- (2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (3- metil- 4- ((2-nitrofenil)sulfonil)piperazin- 1- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)pentano- 1,3-diona;

(*R*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (3- metil- 4- ((2- nitrofenil)sulfonil)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3-d]pirimidina;

(*R*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (3- metilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (4- (6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8-tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (4- cloro- 3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1H-indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*S*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1H- indol- 4- il)- 4- (2-metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- ((3R,4R)- 4- metoxi- 3- metilpiperidin-1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1-il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8-tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperidin- 4- ol racémico;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (3- metoxipropoxi)- 5,6,7,8-tetrahidropirido[4,3- *d*]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8-tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 4- metil- 6- (o- tolil)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 5,6,7,8-tetrahidro- 1,6- naftiridina2- (2,6- dietilfenil)- 6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4-metil- 5,6,7,8-

tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (1,3- dimetil- 1H- pirazol- 5- il)- 4- metil- 5,6,7,8- tetrahidro-1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (5- metoxi- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6-naftiridina;

2- (2,6- dietilfenil)- 6- (2,5- dimetilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (1- etil- 3- metil- 1H- pirazol- 5- il)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (2,4- dimetilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (5- ciclopropil- 2- metilfenil)- 2- (2,6- dietilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (5- cloro- 2- metilfenil)- 2- (2,6- dietilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 4- metil- 6- (1,3,5- trimetil- 1H- pirazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (5- fluoro- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (3- metil- 1H- indol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro($^2H_2$)- 1,6- naftiridina.;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (3- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2- cloro- 5- metoxifenil)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (5- isopropil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

4- metil- 2- (5- metil- 1H- indazol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dietilfenil)- 4,7- dimetil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dietilfenil)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (5- isopropil- 2- metilfenil)- 4,7- dimetil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (3- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (2,4- dimetilpiridin- 3- il)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (3- metil- 1H- indol- 4- il)- 6- (2,6- dimetilfenil)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina ;

6- (5- metoxi- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (5- isopropil- 1H- indazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (5- isopropil- 1H- indazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (3- metil- 1H- indol- 4- il)- 6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (2,6- dietilfenil)- 4- metil- 6- (1- metil- 1H- tetrazol- 5- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- metoxi- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- metoxi- 5,6,7,8- tetrahidro(5,5- ^{2}- 1,6- naftiridina;

(*S*)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

2- (2,6- dimetilfenil)- 4- ((2- hidroxi- 2- metilpropil)(metil)amino)- 6- (5- isopropil- 2- metilfenil)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

4- ((ciclopropilmetil)(propil)amino)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2- metoxietil)(metil)amino)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

(*S*)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

1- ((2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidro- 1,6- naftiridin- 4- il)(metil)amino)- 2- metilpropan- 2- ol;

N- (ciclopropilmetil)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- N- propil- 5,6,7,8- tetrahidro- 1,6- naftiridin- 4- amina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- N- (2- metoxietil)- N- metil- 5,6,7,8- tetrahidro- 1,6- naftiridin- 4- amina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- etoxi- 2- metilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- (difluorometil)- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (4- cloro- 3- (difluorometil)- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- etoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- metil- 1*H*- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(S)- 6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(R)- 6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina; y

(R)- 6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(S)- 6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(cis)- 3- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (1- metil- 3- (trifluorometil)- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 1- metil- 7- oxa- 3- azabiciclo[4.2.0]octano racémico;

(R)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- ciclopropil- 2- (2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((4*S*,6*R*)- 6- metil- 1- oxa- 7- azaspiro[3.5]nonan- 7- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)benzonitrilo;

(R)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- metoxi- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina;

(R)- 6- (4- cloro- 1- metil- 3- (trifluorometil)- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(R)- 6- (3- (difluorometil)- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(R)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (4- fluoro- 1- metil- 3- (trifluorometil)- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- fluoroetoxi)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (2,2- difluoroetoxi)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- ((2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)oxi)etanamina;

2- ((2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)oxi)- N- metiletanamina;

(S)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((1- metilpirrolidin- 2- il)metoxi)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (2- ((2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)oxi)etil)morfolina;

(*R*)- 3- ((2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)oxi)propano- 1,2- diol;

1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina;

(*R*)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina;

1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3,3- difluoropiperidin- 4- ol;

(*R*)- 1- (2- (3,5- dimetil- 1H- pirazolo[3,4- b]piridin- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina;

(3S,4S)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- metoxi- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(3R,4R)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- metoxi- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(3R,4R)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(3S,4S)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(*R*)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 4- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilmorfolina;

2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- (metilsulfonil)piperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 4- (2,2- difluoroetoxi)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (3- etoxiazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina;

(R)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(S)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(3R,4R)- 1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(3S,4S)- 1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(trans)- 1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilazetidin- 3- ol racémico;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((*trans)*- 3- metoxi- 2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémico;

1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2,4- dimetilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(1*S**,6*S**)- 3- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 1- metil- 7- oxa- 3- azabiciclo[4.2.0]octano racémico;

(*cis*)- 3- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 7- oxa- 3- azabiciclo[4.2.0]octano racémico;

(*R*)- 4- (6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilmorfolina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 4- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilmorfolina;

1- (6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina;

(*R*)- 6- (3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- ciclopropil- 1- etil- 4- fluoro- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 3- (difluorometil)- 5- (2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)- 1- metil- 1H- pirazol- 4- carbonitrilo

(1*S**,6*S**)- 3- (6- (3- (difluorometil)- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 1- metil- 7- oxa- 3- azabiciclo[4.2.0]octano racémico;

(*R*)- 4- (6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilmorfolina;

(R)- 6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina; y

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.

En una decimocuarta realización, se proporciona una composición farmacéutica que comprende uno o más vehículos farmacéuticamente aceptables y una cantidad terapéuticamente eficaz de un compuesto de una cualquiera de las realizaciones 1 a 13.

En una decimoquinta realización, se proporciona una combinación, en particular una combinación farmacéutica, que comprende una cantidad terapéuticamente eficaz del compuesto según cualquiera de las realizaciones 1 a 13 y un segundo agente terapéuticamente activo.

En una decimosexta realización, se proporciona un método de inhibición de anafilaxia inducida por C5a en un sujeto, el método comprende administrar al sujeto una cantidad terapéuticamente eficaz del compuesto según cualquiera de las realizaciones 1 a 13.

En una decimoseptima realización, se proporciona un método para tratar un trastorno o enfermedad en un sujeto mediada por la activación del complemento, en particular mediada por la activación de C5a, el método comprende administrar al sujeto una cantidad terapéuticamente eficaz del compuesto según cualquiera de realizaciones 1 a 13.

En una decimooctava realización, se proporciona el método de la decimo séptima realización en la cual la enfermedad o trastorno se selecciona del grupo que consta de degeneración macular relacionada con la edad, atrofia geográfica, retinopatía diabética, uveítis, retinitis pigmentosa, edema macular, uveítis de Behcet, coroiditis multifocal, síndrome de Vogt-Koyanagi-Harada, uveítis intermedia, retinocorioiditis en perdigonada, oftalmía simpatética, penfigoide cicatricial ocular, pénfigo ocular, neuropatía óptica isquémica no artérica, inflamación post-operatoria, oclusión venosa de la retina, alteraciones neurológicas, esclerosis múltiple, accidente cerebro vascular, síndrome de Guillain Barre, lesión cerebral traumática, enfermedad de Parkinson, trastornos de la activación del complemento inadecuados o indeseables, complicaciones en hemodiálisis, rechazo del aloinjerto hiperagudo, rechazo de xenoinjertos, toxicidad inducida por interleucina-2 durante terapia de IL-2, enfermedades inflamatorias, inflamación de enfermedades autoinmunes, enfermedad de Crohn, síndrome de distrés respiratorio agudo del adulto (SDRA), miocarditis, condiciones de reperfusión pos-isquémica, infarto de miocardio, angioplastia con balón, síndrome pos-perfusión en bypass renal o bypass cardiopulmonar, aterosclerosis, hemodiálisis, isquemia renal, reperfusión de la arteria mesentérica después de la reconstrucción aórtica, enfermedad infecciosa o sepsis,

transtornos complejos inmunes y trastornos autoinmunes, artritis reumatoide, lupus eritematoso sistémico (LES), nefritis por lupus, nefritis proliferativa, fibrosis hepática, anemia hemolítica, miastenia gravis, regeneración de tejidos, regeneración neuronal, disnea, hemoptisis, SDRA, asma, enfermedad pulmonar obstructiva crónica obstructiva crónica (EPOC), enfisema, embolia pulmonar e infartos, neumonía, enfermedades originadas por polvo fibrogénico, fibrosis pulmonar, asma, alergia, broncoconstricción, neumonitis por hipersensibilidad, enfermedades parasitarias, síndrome de Goodpasture, vasculitis pulmonar, vasculitis pauci-inmune, inflamación asociada con complejos inmunes, síndrome antifosfolípido, glomerulonefritis y la obesidad.

En una decimonovena realización, se proporciona un método de tratamiento de la degeneración macular relacionada con la edad, el método comprende administrar a un sujeto que lo necesita una cantidad eficaz de una composición que comprende un compuesto de cualquiera de las reivindicaciones 1 a 14.

En una vigesima realización, se proporciona un compuesto según cualquiera de las realizaciones 1 a 13 para su uso como un medicamento.

En una vigesimoprimera realización se proporciona el uso de un compuesto según cualquiera de las realizaciones 1 a 13 en la fabricación de un medicamento para el tratamiento de un trastorno o enfermedad en un sujeto mediado por la activación del complemento o activación de la vía alternativa del complemento.

En una vigesimo segunda realización, se proporciona el uso de un compuesto según cualquiera de las realizaciones 1 a 13 para el tratamiento de la degeneración macular relacionada con la edad.

En otra realización, se proporcionan composiciones farmacéuticas que comprenden uno o más vehículos farmacéuticamente aceptable y una cantidad terapéuticamente eficaz de un compuesto de una cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una subfórmula del mismo, por ejemplo, un compuesto de una cualquiera de las realizaciones uno a once listadas anteriormente.

En otra realización, se proporcionan combinaciones, en particular combinaciones farmacéuticas que comprenden una cantidad terapéuticamente eficaz del compuesto de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V) , (VI), (VII), o una sub fórmula de los mismos, por ejemplo, un compuesto de una cualquiera de las realizaciones uno a once listadas anteriormente.

En otra realización, se proporcionan métodos de modulación de la actividad del complemento en un sujeto que comprenden administrar al sujeto una cantidad terapéuticamente eficaz del compuesto de una cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI),

(VII), o una sub fórmula del mismo, por ejemplo, un compuesto de una cualquiera de las realizaciones uno a once listadas anteriormente.

En otras realizaciones, se proporcionan métodos de tratamiento de un trastorno o enfermedad en un sujeto mediada por la activación del complemento, en particular, mediada por la activación del sistema del complemento, dichos métodos comprenden administrar al sujeto una cantidad terapéuticamente eficaz del compuesto de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una sub fórmula del mismo, por ejemplo, un compuesto de cualquiera de las realizaciones uno a once listadas anteriormente.

En otra realización, se proporcionan métodos de tratamiento de la degeneración macular relacionada con la edad en un sujeto que comprenden administrar al sujeto una cantidad terapéuticamente eficaz del compuesto de una cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una sub fórmula del mismo, por ejemplo, un compuesto de cualquiera de las realizaciones uno a once listadas anteriormente.

En otro aspecto, la invención proporciona el uso de compuestos de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una sub fórmula de los mismos, por ejemplo, un compuesto de una cualquiera de las realizaciones uno a once listadas anteriormente, para su uso en la preparación de un medicamento y más particularmente para su uso en la fabricación de un medicamento para el tratamiento de un trastorno o enfermedad en un sujeto mediada por la activación del complemento o la activación del sistema del complemento. En ciertos aspectos, la invención proporciona el uso de un compuesto según cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una sub fórmula de los mismos, por ejemplo, un compuesto de cualquiera de las realizaciones uno a once listadas anteriormente, en el tratamiento de la degeneración macular relacionada con la edad.

En una realización, la invención proporciona una combinación, en particular, una combinación farmacéutica, que comprende una cantidad terapéuticamente efectiva del compuesto según la definición de la fórmula (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una sub fórmulas del mismo, por ejemplo, un compuesto de una cualquiera de las realizaciones uno a once listadas anteriormente, o cualquiera de los compuestos específicamente descritos de la invención y uno o más agentes terapéuticamente activos (preferiblemente seleccionados de aquellos listados más adelante).

En una vigesimotercera realización, la invención es una forma solvatada del Ejemplo 19-F aislado a partir de MTBE.

En una vigesmocuarta realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de MTBE caracterizado por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 6,369 ± 0,2 °, 7,058

± 0,2 ° , 9,306 ± 0,2 °, ± 0.2 ° 10.522, 11.908 ± 0.2 °, ± 0,2 ° 12.511, 13.434 ± 0,2 °, ± 0,2 ° 15.527, 16.385 ± 0,2 °, ± 0,2 ° 17.390, 18.883 ± 0,2 °, 20,285 ± 0,2 ° , 22,351 ± 0,2 ° y 23,297 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una vigesimoquinta realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de MTBE caracterizado por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 6,369 ± 0,2 °, 7,058 ± 0,2 ° , 9,306 ± 0,2 °, ± 0,2 ° 10.522, 11.908 ± 0,2 °, ± 0,2 ° 12.511, 13.434 ± 0,2 °, ± 0,2 ° 15.527, 16.385 ± 0,2 °, ± 0,2 ° 17.390, 18.883 ± 0,2 °, 20,285 ± 0,2 ° , 22,351 ± 0,2 ° y 23,297 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una vigesimosexta realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de MTBE que tiene un espectro de difracción de rayos X sustancialmente igual que el espectro de difracción de rayos-x de polvos mostrado en la figura. 1.

En una vigesimoseptima realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de MTBE que tiene un termograma de calorimetría diferencial de barrido (DSC) sustancialmente igual que el mostrado en la figura. 2.

En una vigesimooctava realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de MTBE que tiene un diagrama de análisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura. 2.

En una trigésima realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de Me-THF.

En una trigesimoprimera realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de Me-THF caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 6,959 ± 0,2 °, 8,629 ± 0,2 ° ± 0,2 ° 11.310, 13.387 ± 0,2 °, ± 0,2 ° 16.778, 17.287 ± 0,2 °, ± 0,2 ° 17.865, 18.849 ± 0,2 °, ± 0,2 ° 19.452, 22.353 ± 0,2 °, ± 0,2 ° 22.830 y 26.312 ± 0,2 ° a una temperatura de aproximadamente 22 ° C.

En una trigesimosegunda realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de Me-THF caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 6,959 ± 0,2 °, 8,629 ± 0,2 ° ± 0,2 ° 11.310, 13.387 ± 0,2 °, ± 0,2 ° 16.778, 17.287 ± 0,2 °, ± 0,2 ° 17.865, 18.849 ± 0,2 °, ± 0,2 ° 19.452, 22.353 ± 0,2 °, ± 0,2 ° 22.830 y 26.312 ± 0,2 ° a una temperatura de aproximadamente 22 ° C.

En una trigesimotercera realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de Me-THF que tiene un espectro de difracción de rayos X sustancialmente igual que el espectro difracción de de rayos X de polvos mostrado en la figura 3.

En una trigesimocuarta realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de Me-THF que tiene un termograma de calorimetría de barrido diferencial (DSC) termograma sustancialmente igual que aquel mostrado en la figura 4.

En una trigesimoquinta realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de Me-THF que tiene un diagrama de análisis termo gravimétrico (TGA) sustancialmente igual a aquel mostrado en la figura. 4.

En una trigesimosexta realización, la invención es una forma solvatada del Ejemplo 19-F aislado a partir de tolueno.

En trigesimoséptima realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de tolueno caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 7,431 ± 0,2 °, 9,970 ± 0,2 °, 10,975 ± 0,2 °, 11,562 ± 0,2 °, 12,209 ± 0,2 °, 13,632 ± 0,2 ° ± 0,2 ° 14.448, 15.032 ± 0,2 °, 15,865 ± 0,2 °, 16,974 ± 0,2 °, 17,280 ± 0,2 °, 18,829 ± 0,2 °, 22,402 ± 0,2 ° y 23,165 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una trigesimooctava realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de tolueno caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 7,431 ± 0,2 °, 9,970 ± 0,2 ° , 10,975 ± 0,2 °, ± 0,2 ° 11.562, 12.209 ± 0,2 °, 13,632 ± 0,2 ° ± 0,2 ° 14.448, 15.032 ± 0,2 °, ± 0,2 ° 15.865, 16.974 ± 0,2 °, ± 0,2 ° 17.280, 18.829 ± 0,2 °, 22,402 ± 0,2 ° y 23,165 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una trigesimonovena realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de tolueno que tiene un espectro de difracción de rayos X sustancialmente igual que el espectro de difracción de rayos X de polvos mostrado en la figura. 6.

En una cuadragésima realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de tolueno que tiene un termograma de calorimetría diferencial de barrido (DSC) sustancialmente igual a aquel mostrado en figura. 7.

En una cuadragesima primera realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de tolueno que tiene un diagrama de análisis gravimétrico (TGA) sustancialmente igual a aquel mostrado en la figura. 7.

En una cuadragesimasegunda realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de EtOAc.

En una cuadragesimatercera realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de EtOAc caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 7,430 ± 0,2 °, 9,171 ± 0,2 ° , 10,048 ± 0,2 °, ± 0,2 ° 11.070, 11.555 ± 0,2 °, ± 0,2 ° 12.318, 13.778 ± 0,2

°, ± 0,2 ° 14.490, 15.972 ± 0,2 °, ± 0,2 ° 17.394, 19.025 ± 0,2 ° y 23,283 ± 0,2 ° , a una temperatura de aproximadamente 22 ° C.

En una cuadragesimacuarta realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de EtOAc caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 7,430 ± 0,2 °, 9,171 ± 0,2 ° , 10,048 ± 0,2 °, ± 0,2 ° 11.070, 11.555 ± 0,2 °, ± 0,2 ° 12.318, 13.778 ± 0,2 °, ± 0,2 ° 14.490, 15.972 ± 0,2 °, ± 0,2 ° 17.394, 19.025 ± 0,2 ° y 23,283 ± 0,2 ° , a una temperatura de aproximadamente 22 ° C.

En una cuadragesimaquinta realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de EtOAc que tiene un espectro de difracción de rayos X sustancialmente igual al espectro de difracción de rayos X de polvos mostrado en la figura. 8.

En una cuadragesima sexta realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de EtOAc que tiene un termograma de calorimetría diferencial de barrido (DSC) sustancialmente igual al mostrado en la figura. 9.

En una cuadragesimaséptima realización, la invención es una forma solvatada del Ejemplo 19-F aislada a partir de EtOAc que tiene diagrama de análisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura. 9.

En una cuadragesimaoctava realización, la invención es una forma cristalina de clorhidrato A del Ejemplo 19-F.

En una cuadragesima novena realización, la invención es una forma cristalina de clorhidrato A del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 6,928 ± 0,2 °, 7,630 ± 0,2 °, 9,394 ± 0,2 °, 10,875 ± 0,2 °, 12,252 ± 0,2 °, 14,236 ± 0,2 °, 15,378 ± 0,2 °, 17,227 ± 0,2 °, 18,146 ± 0,2 °, 19,187 ± 0,2 ° y 0,2 ° ± 26,521, a una temperatura de alrededor de 22 ° C.

En una quincuagésima realización, la invención es una forma cristalina de clorhidrato A del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 6,928 ± 0,2 °, 7,630 ± 0,2 °, 9,394 ± 0,2 °, ± 0,2 ° 10.875, 12.252 ± 0,2 °, ± 0,2 ° 14.236, 15.378 ± 0,2 °, ± 0,2 ° 17.227, 18.146 ± 0,2 °, ± 0,2 ° 19.187 y 26.521 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una quincuagésimaprimera realización, la invención es una forma cristalina de clorhidrato A del Ejemplo 19-F que tiene un espectro de difracción de rayos X sustancialmente igual que el espectro de difracción de rayos X de polvos mostrado en la figura. 11.

En una quincuagésimasegunda realización, la invención es una forma cristalina de clorhidrato A del Ejemplo 19-F que tiene un termograma de calorimetría diferencial de barrido (DSC) sustancialmente igual al mostrado las FIG. 13 y 14.

En una quincuagésimatercera realización, la invención es una forma cristalina de clorhidrato A del Ejemplo 19-F que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura. 12.

En una quincuagésimacuarta realización, la invención es una forma cristalina de clorhidrato B del Ejemplo 19-F.

En una quincuagésimaquinta realización, la invención es una forma cristalina de clorhidrato B del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 7,407 ± 0,2 °, 8,041 ± 0,2 °, 8,368 ± 0,2 °, 9,681 ± 0,2 °, 9,983 ± 0,2 °, 13,252 ± 0,2 °, 15,006 ± 0,2 °, 15,554 ± 0,2 °, 19,271 ± 0,2 ° y 0,2 ° ± 20,137, a una temperatura de aproximadamente 22 ° C.

En una quincuagésimasexta realización, la invención es una forma cristalina de clorhidrato B del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 7,407 ± 0,2 °, 8,041 ± 0,2 °, 8,368 ± 0,2 °, 9,681 ± 0,2 °, 9,983 ± 0,2 °, 13,252 ± 0,2 °, 15,006 ± 0,2 °, 15,554 ± 0,2 °, 19,271 ± 0,2 ° y 0,2 ° ± 20,137, a una temperatura de aproximadamente 22 ° C.

En quincuagésimaséptima realización, la invención es una forma cristalina de clorhidrato B del Ejemplo 19-F que tiene un espectro de difracción de rayos X sustancialmente igual que el espectro de difracción de rayos X de polvos mostrado en la figura. 15.

En una quincuagésimaoctava realización, la invención es una forma cristalina de clorhidrato B del Ejemplo 19-F que tiene un termograma de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura. 17.

En una quincuagésimanovena realización, la invención es una forma cristalina de clorhidrato B del Ejemplo 19-F que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura. 16.

En una sexagésima realización, la invención es una forma cristalina de fosfato A del Ejemplo 19-F.

En una sexagésima primera realización, la invención es una forma cristalina de fosfato A del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 4,730 ± 0,2 °, 7,956 ± 0,2 °, 9,584 ± 0,2 °, 10,644 ± 0,2 °, 13,588 ± 0,2 °, 14,548 ± 0,2 °, 16,287 ± 0,2 °, 17,266 ± 0,2 °, 11,835 ± 0,2 ° y 0,2 ° ± 18,948, a una temperatura de aproximadamente 22 ° C.

En una sexagésimasegunda realización, la invención es una forma cristalina de fosfato A del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 7,956 ± 0,2 °, 9,584 ± 0,2 °, 10,644 ± 0,2 °, 13,588 ± 0,2 °, 14,548 ± 0,2 °, 16,287 ± 0,2 °, 17,266 ± 0,2 °, 11,835 ± 0,2 ° y 0,2 ° ± 18,948, a una temperatura de aproximadamente 22 ° C.

En una sexagésimatercera realización, la invención es una forma cristalina de fosfato A del Ejemplo 19-F que tiene un espectro de difracción de rayos X sustancialmente igual que el espectro de difracción de rayos X de polvos mostrado en la figura. 18.

En una sexagésimacuarta realización, la invención es una forma cristalina de fosfato A del Ejemplo 19-F que tiene un termograma de calorimetría de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura. 19.

En una sexagésimaquinta realización, la invención es una forma cristalina de fosfato B del Ejemplo 19-F.

En una sexagésimasexta realización, la invención es una forma cristalina de fosfato B del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2q seleccionados del grupo que consta de 5,873 ± 0,2 °, 7,086 ± 0,2 °, 7,993 ± 0,2 °, 10,188 ± 0,2 °, 11,865 ± 0,2 °, 13,382 ± 0,2 °, 14,434 ± 0,2 °, 16,946 ± 0,2 °, 18,742 ± 0,2 °, 20,709 ± 0,2 °, 21,718 ± 0,2 ° y 0,2 ° ± 22,728, a una temperatura de aproximadamente 22 ° C.

En una sexagésimaséptima realización, la invención es una forma cristalina de fosfato B del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 5,873 ± 0,2 °, 7,086 ± 0,2 °, 7,993 ± 0,2 °, 10,188 ± 0,2 °, 11,865 ± 0,2 °, 13,382 ± 0,2 °, 14,434 ± 0,2 °, 16,946 ± 0,2 °, 18,742 ± 0,2 °, 20,709 ± 0,2 °, 21,718 ± 0,2 ° y 0,2 ° ± 22,728, a una temperatura de aproximadamente 22 ° C.

En una sexagésimaoctava realización, la invención es una forma cristalina de fosfato B del Ejemplo 19-F que tiene un espectro de difracción de rayos X sustancialmente igual que el espectro de difracción de rayos X de polvos mostrado en la figura. 20.

En una sexagésimanovena realización, la invención es una forma cristalina de fosfato B del Ejemplo 19-F que tiene un termograma de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura. 21.

En una septuagésima realización, la invención es un Forma cristalina de fosfato C del Ejemplo 19-F.

En una septuagésimaprimera realización, la invención es un Forma cristalina de fosfato C del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que

comprende cuatro o más valores 2θ seleccionados del grupo que consta de 7,93 ± 0,2 °, 8,65 ± 0,2 °, 10,63 ± 0,2 °, 12,00 ± 0,2 °, 13,85 ± 0,2 °, 15,35 ± 0,2 °, 16,06 ± 0,2 °, 17,65 ± 0,2 ° C y 18,82 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una septuagésima segunda realización, la invención es un forma cristalina de fosfato C del Ejemplo 19-F caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 4,50 ± 0,2 °, 7,93 ± 0,2 °, 8,65 ± 0,2 °, 10,63 ± 0,2 °, 12,00 ± 0,2 °, 13,85 ± 0,2 °, 15,35 ± 0,2 °, 16,06 ± 0,2 °, 17,65 ± 0,2 ° C y 18,82 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una septuagésimatercera realización, la invención es una forma cristalina de fosfato C del Ejemplo 19-F que tiene un espectro de difracción de rayos X sustancialmente igual al espectro de difracción de rayos X de polvos mostrado en la figura. 22.

En una septuagésima cuarta realización, la invención es una forma cristalina de fosfato C del Ejemplo 19-F que tiene un termograma de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura. 23.

En una septuagésima quinta realización, la invención es una forma cristalina de clorhidrato C del Ejemplo 19-F que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura. 24.

En una septuagésima sexta realización, la invención es una forma solvatada del Ejemplo 55-G aislada a partir de EtOAc en heptano.

En una septuagésima séptima realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de EtOAc en heptano caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 7,752 ± 0,2 °, 8,750 ± 0.2 °, ± 0,2 ° 10.211, 10.909 ± 0,2 °, ± 0,2 ° 11.635, 12.485 ± 0,2 °, ± 0,2 ° 12.972, 14.159 ± 0,2 °, ± 0,2 ° 14.831, 15.714 ± 0,2 °, ± 0,2 ° 16.227, 17.249 ± 0.2 °, ± 0,2 ° 17.899, 18.411 ± 0,2 °, ± 0,2 ° 19.351, 20.094 ± 0,2 °, ± 0,2 ° 22.443, 23.089 ± 0,2 °, ± 0,2 ° 23.813, 24.303 ± 0,2 °, ± 0,2 ° 25.326, 25.809 ± 0,2 °, 27,193 ± 0,2 °, 27,973 y 28,863 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una septuagésima octava realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de EtOAc en heptano caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 7,752 ± 0,2 °, 8,750 ± 0.2 °, ± 0,2 ° 10.211, 10.909 ± 0,2 °, ± 0,2 ° 11.635, 12.485 ± 0,2 °, ± 0,2 ° 12.972, 14.159 ± 0,2 °, ± 0,2 ° 14.831, 15.714 ± 0,2 °, ± 0,2 ° 16.227, 17.249 ± 0.2 °, ± 0,2 ° 17.899, 18.411 ± 0,2 °, ± 0,2 ° 19.351, 20.094 ± 0,2 °, ± 0,2 ° 22.443, 23.089 ± 0,2 °, ± 0,2 ° 23.813, 24.303 ± 0,2 °, ± 0,2 ° 25.326, 25.809 ± 0,2 °, 27,193 ± 0,2 °, 27,973 y 28,863 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una septuagésima novena realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de EtOAc en heptano que tiene un espectro de difracción de rayos X sustancialmente igual al espectro de difracción de rayos X de polvos mostrado en la figura. 26.

En una octogésima realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de EtOAc en heptano que tiene un termograma de calorimetría de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura. 27.

En una octogésima primera realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de EtOAc en heptano que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura. 27.

En una octogésima segunda realización, la invención es una forma de tri-hidrato del Ejemplo 55-T aislada a partir de MeOH al 50% en agua.

En una octogésima tercera realización, la presente invención es una forma de tri-hidrato del Ejemplo 55-T aislada a partir de MeOH al 50% en agua caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 8,161 ± 0,2 °, 9,746 ± 0,2 °, ± 0,2 ° 12.689, 13.109 ± 0,2 °, ± 0,2 ° 13.910, 14.544 ± 0,2 °, ± 0,2 ° 16.441, 16.999 ± 0,2 °, ± 0,2 ° 17.517, 19.318 ± 0,2 °, 21,222 ± 0,2 °, 22,710 ± 0,2 °, 23,065 ± 0,2 °, 24,253 ± 0,2 °, 25,351 ± 0,2 ° y 27,787 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una octogésima cuarta realización, la invención es una forma de tri-hidrato del Ejemplo 55-T aislada a partir de MeOH al 50% de en agua caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 6,602 ± 0,2 °, 8,161 ± 0,2 °, 9,746 ± 0,2 °, ± 0,2 ° 12.689, 13.109 ± 0,2 °, ± 0,2 ° 13.910, 14.544 ± 0,2 °, ± 0,2 ° 16.441, 16.999 ± 0,2 °, ± 0,2 ° 17.517, 19.318 ± 0,2 °, ± 0,2 ° 21.222, 22.710 ± 0,2 °, ± 0,2 ° 23.065, 24.253 ± 0,2 °, ± 0,2 ° 25.351 y 27.787 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una octogésima quinta realización, la invención es una forma de tri-hidrato del Ejemplo 55-T aislada a partir de MeOH al 50% en agua que tiene un espectro de difracción de rayos X sustancialmente igual al espectro de difracción de rayos X de polvos mostrado en la figura. 28.

En una octogésima sexta realización, la invención es una forma de tri-hidrato del Ejemplo 55-T aislada a partir de MeOH al 50% en agua que tiene un termograma de calorimetría diferencial de barrido (DSC) sustancialmente igual al mostrado en las figuras 29 y 30.

En una octogésima séptima realización, la invención es una forma de tri-hidrato del Ejemplo 55-T aislada a partir de MeOH al 50% en agua que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura. 30.

En una octogésima octava realización, la invención es una forma cristalina de sulfato del Ejemplo 55-G.

En una octogésima novena realización, la invención es una forma cristalina de sulfato del Ejemplo 55-T caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 6,198 ± 0,2 °, 8,648 ± 0,2 °, 10,047 ± 0,2 °, ± 0,2 ° 11.452, 12.769 ± 0,2 °, ± 0,2 ° 14.551, 16.203 ± 0,2 °, ± 0,2 ° 17.059, 17.827 ± 0,2 ° ± 0,2 ° 19.214 y el 19.952 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una nonagésima realización, la invención es una forma cristalina de sulfato del Ejemplo 55-T caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 6,198 ± 0,2 °, 8,648 ± 0,2 °, 10,047 ± 0.2 °, ± 0,2 ° 11.452, 12.769 ± 0,2 °, ± 0,2 ° 14.551, 16.203 ± 0,2 °, ± 0,2 ° 17.059, 17.827 ± 0,2 ° ± 0,2 ° 19.214 y el 19.952 ± 0,2 °, a una temperatura de aproximadamente 22 ° C .

En una nonagésima primera realización, la invención es una forma cristalina de sulfato del Ejemplo 55-T que tiene un espectro de difracción de rayos X sustancialmente igual al espectro de difracción de rayos X de polvos mostrado en la figura. 31.

En una nonagésima segunda realización, la invención es una forma cristalina de sulfato del Ejemplo 55-T que tiene un termograma de calorimetría de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura. 32.

En una nonagésima tercera realización, la invención es una forma cristalina de sulfato del Ejemplo 55-T que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura 32.

En una nonagésima cuarta realización, la invención es una forma cristalina de tosilato del Ejemplo 55-G.

En una nonagésima quinta realización, la invención es una forma cristalina de tosilato del Ejemplo 55-T caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 6,405 ± 0,2 °, 8,264 ± 0,2 °, 9,769 ± 0,2 °, ± 0,2 ° 12.366, 13.724 ± 0,2 °, ± 0,2 ° 14.639, 16.026 ± 0,2 °, 18,069 y 18,889 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una nonagésima sexta realización, la invención es una forma cristalina de tosilato del Ejemplo 55-T caracterizada por un patrón de difracción de rayos X de polvos que comprende

cinco o más valores 2q seleccionados del grupo que consta de 6,405 ± 0,2 °, 8,264 ± 0,2 °, 9,769 ± 0,2 °, ± 0,2 ° 12.366, 13.724 ± 0,2 °, ± 0,2 ° 14.639, 16.026 ± 0,2 °, 18,069 y 18,889 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una nonagésima séptima realización, la invención es una forma cristalina de tosilato del Ejemplo 55-T que tiene un espectro de difracción de rayos X sustancialmente igual al espectro de difracción de rayos X de polvos mostrado en la figura 33.

En una nonagésima octava realización, la invención es una forma cristalina de tosilato del Ejemplo 55-T que tiene un termograma de calorimetría de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura 34.

En una nonagésima novena realización, la invención es una forma cristalina de tosilato del Ejemplo 55-T que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura 34.

En una centésima realización, la invención es una forma cristalina de besilato del Ejemplo 55-G.

En una centésima primera realización, la invención es una forma cristalina de besilato del Ejemplo 55-T caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 7,624 ± 0,2 °, 8,215 ± 0,2 °, 9,196 ± 0,2 °, 10,674 ± 0,2 °, 11,177 ± 0,2 °, 11,715 ± 0,2 °, 13,324 ± 0,2 °, 13,710 ± 0,2 °, 14,352 ± 0,2 °, 14,912 ± 0,2 °, 15,358 ± 0,2 °, 16,169 ± 0,2 °, 16,706 ± 0,2 °, 17,160 ± 0,2 °, 17,465 ± 0,2 °, 17,737 ± 0,2 °, 18,952 ± 0,2 °, 19,915 ± 0,2 °, 21,568 ± 0,2 °, 22,119 ± 0,2 °, 22,422 ± 0,2 °, 23,656 ± 0,2 °, 24,450 ± 0,2 °, 25,535 ± 0,2 °, 27,668 ± 0,2 °, 28,393 ± 0,2 °, 29,209 ± 0,2 °, 29,832, 30,595 y 33,143 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una centésima segunda realización, la invención es una forma cristalina de besilato del Ejemplo 55-T caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 7,624 ± 0,2 °, 8,215 ± 0,2 °, 9,196 ± 0,2 °, 10,674 ± 0,2 °, 11,177 ± 0,2 °, 11,715 ± 0,2 °, 13,324 ± 0,2 °, 13,710 ± 0,2 °, 14,352 ± 0,2 °, 14,912 ± 0,2 °, 15,358 ± 0,2 °, 16,169 ± 0,2 °, 16,706 ± 0,2 °, 17,160 ± 0,2 °, 17,465 ± 0,2 °, 17,737 ± 0,2 °, 18,952 ± 0,2 °, 19,915 ± 0,2 °, 21,568 ± 0,2 °, 22,119 ± 0,2 °, 22,422 ± 0,2 °, 23,656 ± 0,2 °, 24,450 ± 0,2 °, 25,535 ± 0,2 °, 27,668 ± 0,2 °, 28,393 ± 0,2 °, 29,209 ± 0,2 °, 29,832, 30,595 y 33,143 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una centésima tercera realización, la invención es una forma cristalina de besilato del Ejemplo 55-T que tiene un espectro de difracción de rayos X sustancialmente igual al espectro de difracción de rayos X de polvos mostrado en la figura 35.

En una centésima cuarta realización, la invención es una forma cristalina de besilato del Ejemplo 55-T que tiene un termograma de calorimetría de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura 36.

En una centésima quinta realización, la invención es una forma cristalina de besilato del Ejemplo 55-T que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura. 36.

En una centésima sexta realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de MTBE.

En una centésima séptima realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de MTBE caracterizada por un patrón de difracción de rayos X de polvos que comprende cuatro o más valores 2θ seleccionados del grupo que consta de 6,728 ± 0,2 °, 7,659 ± 0,2 °, 8,627 ± 0,2 °, ± 0,2 ° 10.148, 10.853 ± 0,2 °, ± 0,2 ° 11.418, 12.313 ± 0,2 °, ± 0,2 ° 12.889, 14.043 ± 0,2 °, ± 0,2 ° 14.684, 15.969 ± 0,2 °, 16,689 ± 0,2 °, ± 0,2 ° 17.149, 17.842 ± 0,2 °, ± 0,2 ° 18.338, 19.119 ± 0,2 °, ± 0,2 ° 19.752, 23.113 ± 0,2 °, ± 0,2 ° 24.397, 25.187 ± 0,2 °, ± 0,2 ° 25.794 y 27.159 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una centésima octava realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de MTBE caracterizada por un patrón de difracción de rayos X de polvos que comprende cinco o más valores 2θ seleccionados del grupo que consta de 6,728 ± 0,2 °, 7,659 ± 0,2 °, 8,627 ± 0,2 °, ± 0,2 ° 10.148, 10.853 ± 0,2 °, ± 0,2 ° 11.418, 12.313 ± 0,2 °, ± 0,2 ° 12.889, 14.043 ± 0,2 °, ± 0,2 ° 14.684, 15.969 ± 0,2 °, 16,689 ± 0,2 °, ± 0,2 ° 17.149, 17.842 ± 0,2 °, ± 0,2 ° 18.338, 19.119 ± 0,2 °, ± 0,2 ° 19.752, 23.113 ± 0,2 °, ± 0,2 ° 24.397, 25.187 ± 0,2 °, ± 0,2 ° 25.794 y 27.159 ± 0,2 °, a una temperatura de aproximadamente 22 ° C.

En una centésima novena realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de MTBE que tiene un espectro de difracción de rayos X sustancialmente igual al espectro de difracción de rayos X de polvos mostrado en la figura 37.

En una centésima décima realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de MTBE que tiene un termograma de calorimetría de barrido diferencial (DSC) sustancialmente igual al mostrado en la figura 38.

En una centésima undécima realización, la invención es una forma solvatada del Ejemplo 55-T aislada a partir de MTBE que tiene un diagrama de ánalisis termo gravimétrico (TGA) sustancialmente igual al mostrado en la figura 38.

Para propósitos de interpretar esta especificación, las siguientes definiciones se aplicarán y cuando sea apropiado, los términos utilizados en forma singular también incluirán la forma plural y viceversa.

Como se utiliza en la presente, el término "alquilo" se refiere a una fracción de hidrocarburo ramificada o no ramificada completamente saturada que tiene hasta 20 átomos de carbono. A menos que se indique lo contrario, alquilo se refiere a fracciones de hidrocarburo que tienen 1 a 12 átomos de carbono 1 a 10 átomos de carbono, 1 a 7 átomos de carbono, o 1 a 4 átomos de carbono. Ejemplos representativos de alquilo incluyen, pero no se limitan a, metilo, etilo, n- propilo, iso- propilo, n- butilo, sec- butilo, iso- butilo, tert- butilo, n- pentilo, isopentilo, neopentilo, n- hexilo, 3- metilhexilo, 2,2- dimetilpentilo, 2,3- dimetilpentilo, n- heptilo, n- octilo, n- nonilo, n- decilo y similares.

Como se utiliza en la presente, el término “alquileno” se refiere a un grupo alquilo divalente como se definió en la presente anteriormente que tiene 1 a 20 átomos de carbono. Este comprende 1 a 20 átomos de carbono, A menos que se indique lo contrario, alquileno se refiere a fracciones que tienen 1 a 12 átomos de carbono, 1 a 10 átomos de carbono, 1 a 7 átomos de carbono, o 1 a 4 átomos de carbono. Ejemplos representativos de alquileno incluyen, pero no se limitan a, metileno, etileno, n- propileno, iso- propileno, n- butileno, sec- butileno, iso- butileno, tert- butileno, n- pentileno, isopentileno, neopentileno, n- hexileno, 3- metilhexileno, 2,2- dimetilpentileno, 2,3- dimetilpentileno, n- heptileno, n- octileno, n- nonileno, n- decileno y similares.

Como se utiliza en la presente, el término “haloalquilo” se refiere a un alquilo como se define en la presente el cual es sustituido por uno o más grupos halo como se define en la presente. El haloalquilo puede ser monohaloalquilo, dihaloalquilo, o polihaloalquilo, incluyendo perhaloalquilo. Un monohaloalquilo puede tener un yodo, bromo, cloro ó fluoro dentro del grupo alquilo. Los grupos dihaloalquilo y polihaloalquilo pueden tener dos o más de los mismos átomos halo o una combinación de diferentes grupos halo dentro del alquilo Típicamente el polihalolaquilo contiene hasta 12, o 10, o 8, o 6, o 4, o 3, o 2 grupos halo. Ejemplos no limitantes de haloalquilo incluyen fluorometilo, difluorometilo, trifluorometilo, clorometilo, diclorometilo, triclorometilo, pentafluoroetilo, heptafluoropropilo, difluoroclorometilo, diclorofluorometilo, difluoroetilo, difluoropropilo, dicloroetilo y dicloropropilo. Un perhaloalquilo se refiere a un alquilo que tiene todos los átomos de hidrógeno reemplazados por átomos halo.

El término "arilo" se refiere a un grupo hidrocarbono aromático que tiene 6-20 átomos de carbono en la porción cíclica. Típicamente, arilo es arilo monocíclico, bicíclico o tricíclico que tiene 6-20 átomos de carbono.

Además, el término "arilo” como se utiliza en la presente, se refiere a un sustituyente aromático el cual puede ser un único anillo aromático, o múltiples anillos aromáticos que son fusionados juntos.

Ejemplos no limitantes incluyen fenilo, naftilo o tetrahidronaftilo, cada uno de los cuales puede opcionalmente sustituirse por 1- 4 sustituyentes, tales como alquilo, trifluorometilo, cicloalquilo, halógeno, hidroxilo, alcoxilo, acilo, alquilo- C(O)- O- , arilo- O- , heteroarilo- O- , amino, tiol, alquilo- S- , arilo- S- , nitro, ciano, carboxilo, alquilo- O- C(O)- , carbamoilo, alquilo- S(O)- , sulfonilo, sulfonamido, fenilo, y heterociclilo.

Como se utiliza en la presente, el término “alcoxilo” se refiere a alquilo-O-, en donde alquilo se definió en la presente anteriormente. Ejemplos representativos de alcoxilo incluyen, pero no se limitan a, metoxilo, etoxilo, propoxilo, 2-propoxilo, butoxilo, *tert*-butoxilo, pentiloxilo, hexiloxilo, ciclopropiloxilo-, ciclohexiloxilo- y similares. Típicamente, los grupos alcoxilo tienen aproximadamente 1-7, más preferiblemente 1-4 carbonos aproximadamente.

Tal como se utiliza en la presente, el término "heterociclo" o "heterociclilo" se refiere a un anillo no aromático saturado o insaturado o sistema cíclico, por ejemplo, el cual es un sistema de anillo monocíclico de 4- , 5- , 6- , o 7 miembros, bicíclico de 7- , 8- , 9- , 10- , 11- , o 12- miembros o tricíclico de 10- , 11- , 12- , 13- , 14- o 15- miembros y contiene al menos un heteroátomo seleccionado entre O, S y N , donde el N y S también pueden opcionalmente ser oxidados a varios estados de oxidación. El grupo cicloheteroalquilo puede fijarse en un heteroátomo o un átomo de carbono. El heterociclilo puede incluir anillos fusionados o unidos así como también anillos espirocíclicos. Ejemplos de heterociclos incluyen tetrahidrofurano (THF), dihidrofurano, 1,4- dioxano, morfolina, 1,4- ditiano, piperazina, piperidina, 1,3- dioxolano, imidazolidina, imidazolina, pirrolina, pirrolidina, tetrahidropirano, dihidropirano, oxatiolano, ditiolano, 1,3- dioxano, 1,3- ditiano, oxatiano, tiomorfolina, y similares.

El término “heterociclilo” además se refiere a grupos heterocíclicos como se definen en la presente sustituidos por 1 a 5 sustituyentes independientemente seleccionados a partir de los grupos que constan de los siguientes:

(a) alquilo;

(b) hidroxilo (o hidroxilo protegido);

(c) halo;

(d) oxo, es decir, =O;

(e) amino, alquilamino o dialquilamino;

(f) alcoxilo;

(g) cicloalquilo;

(h) carboxilo;

(i) heterociclooxi, en donde heterociclooxi denota un grupo heterocíclico unido a través de un puente de oxígeno;

(j) alquilo- O- C(O)- ;

(k) mercapto;

(l) nitro;

(m) ciano;

(n) sulfamoilo o sulfonamido;

(o) arilo;

(p) alquilo- C(O)- O- ;

(q) arilo- C(O)- O- ;

(r) arilo- S- ;

(s) ariloxilo;

(t) alquilo- S- ;

(u) formilo, es decir, HC(O)- ;

(v) carbamoilo;

(w) aril- alquilo- ; y

(x) arilo sustituido con alquilo, cicloalquilo, alcoxilo, hidroxilo, amino, alquilo- C(O)- NH- , alquilamino, dialquilamino o halógeno.

Como se utiliza en la presente, el término "cicloalquilo" se refiere a grupos hidrocarburos monocíclicos, bicíclicos o tricíclicos saturados o no saturados de 3- 12 átomos de carbono. A menos que se indique lo contrario, cicloalquilo se refiere a grupos hidrocarburo cíclicos que tienen entre 3 y 9 átomos de carbono cíclicos o entre 3 y 7 átomos de carbono cíclicos, cada uno de los cuales puede opcionalmente sustituirse por uno, o dos, o tres, o más sustituyentes independientemente seleccionados a partir del grupo que consta de alquilo, halo, oxo, hidroxilo, alcoxilo, alquilo- C(O)- , acilamino, carbamoilo, alquilo- NH- , (alquilo)2N- , tiol, alquilo- S- , nitro, ciano, carboxilo, alquilo- O- C(O)- , sulfonilo, sulfonamido, sulfamoilo, y heterociclilo. Grupos hidrocarbono monocíclicos de ejemplo incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexili y ciclohexenilo y similares. Grupos hidrocarburo bicíclicos de ejemplo incluyen bornilo, indilo, hexahidroindilo, tetrahidronaftilo, decahidronaftilo, biciclo[2.1.1]hexilo, biciclo[2.2.1]heptilo, biciclo[2.2.1]heptenilo, 6,6-dimetilbiciclo[3.1.1]heptilo, 2,6,6-trimetilbiciclo[3.1.1]heptilo, biciclo[2.2.2]octilo y similares. Grupos hidrocarburo tricíclicos de ejemplo incluyen adamantilo y similares.

Como se utiliza en la presente, el término “ariloxilo” se refiere a ambos un grupo - O- arilo y un grupo - O- heteroarilo, en donde arilo y heteroarilo se definen en la presente.

Como se utiliza en la presente, el término "heteroarilo" se refiere a un sistema de anillo monocíclico o bicíclico- o tricíclico-aromático de 5-14 miembros, que tiene 1 to 8 heteroátomos seleccionados a partir de N, O ó S. Típicamente, el heteroarilo es un sistema de anillo de 5-10 miembros (ej., monociclo de 5-7 miembros o un biciclo de 8-10 miembros) o un sistema de anillo de 5-7 miembros. Grupos heteroarilo típicos incluyen 2- o 3-tienilo, 2- o 3-furilo, 2- o 3-

pirrolilo, 2-, 4-, ó 5-imidazolilo, 3-, 4-, o 5- pirazolilo, 2-, 4-, o 5-tiazolilo, 3-, 4-, o 5-isotiazolilo, 2-, 4-, o 5-oxazolilo, 3-, 4-, o 5-isoxazolilo, 3- o 5-1,2,4-triazolilo, 4- o 5-1,2, 3-triazolilo, tetrazolilo, 2-, 3-, o 4-piridilo, 3- o 4-piridazinilo, 3-, 4-, o 5-pirazinilo, 2-pirazinilo, y 2-, 4-, o 5-pirimidinilo.

El término "heteroarilo" también se refiere a un grupo en el cual un anillo heteroaromático es fusionado a uno más anillos arilo, cicloalifáticos, o heterocíclicos, donde el radical o punto de fijación está sobre el anillo heteroaromático. Ejemplos no limitantes incluyen 1-, 2-, 3-, 5-, 6-, 7-, o 8- indolizinilo, 1-, 3-, 4-, 5-, 6-, o 7-isoindolilo, 2-, 3-, 4-, 5-, 6-, o 7-indolilo, 2-, 3-, 4-, 5-, 6-, o 7-indazolilo, 2-, 4-, 5-, 6-, 7-, o 8- purinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, o 9-quinolizinilo, 2-, 3-, 4-, 5-, 6-, 7-, o 8-quinoliilo, 1-, 3-, 4-, 5-, 6-, 7-, o 8-isoquinoliilo, 1-, 4-, 5-, 6-, 7-, o 8-ftalazinilo, 2-, 3-, 4-, 5-, o 6-naftiridinilo, 2-, 3- , 5-, 6-, 7-, o 8-quinazolinilo, 3-, 4-, 5-, 6-, 7-, o 8-cinnolinilo, 2-, 4-, 6-, o 7-pteridinilo, 1-, 2-, 3-, 4-, 5-, 6-, 7-, o 8-4aH carbazolilo, 1-, 2-, 3-, 4-, 5-, 6-, 7-, o 8-carbazolilo, 1-, 3-, 4-, 5-, 6-, 7-, 8-, o 9-carbolinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, o 10-fenantridinilo, 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, o 9-acridinilo, 1-, 2-, 4-, 5-, 6-, 7-, 8-, o 9-perimidinilo, 2-, 3-, 4-, 5-, 6-, 8-, 9-, o 10-fenatrolinilo, 1-, 2- , 3-, 4-, 6-, 7-, 8-, o 9-fenazinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, o 10-fenotiazinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, o 10-fenoxazinilo, 2-, 3-, 4-, 5-, 6-, o l-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, o 10- benzisoquinolinilo, 2-, 3-, 4-, o tieno[2,3-b]furanilo, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, o 11-7H-pirazino[2,3-c]carbazolilo,2-, 3-, 5-, 6-, o 7-2H- furo[3,2-b]-piranilo, 2-, 3-, 4-, 5-, 7-, o 8-5H-pirido[2,3-d]-o-oxazinilo, 1-, 3-, o 5-1H-pirazolo[4,3-d]-oxazolilo, 2-, 4-, o 54H-imidazo[4,5-d] tiazolilo, 3-, 5-, o 8-pirazino[2,3-d]piridazinilo, 2-, 3-, 5-, o 6- imidazo[2,1-b] tiazolilo, 1-, 3-, 6-, 7-, 8-, o 9-furo[3,4-c]cinolinilo, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10, o 11-4H-pirido[2,3-c]carbazolilo, 2-, 3-, 6-, o 7-imidazo[1,2-b][1,2,4]triazinilo, 7-benzo[b]tienilo, 2-, 4-, 5- , 6-, o 7-benzoxazolilo, 2-, 4-, 5-, 6-, o 7-benzimidazolilo, 2-, 4-, 4-, 5-, 6-, o 7-benzotiazolilo, 1-, 2-, 4-, 5-, 6-, 7-, 8-, o 9- benzoxapinilo, 2-, 4-, 5-, 6-, 7-, o 8-benzoxazinilo, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, o 11-1H-pyrrolo[1,2-b][2]benzazapinilo. Grupos heteroarilo fusionados típicos incluyen, pero no se limitan a 2- , 3- , 4- , 5- , 6- , 7- , ó 8- quinolinilo, 1- , 3- , 4- , 5- , 6- , 7- , o 8- isoquinolinilo, 2- , 3- , 4- , 5- , 6- , 7 o indolilo, 2- , 3- , 4- , 5- , 6- , 7 o benzo- [b] tienilo , 2- , 4- , 5- , 6- , o 7- benzoxazolilo, 2- , 4- , 5- , 6- , 7 o bencimidazolilo, y 2- , 4- , 5- , 6- , 7 o- benzotiazolilo.

Un grupo heteroarilo puede sustituirse con 1 a 5 sustituyentes independientemente seleccionados a partir de los grupos que constan de los siguientes:

(a) alquilo;

(b) hidroxilo (o hidroxilo protegido);

(c) halo;

(d) oxo, es decir, =O;

(e) amino, alquilamino o dialquilamino;

(f) alcoxilo;

(g) cicloalquilo;

(h) carboxilo;

(i) heterociclooxi, en donde heterociclooxi denota un grupo heterocíclico unido a través de un puente de oxígeno;

(j) alquilo- O- C(O)- ;

(k) mercapto;

(l) nitro;

(m) ciano;

(n) sulfamoilo o sulfonamido;

(o) arilo;

(p) alquilo- C(O)- O- ;

(q) arilo- C(O)- O- ;

(r) arilo- S- ;

(s) ariloxilo;

(t) alquilo- S- ;

(u) formilo, es decir, HC(O)- ;

(v) carbamoilo;

(w) aril- alquilo- ; y

(x) arilo sustituido con alquilo, cicloalquilo, alcoxilo, hidroxilo, amino, alquilo-C(O)- NH- , alquilamino, dialquilamino o halógeno.

Como se utiliza en la presente, el término “halógeno” o “halo” se refiere a fluoro, cloro, bromo, y yodo.

Como se utiliza en la presente, el término “opcionalmente sustituido” a menos que se especifique lo contrario se refiere a un grupo que no es sustituido o es sustituido por uno o más, típicamente 1, 2, 3 o 4, sustituyentes no hidrogéno apropiados, cada uno de los cuales es independientemente seleccionado del grupo que consta de:

(a) alquilo;

(b) hidroxilo (o hidroxilo protegido);

(c) halo;

(d) oxo, es decir, =O;

(e) amino, alquilamino o dialquilamino;

(f) alcoxilo;

(g) cicloalquilo;

(h) carboxilo;

(i) heterociclooxi, en donde heterociclooxi denota un grupo heterocíclico unido a través de un puente de oxígeno;

(j) alquilo- O- C(O)- ;

(k) mercapto;

(l) nitro;

(m) ciano;

(n) sulfamoilo o sulfonamido;

(o) arilo;

(p) alquilo- C(O)- O- ;

(q) arilo- C(O)- O- ;

(r) arilo- S- ;

(s) ariloxilo;

(t) alquilo- S- ;

(u) formilo, es decir, HC(O)- ;

(v) carbamoilo;

(w) aril- alquilo- ; y

(x) arilo sustituido con alquilo, cicloalquilo, alcoxilo, hidroxilo, amino, alquilo- C(O)- NH- , alquilamino, dialquilamino o halógeno.

Como se utiliza en la presente, el término “isómeros” se refiere a diferentes compuestos que tienen la misma fórmula molecular pero difieren en disposición y configuración de los átomos. También como se utiliza en la presente, el término “un isómero óptico” o “un estereoisómero” se refiere a cualquiera de las diferentes configuraciones estereoisoméricas que pueden existir para un compuesto dado del presente invento e incluyen isómeros geométricos. Se entiende que un sustituyente será fijado a un centro quiral de un átomo de carbono. Por lo tanto, el invento incluye enantiómeros, diastereoisómeros o racematos del compuesto. Los “enantiómeros” son un par de estereoisómeros que son imágenes especulares que no pueden ser superpuestas entre sí. Una mezcla 1:1 de un par de enantiómeros es una mezcla "racémica”. El término se utiliza para designar una mezcla racémica donde sea apropiado. El asterisco (*) indicado en el nombre de un compuesto designa una mezcla racémica. Los "diaestereoisómeros” son estereoisómeros que tienen al menos dos átomos asimétricos, pero los cuales no son imágenes especulares entre sí. La estereoquímica absoluta es especificada según el sistema R-S de Cahn- lngold- Prelog. Cuando un compuesto es un enantiómero puro la estereoquímica de cada carbono quiral puede especificarse por cualquiera R o S. Compuestos resueltos cuya configuración absoluta se desconoce pueden designarse (+) o (-) dependiendo de la dirección (dextro- o levorotatoria) que rotan el plano de luz polarizada según la longitud de onda de la línea D del sodio. Ciertos de los compuestos descritos en la presente contienen uno

o más centros o ejes asimétricos y pueden por lo tanto dar origen a enantiómeros, diastereoisómeros, y otras formas estereoisoméricas que pueden ser definidas, en términos de estereoquímica absoluta, como (R)- o (S)-. El presente invento pretende incluir todos éstos isómeros posibles, incluyendo mezclas racémicas, formas ópticamente puras y mezclas intermedias. Isómeros ópticamente activos (R)- y (S)- pueden prepararse utilizando sintones quirales o reactivos quirales, o resolverse utilizando técnicas convencionales. Si el compuesto contiene un enlace doble, el sustituyente puede ser de configuración E o Z. Si el compuesto contiene un cicloalquilo disustituido, el sustituyente cicloalquilo puede tener una configuración cis- o - trans. Todas las formas tautoméricas también son incluidas.

Tal como se utiliza en la presente, el término "sales farmacéuticamente aceptables" se refiere a sales que retienen la eficacia biológica y propiedades de los compuestos de esta invención y, que normalmente no son biológicamente o de otro modo indeseables. En muchos casos, los compuestos del presente invento son capaces de formar sales ácidas y/o alcalinas en virtud de la presencia de grupos amino y/o carboxilo o grupos similares de los mismos.

Sales de adición ácida farmacéuticamente aceptables pueden formarse con ácidos inorgánicos y ácidos orgánicos, ej., acetato, aspartato, benzoato, besilato, bromuro/hidrobromuro, bicarbonato/carbonato, bisulfato/sulfato, canforsulfornato, cloruro/hidrocloruro, clorteofilonato, citrato, etanodisulfonato, fumarato, gluceptato, gluconato, glucuronato, hipurato, hidroyoduro/yoduro, isetionato, lactato, lactobionato, laurilsulfato, malato, maleato, malonato, mielato, misilato, metilsulfato, naftoato, napsilato, nicotinato, nitrato, octadecanoato, oleato, oxalato, palmitato, pamoato, fosfato/fosfato de hidrógeno/fosfato de dihidrógeno, poligalacturonato, propionato, estearato, succinato, sulfosalicilato, tartrato, tosilato y sales de trifluoroacetato. Ácidos inorgánicos a partir de los cuales las sales pueden derivarse incluyen, por ejemplo, ácido clorhídrico, ácido hidrobrómico, ácido sulfúrico, ácido nítrico, y ácido fosfórico. Ácidos orgánicos de tales sales pueden derivarse incluyendo, por ejemplo, ácido acético, ácido propiónico, ácido glicólico, ácido oxálico, ácido maléico, ácido manólico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzóico, ácido mandélico, ácido metanosulfónico, ácido etanosulfónico, ácido toluensulfónico, ácido sulfosalicílico, y similares.

Las Sales de adición alcalina farmacéuticamente aceptables pueden formarse con bases inorgánicas y orgánicas. Bases inorgánicas a partir de las cuales las sales pueden derivarse incluyen, por ejemplo, sales y metales de amonio de las columnas I a XII de la tabla periódica. En ciertas realizaciones, las sales se derivan a partir de sodio, potasio, amonio, calcio, magnesio, hierro, plata, zinc, y cobre; sales particularmente apropiadas incluyen sales de amonio, potasio, sodio, calcio y magnesio. Bases orgánicas a partir de las cuales pueden derivarse las sales incluyen, por ejemplo, aminas primarias, secundarias y terciarias, aminas

sustituidas incluyendo aminas sustituidas de ocurrencia natural, aminas cíclicas, resinas de intercambio de iones alcalinos, y similares. Ciertas aminas orgánicas incluyen esopropilamina, benzatina, colinato, dietanolamina, dietilamina, lisina, meglumina, piperazina y trometamina.

Las sales farmacéuticamente aceptables del presente invento pueden sintetizarse a partir de un compuesto precursor, una fracción alcalina o ácida, mediante métodos químicos convencionales. Generalmente, tales sales pueden prepararse al reaccionar formas ácidas libres de estos compuestos con una cantidad estequiométrica de la base apropiada (tales como hidróxido, carbonato, bicarbonato de Na, Ca, Mg, o K o similares), o al reaccionar formas alcalinas libres de estos compuestos con una cantidad estequiométrica del ácido apropiado. Típicamente, tales reacciones se realizan en agua o en un solvente orgánico, o en una mezcla de los dos. Generalmente, el uso de medios no acuosos tipo éter, acetato de etilo, etanol, isopropanol, o acetonitrilo es deseable, donde pueda realizarse. Listas de sales apropiadas adicionales pueden encontrarse, ej., en "*Remington's Farmaceutical Sciences*", 20th ed., Mack Publishing Company, Easton, Pa., (1985); y en "*Handbook of Farmaceutical Salts: Properties, Selection, and Use*" de Stahl y Wermuth (Wiley-VCH, Weinheim, Alemania, 2002).

Cualquiera fórmula dada en la presente también tiene el propósito de representar formas no rotuladas así como también formas isotopicamente rotuladas de los compuestos. Los compuestos isotopicamente rotulados tienen estructuras representadas por las fórmulas dadas en la presente excepto que uno o más átomos son reemplazados por un átomo que tiene un número de masa o masa atómica seleccionada. Ejemplos de isótopos que pueden incorporarse en compuestos del invento incluyen isótopos de hidrógeno, carbono, nitrógeno, oxigeno, fósforo, flúor, y cloro, tales como ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectivamente. El invento incluye varios compuestos isotópicamente rotulados como se definió en la presente, por ejemplo aquellos en los cuales los isótopos radioactivos, tales como ^{3}H, ^{13}C, y ^{14}C , están presentes. Tales compuestos rotulados isotópicamente son útiles en estudios metabólicos (con ^{14}C), estudios cinéticos de reacción (con, por ejemplo ^{2}H o ^{3}H), técnicas de detección o visualización, tales como tomografía de emisión de positrones (PET) o tomografía computarizada de emisión de fotones individuales (SPECT) incluyen ensayo de distribución tisular de sustratos o fármacos, o tratamientos radioactivos de pacientes. En particular, un ^{18}F o un compuesto rotulado pueden ser particularmente deseados para estudios PET o SPECT. Los compuestos isotópicamente rotulados de este invento y profármacos de los mismos generalmente pueden prepararse mediante la realización de los procedimientos divulgados en los esquemas o en los ejemplos y preparaciones descritos a continuación al sustituir un reactivo isotopicamente rotulado fácilmente disponible por un reactivo no isotopicamente rotulado.

Además, la sustitución con isótopos más pesados, particularmente deuterio (es decir,., ^{2}H o D) pueden proporcionar ciertas ventajas terapéuticas que resultan a partir de la mayor

estabilidad metabólica, por ejemplo vida media *in vivo* aumentada o requerimientos de dosificación reducidos o una mejora en el índice terapéutico. Se entiende que deuterio en este contexto es considerado como un sustituyente de un compuesto de la Fórmula (I). La concentración de tal isótopo más pesado, específicamente deuterio, será definida por el factor de enriquecimiento isotópico. El término "factor de enriquecimiento isotópico" como se utiliza en la presente se refiere a la relación entre la abundancia isotópica y la abundancia natural de un isótopo específico. Si un sustituyente en un compuesto de este invento se denota deuterio, tal compuesto tiene un factor de enriquecimiento isotópico para cada átomo de deuterio designado de al menos 3500 (52.5% de incorporación de deuterio en cada átomo de deuterio designado), al menos 4000 (60% de incorporación de deuterio), al menos 4500 (67.5% de incorporación de deuterio), al menos 5000 (75% de incorporación de deuterio), al menos 5500 (82.5% de incorporación de deuterio), al menos 6000 (90% de incorporación de deuterio), al menos 6333.3 (95% de incorporación de deuterio), al menos 6466.7 (97% de incorporación de deuterio), al menos 6600 (99% de incorporación de deuterio), o al menos 6633.3 (99.5% de incorporación de deuterio).

En ciertas realizaciones, la deuteración selectiva de compuestos de la Fórmula (I) incluye aquellos compuestos en los cuales R^6 es deuterio. En ciertas realizaciones adicionales, los compuestos de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una sub fórmula de los mismos, ej. Un compuesto de cualquiera de las realizaciones uno a once listadas anteriormente pueden ser bis-deuterados en la posición 5 de bien sea el sistema de anillo de tetrahidropirido-piridina o tetrahidro-pirimidina.

Compuestos isotópicamente rotulados de la fórmula (I) pueden generalmente prepararse mediante técnicas convencionales conocidas por aquellos con experiencia en el estado de la técnica o mediante procesos análogos a aquellos descritos en los Ejemplos y Preparaciones anexos utilizando un reactivo isotópicamente rotulado apropiado en cambio del reactivo no rotulado previamente empleado.

Los compuestos de la presente invención pueden inherentemente o por diseño formar solvatos con solventes (incluyendo agua) Por lo tanto, se pretende que la invención contemple ambas formas solvatadas y no solvatadas. El término "solvato" se refiere a un complejo molecular de un compuesto de la presente invención (incluyendo sales de los mismos) con una o más moléculas solventes. Tales moléculas solventes son aquellas comúnmente utilizadas en el estado de la técnica farmacéutica, las cuales son conocidas por ser inocuas para el receptor, ej., agua, etanol, dimetilsulfóxido, acetona y otros solventes orgánicos comunes. El término “hidrato”se refiere a un complejo molecular que comprende un compuesto de la invención y agua. Solvatos farmacéuticamente aceptables según la invención incluyen aquellos en donde la cristalización del solvente puede sustituirse isotópicamente, ej. D20, d6-acetona, d6-DMSO.

Los compuestos de la invención, es decir, los compuestos de la fórmula (I) que contienen grupos capaces de actuar como donantes y/o aceptores de enlaces de hidrógeno pueden ser capaces de formar co- cristales con formadores de co- cristales adecuados. Estos co-cristales pueden prepararse de compuestos de la fórmula (I) mediante procedimientos de formación de co- cristales conocidos. Tales procedimientos incluyen trituración, calentamiento, co- sublimación, co- fundición, o poner en contacto en solución compuestos de la fórmula (I) con el formador de co- cristales bajo condiciones de cristalización y aislamiento de co- cristales así formados. Formadores de co- cristales apropiados incluyen aquellos descritos en WO 2004/078163. Por lo tanto la invención además proporciona co-cristales que comprenden un compuesto de la fórmula (I).

Como se utiliza en la presente, el término " vehículo farmacéuticamente aceptable" incluye cualquiera y todos los solventes, medios de dispersión, recubrimientos, surfactantes, antioxidantes, preservativos (ej., agentes antibacterianos , agentes antimicóticos), agentes isotónicos, agents retardantes de absorción, preservativos, fármacos, fármacos estabilizadores, aglutinantes, excipientes, agentes de desintegración, lubricantes, edulcorantes, agentes sapófiros, tintes, y similares y combinaciones de los mismos, como se conocerá por aquellos con experiencia en el estado de la técnica (ver, por ejemplo, *Remington's Pharmaceutical Sciences*, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Excepto en lo que respecta a cualquier vehículo convencional incompatible con el ingrediente activo, su uso es contemplado en las composiciones terapéuticas o farmacéuticas.

El término "una cantidad terapéuticamente eficaz" de un compuesto de la presente invención se refiere a una cantidad del compuesto de la presente invención que producirá la respuesta biológica o médica de un sujeto, por ejemplo, reducción o inhibición de una enzima o actividad de una proteína , o mejorar los síntomas, aliviar condiciones, retardar la progresión de la enfermedad, o prevenir una enfermedad, etc. En una realización no limitante, el término "una cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a un sujeto, es eficaz para (1) al menos parcialmente, aliviar, inhibir, prevenir y/o mejorar una condición o un trastorno, o una enfermedad o un proceso biológico (por ejemplo, regeneración y reproducción de tejidos) (i) mediada por actividad del receptor de C5a, o (ii) actividad asociada del receptor de C5a, o (iii) caracterizada por la actividad (normal o anormal) del sistema del complemento, o (2) reducir o inhibir la actividad de la actividad del receptor de C5a, o (3) reducir o inhibir la activación del sistema del complemento y en particular reducir o inhibir la interacción de C5a y su receptor.

En otra realización no limitante, el término "una cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a una

célula, tejido, o un material biológico no celular, o un medio, es eficaz, al menos parcialmente para reducir o inhibir la actividad del receptor de C5a y/o el sistema del complemento.

Como se utiliza en la presente, el término “sujeto” se refiere a un animal. Típicamente el animal es un mamífero. Un sujeto también se refiere a por ejemplo, primates (*ej.*, humanos), vacas, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones, peces, aves y similares. En ciertas realizaciones, el sujeto es un primate. En aún otras realizaciones, el sujeto es un humano.

Como se utiliza en la presente, el término "inhibir" o "inhibición" se refiere a la reducción o supresión de una condición, síntoma, o trastorno, o enfermedad dada, o una disminución significativa en la actividad inicial de una actividad o proceso biológico.

Como se utiliza en la presente, el término “tratar”, o "tratamiento" de cualquier enfermedad o trastorno se refiere en una realización, a mejorar la enfermedad o trastorno (es decir, retardar o detener o reducir el desarrollo de la enfermedad o al menos uno de los síntomas clínicos de la misma). En otra realización “tratar” o “tratamiento” se refiere a aliviar o mejorar al menos parámetro físico incluyendo aquellos los cuales pueden ser no discernibles por el paciente. En aún otra realización, “tratar” o “tratamiento” se refiere a modular la enfermedad o trastorno, bien sea físicamente, (*ej.*, estabilización de un síntoma discernible), fisiológicamente, (*ej.*, estabilización de un parámetro físico), o ambos. En aún otra realización, “tratar” o “tratamiento” se refiere a prevenir o retardar el comienzo o desarrollo o progresión de la enfermedad o trastorno.

Como se utiliza en la presente, un sujeto esta “en necesidad de” un tratamiento si tal sujeto se beneficia biológicamente, médicamente o mejora su calidad de vida a partir de tal tratamiento.

Como se utiliza en la presente, el término "un," "una," "el", “los” y términos similares se utilizan en el contexto del presente invento (especialmente en el contexto de las reivindicaciones) para cubrir formas tanto singulares como plurales a menos que se indique lo contrario o claramente sea contradicho por el contexto.

Todos los métodos descritos en la presente pueden realizarse en cualquier orden apropiado a menos que se indique lo contrario en la presente o de otra manera sea contradicho claramente por el contexto. El uso de cualquiera y todos los Ejemplos, o terminología de ejemplo (*ej.,* "tal como") proporcionada en la presente pretende solamente ilustrar mejor el invento y no implica limitación sobre el alcance del invento de otra manera reivindicado.

Cualquier átomo asimétrico (ej., carbono o similares) de los compuestos del presente invento puede presentarse en la configuración racémica o enantioméricamente enriquecida, por ejemplo la configuración (*R*)-, (*S*)- o (*R,S*)-. En ciertas realizaciones, cada átomo asimétrico tiene al menos 50% de exceso enantiomérico, al menos 60 % de exceso enantiomérico, al

menos 70 % de exceso enantiomérico, al menos 80 % de exceso enantiomérico, al menos 90 % de exceso enantiomérico, al menos 95 % de exceso enantiomérico, o al menos 99 % de exceso enantiomérico en la configuración (*R*)- o (*S*)-. Los sustituyentes en átomos con enlaces no saturados pueden, si es posible, estar presentes en la forma *cis*- (*Z*)- o *trans*- (*E*)-.

En consecuencia, como se utiliza en la presente un compuesto del presente invento puede estar en la forma de uno de los posibles isómeros, rotámeros, atropisómeros, tautómeros o mezclas de los mismos, por ejemplo, como isómeros geométricos sustancialmente puros (*cis* o *trans*), diastereomeros, isómeros ópticos (antípodos), racematos o mezclas de los mismos.

Cualquier mezcla resultante de isómeros puede ser separada sobre la base de las diferencias fisicoquímicas de los constituyentes, en isómeros geométricos u ópticos puros o sustancialmente puros, diastereoisómeros, racematos, por ejemplo, mediante cromatografía y/o cristalización fraccional.

Los racematos resultantes de los productos finales o intermedios pueden ser resueltos en los antípodos ópticos mediante métodos conocidos, *ej.*, mediante separación de las sales diastereoisoméricas de los mismos, obtenidas con un ácido o base óptimamente activos, y liberando el compuesto ácido o alcalino ópticamente activo. En particular, una fracción alcalina puede emplearse para separar los compuestos del presente invento en sus antípodos ópticos, *ej.*, mediante cristalización fraccional de una sal formada con un ácido ópticamente activo, *ej.*, ácido tartárico, ácido dibenzoil tartárico, ácido diacetil tartárico, ácido di-O,O'-*p*-toluoil tartárico, ácido mandélico, ácido málico o ácido canfor-10-sulfónico. Los productos racémicos también pueden separarse mediante cromatografía quiral, *ej.*, cromatografía líquida de alta presión (HPLC) utilizando un absorbente quiral.

Los compuestos del presente invento son obtenidos ya sea en la forma libre, como una sal de los mismos, ó como derivados profarmacológicos de los mismos.

Cuando ambos un grupo alcalino y un grupo ácido están presentes en la misma molécula, los compuestos del presente invento también pueden formar sales internas, ej.,, moléculas zwiteriónicas.

El presente invento también proporciona pro- fármacos de los compuestos del presente invento que se convierten *in vivo* en los compuestos del presente invento. Un pro- fármaco es un compuesto activo o inactivo que es modificado químicamente a través de acción fisiológica *in vivo*, tal como hidrólisis, metabolismo y similares, en un compuesto de este invento después de administración del profármaco a un sujeto. La conveniencia y técnicas involucradas en la preparación y utilización de pro-fármacos son bien conocidas por aquellos con experiencia en el estado de la técnica. Los profármacos pueden dividirse conceptualmente en dos categorías no exclusivas, profármacos bioprecursores o profármacos vehículos. Ver *The Practice of Medicinal Chemistry*, Capítulo. 31- 32 (Ed. Wermuth, Academic Press, San Diego, Calif.,

2001). Generalmente, los profármacos bioprecursores son compuestos, los cuales son inactivos o tienen baja actividad en comparación con el compuesto farmacológico activo correspondiente, que contiene uno o más grupos protectores y son convertidos en una forma activa mediante metabolismo o solvólosis. Tanto la forma farmacológica activa como cualquier producto metabólico liberado deben tener toxicidad aceptablemente baja.

Profármacos vehículos son compuestos farmacológicos que contienen una fracción transportadora, *ej.*, que mejoran la captación y/o distribución localizada a un sitio de acción. Deseablemente para tal pro fármaco vehículo, la conexión entre la fracción farmacológica y la fracción transportadora es un enlace covalente, el profármaco es inactivo o menos activo que el compuesto farmacológico, y cualquier fracción transportadora liberada es aceptablemente no tóxica. Para profármacos donde la fracción transportadora pretende mejorar la absorción, típicamente la liberación de la fracción transportadora debe ser rápida. En otros casos, es deseable utilizar una fracción que proporciona liberación lenta, *ej.*, ciertos polímeros u otras fracciones, tales como ciclodextrinas. Por ejemplo, los profármacos vehículos pueden utilizarse para mejorar una o más de las siguientes propiedades: lipofilicidad aumentada, duración aumentada de efectos farmacológicos, especificidad a sitio aumentada, toxicidad disminuida y reacciones adversas, y/o mejoría en la formulación farmacológica (*ej.*, estabilidad, solubilidad en agua, supresión de una propiedad organoléptica o fisioquímica no deseada). Por ejemplo, la lipofilicidad puede aumentarse mediante esterificación de (a) grupo hidroxilo con ácidos carboxílicos lipofílicos (ej., un ácido carboxílico que tiene al menos una fracción lipofílica), o (b) grupos ácidos carboxílicos con alcoholes lipofílicos (ej., un alcohol que tiene al menos una fracción lipofílica, por ejemplo alcoholes alifáticos).

Profármacos de ejemplo son, *ej.*, ésteres de ácidos carboxílicos libres y derivados S-acilo de tioles y derivados O- acilo de alcoholes o fenoles, en donde acilo tiene un significado como se definió en la presente. Profármacos apropiados son a menudo derivados de éster farmacéuticamente aceptables convertibles mediante solvólosis bajo condiciones fisiológicas en el ácido carboxílico precursor, *ej.*, ésteres de alquilo menor, ésteres de cicloalquilo, ésteres de alquenilo menor, ésteres de bencilo, ésteres de alquilo menor mono- o di- sustituidos, tales como los ω-(amino, mono- o di- alquilamino menor, carboxilo, alcoxicarbonilo menor)-alquilésteres menores, los α (alcanoiloxilo menor, alcoxicarbonilo menor o di-alquilaminocarbonilo menor)- alquilésteres menores, tal como el éster de pivaloiloximetilo y similares convencionalmente utilizados en el estado de la técnica. Además, se han enmascarado las aminas como derivados sustituidos de arilcarboniloximetilo los cuales son escindidos mediante esterasas *en vivo* liberando el fármaco libre y formaldehído (Bundgaard, *J. Med. Chem*. 2503 (1989)) Además, los fármacos que contienen un grupo NH ácido, tales como

imidazol, imida, indol y similares, han sido enmascarados con grupos N-aciloximetilo (Bundgaard, *Design de Profármacos*, Elsevier (1985)). Los grupos hidroxilo han sido enmascarados como ésteres y éteres. EP 039,051 (Sloan y Little) divulga profármacos de ácido hidroxámico con base Mannich, su preparación y uso.

Además, los compuestos del presente invento, incluyendo sus sales, también pueden obtenerse en la forma de sus hidratos, o incluir otros solvatos utilizados para su cristalización.

Dentro del alcance de este texto, solamente un grupo fácilmente removible que no es un constituyente del producto final deseado particular de los compuestos del presente invento se designa un "grupo protector", a menos que el contexto indique lo contrario. La protección de grupos funcionales mediante tales protectores de grupo, los protectores de grupo mismos, y sus reacciones de escisión se describen por ejemplo en trabajos de referencia estándar, tal como J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London y New York 1973, en T. W. Greene y P. G. M. Wuts, "Protective Groups in Organic Synthesis", Tercera edición, Wiley, New York 1999, en "Los Péptidos "; Volume 3 (editors: E. Gross y J. Meienhofer), Academic Press, London y New York 1981, en "Methoden der organischen Chemie" (Métodos de Química Orgánica), Houben Weyl, 4th edición, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, en H.- D. Jakubke y H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Aminoacidos, Péptidos, Proteínas), Verlag Chemie, Weinheim, Deerfield Beach, y Basel 1982, y en Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Quimica de Carbohidratos: Monosacaridos y Derivados), Georg Thieme Verlag, Stuttgart 1974. Una característica de protectores de grupo es que estos se pueden retirar de manera fácil (es decir sin la ocurrencia de reacciones secundarias indeseadas) por ejemplo mediante solvólisis, reducción, fotolisis o alternativamente bajo condiciones fisiológicas (*ej.,* mediante escisión enzimática).

Sales de compuestos del presente invento que tienen al menos un grupo formador de sal pueden prepararse en una forma conocida por aquellos con experiencia en el estado de la técnica. Por ejemplo, sales de compuestos del presente invento que tienen grupos ácidos pueden formarse, por ejemplo, al tratar los compuestos con compuestos metálicos, tal como sales de metales alcalinos de ácidos carboxílicos orgánicos apropiados, ej., la sal de sodio de ácido 2-etilhexanóico, con compuestos orgánicos de metales alcalinos o alcalinotérreos, tal como los hidróxidos correspondientes, carbonatos o carbonatos de hidrógeno, tales como hidróxido de sodio o potasio, carbonato o carbonato de hidrógeno, con compuestos de calcio correspondientes o con amoniaco o una amina orgánica apropiada, cantidades estoiquiométricas o solamente un pequeño exceso del agente formador de sales preferiblemente siendo utilizado. Las sales de adición ácida de los compuestos del presente invento son obtenidas en forma habitual, *ej.,* al tratar los compuestos con un ácido o un reactivo de intercambio aniónico

apropiado. Las sales internas de compuestos de la presente invención que contienen grupos formadores de sales ácidas y básicas, *ej.,* un grupo carboxilo libre y un grupo amino libre, pueden formarse, *ej.,* mediante la neutralización de sales, tales como sales de adición ácida, hacia el punto isoeléctrico, *ej.,* con bases débiles, o mediante tratamiento con intercambiadores de iones.

Las sales pueden convertirse en los compuestos libres según métodos conocidos por aquellos con experiencia en el estado de la técnica. Las sales metálicas y de amonio pueden convertirse, por ejemplo, mediante tratamiento con ácidos apropiados, y sales de adición ácida, por ejemplo, mediante tratamiento con un agente alcalino apropiado.

Las mezclas de isoméros obtenibles según la invención pueden separarse en una forma conocida por aquellos con experiencia en el estado de la técnica en los isómeros individuales; los diastereoisómeros pueden separarse, por ejemplo, al particionar entre mezclas solventes polifásicas, recristalización y/o separación cromatográfica, por ejemplo sobre gel de sílice o por *ej.,* cromatografía líquida de mediana presión sobre una columna de fase invertida, y los racematos pueden separarse, por ejemplo, mediante la formación de sales con reactivos formadores de sales ópticamente puras y separación de la mezcla de diastereoisómeros así obtenible, por ejemplo por medio de cristalización fraccional, o mediante cromatografía sobre materiales de columna ópticamente activa.

Intermedios y productos finales pueden purificarse según métodos estándar, ej., utilizando métodos cromatográficos, métodos de distribución, (re)- cristalización, y similares.

Lo siguiente aplica en general a todos los procesos mencionados en la presente antes y de aquí en adelante.

Todos los pasos de proceso antes mencionados pueden realizarse bajo condiciones de reacción que son conocidas por aquellos con experiencia en el estado de la técnica, incluyendo aquellas específicamente mencionadas, en ausencia o, comúnmente, en presencia de solventes o diluyentes, incluyendo, por ejemplo, solventes o diluyentes que son inertes a los reactivos utilizados y disolverlos, en ausencia o presencia de catalizadores, agentes de condensación o neutrolizadores, por ejemplo intercambiadores de iones, tales como intercambiadores de cationes, *ej.,* en la forma H+, dependiendo de la naturaleza de la reacción y/o de los reactivos a temperatura reducida, normal o elevada, por ejemplo en un rango de temperatura dentro - 100 ºC y 190 ºC aproximadamente, incluyendo, por ejemplo, desde - 80 ºC a 150 ºC aproximadamente, por ejemplo entre - 80 y - 60 ºC aproximadamente, a temperatura ambiente, desde - 20 a 40 ºC aproximadamente o a temperatura de reflujo, bajo presión atmosférica o en un recipiente cerrado, donde sea apropiado bajo presión, y/o en una atmósfera inerte, por ejemplo bajo una atmósfera de argón o nitrógeno.

En todas las etapas de las reacciones, las mezclas de isoméros que se forman pueden separarse en los isómeros individuales, por ejemplo diastereoisómeros o enantiomeros, o en cualquiera de las mezclas deseadas de isoméros, por ejemplo racematos o mezclas de diastereoisómeros, por ejemplo de manera análoga a los métodos descritos bajo "pasos de proceso adicionales".

Los solventes desde los cuales estos solventes que son apropiados para cualquier reacción particular pueden seleccionarse incluyen aquellos específicamente mencionados o, por ejemplo, agua, ésteres, tales como alquilo inferior- alcanoatos inferiores, por ejemplo acetato de etilo, éteres, tal como éteres alifáticos, por ejemplo éter dietílico, o éteres cíclicos, por ejemplo tetrahidrofurano o dioxano, hidrocarburos aromáticos líquidos, tales como benceno o tolueno, alcoholes, tales como metanol, etanol o 1- o 2- propanol, nitrilos, tal como acetonitrilos, hidrocarburos halogenados, tales como cloruro de metileno o cloroformo, amidas ácidas, tales como dimetilformamida o acetamida de dimetilo, bases, tales como bases de nitrógeno heterocíclico, por ejemplo piridina o *N*- metilpirrolidin- 2- ona, anhidridos de ácido carboxílicos, tales como anhidridos de ácido alcanoico inferior, por ejemplo anhídrido acético, hidrocarburos cíclicos, lineales o ramificados, tales como ciclohexano, hexano o isopentano, meticiclohexano, o mezclas de estos solventes, por ejemplo soluciones acuosas, a menos que se indique lo contrario en la descripción de los procesos. Tales mezclas solventes también pueden utilizarse en tratamientos finales, por ejemplo mediante cromatografía o particionamiento.

Los compuestos, incluyendo sus sales, también pueden obtenerse en la forma de hidratos, o sus cristales pueden, por ejemplo, incluir el solvente utilizado para cristalización. Diferentes formas cristalinas pueden estar presentes.

La invención también se relaciona con aquellas formas del proceso en las cuales un compuesto obtenible como un intermedio cualquier etapa del proceso se utiliza como material de inicio y se realizan los restantes pasos del proceso, o en los cuales un material de inicio se forma bajo las condiciones de reacción o se utiliza en la forma de un derivado, por ejemplo en una forma protegida o en la forma de una sal, o un compuesto obtenible por el proceso según el invento se produce bajo las condiciones de proceso y se procesa adicionalmente in situ.

En otro aspecto, el presente invento proporciona una composición farmacéutica que comprende a compuesto del presente invento y un vehículo farmacéuticamente aceptable. La composición farmacéutica puede formularse para vías particulares de administración tales como administración oral, administración parenteral, y administración oftálmica, etc. Además, las composiciones farmacéuticas de la presente invención pueden integrarse en una forma sólida (incluyendo sin limitación cápsulas, tabletas, píldoras, gránulos, polvos o supositorios), o en una forma líquida (incluyendo sin limitación soluciones, suspensiones o emulsiones, cada uno de los cuales puede ser apropiado para administración oftálmica). Las composiciones

farmacéuticas pueden someterse a operaciones farmacéuticas convencionales tales como esterilización y/o pueden contener diluyentes inertes convencionales, agentes lubricantes, o agentes amortiguadores, así como también adyuvantes, tales como preservativos, estabilizadores, agentes humectantes, emulsificadores y buffers, etc.

Típicamente, las composiciones farmacéuticas son comprimidos o cápsulas de gelatina que comprenden el ingrediente activo junto con

a) diluyentes, *ej*., lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa y/o glicina;

b) lubricantes, ej., silicio, talco, ácido estearico, su sal de magnesio o calcio y/o glicol de polietileno; para tabletas también

c) aglutinantes, ej, silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa de sodio y/o polivinilpirrolidona; si se desea

d) desintegrantes, ej., almidones, agar, ácido algínico o su sal de sodio, o mezclas efervescentes; y/o

e) absorbentes, colorantes, agentes sapófiros y edulcorantes.

Las tabletas pueden tener revestimiento de película o revestimiento entérico según métodos conocidos en el estado de la técnica.

Composiciones adecuadas para administración oral incluyen una cantidad efectiva de un compuesto del presente invento en la forma de comprimidos, grageas, suspensiones acuosas o aceitosas, polvos o gránulos dispersables, emulsión, cápsulas duras o blandas, o jarabes o elixires. Las composiciones para uso oral son preparadas según cualquier método conocido en el estado de la técnica para la fabricación de composiciones farmacéuticas y tales composiciones pueden contener uno o más agentes seleccionados del grupo que consta de agentes endulzantes, agentes saborizantes, agentes colorantes y agentes preservativos con el objeto de proporcionar preparaciones farmacéuticamente elegantes y de sabor agradable. Las tabletas pueden contener el ingrediente activo en mezcla con excipientes farmacéuticamente aceptables no tóxicos los cuales son apropiados para la fabricación de tabletas. Estos excipientes son, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes granulantes y desintegrantes, por ejemplo, almidón de maíz, o ácido algínico; agentes aglomerantes, por ejemplo, almidón, gelatina o acacia; y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o talco. Las tabletas son revestidas o no revestidas mediante técnicas conocidas para retardar desintegración y absorción en el tracto gastrointestinal y proporcionar así una acción sostenida durante un periodo más largo de tiempo. Por ejemplo, puede utilizarse un material retardante tal como monoestearato de glicerilo o diestearato de glicerilo. Las formulaciones para uso oral

pueden presentarse como cápsulas de gelatina dura en donde el ingrediente activo es mezclado con un diluyentes sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolina, o como cápsulas de gelatina suave en donde el ingrediente activo es mezclado con agua o un medio de aceite, por ejemplo, aceite de coco, parafina líquida o aceite de oliva.

Ciertas composiciones inyectables son soluciones o suspensiones acuosas isotónicas, y los supositorios son ventajosamente preparados a partir de emulsiones o suspensiones grasas. Dichas composiciones pueden ser esterilizadas y/o contener adyuvantes, tales como agentes preservantes, estabilizantes, humectantes o emulsificantes, promotores de solución, sales para regular la presión osmótica y/o buffers. Además, también pueden contener otras sustancias terapéuticamente valiosas. Dichas composiciones son preparadas según métodos convencionales de mezclado, granulación o revestimiento, respectivamente, y contienen 0.1-75% aproximadamente, o contienen 1-50% aproximadamente, del ingrediente activo.

Composiciones apropiadas para aplicación transdérmica incluyen una cantidad efectiva de un compuesto del invento con un vehículo apropiado. Vehículos apropiados para liberación transdérmica incluyen solvatos farmacológicamente aceptables absorbentes para asistir en el pasaje a través de la piel del huésped. Por ejemplo, los dispositivos transdérmicos están en la forma de un vendaje que comprende un miembro de soporte, un depósito que contiene el compuesto opcionalmente con vehículos, opcionalmente una barrera controladora de tasa para liberar el compuesto de la piel del huésped a una tasa controlada y predeterminada durante un periodo de tiempo prolongado, y medios para asegurar el dispositivo a la piel.

Composiciones apropiadas para aplicación tópica, *ej.*, a la piel y ojos, incluyen soluciones acuosas, suspensiones, ungüentos, cremas, geles o formulaciones en atomizador, *ej.*, para liberación mediante aerosol o similares. Tales sistemas de liberación tópica en particular serán apropiados para aplicación oftálmica, ej., para el tratamiento de enfermedades oculares, ej., para uso terapéutico o profiláctico en el tratamiento de degeneración macular relacionada con la edad y otros trastornos oftálmicos mediados por complemento. Estos pueden contener solubilizantes, estabilizadores, agentes mejoradotes de tonicidad, buffer y preservativos.

Como se utiliza en la presente una aplicación tópica también se refiere a una inhalación o a una aplicación intranasal. Estas pueden ser convenientemente liberadas en la forma de un polvo seco (bien sea solo, como una mezcla, por ejemplo una mezcla seca con lactosa, o como partículas de componentes mixtos, por ejemplo con fosfolípidos) a partir de un inhalador de polvo seco o una presentación de aerosol a partir de un recipiente presurizado, bomba, atomizador, atomizador o nebulizador, con o sin el uso de un propelente apropiado.

Formas de dosificación para la administración tópica o transdérmica de un compuesto de este invento incluyen polvos, aerosoles, ungüentos, pastas, cremas, lociones, geles, soluciones, parches e inhaladores. El compuesto activo puede mezclarse bajo condiciones

estériles con un vehículo farmacéuticamente aceptable, y con cualquiera de los preservativos, buffers, o propulsores que puedan ser deseables.

Los ungüentos, pastas, cremas y geles pueden contener, además de un compuesto activo de este invento, excipientes, tales como grasas animales y vegetales, aceites, ceras, parafinas, almidón, tragacanto, derivados de celulosa, glicoles de polietileno, siliconas, bentonitas, ácido silícico, talco y óxido de zinc, o mezclas de los mismos.

Polvos y aerosoles pueden contener, además de un compuesto de este invento, excipientes tales como lactosa, talco, ácido silícico, hidróxido de aluminio, silicatos de calcio y polvo de poliamida, o mezclas de estas sustancias. Los aerosoles pueden contener adicionalmente propulsores habituales, tales como clorofluorohidrocarburos e hidrocarburos no sustituidos volátiles, tales como butano y propano.

Los parches transdérmicos tienen la ventaja agregada de proporcionar liberación controlada de un compuesto del presente invento al cuerpo. Tales formas de dosificación pueden prepararse al disolver o dispersar el compuesto en el medio apropiado. También pueden utilizarse mejoradores de absorción para aumentar el flujo del compuesto a través de la piel. La tasa de tal flujo puede controlarse mediante cualquiera proporcionar una membrana controladora de tasa o dispersar el compuesto activo en una matriz o gel polimérico.

También se contemplan dentro del alcance de este invento las formulaciones oftalmicas, ungüentos oculares, polvos, soluciones y similares.

El presente invento además proporciona composiciones farmacéuticas anhídridas y formas de dosificación que comprenden los compuestos del presente invento como ingredientes activos, puesto que el agua puede facilitar la degradación de ciertos compuestos.

Composiciones farmacéuticas anhídridas y formas de dosificación del invento pueden prepararse utilizando ingredientes anhidros o que contiene baja humedad y condiciones de baja humedad. Una composición farmacéutica anhídrida puede prepararse y almacenarse tal que su naturaleza anhídrida sea mantenida. Por consiguiente, composiciones anhídridas son empacadas utilizando materiales conocidos para prevenir exposición al agua tal que éstas puedan incluirse en kits de formulación apropiados. Ejemplos de empaques apropiados incluyen, pero no están limitados a aluminios herméticamente sellados, plásticos, recipientes de dosis unitaria (ej., viales), empaques blister, y empaques de tira.

El invento además proporciona composiciones farmacéuticas y formas de dosificación que comprenden uno o más agentes que reducen la tasa mediante la cual el compuesto del presente invento como un ingrediente activo se descompondrá. Tales agentes, los cuales se conocen en la presente como "estabilizadores," incluyen, pero no están limitados a, antioxidantes tales como ácido ascórbico, buffers de pH, o buffers de sales, etc.

Usos profilácticos y Terapéuticos

Los compuestos de la Fórmula I en forma libre o en forma de sal farmacéuticamente aceptable, exhiben valiosas propiedades farmacológicas, por ejemplo propiedades moduladores del receptor de C5a, propiedades moduladores de la vía del complemento y modulación del sistema del complemento, por ejemplo, como se indica en pruebas in vitro e in vivo como se proporciona en las siguientes secciones y por lo tanto se indican para terapia.

La presente invención proporciona métodos para tratar una enfermedad o trastorno asociado con la actividad aumentada del complemento mediante la administración a un sujeto que lo necesita una cantidad eficaz de los compuestos de la Fórmula (I) de la invención. En ciertos aspectos, se proporcionan métodos para el tratamiento de enfermedades asociadas con una actividad aumentada del bucle de amplificación C3 de la vía del complemento. En ciertas realizaciones, se proporcionan métodos de tratamiento o prevención de enfermedades mediadas por complemento, en los cuales la activación del complemento es inducida por interacciones antígeno-anticuerpo, por un componente de una enfermedad autoinmune, o por daño isquémico.

En una realización específica, la presente invención proporciona un método de tratamiento o prevención de degeneración macular relacionada con la edad (AMD) mediante la administración a un sujeto que lo necesita, una cantidad eficaz del compuesto de Fórmula (I) de la invención. En ciertas realizaciones, los pacientes que se encuentran actualmente asintomáticos, pero están en riesgo de desarrollar un trastorno relacionado con degeneración macular sintomática son apropiados para la administración con un compuesto de la invención. Los métodos de tratamiento o prevención de AMD incluyen, pero no se limitan a métodos de tratamiento o prevención de uno o más síntomas o aspectos de AMD seleccionados a partir de la formación de drusa ocular, inflamación ocular, o inflamación de tejido ocular, pérdida de células fotoreceptoras, pérdida de la visión (incluyendo pérdida de la agudeza visual o del campo visual), neovascularización (incluyendo CNV), desprendimiento de la retina, degeneración de los fotoreceptores, degeneración RPE, degeneración de la retina, degeneración corioretiniana, degeneración de los conos, disfunción de la retina, daño en la retina en respuesta a exposición a la luz, daño de la membrana de Bruch, y/o pérdida de función EPR.

El compuesto de la Fórmula (I) de la invención puede utilizarse, entre otras cosas, para prevenir la aparición de AMD, para prevenir la progresión de AMD precoz a formas avanzadas de AMD incluyendo AMD neovascular o atrofia geográfica, para retardar y/o prevenir la progresión de la atrofia geográfica, para tratar o prevenir el edema macular por AMD u otras condiciones (tales como retinopatía diabética, uveítis o trauma pos-quirúrgico o no quirúrgico), para prevenir o reducir la pérdida de la visión por AMD, y para mejorar la visión perdida debido a AMD precoz pre-existente o avanzada. También se puede utilizar en combinación con terapias anti-VEGF para el tratamiento de pacientes con AMD neovascular o para la prevención

de AMD neovascular. La presente invención proporciona además métodos para tratar una enfermedad o trastorno relacionado con el complemento mediante la administración a un sujeto que lo necesita una cantidad eficaz del compuesto (s) de la invención, en donde dicha enfermedad o trastorno se selecciona entre uveítis, degeneración macular del adulto, retinopatía diabética, retinitis pigmentosa, edema macular, uveítis de Behcet, coroiditis multifocal, síndrome de Vogt-Koyanagi-Harada, uveítis intermedia, retinocoroiditis en perdigonada, oftalmía simpatética, penfigoide cicatricial ocular, pénfigo ocular, neuropatía óptica isquémica no arterítica, inflamación post-operatoria, y oclusión venosa de la retina.

En algunas realizaciones, la presente invención proporciona métodos para tratar una enfermedad o trastorno relacionado con el complemento mediante la administración a un sujeto que lo necesita una cantidad eficaz de los compuestos de la invención. Ejemplos de enfermedades o trastornos relacionados con complemento que se conocen incluyen: trastornos neurológicos, esclerosis múltiple, accidente cerebro vascular, síndrome de Guillain Barré, lesión cerebral traumática, enfermedad de Parkinson, trastornos de la activación inadecuada o indeseable del complemento, complicaciones en hemodiálisis, rechazo hiperagudo del aloinjertos, rechazo de xenoinjertos, toxicidad inducida por la interleucina-2 durante terapia con IL-2, enfermedades inflamatorias, inflamación de enfermedades autoinmunes, enfermedad de Crohn, síndrome de distrés respiratorio del adulto, lesión térmica incluyendo quemaduras o congelación, miocarditis, condiciones de reperfusión post-isquémica, infarto de miocardio, angioplastia con balón, síndrome pos-perfusión en bypass renal o bypass cardiopulmonar, aterosclerosis, hemodiálisis, isquemia renal, reperfusión de la arteria mesentérica después de reconstrucción aórtica, enfermedad infecciosa o la sepsis, trastornos complejos inmunes y enfermedades autoinmunes, artritis reumatoide, lupus eritematoso sistémico (LES), nefritis por lupus, nefritis proliferativa, fibrosis hepática , anemia hemolítica, miastenia gravis, regeneración de tejidos y regeneración neuronal. Además, otras enfermedades conocidas relacionadas con complemento son las enfermedades y trastornos pulmonares, tales como disnea, hemoptisis, SDRA, asma, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, embolia pulmonar e infartos, neumonía, enfermedades originadas por polvo fibrogénico, polvos inertes y minerales (por ejemplo, silicio, polvo de carbón, berilio, y asbesto), fibrosis pulmonar, enfermedades orgánicas por polvo, daño químico (debido a gases irritantes y productos químicos, por ejemplo, cloro, fosgeno, dióxido de azufre, sulfuro de hidrógeno, dióxido de nitrógeno, amoníaco y ácido clorhídrico), lesión por humo, lesión térmica (por ejemplo, quemadura, congelación), asma, alergia, broncoconstricción, neumonitis por hipersensibilidad, enfermedades parasitarias, síndrome de Goodpasture, vasculitis pulmonar, vasculitis pauci-inmune, inflamación asociada de complejo inmune, uveítis (incluida la enfermedad de Behçet y otros sub-tipos de uveítis), síndrome antifosfolípido.

En una realización específica, la presente invención proporciona métodos para tratar una enfermedad o trastorno relacionado con el complemento mediante la administración a un sujeto que lo necesita, de una cantidad eficaz de los compuestos de la invención, en donde dicha enfermedad o trastorno es asma, artritis (por ejemplo, artritis reumatoide), enfermedad cardiaca autoinmune, esclerosis múltiple, enfermedad inflamatoria intestinal, lesiones por isquemia-reperfusión, síndrome de Barraquer-Simons, hemodiálisis, lupus sistémico, lupus eritematoso, psoriasis, esclerosis múltiple, trasplante, enfermedades del sistema nervioso central como la enfermedad de Alzheimer y otras enfermedades neurodegenerativas, síndrome urémico hemolítico atípico (aHUS), glomerulonefritis (incluyendo glomerulonefritis proliferativa de membrana), enfermedades cutáneas ampollosas (incluyendo penfigoide ampolloso, pénfigo, y epidermólisis bullosa), penfigoide cicatrical ocular o MPGN II.

En una realización específica, la presente invención proporciona métodos de tratamiento de glomerulonefritis mediante la administración a un sujeto que lo necesita, de una cantidad eficaz de una composición que comprende un compuesto de la presente invención. Los síntomas de la glomerulonefritis incluyen, pero no se limitan a, proteinuria, tasa de filtración glomerular reducida (TFG); cambios de electrolitos séricos, incluyendo azotemia (uremia, excesivo nitrógeno ureico en sangre - BUN) y retención de sal, dando lugar a retención de agua resultando en hipertensión y edema; hematuria y sedimentos urinarios anormales, incluyendo cilindros eritrocitarios, hipoalbuminemia, hiperlipidemia, y lipiduria. En una realización específica, la presente invención proporciona métodos de tratamiento de hemoglobinuria paroxística nocturna (HPN) mediante la administración a un sujeto que lo necesita, de una cantidad eficaz de una composición que comprende un compuesto de la presente invención, con o sin administración concomitante de un inhibidor C5 del complemento o inhibidor C5 de convertasa, tal como Soliris.

En una realización específica, la presente invención proporciona métodos para reducir la disfunción de los sistemas inmunes y/o hemostáticos asociados con la circulación extracorpórea mediante la administración a un sujeto que lo necesita de una cantidad eficaz de una composición que comprende un compuesto de la presente invención. Los compuestos de la presente invención se pueden utilizar en cualquier procedimiento que implica circular la sangre del paciente desde un vaso sanguíneo del paciente, a través de un conducto, y de vuelta a un vaso sanguíneo del paciente, el conducto con una superficie luminal que comprende un material capaz de causar al menos uno entre activación del complemento, activación de las plaquetas, activación de leucocitos, o adhesión de plaquetas-leucocitos. Tales procedimientos incluyen, pero no se limitan a, todas las formas de ECC, así como procedimientos que implican la introducción de un órgano, tejido o vaso artificial o extraño, en el circuito sanguineo de un paciente. Más particularmente, tales procedimientos incluyen, pero no se limitan a,

procedimientos de trasplante, incluyendo procedimientos de trasplante de riñón, hígado, pulmón o corazón y procedimientos de trasplante de células de islotes pancreáticos.

En otras realizaciones, los compuestos de la invención son adecuados para utilizar en el tratamiento de enfermedades y trastornos asociados con el metabolismo de ácidos grasos, incluyendo la obesidad y otros trastornos metabólicos.

En otra realización, los compuestos de la invención pueden utilizarse en ampollas de sangre, equipos de diagnóstico y otros equipos utilizados en la recolección y el muestreo de sangre. El uso de los compuestos de la invención en tales equipos de diagnóstico pueden inhibir la activación ex vivo de la vía del complemento asociada con el muestreo de sangre.

La composición farmacéutica o combinación de la presente invención puede ser en dosificación unitaria de 1-1000 mg aproximadamente de ingrediente activo para un sujeto de 50-70 kg aproximadamente, o 1-500 mg aproximadamente o 1-250 mg aproximadamente o 1-150 mg aproximadamente o 0.5-100 mg aproximadamente, o 1-50 mg aproximadamente de ingredientes activos. La dosificación terapéuticamente efectiva de un compuesto, la composición farmacéutica, o las combinaciones de los mismos, es dependiente de la especie del sujeto, el peso corporal, edad y condición individual, el trastorno o enfermedad o la severidad de la misma. Un médico, médico clínico o veterinario con experiencia común puede fácilmente determinar la cantidad efectiva de cada uno de los ingredientes activos necesarios para prevenir, tratar o inhibir el progreso del trastorno o enfermedad.

Las propiedades de dosificación antes citadas son demostrables en pruebas *in vitro* y *in vivo* utilizando de manera ventajosa mamíferos, *ej.*, ratones, ratas, perros, monos u órganos aislados, tejidos y preparaciones de los mismos. Los compuestos del presente invento pueden aplicarse *in vitro* en la forma de soluciones, *ej.*, soluciones acuosas, e *in vivo* bien sea de manera entérica, parenteral, de manera ventajosa, intravenosamente, *ej.*, como una suspensión o en solución acuosa. La dosificación *in vitro* puede estar en el rango entre concentraciones 10^{-3} molar y 10^{-9} molar aproximadamente. Una cantidad terapéuticamente efectiva *in vivo* puede estar en el rango dependiendo de la vía de administración, entre 0.1 y 500 mg/kg aproximadamente, o entre 1 y 100 mg/kg aproximadamente.

La actividad de un compuesto según el presente invento puede evaluarse mediante los siguientes métodos *in vitro & in vivo*.

Los compuestos del presente invento pueden administrarse bien sea simultáneamente con, o antes de o después de, uno o más agentes terapéuticos. Los compuestos del presente invento pueden administrarse de manera separada, mediante la misma o diferente vía de administración, o juntos en la misma composición farmacéutica como los otros agentes.

En una realización, la invención proporciona un producto que comprende un compuesto de la fórmula (I) y al menos otro agente terapéutico como una preparación combinada para uso

simultaneo, separado o secuencial en terapia. En una realización, la terapia es el tratamiento de una enfermedad o condición mediada la activación del complemento. Los productos proporcionados como una preparación combinada incluyen una composición que comprende el compuesto de la fómrula (I) y los otros agentes terapéuticos en forma separada, *ej.* en la forma de un kit.

En una realización, el invento proporciona una composición farmacéutica que comprende un compuesto de la fórmula (I) y otros agentes terapéuticos. Opcionalmente, la composición farmacéutica puede comprender un excipiente farmacéuticamente aceptable, como se describió anteriormente.

En una realización, el invento proporciona un kit que comprende dos o más composiciones farmacéuticas separadas, al menos una de las cuales contiene un compuesto de la fórmula (I). En una realización, el kit comprende medios para retener de manera separada dichas composiciones, tales como un recipiente, botella dividida, o empaque dividido en aluminio. Un ejemplo de tal kit es paquete blister, como el que típicamente se utiliza para empacar tabletas, cápsulas y similares.

El kit del invento puede utilizarse para administrar diferentes formas de dosificación, por ejemplo, oral y parenteral, para administrar las composiciones separadas a diferentes intervalos de dosificación, o para titular las diferentes composiciones entre sí. Para ayudar en el cumplimiento terapéutico, el kit del invento típicamente comprende pautas para administración.

En las terapias de combinación del invento, el compuesto del invento y el otro agente terapéutico pueden fabricarse y/o formularse por los mismos o diferentes fabricantes. Además, el compuesto del invento y el otro terapéutico serán llevados juntos en una terapia de combinación: (i) antes de entregar el producto de combinación a los médicos (*ej.* en el caso de un kit que comprende el compuesto del invento y el otro agente terapéutico); (ii) por los médicos mismos (o bajo la pauta del médico) poco antes de administración; (iii) en los pacientes mismos, *ej.* durante administración secuencial del compuesto del invento y el otro agente terapéutico.

Por consiguiente, la invención proporciona el uso de un compuesto de la fórmula (I) para tratar una enfermedad o condición mediada por el sistema del complemento, en donde el medicamento es preparado para administración con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico para el tratamiento de una enfermedad o condición mediada por el sistema del complemento, en donde el medicamento se administra con un compuesto de la fórmula (I).

La invención también proporciona un compuesto de la fórmula (I) para uso en un método de tratamiento de una enfermedad o condición mediada por el sistema del complemento, en donde el compuesto de la fórmula (I) se prepara para su administración con

otro agente terapéutico. La invención también proporciona otro agente terapéutico para su uso en un método de tratamiento de una enfermedad o condición mediada por el sistema del complemento y/o, en el que el otro agente terapéutico se prepara para su administración con un compuesto de la fórmula (I). La invención también proporciona un compuesto de la fórmula (I) para utilizar en un método de tratamiento de una enfermedad o condición mediada por el sistema del complemento y/o la inflamación mediada por C5a, en donde el compuesto de la fórmula (I) se administra con otro agente terapéutico. La invención también proporciona otro agente terapéutico para su uso en un método de tratamiento de una enfermedad o condición mediada por el sistema del complementoy/o la inflamación mediada por C5a, en el que el otro agente terapéutico se administra con un compuesto de la fórmula (I).

La invención también proporciona el uso de un compuesto de la fórmula (I) para el tratamiento de una enfermedad o condición mediada por el sistema del complementoy/o inflamación mediada por C5a, en el que el paciente ha sido tratado previamente (por ejemplo, dentro de 24 horas) con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico para el tratamiento de una enfermedad o condición mediada por el sistema del complemento y/o la inflamación mediada por C5a en el cual el paciente ha sido tratado previamente (por ejemplo, dentro de 24 horas) con un compuesto de la fórmula (I).

Las composiciones farmacéuticas se pueden administrar solas o en combinación con otras moléculas conocidas por tener un efecto beneficioso en la fijación retinal o tejido retinal dañado, incluyendo moléculas capaces de reparar y regenerar tejidos y/o inhibir la inflamación. Ejemplos de cofactores útiles incluyen agentes anti-VEGF (tales como un anticuerpo o FAB contra el VEGF, por ejemplo, Lucentis o Avastin), factor de crecimiento de fibroblastos básico (bFGF), factor neurotrófico ciliar (CNTF), axoquina (una muteína de CNTF), factor inhibidor de leucemia (LIF), neurotrofina 3 (NT-3), neurotrofina-4 (NT-4), factor de crecimiento nervioso (NGF), factor de crecimiento tipo insulina II, prostaglandina E2, factor de supervivencia 30 kD, taurina y vitamina A. Otros cofactores útiles incluyen cofactores para el alivio de síntomas, incluyendo antisépticos, antibióticos, agentes antivirales y antimicóticos y analgésicos y anestésicos. Los agentes adecuados para el tratamiento de combinación con los compuestos de la invención incluyen agentes conocidos en el estado de la técnica que son capaces de modular las actividades de los componentes del complemento.

Un régimen de terapia de combinación puede ser aditivo, o puede producir resultados sinérgicos (por ejemplo, reducciones de la actividad de la vía del complemento más de lo esperado para el uso combinado de los dos agentes). En algunas realizaciones, la presente invención proporciona una terapia de combinación para prevenir y/o tratar AMD u otra enfermedad ocular relacionada con complemento como se describió anteriormente con un

compuesto de la invención y un anti-angiogénico, tal como agente anti-VEGF (incluyendo Lucentis y Avastin) o la terapia fotodinámica (tal como verteporfina).

En algunas realizaciones, la presente invención proporciona una terapia de combinación para prevenir y/o tratar la enfermedad autoinmune, como se ha descrito anteriormente, con un compuesto de la invención y un agente de modulación de células B o T (por ejemplo ciclosporina o análogos de la misma, rapamicina, RAD001 o análogos de los mismos, y similares). En particular, para esclerosis múltiple, terapia puede incluir la combinación de un compuesto de la invención y un segundo agente MS seleccionado a partir de fingolimod, cladribina, tysabri, laquinimod, rebif, avonex y similares.

En una realización, la invención proporciona un método de modulación de la actividad del sistema del complemento en un sujeto, en donde el método comprende administrar al sujeto una cantidad terapéuticamente efectiva del compuesto según la definición de la fórmula (I). La invención proporciona además métodos de modulación de la actividad del sistema del complemento en un sujeto mediante la modulación de la actividad del receptor de C5a, en donde el método comprende administrar al sujeto una cantidad terapéuticamente efectiva del compuesto según la definición de la fórmula (I).

En una realización, la invención proporciona un compuesto según la definición de las fórmulas (I), (Ia), (VII) o cualquier sub fórmula de las mismas, para su uso como un medicamento.

En una realización, la invención proporciona el uso de un compuesto según la definición de la fórmula (I), (Ia), (VII) o cualquier sub fórmula de las mismas, para el tratamiento de un trastorno o enfermedad en un sujeto mediada por la activación del complemento. En particular, la invención proporciona el uso de un compuesto según la definición de las fórmulas (I), (Ia), (VII) o cualquier sub fórmula de las mismas, para el tratamiento de un trastorno o enfermedad mediada por la activación del sistema del complemento.

En una realización, la invención proporciona el uso de un compuesto según la definición de la fórmula (I), (Ia), en la fabricación de un medicamento para el tratamiento de un trastorno o enfermedad en un sujeto caracterizado por la activación del sistema del complemento. Más particularmente en la fabricación de un medicamento para el tratamiento de una enfermedad o trastorno en un sujeto caracterizado por la sobre-activación del sistema del complemento.

En una realización, la invención proporciona el uso de un compuesto según la definición de la fórmula (I), (Ia), o sub fórmulas de las mismas para el tratamiento de un trastorno o enfermedad en un sujeto caracterizado por la activación del sistema del complemento. Más particularmente, la invención proporciona usos de los compuestos proporcionados en la presente en el tratamiento de una enfermedad o trastorno caracterizado por sobre-activación del sistema del complemento o el bucle de amplificación C3 del sistema. En ciertas realizaciones,

el uso es en el tratamiento de una enfermedad o trastorno seleccionada a partir de enfermedades de la retina (como la degeneración macular relacionada con la edad).

La presente invención proporciona el uso de los compuestos de la invención para el tratamiento de una enfermedad o trastorno asociado con la actividad aumetada del complemento mediante la administración a un sujeto que lo necesita una cantidad eficaz de los compuestos de la fórmula (I) de la invención. En ciertos aspectos, los usos se proporcionan para el tratamiento de enfermedades asociadas con una mayor actividad del bucle de amplificación C3 de la vía del complemento. En ciertas realizaciones, se proporcionan usos para tratar o prevenir enfermedades mediadas por complemento en los que la activación del complemento es inducida por la interacción antígeno-anticuerpo, por un componente de una enfermedad autoinmune, o por daño isquémico.

En una realización específica, la presente invención proporciona el uso de los compuestos de la invención para el tratamiento o prevención de la degeneración macular relacionada con la edad (AMD). En ciertas realizaciones, los pacientes que se encuentran actualmente asintomáticos, pero están en riesgo de desarrollar un trastorno relacionado con la degeneración macular sintomática son adecuados para la administración con un compuesto de la invención. El uso en el tratamiento o prevención de AMD incluyen, pero no se limitan a, usos en el tratamiento o prevención de uno o más síntomas o aspectos de AMD seleccionados a partir de la formación de drusas oculares, inflamación ocular o del tejido ocular, pérdida de células fotoreceptoras, pérdida de la visión (incluyendo pérdida de la agudeza visual o del campo visual), neovascularización (incluyendo CNV), desprendimiento de retina, degeneración de los fotoreceptores, degeneración RPE, degeneración de la retina, degeneración coriorretiniana, degeneración de los conos, disfunción de retina, daño en la retina en respuesta a la exposición a la luz, daño de la membrana de Bruch, y/o pérdida de función RPE.

El compuesto de la fórmula (I) de la invención se puede utilizar, entre otras cosas, para prevenir la aparición de AMD, para prevenir la progresión de AMD precoz a formas avanzadas de AMD, incluyendo AMD neovascular o atrofia geográfica, para retardar y/o prevenir la progresión de la atrofia geográfica, para tratar o prevenir el edema macular de AMD u otras condiciones (tales como retinopatía diabética, uveítis o trauma post quirúrgico o no quirúrgico), para prevenir o reducir la pérdida de la visión a partir de AMD, y para mejorar la perdida de visión debido a AMD pre-existente precoz o avanzada. También se puede utilizar en combinación con terapias anti-VEGF para el tratamiento de pacientes con AMD neovascular o para la prevención de AMD neovascular. La presente invención proporciona además métodos para tratar una enfermedad o trastorno relacionado con el complemento mediante la administración a un sujeto que lo necesita de una cantidad eficaz del compuesto(s) de la invención, en donde dicha enfermedad o trastorno se selecciona de uveítis, degeneración

macular adulta, retinopatía diabética, retinitis pigmentosa, edema macular, uveítis de Behcet, coroiditis multifocal, síndrome de Vogt-Koyanagi-Harada, uveítis intermedia, retinocoroiditis en perdigonada, oftalmía simpática, penfigoide cicatricial ocular, pénfigo ocular, neuropatía óptica isquémica no arterítica, inflamación post-operatoria, y oclusión venosa de la retina.

En algunas realizaciones, la presente invención proporciona usos para el tratamiento de una enfermedad o trastorno relacionado con el complemento. Ejemplos de enfermedades o trastornos conocidos relacionados con complemento incluyen: trastornos neurológicos, esclerosis múltiple, accidente cerebro vascular, síndrome de Guillain Barré, lesión cerebral traumática, enfermedad de Parkinson, trastornos de la activación del complemento inadecuada o indeseable, complicaciones de hemodiálisis, rechazo del aloinjerto hiperagudo, rechazo de xenoinjertos, toxicidad inducida por interleucina-2 durante terapia de IL-2, enfermedades inflamatorias, inflamación de enfermedades autoinmunes, enfermedad de Crohn, síndrome de distrés respiratorio del adulto, lesión térmica que incluye quemaduras o congelación, miocarditis, condiciones de reperfusión post-isquémica, infarto del miocardio, angioplastia con balón, síndrome pos-perfusión en bypass renal o bypass cardiopulmonar, aterosclerosis, hemodiálisis, isquemia renal, reperfusión de la arteria mesentérica después de reconstrucción aórtica, enfermedad infecciosa o sepsis, trastornos inmunes complejos y enfermedades autoinmunes, artritis reumatoide, lupus eritematoso sistémico (LES), nefritis de lupus eritematoso sistémico, nefritis proliferativa, fibrosis hepática, anemia hemolítica, miastenia gravis, regeneración de tejidos y regeneración neuronal. Además, otras enfermedades conocidas relacionadas con complemento son las enfermedades pulmonares y trastornos, tales como disnea, hemoptisis, SDRA, asma, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, embolia pulmonar e infartos, neumonía, enfermedades originadas por polvos fibrogénicos, polvos inertes y minerales (por ejemplo, silicio, polvo de carbón, berilio, y asbesto), fibrosis pulmonar, enfermedades de polvo orgánico, daño químico (debido a gases irritantes y productos químicos, por ejemplo, cloro, fosgeno, dióxido de azufre, sulfuro de hidrógeno, dióxido de nitrógeno, amoníaco y ácido clorhídrico), lesiones por humo, lesión térmica (por ejemplo, quemadura, congelación), asma, alergia, broncoconstricción, neumonitis por hipersensibilidad, enfermedades parásitarias, síndrome de Goodpasture, vasculitis pulmonar, vasculitis pauci-inmune por inflamación asociada con complejos inmunes, uveítis (incluyendo la enfermedad de Behcet y otros sub-tipos de uveítis), síndrome antifosfolípido.

En una realización específica, la presente invención proporciona el uso de los compuestos de la invención para el tratamiento de una enfermedad o trastorno relacionado con el complemento, en donde dicha enfermedad o trastorno es asma, artritis (por ejemplo, artritis reumatoide), enfermedad cardíaca autoinmune, esclerosis múltiple, enfermedad inflamatoria del intestino , lesiones de isquemia-reperfusión, síndrome de Barraquer-Simons, hemodiálisis,

lupus sistémico, lupus eritematoso, psoriasis, esclerosis múltiple, trasplante, enfermedades del sistema nervioso central como la enfermedad de Alzheimer y otras enfermedades neurodegenerativas, síndrome urémico hemolítico atípico (aHUS), glomerulonefritis (incluyendo glomerulonefritis proliferativa de membrana), enfermedades cutáneas ampollosas (incluyendo penfigoide ampolloso, pénfigo, y epidermólisis bullosa), penfigoide cicatrical ocular o MPGN II.

En una realización específica, la presente invención proporciona el uso de los compuestos de la invención para el tratamiento de la glomerulonefritis. Los síntomas de la glomerulonefritis incluyen, pero no se limitan a, proteinuria, tasa de filtración glomerular (TFG) reducida, cambios de los electrolitos séricos, incluyendo azotemia (uremia, excesivo nitrógeno ureico en sangre - BUN) y retención de sal, dando lugar a retención de agua resultando en hipertensión y edema; hematuria y sedimentos urinarios anormales, incluyendo cilindros eritrocitarios, hipoalbuminemia, hiperlipidemia, y lipiduria. En una realización específica, la presente invención proporciona métodos de tratamiento de hemoglobinuria paroxística nocturna (HPN) mediante la administración a un sujeto que lo necesita de una cantidad eficaz de una composición que comprende un compuesto de la presente invención, con o sin la administración concomitente de un inhibidor del complemento C5 o inhibidor de la convertasa C5 tal como Soliris.

En una realización específica, la presente invención proporciona el uso de los compuestos de la invención para reducir la disfunción de los sistemas inmunológicos y/o hemostáticos asociados con la circulación extracorpórea. Los compuestos de la presente invención se pueden utilizar en cualquier procedimiento que implique la circulación de la sangre del paciente de un vaso sanguíneo del paciente, a través de un conducto, y de nuevo a un vaso sanguíneo del paciente, el conducto que tiene una superficie luminal que comprende un material capaz de producir al menos una entre activación del complemento, activación de plaquetas, activación de leucocitos, o adhesión de plaquetas-leucocitos. Tales procedimientos incluyen, pero no se limitan a, todas las formas de ECC, así como procedimientos que implican la introducción de un órgano, tejido o vaso artificial o extraño en el circuito de sangre de un paciente. Más particularmente, tales procedimientos incluyen, pero no se limitan a, los procedimientos de trasplante, incluyendo procedimientos de trasplante de riñón, hígado, pulmón o corazón y de procedimientos de trasplante de células de islotes pancreáticos.

Los siguientes ejemplos pretenden ilustrar la invención y no deben ser interpretados como limitaciones al respecto. Las temperaturas se dan en grados centígrados (°C). Si no se menciona lo contrario, todas las evaporaciones se realizan bajo presión reducida, típicamente entre aproximadamente 15 mm de Hg y 100 mm de Hg (= 20-133 mbar). La estructura de los productos finales, compuestos intermedios y materiales de inicio se confirma mediante métodos

analíticos estándar, por ejemplo, microanálisis y características espectroscópicas, por ejemplo, MS, IR, RMN. Las abreviaturas utilizadas son aquellas convencionales en la técnica.

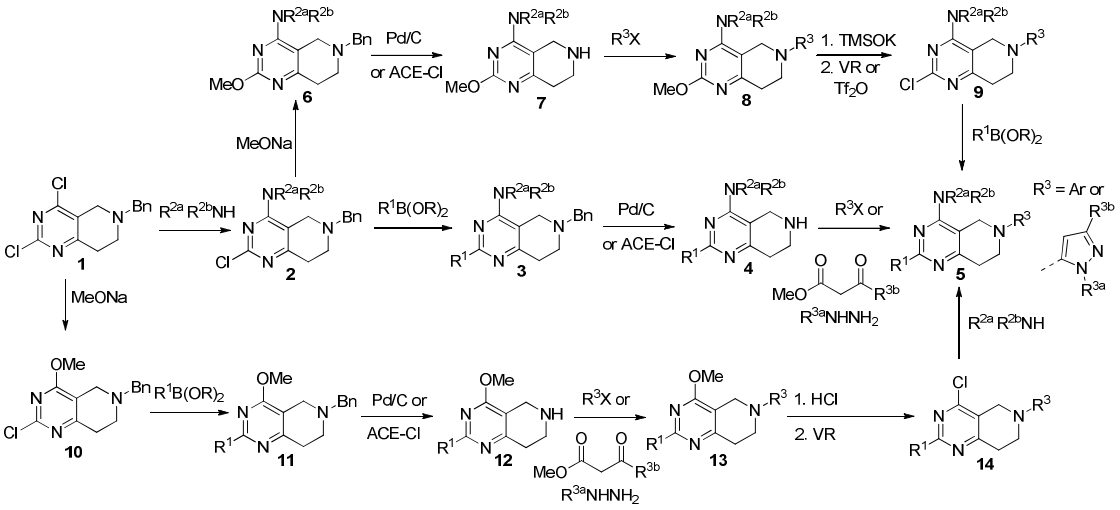
Todos los materiales de inicio, componentes fundamentales (materia prima), reactivos, ácidos, bases, agentes deshidratantes, solventes y catalizadores utilizados para sintetizar los compuestos del presente invento están comercialmente disponibles o pueden producirse mediante métodos de síntesis orgánica conocidos por alguien con habilidad común en el estado de la técnica (Houben- Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Además, los compuetos de la presente invención pueden producirse mediante métodos de síntesis orgánica conocidos por un experto en el estado de la técnica como se muestra en los siguientes ejemplos.

Los siguientes ejemplos sirven para ilustrar la invención sin limitar su alcance.

ASPECTOS SINTETICOS GENERALES

Típicamente, los compuestos de la fórmula (I) pueden prepararse según los Esquemas proporcionados a continuación.

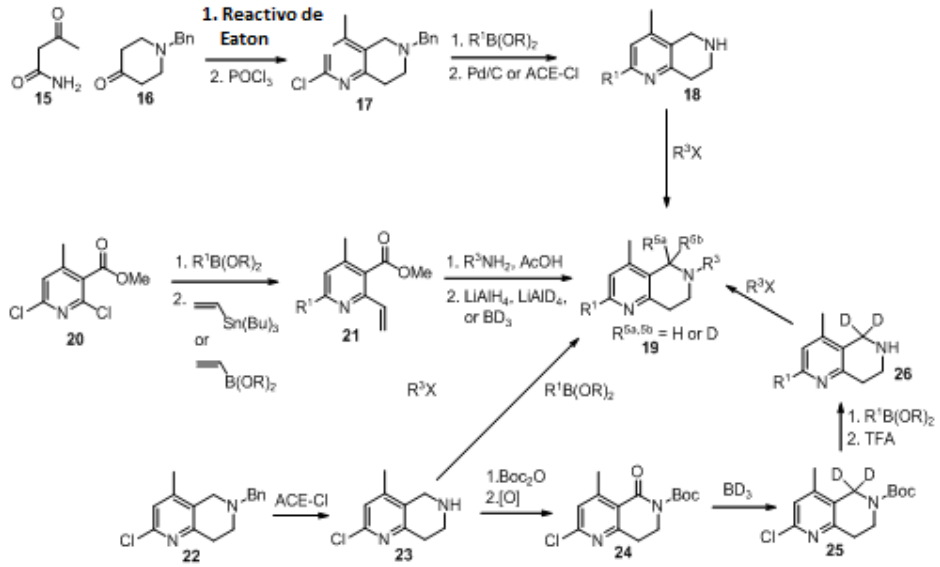
Esquema1



La aminación del núcleo de pirimidina, para proporcionar productos intermedios tales como 2, se puede lograr mediante el tratamiento de dicloropirimidina 1 con aminas primarias o secundarias ($R^{2a}R^{2b}NH$) y DIEA o TEA en disolventes tales como DMA o IPA a temperatura elevada. En una forma similar, el tratamiento con dicloropirimidina **1** con MeONa en MeOH proporciona el derivado de metoxilo **10**. La instalación de R^1 en cualquiera el intermedio **2** o **10** se puede lograr con acoplamiento cruzado catalizado por paladio de ácidos borónicos o los ésteres de borato correspondientes para proporcionar 3 y 12 respectivamente. Alternativamente, **2** puede hacerse reaccionar con MeONa a temperatura elevada para proporcionar el intermedio

de metoxilo **6**. La eliminación del grupo protector bencilo **3**, **11**, o **6** puede llevarse a cabo por tratamiento con ACE-Cl o hidrogenolisis catalizada por paladio para proporcionar las correspondientes aminas secundarias **4**, **7** ó **12**. El grupo R^3 puede luego ser instalado por una aminación catalizada por paladio con el triflato de arilo apropiado o haluro de arilo y uno de **4**, **7**, o **12** para proporcionar **5**, **8** o **13**. Alternativamente, un R^3 pirazol puede ser construido mediante la reacción de aminas **4**, **7**, o **12** con el β-cetoéster apropiado y luego la posterior condensación de intermedio de β-cetoamida con alquilhidrazina facilitada por el reactivo de Lawesson. El grupo metoxilo de **8** puede ser eliminado por tratamiento con TMSOK a temperatura elevada y la pirimidina de hidroxilo se convierte a continuación en cloruro por reacción con el Reactivo de Vilsmeier, $POCl_3$, PPh3/CCl_4 o similares. Una secuencia análoga se emplea con el intermedio de metoxilo **13** para proporcionar la 4-cloropirimidina **14**. La 2-cloropirimidina **9** puede entonces someterse a la instalación del grupo R^1 como se describió anteriormente para proporcionar **5**. La 4-cloropirimidina **14** puede soportar desplazamiento nucleofílico de aminas primarias o secundarias ($R^{2a}R^{2b}NH$), y DIEA o TEA en disolventes tales como DMA o IPA a temperatura elevada para proporcionar **5**.

Esquema 2



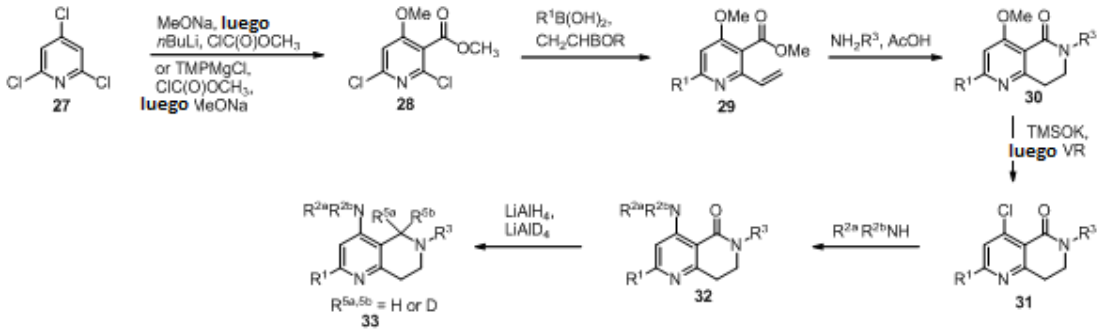
El núcleo de piridina **17** puede prepararse por la condensación de **15** y **16** en el Reactivo de Eaton a temperatura elevada seguido de cloración de la hidroxipiridina resultante con POCl3. La reacción de acoplamiento cruzado catalizada por paladio de cloropiridina **17** con el ácido borónico R^1 apropiado o éster permite la instalación de R^1. La eliminación del grupo protector bencilo desde **17** puede llevarse a cabo por tratamiento con ACE-Cl o hidrogenolisis catalizada por paladio para proporcionar las correspondientes aminas secundarias **18**. El grupo R^3 puede luego ser instalado por una aminación catalizada por paladio con el triflato de arilo

apropiado o haluro de arilo y **18** para proporcionar **19**. Alternativamente, un R^3 pirazol puede ser construido mediante la reacción de aminas **18** con el β-cetoéster apropiado y luego la posterior condensación del intermedio β-cetoamida con alquilhidrazina facilitada por el reactivo de Lawesson para proporcionar **19**.

El intermedio **19** también se puede preparar a partir de **20** reacción de acoplamiento cruzado catalizada por paladio con el ácido borónico R^1 apropiado o éster para instalar R^1, una segunda reacción de acoplamiento cruzado catalizada por paladio, ya sea con un éster de vinil borato o reactivo de vinil estannano para proporcionar **21**. El calentamiento de la amina apropiada R^3 con **21** en AcOH facilita la formación de anillo para proporcionar el intermedio lactama correspondiente a **19**. La lactama puede luego reducirse con LiAlH 4, LiAlD4, o BD_3 para proporcionar los compuestos deseados **19**. Un enfoque alternativo a **19** utiliza una aminación selectiva catalizada por paladio de **23** con un triflato de arilo apropiado o bromuro de arilo seguido por acoplamiento cruzado catalizado por paladio para instalar R^1.

El intermedio deuterados puede ser accesado por la secuencia de protección, oxidación, y reducción a partir de **23 a 25**. El grupo R^1 es instalado como antes sobre el intermedio **25** y a continuación la desprotección proporciona **26**. La aminación catalizada por paladio como se describió anteriormente proporciona **19**.

Esquema 3



El tratamiento de **27** con MeONa y luego cloroformiato de *n*butil-litio y metilo proporciona dicloropiridina **28**. Alternativamente, **28** puede prepararse a partir de **27** por metalación con TMPMgCl, esterificación, y luego metanólisis con MeONa. El grupo R^1 se puede instalar con acoplamiento cruzado catalizado por paladio con el éster o ácido bórico correspondiente. En una segunda etapa de acoplamiento cruzado el grupo vinilo se puede instalar para proporcionar **29**. Como se describió anteriormente, **29** soporta ciclación por reacción con la amina correspondiente en ácido acético a temperatura elevada para proporcionar la lactama **30**. Luego la 4-metoxipiridina se convierte en una 4-cloropiridina **31** por tratamiento con TMSOK y luego Reactivo de Vilsmeier. El desplazamiento del grupo cloro se facilita por calentamiento de **31** con la amina primaria o secundaria apropiada para proporcionar la lactama

intermedia, que a continuación se somete a reducción como se describió anteriormente para proporcionar **33**.

La invención también incluye cualquier variante de estos procesos, en los cuales un producto intermedio obtenible en cualquier etapa de los mismos se utiliza como material de partida y el resto de pasos se llevan a cabo, o en los que los materiales de partida se forman *in situ* bajo condiciones de reacción, o en los cuales los componentes de reacción se utilizan en la forma de sus sales o antípodas ópticamente puros.

Los compuestos de la invención y productos intermedios también se pueden convertir unos en otros según métodos generalmente conocidos *per se*.

Con los grupos de compuestos preferidos de fórmula I mencionados en lo sucesivo, las definiciones de los sustituyentes a partir de las definiciones generales mencionadas anteriormente se pueden utilizar de manera razonablemente, por ejemplo, para reemplazar una o más hasta todas las definiciones más generales con las definiciones más específicas o especialmente con las definiciones caracterizadas como preferidas.

Los compuestos de la fórmula I se preparan de forma análoga a los métodos que, para otros compuestos, son en principio conocidos en la técnica, pero son nuevos cuando se aplican en la fabricación de los compuestos de la presente invención, y son especialmente preparados según los métodos descritos a continuación bajo "Ejemplos" o mediante métodos análogos.

Los derivados de profármacos de los compuestos de la invención pueden prepararse por métodos conocidos por los expertos en la técnica (por ejemplo, para más detalles véase Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, vol. 4, pág. 1985). Por ejemplo, profármacos adecuados pueden prepararse haciendo reaccionar un compuesto no derivatizado de la invención con un agente carbamilante adecuado (por ejemplo, 1,1-aciloxialquilcarbanocloridato, para-nitrofenil carbonato, o similares).

Derivados protegidos de los compuestos de la invención pueden prepararse por medios conocidos por los expertos en la técnica. Una descripción detallada de las técnicas aplicables a la creación de grupos protectores y su eliminación se puede encontrar en TW Greene, "Protecting Groups in Organic Chemistry", tercera edición, John Wiley and Sons, Inc., 1999. Grupos protectores correspondientes pueden introducirse, utilizarse y eliminarse en las etapas apropiadas en cualquier etapa en la fabricación de un compuesto de la fórmula I.

Los compuestos de la presente invención pueden prepararse o formarse convenientemente durante el proceso de la invención, en forma solvatadas (por ejemplo, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar convenientemente por recristalización a partir de una mezcla acuosa/orgánica de disolvente, utilizando disolventes orgánicos tales como acetonitrilo, metanol, etanol, acetato de etilo, heptano o tetrahidrofurano.

Los intermedios y productos finales pueden purificarse según métodos estándar, por ejemplo utilizando métodos cromatográficos, métodos de distribución, (re-) cristalización, y similares.

Abreviaturas

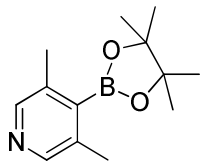
ACECl	cloroformato de 2-cloroetilo
app	aparente
aq	acuoso
atm	*atmósfera*
BHT	2,6-di-terc-butil-4-metilfenol
BINAP	2,2 '-bis (difenilfosfino) -1,1'-binaftaleno
Bn	bencilo
BOC	butil carboxilo terciario
br	general
BSA	albúmina de suero bovino
Cbz	carbobenciloxilo
C5aR	receptor de C5a
d	doblete
D	deuterio
DCE	1,2-dicloroetano
dd	doblete de dobletes
DCM	diclorometano
DEA	dietilamina
DIEA, DIPEA	diisopropiletilamina
DMA	N, N-dimetilacetamida
DMAP	4,4-dimetilaminopiridina
DME	1,2-dimetoxietano
DMEM	Medio Eagle modificado de Dulbecco
DMF	N, N-dimetilformamida
DMSO	dimetilsulfóxido
ee	exceso enantiomérico
ESI	ionización por electrospray
EtOAc	acetato de etilo
FACS	citofluorometría de flujo
FCC	Cromatografía en columna ultra-rápida
FITC	isotiocianato de fluoresceína

FLIPR	Lector de Placas de Imagenes Fluorescentes
g	gramos
h	hora (s)
HBSS	Solución Salina Equilibrada de Hanks
HEPES	ácido 4 - (2-hidroxietil)-1-piperazina etanosulfónico
HPLC	cromatografía líquida de alta presión
IR	espectroscopía infrarroja
LDA	deuteruro de litio y aluminio
LAH	hidruro de litio y aluminio
Reactivo de Lawesson	2,4-bis-(4-metoxifenil) -1,3-ditia-2 ,4-difosfetano 2,4-disulfuro
LCMS	cromatografía líquida y espectrometría de masas
LTMP	2,2 ', 6,6'-tetrametilpiperidina de litio
M	molar
m	multiplete
MeCN, CH3CN	acetonitrilo
MeOH	metanol
Me-THF	2-metilo- Tetrahidrofurano
MTBE	Metil terc-butil éter
min	minutos
ml	mililitro (s)
mmol	milimoles
MS	espectrometría de masas
MSOH	ácido metanosulfónico
MW	microondas
m/z	relación masa a carga
N	normal
NCS	*N*-clorosuccinimida
RMN	resonancia magnética nuclear
obs	oscuro, parcialmente oscuro
PBS	solución buffer de fosfato
Pd/C	paladio sobre carbono
ppm	partes por millón
rac	racémica
rt	a temperatura ambiente
Carr.	tiempo de retención
s	sencillo

sat	saturado
SFC	Cromatografía de fluidos supercríticos
S-Phos	2-diciclohexilfosfino-2 ',6'-dimetoxibifenil
t	tripleta
TBSCl	cloruro de *terc*-butildimetilsililo
Tf	trifluorometanosulfonato
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TMP	2,2,6,6-tetrametilpiperidina
TMS	trimetilsililo
Ts, Tos	tosilo
VR	Reactivo de Vilsmeier; cloruro de (Clormetileno) dimetilamonio
X-Phos	2-diciclohexilfosfino-2 ', 4', 6'-triisopropil-bifenilo

Ejemplo 1

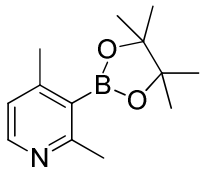
3,5- Dimetil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il) piridina.



A una solución de 4- bromo- 3 ,5- dimetilpiridina (600 mg, 2.70 mmol) en dioxano (9 ml) se añadió bis (pinocolato) diboro (1.37 g, 5.39 mmoles), acetato de potasio (1.06 g, 10.8 mmol) , S- fosfato (221 mg, 0.539 mmol) y $PdCl_2$ (MeCN) 2 (35 mg, 0.14 mmol). La reacción se calentó a 95 °C durante 16 h. Se añadió agua y la fase acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron bajo presión reducida. El residuo se purificó a través de FCC (40-60% EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 234.1 (M+H)+.

Ejemplo 2

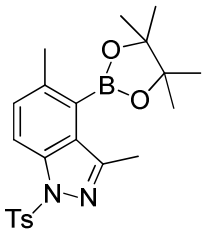
2,4- dimetil- 3- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il) piridina.



A una solución de 3- bromo- 2 ,4- dimetilpiridina (476 mg, 2.56 mmol) en DMSO (14 mL) se añadió bis (pinocolato) diboro (3.25 g, 12.8 mmol), acetato de potasio (1.26 g, 12.8 mmol) y $PdCl_2$ (dppf)·CH_2Cl_2 aducto (209 mg, 0.256 mmol). La reacción se calentó a 95 °C durante 16 h. Se añadió agua y la fase acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron bajo presión reducida. El residuo se purificó a través deFCC (40- 70% de EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$)δ ppm 8,35 (d, J = 5,1 Hz, 1 H), 6,91 (d, J = 5,1 Hz, 1 H), 2,64 (s, 3 H), 2,42 (s, 3 H); 1,43 (s, 12 H) ; MS (ESI +) m/z 234.1 (M+H)+.

Ejemplo 3

3,5- Dimetil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1- tosil- 1H- indazol.



Una solución de 1 - (2- cloro- 6- fluoro- 3- metilfenil) etanona (10 g, 53.6 mmol) e hidrazina (5.05 ml, 161 mmol) en DMSO (50 ml) se calentó a 80 °C durante la noche. La mezcla de reacción se repartió entre EtOAc y agua. La capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron para proporcionar 4- cloro- 3 ,5- dimetil- 1H- indazol crudo como un sólido blanco, que se utilizó en la siguiente etapa directamente. MS (ESI+) m/z 180.9 (M+H)+.

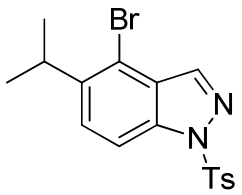
NaH (60% de dispersión en aceite mineral, 3.87 g, 97 mmol) se añadió en porciones a una solución de 4- cloro- 3 ,5- dimetil- 1H- indazolcrudo (9.7 g, 53.7 mmol) en THF (200 ml) a - 20 °C. La mezcla se dejó calentar a 0 °C y se agito durante 20 min, luego TsCl (14.33 g, 75 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante la

noche. La mezcla de reacción se enfrió a - 20 °C y se añadió solución acuosa de NH_4Cl saturadopara apagar el exceso de base. La mezcla resultante se extrajo con CH_2Cl_2 (2X). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron. El residuo se trituró con EtOAc y se filtró para proporcionar 4- cloro- 3 ,5- dimetil- 1- tosil- 1H- indazol. ^{1}H RMN (400 MHz, $CDCl_3$)δ ppm 7,98 (d, J = 8,34 Hz, 1 H) 7,84 (m, J = 8,34 Hz, 2 H) 7,39 (d, J = 8,59 Hz, 1 H) 7,25 (m, J = 7,83 Hz, 2 H) 2,73 (s, 3 H) 2,46 (s, 3 H) 2,38 (s, 3 H), MS (ESI+) m/z 334.7 (M+H)+.

Una mezcla de 4- cloro- 3 ,5- dimetil- 1- tosil- 1H- indazol (1.5 g, 4.48 mmol), dioxaborolano (3.41 g, 13.44 mmol), S- fofopaladaciclo (CAS: 1028206- 58- 7, 0.151 g, 0.224 mmol), y K_3PO_4 (2.85 g, 13.44 mmol) en DMSO (20 mL) se calentó a 110 °C durante 70 min. La mezcla de reacción se particionó entre DCM y agua. La capa acuosa se extrajo con DCM (2X). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron. El residuo se purificó mediante FCC (0- 30% de EtOAc/heptanos) para proporcionar 3,5- dimetil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il) - 1 - tosil- 1H- indazol. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,09 ppm (d,J = 8,59 Hz, 1 H) 7,78 (m, J = 8,34 Hz, 2 H) 7,35 (d, J = 8,84 Hz, 1 H) 7,19 (m, J = 8,08 Hz, 2 H) 2,59 (s, 3 H) 2,54 (s, 3 H) 2,35 (s, 3 H) 1,44 (s, 12 H);(ESI+) m/z 426.9 (M+H)+.

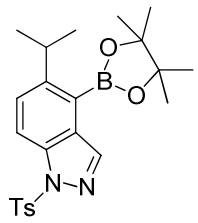
Ejemplo 4

4- A. 4- bromo- 5- isopropil- 1- tosil- 1H- indazol.



Se agregó NaH (60% de dispersión en aceite mineral, 241 mg, 6.02 mmol) a una solución de 4- bromo- 5- isopropil- 1H- indazol (720 mg, 3.01 mmol) en THF (15 ml) a 0 °C. Después de 10 minutos, se añadio TsCl (861 mg, 4,52 mmol) y la mezcla resultante se agitó a 0 °C durante 1 h, después a temperatura ambiente durante la noche. Se añadió NH_4Cl saturada acuosa y la mezcla se extrajo con EtOAc (2X). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (0- 30% de EtOAc/heptanos) para proporcionar 4- bromo- 5- isopropil- 1- tosil- 1H- indazol. MS (ESI+) m/z 394.8 (M+H)+.

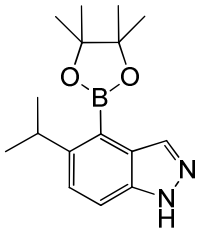
4- B. 5- isopropil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1- tosil- 1H- indazol.



Una mezcla de 4- bromo- 5- isopropil- 1- tosil- 1H- indazol (550 mg, 1.398 mmol), bis (pinacolato)diboro (710 mg, 2.80 mmol), aducto $PdCl_2$ (dppf)·CH_2Cl_2 (91 mg, 0.112 mmol) y acetato de potasio (412 mg, 4.20 mmol) en DMSO (8 ml) se calentó a 110 °C durante 24 h. La mezcla de reacción se particionó entre EtOAc y agua. La capa acuosa se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (0- 30% de EtOAc/heptano) para proporcionar 5- isopropil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il) - 1 - tosil- 1H- indazol. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 8,57 (s, 1 H) 8,24 (d, J = 8,84 Hz, 1 H) 7,87 (d, J = 8,59 Hz, 2 H) 7,57 (d, J = 8,84 Hz, 1 H) 7,24 (d, J = 8,59 Hz, 2 H) 3.71- 3.88 (m, 1 H) 2,38 (s, 3 H) 1,41 (s, 12 H) 1.29- 1.32 (m, 6 H), MS (ESI+) m/z 440.9 (M+H)+.

Ejemplo 5

5- isopropil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1H- indazol.

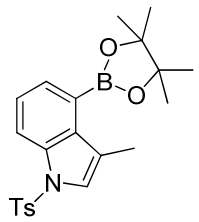


Una suspensión de 4- bromo- 5- isopropil- 1H- indazol (396 mg, 1.656 mmol), bis (pinacolato)diboro (841 mg, 3.31 mmol), KOAc (488 mg, 4.97 mmol), $PdCl_2$ $(CH_3CN)_2$(21.48 mg, mmol 0.083) y S- Phos (136 mg, 0.331 mmol) en DMSO (6 mL) se dejó en agitación a 110 °C durante 23 horas bajo nitrógeno. La mezcla de reacción se enfrió a temperatura ambiente, y se diluyó con EtOAc y salmuera saturada. Los productos se extrajeron tres veces con EtOAc. La capa orgánica combinada se lavó con salmuera, y se concentró. Después el residuo se diluyó con THF (10 mL) y MeOH (1.5 mL), se añadió 1 M acuoso LiOH (4.5 mL).

Después de agitar durante 0.5 h, la reacción se inactivó con NH_4Cl acuoso saturado y se diluyó con EtOAc y salmuera. La mezcla se extrajo dos veces con EtOAc. La capa orgánica combinada se lavó con una solución 1:1 de solución acuosa saturada de NH_4Cl y salmuera saturada, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 40 g de gel de sílice (0- 20% EtOAc/heptano) para proporcionar 5- isopropil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1H- indazol junto con 20% molar de producto desbrominado (345 mg) como un sólido amarillo. ^1H RMN (400 MHz, $CDCl_3$, el éster borónico deseado) δ ppm 9,93 (br s, 1 H), 8,39 (d, J = 1,01 Hz, 1 H), 7,50 - 7,52 (m, 1 H), 7,41 (d, J = 8,84 Hz, 1 H), 3,75 - 3,85 (m, 1 H), 1,42 (s, 12 H), 1,28 (d, J = 6,82 Hz, 6 H), MS (ESI+) m/z 287.30 (M+H)+. El material obtenido se utilizó sin purificación adicional.

Ejemplo 6

3- metil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1- tosil- 1H- indol.



A una solución de 4- bromo- 1H- indol- 3- carbaldehído (7.5 g, 66.9 mmol) en THF (125 mL) se añadió $LiAlH_4$ (40 ml, 1.0 M THF) por goteo a temperatura ambiente. La mezcla se calentó luego a reflujo durante 2 horas y después se enfrió a 0 °C. En ese punto se añadió NaOH al 15% (2 mL) y agua (7 mL) en secuencia y la mezcla se agitó vigorosamente durante 1 h. En ese punto, la suspensión se filtró sobre Celite ® y el filtrado se concentró para proporcionar de 4- bromo- 3- metil- 1H- indolcrudo, el cual fue llevado al siguiente paso.

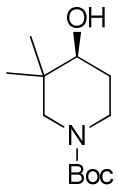
Una solución de 4- bromo- 3- metil- 1H- indol crudo (14.0 g, 66.9 mmol) en THF (50 mL) se añadió a una suspensión de NaH (2.94 g, 73.6 mmol, 60% en aceite mineral) en THF (200 mL) a 0 °C. La mezcla se agitó durante 0.5 horas a esa temperatura antes se añadió una solución de p- tolueno sulfonilcloruro (13.4 g, 70.2 mmol) en THF (50 mL). Después de agitar durante 1 hora másse añadió lentamente NH_4Cl acuoso saturada. La mezcla de reacción se diluyó con EtOAc y NH_4Cl acuoso saturado ylas capas se separaron. La capa orgánica se secó

(Na_2SO_4), se filtraron y se concentraron. Luego el residuo se purificó mediante FCC (0- 50% de EtOAc/heptano) para proporcionar 4- bromo- 3- metil- 1- tosil- 1H- indol.

A una solución de 4- bromo- 3- metil- 1- tosil- 1H- indol (8.66 g, 23.8 mmol) en DMSO (100 mL), 4,4,4',4',5,5,5',5'- octametil- 2,2'- bi(1,3,2- dioxaborolano) (7.85 g, 30.9 mmol), se añadió acetato de potasio (3.50 g, 35.7 mmol) y $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.97 g, 1.19 mmol). La mezcla de reacción se colocó bajo una atmósfera de nitrógeno y luego se calentó a 100 °C durante 4 h. La mezcla se dejó entonces enfriar a temperatura ambiente y luego se vertió en agua con hielo (600 mL). El precipitado se filtró y luego el sólido se purificó mediante FCC (0- 25% EtOAc/heptanos) para proporcionar3- metil- 4- (4,4,5,5- tetrametil- 1,3,2- dioxaborolan- 2- il)- 1- tosil- 1H- indol. MS (ESI+) m/z 412.2 (M+H)+.

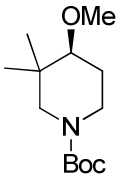
Ejemplo 7

7- A. 4- hidroxi- 3 ,3- dimetilpiperidina- 1- carboxilato de (S)- terc- butilo



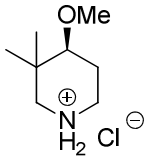
A una solución de 3,3- dimetil- 4- oxopiperidina- 1- carboxilato de terc- butilo (10.0 g, 44.0 mmol) en THF (45 mL) a 0 °C se añadió por goteo (-)- DIP- Cloruro de (50- 65% por peso en heptano, 48.9 ml, 79.0 mmol), y la mezcla de reacción se agitó a 5 °C durante 4 días. La mezcla de reacción se diluyó entonces con Et_2O (250 mL) yse añadió dietanolamina (8.0 g) para proporcionar una cantidad masiva de precipitado blanco. La mezcla resultante se agitó vigorosamente a temperatura ambiente durante 3 h. Luego la mezcla heterogénea se filtró a través de un embudo Buchner embalado con Celite ®, y el filtrado resultante se concentró para proporcionar un residuo amarillo. El residuo se purificó mediante cromatografía en gel de sílice (25- 70% EtOAc/heptano) para proporcionar 4- hidroxi- 3 ,3- dimetilpiperidina- 1- carboxilato de (S)- terc- butilo. (90% ee). El exceso enantiomérico determinado mediante análisis de Mosher éster. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3,79 - 3,94 (m, 1 H), 3,53 (d, J = 13,4 Hz, 1 H), 3,42 (dd, J = 9,2, 4,2 Hz, 1 H), 3,05 (ddd, J = 13,2, 9,8, 3,5 Hz, 1 H), 2,74 (d, J = 13,1 Hz, 1 H), 1,69 - 1,80 (m, 2 H), 1,58 (m, 1 H), 1,46 (s, 9 H), 0,97 (s, 3 H), 0,90 (s, 3 H).

7- B. 4- hidroxi- 3 ,3- dimetilpiperidina- 1- carboxilato de (S)- terc- butilo



A una solución de 4- hidroxi- 3 ,3- dimetilpiperidina- 1- carboxilato de (S)- terc- butilo (6.43 g, 28.0 mmol) en DMF (100 mL) a 0 °C se añadió NaH (60% de dispersión en el mineral aceite, 2.24 g, 56.1 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 15 min. Luego, se añadió por goteoMeI (3.16 ml, 50.5 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 1.5 h. La mezcla de reacción se enfrió a 0 °C y se añadió lentamente NH_4Cl acuoso saturado y se agitó durante 5 min. La solución se calentó a temperatura ambiente y se diluyó con agua (250 mL) y se extrajo con Et_2O (3 x 200 mL). Los extractos orgánicos combinados se lavaron con salmuera (100 mL), se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (5-30% de EtOAc/heptano) para proporcionar 4- metoxi- 3 ,3- dimetilpiperidina- 1- carboxilato de (S)- terc- butilo. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3,75 (br. s., 1 H), 3,41 (d, J = 13,1 Hz, 1 H), 3,35 (s, 3 H), 3,09 (ddd, J = 13,3, 9,3, 3,7 Hz, 1 H), 2,86 (dd, J = 8,5, 3,7 Hz, 1 H), 2,80 (d, J = 13,1 Hz, 1 H), 1,74 a 1,85 (m, 1 H), 1,48 - 1,59 (m, 1 H), 1,46 (s, 9 H), 0,94 (s, 3 H), 0,88 (s, 3 H).

7- C. Cloruro de (S)- 4- metoxi- 3 ,3- dimetilpiperidin- 1- io

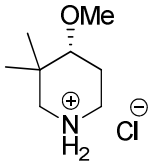


A 4- metoxi- 3 ,3- dimetilpiperidina- 1- carboxilato de (S)- terc- butilo puro (5.87 g, 24.1 mmol) se añadió HCl 4.0 M en dioxano (24.1 ml, 96.0 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. Luego la mezcla de reacción se diluyó con heptanos (60 mL) y Et_2O (10 mL) y se agitó a temperatura ambiente hasta precipitarse en un sólido blanco. La mezcla heterogénea se filtró y el sólido blanco se recogió para producir cloruro de (S)- 4- metoxi- 3 ,3- dimetilpiperidin- 1- io. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 9,58 (s ancho, 1 H)., 9,23 (br. s., 1 H.), 3,34 (s, 3 H), 3,09 - 3,24 (m, 2 H), 3,05 (t, J = 10,0 Hz, 1 H), 2,97 (dd, J = 5,4, 2,4 Hz, 1 H), 2,76 (d, J = 13,1 Hz, 1 H), 2,04 a 2,17 (m, 1 H) , 1,84 - 1,96 (m, 1 H), 1,19 (s, 3 H), 1,05 (s, 3 H).

La correspondiente sal de TFA se preparó también con un método similar utilizando TFA en DCM.

Los siguientes compuestos se prepararon de una manera similar.

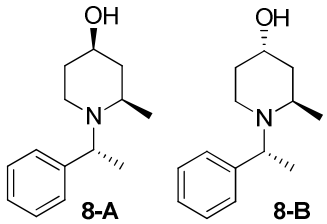
7- D. Cloruro de (R)- 4- metoxi- 3 ,3- dimetilpiperidin- 1- io.



^{1}H RMN (400 MHz·CD_2Cl_2) δ ppm 9,62 (br. s., 1 H) 9,36 (br. s., 1 H) 3,33 (s, 3 H) 3,15 (d, J = 8,84 Hz, 1 H) 2,90 - .. 3.08 (m, 3 H) 2.65- 2.77 (m, 1 H) 1.98 - 2,11 (m, 1 H) 1.81- 1.93 (m, 1 H) 1,15 (s, 3 H) 1,04 (s, 3 H).

Ejemplo 8

8- A. (2R, 4R)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ol y 8- B. (2R, 4S)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ol.



8-A 8-B

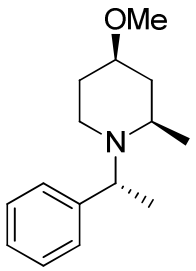
Preparación de (R)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ona y (S)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ona hecha como se describe en WO2004/94380. La mezcla de diastereómeros se separó mediante FCC (0- 15% de EtOAc/heptano) para proporcionar (R)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ona como el primer diastereómero de eluición. Los datos analíticos para (R)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ona: ^{1}H RMN (400 MHz, $CDCl^3$) δ ppm 7,46 (d, J = 7,07 Hz, 2 H) 7,35 (t, J = 7,45 Hz, 2 H) 7.23 - 7.28 (m, 1 H) 4.02 (q, J = 6,57 Hz, 1 H) 3,39 (m, 1 H) 2,73- 2,83 (m, 1 H) 2.61 - 2.72 (m, 2 H) 2,30 - 2,40 (m, 1 H) 2.16 a 2.30 (m, 2 H) 1,35 (d, J = 6,82 Hz, 3 H) 1,15 (d, J = 6,57 Hz, 3 H); $[\alpha]^{25}$D +46.28 (c 1.0, MeOH).

Para una solución preenfriada (0 °C) de (R)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ona, preparada como anteriormente, (2.64 g, 12.1 mmol) en EtOH (50 mL) se añadió borohidruro de sodio (551 mg, 14.6 mmol). Después de 2 horas, la reacción se apagó con una solución saturada de cloruro amónico y se dejó calentar a temperatura ambiente. El pH se ajustó entonces a 9 por la adición de NaOH 4 N y luego se extrajo con EtOAc (3 x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron bajo presión reducida. Los diastereómeros 8- A y 8- Bluego se purificaron mediante FCC(0- 50% EtOAc/heptano) con 8- A. Siendo el producto principal y el primer diastereómero de elución seguido por **8- B** como el producto diastereoisómero menor

8- A: ^{1}H RMN (400 MHz,$CDCl_3$)δ ppm 7,49 (d, J = 8,1 Hz, 2 H), 7,31 - 7,40 (m, 2 H), 7,21 a 7,28 (m, 1 H), 4,34 (q, J = 6,8 Hz, 1 H), 3,62 (tq , J = 10,5, 5,1 Hz, 1 H), 2,60 - 2,72 (m, 1 H), 2,47 (dt, J = 11,8, 3,7 Hz, 1 H), 2,13 (td, J = 11,9, 2,3 Hz, 1 H), 2,00 (ddt, J = 11,9, 4,7, 2,5 Hz, 1 H), 1,74 - 1,85 (m, 1 H), 1,36 - 1,45 (m, 1 H), 1,30 - 1,36 (m, 2 H), 1,23 - 1,30 (m, 6 H), MS (ESI+) m/z 220.2 (M+H)+; [α] ^{25}D - 51,66 (c 1.0, MeOH).

8- B:^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,40 - 7,46 (m, 2 H), 7,33 (t, J = 7,6 Hz, 2 H), 7,21 a 7,27 (m, 1 H), 3,99 (br. s., 1 H.), 3,89 (q, J = 6,7 Hz, 1 H), 3,32 (sxt, J = 6,0 Hz, 1 H), 2,48 - 2,58 (m, 1 H), 2,32 (ddd, J = 12,1, 8,5, 3,4 Hz, 1 H), 1,77 (t, J = 5,6 Hz, 2 H), 1,66 - 1,74 (m, J = 12,6, 3,4, 3,4 Hz, 1 H), 1,47 (dtd, J = 12,3, 8,1, 3,8 Hz, 1 H), 1,29 - 1,35 (m, 4 H), 1,13 (d, J = 6,6 Hz, 3 H), MS (ESI+) m/z 220.2 (M+H)+.

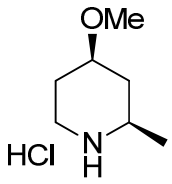
8- C. (2R, 4R)- 4- metoxi- 2- metil- 1- ((R)- 1- feniletil) piperidina.



Se añadió hidruro de sodio (710 mg, 17.7 mmol; dispersión al 60% en aceite mineral) a una solución de (2R, 4R)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ol (1.95 g, 8.87 mmol) en DMF (47 mL) a 0 °C. Después de 15 minutos, se añadió yodometano (666 µl, 10.7 mmol) y la solución se dejó calentar a temperatura ambiente. Después de 1 hora, se añadió agua lentamente a 0 °C. La fase acuosa se extrajo con una mezcla 4:1 de acetato de etilo/n- heptano (3 x). Las capas orgánicas combinadas se lavaron con salmuera (3 x), se secaron sobre sulfato de sodio anhidro, se filtraron y se concentró bajo presión reducida. El residuo se purificó a través de

FCC (0- 30% de EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,49 (d, J = 7,8 Hz, 2 H), 7,35 (t, J = 7,6 Hz, 2 H), 7,21 a 7,28 (m, 1 H), 4,33 (q, J = 6,8 Hz, 1 H), 3,36 (s, 3 H), 3,11 a 3,22 (m, 1 H), 2,59 - 2,71 (m, 1 H), 2,49 (dt, J = 11,9, 3,8 Hz, 1 H), 1,99 - 2,16 (m, 2 H), 1,85 (d, J = 12,1 Hz, 1 H), 1,33 - 1,42 (m, 1 H), 1,28 (d, J = 7,1 Hz, 4 H), 1,25 (d, J = 6,3 Hz, 3 H), MS (ESI+) m/z 234.2 (M+H)+; [α] ^{25}D - 49.17 (c 1.0, MeOH).

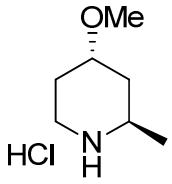
8- D. Hidrocloruro de (+) - (2R, 4R)- 4- metoxi- 2- metilpiperidina.



Se agregó paladio sobre carbono (5%) (857 mg, 0.403 mmol) y HCl (concentrado) (734 l, 24.3 mmol) a (2R, 4R)- 4- metoxi- 2- metil- 1- ((R) - 1- feniletil) piperidina (1.88 g, 8.05 mmol) en MeOH (80 mL). Se burbujeó hidrógeno a través de la mezcla reacción durante 15 min. Después de 1 hora, la mezcla de reacción se filtró a través de Celite ®. El filtrado se lavó con una solución de DCM/MeOH (4:1) y se concentró al vacío para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, MeOD) δ ppm 3,40 - 3,51 (m, 2 H), 3,38 (s, 3 H), 3,19 - 3,28 (m, 1 H), 3,01 (td, J = 13,5, 2,7 Hz, 1 H), 2,19 - 2,36 (m, 2 H), 1,48 (tdd, J = 13,7, 10,7, 4,5 Hz, 1 H), 1,35 (d, J = 6,6 Hz, 3 H), 1,25 - 1,33 (m, 1 H); [α] ^{25}D 15.03 (c 1.0, MeOH).

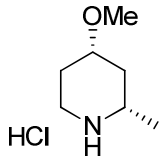
Los siguientes compuestos se prepararon de una manera similar.

8- E. Hidrocloruro de (2R, 4S)- 4- metoxi- 2- metilpiperidina.



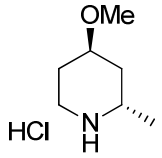
^{1}H RMN (400 MHz,MeOD)δ ppm 3.66 (quin, J = 2,9 Hz, 1 H), 3,39 - 3,47 (m, 1 H), 3,35 (s, 3 H), 3,16 - 3,23 (m, 2 H), 2,03 - 2,18 (m, 2 H), 1,69 - 1,82 (m, 1 H), 1,53 - 1,63 (m, 1 H), 1,29 (d, J = 6,6 Hz, 3 H).

8- F. Hidrocloruro de (2S, 4S)- 4- metoxi- 2- metilpiperidina.



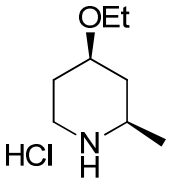
^{1}H RMN (400 MHz,$CDCl_3$)δ 9,88 ppm (br. s., 1 H), 9,41 (br. s., 1 H), 3,54 (br. s., 1 H), 3,38 (s, 3 H), 3,38 (m obs, 1 H) 3,21 (br. s., 1 H), 2,88 (br. s., 1 H), 2,21 (d, J = 11,9 Hz, 2 H), 1,91 (br. s., 1 H), 1,71 (br. s., 1 H), 1,61 (br. s., 3 H).

8- G. Hidrocloruro de (2S, 4R)- 4- metoxi- 2- metilpiperidina.



^{1}H RMN (400 MHz,$CDCl_3$)δ ppm 9,50 (br. s., 1 H)., 9,17 (br. s., 1 H.), 3,77 (q, J = 7,0 Hz, 1 H), 3,66 (br. s., 1 H)., 3,48 - 3,61 (m, 1 H), 3,35 (s, 3H), 3,26 (br. S., 1 H), 2,06 (d, J = 8,8 Hz, 2 H), 1,17 - 1,34 (m, 3 H).

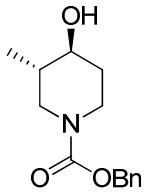
8- H. Hidrocloruro de (2R, 4R)- 4- etoxi- 2- metilpiperidina.



^{1}H RMN (400 MHz,MeOD)δ ppm ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 9.18 (br.s, 1H) 8.80 (br.s., 1H) 3.46 (q, J = 6,99 Hz, 3 H) 3.19 - 3.30 (m, 1 H) 03.03 - 03.16 (m, 1 H) 2,75 - 2,90 (m, 1 H) 1,98- 2,14 (m, 2 H) 1,40- 1,55 (m, 1 H) 1.28- 1.37 (m, 1 H) 1,25 (d, J = 6,57 Hz, 3 H) 1,09 (t, J = 6,95 Hz, 3 H).

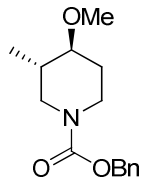
Ejemplo 9

9- A. 4- hidroxi- 3- metilpiperidina- 1- carboxilato de (3S, 4S)- bencilo



A una solución de pivalato de (3S, 4S)- 3- metilpiperidin- 4- ilo[6.6 g, 33.1 mmol (CAS# 863249- 31- 4; preparado como se describe en el documento WO 2005077932)] en THF (200 ml) a 0 °C bajo una atmósfera de argón, se añadió $LiAlH_4$ (2.51 g, 66.2 mmol) en 3 porciones. La mezcla de reacción se dejó calentar a temperatura ambiente y luego se calentó a 55 °C durante aproxidamente 14 horas. La mezcla de reacción se enfrió a 0 °C y se apagó mediante adición lenta por goteo de una mezcla 9:1 de THF/H_2O (20 ml). Luego se añadió NaOH 2 N acuoso. (7 ml) y la reacción se colocó a temperatura ambiente. Luego, se añadio agua (13.2 ml) y THF (60 mL) y la mezcla se agitó durante 10 minutos. Se añadió Celite ® (30 gramos) y la mezcla heterogénea se agito durante 2 minutos y luego se filtró a través de FCC través de una almohadilla de Celite ®, lavando la almohadilla con MeOH al 10%/THF (200 ml). Luego el eluyente se concentró para proporcionar un semi- sólido que se disolvió en agua (165 ml). A la solución resultante se añadió Na_2CO_3 2N acuoso. (99 ml, 198 mmol), luego CbzCl (9.42 ml, 66.0 mmol). La mezcla se agitó a temperatura ambiente durante 3.5 h. Luego la mezcla se vertió en diclorometano y las capas resultantes se separaron. La capa acuosa se volvió a extraer con diclorometano y las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (35- 80% {Et_2O (2% EtOH)}/DCM) para proporcionar: 4- hidroxi- 3- metilpiperidina- 1- carboxilato de (3S, 4S)- bencilo. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 0,98 (d, J = 6,6 Hz, 3 H) 1.31- 1.53 (m, 2 H) 1,89 (dq, J = 12,8, 3,6 Hz, 1 H) 2,54 (br. s., 1 H) 2.73- 3.02 (m, 1 H) 3,28 (td, J = 9,7, 4,3 Hz, 1 H) 3,89 - 4,20 (m, 2 H) 4.93- 5.23 (m, 2 H) 7,19 - 7,47 (m, 5 H), MS (ESI+) m/z 250.1 (M+H)+.

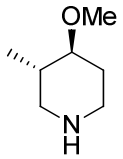
9- B. 4- metoxi- 3- metilpiperidina- 1- carboxilato de (3S, 4S)- bencilo



A una solución de 4- metoxi- 3- metilpiperidina- 1- carboxilato de (3S, 4S)- bencilo (4.45 g, 17.85 mmol) en DMF (100 mL) a 0 °C se añadió NaH (60% de dispersión en aceite,

1.285 g, 32.1 mmol). Luego la mezcla de reacción se dejó a temperatura ambiente durante 10 minutos y luego se volvió a enfriar a 0 °C. Luego se añadió MeI (1.674 ml, 26.8 mmol) y la reacción se dejó calentar a temperatura ambiente. Después de agitar durante 40 minutos aproximadamente la mezcla de reacción se enfrió a 0 °C y se apagó con solución saturada de NH_4Cl acuoso y se diluyó con Et_2O. La mezcla se diluyó adicionalmente con agua y las capas resultantes se separaron. La capa acuosa se volvió a extraer con Et_2O y las capas orgánicas se combinaron, se lavaron con salmuera, después se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (50% Et_2O/Heptano) para proporcionar: 4- metoxi- 3- metilpiperidina- 1- carboxilato de (3S, 4S)- bencilo. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 0,95 (d, J = 6,6 Hz, 3 H) 1.25 - 1,40 (m, 1 H) 1.56- 1.68 (m, 1 H) 1.94 a 2.05 (m, 1 H) 2.67 (br. S., 1 H) 2,87 (td, J = 8,8, 4,0 Hz, 1 H) 2.97 (ddd, J = 13,6, 10,8, 3,2 Hz, 1 H) 3,33 (s, 3 H) 3,79 - 4,10 (m, 2 H) 4.96- 5.18 (m, 2 H) 7.20- 7.46 (m, 5 H), MS (ESI+) m/z 264.0 (M+H)+.

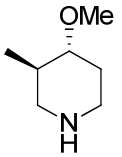
9- C. (3S, 4S)- 4- metoxi- 3- metilpiperidina.



A una solución de 4- metoxi- 3- metilpiperidina- 1- carboxilato de (3S, 4S)- bencilo (4.0 g, 15.19 mmol) en MeOH (150 mL) bajo una atmósfera de argón se añadió de Pd/Chúmedo [(5% base seca) (1.617 g, 0.759 mmol)]. La atmosfera fue reemplazada con gas hidrógeno a través de un globo. La mezcla heterogénea se agitó durante 1 hora a temperatura ambiente, y luego se filtró a través de Celite ®. La torta del filtro se lavó con diclorometano (150 mL), seguido por 20% de MeOH/DCM (150 mL). El eluyente se concentró para proporcionar (3S, 4S)- 4- metoxi- 3- metilpiperidina el cual se utilizó sin la necesidad de purificación adicional. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 0,91 (d, J = 6,6 Hz, 3 H) 1,20 (tdd, J = 12,2, 12,2, 10,5, 4,3 Hz, 1 H) 1.37- 1.55 (m, 1 H) 2.03 (ddt, J = 12,6, 4,2, 3,0, 3,0 Hz, 1 H) 2,21 (dd, J = 12,6, 10,6 Hz, 1 H) 2,53 (td, J = 12,4, 2,8 Hz, 1 H) 2,70- 2,81 (m , 1 H) 2.95 (ddd, J = 12,5, 4,3, 1,6 Hz, 1 H) 3.1 - 3.11 (m, 1 H) 3,31 (s, 3 H).

Los siguientes compuestos se prepararon mediante un método similar.

9- D. (3R, 4R)- 4- metoxi- 3- metilpiperidina.

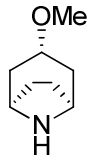


Los mismos procedimientos empleados para sintetizar (3S, 4S)- 4- metoxi- 3- metilpiperidina

Ejemplos 9- C se utilizaron, sin embargo, el material de inicio utilizado fuepivalato de (3R, 4R)- 3- metilpiperidin- 4- il (CAS# 863249 - 35- 8, preparado como se describe en el documento WO 2005077932). ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 0,92 (d, J = 6,6 Hz, 3 H) 1,22 (tdd, J = 12,3, 12,3, 10,4, 4,3 Hz, 1 H) 1,39 - 1,55 (m, 1 H) 2,04 (dq, J = 12,4, 3,5 Hz, 1 H) 2,23 (dd, J = 12,6, 10,6 Hz, 1 H) 2,55 (td, J = 12,4, 2,8 Hz, 1 H) 2,75 (td, J = 9,7, 4,2 Hz, 1 H) 2.96 (ddd, J = 12,6, 4,2, 1,4 Hz, 1 H) 03.02 - 03.11 (m, 1 H) 3,31 (s, 3 H).

Ejemplo 10

(3- endo)- 3- metoxi- 8- azabiciclo[3.2.1] octano.



Una solución de nortropina (5 g, 39.3 mmol) y Boc_2O (9.44g, 43.2 mmol) en THF (100 mL) se agitó a temperatura ambiente durante la noche. La mezcla se concentró bajo presión reducida y el residuo se trituró con heptanos para proporcionar 3- hidroxi- 8- azabiciclo [3.2.1] octano- 8- carboxilato de (3- endo)- terc- butilo como un sólido blanquecino. MS (ESI+) m/z 228.0 (M+H)+.

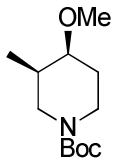
Se añadió NaH (60% de dispersión en aceite mineral, 1.5 g, 38 mmol) en porciones a una solución de 3- hidroxi- 8- azabiciclo [3.2.1] octano- 8- carboxilato de (3- endo)- terc- butilo crudo (4.3 g, 19 mmol) en DMF (43 mL) a 0 °C. Después de 30 min se añadió (4.8 g, 34.1 mmol) y la mezcla se dejó calentar a temperatura ambiente. Después de 1.5 horas la mezcla de reacción se enfrió a 0 °C y se añadió lentamente solución acuosa de NH_4Cl saturadopara apagar el exceso de base. La mezcla resultante se diluyó con H_2O (100 mL) y Et_2O (100 mL). Luego

las capas se mezclaron y se separaron. La capa acuosa se extrajo adicionalmente con Et_2O (2 x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron para proporcionar 3- metoxi- 8- azabiciclo [3.2.1] octano- 8- carboxilato de (3-endo)- terc- butilo crudo. MS (ESI+) m/z 242.0 (M+H)+.

Una solución de 3- metoxi- 8- azabiciclo [3.2.1] octano- 8- carboxilato de (3- endo)- terc-butilo (1.9 g, 8.0 mmol en DCM (20 mL) y TFA (10 mL) se agitó a temperatura ambiente durante 3 h. Luegola mezcla de reacción se concentró al vacío para proporcionar sal TFA (3-endo)- 3- metoxi- 8- azabiciclo[3.2.1]octano. ^{1}H RMN (400 MHz, DMSO)δ ppm 3,91 (s, 2 H) 3,46 (t,J = 2,78 Hz, 1 H) 3,22 (s, 3 H) 2,10 (d, J = 7,33 Hz, 2 H) 2,00 (t, J = 3,03 Hz, 4 H) 1.84-1.92 (m, 2 H).

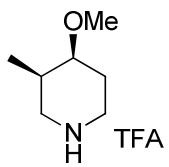
Ejemplo 11

11- A 4- metoxi- 3- metilpiperidina- 1- carboxilato de (cis)- terc- butilo racémico



A una solución de 4- hidroxi- 3- metilpiperidina- 1- carboxilato de (cis)- terc- butilo racémico (310 mg, 1.44 mmol) (CAS# 955028- 93- 0; preparado como se describe en US20070249589)] en DMF (5 mL) a 0 °C se añadió NaH (60% de dispersión en aceite mineral, 75 mg, 1.87 mmol). La mezcla de reacción se agitó a 0 °C durante 10 minutos y se añadió Mei (0.13 ml, 2.02 mmol). Después de 2 h, la reacción se apagó con NH_4Cl acuoso saturado. Lafase acuosa se lavó tres veces con EtOAc.Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobreNa_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 100% de EtOAc/heptanos) para proporcionar 4- metoxi- 3- metilpiperidina- 1- carboxilato de (cis)-terc- butilo racémico. ^{1}H RMN (400 MHz, $CDCl_3$)δ ppm 3,36 - 3,50 (m, 6 H), 3,34 (dt, J = 6,6, 3,3 Hz, 1 H), 3,22 - 3,29 (m, 1 H), 1,78 - 1,96 (m, 2 H), 1,49 (s, 9 H), 0,95 (d, J = 6,8 Hz, 3 H).

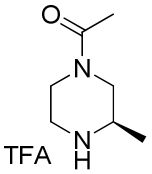
11- B. 2,2,2- trifluoroacetato de (cis)- 4- metoxi- 3- metilpiperidina racémico



Una solución de 4- metoxi- 3- metilpiperidina- 1- carboxilato de (cis)- terc- butilo racémico (230 mg, 1.0 mmol) en DCM (2 mL) con TFA (0.23 ml, 3.01 mmol) se agitó a temperatura ambiente durante la noche. Luego la mezcla de reacción se concentrópara proporcionar 2,2,2- trifluoroacetato de (cis)- 4- metoxi- 3- metilpiperidina racémico.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 3,27 (s, 3 H), 3,01 - 3,09 (m, 1 H), 2,93 - 3,00 (m, 1 H), 2,81 - 2,93 (m, 1 H), 2,69 - 2,77 (m, 1 H), 1,90 - 2,08 (m, 2 H), 1,57 - 1,67 (m, 1 H), 0,90 (d, J = 7,1 Hz, 3 H).

Ejemplo 12

2,2,2- trifluoroacetato de (R) - 1 - (3- metilpiperazin- 1- il) etanona.

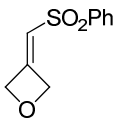


Una mezcla de 2- metilpiperazina- 1- carboxilato de (R)- terc- butilo (4.8 g, 23.97 mmol), Ac_2O (3.39 ml, 36.0 mmol) y piridina (3.88 ml, 47.9 mmol) en DCM (30 mL) se agitó a temperatura ambiente durante 30 min. La reacción se diluyó con EtOAc, se lavó con HCl diluido, salmuera y $NaHCO_3$ saturado, salmuera, y se secó sobre Na_2SO_4, se concentró. El residuo resultante se trató con NaOH 1N en éter, se extrajo con éter, se lavó con salmuera, se secó sobre Na_2SO_4, se concentró y se purificó mediante FCC (0- 10% MeOH en DCM) para proporcionar 4- acetil- 2 - metilpiperazina- 1- carboxilato de (R)- terc- butilo. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 4,14 - 4,46 (m, 2 H) 3.74- 3.91 (m, 1 H) 3.46- 3.72 (m, 1 H) 2.92 - 3.35 (m, 2 H) 2,56- 2,91 (m, 1 H) 2,05 (d, J = 16,67 Hz, 3 H) 1,44 (s, 9 H) 01.03 - 01.18 (m, 3 H). MS (ESI+) m/z 243.2 (M+H)+.

Una mezcla de 4- acetil- 2- metilpiperazina- 1- carboxilato de (R)- terc- butilo (1.34 g, 5.53 mmol) y TFA (10 ml, 130 mmol) en DCM (30 mL) se agitó a temperatura ambiente durante 45 min , luego se concentró, se diluyó con DCM, y luego se concentró de nuevo lo cual se repitió 3 veces. Se secó al vacío a 80 °Cpara proporcionar 2,2,2- trifluoroacetato de (R) - 1 - (3- metilpiperazin- 1- il)etanona(1.95 g). MS (ESI+) m/z 143.0 (M+H)+.

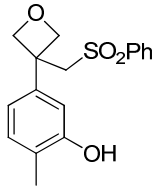
Ejemplo 13

13- A. 3 - ((fenilsulfonil)metileno)oxetano.



Se añadió una solución de BuLi (2.5 M en hexanos, 22.5 ml, 56.3 mmol) durante 10 min a una solución de metilfenilsulfono (4.00 g, 25.6 mmol) en THF (70 mL) a 0 °C. La solución fue de verde claro a una suspensión amarilla heterogénea. La mezcla se agitó durante 30 min a 0 °C y luego se añadió por goteo clorodietilfosfonato (4.46 ml, 30.7 mmol) y se continuó la agitación durante 30 minutos, momento en el cual la solución se volvió de color naranja claro. La mezcla de reacción se enfrió a - 78 °C y se añadió oxetan- 3- ona (1.85 g, 25.6 mmol) en THF (3 mL). La mezcla de reacción se tornó marrónpálido/amarillo. Después de agitar durante otra 1.5 h, la mezcla de reacción se filtró a través de un tapón de gel de sílice. El filtrado se trituró con NH_4Cl sólido hasta que se alcanzó un pH 7. La mezcla se filtró y el filtrado se concentró. El residuo se purificó mediante cromatografía en gel de sílice (0- 60% de EtOAc/heptano) para proporcionar 3 - ((fenilsulfonil)metileno)oxetano. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,86 - 7,99 (m, 2 H) 7,68 - 7,77 (m, 1 H) 7.57- 7.68 (m, 2 H) 6,18 (t, J = 2,40 Hz, 1 H) 5.59 - 5,70 (m, 2 H) 5,30 (td, J = 3,41, 2,27 Hz, 2 H)

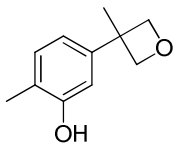
13- B. 2- metil- 5- (3 - ((fenilsulfonil)metil)oxetan- 3- il)fenol.



Una solución de KOH (1.5 M en agua, 14.2 ml, 21.3 mmol) se añadió a una solución de $[Rh(COD)Cl]_2$ (0.525 g, 1.07 mmol) en dioxano (60 mL). La solución amarilla resultante se agitó durante 1 min. Luego, se añadió ácido 3- hidroxi- 4- metilfenilborónico (6.48 g, 42.6 mmol) y una solución de 3 - ((fenilsulfonil)metileno)oxetano (4.48 g, 21.3 mmol) en dioxano (40 mL)en ese orden. Después de 1 h, se añadió una solución de KOH (1.5 M en agua, 14.2 ml, 21.3 mmol). Después de otros 10 minutos, $[Rh(COD)Cl]_2$ (0.525 g, 1.07 mmol). La mezcla resultante se agitó a temperatura ambiente durante la noche, y luego se particionó entre Et_2O y NH_4Cl acuoso. La capa acuosa se extrajo con Et_2O (3X). (Durante extracciones, algunos sólidos se precipitaron en la capa orgánica, pero retornaron a la solución con el tiempo). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo naranja oscuro se purificó mediante cromatografía en gel de sílice (30- 100% EtOAc/heptano) para proporcionar 2- metil- 5- (3 - ((fenilsulfonil) metil)oxetan- 3- il)fenol. ^{1}H RMN (400 MHz,

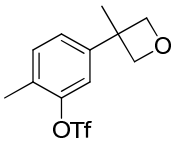
CD_2Cl_2) dδ ppm 7,52 - 7,63 (m, 3 H) 7,41 (t, J = 7,71 Hz, 2 H) 6,99 (d, J = 7,83 Hz, 1 H) 6,57 (dd, J = 7,83, 1,77 Hz, 1 H) 6.50 (d, J = 2,02 Hz, 1 H) 4,99 (d, J = 6,57 Hz, 2 H) 4,91 (d, J = 6,57 Hz, 2 H) 4,03 (s, 2 H) 2,20 (s, 3 H)

13- C. 2- metil- 5- (3- metiloxetan- 3- il)fenol.



Se añadió magnesio (granulado) (8.70 g, 358 mmol) a una solución de 2- metil- 5- (3 - ((fenilsulfonil)metil)oxetan- 3- il)fenol (7.6 g, 23.9 mmol) en MeOH (100 mL). La mezcla resultante se agitó durante 2 min en un baño de ultrasonidos. Luego el matraz se equipó con un condensador. Se continuó la agitación durante 3 h, momento en el cual la mezcla de reacción se tornó turbia y de color blancuzco. La reacción fue exotérmica, lo que causó que el solvente entrara en reflujo. Se añadió un baño de agua para bajar la temperatura de la mezcla de reacción a temperatura ambiente. Luegola mezcla de reacción se agitódurante la noche y se volvió heterogénea y de color naranja pálido. Se añadió Et_2O (525 mL), seguido por $Na_2SO_4 \cdot 10H_2O$ (85 g). La mezcla resultante se agitó durante 2 horas a temperatura ambiente y luego se añadió Celite ®. La mezcla resultante se agitó durante 1h y se filtró a través de un embudo Buchner embalado con Celite ®. La torta se lavó con EtOAc (2X) y MeOH (1X). El filtrado amarillo concentró se concentró y el residuo se trituro con $CHCl_3$ (220 mL) y se filtró. El filtrado se concentró para proporcionar 2- metil- 5- (3- metiloxetan- 3- il) fenol. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,14 (d, J = 7,83 Hz, 1 H) 6,73 (d, J = 7,58 Hz, 1 H) 6,69 (d, J = 1,77 Hz, 1 H) 4,92 (d, J = 5,31 Hz, 2 H) 4,61 (d, J = 5,56 Hz, 2 H) 2,26 (s, 3 H) 1,72 (s, 3 H)

13- D. Trifluorometanosulfonato de 2- metil- 5- (3- metiloxetan- 3- il)fenilo.

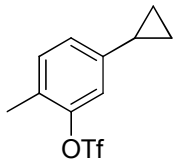


Se añadió por goteo Tf_2O (3,07 ml, 18,2 mmol) a una solución de 2- metil- 5- (3- metiloxetan- 3- il) fenol (2.70 g, 15.2 mmol) y piridina (1.71 ml, 21.2 mmol) en DCM (25 mL) a 0 °C. La mezcla de color rojo/naranja se agitó a 0 °C durante 1.5 h, después se particionó entre DCM y agua. La capa acuosa se extrajo con DCM (2X). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó mediante

cromatografía en gel de sílice (0- 40% de EtOAc/heptano) para proporcionar trifluorometanosulfonato de 2- metil- 5- (3- metiloxetan- 3- il)fenilo. ^{1}H RMN (400 MHz, CD_2Cl_2)δ ppm 7,38 (d, J = 8,08 Hz, 1 H) 7,26 (dd, J = 7,96, 1,89 Hz, 1 H) 7,14 (d, J = 1,77 Hz, 1 H) 4,89 (d, J = 5,56 Hz, 2 H) 4,66 (d, J = 5,81 Hz, 2 H) 2,41 (s, 3 H) 1,75 (s, 3 H).

Ejemplo 14

Trifluorometanosulfonato de 5- ciclopropil- 2- metilfenilo.

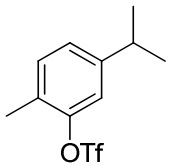


Una solución de 5- bromo- 2- metilfenol (2.00 g, 10.7 mmol), ciclopropiltrifluoroborato de potasio (2.85 g, 19.2 mmol), bis (di- terc- butilo(4- dimetilaminofenil)fosfina)dicloropaladio (II) (0.379 g, 0.535 mmol) y K_3PO_4 (5.67 g, 26.7 mmol) en tolueno (40mL) y agua (10 mL) se dejó en agitación a 100 °C durante 17 horas bajo nitrógeno. La reacción se monitoreo mediante^{1}H RMN. La mezcla se enfrió a temperatura ambiente, y se diluyó con HCl acuoso 1 M (100 mL), salmuera y EtOAc. Los productos se extrajeron dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraronpara proporcionar crudo como aceite de color rojo (1.73 g). El crudo se utilizó sin purificación adicional.

A una solución del producto bruto (1.73 g) y piridina (1.21 ml, 15.0 mmol) en DCM (15 ml), Tf_2O (2.17 ml, 12.8 mmol) se añadió a 0 °C bajo nitrógeno. La mezcla se dejó en agitación durante 1 h. La reacción se monitoreo mediante TLC (25% EtOAc/heptano). La mezcla se diluyó con salmuera y DCM. La capa orgánica se separó y se concentró. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 40 g gel de sílice (con 15 g de pre-columna de gel de sílice; eluyente: heptano/acetato de etilo = 100:0 a 85:15) para proporcionar 5- ciclopropil- 2- metilfenil trifluorometanosulfonato. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,16 (d, J = 7,87 Hz, 1 H), 6,96 (dd, J = 1,64, 7,87 Hz, 1 H), 6,92 (d, J = 1,64 Hz, 1 H) , 2,32 (s, 3 H), 1,85 - 1,92 (m, 1 H), 0,97 - 1,01 (m, 2 H), 0,65 - 0,69 (m, 2 H).

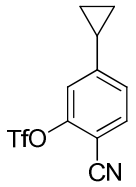
Ejemplo 15

15- A. trifluorometanosulfonato de 5- isopropil- 2- metilfenilo.



A una solución de la carvacrol (5.0 g, 33.3 mmol) y piridina (20 mL) en DCM (40 ml) se añadió Tf_2O (8.44 ml, 33.3 mmol) a 0 °C bajo nitrógeno. La solución se agitó durante 0.5 horas a esta temperatura y luego 0.5 h a temperatura ambiente. En ese momento la reacción se diluyó con DCM (250 ml) y HCl 1 M (250 ml). Las capas se mezclaron y luego se separó. La capa acuosa se extrajo adicionalmente con DCM (250 mL) y las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. Luego el residuo se purificó mediante FCC (10- 30% de EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,19 a 7,24 (m, 1 H) 7.12 - 7,17 (m, 1 H) 7,08 (d, J = 1,52 Hz, 1 H) 2.92 (spt, J = 6,91 Hz, 1 H) 2,35 (s, 3 H) 1,25 (d, J = 6,82 Hz, 6 H).

15- B. trifluorometanosulfonato de 2- ciano- 5- ciclopropilfenilo

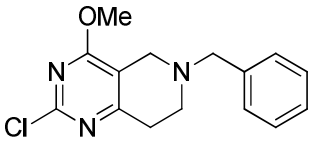


Paso 1: Una solución de 4- bromo- 2- hidroxibenzonitrilo (1 g, 5.05 mmol), ciclopropiltrifluoroboratode potasio (1.495 g, 10.10 mmol), K_3PO_4 (5.05 ml, 15.15 mmol) y $PdCl_2$ $(Amphos)_2$ (0.358 g, 0.505 mmol) en tolueno (25 ml) se dejó en agitación a 100 °C bajo nitrógeno durante la noche. La mezcla se enfrió luego a temperatura ambiente, se diluyó con EtOAc/NH_4Cl (acuoso), y se filtró a través de una almohadilla de Celite. La capa orgánica fue separada, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante FCC (0- 50% de EtOAc/heptano) para proporcionar 4- ciclopropil- 2- hidroxibenzonitrilo, ^{1}H RMN (400 MHz, CH_2Cl_2) δ 12,17 (br. s., 1H), 7,23 (d, J = 8,34 Hz, 1H), 6,51 - 6,58 (m, 2H), 1,82 (tt, J = 5,02, 8,37 Hz, 1H), 0,94 - 1,00 (m, 2H), 0,68 - 0,73 (m, 2H).

Paso 2: El compuesto del título se preparó a partir de 4- ciclopropil- 2- hidroxibenzonitrilo en una manera similar al ejemplo **15- A**. ^{1}H RMN (400 MHz, CD_3Cl) δ ppm 7,63 (d, J = 8,08 Hz, 1H), 7,16 (dd, J = 1,52, 8,08 Hz, 1H), 7,13 (d, J = 1,77 Hz, 1H), 2,01 (tt, J = 4,93, 8,34 Hz, 1H), 1,19 - 1,26 (m, 2H), 0,82 - 0,88 (m, 2H).

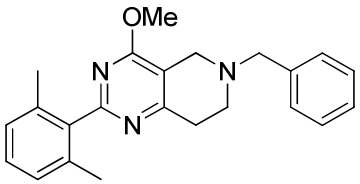
Ejemplo 16

16- A. 6- Bencil- 2- cloro- 4- metoxi- 5 ,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de 6- bencil- 2 ,4- dicloro- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (6.38 g, 21.69 mmol) en metanol anhidro (100 ml), se añadió lentamentemetóxido de sodio 4.67 N (5.57 ml, 26 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 15 minutos, luego a temperatura ambiente durante 30 min. La mezcla de reacción se concentró bajo presión reducida. El residuo se disolvió en DCM y se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar 6- bencil- 2- cloro- 4- metoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina el cual se utilizó sin necesidad de purificación. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,31 - 7,40 (m, 4 H), 7,23 - 7,31 (m, 1 H), 3,95 (s, 3 H), 3,72 (br. s., 2 H), 3,43 (br. s., 2 H), 2,84 (d, J = 4,5 Hz, 2 H), 2,78 (d, J = 4,0 Hz, 2 H). MS (ESI+) m/z 290.4 (M+H)+.

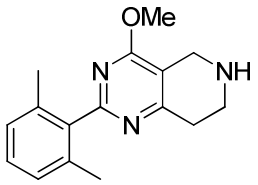
16- B. 6- Bencil- 2- (2,6- dimetilfenil)- 4- metoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina.



A una suspensión de 6- bencil- 2- cloro- 4- metoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (6.52 g, 22.5 mmol) y ácido 2,6 dimetilfenilboronico (3.90 g , 26.0 mmol) en 1,2- dimetoxietano (175 ml), se añadió $Na_2CO_3$2 M acuoso (35.2 ml, 70.5 mmol) y tetrakis (trifenilfosfina) paladio (0) (0.751 g, 0.651 mmol). La reacción se lavó con nitrógeno, luego se calentó a 100 °C durante 48 h. La mezcla de reacción se enfrió a temperatura ambiente, luego se añadió acetato de etilo y salmuera. La capa acuosa se extrajo con acetato de etilo dos veces. Las capas combinadas de acetato de etilo se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó a través de FCC de gel sílice (0- 40% de EtOAc/heptano) para proporcionar 6- bencil- 2- (2,6- dimetilfenil)- 4- metoxi- 5 ,6,7,8- tetrahidropirido[4, 3- d] pirimidina. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,23 - 7,46 (m, 5 H), 7,12 - 7,21 (m, 1 H), 7,04 - 7,10 (m, 1 H), 6,97 (d, J = 7,6 Hz, 1 H), 3,94 (d, J = 10,1 Hz, 3 H),

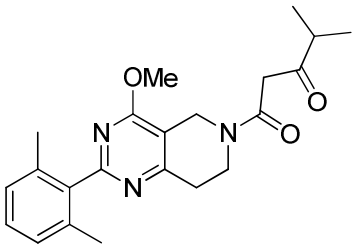
3,73 (d, J = 16,4 Hz, 2 H), 3,36 - 3,56 (m, 2 H), 2,91 (d, J = 4,8 Hz, 1 H), 2,84 (br. s., 2 H), 2,77 (t, J = 5,4 Hz, 1 H), 2,35 (s, 3 H), 2,08 (s, 3 H). MS (ESI+) m/z 360.3 (M+H)+.

16- C. 2 - (2,6- dimetilfenil)- 4- metoxi- 5 ,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de 6- bencil- 2- (2,6- dimetilfenil)- 4- metoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (7.08 g, 19.70 mmol) en THF (100 ml) yH_2O (12.50 ml), se añadió 20% $Pd(OH)_2$ húmedo (50% base seca, 2.77 g, 1.970 mmol), seguido por el ácido acético (2.26 ml, 39.4 mmol). La reacción se agitó a temperatura ambiente en atmósfera de hidrógeno durante 30 minutos, después se calentó a 40 °C durante 16 h. La mezcla de reacción se enfrió a temperatura ambiente. y se filtró a través de una almohadilla de Celite ® la cual se lavó con metanol. El disolvente orgánico en el filtrado se eliminó bajo presión reducida. La mezcla de reacción se diluyó en 200 ml de DCM y se neutralizó mediante $NaHCO_3$acuoso saturado. La mezcla se extrajo dos veces mediante DCM. Las capas orgánicas combinadas se secaron sobre Na_2SO_4. Después de la filtración y concentración, el residuo resultante se purificó a través de FCC de gel sílice (metanol/DCM = 0 a 10%) para proporcionar 2 - (2,6- dimetilfenil)- 4- metoxi- 5 ,6,7,8- tetrahidropirido [4,3- d]pirimidina. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,14 - 7,22 (m, 1 H), 7,05 - 7,11 (m, 2 H), 5,75 (s, 1 H), 3,88 (s, 3 H), 3,72 (s, 2 H), 3,01 (t, J = 5,8 Hz, 2 H), 2,68 (t, J = 5,7 Hz, 2 H), 2,03 (s, 6 H). MS (ESI+) m/z 270.5 (M+H)+.

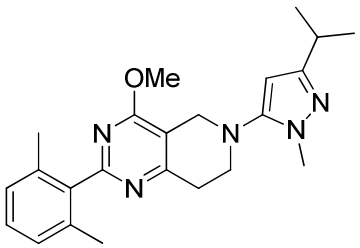
16- D. 1- (2- (2,6- Dimetilfenil)- 4- metoxi- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)- 4- metilpentano- 1,3- diona.



Una mezcla de 2 - (2,6- dimetilfenil)- 4- metoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (4.8 g, 17.82 mmol), 4- metil- 3- oxopentanoato (5.14 g, 35.6 mmol), y DMAP (0.327 g, 2.67 mmol) se disolvió en tolueno (70 mL). La mezcla se dividió equitativamente en

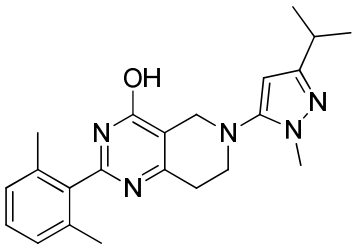
cuatro viales de microondas de 20 mL. Cada vial se calentó a 150 °C durante 30 min a través de la irradiación de microondas. Las mezclas de reacción se combinaron y se concentraron directamente. El residuo resultante se purificó a través de gel de sílice FCC (0- 80% de EtOAc/heptano) para proporcionar MS (ESI+) m/z 382.3 (M+H)+.

16- E.2- (2,6- Dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- metoxi- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina.



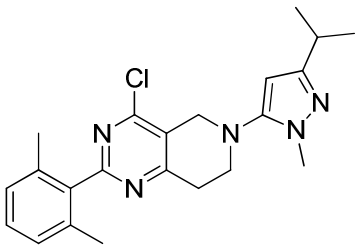
A una solución de 2-(2,6-dimetilfenil)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina (4.8 g, 17.82 mmol), 4-metil-3-oxopentanoato de metilo (5.92 g, 15.52 mmol) en THF (80 ml) se añadió piridina (5 ml). la solución resultante se dividió uniformemente en cuatro viales demicroondas de 20 mL. A cada uno se añadió por microondas, hidrazina de metilo (0.312 ml, 5.81 mmol) y 2,4- disulfuro de 2,4- bis (4- metoxifenil) - 1,3,2,4- ditiadifosfetano(reactivo de Lawesson) (1.88 g, 4.66 mmol). Los viales se taparon inmediatamente y se calentaron a 125 °C durante 10 min a través de la irradiación de microondas. Los viales de reacción se enfriaron a temperatura ambiente y las mezclas de reacción se combinaron y se diluyeron con salmuera. La mezcla se extrajo con DCM tres veces. Las capas orgánicas combinadas se secaron sobre Na_2SO_4. Después de la filtración y concentración, el residuo resultante se purificó a través de FCC de gel de sílice ((1% de MeOH en EtOAc): n- heptano = 0 a 100%) para proporcionar ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,15 - 7,24 (m, 1 H), 7,05 - 7,12 (m, 2 H), 5,77 (s, H 1), 4,00 - 4,04 (m, 2 H), 3,98 (s, 3 H), 3,70 (s, 3 H), 3,28 (t, J = 5,8 Hz, 2 H), 3,05 (t, J = 5,8 Hz, 2 H), 2,87 (dt, J = 13,9, 6,9 Hz , 1 H), 2,12 (s, 6 H), 1,23 (d, J = 7,1 Hz, 6 H). MS (ESI+) m/z 392.4 (M+H)+.

16- F. 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- ol.



A una solución de2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- metoxi- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina (3.3 g, 8.51 mmol) en EtOH (30 mL) en un tubo de 150 ml sellado se añadió hidrocloruro concentrado (21 mL). El tubo se selló, se agitó, y se calentó a 90 °C durante 16 h. La mezcla de reacción se enfrió a temperatura ambiente y se vertió sobre hielo- agua. Se añadió $NaHCO_3$ sólido para neutralizar la mezcla. La mezcla se extrajo mediante DCM tres veces. Las capas orgánicas combinadas se secaron sobre Na_2SO_4. Después de la filtración y concentración, el residuo resultante se purificó a través de FCC de gel de sílice (0- 100% de EtOAc/heptano) para proporcionar2-(2,6-dimetilfenil)-6-(3-isopropil-1-metil-1*H*-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-ol.^{1}H RMN (400 MHz, CD_2Cl_2) dδ ppm 9,95 (br. S., 1 H), 7,21 a 7,36 (m, 1 H), 7,13 (d, J = 7,3 Hz, 2 H), 5,76 (s, 1 H), 3,87 (s, 2 H), 3,68 (s, 3 H), 3,22 (t, J = 5,7 Hz, 2 H), 2,77 - 2,97 (m, 3 H), 2,22 (s, 6 H), 1,22 (d, J = 7,1 Hz, 6 H). MS (ESI+) m/z 378.3 (M+H)+.

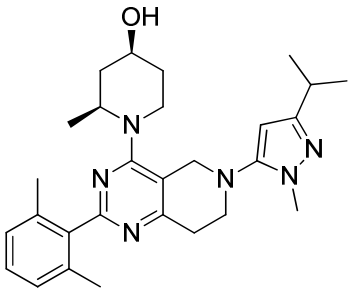
16- G.4- Cloro- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina.



A una solución de2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- ol (2.38 g, 6.3 mmol) en DCM (50 ml) a 0 °C, se añadió cloruro (1- cloro- etilideno)- dimetilamonio (reactivo de Vilsmeier) (2.421 g, 18.91 mmol). La reacción se agitó a 0 °C durante 5 minutos, luego a temperatura ambiente durante 30 minutos. Se añadió $NaHCO_3$ acuoso saturadopara apagar la reacción. El mezcla se extrajo con DCM tres veces. Las capas orgánicas combinadas se secaron sobre Na_2SO_4. Después de la filtración y concentración, el residuo resultante se purificó a través de FCC de gel de sílice (0- 100% EtOAc/heptano) para proporcionar4-cloro-2-(2,6-dimetilfenil)-6-(3-isopropil-1-metil-1*H*-

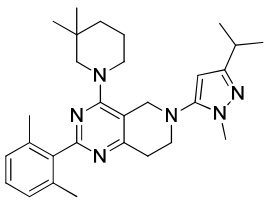
pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina.^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,19 - 7,27 (m, 1 H), 7,11 (d, J = 7,6 Hz, 2 H), 5,80 (s, 1 H), 4,16 (s, 2 H), 3,72 (s, 3 H), 3,32 (t, J = 5,9 Hz, 2 H), 3,16 (t, J = 5,8 Hz, 2 H), 2,88 (dt, J = 13,9, 6,9 Hz, 1 H), 2,11 (s, 6 H), 1,23 (d, J = 6,8 Hz, 6 H). MS (ESI+) m/z 396.3 (M+H)+.

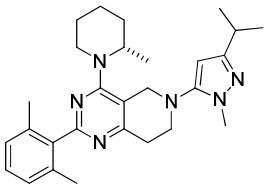
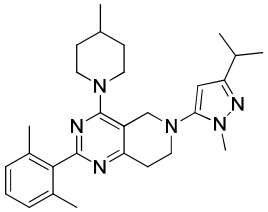
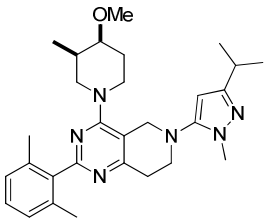
16- H. (±)- 1- (2- (2,6- Dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperidin- 4- ol.

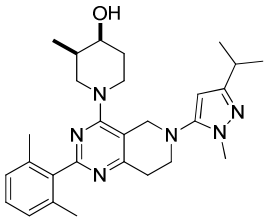
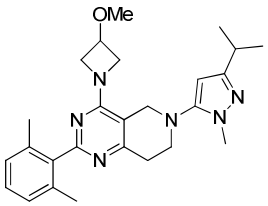
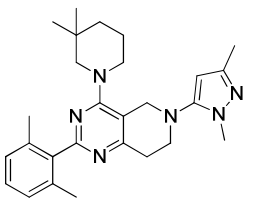
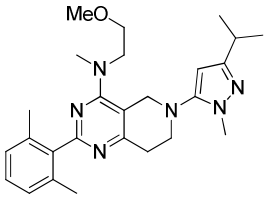


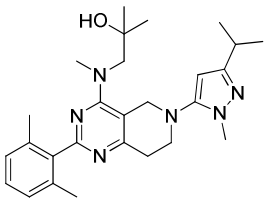
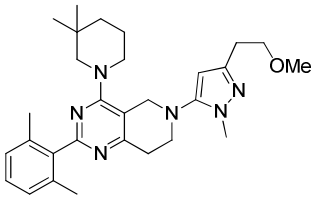
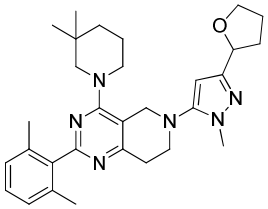
A una solución de 4- cloro- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina (40 mg, 0.101 mmol) en N, N- dimetilacetamida (1,5 ml), se añadió diisopropiletilamina (0.141 ml, 0.808 mmol) y hidrocloruro de cis racémico- 2- metilpiperidin- 4- ol, (CAS#, 344329- 35- 7 30.6 mg, 0.202 mmol). La reacción se calentó a 125 °C durante 42 h. Después de enfriar, la mezcla se purificó directamente a través de HPLC ((hidróxido amónico al 0.1% en acetonitrilo/agua 35% - 100) para proporcionar 26 mg del producto. ^{1}H RMN (400 MHz, CD_2Cl_2)δ ppm 7,14 - 7,24 (m, 1 H), 7,04 - 7,12 (m, 2 H), 5,70 (s, 1 H), 4,15 (d, J = 15,2 Hz, 1 H), 3,94 (d, J = 15,4 Hz , 1 H), 3,78 - 3,91 (m, 1 H), 3,69 (s, 3 H), 3,57 - 3,67 (m, 1 H), 3,27 - 3,39 (m, 2 H), 3,19 - 3,27 (m, 1 H), 3,02 - 3,12 (m, 2 H), 2,96 (ddd, J = 12,8, 9,3, 3,2 Hz, 1 H), 2,86 (ddd, J = 13,8, 7,1, 6,9 Hz, 1 H), 2,09 (s , 6 H), 1,87 - 2,02 (m, 2 H), 1,82 (d, J = 3,0 Hz, 1 H), 1,56 a 1,71 (m, 1 H), 1,49 (dt, J = 12,9, 8,3 Hz, 1 H), 1,22 (d, J = 7,1 Hz, 6 H), 1,14 (d, J = 6,3 Hz, 3 H), MS (ESI+) m/z 475.4 (M+H)+.

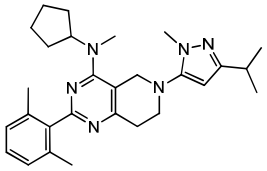
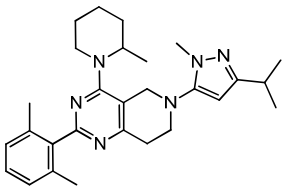
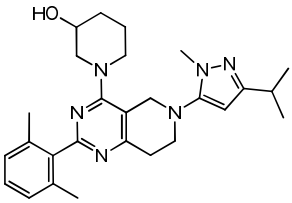
Los siguientes compuestos se prepararon de una manera similar.

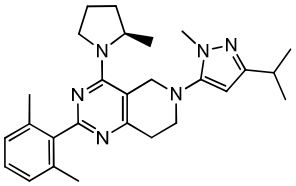
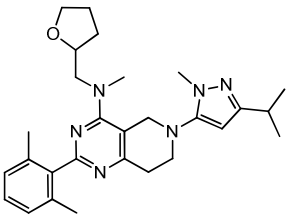
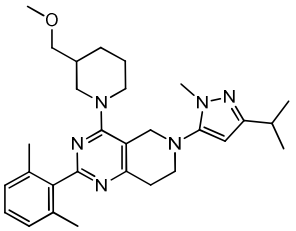
	Estructura	Nombre Quimico y Datos Analiticos
16- I		2- (2,6- Dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. Sal de HCl ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.39 - 7.43 (m, 1 H), 7.25 (d, *J*=7.8 Hz, 2 H), 5.76 (s, 1 H), 4.15 (s, 2 H), 3.73 (br. s., 2 H), 3.61 (s, 3 H), 3.31 (t, *J*=5.8 Hz, 2 H), 3.01 (br.

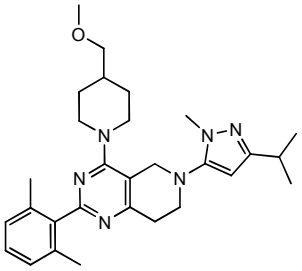
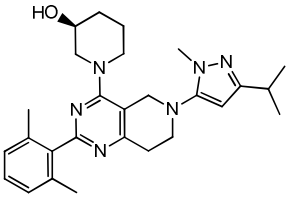
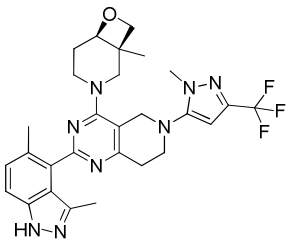
		s., 2 H), 2.77 (spt, *J*=6.9 Hz, 1 H), 2.17 (s, 6 H), 1.68 (br. s., 2 H), 1.48 (br. s., 2 H), 1.15 (d, *J*=7.1 Hz, 6 H), 0.89 (s, 6 H); MS (ESI+) *m/z* 473.2 $(M+H)^+$.
16- J		(*S*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.8 Hz, 2 H), 5.78 (s, 1 H), 4.26 (d, *J*=14.1 Hz, 2 H), 3.96 (d, *J*=14.9 Hz, 2 H), 3.62 (s, 3 H), 3.29 - 3.43 (m, 3 H), 3.18 - 3.29 (m, 1 H), 2.91 - 3.13 (m, 3 H), 2.72 - 2.82 (m, 1 H), 2.18 (s, 6 H), 1.67 - 1.82 (m, 3 H), 1.55 - 1.67 (m, 2 H), 1.50 (dd, *J*=14.9, 5.3 Hz, 1 H), 1.32 (d, *J*=6.6 Hz, 3 H), 1.16 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 459.5 $(M+H)^+$.
16- K		2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.8 Hz, 2 H), 5.83 (s, 1 H), 4.19 - 4.43 (m, 2 H), 4.11 (s, 2 H), 3.61 (s, 3 H), 3.14 - 3.33 (m, 4 H), 3.02 (t, *J*=5.7 Hz, 2 H), 2.73 - 2.83 (m, 1 H), 2.18 (s, 6 H), 1.70 - 1.83 (m, 4 H), 1.18 - 1.24 (m, 1 H), 1.16 (d, *J*=7.1 Hz, 6 H), 0.92 (d, *J*=6.1 Hz, 3 H); MS (ESI+) *m/z* 459.5 $(M+H)^+$.
16- L		(±)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.25 (d, *J*=7.8 Hz, 2 H), 5.80 (s, 1 H), 4.05 - 4.25 (m, 2 H), 3.64 - 3.84 (m, 3 H), 3.62 (s, 3 H), 3.53 - 3.61 (m, 1 H), 3.40 - 3.49 (m, 1 H), 3.22 - 3.37 (m, 5 H), 3.03 (t, *J*=5.9 Hz, 2 H), 2.72 - 2.84 (m, 1 H), 2.18 (s, 6 H), 1.99 - 2.11 (m, 1 H), 1.81 - 1.94 (m, 1 H), 1.63 - 1.77 (m, 1 H), 1.17 (d, *J*=7.1 Hz, 6 H), 0.86 (d, *J*=6.8 Hz, 3 H); MS (ESI+) *m/z* 489.5 $(M+H)^+$.

16- M		1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidin- 4- ol racémico. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.6 Hz, 2 H), 5.79 (s, 1 H), 4.05 - 4.22 (m, 2 H), 3.75 - 3.98 (m, 3 H), 3.63 - 3.75 (m, 1 H), 3.61 (s, 3 H), 3.48 (dd, *J*=12.6, 9.9 Hz, 1 H), 3.21 - 3.38 (m, 2 H), 3.01 (t, *J*=5.9 Hz, 2 H), 2.77 (quin, *J*=6.9 Hz, 1 H), 2.18 (s, 6 H), 1.79 - 1.92 (m, 1 H), 1.67 - 1.78 (m, 2 H), 1.16 (d, *J*=6.8 Hz, 6 H), 0.86 (d, *J*=6.8 Hz, 3 H); MS (ESI+) *m/z* 475.5 $(M+H)^+$.
16- N		2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (3- metoxiazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. Sal de TFA^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.23 (d, *J*=7.6 Hz, 2 H), 5.92 (s, 1 H), 4.59 - 5.13 (m, 2 H), 4.36 - 4.59 (m, 1 H), 4.26 - 4.36 (m, 1 H), 4.18 (br. s., 2 H), 3.88 - 4.13 (m, 1 H), 3.62 (s, 3 H), 3.25 (s, 3 H), 3.18 (t, *J*=5.7 Hz, 2 H), 2.95 (t, *J*=4.3 Hz, 2 H), 2.78 (quin, *J*=6.9 Hz, 1 H), 2.17 (s, 6 H), 1.17 (d, *J*=6.9 Hz, 6 H); MS (ESI+) *m/z* 447.5 $(M+H)^+$.
16- O		6- (1,3- dimetil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. Sal de TFA^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.34 (t, *J*=7.6 Hz, 1 H), 7.16 (d, *J*=7.6 Hz, 2 H), 5.86 (s, 1 H), 4.05 (s, 2 H), 3.82 (s, 3 H), 3.73 (app. t, *J*=5.1 Hz, 2 H), 3.53 (s, 2 H), 3.40 (br. s., 4 H), 2.33 (s, 3 H), 2.22 (s, 6 H), 1.73 - 1.81 (m, 2 H), 1.52 - 1.58 (m, 2 H), 0.94 (s, 6 H); MS (ESI+) *m/z* 445.3 $(M+H)^+$.
16- P		2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- N- (2- metoxietil)- N- metil- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina. ^{1}H NMR Sal de HCl (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=8.6 Hz, 1 H), 7.24 (d, *J*=7.6 Hz, 2 H), 5.88 (br. s., 1 H), 4.35 (br.

		s., 2 H), 3.66 (s, 3 H), 3.56 - 3.63 (m, 2 H), 3.38 - 3.45 (m, 3 H), 3.31 (br. s., 2 H), 3.23 (s, 3 H), 3.04 (br. s., 2 H), 2.81 (spt, *J*=6.6 Hz, 1 H), 2.18 (s, 6 H), 1.18 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 449.2 $(M+H)^+$.
16- Q		1- ((2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.12 - 7.19 (m, 1 H), 7.06 (d, *J*=7.6 Hz, 2 H), 5.55 (s, 1 H), 4.64 (s, 1 H), 4.15 (br. s, 2 H), 3.63 (s, 2 H), 3.60 (s, 3 H), 3.28 – 3.33 (m, 2 H), 2.84 (t, *J*=5.7 Hz, 2 H), 2.74 (spt, *J*=7.1 Hz, 1 H), 2.02 (s, 6 H), 1.11 (d, *J*=6.8 Hz, 6 H), 1.02 (s, 6 H);MS (ESI+) *m/z* 463.2 $(M+H)^+$.
16- R		2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (3- (2- metoxietil)- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.17 (m, *J*=7.1 Hz, 1 H), 7.08 (d, *J*=7.6 Hz, 2 H), 5.73 (s, 1 H), 4.00 (s, 2 H), 3.59 (s, 3 H), 3.51 (t, *J*=7.1 Hz, 2 H), 3.22 - 3.32 (m, 7 H), 3.04 (s, 2 H), 2.93 (t, *J*=5.9 Hz, 2 H), 2.66 (t, *J*=7.1 Hz, 2 H), 2.04 (s, 6 H), 1.58 - 1.68 (m, 2 H), 1.39 (t, *J*=5.8 Hz, 2 H), 0.91 (s, 6 H); MS (ESI+) *m/z* 489.3 $(M+H)^+$.
16- S		2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (tetrahidrofuran- 2- il)- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.17 (dd, *J*=8.6, 7.1 Hz, 1 H), 7.07 (d, *J*=7.6 Hz, 2 H), 5.80 (s, 1 H), 4.63 - 4.68 (m, 1 H), 4.02 (br. s, 2 H), 3.76 - 3.84 (m, 1 H), 3.66 - 3.74 (m, 1 H), 3.62 (s, 3 H), 3.24 - 3.32 (m, 4 H), 3.05 (d, *J*=2.8 Hz, 2 H), 2.92 (t, *J*=6.1 Hz, 2 H), 2.06 - 2.15 (m, 1 H), 2.04 (s, 6 H), 1.84 - 1.96 (m, 3 H), 1.58 - 1.67 (m, 2 H), 1.37 – 1.41 (m, 2 H), 0.90 (s, 6 H); MS (ESI+) *m/z* 501.3 $(M+H)^+$.

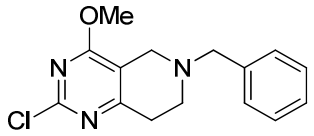
16- T		*N*- ciclopentil- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- *N*- metil- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- amina. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.41 (t, *J*=7.8 Hz, 1 H), 7.25 (d, *J*=7.6 Hz, 2 H), 5.79 (s, 1 H), 4.88 (br. s., 1 H), 4.25 (s, 3 H), 3.62 (s, 3 H), 3.29 (t, *J*=5.9 Hz, 2 H), 3.18 (s, 2 H), 2.94 - 3.08 (m, 2 H), 2.72 - 2.84 (m, 1 H), 2.18 (s, 6 H), 1.79 - 1.93 (m, 1 H), 1.79 - 1.94 (m, 2 H), 1.62 - 1.79 (m, 4 H), 1.46 - 1.62 (m, 2 H), 1.17 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 459.5 $(M+H)^+$.
16- U		2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.25 (d, *J*=7.6 Hz, 2 H), 5.78 (s, 1 H), 4.70 (br. s., 1 H), 3.87 - 4.37 (m, 2 H), 3.62 (s, 3 H), 3.36 (ddd, *J*=12.3, 6.1, 5.9 Hz, 2 H), 3.15 - 3.29 (m, 1 H), 2.91 - 3.15 (m, 3 H), 2.72 - 2.85 (m, 1 H), 2.18 (s, 6 H), 1.65 - 1.84 (m, 3 H), 1.54 - 1.65 (m, 2 H), 1.42 - 1.54 (m, 1 H), 1.33 (d, *J*=6.6 Hz, 3 H), 1.16 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 459.4 $(M+H)^+$.
16- V		1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol racémico. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.25 (d, *J*=7.6 Hz, 2 H), 5.81 (s, 1 H), 4.27 (d, *J*=14.7 Hz, 1 H), 4.01 (d, *J*=14.9 Hz, 1 H), 3.79 - 3.98 (m, 2 H), 3.73 (br. s., 1 H), 3.66 (br. s., 1 H), 3.61 (s, 3 H), 3.49 (br. s., 1 H), 3.18 - 3.39 (m, 2 H), 3.03 (t, *J*=5.3 Hz, 2 H), 2.71 - 2.84 (m, 1 H), 2.18 (s, 6 H), 1.85 (d, *J*=8.6 Hz, 2 H), 1.41 - 1.65 (m, 2 H), 1.16 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 461.4 $(M+H)^+$.

16-W		(*R*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*-pirazol- 5- il)- 4- (2- metilpirrolidin- 1- il)- 5,6,7,8-tetrahidropirido[4,3- *d*]pirimidina. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.41 (t, *J*=7.6 Hz, 1 H), 7.26 (d, *J*=7.8 Hz, 2 H), 5.88 (s, 1 H), 4.52 (br. s., 1 H), 4.20 - 4.44 (m, 2 H), 3.89 - 4.18 (m, 2 H), 3.63 (s, 3 H), 3.22 - 3.36 (m, 1 H), 2.87 - 3.21 (m, 2 H), 2.73 - 2.87 (m, 1 H), 2.19 (s, 6 H), 1.78 - 2.13 (m, 4 H), 1.62 (br. s., 1 H), 1.22 (d, *J*=6.1 Hz, 3 H), 1.18 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 445.4 $(M+H)^+$.
16- X		2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*-pirazol- 5- il)- *N*- metil- *N*- ((tetrahidrofuran- 2- il)metil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- amina. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.23 (d, *J*=7.6 Hz, 2 H), 5.76 (s, 1 H), 4.32 - 4.45 (m, 1 H), 4.23 (d, *J*=14.9 Hz, 1 H), 4.10 - 4.20 (m, 1 H), 3.73 - 3.86 (m, 2 H), 3.63 - 3.73 (m, 1 H), 3.55 - 3.63 (m, 4 H), 3.41 (s, 3 H), 3.26 (t, *J*=5.9 Hz, 2 H), 2.99 (t, *J*=4.9 Hz, 2 H), 2.69 - 2.83 (m, 1 H), 2.16 (s, 6 H), 1.87 - 2.01 (m, 1 H), 1.68 - 1.87 (m, 2 H), 1.43 - 1.60 (m, 1 H), 1.14 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 475.5 $(M+H)^+$.
16- Y		2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*-pirazol- 5- il)- 4- (3- (metoximetil)piperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina racémico. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.25 (d, *J*=7.6 Hz, 2 H), 5.80 (s, 1 H), 4.25 (br. s., 2 H), 4.19 (d, *J*=15.2 Hz, 1 H), 4.02 - 4.10 (m, 1 H), 3.62 (s, 3 H), 3.22 - 3.39 (m, 4 H), 3.16 - 3.22 (m, 4 H), 3.09 - 3.16 (m, 1 H), 2.93 - 3.08 (m, 2 H), 2.72 - 2.85 (m, 1 H), 2.19 (s, 6 H), 1.89 - 2.06 (m, 1 H), 1.71 - 1.86 (m, 2 H), 1.47 - 1.65 (m, 1 H), 1.28 - 1.44 (m, 1 H), 1.17 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 489.4 $(M+H)^+$.

16- Z		2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (4- (metoximetil)piperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.8 Hz, 2 H), 5.82 (s, 1 H), 4.33 (d, *J*=13.6 Hz, 2 H), 4.12 (s, 2 H), 3.61 (s, 3 H), 3.24 - 3.34 (m, 4 H), 3.23 (s, 3 H), 3.20 (d, *J*=6.3 Hz, 2 H), 3.02 (t, *J*=5.7 Hz, 2 H), 2.77 (quin, *J*=6.9 Hz, 1 H), 2.17 (s, 6 H), 1.86 - 2.02 (m, 1 H), 1.81 (d, *J*=14.1 Hz, 2 H), 1.19 - 1.34 (m, 2 H), 1.16 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 489.5 $(M+H)^+$.
16- AA		(*S*)- 1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol. Sal de TFA ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.24 (d, *J*=7.6 Hz, 2 H), 5.80 (s, 1 H), 4.27 (d, *J*=15.2 Hz, 1 H), 4.01 (d, *J*=14.7 Hz, 1 H), 3.93 (d, *J*=14.9 Hz, 1 H), 3.78 - 3.90 (m, 1 H), 3.70 - 3.78 (m, 1 H), 3.62 - 3.70 (m, 1 H), 3.61 (s, 3 H), 3.42 - 3.55 (m, 1 H), 3.18 - 3.38 (m, 2 H), 2.97 - 3.08 (m, 2 H), 2.73 - 2.81 (m, 1 H), 2.18 (s, 6 H), 1.85 (d, *J*=11.4 Hz, 2 H), 1.42 - 1.63 (m, 2 H), 1.16 (d, 6 H); MS (ESI+) *m/z* 461.5 $(M+H)^+$.
16- AB LLN036		*(cis)*- 3- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (1- metil- 3- (trifluorometil)- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 1- metil- 7- oxa- 3- azabiciclo[4.2.0]octano *racémico*. ^{1}H NMR (400 MHz,CD_2Cl_2) δ ppm 9.78 (br. s, 1H), 7.27 (d, *J* = 8.59 Hz, 1H), 7.16 (d, *J* = 8.59 Hz, 1H), 6.08 (s, 1H), 4.57 (t, *J* = 3.03 Hz, 1H), 4.44 (d, *J* = 5.81 Hz, 1H), 4.23 (d, *J* = 6.06 Hz, 1H), 4.12 (q, *J* = 14.70 Hz, 2H), 3.89 - 4.00 (m, 1H), 3.73 (s, 3H), 3.65 (d, *J* = 13.64 Hz, 1H), 3.43 (td, *J* = 4.36, 11.24 Hz, 1H), 3.24 - 3.37 (m, 2H), 3.20 (d, *J* = 13.64 Hz, 1H), 2.92 - 3.09 (m, 2H), 2.19 (s, 3H), 1.88 - 1.97 (m, 2H), 1.92 (s, 3H), 1.18 (s, 3H); MS (ESI+) *m/z* 553.3 $(M+H)^+$.

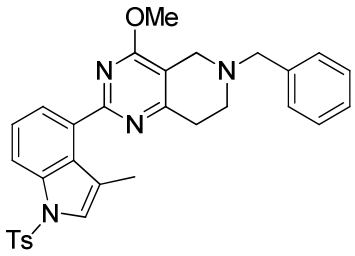
Ejemplo 17

17- A. 6- Bencil- 2- cloro- 4- metoxi- 5 ,6,7,8- tetrahidropirido[4,3- d] pirimidina.



A una solución de 6- bencil- 2 ,4- dicloro- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (CAS# 778574- 06- 4 2.0 g, 6.80 mmol) en MeOH (70 ml) a 0 °C se añadió metóxido sódico al 25% en metanol (1.9 ml, 8.2 mmol) para proporcionar una suspensión. Después de 15 minutos la reacción se volvió una solución homogénea, en cuyo momento se añadió una alícuota adicional de metóxido de sodio al 25% en metanol (0.25 ml, 1.1 mmol) y la reacción se agitó durante 15 minutos. Luego la reacción se diluyó con agua y éter dietílico y las capas resultantes se separaron. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El aceite amarillo resultante se utilizó sin purificación adicional. ^1H RMN (400 MHz, CD_2Cl_2) δ ppm 2,71 - 2,91 (m, 4 H) 3,43 (m, 2 H) 3,72 (m, 2 H), 3,95 (s, 3 H) 7,24- 7,42 (m, 5 H). MS (ESI+) m/z 290.2 (M+H)+.

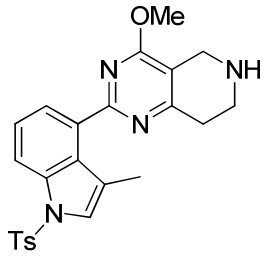
17- B. 6- Bencil- 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.



A una solución de 6- bencil- 2- cloro- 4- metoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (1.0 g, 3.45 mmol) en DME (10.0 ml) en un vial de microondas de reacción20 mL se añadió 3- metil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1- tosil- 1H- indol (1.57 g, 3.80 mmol). Luego se añadió Na_2CO_3 2 M acuoso (5.6 ml, 11.22 mmol). La mezcla de reacción se dagasificó a través de una serie de 3 ciclos de argón/vacío y luego se colocó bajo una atmósfera de argón. Luego se añadió $Pd(Ph_3P)_4$ (0.399 g, 0.345 mmol) y el vial se selló y se calentó a través de la irradiación de microondas a 140 °C durante 90 minutos. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con Et_2O y agua. Las capas se separaron

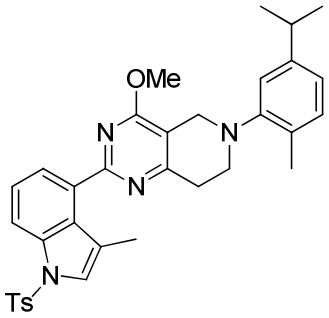
y la capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (27- 48% acetato de etilo/heptanos) para proporcionar 6- bencil- 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina como un sólido blanco. MS (ESI+) m/z 539.3 (M+H)+.

17- C. 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina



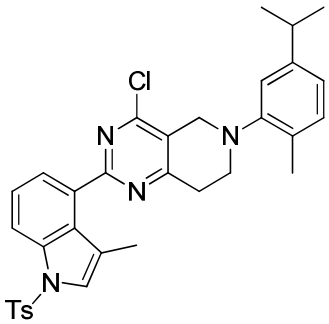
A una solución de 6- bencil- 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina (1.1 g, 2.0 mmol) en THF (15 mL) se añadió agua (3.75 ml) y ácido acético (0.34 ml, 5.9 mmol), luego $Pd(OH)_2$/ 20% mol sobre carbón (50% húmedo) (0.86 g, 0.61 mmol). La mezcla de reacción se colocó bajo una atmósfera de gas hidrógeno a través de un globo. Después de 1.5 horas la mezcla se diluyó con acetato de etilo y se neutralizó con $NaHCO_3$ acuoso saturado. La mezcla se filtró a través de una almohadilla de Celite ®. Luego el eluyente sediluyó con acetato de etilo y salmuera ylas capas se separaron. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 20% MeOH/DCM) para proporcionar 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il) - 5,6,7 ,8- tetrahidropirido [4,3- d] pirimidina. ^{1}H RMN (400 MHz, DMSO- d6) δ ppm 1,91 (d, J = 1,0 Hz, 3 H) 2,32 (s, 3 H) 2,68 (t, J = 5,6 Hz, 2 H) 3,00 (t, J = 5,7 Hz, 2 H) 3,72 (s, 2 H) 3,92 (s, 3 H) 7,30 - 7,48 (m, 4 H) 7,65 (d, J = 1,0 Hz, 1 H) 7,85 (d, J = 8,3 Hz, 2 H) 8,04 (dd, J = 7,3, 2,0 Hz, 1 H). MS (ESI+) m/z 449.2 (M+H)+.

17- D. 6- (5- Isopropil- 2- metilfenil)- 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina (1.32 g, 2.94 mmol) en THF (11 mL) en un vial de microondas de 20 ml se añadió trifluorometanosulfonato de 5- isopropil- 2- metilfenilo, preparado como se describe en el Ejemplo 15 (1.25 g, 4.41 mmol). Luego se añadió carbonato de cesio (2.4 g, 7.36 mmol) seguido por X- Phos (CAS# 564483- 18- 7, 0.28 g, 0.59 mmol). La mezcla de reacción se degasificó a través de variosciclos de vacío/nitrógeno y luego se añadió $Pd(OAc)_2$ (53 mg, 0.235 mmol). El vial se cerró herméticamente y se calentó a través de la irradiación de microondas a 120 °C durante 90 minutos. Luegola reacción se diluyó con acetato de etilo y agua. Las capas se separaron y la capa acuosa se extrajo dos veces más con acetato de etilo. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtró y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 50% acetato de etilo/heptanos) para proporcionar: 6-(5-isopropil-2-metilfenil)-4-metoxi-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina MS (ESI+) m/z 581.2 (M+H)+.

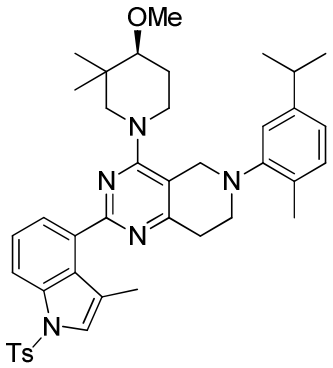
17- E. 4- Cloro- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



Se añadió etanol (4 ml) a6- (5- isopropil- 2- metilfenil)- 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (0.92 g, 1.58 mmol) y luego se añadió HC 12 N acuoso (2 ml, 24 mmol) y la mezcla se calentó a 68 °C durante aproxidamente 15 horas. La reacción se enfrió luego a temperatura ambiente, se diluyó con diclorometano, y se

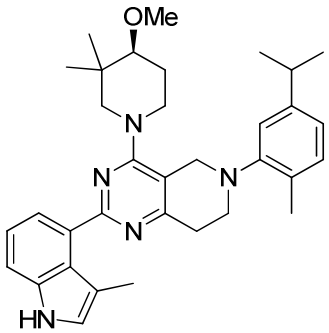
neutralizó mediante la adición lenta de bicarbonato de sodio acuoso saturado. Las capas resultantes se separaron y la capa acuosa se extrajo dos veces más con diclorometano. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. Luego el residuo resultante se disolvió después en diclorometano (20 mL) y se enfrió a 0 °C y se añadiócloruro de N- clorometileno- N, N- dimetilamonio (reactivo de Vilsmeier) (0.41 g, 3.21 mmol). Luego la reacción se colocó a la temperatura ambiente durante 25 minutos. La reacción se diluyó con diclorometano y bicarbonato sódico acuoso saturado. Las capas resultantes se separaron y la capa acuosa se extrajo una vez con diclorometano adicional. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4 filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 45% acetato de etilo/heptanos) para proporcionar 4-cloro-6-(5-isopropil-2-metilfenil)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI+) m/z 585.2 (M+H)+.

17- F.(*S*)- 6- (5- Isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



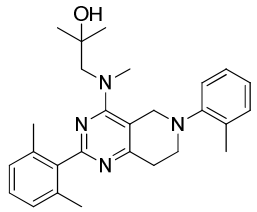
Se añadió isopropanol (2 ml) a un vial de microondas que contiene una mezcla de4-cloro- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8-tetrahidropirido[4,3- d]pirimidina (150 mg, 0.256 mmol) y la sal de ácido trifluoroacético de (S)- 4- metoxi- 3 ,3- dimetilpiperidina (120 mg, 0.461 mmol). Luego se añadió diisopropiletilamina (0.32 ml, 1.8 mmol) y el vial se selló y se calentó a través de la irradiación de microondas a 125 °C durante 3.5 horas. Luego la reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo y $NaHCO_3$ acuoso saturado. Las capas se separaron y la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se purificó mediante cromatografía en gel de sílice (0- 60% acetato de etilo/heptanos) para proporcionar: (*S*)-6-(5-isopropil-2-metilfenil)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI+) m/z 692.5 (M+H)+.

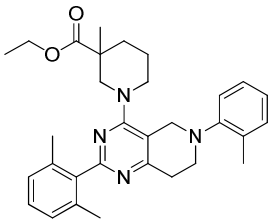
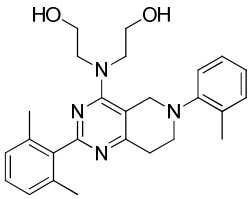
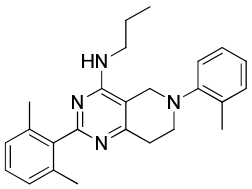
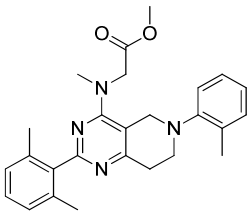
17- G.(*S*)- 6- (5- Isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.

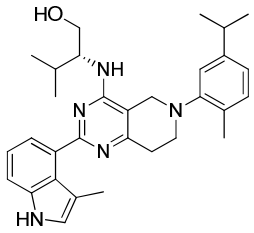
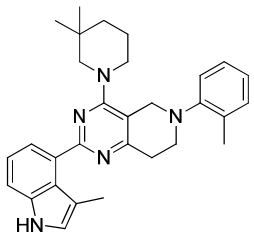
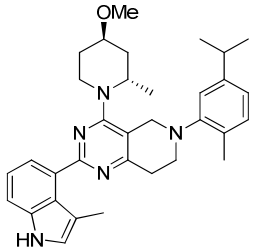


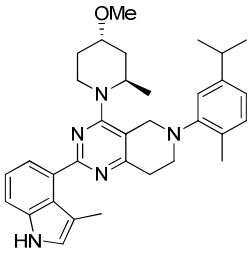
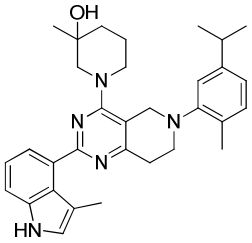
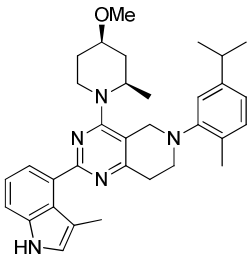
A una solución de (*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (135 mg, 0.195 mmol) en metanol (2 mL) en un vial de microondas se añadió KOH (100 mg, 1.75 mmol) seguido de hidróxido amónico al 28% en agua (1 ml, 7.25 mmol). El vial se cerró herméticamente y se calentó a través de la irradiación de microondas a 80 °C durante 75 minutos. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con diclorometano y salmuera. Las capas se separaron y la capa acuosa se extrajo dos veces más con diclorometano. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 70% acetato de etilo/heptanos) para proporcionar(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina^{1}H RMN (400 MHz, DMSO- d6) δ ppm 0,92 (s, 3 H) 0,98 (s, 3 H) 1,18 (d, J = 6,8 Hz, 6 H) 1,51 - 1,62 (m, 1 H) 1,91 - 1,99 (m, 1 H) 2,01 (s, 3 H) 2,21 (s, 3 H) 2,78 - 2,88 (m, 2 H) 2.91- 3.08 (m, 4 H) 3,29 (s, 3 H) 3.31- 3.41 (m , 3 H) 3.60- 3.71 (m, 1 H) 4,07 (s, 2 H) 6,86 (d, J = 7,3 Hz, 1 H) 6,96 (s, 1 H) 7.7 - 7.15 (m, 3 H) 7,20 (d, J = 7,1 Hz, 1 H) 7,41 (d, J = 7,8 Hz, 1 H) 10,89 (br. S., 1 H);. MS (ESI+) m/z 538.4 (M+H)+.

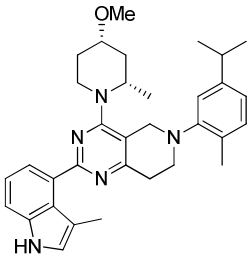
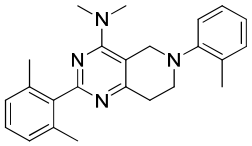
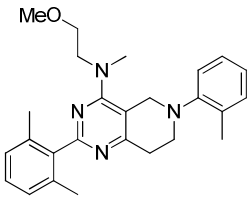
Los siguientes compuestos se prepararon de una manera similar.

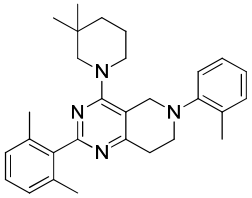
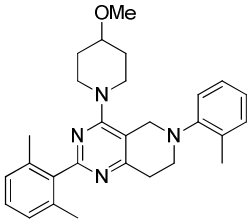
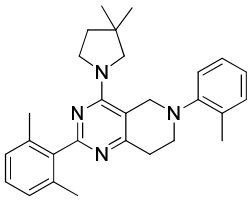
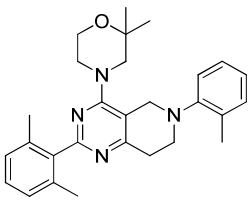
	Estructura	Nombre Quimico y Datos Analiticos
17- H		1- ((2- (2,6- Dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.13 - 7.26 (m, 4 H), 7.00 - 7.11 (m, 3 H), 4.17 (s, 2 H), 3.54 (s, 2 H), 3.26 - 3.32 (m, 5 H), 3.05 (t, *J*=5.8 Hz, 2

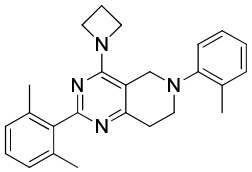
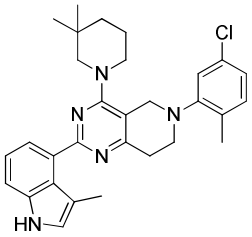
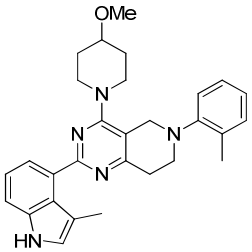
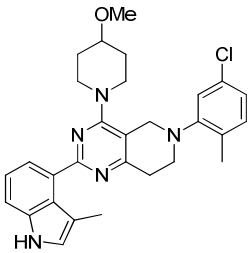
		H), 2.34 (s, 3 H), 2.11 (s, 6 H), 1.14 (s, 6 H); MS (ESI+) *m/z* 431.2 $(M+H)^+$.
17- I		1- (2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidina- 3- de etilo. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.14 - 7.25 (m, 4 H), 7.08 (d, *J*=7.6 Hz, 2 H), 7.01 (t, *J*=7.1 Hz, 1 H), 4.03 - 4.15 (m, 2 H), 3.81 - 3.96 (m, 2 H), 3.77 (d, *J*=14.4 Hz, 1 H), 3.58 - 3.67 (m, 1 H), 3.19 - 3.28 (m, 1 H), 2.85 - 3.05 (m, 4 H), 2.24 (s, 3 H), 2.08 - 2.16 (m, 1 H), 2.05 (s, 6 H), 1.57 - 1.67 (m, 2 H), 1.35 - 1.44 (m, 1 H), 1.09 (s, 3 H), 0.97 (t, *J*=7.1 Hz, 3 H);MS (ESI+) *m/z* 499.2 $(M+H)^+$.
17- J		2,2'- ((2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)azanediil)dietanol. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.14 - 7.23 (m, 4 H), 7.07 (d, *J*=7.6 Hz, 2 H), 6.97 - 7.02 (m, 1 H), 4.76 (t, *J*=5.1 Hz, 2 H), 4.11 (s, 2 H), 3.49 - 3.60 (m, 8 H), 3.23 (t, *J*=5.9 Hz, 2 H), 2.92 (t, *J*=5.7 Hz, 2 H), 2.27 (s, 3 H), 2.04 (s, 6 H);MS (ESI+) *m/z* 433.1 $(M+H)^+$.
17- K		2- (2,6- dimetilfenil)- N- propil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.12 - 7.29 (m, 4 H), 6.98 - 7.10 (m, 3 H), 3.80 (s, 2 H), 3.19 (t, *J*=5.7 Hz, 2 H), 2.78 - 2.86 (m, 2 H), 2.31 (s, 3 H), 2.07 (br. s., 6 H), 1.53 (sxt, *J*=7.1 Hz, 2 H), 0.85 (t, *J*=7.3 Hz, 3 H); MS (ESI+) *m/z* 387.2 $(M+H)^+$.
17- L		metil 2- ((2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)acetato. ^{1}H NMR Sal de HCl (400 MHz, DMSO- d_6) ppm 7.39 (t, *J*=7.7 Hz, 1 H), 7.19 - 7.27 (m, 5 H), 7.02 - 7.08 (m, 1 H), 4.47 (br. s., 2 H), 4.34 (br. s., 2 H), 3.61 (s, 3 H), 3.26 (t, *J*=5.6 Hz, 2 H), 3.04 (br. s., 2 H), 2.28 (s, 3 H), 2.11 (s, 6 H);MS (ESI+) *m/z* 431.2 $(M+H)^+$.

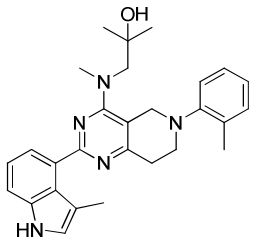
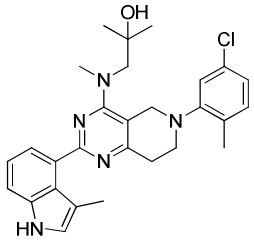
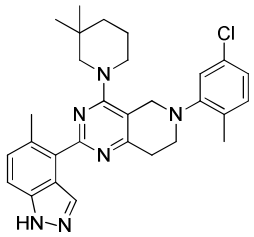
17- M		(*R*)- 2- ((6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)amino)- 3- metilbutan- 1- ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.52 (br. s., 1 H), 7.35 (d, *J*=6.6 Hz, 1 H), 7.19 - 7.23 (m, 1 H), 7.16 (d, *J*=7.8 Hz, 1 H), 7.08 - 7.14 (m, 2 H), 6.95 (dd, *J*=7.8, 1.8 Hz, 1 H), 3.72 - 3.87 (m, 3 H), 3.26 (br. s., 1 H), 3.06 (br. s., 2 H), 2.90 (spt, *J*=6.3 Hz, 1 H), 2.30 (s, 3 H), 2.13 (s, 3 H), 2.04 (spt, *J*=6.6 Hz, 1 H), 1.26 (d, *J*=7.1 Hz, 6 H), 0.99 (d, *J*=6.8 Hz, 3 H), 0.96 (d, *J*=6.8 Hz, 3 H); MS (ESI+) *m/z* 498.3 $(M+H)^+$.
17- N		4- (3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm7.46 - 7.54 (m, 1 H), 7.37 - 7.44 (m, 1 H), 7.22 - 7.30 (m, 3 H), 7.14 - 7.19 (m, 1 H), 7.09 (d, *J*=12.9 Hz, 2 H), 4.03 (s, 2 H), 3.40 (br. s., 1 H), 3.35 (t, *J*=5.9 Hz, 2 H), 3.20 (br. s., 4 H), 2.33 (s, 3 H), 2.10 (s, 3 H), 1.69 - 1.75 (m, 2 H), 1.45 - 1.51 (m, 2 H), 1.01 (s, 6 H); MS (ESI+) *m/z* 466.3 $(M+H)^+$.
17- O		6- (5- isopropil- 2- metilfenil)- 4- ((2*S*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 9.96 - 10.13 (br. s., 1 H), 7.47 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.39 (dd, *J*=7.3, 1.0 Hz, 1 H), 7.13 - 7.20 (m, 3 H), 7.11 (d, *J*=1.8 Hz, 1 H), 6.92 (dd, *J*=7.6, 1.8 Hz, 1 H), 4.34 - 4.42 (m, 1 H), 4.02 - 4.20 (m, 2 H), 3.82 (dt, *J*=13.5, 4.2 Hz, 1 H), 3.62 - 3.72 (m, 1 H), 3.40 - 3.46 (m, 2 H), 3.33 (s, 3 H), 3.08 (t, *J*=6.2 Hz, 2 H), 2.91 (dt, *J*=13.9, 6.9 Hz, 1 H), 2.76 (m, 2 H), 2.30 (s, 3 H), 2.18 (s, 3 H), 1.94 - 2.01 (m, 1 H), 1.66 (ddd, *J*=12.6, 10.4, 5.3 Hz, 1 H), 1.55 (m, 1 H), 1.32 (d, *J*=6.8 Hz, 3 H), 1.26 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.

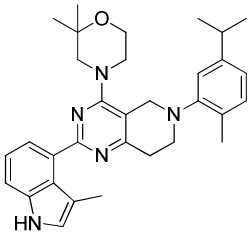
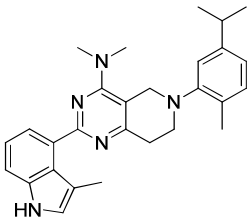
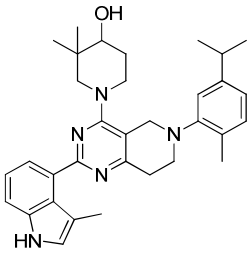
17- P		6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*S*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 9.96 - 10.13 (br. s., 1 H), 7.47 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.39 (dd, *J*=7.3, 1.0 Hz, 1 H), 7.13 - 7.20 (m, 3 H), 7.11 (d, *J*=1.8 Hz, 1 H), 6.92 (dd, *J*=7.6, 1.8 Hz, 1 H), 4.34 - 4.42 (m, 1 H), 4.02 - 4.20 (m, 2 H), 3.82 (dt, *J*=13.5, 4.2 Hz, 1 H), 3.62 - 3.72 (m, 1 H), 3.40 - 3.46 (m, 2 H), 3.33 (s, 3 H), 3.08 (t, *J*=6.2 Hz, 2 H), 2.91 (dt, *J*=13.9, 6.9 Hz, 1 H), 2.76 (m, 2 H), 2.30 (s, 3 H), 2.18 (s, 3 H), 1.94 - 2.01 (m, 1 H), 1.66 (ddd, *J*=12.6, 10.4, 5.3 Hz, 1 H), 1.55 (m, 1 H), 1.32 (d, *J*=6.8 Hz, 3 H), 1.26 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.
17- Q		1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1*H*- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3- metilpiperidin- 3- ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.47 (d, *J*=8.1 Hz, 1 H), 7.32 (d, *J*=7.1 Hz, 1 H), 7.18 - 7.26 (m, 1 H), 7.14 (d, *J*=7.8 Hz, 1 H), 7.07 (d, *J*=1.3 Hz, 1 H), 7.00 (d, *J*=1.8 Hz, 1 H), 6.92 (dd, *J*=7.7, 1.6 Hz, 1 H), 3.98 - 4.13 (m, 2 H), 3.83 - 3.98 (m, 2 H), 3.35 - 3.46 (m, 1 H), 3.25 - 3.34 (m, 1 H), 3.12 - 3.25 (m, 2 H), 2.96 - 3.12 (m, 2 H), 2.89 (dt, *J*=13.8, 6.9 Hz, 1 H), 2.27 (s, 3 H), 2.10 (s, 3 H), 1.81 - 1.96 (m, 1 H), 1.76 (d, *J*=15.2 Hz, 1 H), 1.42 - 1.65 (m, 2 H), 1.25 (d, *J*=7.1 Hz, 6 H), 1.20 (s, 3 H); MS (ESI+) *m/z* 510.2 $(M+H)^+$.
17- R		6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.81 - 11.02 (m, 1 H), 7.33 - 7.52 (m, 1 H), 7.22 (d, *J*=1.0 Hz, 1 H), 7.07 - 7.16 (m, 3 H), 6.96 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.04 - 4.13 (m, 1 H), 3.93 - 4.02 (m, 1 H), 3.76 - 3.87 (m, 1 H), 3.41 - 3.50 (m, 1 H), 3.31 - 3.37 (m, 3

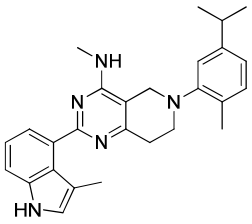
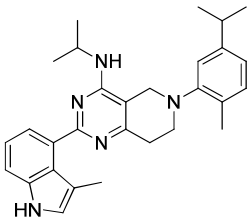
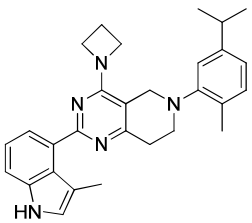
		H), 3.26 (s, 3 H), 3.11 - 3.23 (m, 1 H), 2.96 (t, *J*=5.7 Hz, 2 H), 2.84 (dt, *J*=13.9, 6.9 Hz, 1 H), 2.22 (s, 3 H), 2.02 (s, 3 H), 1.84 - 1.95 (m, 2 H), 1.52 - 1.67 (m, 2 H), 1.15 - 1.23 (m, 9 H); MS (ESI+) *m/z* 524.2 $(M+H)^+$.
17- S		6- (5- isopropil- 2- metilfenil)- 4- ((2*S*,4*S*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ ppm 10.07 (br. s., 1 H), 7.48 (d, *J*=9.1 Hz, 1 H), 7.41 (d, *J*=7.3 Hz, 1 H), 7.13 - 7.22 (m, 3 H), 7.10 (d, *J*=1.5 Hz, 1 H), 6.93 (dd, *J*=1.6, 7.7 Hz, 1 H), 4.03 - 4.28 (m, 2 H), 3.90 (dd, *J*=6.3, 10.9 Hz, 1 H), 3.49 (dt, *J*=3.5, 7.2 Hz, 1 H), 3.39 - 3.46 (m, 2 H), 3.35 (s, 3 H), 3.18 - 3.26 (m, 1 H), 3.06 - 3.13 (m, 2 H), 2.91 (td, *J*=6.9, 13.8 Hz, 1 H), 2.79 (d, *J*=13.6 Hz, 2 H), 2.32 (s, 3 H), 2.18 (d, *J*=0.8 Hz, 3 H), 1.98 – 2.04 (m, 1 H), 1.68 - 1.76 (m, 1 H), 1.59 - 1.68 (m, 1 H), 1.24 - 1.30 (m, 9 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.
17- T		2- (2,6- dimetilfenil)- N,N- dimetil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.14 - 7.23 (m, 4 H), 7.07 (d, *J*=7.6 Hz, 2 H), 6.96 - 7.04 (m, 1 H), 4.08 (s, 2 H), 3.24 (t, *J*=5.9 Hz, 2 H), 3.01 (s, 6 H), 2.91 (t, *J*=5.8 Hz, 2 H), 2.26 (s, 3 H), 2.06 (s, 6 H); MS (ESI+) *m/z* 373.2 $(M+H)^+$.
17- U		2- (2,6- dimetilfenil)- N- (2- metoxietil)- N- metil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina. Sal de HCl^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.39 (t, *J*=7.1 Hz, 1 H), 7.17 - 7.28 (m, 5 H), 6.99 - 7.09 (m, 1 H), 4.31 (br. s., 2 H), 3.89 (t, *J*=4.8 Hz, 2 H), 3.53 - 3.62 (m, 5 H), 3.19 - 3.29 (m, 5 H), 3.01 - 3.10 (m, 2 H), 2.28 (s, 3 H), 2.19 (s, 6 H); MS (ESI+) *m/z* 417.3 $(M+H)^+$.

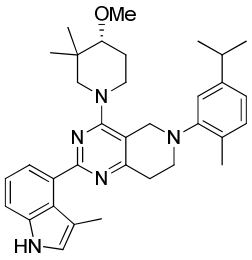
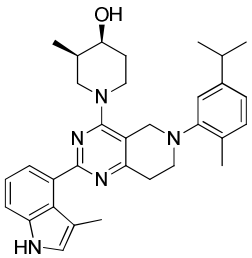
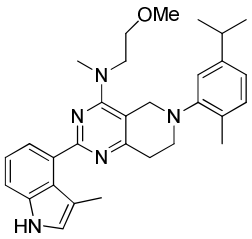
17- V		2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. Sal de HCl ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=6.8 Hz, 1 H), 7.19 - 7.28 (m, 5 H), 7.05 (td, *J*=6.9, 2.0 Hz, 1 H), 4.16 (s, 2 H), 3.76 (br. s., 2 H), 3.59 (s, 2 H), 3.29 (t, *J*=5.6 Hz, 2 H), 3.05 - 3.14 (m, 2 H), 2.28 (s, 3 H), 2.19 (s, 6 H), 1.62 - 1.73 (m, 2 H), 1.47 (t, *J*=5.6 Hz, 2 H), 0.89 (s, 6 H); MS (ESI+) *m/z* 441.3 $(M+H)^+$.
17- W		2- (2,6- dimetilfenil)- 4- (4- metoxipiperidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.39 (t, *J*=7.6 Hz, 1 H), 7.17 - 7.30 (m, 5 H), 7.01 - 7.09 (m, 1 H), 4.14 (br. s., 2 H), 3.95 - 4.06 (m, 2 H), 3.64 - 3.73 (m, 2 H), 3.21 - 3.31 (m, 4 H), 3.10 (br. s., 2 H), 2.28 (s, 3 H), 2.20 (s, 6 H), 1.88 - 2.01 (m, 2 H), 1.59 (s, 3 H); MS (ESI+) *m/z* 443.3 $(M+H)^+$.
17- X		2- (2,6- dimetilfenil)- 4- (3,3- dimetilpirrolidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.18 - 7.27 (m, 3 H) 7.14 (d, J=7.3 Hz, 1 H) 7.06 (d, J=7.6 Hz, 2 H) 7.02 (br. s., 1 H) 4.23 (s, 2 H) 3.74 (t, J=7.0 Hz, 2 H) 3.10 - 3.24 (m, 3 H) 2.87 (t, J=5.3 Hz, 2 H) 2.28 (s, 3 H) 2.07 (s, 6 H) 1.65 (t, J=7.0 Hz, 2 H) 1.05 (s, 6 H); MS (ESI+) *m/z* 427.29 $(M+H)^+$.
17- Y		4- (2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,2- dimetilmorfolina. Sal de HCl ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=7.8 Hz, 1 H), 7.19 - 7.29 (m, 5 H), 7.05 (dd, *J*=7.6, 6.8 Hz, 1 H), 4.16 (s, 2 H), 3.84 (br. s., 2 H), 3.71 (br. s., 4 H), 3.21 - 3.29 (m, 2 H), 3.09 (br. s., 2 H), 2.28 (s, 3 H), 2.18 (s, 6 H), 1.16 (s, 6 H); MS (ESI+) *m/z* 443.3 $(M+H)^+$.

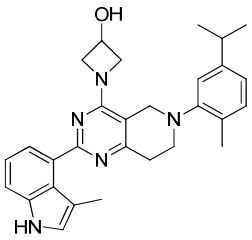
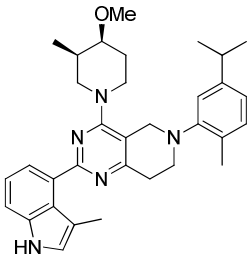
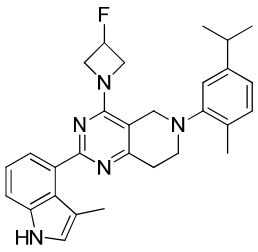
17- Z		4- (azetidin- 1- il)- 2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. Sal de HCl ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 (t, *J*=7.6 Hz, 1 H), 7.18 - 7.29 (m, 5 H), 7.01 - 7.09 (m, 1 H), 4.83 - 4.92 (m, 2 H), 4.22 - 4.31 (m, 2 H), 4.20 (s, 2 H), 3.15 - 3.21 (m, 2 H), 2.92 - 2.98 (m, 2 H), 2.32 - 2.41 (m, 2 H), 2.30 (s, 3 H), 2.19 (s, 6 H); MS (ESI+) *m/z* 385.3 $(M+H)^+$.
17- AA		6- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.46 (d, *J*=7.8 Hz, 1 H), 7.33 - 7.40 (m, 1 H), 7.19 - 7.25 (m, 1 H), 7.17 (d, *J*=8.1 Hz, 1 H), 7.05 - 7.11 (m, 2 H), 7.02 (dd, *J*=8.1, 2.0 Hz, 1 H), 4.00 (s, 2 H), 3.30 - 3.46 (m, 4 H), 3.09 - 3.28 (m, 4 H), 2.29 (s, 3 H), 2.10 (s, 3 H), 1.68 - 1.77 (m, 2 H), 1.42 - 1.48 (m, 2 H), 0.98 (s, 6 H); MS (ESI+) *m/z* 500.3 $(M+H)^+$.
17- AB		4- (4- metoxipiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.26 (br. s., 1 H), 7.46 (d, *J*=9.3 Hz, 1 H), 7.38 (d, *J*=6.3 Hz, 1 H), 7.19 - 7.24 (m, 3 H), 7.13 (d, *J*=6.8 Hz, 1 H), 7.07 (s, 1 H), 7.02 - 7.05 (m, 1 H), 4.01 (s, 2 H), 3.76 (br. s., 2 H), 3.43 (br. s., 1 H), 3.30 - 3.37 (m, 6 H), 3.12 - 3.28 (br. s., 3 H), 2.32 (s, 3 H), 2.10 (s, 3 H), 1.93 - 2.01 (m, 2 H), 1.60 - 1.71 (m, 2 H); MS (ESI+) *m/z* 468.3 $(M+H)^+$.
17- AC		6- (5- cloro- 2- metilfenil)- 4- (4- metoxipiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.20 – 8.29 (br. s., 1 H), 7.45 (d, *J*=7.8 Hz, 1 H), 7.37 (d, *J*=7.3 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.16 (d, *J*=0.5 Hz, 1 H), 7.11 (d, *J*=2.3 Hz, 1 H), 7.07 (s, 1 H), 7.02 (dd, *J*=7.8, 2.0 Hz, 1 H), 3.98 (s, 2 H), 3.69 - 3.79 (m, 2 H), 3.39 - 3.46 (m, 1 H), 3.31 - 3.37 (m, 5

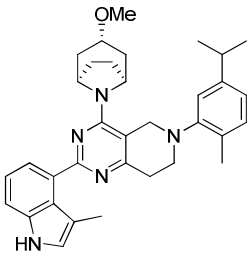
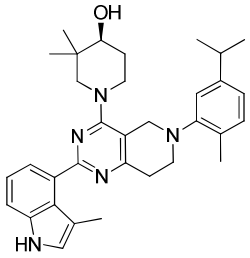
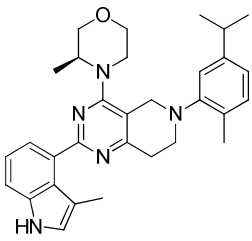
		H), 3.11 - 3.27 (m, 4 H), 2.28 (s, 3 H), 2.10 (d, *J*=0.8 Hz, 3 H), 1.94 - 2.02 (m, 2 H), 1.60 - 1.70 (m, 2 H); MS (ESI+) *m/z* 502.3 $(M+H)^+$.
17-AD		2- metil- 1- (metil(2- (3- metil- 1H- indol- 4- il)- 6- (o-tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)amino)propan- 2- ol. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.89 (br. s., 1 H), 7.37 (d, *J*=10.1 Hz, 1 H), 7.07 - 7.22 (m, 6 H), 7.00 - 7.03 (m, 1 H), 4.71 (s, 1 H), 4.09 (s, 2 H), 3.67 (s, 2 H), 3.19 (s, 3 H), 2.94 (s, 2 H), 2.26 (s, 3 H), 2.00 (s, 3 H), 1.05 (s, 6 H); MS (ESI+) *m/z* 456.2 $(M+H)^+$.
17-AE		1- ((6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.90 (br. s, 1 H), 7.39 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.23 (d, *J*=8.1 Hz, 1 H), 7.03 - 7.16 (m, 5 H), 4.71 (s, 1 H), 4.15 (s, 2 H), 3.69 (s, 2 H), 3.19 (s, 3 H), 2.91 (t, *J*=5.7 Hz, 2 H), 2.24 (s, 3 H), 1.99 (s, 3 H), 1.06 (s, 6 H); MS (ESI+) *m/z* 490.2 $(M+H)^+$.
17- AF		6- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.83 - 7.87 (m, 1 H), 7.28 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.1 Hz, 1 H), 7.12 - 7.17 (m, 2 H), 7.09 (dd, *J*=8.1, 2.0 Hz, 1 H), 4.02 (s, 2 H), 3.73 - 3.78 (m, 2 H), 3.58 - 3.64 (m, 2 H), 3.55 (s, 2 H), 3.37 (t, *J*=5.8 Hz, 2 H), 2.67 (s, 3 H), 2.31 (s, 3 H), 1.75 - 1.81 (m, 2 H), 1.50 - 1.56 (m, 2 H), 0.95 (s, 6 H); MS (ESI+) *m/z* 501.2 $(M+H)^+$.

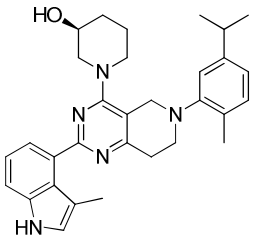
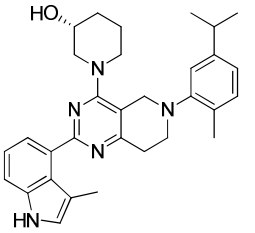
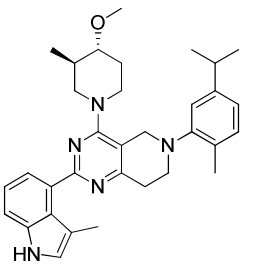
17-AG		4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,2- dimetilmorfolina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.24 (s, 3 H) 1.26 (s, 3 H) 1.28 (s, 6 H) 2.10 (s, 3 H) 2.29 (s, 3 H) 2.89 (dt, *J*=13.9, 7.0 Hz, 1 H) 3.10 - 3.21 (m, 2 H) 3.22 - 3.31 (m, 2 H) 3.37 (t, *J*=5.9 Hz, 2 H) 3.40 - 3.45 (m, 2 H) 3.78 - 3.87 (m, 2 H) 4.04 (s, 2 H) 6.91 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.97 (d, *J*=1.5 Hz, 1 H) 7.07 (s, 1 H) 7.14 (d, *J*=8.1 Hz, 1 H) 7.22 (t, *J*=7.7 Hz, 1 H) 7.36 (d, *J*=7.1 Hz, 1 H) 7.45 (d, *J*=8.1 Hz, 1 H) 8.21 (br. s., 1 H); MS (ESI+) *m/z* 510.3 $(M+H)^+$.
17-AH		6- (5- isopropil- 2- metilfenil)- N,N- dimetil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.25 (d, *J*=6.8 Hz, 6 H) 2.12 (s, 3 H) 2.28 (s, 3 H) 2.89 (spt, *J*=6.9 Hz, 1 H) 3.06 - 3.24 (m, 8 H) 3.34 (t, *J*=5.9 Hz, 2 H) 4.09 (s, 2 H) 6.92 (dd, *J*=7.7, 1.6 Hz, 1 H) 7.01 (d, *J*=1.8 Hz, 1 H) 7.06 (d, *J*=1.0 Hz, 1 H) 7.14 (d, *J*=7.6 Hz, 1 H) 7.21 (t, *J*=7.7 Hz, 1 H) 7.38 (d, *J*=7.1 Hz, 1 H) 7.45 (d, *J*=8.1 Hz, 1 H) 8.27 (br. s., 1 H); MS (ESI+) *m/z* 440.2 $(M+H)^+$.
17- AI		1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3,3- dimetilpiperidin- 4- ol. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 0.90 (s, 3 H) 0.93 (s, 3 H) 1.18 (d, *J*=6.8 Hz, 6 H) 1.52 - 1.65 (m, 1 H) 1.70 - 1.78 (m, 1 H) 2.01 (s, 3 H) 2.21 (s, 3 H) 2.74 (d, *J*=12.9 Hz, 1 H) 2.83 (dt, *J*=13.6, 6.8 Hz, 1 H) 2.90 - 3.05 (m, 3 H) 3.26 - 3.36 (m, 3 H) 3.42 (d, *J*=13.1 Hz, 1 H) 3.61 - 3.70 (m, 1 H) 4.06 (s, 2 H) 4.63 (d, *J*=4.8 Hz, 1 H) 6.86 (dd, *J*=7.6, 1.3 Hz, 1 H) 6.96 (s, 1 H) 7.07 - 7.15 (m, 3 H) 7.19 (dd, *J*=7.1, 1.0 Hz, 1 H) 7.40 (dd, *J*=8.0, 0.9 Hz, 1 H) 10.89 (br. s., 1 H); MS (ESI+) *m/z* 524.4 $(M+H)^+$.

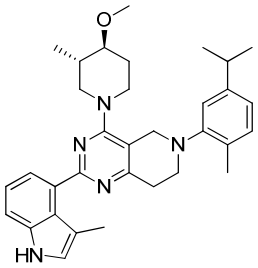
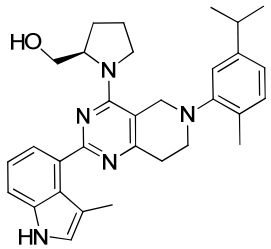
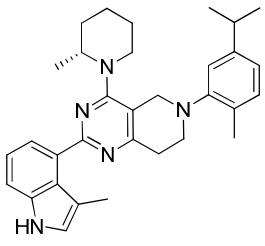
17- AJ		6- (5- isopropil- 2- metilfenil)- N- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 8.23 (br. s., 1 H), 7.42 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.34 (dd, *J*=7.3, 1.0 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.16 (d, *J*=7.8 Hz, 1 H), 7.03 - 7.07 (m, 2 H), 6.93 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.56 (br. s., 1 H), 3.85 (s, 2 H), 3.28 (t, *J*=5.7 Hz, 2 H), 3.09 (d, *J*=4.8 Hz, 3 H), 3.02 (t, *J*=5.6 Hz, 2 H), 2.89 (spt, *J*=6.9 Hz, 1 H), 2.32 (s, 3 H), 2.12 (d, *J*=1.0 Hz, 3 H), 1.26 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 426.2 $(M+H)^+$.
17- AK		N- isopropil- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina. ^{1}H NMR (400 MHz, DICLOROMETANO- d_6) δ ppm 8.23 (br. s., 1 H), 7.42 (dd, *J*=8.1, 0.8 Hz, 1 H), 7.33 (d, *J*=7.1 Hz, 1 H), 7.15 - 7.23 (m, 2 H), 7.08 (d, *J*=1.8 Hz, 1 H), 7.05 (d, *J*=1.0 Hz, 1 H), 6.94 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.48 - 4.57 (m, 1 H), 3.80 (s, 2 H), 3.28 (t, *J*=5.7 Hz, 2 H), 2.99 - 3.07 (m, 2 H), 2.90 (spt, *J*=6.9 Hz, 1 H), 2.33 (s, 3 H), 2.12 (d, *J*=1.0 Hz, 3 H), 1.23 - 1.28 (m, 12 H); MS (ESI+) *m/z* 454.2 $(M+H)^+$.
17- AL		4- (azetidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.16 - 8.22 (m, 1 H), 7.41 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.29 - 7.32 (m, 1 H), 7.16 - 7.21 (m, 1 H), 7.14 (d, *J*=7.6 Hz, 1 H), 7.02 - 7.05 (m, 1 H), 6.99 (d, *J*=1.8 Hz, 1 H), 6.90 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.29 (t, *J*=7.6 Hz, 4 H), 4.06 (s, 2 H), 3.28 (t, *J*=5.7 Hz, 2 H), 2.99 - 3.05 (m, 2 H), 2.88 (spt, *J*=6.9 Hz, 1 H), 2.29 - 2.40 (m, 5 H), 2.10 (d, *J*=0.8 Hz, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 452.1 $(M+H)^+$.

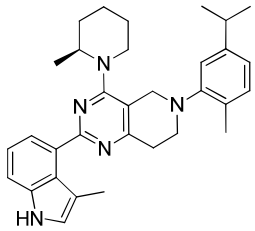
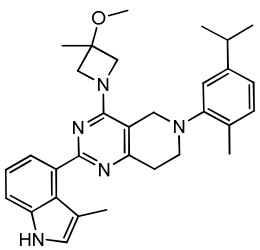
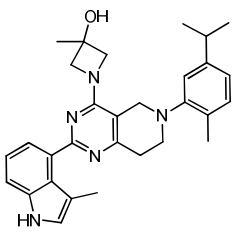
17-AM		(*R*)- 6- (5- Isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 0.94 - 0.99 (m, 3 H) 1.01 (s, 3 H) 1.25 (d, *J*=7.1 Hz, 6 H) 1.63 - 1.76 (m, 1 H) 1.91 - 2.03 (m, 1 H) 2.10 (s, 3 H) 2.28 (s, 3 H) 2.81 - 3.03 (m, 3 H) 3.11 - 3.25 (m, 3 H) 3.34 (s, 3 H) 3.35 - 3.39 (m, 2 H) 3.41 - 3.53 (m, 1 H) 3.74 (dd, *J*=11.4, 6.3 Hz, 1 H) 4.05 (s, 2 H) 6.91 (dd, *J*=7.6, 1.5 Hz, 1 H) 6.97 (d, *J*=1.5 Hz, 1 H) 7.06 (d, *J*=1.0 Hz, 1 H) 7.14 (d, *J*=7.8 Hz, 1 H) 7.19 - 7.25 (m, 1 H) 7.36 (d, *J*=7.1 Hz, 1 H) 7.45 (d, *J*=8.1 Hz, 1 H) 8.27 (br. s., 1 H); MS (ESI+) *m/z* 538.4 $(M+H)^+$.
17-AN		*racémico*- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidin- 4- ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.24 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.35 (d, *J*=7.1 Hz, 1 H), 7.19 - 7.23 (m, *J*=7.6 Hz, 1 H), 7.13 (d, *J*=7.8 Hz, 1 H), 7.06 (d, *J*=1.0 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.90 (dd, *J*=8.1, 1.5 Hz, 1 H), 4.03 (d, *J*=7.1 Hz, 2 H), 3.93 (br. s., 1 H), 3.39 - 3.61 (m, 1 H), 3.35 (t, *J*=6.3 Hz, 2 H), 3.24 (app t, *J*=11.9 Hz, 1 H), 3.15 (br. s., 1 H), 2.89 (spt, *J*=7.1 Hz, 1 H), 2.27 (s, 3 H), 2.10 (s, 1 H), 1.92 - 2.00 (m, 1 H), 1.78 - 1.88 (m, 2 H), 1.25 (d, *J*=7.1 Hz, 6 H), 0.99 (d, *J*=7.1 Hz, 3 H); MS (ESI+) *m/z* 510.2 $(M+H)^+$.
17-AO		6- (5- isopropil- 2- metilfenil)- N- (2- metoxietil)- N- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.37 (br. s., 1 H), 7.43 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.36 (dd, *J*=7.1 Hz, 1 H), 7.17 - 7.23 (m, 1 H), 7.14 (d, *J*=7.6 Hz, 1 H), 7.05 (d, *J*=1.3 Hz, 1 H), 7.00 (d, *J*=1.8 Hz, 1 H), 6.91 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.11 (s, 2 H), 3.72 (br. s., 2 H), 3.62 (app. t, *J*=5.8 Hz, 2 H), 3.33 (app. t, *J*=5.8 Hz, 2 H), 3.30 (s, 3 H), 3.20 (br. s., 4 H), 2.89 (spt, *J*=7.1 Hz, 1 H), 2.27 (s, 3 H), 2.11

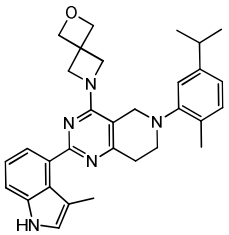
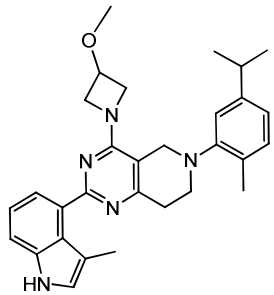
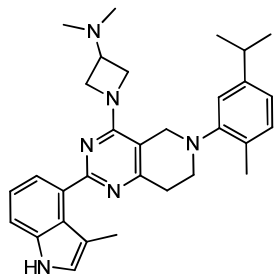
		(d, *J*=0.8, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 484.22 $(M+H)^+$.
17- AP		1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)azetidin- 3- ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.43 (d, *J*=7.3 Hz, 1 H), 7.31 (d, *J*=7.3 Hz, 1 H), 7.15 - 7.19 (m, 2 H), 7.05 (s, 1 H), 6.99 (d, *J*=1.8 Hz, 1 H), 6.93 (dd, *J*=8.1, 1.5 Hz, 1 H), 4.65 - 4.74 (m, 1 H), 4.47 (dd, *J*=8.6, 6.8 Hz, 2 H), 4.14 (br. s., 2 H), 4.01 (s, 2 H), 3.25 (t, *J*=5.6 Hz, 2 H), 3.01 - 3.09 (m, 2 H), 2.89 (spt, *J*=6.6 Hz, 1 H), 2.30 (s, 3 H), 2.09 (s, 3 H), 1.26 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 468.3 $(M+H)^+$.
17- AQ		6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémico. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.21 (br. s., 1 H), 7.43 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.34 (d, *J*=6.6 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.13 (d, *J*=7.8 Hz, 1 H), 7.05 (dd, *J*=2.0, 1.0 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.90 (dd, *J*=7.6, 1.8 Hz, 1 H), 4.03 (AB q, *J*=6.1 Hz, 2 H), 3.41 - 3.52 (m, 1 H), 3.29 - 3.40 (m, 9 H), 3.11 (br. s., 2 H), 2.89 (spt, *J*=7.3 Hz, 1 H), 2.27 (s, 3 H), 2.09 (s, 3 H), 2.01 - 2.08 (m, 1 H), 1.89 - 1.99 (m, 1 H), 1.66 - 1.77 (m, 1 H), 1.25 (d, *J*=6.8 Hz, 6 H), 0.98 (d, *J*=6.8 Hz, 3 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.
17- AR		4- (3- fluoroazetidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.92 (br. s., 1 H), 7.41 (d, *J*=8.1 Hz, 1 H), 7.21 (d, *J*=8.1 Hz, 1 H), 7.06 - 7.16 (m, 3 H), 7.02 (d, *J*=1.5 Hz, 1 H), 6.89 (dd, *J*=7.8, 1.5 Hz, 1 H), 5.35 - 5.59 (m, 1 H), 4.49 - 4.66 (m, 2 H), 4.23 - 4.38 (m, 2 H), 4.05 (s, 2 H), 3.23 (t, *J*=5.7 Hz, 2 H), 2.81 - 2.94 (m, 3 H), 2.24 (s, 3 H), 2.03 (d, *J*=0.8 Hz, 3 H), 1.20 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 470.1 $(M+H)^+$.

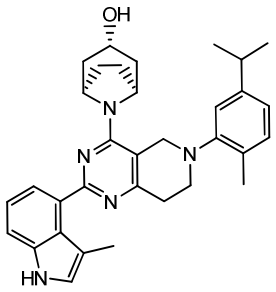
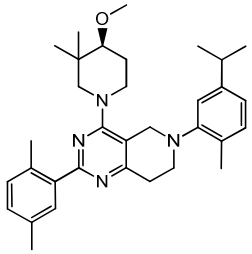
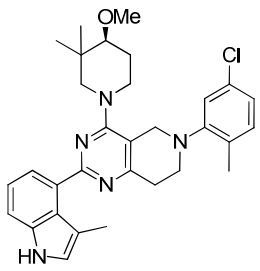
17- AS		6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR Sal de TFA (400 MHz, DMSO- d_6) δ ppm 10.88 - 10.92 (br. s., 1 H), 7.39 (dd, *J*=8.0, 1.1 Hz, 1 H), 7.19 (dd, *J*=7.2, 1.1 Hz, 1 H), 7.13 (s, 1 H), 7.07 - 7.13 (m, 2 H), 7.01 (d, *J*=1.5 Hz, 1 H), 6.88 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.47 (br. s., 2 H), 4.02 (s, 2 H), 3.47 (br. s., 1 H), 3.21 (s, 3 H), 2.92 (t, *J*=5.9 Hz, 2 H), 2.85 (quin, *J*=6.9 Hz, 1 H), 2.22 (s, 3 H), 1.95 - 2.06 (m, 9 H), 1.79 - 1.95 (m, 4 H), 1.16 - 1.22 (m, 6 H); MS (ESI+) *m/z* 536.2 $(M+H)^+$.
17- AT		(*S*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3,3- dimetilpiperidin- 4- ol. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 0.90 (s, 3 H) 0.93 (s, 3 H) 1.18 (d, *J*=6.8 Hz, 6 H) 1.52 - 1.65 (m, 1 H) 1.70 - 1.78 (m, 1 H) 2.01 (s, 3 H) 2.21 (s, 3 H) 2.74 (d, *J*=12.9 Hz, 1 H) 2.83 (dt, *J*=13.6, 6.8 Hz, 1 H) 2.90 - 3.05 (m, 3 H) 3.26 - 3.36 (m, 3 H) 3.42 (d, *J*=13.1 Hz, 1 H) 3.61 - 3.70 (m, 1 H) 4.06 (s, 2 H) 4.63 (d, *J*=4.8 Hz, 1 H) 6.86 (dd, *J*=7.6, 1.3 Hz, 1 H) 6.96 (s, 1 H) 7.07 - 7.15 (m, 3 H) 7.19 (dd, *J*=7.1, 1.0 Hz, 1 H) 7.40 (dd, *J*=8.0, 0.9 Hz, 1 H) 10.89 (br. s., 1 H); MS (ESI+) *m/z* 524.4 $(M+H)^+$.
17- AU		(*S*)- 4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3- metilmorfolina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.25 (d, *J*=7.6 Hz, 6 H) 1.28 (d, *J*=6.3 Hz, 3 H) 2.11 (s, 3 H) 2.28 (s, 3 H) 2.89 (dt, *J*=13.8, 6.9 Hz, 1 H) 3.08 - 3.24 (m, 2 H) 3.29 - 3.43 (m, 3 H) 3.45 - 3.55 (m, 2 H) 3.57 - 3.71 (m, 2 H) 3.78 (dd, *J*=11.2, 2.7 Hz, 1 H) 3.83 - 3.90 (m, 1 H) 3.92 - 4.10 (m, 2 H) 6.91 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.98 (d, *J*=1.5 Hz, 1 H) 7.07 (s, 1 H) 7.14 (d, *J*=7.8 Hz, 1 H) 7.22 (t, *J*=7.8 Hz, 1 H) 7.36 (d, *J*=7.3 Hz,

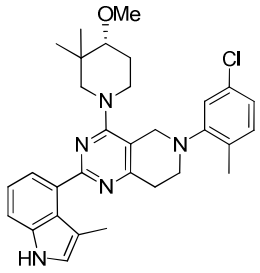
		1 H) 7.45 (d, *J*=7.8 Hz, 1 H) 8.21 (br. s., 1 H); MS (ESI+) *m/z* 496.3 $(M+H)^+$.
17-AV		(*S*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.26 (d, *J*=7.1 Hz, 6 H) 1.55 - 1.60 (m, 1 H) 1.67 - 1.94 (m, 3 H) 2.10 (s, 3 H) 2.26 (s, 3 H) 2.90 (spt, *J*=7.0 Hz, 1 H) 3.08 - 3.16 (m, 2 H) 3.23 - 3.62 (m, 5 H) 3.76 (dd, *J*=13.4, 4.3 Hz, 1 H) 3.86 - 3.94 (m, 1 H) 3.97 - 4.05 (m, 2 H) 6.92 (dd, *J*=7.7, 1.6 Hz, 1 H) 7.01 (d, *J*=1.5 Hz, 1 H) 7.08 (s, 1 H) 7.13 (d, *J*=7.8 Hz, 1 H) 7.17 - 7.27 (m, 1 H) 7.34 (d, *J*=7.3 Hz, 1 H) 7.48 (d, *J*=8.3 Hz, 1 H) 8.43 (s, 1 H); MS (ESI+) *m/z* 496.5 $(M+H)^+$.
17-AW		(*R*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperidin- 3- ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 1.25 (d, *J*=6.8 Hz, 6 H) 1.54 - 1.59 (m, 1 H) 1.66 - 1.93 (m, 3 H) 2.11 (s, 3 H) 2.27 (s, 3 H) 2.89 (dt, *J*=13.7, 6.9 Hz, 1 H) 3.03 - 3.22 (m, 2 H) 3.24 - 3.57 (m, 5 H) 3.75 (dd, *J*=13.5, 4.4 Hz, 1 H) 3.85 - 3.94 (m, 1 H) 4.01 (s, 2 H) 6.91 (dd, *J*=7.7, 1.6 Hz, 1 H) 7.00 (d, *J*=1.5 Hz, 1 H) 7.1 (s, 1 H) 7.14 (d, *J*=7.8 Hz, 1 H) 7.18 - 7.26 (m, 1 H) 7.33 (d, *J*=7.3 Hz, 1 H) 7.46 (d, *J*=8.1 Hz, 1 H) 8.29 (br. s., 1 H); MS (ESI+) *m/z* 496.5 $(M+H)^+$.
17-AX		6- (5- isopropil- 2- metilfenil)- 4- ((3*R*,4*R*)- 4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 0.97 (d, *J*=6.6 Hz, 3 H) 1.19 (d, *J*=6.8 Hz, 6 H) 1.33 - 1.44 (m, 1 H) 1.65 - 1.73 (m, 1 H) 2.02 (s, 3 H) 2.08 - 2.15 (m, 1 H) 2.21 (s, 3 H) 2.76 (dd, *J*=13.1, 9.9 Hz, 1 H) 2.84 (dt, *J*=13.8, 6.9 Hz, 1 H) 2.92 - 3.05 (m, 4 H) 3.28 (s, 3 H) 3.30 - 3.37 (m, 2 H) 3.70 (d, *J*=12.6 Hz, 1 H) 3.80 (d, *J*=13.4 Hz, 1 H) 3.94 - 4.11 (m, 2 H) 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H) 6.98 (s, 1 H) 7.07 - 7.16 (m, 3 H) 7.17 - 7.23 (m, 1 H) 7.41 (dd, *J*=8.1, 1.0

		Hz, 1 H) 10.88 (s, 1 H); MS (ESI+) *m/z* 524.3 $(M+H)^+$.
17-AY		6- (5- isopropil- 2- metilfenil)- 4- ((*3S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 0.97 (d, *J*=6.6 Hz, 3 H) 1.19 (d, *J*=6.8 Hz, 6 H) 1.31 - 1.45 (m, 1 H) 1.63 - 1.74 (m, 1 H) 2.02 (s, 3 H) 2.07 - 2.15 (m, 1 H) 2.21 (s, 3 H) 2.76 (dd, *J*=13.1, 9.9 Hz, 1 H) 2.84 (dt, *J*=13.8, 6.9 Hz, 1 H) 2.91 - 3.06 (m, 4 H) 3.27 (s, 3 H) 3.30 - 3.39 (m, 2 H) 3.70 (d, *J*=11.4 Hz, 1 H) 3.80 (d, *J*=12.4 Hz, 1 H) 3.94 - 4.12 (m, 2 H) 6.87 (d, *J*=7.8 Hz, 1 H) 6.98 (s, 1 H) 7.05 - 7.16 (m, 3 H) 7.20 (dd, *J*=7.1, 0.8 Hz, 1 H) 7.41 (dd, *J*=8.1, 0.8 Hz, 1 H) 10.89 (br. s., 1 H); MS (ESI+) *m/z* 524.4 $(M+H)^+$.
17-AZ		(*R*)- (1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)pirrolidin- 2- il)methanol. ^{1}H (400 MHz, CD_2Cl_2) δ ppm 1.26 (d, *J*=6.8 Hz, 6 H) 1.70 - 1.81 (m, 1 H) 1.84 - 1.94 (m, 1 H) 1.97 - 2.11 (m, 2 H) 2.12 (d, *J*=1.0 Hz, 3 H) 2.29 (s, 3 H) 2.81 - 2.97 (m, 1 H) 3.05 - 3.17 (m, 1 H) 3.18 - 3.29 (m, 2 H) 3.33 - 3.44 (m, 1 H) 3.58 - 3.73 (m, 2 H) 3.76 - 3.87 (m, 2 H) 4.07 - 4.17 (m, 1 H) 4.23 - 4.33 (m, 1 H) 4.54 - 4.67 (m, 1 H) 6.93 (dd, *J*=7.7, 1.64 Hz, 1 H) 7.01 (d, *J*=1.8 Hz, 1 H) 7.07 (s, 1 H) 7.15 (d, *J*=7.8 Hz, 1 H) 7.22 (t, *J*=7.7 Hz, 1 H) 7.34 (d, *J*=7.3 Hz, 1 H) 7.47 (d, *J*=7.8 Hz, 1 H) 8.42 (br. s., 1 H); MS (ESI+) *m/z* 496.1 $(M+H)^+$.
17-BA		(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H (400 MHz, CD_2Cl_2) δ ppm 1.19 - 1.29 (m, 9 H) 1.50 - 1.89 (m, 6 H) 2.11 (s, 3 H) 2.28 (s, 3 H) 2.89 (spt, *J*=6.9 Hz, 1 H) 3.07 - 3.17 (m, 2 H) 3.24 (ddd, *J*=13.5, 10.7, 3.2 Hz, 1 H) 3.32 - 3.41 (m, 2 H) 3.53 - 3.63 (m, 1 H) 3.93 - 4.10 (m, 2 H) 4.11 - 4.21 (m, 1 H) 6.90 (dd, *J*=7.71, 1.6 Hz, 1

		H) 6.98 (d, *J*=1.5 Hz, 1 H) 7.04 (d, *J*=1.1 Hz, 1 H) 7.13 (d, *J*=7.8 Hz, 1 H) 7.17 - 7.24 (m, 1 H) 7.34 (d, *J*=6.6 Hz, 1 H) 7.42 (dd, *J*=8.1, 1.0 Hz, 1 H) 8.22 (br. s., 1 H); MS (ESI+) *m/z* 494.4 $(M+H)^+$.
17- BB		(*S*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H (400 MHz, CD_2Cl_2) δ ppm 1.19 - 1.31 (m, 9 H) 1.47 - 1.88 (m, 6 H) 2.11 (s, 3 H) 2.28 (s, 3 H) 2.83 - 2.96 (m, 1 H) 3.09 - 3.17 (m, 2 H) 3.24 (ddd, *J*=13.5, 10.7, 3.2 Hz, 1 H) 3.32 - 3.41 (m, 2 H) 3.53 - 3.63 (m, 1 H) 3.93 - 4.10 (m, 2 H) 4.12 - 4.20 (m, 1 H) 6.90 (dd, *J*=7.6, 1.8 Hz, 1 H) 6.98 (d, *J*=1.5 Hz, 1 H) 7.03 - 7.07 (m, 1 H) 7.13 (d, *J*=7.6 Hz, 1 H) 7.18 - 7.25 (m, 1 H) 7.34 (d, *J*=7.3 Hz, 1 H) 7.43 (dd, *J*=8.1, 0.8 Hz, 1 H) 8.20 (br. s., 1 H); MS (ESI+) *m/z* 494.1 $(M+H)^+$.
17- BC		6- (5- isopropil- 2- metilfenil)- 4- (3- metoxi- 3- metilazetidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.27 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.35 (d, *J*=7.1 Hz, 1 H), 7.18 - 7.23 (m, 1 H), 7.15 (d, *J*=7.8 Hz, 1 H), 7.05 - 7.07 (m, 1 H), 7.00 (d, *J*=1.5 Hz, 1 H), 6.93 (dd, *J*=7.8, 1.8 Hz, 1 H), 4.26 (d, *J*=8.8 Hz, 2 H), 4.03 - 4.09 (m, 4 H), 3.29 (t, *J*=5.6 Hz, 2 H), 3.24 (s, 3 H), 3.06 - 3.16 (m, 2 H), 2.89 (spt, *J*=6.8 Hz, 1 H), 2.31 (s, 3 H), 2.11 (d, *J*=0.8 Hz, 3 H), 1.51 (s, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z*496.1 $(M+H)^+$.
17- BD		1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilazetidin- 3- ol. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.89 (br. s., 1 H), 7.40 (br. s., 1 H), 7.18 (d, *J*=6.6 Hz, 1 H), 7.06 - 7.20 (m, 3 H), 7.02 (s, 1 H), 6.89 (d, *J*=7.3 Hz, 1 H), 3.97 - 4.13 (m, 5 H), 3.18 - 3.25 (m, 2 H), 2.81 - 2.92 (m, 3 H), 2.24 (s, 3 H), 2.03 (s, 3 H),

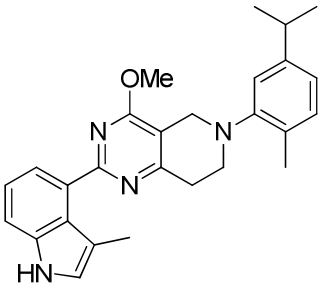
		1.42 (s, 3 H), 1.20 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 482.1 $(M+H)^+$.
17- BE		6- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- oxa- 6- azaspiro[3.3]heptanos. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.45 - 7.56 (m, 2 H), 7.21 (app. t, *J*=7.8 Hz, 1 H), 7.17 (d, *J*=7.6 Hz, 1 H), 7.11 (s, 1 H), 6.94 - 7.01 (m, 2 H), 4.79 (s, 4 H), 4.53 (br. s., 2 H), 4.09 (s, 2 H), 3.46 (br. s., 1 H), 3.28 (t, *J*=8.8 Hz, 2 H), 2.86 - 2.96 (m, 1 H), 2.30 (s, 3 H), 2.14 (s, 3 H), 1.27 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 494.1 $(M+H)^+$.
17- BF		6- (5- isopropil- 2- metilfenil)- 4- (3- metoxiazetidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.32 (br. s., 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.36 (d, *J*=6.8 Hz, 1 H), 7.18 - 7.21 (m, 1 H), 7.05 (d, *J*=0.5 Hz, 1 H), 6.99 (d, *J*=1.5 Hz, 1 H), 6.93 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.46 (br. s., 2 H), 4.25 - 4.32 (m, 1 H), 4.18 (br. s., 2 H), 4.06 (s, 2 H), 3.26 - 3.32 (m, 5 H), 3.12 (br. s., 2 H), 2.88 (spt, *J*=6.3 Hz, 1 H), 2.31 (s, 3 H), 2.11 (s, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 482.1 $(M+H)^+$.
17- BG		1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.19 (br. s., 1 H), 7.41 (dd, *J*=7.1, 1.0 Hz, 1 H), 7.31 (d, *J*=6.8 Hz, 1 H), 7.17 - 7.21 (m, 1 H), 7.15 (d, *J*=7.6 Hz, 1 H), 7.04 (d, *J*=1.0 Hz, 1 H), 7.00 (d, *J*=1.8 Hz, 1 H), 6.92 (dd, *J*= 7.6, 1.8 Hz, 1 H), 4.26 (app. t, *J*=7.6 Hz, 2 H), 4.13 (br. s., 2 H), 4.05 (s, 2 H), 3.29 (t, *J*=5.6 Hz, 2 H), 3.19 (br. s., 1 H), 3.03 (br. s., 2 H), 2.89 (spt, *J*=7.1 Hz, 1 H), 2.31 (s, 3 H), 2.18 (br. s., 6 H), 2.10 (s, 3 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 495.2 $(M+H)^+$.

17-BH		(3- *endo*)- 8- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 8- azabiciclo[3.2.1]octan- 3- ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.28 (br. s, 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.34 (d, *J*=7.6 Hz, 1 H), 7.22 - 7.18 (m, 1 H), 7.14 (d, *J*=7.6 Hz, 1 H), 7.04 (d, *J*=1.0 Hz, 1 H), 7.00 (d, *J*=1.5 Hz, 1 H), 6.92 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.61 (br. s., 2 H), 4.11 (br. s., 1 H), 4.03 (s, 2 H), 3.34 (t, *J*=5.8 Hz, 2 H), 3.15 (br. s., 2 H), 2.89 (spt, *J*=7.1 Hz, 1 H), 2.29 (s, 3 H), 2.20 - 2.27 (m, 4 H), 2.10 (s, 3 H), 1.95 - 2.03 (m, 1 H), 1.79 (d, *J*=14.4 Hz, 2 H), 1.25 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 522.2 $(M+H)^+$.
17- BI		(*S*)- 2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.58 (s, 1 H), 7.05 - 7.18 (m, 3 H), 6.97 (d, *J*=1.8 Hz, 1 H), 6.89 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.00 (s, 2 H), 3.69 (d, *J*=10.6 Hz, 1 H), 3.27 - 3.42 (m, 6 H), 3.01 - 3.15 (m, 3 H), 2.91 - 2.99 (m, 1 H), 2.79 - 2.91 (m, 2 H), 2.49 (s, 3 H), 2.36 (s, 3 H), 2.27 (s, 4 H), 1.89 - 2.07 (m, 1 H), 1.60 - 1.78 (m, 1 H), 1.25 (d, *J*=6.8 Hz, 7 H), 1.00 (s, 3 H), 0.96 (s, 3 H); MS (ESI+) *m/z* 513.3 $(M+H)^+$.
17- BJ		(*S*)- 6- (5- cloro- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_3CN) δ ppm 9.13 (br. s., 1 H) 7.45 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.22 - 7.26 (m, 1 H) 7.14 - 7.22 (m, 3 H) 7.01 - 7.09 (m, 2 H) 3.98 - 4.10 (m, 2 H) 3.64 - 3.75 (m, 1 H) 3.33 - 3.40 (m, 3 H) 3.32 (s, 3 H) 3.01 - 3.12 (m, 3 H) 2.98 (dd, *J*=9.09, 4.04 Hz, 1 H) 2.86 (d, *J*=12.88 Hz, 1 H) 2.27 (s, 3 H) 2.02 (d, *J*=1.01 Hz, 3 H) 1.99 (dd, *J*=5.43, 3.92 Hz, 1 H) 1.65 (dddd, *J*=13.14, 9.60, 9.47, 3.92 Hz, 1 H) 0.98 (s, 3 H) 0.92 (s, 3 H); MS (ESI+) *m/z* 530.3 $(M+H)^+$.

17- **BK**		(*R*)- 6- (5- cloro- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.89 (s, 1 H) 7.41 (dd, *J*=8.1, 1.01 Hz, 1 H) 7.23 (d, *J*=8.1 Hz, 1 H) 7.20 (dd, *J*=7.3, 1.01 Hz, 1 H) 7.08 - 7.16 (m, 3 H) 7.06 (dd, *J*=8.1, 2.0 Hz, 1 H) 3.96 - 4.14 (m, 2 H) 3.66 (d, *J*=13.1 Hz, 1 H) 3.32 - 3.40 (m, 3 H) 3.28 (s, 3 H) 2.94 - 3.09 (m, 4 H) 2.83 (d, *J*=12.9 Hz, 1 H) 2.23 (s, 3 H) 1.90 - 2.04 (m, 4 H) 1.50 - 1.64 (m, 1 H) 0.97 (s, 3 H) 0.89 (s, 3 H); MS (ESI+) *m/z* 530.3 $(M+H)^+$.

Ejemplo 18

6- (5- Isopropil- 2- metilfenil)- 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.

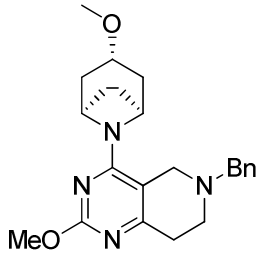


A una solución de 4- cloro- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina preparado como se describe en el Ejemplo 17 (110 mg, 0.188 mmol) en metanol (5 ml) se añadió metóxido sódico al 25% en metanol (40.6 mg, 0.188 mmol). La reacción se agitó durante aproximadamente 40 minutos a temperatura ambiente en cuyo momento la mezcla se diluyó con EtOAc y agua. Las capas se separaron y la capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se añadió a un vial de microondas, y se diluyó con EtOH (2 ml) y se cargo con KOH (aproximadamente. 100 mg, 1.75 mmol) y hidróxido de amônio al 28% en agua (1 ml, 7.25 mmol). El vial se cerró herméticamente y se calentó a través de la irradiación de microondas a 100 °C durante 45 minutos. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con diclorometano y salmuera. Las capas se separaron y la capa acuosa se extrajo dos veces más con diclorometano. Las capas orgánicas se combinaron, se secaron sobre

Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 100% acetato de etilo/heptanos) y luego se purificó adicionalmente mediante HPLC de fase inversa (20- 100% MeCN/0.1% NH_4OH en agua para proporcionar 6-(5-isopropil-2-metilfenil)-4-metoxi-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 8,16 (s ancho, 1 H). 7.37- 7.46 (m, 1 H) 7,27- 7,38 (m, 1 H) 7.11 - 7.21 (m, 1 H) 7,07 (d , J = 7,6 Hz, 1 H) 6.98- 7.05 (m, 1 H) 6,96 (s, 1 H) 6.76- 6.90 (m, 1 H) 4,00 (s, 3 H) 3,34 (s, 1 H) 3.17 - 3,28 (m, 1 H) 2.90 - 3.17 (m, 1 H) 2,76 - 2,90 (m, 1 H) 2,24 (s, 2 H) 2,05 (s, 2 H) 01.09 - 01.28 (m, 6 H), MS (ESI+) m/z 427.25 (M+H)+.

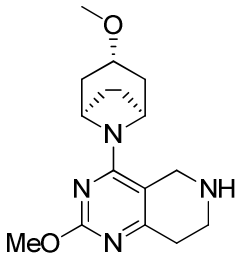
Ejemplo 19

19- A. 19- A. 6- Bencil- 2- metoxi- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



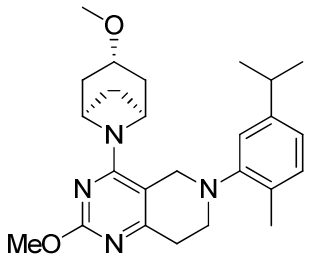
A un vial de microondas que contiene 6- bencil- 2- cloro- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina(1.6 g, 4.0 mmol), preparado de una manera similar al descrito en el **Ejemplo 21** más adelante, se añadió una solución 0.5 M de NaOMe en THF (40 ml, 20.0 mmol). El vial se cerró herméticamente y se calentó en un reactor de microondas a 130 °C durante 30 min. La mezcla de reacción se enfrió y se concentró. El residuo se diluyó con DCM y se lavó con solución de NH_4Cl acuoso saturado. La capa acuosa se extrajo con DCM (2x). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar6- bencil- 2- metoxi- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina el cual se utilizó en la siguiente etapa sin purificación adicional. MS (ESI+) m/z 395.3 (M+H)+.

19- B.2- Metoxi- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



Una mezcla de 6- bencil- 2- metoxi- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (Crudo, 4 mmol), 20% de Pd (OH) 2 sobre carbono (húmedo) (2,25 g, 3,2 mmol) en THF (40 mL), agua (10 mL) y ácido acético (0.69 mL) se agitó bajo unaatmósfera hidrógeno a temperatura ambiente durante 2 h. La mezcla de reacción se filtró a través de Celite ® y el sólido se lavó con DCM. El filtrado combinado se lavó con solución acuoso saturada de $NaHCO_3$. Las capas se separaron y la capa acuosa se extrajo con DCM. Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentróron. El residuo se purificó mediante cromatografía en gel de sílice (0- 10% MeOH (10% NH_4OH)/DCM) para proporcionar 2-metoxi-4-((3-*endo*)-3-metoxi-8-azabiciclo[3.2.1]octan-8-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI+) m/z 305.0 (M+H)+.

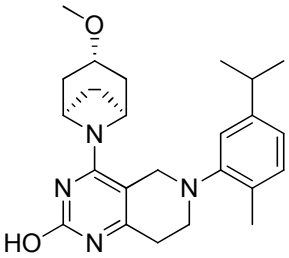
19- C. 6- (5- Isopropil- 2- metilfenil)- 2- metoxi- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



Una mezcla de2- metoxi- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (0.88 g, 2.89 mmol), trifluorometanosulfonatode 5- isopropil- 2- metilfenilo (1.22 g, 4.34 mmol), aducto de cloro(2- diciclohexilfosfino- 2'- 4'- 6'- triisopropil- 1,1'- bifenil)[2- (2- aminoetil)fenil]paladio(II)–metil- *t*- butileter (CAS # 1028206- 56- 5, 0.21 g, 0.30 mmol), y Cs_2CO_3 (1.88 g, 5.78 mmol) en THF (3 mL) se calentó en un reactor de microondas a 140 °C durante 2 h. La mezcla de reacción se particionió entre EtOAc y agua. La capa orgánica se lavó con salmuera, se secó (Na_2SO_4) y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (0- 50% de EtOAc/heptano) para proporcionar 6- (5- isopropil- 2- metilfenil)- 2- metoxi- 4- ((3-

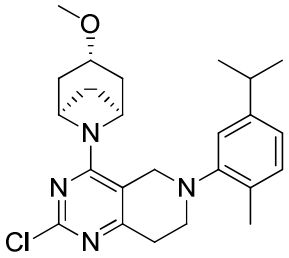
endo)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3-d]pirimidina MS (ESI+) m/z 437.1 (M+H)+.

19- D. 6- (5- Isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 2- ol.



Una mezcla de6- (5- isopropil- 2- metilfenil)- 2- metoxi- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (0.9 g, 2.06 mmol), y KOTMS (2.65 g, 20.6 mmol) en 1,4- dioxano (20 mL) se calentó en un tubo sellado a 140 °C durante 24 h. La mezcla de reacción se diluyó con DCM y se apagó con NH_4Cl acuoso saturado. La capa acuosa se extrajo con DCM. Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 2- ol, el cual se utilizó en la siguiente etapa sin purificación adicional. MS (ESI+) m/z 423.0 (M+H) +.

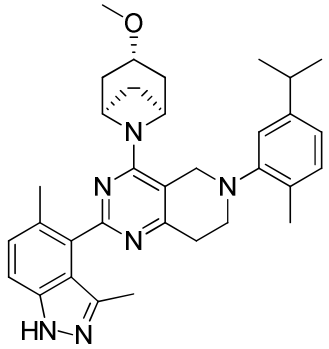
19- E.2- Cloro- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 2- ol (Crudo, 2.06 mmol) en DCE se añadió reactivo de Vilsmeier (1.3 g, 10.3 mmol) y la mezcla de reacción se calentó a 40 °C durante 18 h. La mezcla de reacción se lavó con agua y la capa acuosa se extrajo con DCM (2x). Los extractos orgánicos combinados se lavaron con salmuera, se

secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (0- 100% EtOAc/heptano) para proporcionar MS (ESI+) m/z 441.0 (M+H)+.

19- F. 2- (3,5- Dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3-*endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3-d]pirimidina.

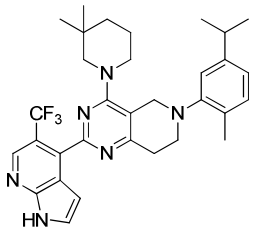
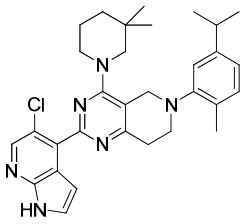
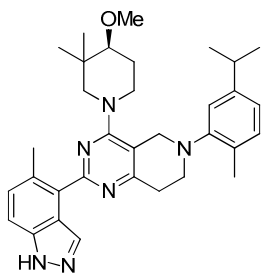


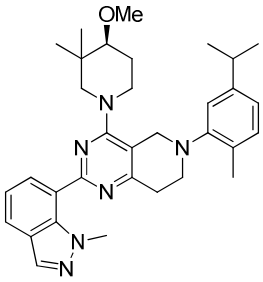
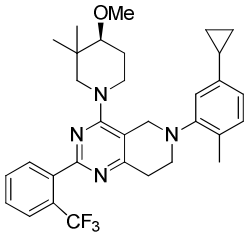
Una mezcla de 2- cloro- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (26 mg, 0.06 mmol), 3,5- dimetil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1- tosil- 1H- indazol (25 mg , 0.06 mmol), $Pd(PPh_3)_4$ (7.0 mg, 0.006 mmol), y de Na_2CO_3 (2 M, 0.09 ml, 0.18 mmol) en DME (2 mL) se calentó en un reactor de microondas a 140 °C durante 30 min. La mezcla de reacción se particionió entre EtOAc y agua. La capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (20- 100% EtOAc/heptano) para proporcionar 2- (3,5- dimetil- 1- tosil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina,el cual se utilizó en la siguiente etapa sin purificación adicional. MS (ESI+) m/z 705.0 (M+H)+.

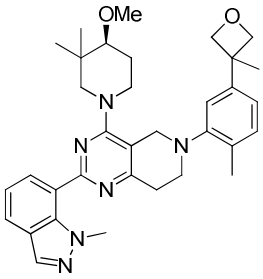
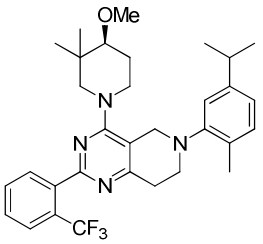
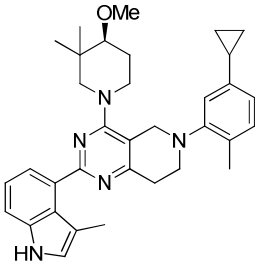
Una suspensión de 2- (3,5- dimetil- 1- tosil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (del paso anterior, teóricamente mmoles 0.06) y K_2CO_3 (82 mg, 0.6 mmol) en MeOH (5 ml) se calentó a 50 °C durante 1 h. La mezcla de reacción se filtró y se lavó con MeOH. El filtrado se concentró y el residuo se purificó mediante HPLC (CH_3CN-agua con 0.1% NH_4OH 10- 100%) para proporcionar 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 9.83 (br. s., 1 H) 7,35 (d, J = 8,60 Hz, 1 H) 7,25 (d, J = 8,60 Hz, 1 H) 7,15 (d, J = 7,83 Hz, 1 H) 7,00 (d, J

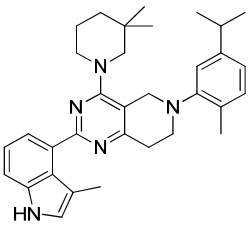
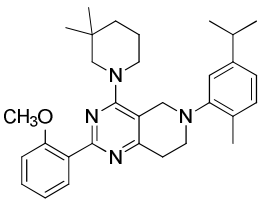
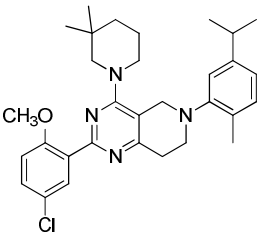
= 1,77 Hz, 1 H) 6,92 (dd, J = 7,71, 1,64 Hz, 1 H) 4,47 (br. s., 2 H) 4,05 (s, 2 H) 3,46 (t, J = 4,80 Hz, 1 H) 3,36 (t, J = 5,94 Hz, 2 H) 3,25 (s, 3 H) 3.1 - 3.10 (m, 2 H) 2,89 (spt, J = 6,95 Hz, 1 H) 2,30 (s, 3 H) 2,29 (s, 3 H) 02.02 - 02.14 (m, 4 H) 2,00 (s, 3 H) 1.87- 1.96 (m, 4 H) 1,26 (d, J = 6,82 Hz, 6 H), MS (ESI+) m/z 551.1 (M+H)+.

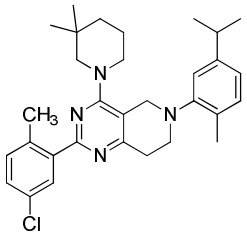
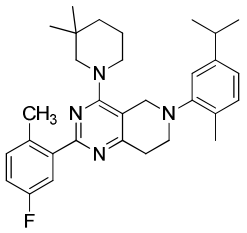
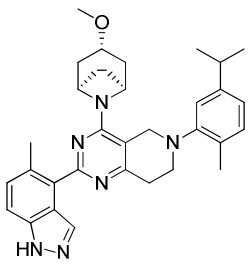
Los siguientes compuestos se prepararon de una manera similar.

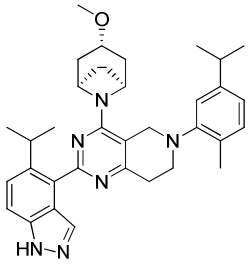
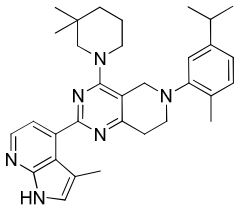
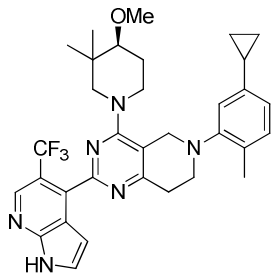
	Estructura	Nombre Quimico y Datos Analiticos
19-G		4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.22 (br.s., 1 H), 8.63 (s, 1 H), 7.11 (d, *J*=7.6 Hz, 1 H), 6.94 (s, 1 H), 6.87 (d, *J*=7.6 Hz, 1 H), 6.44 (d, *J*=3.3 Hz, 1 H), 4.09 (s, 2 H), 3.38 - 3.32 (m, 2 H), 3.10 (s, 2 H), 2.95 (t, *J*=5.9 Hz, 2 H), 2.83 (td, *J*=7.0, 14.0 Hz, 1 H), 2.23 (s, 3 H), 1.69 - 1.58 (m, 2 H), 1.44 - 1.34 (m, 2 H), 1.18 (d, *J*=7.1 Hz, 6 H), 0.94 (s, 6 H); MS (ESI+) *m/z* 563.3 $(M+H)^+$.
19-H		2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 11.94 (br. s., 1 H), 8.30 (s, 1 H), 7.50 - 7.60 (m, 1 H), 7.11 (d, *J*=7.8 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 6.41 (d, *J*=5.3 Hz, 1 H), 4.08 (s, 2 H), 3.32 - 3.38 (m, 4 H), 3.11 (s, 2 H), 2.98 (t, *J*=5.8 Hz, 2 H), 2.84 (dt, *J*=13.7, 6.9 Hz, 1 H), 2.22 (s, 3 H), 1.65 (m, 2 H), 1.40 (t, *J*=5.7 Hz, 2 H), 1.19 (d, *J*=7.1 Hz, 6 H), 0.96 (s, 6 H); MS (ESI+) *m/z* 529.2 $(M+H)^+$.
19- I		(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_3CN) δ ppm 8.00 (s, 1 H), 7.67 (d, *J*=13.4 Hz, 1 H), 7.38 (d, *J*=8.6 Hz, 1 H), 7.20 - 7.20 (m, 1 H), 7.15 (d, *J*=7.8 Hz, 1 H), 7.07 (d,

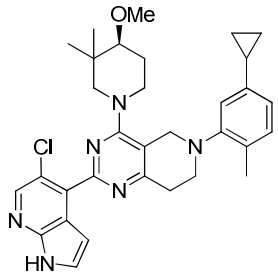
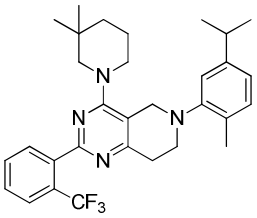
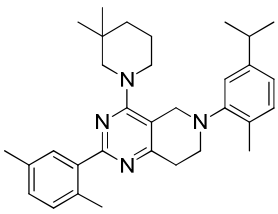
		J=1.8 Hz, 1 H), 6.95 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.09 (s, 2 H), 3.91 - 3.99 (m, 1 H), 3.70 (d, *J*=12.6 Hz, 1 H), 3.48 - 3.57 (m, 1 H), 3.25 - 3.40 (m, 6 H), 3.14 (t, *J*=5.8 Hz, 2 H), 3.07 (dd, *J*=8.0, 3.7 Hz, 1 H), 2.91 (dt, *J*=13.6, 6.8 Hz, 1 H), 2.53 (s, 3 H), 2.50 (s, 3 H), 1.64 - 1.75 (m, 1 H), 1.25 (d, *J*=6.8 Hz, 6 H), 0.98 (s, 3 H), 0.91 (s, 3 H); MS (ESI+) *m/z* 539.2 $(M+H)^+$.
19- J		(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (1- metil- 1H- indazol- 7- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 8.17 (s, 1 H), 7.87 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.69 (dd, *J*=7.1, 1.01Hz, 1 H), 7.23 (dd, *J*=8.0, 7.2 Hz, 1 H), 7.11 (d, *J*=8.1 Hz, 1 H), 7.00 (d, *J*=1.3 Hz, 1 H), 6.87 (dd, *J*=7.7, 1.4 Hz, 1 H), 4.07 (s, 2 H), 3.90 (s, 3 H), 3.71 (d, *J*=13.4 Hz, 1 H), 3.42 (d, *J*=12.9 Hz, 1 H), 3.29 (s, 3 H), 3.10 (t, *J*=10.4 Hz, 1 H), 2.97 - 3.04 (m, 3 H), 2.80 - 2.92 (m, 2 H), 2.21 (s, 3 H), 1.93 - 2.02 (m, 1 H), 1.51 - 1.63 (m, 1 H), 1.19 (dd, *J*=7.0, 0.6 Hz, 6 H), 0.99 (s, 3 H), 0.93 (s, 3 H); MS (ESI+) *m/z* 539.2 $(M+H)^+$.
19- K		(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.70 - 7.81 (m, 2 H), 7.64 (t, *J*=7.3 Hz, 1 H), 7.50 - 7.59 (m, 1 H), 7.08 (d, *J*=7.8 Hz, 1 H), 6.83 (d, *J*=1.8 Hz, 1 H), 6.72 (dd, *J*=7.6, 1.8 Hz, 1 H), 3.97 (s, 2 H), 3.71 (d, *J*=12.9 Hz, 1 H), 3.29 - 3.41 (m, 6 H), 3.06 (br. s., 1 H), 2.94 (dd, *J*=8.7, 3.9 Hz, 1 H), 2.85 (d, *J*=11.9 Hz, 1 H), 2.25 (s, 3 H), 1.95 (ddt, *J*=13.3, 6.1, 3.6 Hz, 1 H), 1.87 (tt, *J*=8.5, 5.1 Hz, 1 H), 1.62 - 1.73 (m, 1 H), 0.97 (s, 3 H), 0.93 - 0.97 (m, 2 H), 0.93 (s, 3 H), 0.63 - 0.68 (m, 2 H); MS (ESI+) *m/z* 551.4 $(M+H)^+$.

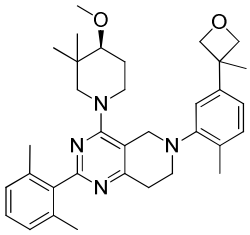
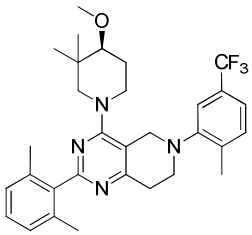
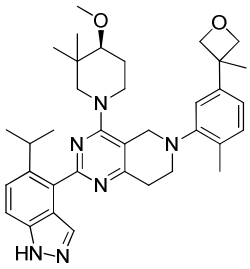
19- L		(*S*)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (1- metil- 1H- indazol- 7- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}HNMR (400 MHz, DMSO- d_6) δ ppm 8.17 (s, 1 H), 7.87 (dd, *J*=8.0, 1.1 Hz, 1 H), 7.69 (dd, *J*=7.1, 1.0 Hz, 1 H), 7.23 (dd, *J*=8.0, 7.2 Hz, 1 H), 7.19 (d, *J*=8.1 Hz, 1 H), 6.98 (d, *J*=1.8 Hz, 1 H), 6.87 (dd, *J*=7.8, 1.8 Hz, 1 H), 4.79 (dd, *J*=5.6, 1.8 Hz, 2 H), 4.52 (dd, *J*=5.6, 1.0 Hz, 2 H), 4.09 (s, 2 H), 3.91 (s, 3 H), 3.70 (d, *J*=13.4 Hz, 1 H), 3.41 (d, *J*=13.4 Hz, 1 H), 3.35 - 3.37 (m, 1 H), 3.29 (s, 3 H), 3.05 - 3.14 (m, 1 H), 2.97 - 3.04 (m, 3 H), 2.88 (d, *J*=13.1 Hz, 1 H), 2.24 (s, 3 H), 1.93 - 2.03 (m, 1 H), 1.62 (s, 3 H), 1.50 - 1.60 (m, 1 H), 0.99 (s, 3 H), 0.92 (s, 3 H); MS (ESI+) *m/z* 567.0 $(M+H)^+$.
19- M		(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.71 - 7.80 (m, 2 H), 7.64 (t, *J*=7.5 Hz, 1 H), 7.55 (t, *J*=1.0 Hz, 1 H), 7.13 (d, *J*=7.8 Hz, 1 H), 6.96 (d, *J*=1.5 Hz, 1 H), 6.90 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.01 (s, 2 H), 3.70 (d, *J*=12.9 Hz, 1 H), 3.30 - 3.41 (m, 6 H), 3.06 (br. s., 2 H), 2.94 (dd, *J*=8.8, 3.8 Hz, 1 H), 2.81 - 2.90 (m, 2 H), 2.26 (s, 3 H), 1.91 - 2.01 (m, 1 H), 1.61 - 1.73 (m, 1 H), 1.48 - 1.52 (m, 1 H), 1.24 (d, *J*=7.1 Hz, 6 H), 0.98 (s, 3 H), 0.94 (s, 3 H); MS (ESI+) *m/z* 553.4 $(M+H)^+$.
19- N		(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.22 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.34 (d, *J*=7.1 Hz, 1 H), 7.21 (t,*J*=7.7 Hz, 1 H), 7.01 - 7.13 (m, 2 H), 6.84 (s, 1 H), 6.72 (d, *J*=7.8 Hz, 1 H), 4.01 (s, 2 H), 3.71 (br. s., 1 H), 3.43 (d, *J*=11.4 Hz, 1 H), 3.28 - 3.37 (m, 5 H), 3.13 (br. s., 3 H), 2.95 (dd, *J*=8.7, 3.9 Hz, 2 H), 2.26 (s, 3 H), 209 (s, 3 H),

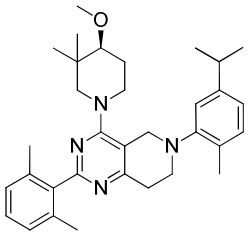
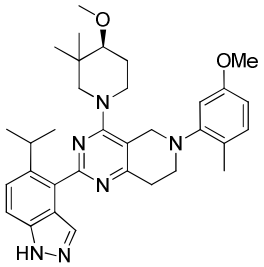
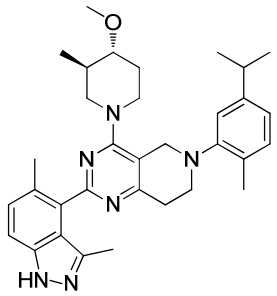
		1.98 (dd, *J*=12.8, 9.2 Hz, 1 H), 1.81 - 1.92 (m, 1 H), 1.63 - 1.74 (m, 1 H), 1.00 (s, 3 H), 0.96 (br. s., 3 H), 0.91 - 0.95 (m, 2 H), 0.62 - 0.69 (m, 2 H); MS (ESI+) *m/z* 536.0 $(M+H)^+$.
19-O		4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (br. s., 1 H), 7.44 (dd, *J*=13.0, 7.7 Hz, 2 H), 7.22 - 7.27 (m, 1 H), 7.19 (d, *J*=7.6 Hz, 1 H), 7.02 (d, *J*=18.9 Hz, 2 H), 6.94 (d, *J*=7.6 Hz, 1 H), 4.12 (s, 2 H), 3.42 (t, *J*=6.1 Hz, 2 H), 3.31 - 3.38 (m, 2 H), 3.12 - 3.19 (m, 4 H), 2.92 (dt, *J*=13.8, 6.8 Hz, 1 H), 2.34 (s, 3 H), 2.17 (s, 3 H), 1.70 - 1.79 (m, 2 H), 1.45 (t, *J*=6.1 Hz, 2 H), 1.30 (d, *J*=6.8 Hz, 6 H), 1.04 (s, 6 H); MS (ESI+) *m/z* 508.4 $(M+H)^+$.
19- P		4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (2- metoxifenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.47 (dd, *J*=7.6, 1.8 Hz, 1 H) 7.36 - 7.43 (m, 1 H) 7.11 (s, 1 H) 7.09 (s, 1 H) 6.98 - 7.04 (m, 2 H) 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H) 3.99 (s, 2 H) 3.76 (s, 3 H) 3.22 - 3.30 (m, 4 H) 3.04 (s, 2 H) 2.93 (t, 2 H) 2.85 (quin, *J*=6.9 Hz, 1 H) 2.20 (s, 3 H) 1.60 - 1.68 (m, 2 H) 1.38 (t, *J*=5.9 Hz, 2 H) 1.20 (d, *J*=7.1 Hz, 6 H) 0.96 (s, 6 H); MS (ESI+) *m/z* 485.1 $(M+H)^+$.
19-Q		2- (5- cloro- 2- metoxifenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ□ppm 7.49 (d, *J*=2.8 Hz, 1 H) 7.45 (dd, *J*=9.2, 2.8 Hz, 1 H) 7.14 (d, *J*=8.8 Hz, 1 H) 7.10 (d, *J*=7.8 Hz, 1 H) 7.01 (d, *J*=1.3 Hz, 1 H) 6.87 (dd, *J*=7.7, 1.6 Hz, 1 H) 3.98 - 4.02 (m, 2 H) 3.77 (s, 3 H) 3.24 - 3.29 (m, 4 H) 3.04 - 3.08 (m, 2 H) 2.94 (t, *J*=5.8 Hz, 2 H) 2.85 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.20 (s, 3 H) 1.59 - 1.68 (m, 2 H) 1.39 (t, *J*=5.8 Hz, 2 H) 1.20 (d, 6 H) 0.95 (s,

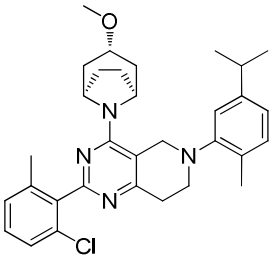
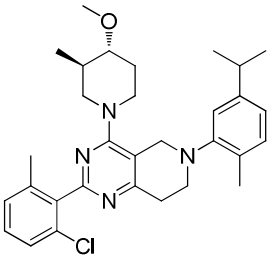
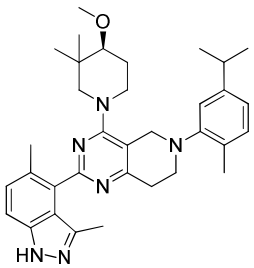
		6 H); MS (ESI+) *m/z* 519.1 $(M+H)^+$.
19-R		2- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.80 (d, *J*=2.3 Hz, 1 H) 7.39 - 7.42 (m, 1 H) 7.38 (d, *J*=2.5 Hz, 1 H) 7.32 (d, *J*=8.4 Hz, 1 H) 7.10 (d, *J*=7.8 Hz, 1 H) 6.99 (d, *J*=1.5 Hz, 1 H) 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H) 4.02 (s, 2 H) 3.26 - 3.31 (m, 4 H) 3.05 - 3.08 (m, 2 H) 2.98 (t, *J*=5.8 Hz, 2 H) 2.84 (dq, *J*=7.1, 6.9 Hz, 1 H) 2.51 - 2.53 (m, 2 H) 2.20 (s, 3 H) 1.62 - 1.70 (m, 2 H) 1.40 (t, *J*=5.9 Hz, 2 H) 1.18 (d, 6 H) 0.96 (s, 6 H); MS (ESI+) *m/z* 503.1 $(M+H)^+$.
19- S		4- (3,3- dimetilpiperidin- 1- il)- 2- (5- fluoro- 2- metilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.57 (dd, *J*=10.2, 2.9 Hz, 1 H) 7.32 (dd, *J*=8.5, 5.9 Hz, 1 H) 7.18 (td, *J*=8.4, 2.9 Hz, 1 H) 7.10 (d, *J*=7.8 Hz, 1 H) 7.00 (d, *J*=1.3 Hz, 1 H) 6.86 (dd, *J*=7.6, 1.5 Hz, 1 H) 4.02 (s, 2 H) 3.33 (s, 3 H) 3.26 - 3.32 (m, 4 H) 3.05 - 3.10 (m, 2 H) 2.97 (t, *J*=5.8 Hz, 2 H) 2.84 (spt, *J*=6.8 Hz, 1 H) 2.20 (s, 3 H) 1.61 - 1.71 (m, 2 H) 1.40 (t, *J*=5.8 Hz, 2 H) 1.19 (d, *J*=6.8 Hz, 6 H) 0.96 (s, 6 H); MS (ESI+) *m/z* 487.1 $(M+H)^+$.
19- T		6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.21 (br. s., 1 H) 7.49 (d, J=8.3 Hz, 1 H) 7.30 - 7.43 (m, 2 H) 7.20 (d, J=8.3 Hz, 1 H) 7.07 (d, J=1.5 Hz, 1 H) 6.97 (dd, J=7.7, 1.6 Hz, 1 H) 4.59 (br. s., 2 H) 4.09 (s, 2 H) 3.53 (t, J=4.8 Hz, 1 H) 3.40 (t, J=5.8 Hz, 2 H) 3.32 (s, 3 H) 3.11 - 3.26 (m, 1 H) 2.96 (dt, J=13.9, 7.0 Hz, 1 H) 2.66 (s, 3 H) 2.35 (s, 3 H) 2.08 - 2.25 (m, 4 H) 1.93 - 2.06 (m, 4 H) 1.31 (d, J=6.8 Hz, 6 H); MS (ESI+) *m/z* 537.0 $(M+H)^+$.

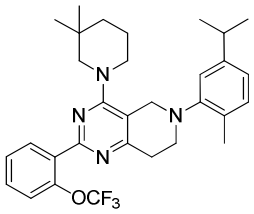
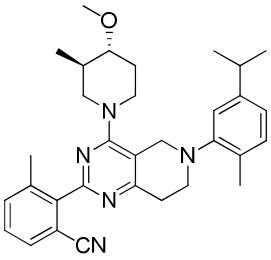
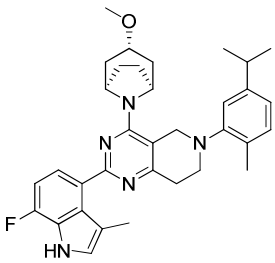
19-U		2- (5- isopropil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 10.24 (br. s., 1 H) 8.05 (s, 1 H) 7.51 - 7.56 (m, 2 H) 7.20 (d, J=7.8 Hz, 1 H) 7.08 (d, J=1.8 Hz, 1 H) 6.97 (dd, J=7.8, 1.8 Hz, 1 H) 4.56 (br. s., 2 H) 4.09 (s, 2 H) 3.68 (quin, J=6.9 Hz, 1 H) 3.52 (t, J=4.8 Hz, 1 H) 3.41 (t, J=5.9 Hz, 2 H) 3.31 (s, 3 H) 3.14 (t, J=5.9 Hz, 2 H) 2.96 (quin, J=6.9 Hz, 1 H) 2.36 (s, 3 H) 2.07 - 2.23 (m, 4 H) 1.92 - 2.04 (m, 4 H) 1.31 (d, J=7.2 Hz, 6 H) 1.33 (d, J=7.2 Hz, 6 H); MS (ESI+) *m/z* 565.1 $(M+H)^+$.
19-V		4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1*H*- pirrolo[2,3- *b*]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.53 (br s, 1 H), 8.35 (d, *J* = 4.80 Hz, 1 H), 7.41 (d, *J* = 4.80 Hz, 1 H), 7.16 (d, *J* = 7.83 Hz, 1 H), 7.11 – 7.12 (m, 1 H), 6.96 (d, *J* = 1.77 Hz, 1 H), 6.92 (dd, *J* = 1.77, 7.58 Hz, 1 H), 4.07 (s, 2 H), 3.39 (app t, *J* = 6.03 Hz, 2 H), 3.34 (br t, *J* = 5.43 Hz, 2 H), 3.12 – 3.14 (m , 4 H), 2.84 – 2.95 (m, 1 H), 2.30 (s, 3 H), 2.21 (d, *J* = 1.01 Hz, 3 H), 1.69 – 1.75 (m, 2 H), 1.44 (t, *J* = 6.06 Hz, 2 H), 1.26 (d, *J* = 7.07 Hz, 6 H), 1.01 (s, 6 H); MS (ESI+) *m/z*509.28 $(M+H)^+$.
19-W		(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.68 (s, 1 H), 7.44 (dd, *J*=3.5, 2.3 Hz, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.85 (d, *J*=1.5 Hz, 1 H), 6.74 (dd, *J*=7.7, 1.6 Hz, 1 H), 6.58 (dd, *J*=3.5, 1.8 Hz, 1 H), 4.02 (s, 2 H), 3.70 - 3.76 (m, 1 H), 3.43 (d, *J*=14.1 Hz, 1 H), 3.34 - 3.38 (m, 2 H), 3.33 (s, 3 H), 3.13 (br. s., 3 H), 2.95 (dd, *J*=8.5, 3.9 Hz, 2 H), 2.27 (s, 3 H), 1.91 - 2.00 (m, 1 H), 1.83 - 1.91 (m, 1 H), 1.63 - 1.74 (m, 1 H), 0.98

		(s, 3 H), 0.94 - 0.97 (m, 2 H), 0.93 (s, 3 H), 0.63 - 0.70 (m, 2 H); MS (ESI+) *m/z* 590.9 $(M+H)^+$.
19-X		(*S*)- 2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.35 (s, 1 H), 7.39 (br. s., 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.86 (d, *J*=1.5 Hz, 1 H), 6.74 (dd, *J*=7.8, 1.5 Hz, 1 H), 6.56 (br. s., 1 H), 4.00 (s, 2 H), 3.73 - 3.83 (m, *J*=8.3 Hz, 1 H), 3.42 - 3.54 (m, 1 H), 3.33 - 3.36 (m, 6 H), 3.12 - 3.26 (m, 2 H), 2.92 - 3.03 (m, 2 H), 2.26 (s, 3 H), 1.93 - 2.02 (m, 1 H), 1.84 - 1.93 (m, 1 H), 1.66 - 1.77 (m, 1 H), 0.99 (s, 3 H), 0.95 - 0.98 (m, 2 H), 0.94 (s, 3 H), 0.64 - 0.69 (m, 2 H); MS (ESI+) *m/z* 556.9 $(M+H)^+$.
19-Y		2- (2,5- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.83 (d, *J*=7.8 Hz, 1 H), 7.71 - 7.78 (m, 2 H), 7.61 - 7.70 (m, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.96 (s, 1 H), 6.86 (d, *J*=9.1 Hz, 1 H), 4.04 (s, 2 H), 3.24 - 3.34 (m, 4 H), 3.08 (s, 2 H), 2.93 (app t, *J*=5.9 Hz, 2 H), 2.77 - 2.88 (m, 1 H), 2.20 (s, 3 H), 1.58 - 1.70 (m, 2 H), 1.34 - 1.43 (m, 2 H), 1.18 (d, *J*=7.1 Hz, 6 H), 0.94 (s, 6 H); MS (ESI+) *m/z* 523.3 $(M+H)^+$.
19- Z		2- (2,5- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 0.99 (s, 6 H) 1.23 (d, *J*=7.07 Hz, 6 H) 1.47 (m, *J*=5.80, 5.80 Hz, 2 H) 1.68 - 1.79 (m, 2 H) 2.26 (s, 3 H) 2.35 (s, 3 H) 2.40 (s, 3 H) 2.79 - 2.91 (m, 1 H) 3.01 (m, *J*=5.80, 5.80 Hz, 2 H) 3.12 - 3.19 (m, 2 H) 3.34 - 3.42 (m, 4 H) 4.02 (s, 2 H) 6.88 (d, *J*=7.58 Hz, 1 H) 6.97 (s, 1 H) 7.05 - 7.19 (m, 3 H) 7.39 (s, 1 H); MS (ESI+) *m/z* 483.3 $(M+H)^+$.

19-AA		(*S*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.15 - 7.22 (m, 2 H), 7.07 (d, *J*=7.6 Hz, 2 H), 6.89 (d, *J*=2.0 Hz, 1 H), 6.86 (dd, *J*=7.8, 1.8 Hz, 1 H), 4.91 (d, *J*=5.6 Hz, 2 H), 4.58 (d, *J*=5.6 Hz, 2 H), 4.03 (s, 2 H), 3.62 – 3.71 (m, 1 H), 3.30 - 3.39 (m, 6 H), 3.01 - 3.13 (m, 3 H), 2.94 (dd, *J*=8.8, 3.8 Hz, 1 H), 2.84 (d, *J*=12.6 Hz, 1 H), 2.30 (s, 3 H), 2.11 (s, 6 H), 1.91 - 1.99 (m, 1 H), 1.69 (s, 3 H), 1.62 - 1.68 (m, 1 H), 0.99 (s, 3 H), 0.94 (s, 3 H); MS (ESI+) *m/z* 541.1 $(M+H)^+$.
19-AB		(*S*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.35 (d, *J*=7.8 Hz, 1 H), 7.28 - 7.31 (m, 2 H), 7.19 - 7.24 (m, 1 H), 7.10 (d, *J*=7.6 Hz, 2 H), 4.03 (s, 2 H), 3.72 (br. s., 1 H), 3.38 (t, *J*=5.8 Hz, 2 H), 3.33 (s, 3 H), 3.16 (br. s., 2 H), 2.96 (dd, *J*=8.3, 3.8 Hz, 1 H), 2.38 (s, 3 H), 2.14 (br. s, 6 H), 1.91 - 2.01 (m, 1 H), 1.63 - 1.75 (m, 1 H), 0.97 (s, 3 H), 0.92 (s, 3 H);MS (ESI+) *m/z* 539.0 $(M+H)^+$.
19-AC		(*S*)- 2- (5- isopropil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.97 (br. s, 1 H), 7.52 (d, *J*=8.3 Hz, 1 H), 7.47 (d, *J*=8.8 Hz, 1 H), 7.22 (d, *J*=8.1 Hz, 1 H), 6.94 (d, *J*=1.5 Hz, 1 H), 6.89 (d, *J*=7.6 Hz, 1 H), 4.92 (d, *J*=5.6 Hz, 2 H), 4.60 (d, *J*=5.6 Hz, 2 H), 4.06 (s, 2 H), 3.71 (br. s., 1 H), 3.35 - 3.43 (m, 3 H), 3.33 (s, 3 H), 3.14 (br. s., 2 H), 2.95 (dd, *J*=8.3, 3.3 Hz, 1 H), 2.32 (s, 3 H), 1.93 - 2.01 (m, 1 H), 1.71 (s, 3 H), 1.64 - 1.70 (m, 1 H), 1.30 (d, *J*=6.6 Hz, 6 H), 0.99 (s, 3 H), 0.96 (s, 3 H); MS (ESI+)

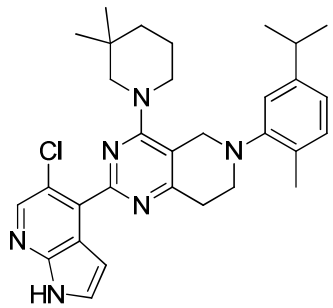
		m/z 595.0 $(M+H)^+$.
19-AD		(*S*)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.16 - 7.22 (m, 1 H), 7.13 (d, *J*=7.6 Hz, 1 H), 7.08 (d, *J*=7.6 Hz, 2 H), 6.95 (d, *J*=1.8 Hz, 1 H), 6.89 (dd, *J*=7.8, 1.5 Hz, 1 H), 4.03 (s, 2 H), 3.69 (br. s., 1 H), 3.30 - 3.39 (m, 6 H), 3.04 (br. s., 3 H), 2.94 (dd, *J*=4.8, 3.8 Hz, 1 H), 2.87 (spt, *J*=6.8 Hz, 1 H), 2.28 (s, 3 H), 2.12 (s, 6 H), 1.91 - 1.99 (m, 1 H), 1.62 - 1.72 (m, 1 H), 1.24 (d, *J*=7.1 Hz, 6 H), 0.99 (s, 3 H), 0.94 (s, 3 H); MS (ESI+) *m/z* 513.3 $(M+H)^+$.
19-AE		(*S*)- 2- (5- isopropil- 1H- indazol- 4- il)- 6- (5- metoxi- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.74 (br s., 1 H), 7.37 (br. s., 2 H) 7.15 (d, *J*=7.8 Hz, 1 H), 6.72 (d, *J*=2.5 Hz, 1 H), 6.63 (d, *J*=7.8 Hz, 1 H), 4.03 (s, 2 H), 3.80 (s, 3 H), 3.31 - 3.38 (m, 6 H), 3.00 (br. s., 1 H), 2.26 (s, 3 H), 1.90 - 2.02 (m, 1 H), 1.73 (br. s., 1 H), 1.32 (br. s, 6 H), 0.96 (s, 3 H), 0.92 (s, 3 H); MS (ESI+) *m/z* 555.0 $(M+H)^+$.
19-AF		2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((*3R,4R*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.59 (s, 1 H) 7.39 (d, *J*=8.6 Hz, 1 H) 7.21 (d, *J*=8.6 Hz, 1 H) 7.11 (d, *J*=8.1 Hz, 1 H) 6.94 (d, *J*=1.3 Hz, 1 H) 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H) 3.96 - 4.16 (m, 2 H) 3.62 - 3.84 (m, 2 H) 3.30 - 3.40 (m, 2 H) 3.26 (s, 3 H) 2.89 - 3.06 (m, 4 H) 2.73 - 2.87 (m, 2 H) 2.21 (s, 3 H) 2.19 (s, 3 H) 2.04 - 2.13 (m, 1 H) 1.87 (s, 3 H) 1.60 - 1.72 (m, 1 H) 1.29 - 1.42 (m, 1 H) 1.18 (d, *J*=7.1 Hz, 6 H) 0.94 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 539.4 $(M+H)^+$.

19-AG		2- (2- cloro- 6- metilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.22 - 7.37 (m, 3 H) 7.11 (d, *J*=7.8 Hz, 1 H) 6.99 (d, *J*=1.3 Hz, 1 H) 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H) 4.35 - 4.44 (m, 2 H) 3.98 - 4.05 (m, 2 H) 3.42 - 3.47 (m, 1 H) 3.29 (t, *J*=5.9 Hz, 2 H) 3.20 (s, 3 H) 2.79 - 2.92 (m, 3 H) 2.22 (s, 3 H) 2.08 (s, 3 H) 1.79 - 2.03 (m, 8 H) 1.18 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 531.3 $(M+H)^+$.
19-AH		2- (2- cloro- 6- metilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((*3R,4R*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.23 - 7.38 (m, 3 H) 7.10 (d, *J*=8.1 Hz, 1 H) 6.93 (d, *J*=1.5 Hz, 1 H) 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H) 3.93 - 4.11 (m, 2 H) 3.62 - 3.81 (m, 2 H) 3.29 - 3.35 (m, 1 H) 3.26 (s, 3 H) 2.94 - 3.06 (m, 2 H) 2.90 (t, *J*=5.8 Hz, 2 H) 2.73 - 2.87 (m, 2 H) 2.20 (s, 3 H) 2.08 (s, 3 H) 1.59 - 1.71 (m, 1 H) 1.30 - 1.42 (m, 1 H) 1.17 - 1.20 (m, 1 H) 1.17 (d, *J*=6.8 Hz, 6 H) 0.95 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 519.4 $(M+H)^+$.
19-AI		(*S*)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.^{1}HNMR (400 MHz, CD2Cl2)δ ppm 7.30 (d, *J*=8.6 Hz, 1 H), 7.17 (d, *J*=8.6 Hz, 1 H), 7.08 (d, *J*=7.6 Hz, 1 H), 6.75 - 6.92 (m, 2 H), 3.98 (s, 2 H), 3.76 (br. s., 1 H), 3.32 (br. s., 3 H), 3.21 - 3.26 (m, 3 H), 2.91 (br. s., 1 H), 2.78 (spt, *J*=6.8 Hz, 1 H), 2.31 (br. s., 2 H), 2.19 (br. s, 3 H), 2.01 (br. s., 3 H), 1.88 (m, *J*=3.5 Hz, 1 H), 1.58 - 1.69 (m, 1 H), 1.17 (d, *J*=6.8 Hz, 6 H), 0.89 (s, 3 H) 0.84 (s, 3 H); MS (ESI+) m/z 553.1 $(M+H)^+$.

19-AJ		4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometoxi)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 0.95 (s, 6 H) 1.18 (d, *J*=6.82 Hz, 6 H) 1.40 (app t, *J*=5.94 Hz, 2 H) 1.65 (br. s., 2 H) 2.75 - 2.88 (m, 1 H) 2.94 (t, *J*=5.94 Hz, 2 H) 3.10 (s, 2 H) 4.03 (s, 2 H) 6.86 (dd, *J*=7.71, 1.39 Hz, 1 H) 6.96 (d, *J*=1.26 Hz, 1 H) 7.10 (d, *J*=7.83 Hz, 1 H) 7.45 (d, *J*=8.08 Hz, 1 H) 7.48 - 7.54 (m, 1 H) 7.55 - 7.63 (m, 1 H) 7.95 (dd, *J*=7.58, 1.77 Hz, 1 H); MS (ESI+) *m/z* 539.3 $(M+H)^+$.
19-AK		2- (6- (5- isopropil- 2- metilfenil)- 4- ((3*R*,4*R*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 2- il)- 3- metilbenzonitrilo. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.75 (d, *J*=7.6 Hz, 1 H) 7.64 (d, *J*=7.3 Hz, 1 H) 7.52 (t, *J*=7.7 Hz, 1 H) 7.10 (d, *J*=8.1 Hz, 1 H) 6.98 (d, *J*=1.5 Hz, 1 H) 6.87 (dd, *J*=7.8, 1.5 Hz, 1 H) 3.92 - 4.15 (m, 2 H) 3.70 - 3.90 (m, 2 H) 3.28 - 3.32 (m, 2 H) 3.27 (s, 3 H) 3.02 - 3.12 (m, 1 H) 2.92 - 3.02 (m, 3 H) 2.75 - 2.89 (m, 2 H) 2.32 (s, 3 H) 2.20 (s, 3 H) 2.06 - 2.16 (m, 1 H) 1.61 - 1.74 (m, 1 H) 1.37 (d, *J*=10.9 Hz, 1 H) 1.18 (d, *J*=6.8 Hz, 6 H) 0.96 (d, *J*=6.6 Hz, 3 H). MS (ESI+) *m/z*510.3 $(M+H)^+$.
19-AL		2- (7- fluoro- 3- metil- 1H- indol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.40 (br. s., 1 H) 7.37 (dd, *J*=8.1, 4.8 Hz, 1 H) 7.19 (d, *J*=7.8 Hz, 1 H) 7.11 (s, 1 H) 7.05 (s, 1 H) 6.92 - 7.01 (m, 2 H) 4.56 (br. s., 2 H) 4.07 (s, 2 H) 3.52 (t, *J*=4.7 Hz, 1 H) 3.39 (t, *J*=6.0 Hz, 2 H) 3.32 (s, 3 H) 3.10 (t, *J*=5.8 Hz, 2 H) 2.94 (dt, *J*=13.6, 6.8 Hz, 1 H) 2.34 (s, 3 H) 2.09 - 2.24 (m, 7 H) 1.92 - 2.06 (m, 4 H) 1.31 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 554.5 $(M+H)^+$.

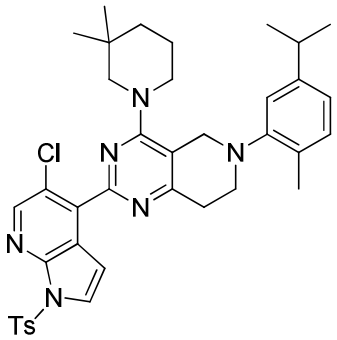
Ejemplo 20

20- A. 2- (5- Cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



El compuesto del título se preparó de una manera similar a la descrita en el **Ejemplo 19**. ^{1}H RMN (400 MHz, DMSO- d_6) δ 11,94 ppm (br. s., 1 H.), 8,30 (s, 1 H), 7,50 - 7,60 (m, 1 H), 7,11 (d, J = 7,8 Hz, 1 H), 6,98 (d, J = 1,5 Hz, 1 H), 6,87 (dd, J = 7,6, 1,5 Hz, 1 H), 6,41 (d, J = 5,3 Hz, 1 H), 4,08 (s, 2 H), 3,32 - 3,38 (m, 4 H), 3,11 (s, 2 H), 2,98 (t, J = 5,8 Hz, 2 H), 2,84 (dt, J = 13,7, 6,9 Hz, 1 H), 2,22 (s, 3 H), 1,65 (m, 2 H), 1,40 (t, J = 5,7 Hz, 2 H), 1,19 (d, J = 7,1 Hz, 6 H), 0,96 (s, 6 H), MS (ESI+) m/z 529.2 (M+H)+.

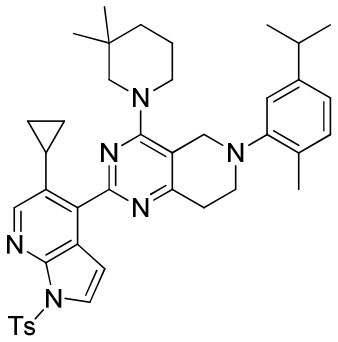
20- B.2- (5- Cloro- 1- tosil- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de 2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (213 mg, 0.403 mmol) en THF (2.4 ml) se añadió NaH 60% en aceite (32 mg, 0.80 mmol) a 0 °C. Después de 15 min se añadió p- toluenosulfonilcloruro (81 mg, 0.42 mmol) y la mezcla se dejó calentar a temperatura ambiente. Después de 16 h, se añadió agua y la fase acuosa se extrajo con EtOAc (3x). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron y se concentró bajo presión reducida. El residuo se

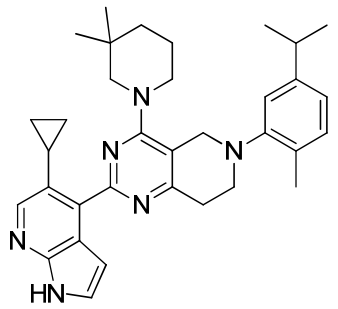
purificó a través de FCC (0- 20% EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 683.2 (M+H)+.

20- C. 2- (5- Ciclopropil- 1- tosil- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina



A una mezcla de 2- (5- cloro- 1- tosil- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (135 mg, 0.198 mmol) en tolueno (2 ml) y agua (0.1 mL) se añadió ciclopropiltrifluoroborato de potasio (58 mg, 0.39 mmol), triciclohexilfosfina (11 mg, 0.04 mmol), Pd $(OAc)_2$ (4 mg, 0.02 mmol) y Cs_2CO_3 (193 mg, 0.593 mmol). La mezcla de reacción se calentó a 100 °C durante 16 h. Después, la mezcla de reacción se filtró y el residuo se purificó a través de FCC (0- 30% EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m / z 689.4 (M+H)+.

20- D. 2 - (5 - Ciclopropil- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.

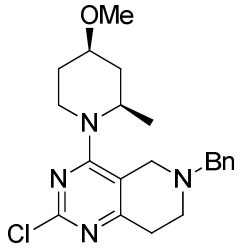


A una solución de 2-(5-ciclopropil-1-tosil-1H-pirrolo[2,3-b]piridin-4-il)-4-(3,3-dimetilpiperidin-1-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (50 mg, 0.073 mmol) en EtOH (1.9 ml) se añadió KOH (24 mg, 0.44 mmol) y NH_4OH acuoso al

28% (303 µl, 7.26 mmol). La mezcla se calentó a 100 °C durante 45 min en un reactor de microondas. Se añadió una solución acuosa saturada de NH_4Cl y la fase acuosa se extrajo con EtOAc (3x). Las fases combinadas se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron y se concentraron bajo presión reducida. Luego la mezcla de reacción se filtró y el residuo se purificó a través de FCC (20- 60% EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 11,53 (br. s., 1 H.), 8,00 (s, 1H), 7,38 - 7,43 (m, 1 H), 7,11 (d, J = 7,8 Hz, 1 H), 6,97 (d, J = 1,3 Hz, 1 H), 6,86 (dd, J = 7,7, 1,4 Hz, 1 H), 6,38 (dd, J = 3,4, 1,9 Hz, 1 H), 4,09 (s, 2 H), 3,34 (t, J = 5,9 Hz, 2 H), 3,08 (s, 2 H), 2,98 (t, J = 5,8 Hz, 2 H), 2,83 (dt, J = 13,6, 6,8 Hz, 1 H), 2,34 - 2,41 (m, 1 H), 2,23 (s, 3H), 1,65 (dt, J = 10,6, 5,5 Hz, 2 H), 1,40 (t, J = 5,9 Hz, 2 H), 1,18 (d, J = 6,8 Hz, 6 H), 0,97 (s, 6 H), 0,73 - 0,82 (m, 2 H), 0,55 - 0,63 (m, 2 H), MS (ESI+) m/z 535.4 (M+H)+.

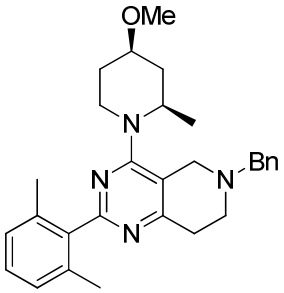
Ejemplo 21

21- A. 6- Bencil- 2- cloro- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



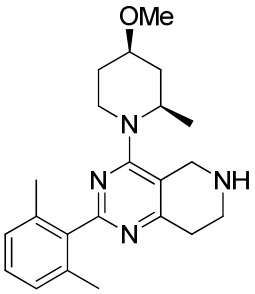
A una solución de 6- bencil- 2 ,4- dicloro- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (3.31 g, 11,2 mmol) en DMA (13 ml) se añadió hidrocloruro de (2R, 4R)- 4- metoxi- 2- metilpiperidina (1.33 g, 8.03 mmol) y DIPEA (7.0 ml, 40 mmol). Luego la mezcla se calentó a 80 °C durante 20 h. En ese punto se añadió agua y la fase acuosa se extrajo con una solución de acetato de etilo/n- heptano (4:1). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron bajo presión reducida. El residuo se purificó a través de FCC (15- 30% EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,34 - 7,39 (m, 4 H), 7,32 (d, J = 4,3 Hz, 1 H), 3,92 - 4,02 (m, 1 H), 3,75 - 3,82 (m, 1 H), 3,61 - 3,69 (m, 1 H), 3,54 (t, J = 3,9 Hz, 1 H), 3,36 - 3,42 (m, 6 H), 2,89 - 2,96 (m, 2 H), 2,73 - 2,89 (m, 2 H), 1,75 - 1,83 (m, 4 H), 1,32 (d, J = 6,6 Hz, 3 H), MS (ESI+) m/z 387.2 (M+H)+.

21- B.6- Bencil- 2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de 6- bencil- 2- cloro- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (775 mg, 2.00 mmol) en DME (7 mL) se añadió ácido 2,6- dimetilfenilboronico (601 mg, 4.01 mmol), $Pd(Ph_3P)_4$ (231 mg, 0.200 mmol) y una solución de carbonato sódico2M (3.0 ml, 6.0 mmol). La reacción se calentó a 130 °C en un reactor de microondas durante 1 hora 15 min. La reacción se filtró y se concentró bajo presión reducida. El residuo se purificó a través de FCC (0- 30% EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,34 - 7,44 (m, 4 H), 7,30 - 7,33 (m, 1 H), 7,12 - 7,19 (m, 1 H), 7,03 - 7,09 (m, 2 H), 3,80 - 3,87 (m, 1 H) , 3,73 - 3,77 (m, 1 H), 3,62 - 3,72 (m, 2 H), 3,39 - 3,51 (m, 2 H), 3,36 (s, 3 H), 3,21 - 3,31 (m, 1 H), 3,04 - 3,14 (m, 1 H), 2,95 - 3,02 (m, 2 H), 2,84 - 2,93 (m, 1 H), 2,75 - 2,84 (m, 1 H), 2,11 (s, 6 H), 1,83 - 1,97 (m, 2 H), 1,63 - 1,71 (m, 1 H), 1,60 (dd, J = 13,4, 6,6 Hz, 1 H), 1,17 (d, J = 6,6 Hz, 3 H), MS (ESI+) m/z 457.3 (M+H)+.

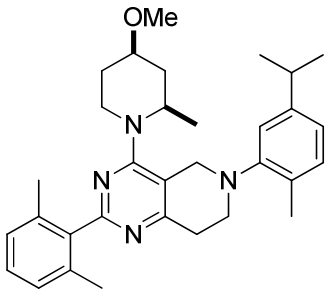
21- C.2- (2,6- Dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de 6- bencil- 2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina(549 mg, 1.20 mmol) en THF (9 ml) y agua (2 mL) se añadió ácido acético (206 l, 3.61 mmol) y $Pd(OH)_2$ (253mg, 0.361 mmol). El hidrógeno se burbujeó a través de la solución durante 15 minutos. Después de 1 hora, se añadió una solución saturada de bicarbonato sódico y la solución se filtró sobre Celite ®, se lavó con una solución de DCM/MeOH (4:1). La fase acuosa se extrajo con DCM. Las capas

orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron bajo presión reducida para obtener el compuesto del título. MS (ESI+) m/z 367.3 (M+H)+.

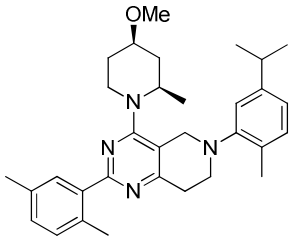
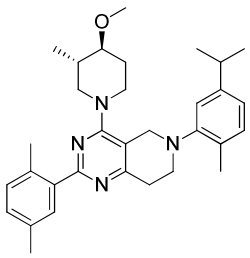
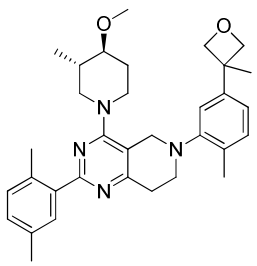
21- D.2- (2,6- Dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.

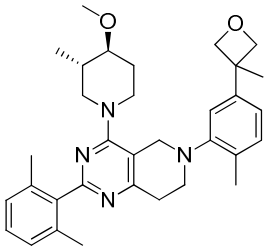
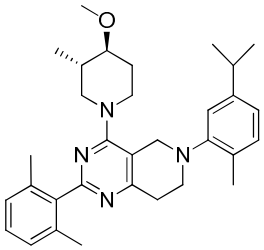
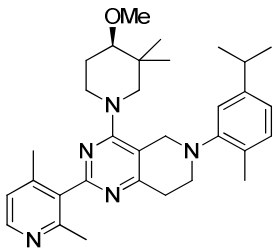


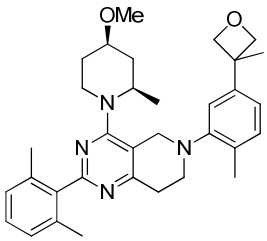
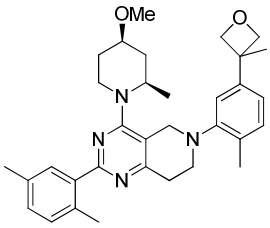
A una solución de 2-(2,6-dimetilfenil)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (45 mg, 0.12 mmol) en dioxano (455 µL) se añadió trifluorometanosulfonato de 5- isopropil- 2- metilfenil (52 mg, 0.18 mmol), Cs_2CO_3 (80 mg, 0.25 mmol) y aductoCloro(2- diciclohexilfosfino- 2'- 4'- 6'- triisopropil- 1,1'- bifenil)[2-(2- aminoetil)fenil]paladio(II)–metil- *t*- butileter (14 mg, 0.020 mmol). La reacción se purgó con argón y se calentó a 90 °C durante 16 h. La mezcla se diluyó con EtOAc y se filtró. El residuo se purificó a través de FCC (0- 30% EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,15 - 7,22 (m, 1 H), 7,05 - 7,13 (m, 3 H), 6,91 (s, 1 H), 6,86 (dd, J = 7,7, 1,4 Hz, 1 H), 4,05 - 4,15 (m, 1) H, 3,92 - 4,01 (m, 1 H), 3,71 - 3,82 (m, 1 H), 3,39 - 3,49 (m, 1 H), 3,31 - 3,36 (m, 2 H), 3,25 (s, 3 H), 3,06 - 3,16 (m, 1 H), 2,91 (t, J = 5,7 Hz, 2 H), 2,82 (quin, J = 6,8 Hz, 1 H), 2,22 (s, 3 H), 2,03 (s, 6 H), 1,86 (dt, J = 13,0, 3,9 Hz, 2 H), 1,54 - 1,67 (m, 2 H), 1,21 - 1,30 (m, 2 H), 1,14 - 1,20 (m, 9 H), MS (ESI+) m/z 499.3 (M+H)+.

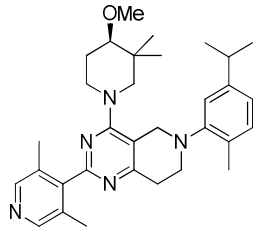
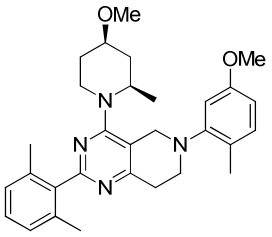
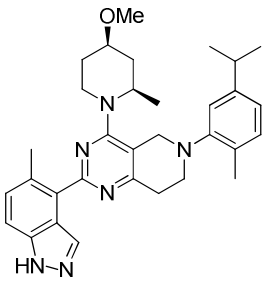
Los siguientes compuestos se prepararon de una manera similar. Para los compuestos que contienen un grupo indazol oindol la síntesis se realizócon los correspondientes intermedios N- tosilo protegidos descritos en los otros ejemplos en este documento y la eliminación del grupo protector tosilo en el último paso se realizócomo se describe en otros ejemplos en este documento.

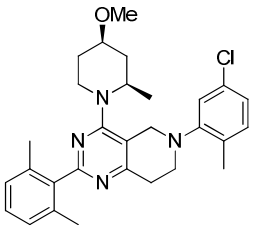
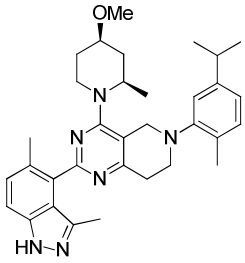
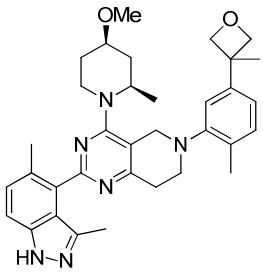
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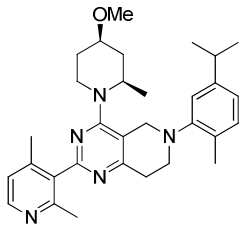
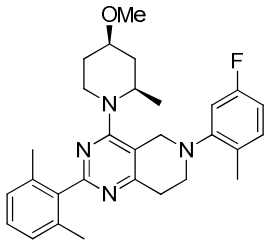
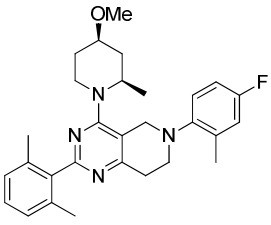
21- E		2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 7.58 (s, 1 H), 7.13 - 7.16 (m, 2 H), 7.08 - 7.13 (m, 1 H), 6.97 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.01 - 4.09 (m, 1 H), 3.87 - 3.96 (m, 1 H), 3.79 - 3.87 (m, 1 H), 3.43 - 3.50 (m, 1 H), 3.27 (s, 3 H), 3.13 - 3.21 (m, 1 H), 2.98 (t, *J*=5.8 Hz, 2 H), 2.80 - 2.94 (m, 1 H), 2.46 (s, 3 H), 2.32 (s, 3 H), 2.20 (s, 3 H), 1.80 - 1.96 (m, 2 H), 1.52 - 1.71 (m, 2 H), 1.28 (d, *J*=6.8 Hz, 3 H), 1.15 - 1.25 (m, 9 H); MS (ESI+) *m/z* 499.4 $(M+H)^+$.
21- F		2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 0.97 (d, *J*=6.6 Hz, 3 H) 1.19 (d, *J*=6.8 Hz, 6 H) 1.30 - 1.43 (m, 1 H) 1.63 - 1.75 (m, 1 H) 2.05 - 2.15 (m, 1 H) 2.19 (s, 3 H) 2.32 (s, 3 H) 2.47 (s, 3 H) 2.75 (dd, *J*=13.1, 9.9 Hz, 1 H) 2.85 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.92 - 3.09 (m, 4 H) 3.22 - 3.38 (m, 2 H), 3.27 (s, 3 H) 3.64 - 3.73 (m, 1 H) 3.78 (m, 1 H) 3.88 - 4.09 (m, 2 H) 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H) 6.99 (d, *J*=1.3 Hz, 1 H) 7.06 - 7.19 (m, 3 H) 7.58 (s, 1 H); MS (ESI+) *m/z* 499.5 $(M+H)^+$.
21- G		2- (2,5- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 0.97 (d, *J*=6.6 Hz, 3 H) 1.31 - 1.43 (m, 1 H) 1.61 (s, 3 H) 1.65 - 1.75 (m, 1 H) 2.07 - 2.15 (m, 1 H) 2.22 (s, 3 H) 2.32 (s, 3 H) 2.46 (s, 3 H) 2.75 (dd, *J*=13.1, 9.9 Hz, 1 H) 2.93 - 3.08 (m, 4 H) 3.28 (s, 3 H) 3.29 - 3.40 (m, 2 H) 3.64 - 3.84 (m, 2 H) 3.90 - 4.11 (m, 2 H) 4.52 (d, *J*=5.6 Hz, 2 H) 4.78 (d, *J*=5.6 Hz, 2 H) 6.87 (dd, *J*=7.8, 1.8 Hz, 1 H) 6.96 (d, *J*=1.8 Hz, 1 H) 7.07 - 7.23 (m, 3 H) 7.58 (s, 1

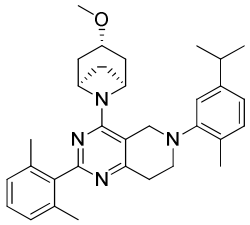
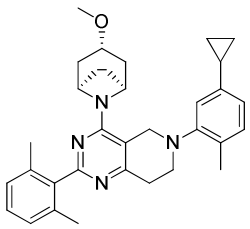
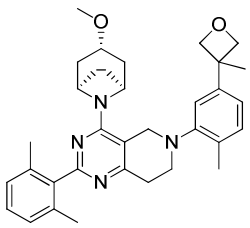
		H); MS (ESI+) *m/z* 527.4 $(M+H)^+$.
21- H		2- (2,6- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 0.95 (d, *J*=6.82 Hz, 3 H) 1.31 - 1.42 (m, 1 H) 1.60 (s, 3 H) 1.62 - 1.72 (m, 1 H) 2.05 (s, 6 H) 2.06 - 2.12 (m, 1 H) 2.24 (s, 3 H) 2.74 (dd, *J*=13.4, 9.9 Hz, 1 H) 2.87 - 2.93 (m, 2 H) 2.94 - 3.03 (m, 2 H) 3.27 (s, 3 H) 3.35 (dq, *J*=12.2, 6.4 Hz, 2 H) 3.60 - 3.67 (m, 1 H) 3.73 (d, *J*=13.9 Hz, 1 H) 3.95 - 4.03 (m, 1 H) 4.06 - 4.14 (m, 1 H) 4.50 (d, *J*=5.6 Hz, 2 H) 4.76 (d, *J*=5.6 Hz, 2 H) 6.83 - 6.92 (m, 2 H) 7.05 - 7.11 (m, 2 H) 7.13 - 7.20 (m, 2 H); MS (ESI+) *m/z*527.3 $(M+H)^+$.
21- I		2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 0.95 (d, *J*=6.57 Hz, 3 H) 1.17 (d, *J*=6.8 Hz, 6 H) 1.30 - 1.41 (m, 1 H) 1.61 - 1.70 (m, 1 H) 2.05 (s, 6 H) 2.08 - 2.13 (m, 1 H) 2.21 (s, 3 H) 2.75 (dd, *J*=13.6, 10.0 Hz, 1 H) 2.82 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.90 (t, *J*=6.1 Hz, 2 H) 2.94 - 3.04 (m, 2 H) 3.27 (s, 3 H) 3.31 - 3.37 (m, 2 H) 3.60 - 3.69 (m, 1 H) 3.71 - 3.78 (m, 1 H) 3.95 - 4.02 (m, 1 H) 4.03 - 4.11 (m, 1 H) 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H) 6.92 (d, *J*=1.5 Hz, 1 H) 7.04 - 7.12 (m, 3 H) 7.14 - 7.22 (m, 1 H). MS (ESI+) *m/z*499.1 $(M+H)^+$.
21- J		(*R*)- 2- (2,4- dimetilpiridin- 3- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 8.32 (d, *J*=5.1 Hz, 1 H), 7.14 (d, *J*=5.1 Hz, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.92 (s, 1 H), 6.86 (dd, *J*=7.8, 1.5 Hz, 1 H), 3.99 - 4.14 (m, 2 H), 3.65 (dt, *J*=10.2, 5.1 Hz, 1 H), 3.32 - 3.40 (m, 3 H), 3.28

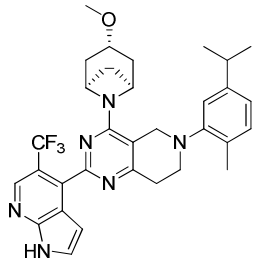
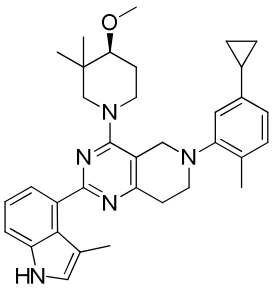
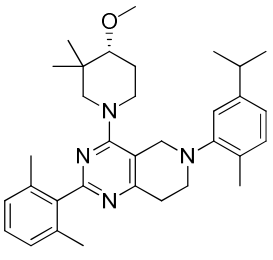
		(s, 3 H), 3.00 - 3.10 (m, 1 H), 2.98 (dd, *J*=9.1, 4.0 Hz, 1 H), 2.91 (t, *J*=5.8 Hz, 2 H), 2.74 - 2.88 (m, 2 H), 2.25 (s, 3 H), 2.21 (s, 3 H), 2.09 (s, 3H), 1.88 - 2.00 (m, 1 H), 1.47 - 1.62 (m, 1 H), 1.17 (d, *J*=7.1 Hz, 6 H), 0.96 (s, 3 H), 0.88 (s, 3 H); MS (ESI+) *m/z*514.4 $(M+H)^+$.
21- K		2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 7.14 - 7.22 (m, 2 H), 7.03 - 7.11 (m, 2 H), 6.82 - 6.90 (m, 2 H), 4.76 (dd, *J*=5.6, 2.8 Hz, 2 H), 4.50 (dd, *J*=5.6, 1.8 Hz, 2 H), 4.08 - 4.17 (m, 1 H), 3.92 - 4.01 (m, 1 H), 3.72 - 3.81 (m, 1 H), 3.41 - 3.49 (m, 1 H), 3.33 - 3.39 (m, 2 H), 3.25 (s, 3 H), 3.06 - 3.18 (m, 1 H), 2.91 (t, *J*=5.6 Hz, 2 H), 2.25 (s, 3 H), 2.03 (s, 6 H), 1.79 - 1.91 (m, 2 H), 1.55 - 1.68 (m, 5 H), 1.24 (d, *J*=6.8 Hz, 1 H), 1.19 (d, *J*=6.6 Hz, 3 H);MS (ESI+) *m/z*527.4 $(M+H)^+$.
21- L		2- (2,5- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 7.58 (d, *J*=0.5 Hz, 1 H), 7.09 - 7.20 (m, 3 H), 6.95 (d, *J*=1.8 Hz, 1 H), 6.87 (dd, *J*=7.8, 1.8 Hz, 1 H), 4.78 (dd, *J*=5.6, 2.8 Hz, 2 H), 4.52 (dd, *J*=5.6, 1.8 Hz, 2 H), 4.08 (d, *J*=14.9 Hz, 1 H), 3.91 (d, *J*=14.4 Hz, 1 H), 3.79 - 3.88 (m, 1 H), 3.42 - 3.50 (m, 1 H), 3.32 - 3.35 (m, 2 H), 3.27 (s, 3 H), 3.13 - 3.23 (m, 1 H), 2.98 (t, *J*=5.9 Hz, 2 H), 2.47 (s, 3 H), 2.32 (s, 3 H), 2.23 (s, 3 H), 1.83 - 1.93 (m, 2 H), 1.55 - 1.70 (m, 6 H), 1.22 (d, *J*=6.6 Hz, 3 H);MS (ESI+) *m/z*527.4 $(M+H)^+$.

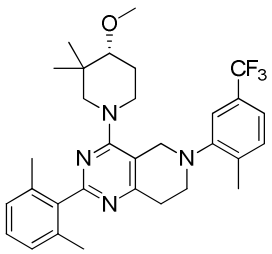
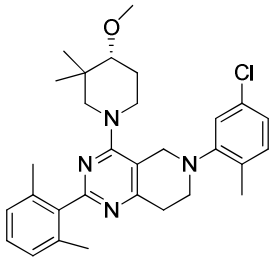
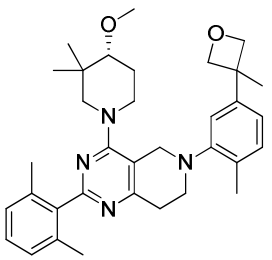
21- M		(*R*)- 2- (3,5- dimetilpiridin- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H (400 MHz, DMSO- d_6) δ ppm 8.34 (s, 2 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.92 (d, *J*=1.5 Hz, 1 H), 6.86 (dd, *J*=7.7, 1.4 Hz, 1 H), 3.95 - 4.14 (m, 2 H), 3.56 - 3.76 (m, 1 H), 3.32 - 3.39 (m, 3 H), 3.28 (s, 3 H), 3.05 (ddd, *J*=13.3, 10.1, 3.2 Hz, 1 H), 2.98 (dd, *J*=9.0, 3.9 Hz, 1 H), 2.91 (t, *J*=5.7 Hz, 2 H), 2.77 - 2.88 (m, 2 H), 2.21 (s, 3 H), 2.08 (s, 6 H), 1.89 - 1.97 (m, 1 H), 1.47 - 1.61 (m, 1 H), 1.17 (d, *J*=6.8 Hz, 6 H), 0.96 (s, 3 H), 0.88 (s, 3 H);MS (ESI+) *m/z*514.3 $(M+H)^+$.
21- N		2- (2,6- dimetilfenil)- 6- (5- metoxi- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.15 - 7.22 (m, 1 H), 7.06 - 7.14 (m, 3 H), 6.68 (d, *J*=2.5 Hz, 1 H), 6.60 (dd, *J*=8.2, 2.4 Hz, 1 H), 4.02 - 4.11 (m, 1 H), 3.88 - 3.96 (m, 1 H), 3.74 - 3.79 (m, 2 H), 3.72 (s, 3 H), 3.40 - 3.48 (m, 1 H), 3.25 (s, 3 H), 3.06 - 3.16 (m, 1 H), 2.96 (t, *J*=5.8 Hz, 2 H), 2.18 (s, 3 H), 2.03 (s, 6 H), 1.80 - 1.90 (m, 2 H), 1.54 - 1.67 (m, 2 H), 1.24 (d, *J*=7.1 Hz, 1 H), 1.16 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z*487.3 $(M+H)^+$.
21- O		6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.97 (s, 1 H), 8.08 (s, 1 H), 7.50 (d, *J*=8.3 Hz, 1 H), 7.28 (d, *J*=8.6 Hz, 1 H), 7.12 (d, *J*=7.8 Hz, 1 H), 6.99 (s, 1 H), 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.06 - 4.16 (m, 1 H), 3.92 - 4.00 (m, 1 H), 3.82 - 3.92 (m, 1 H), 3.44 - 3.53 (m, 1 H), 3.32 - 3.39 (m, 2 H), 3.27 (s, 3 H), 3.00 - 3.06 (m, 2 H), 2.85 (quin, *J*=6.9 Hz, 1 H), 2.55 (s, 3 H), 2.23 (s, 3 H), 1.83 - 1.94 (m, 2 H), 1.59 - 1.72 (m, 2 H), 1.23 (d, *J*=6.6 Hz, 4 H), 1.19 (d, *J*=7.1 Hz, 7 H); MS (ESI+)

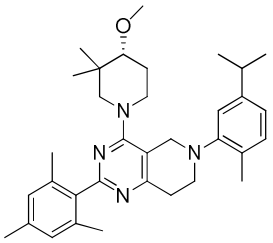
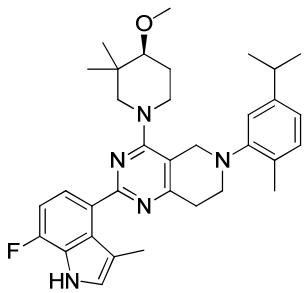
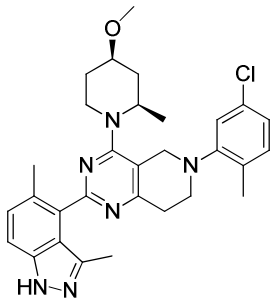
		*m/z*525.1 $(M+H)^+$.
21- P		6- (5- cloro- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm 7.24 (d, *J*=8.3 Hz, 1 H), 7.15 - 7.21 (m, 1 H), 7.13 (d, *J*=2.0 Hz, 1 H), 7.02 - 7.11 (m, 3 H), 4.05 - 4.13 (m, 1 H), 3.93 - 4.01 (m, 1 H), 3.71 - 3.79 (m, 1 H), 3.39 - 3.47 (m, 1 H), 3.25 (s, 3 H), 3.05 - 3.15 (m, 1 H), 2.96 (t, *J*=5.8 Hz, 2 H), 2.24 (s, 3 H), 2.03 (s, 6 H), 1.78 - 1.93 (m, 2 H), 1.51 - 1.67 (m, 2 H), 1.16 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z*491.0 $(M+H)^+$.
21- Q		(+)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm 12.58 (s, 1 H), 7.40 (d, *J*=8.6 Hz, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=7.8 Hz, 1 H), 6.92 (s, 1 H), 6.87 (d, *J*=7.8 Hz, 1 H), 4.07 - 4.19 (m, 1 H), 3.97 - 4.06 (m, 1 H), 3.70 - 3.86 (m, 1 H), 3.41 - 3.52 (m, 1 H), 3.34 - 3.40 (m, 2 H), 3.25 (s, 3 H), 3.10 - 3.21 (m, 1 H), 2.94 (t, *J*=5.7 Hz, 2 H), 2.82 (quin, *J*=6.9 Hz, 1 H), 2.23 (s, 3 H), 2.17 (s, 3 H), 1.76 - 1.91 (m, 5 H), 1.53 - 1.70 (m, 2 H), 1.09 - 1.27 (m, 10 H); MS (ESI+) *m/z*539.4 $(M+H)^+$; $[\alpha]^{25}_D$ +0.85 (c 1.0, MeOH). .
21- R		2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm12.58 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.20 (dd, *J*=10.7, 8.2 Hz, 2 H), 6.81 - 6.94 (m, 2 H), 4.78 (dd, *J*=5.6, 2.5 Hz, 2 H), 4.51 (d, *J*=5.6 Hz, 2 H), 4.08 - 4.21 (m, 1 H), 3.96 - 4.08 (m, 1 H), 3.71 - 3.85 (m, 1 H), 3.42 - 3.51 (m, 1 H), 3.39 (t, *J*=6.1 Hz, 2 H), 3.24 (s, 3 H), 3.12 - 3.22 (m, 1 H), 2.95 (t, *J*=5.4 Hz, 2 H), 2.43 - 2.47

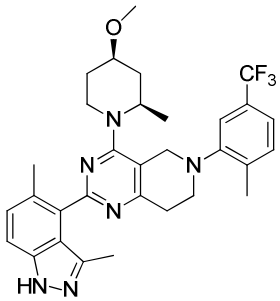
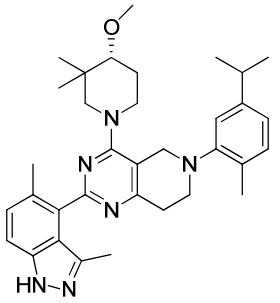
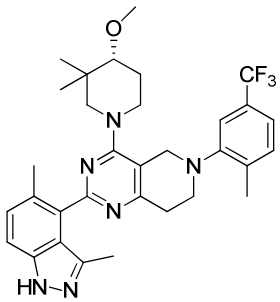
		(m, 1 H), 2.25 (s, 3 H), 2.17 (s, 3 H), 1.78 - 1.90 (m, 5 H), 1.54 - 1.67 (m, 5 H), 1.20 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z*567.3 $(M+H)^+$.
21- S		2- (2,4- dimetilpiridin- 3- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm8.33 (d, *J*=4.8 Hz, 1 H), 7.15 (d, *J*=5.3 Hz, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 6.92 (s, 1 H), 6.86 (d, *J*=7.8 Hz, 1 H), 4.05 - 4.17 (m, 1 H), 3.95 (d, *J*=14.9 Hz, 1 H), 3.76 - 3.87 (m, 1 H), 3.42 - 3.51 (m, *J*=3.5 Hz, 1 H), 3.32 - 3.37 (m, 2 H), 3.13 - 3.23 (m, 1 H), 2.93 (t, *J*=5.7 Hz, 2 H), 2.83 (dt, *J*=13.7, 6.9 Hz, 1 H), 2.18 - 2.29 (m, 7 H), 2.08 (s, 3 H), 1.77 - 1.90 (m, 2 H), 1.55 - 1.71 (m, 3 H), 1.19 - 1.24 (m, 4 H), 1.17 (d, *J*=6.8 Hz, 7 H); MS (ESI+) *m/z*500.3 $(M+H)^+$.
21- T		2- (2,6- dimetilfenil)- 6- (5- fluoro- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm7.20 - 7.27 (m, 1 H), 7.18 (d, *J*=8.1 Hz, 1 H), 7.05 - 7.12 (m, 2 H), 6.98 (dd, *J*=11.4, 2.5 Hz, 1 H), 6.83 (td, *J*=8.3, 2.5 Hz, 1 H), 4.03 - 4.12 (m, 1 H), 3.90 - 4.00 (m, 1 H), 3.71 - 3.81 (m, 1 H), 3.39 - 3.48 (m, 1 H), 3.25 (s, 3 H), 3.05 - 3.16 (m, 1 H), 2.98 (t, *J*=5.7 Hz, 2 H), 2.42- 2.46 (m, 1 H), 2.23 (s, 3 H), 2.03 (s, 6 H), 1.78 - 1.93 (m, 2 H), 1.50 - 1.72 (m, 3 H), 1.20 - 1.31 (m, 1 H), 1.16 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z*475.3 $(M+H)^+$.
21- U		2- (2,6- dimetilfenil)- 6- (4- fluoro- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm7.20 - 7.25 (m, 1 H), 7.16 - 7.19 (m, 1 H), 7.06 - 7.11 (m, 2 H), 7.03 (td, *J*=8.6, 3.0 Hz, 1 H), 3.97 - 4.06 (m, 1 H), 3.87 - 3.94 (m, 1 H), 3.74 (dt, *J*=6.8, 5.5 Hz, 1 H), 3.38 - 3.46 (m, 1 H), 3.24 (s, 4 H), 3.04 - 3.13 (m, 1 H), 2.98 (t, *J*=5.9 Hz, 1 H), 2.42 -

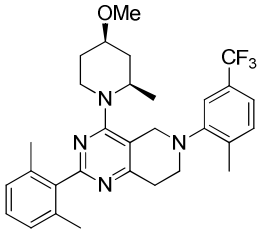
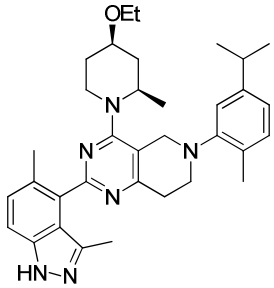
		2.46 (m, 1 H), 2.27 (s, 2 H), 2.03 (s, 3 H), 1.78 - 1.91 (m, 1 H), 1.52 - 1.66 (m, 1 H), 1.22 - 1.26 (m, 0 H), 1.14 (d, *J*=6.3 Hz, 2 H); MS (ESI+) *m/z*475.3 $(M+H)^+$.
21- V		2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.15 - 7.21 (m, 1 H) 7.05 - 7.14 (m, 3 H) 6.99 (d, J=1.8 Hz, 1 H) 6.89 (dd, J=7.7, 1.6 Hz, 1 H) 4.52 (br. s., 2 H) 4.03 (s, 2 H) 3.48 (t, J=4.4 Hz, 1 H) 3.35 (t, J=5.9 Hz, 2 H) 3.28 (s, 3 H) 2.93 (t, J=5.9 Hz, 2 H) 2.85 (ddd, J=13.8, 7.1, 7.0 Hz, 1 H) 2.27 (s, 3 H) 2.10 (s, 6 H) 2.02 - 2.19 (m, 4 H) 1.87 - 2.01 (m, 4 H) 1.23 (d, J=7.1 Hz, 6 H); MS (ESI+) *m/z*511.4 $(M+H)^+$.
21- W		6- (5- ciclopropil- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.15 - 7.21 (m, 1 H) 7.04 - 7.11 (m, 3 H) 6.86 (d, *J*=1.8 Hz, 1 H) 6.72 (dd, *J*=7.6, 1.8 Hz, 1 H) 4.52 (br. s., 2 H) 4.01 (s, 2 H) 3.49 (t, *J*=4.3 Hz, 1 H) 3.31 - 3.36 (m, 2 H) 3.28 (s, 3 H) 2.93 (t, *J*=5.8 Hz, 2 H) 2.26 (s, 3 H) 2.10 (s, 6 H) 2.02 - 2.19 (m, 4 H) 1.82 - 2.00 (m, 5 H) 0.91 (dt, *J*=10.6, 4.2 Hz, 2 H) 0.61 (dd, *J*=5.1, 2.1 Hz, 2 H); MS (ESI+) *m/z*509.1 $(M+H)^+$.
21- X		2- (2,6- dimetilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 (d, J=7.8 Hz, 1 H) 7.16 - 7.22 (m, 1 H) 7.1 - 7.14 (m, 2 H) 6.98 (d, J=1.8 Hz, 1 H) 6.92 - 6.96 (m, 1 H) 5.00 (d, J=5.6 Hz, 2 H) 4.68 (d, J=5.6 Hz, 2 H) 4.49 (br. s., 2 H) 4.05 (s, 2 H) 3.48 - 3.55 (m, 1 H) 3.40 (t, J=5.8 Hz, 2 H) 3.31 (s, 3 H) 3.05 - 3.14 (m, 2 H) 2.38 (s, 3 H) 2.20 (s, 6 H) 2.03 - 2.17 (m, 4 H) 1.89 - 2.02 (m, 4 H) 1.77 (s, 3

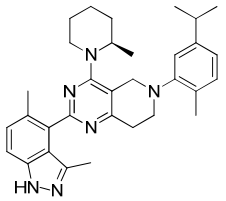
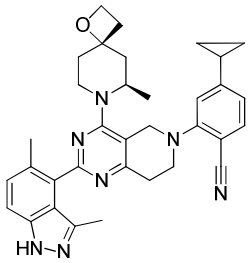
		H); MS (ESI+) *m/z*540.0 $(M+H)^+$.
21- Y		6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.67 (s, 1 H) 7.44 (d, J=3.8 Hz, 1 H) 7.14 (d, J=8.3 Hz, 1 H) 7.00 (d, J=1.8 Hz, 1 H) 6.92 (dd, J=7.8, 1.8 Hz, 1 H) 6.57 (d, J=3.5 Hz, 1 H) 4.49 (br. s., 2 H) 4.04 (s, 2 H) 3.46 (t, J=4.8 Hz, 1 H) 3.35 (t, J=6.0 Hz, 2 H) 3.25 (s, 3 H) 3.06 (t, J=6.0 Hz, 2 H) 2.90 (ddd, J=13.8, 7.1, 7.0 Hz, 1 H) 2.30 (s, 3 H) 2.00 - 2.16 (m, 4 H) 1.83 - 1.96 (m, 4 H) 1.26 (d, J=6.8 Hz, 6 H); MS (ESI+) *m/z*591.0 $(M+H)^+$.
21- Z		(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina **.** ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.22 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.34 (d, *J*=7.1 Hz, 1 H), 7.19 - 7.23 (m, 1 H), 7.01 - 7.13 (m, 2 H), 6.84 (s, 1 H), 6.72 (d, *J*=7.8 Hz, 1 H), 4.01 (s, 2 H), 3.71 (br. s., 1 H), 3.38 - 3.43 (m, 1 H), 3.34 (br. s., 5 H), 3.13 (br. s., 3 H), 2.95 (dd, *J*=8.7, 3.9 Hz, 2 H), 2.26 (s, 3 H), 2.09 (s, 3 H), 1.92 – 2.01 (m, 1 H), 1.81 - 1.92 (m, 1 H), 1.63 - 1.74 (m, 1 H), 1.00 (s, 3 H), 0.96 (br. s., 3 H), 0.91 - 0.95 (m, 2 H), 0.62 - 0.69 (m, 2 H); MS (ESI+) *m/z* 536.0 $(M+H)^+$.
21- AA		(*R*)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.15 - 7.20 (m, 1 H) 7.06 - 7.12 (m, 3 H) 6.91 (d, *J*=1.52 Hz, 1 H) 6.85 (dd, *J*=7.83, 1.52 Hz, 1 H) 4.06 (d, *J*=6.06 Hz, 2 H) 3.62 (br. s., 1 H) 3.31 - 3.36 (m, 3 H) 2.95 - 3.07 (m, 2 H) 2.86 - 2.92 (m, 2 H) 2.78 - 2.86 (m, 2 H) 2.21 (s, 3 H) 2.04 (s, 6 H) 1.89 - 1.98 (m, 1 H) 1.49 - 1.62 (m, 1 H) 1.17 (d,

		J=7.07 Hz, 6 H) 0.96 (s, 3 H) 0.88 (s, 3 H); MS (ESI+) *m/z*513.4 $(M+H)^+$.
21-AB		(*R*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.43 (d, *J*=7.83 Hz, 1 H) 7.29 - 7.35 (m, 2 H) 7.15 - 7.20 (m, 1 H) 7.05 - 7.10 (m, 2 H) 4.13 (q, *J*=14.65 Hz, 2 H) 3.64 (d, *J*=12.63 Hz, 1 H) 3.40 (t, *J*=6.44 Hz, 2 H) 3.33 (dd, *J*=13.14, 1.26 Hz, 1 H) 3.28 (s, 3 H) 2.99 - 3.08 (m, 1 H) 2.97 (dd, *J*=8.97, 3.92 Hz, 1 H) 2.88 - 2.95 (m, 2 H) 2.84 (d, *J*=12.88 Hz, 1 H) 2.34 (s, 3 H) 2.04 (s, 6 H) 1.89 - 1.96 (m, 1 H) 1.49 - 1.60 (m, 1 H) 0.95 (s, 3 H) 0.86 (s, 3 H); MS (ESI+) *m/z*539.3 $(M+H)^+$.
21-AC		(*R*)- 6- (5- cloro- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.23 (d, *J*=8.59 Hz, 1 H) 7.13 - 7.20 (m, 2 H) 7.04 - 7.10 (m, 3 H) 4.03 - 4.11 (m, 1 H) 3.95 - 4.03 (m, 1 H) 3.67 (d, *J*=14.15 Hz, 1 H) 3.34 (d, *J*=9.60 Hz, 2 H) 2.90 - 3.09 (m, 4 H) 2.85 (d, *J*=13.14 Hz, 1 H) 2.53 - 2.58 (m, 1 H) 2.23 (s, 3 H) 2.04 (s, 6 H) 1.88 - 1.96 (m, 1 H) 1.49 - 1.61 (m, 1 H) 0.94 (s, 3 H) 0.84 (s, 3 H); MS (ESI+) *m/z*505.3 $(M+H)^+$.
21-AD		(*R*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.14 - 7.23 (m, 2 H) 7.08 (d, *J*=7.58 Hz, 2 H) 6.84 - 6.92 (m, 2 H) 4.90 (d, *J*=5.56 Hz, 2 H) 4.58 (d, *J*=5.56 Hz, 2 H) 4.04 (s, 2 H) 3.67 (d, *J*=15.92 Hz, 1 H) 3.29 - 3.40 (m, 6 H) 3.05 (br. s., 3 H) 2.94 (dd, *J*=8.84, 3.79 Hz, 1 H) 2.84 (d, *J*=14.40 Hz, 1 H) 2.31 (s, 3 H) 2.12 (s, 6 H) 1.90 - 2.01 (m, 1 H) 1.61 - 1.73 (m, 4 H) 0.97 (d, *J*=16.93 Hz, 6 H); MS (ESI+) *m/z*541.3 $(M+H)^+$.

21-AE		(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- mesityl- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.09 (d, *J*=7.83 Hz, 1 H) 6.91 (s, 1 H) 6.89 (s, 2 H) 6.85 (dd, *J*=7.71, 1.39 Hz, 1 H) 3.99 - 4.11 (m, 2 H) 3.58 - 3.68 (m, 1 H) 3.33 (d, *J*=6.06 Hz, 3 H) 3.28 (s, 3 H) 2.95 - 3.06 (m, 2 H) 2.86 - 2.91 (m, 2 H) 2.77 - 2.85 (m, 2 H) 2.27 (s, 3 H) 2.21 (s, 3 H) 2.02 (s, 6 H) 1.93 (dd, *J*=13.14, 3.79 Hz, 1 H) 1.49 - 1.61 (m, 1 H) 1.16 (d, *J*=6.82 Hz, 6 H) 0.96 (s, 3 H) 0.88 (s, 3 H). MS (ESI+) *m/z*527.4(M+H)$^+$.
21-AF		(*S*)- 2- (7- fluoro- 3- metil- 1H- indol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.25 (br. s., 1 H) 7.22 (dd, J=8.1, 4.8 Hz, 1 H) 7.03 (d, J=7.8 Hz, 1 H) 6.98 (d, J=1.0 Hz, 1 H) 6.88 (d, J=1.5 Hz, 1 H) 6.76 - 6.86 (m, 2 H) 3.95 (s, 2 H) 3.50 - 3.67 (m, 1 H) 3.19 - 3.36 (m, 6 H) 2.94 - 3.06 (m, 3 H) 2.69 - 2.91 (m, 3 H) 2.18 (s, 3 H) 2.03 (s, 3 H) 1.82 - 1.95 (m, 1 H) 1.51 - 1.68 (m, 1 H) 1.16 (d, J=6.8 Hz, 6 H) 0.92 (s, 3 H) 0.89 (s, 3 H); MS (ESI+) m/z 556.4 (M+H)$^+$.
21-AG		6- (5- cloro- 2- metilfenil)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.58 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.23 (t, *J*=8.1 Hz, 2 H), 7.10 (d, *J*=2.0 Hz, 1 H), 7.06 (dd, *J*=8.1, 1.8 Hz, 1 H), 4.07 - 4.17 (m, 1 H), 3.99 - 4.07 (m, 1 H), 3.74 - 3.84 (m, 1 H), 3.42 - 3.49 (m, 1 H), 3.34 - 3.39 (m, 2 H), 3.25 (s, 3 H), 3.11 - 3.21 (m, 1 H), 2.96 (t, *J*=5.9 Hz, 2 H), 2.25 (s, 3 H), 2.17 (s, 3 H), 1.86 - 1.90 (m, 1 H), 1.84 (s, 3 H), 1.56 - 1.69 (m, 2 H), 1.24 (br. s., 1 H), 1.18 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z*531.2 (M+H)$^+$.

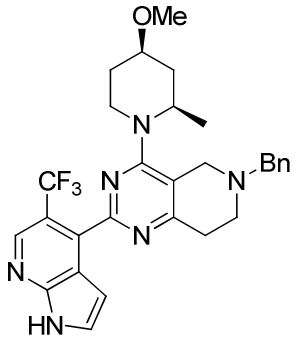
21-AH		2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d*$_6$) δ ppm 12.58 (s, 1 H), 7.45 (d, *J*=7.8 Hz, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.34 (d, *J*=8.3 Hz, 1 H), 7.28 (s, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 4.16 - 4.24 (m, 1 H), 4.06 - 4.15 (m, 1 H), 3.75 - 3.82 (m, 1 H), 3.44 (t, *J*=5.7 Hz, 2 H), 3.25 (s, 3 H), 3.11 - 3.20 (m, 1 H), 2.95 (t, *J*=6.3 Hz, 2 H), 2.44 - 2.47 (m, 1 H), 2.36 (s, 3 H), 2.17 (s, 3 H), 1.86 - 1.90 (m, 2 H), 1.83 (s, 3 H), 1.56 - 1.66 (m, 2 H), 1.24 (d, *J*=3.0 Hz, 1 H), 1.19 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z*565.3 $(M+H)^+$.
21-AI		(*R*)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d*6) δ ppm 12.57 (s, 1 H) 7.39 (d, *J*=8.34 Hz, 1 H) 7.21 (d, *J*=8.84 Hz, 1 H) 7.11 (d, *J*=7.83 Hz, 1 H) 6.93 (s, 1 H) 6.84 - 6.89 (m, 1 H) 4.02 - 4.17 (m, 2 H) 3.65 (d, *J*=13.14 Hz, 1 H) 3.33 - 3.41 (m, 3 H) 3.27 (s, 3 H) 3.00 - 3.13 (m, 1 H) 2.98 (dd, *J*=8.97, 3.92 Hz, 1 H) 2.89 - 2.95 (m, 2 H) 2.77 - 2.87 (m, 2 H) 2.22 (s, 3 H) 2.19 (s, 3 H) 1.89 - 1.97 (m, 1 H) 1.87 (s, 3 H) 1.49 - 1.61 (m, 1 H) 1.18 (d, *J*=6.82 Hz, 6 H) 0.96 (s, 3 H) 0.89 (s, 3 H); MS (ESI+) *m/z*553.3 $(M+H)^+$.
21-AJ		(*R*)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d*6) δ ppm 12.57 (s, 1 H) 7.44 (d, *J*=8.08 Hz, 1 H) 7.39 (d, *J*=8.34 Hz, 1 H) 7.27 - 7.36 (m, 2 H) 7.21 (d, *J*=8.59 Hz, 1 H) 4.10 - 4.25 (m, 2 H) 3.62 - 3.70 (m, 1 H) 3.44 (t, *J*=6.19 Hz, 2 H) 3.36 (d, *J*=13.64 Hz, 1 H) 3.27 (s, 3 H) 3.01 - 3.10 (m, 1 H) 2.98 (dd, *J*=9.09, 3.79 Hz, 1 H) 2.93 (t,

		J=6.32 Hz, 2 H) 2.85 (d, *J*=13.14 Hz, 1 H) 2.35 (s, 3 H) 2.18 (s, 3 H) 1.93 (dd, *J*=13.64, 4.04 Hz, 1 H) 1.85 (s, 3 H) 1.49 - 1.61 (m, 1 H) 0.95 (s, 3 H) 0.87 (s, 3 H); MS (ESI+) *m/z*579.3 $(M+H)^+$.
21-AK		2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm 7.44 (d, *J*=7.8 Hz, 1 H), 7.34 (d, *J*=8.6 Hz, 1 H), 7.29 (s, 1 H), 7.15 - 7.22 (m, 1 H), 7.05 - 7.12 (m, 2 H), 4.11 - 4.21 (m, 1 H), 4.00 - 4.09 (m, 1 H), 3.71 - 3.81 (m, 1 H), 3.42 - 3.48 (m, 1 H), 3.40 (t, *J*=6.1 Hz, 2 H), 3.25 (s, 3 H), 3.11 (ddd, *J*=13.8, 6.6, 4.3 Hz, 1 H), 2.94 (t, *J*=5.9 Hz, 2 H), 2.35 (s, 3 H), 2.03 (s, 6 H), 1.80 - 1.91 (m, 2 H), 1.54 - 1.67 (m, 2 H), 1.18 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z*525.2 $(M+H)^+$.
21-AL		2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((2R,4R)- 4- etoxi- 2- metilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm 12.58 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=7.6 Hz, 1 H), 6.92 (s, 1 H), 6.87 (dd, *J*=7.7, 1.4 Hz, 1 H), 4.08 - 4.18 (m, 1 H), 3.96 - 4.05 (m, 1 H), 3.74 - 3.84 (m, 1 H), 3.55 (t, *J*=5.7 Hz, 1 H), 3.40 - 3.49 (m, 2 H), 3.34 - 3.40 (m, 3 H), 3.11 - 3.21 (m, 1 H), 2.94 (t, *J*=5.7 Hz, 2 H), 2.82 (dt, *J*=13.6, 6.8 Hz, 1 H), 2.23 (s, 3 H), 2.17 (s, 3 H), 1.77 - 1.90 (m, 5 H), 1.55 - 1.66 (m, 2 H), 1.15 - 1.23 (m, 9 H), 1.10 (t, *J*=6.9 Hz, 3 H); MS (ESI+) *m/z* 553.5 $(M+H)^+$.

21-AM		(*R*)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=8.1 Hz, 1 H), 6.93 (d, *J*=1.5 Hz, 1 H), 6.86 (dd, *J*=7.6, 1.5 Hz, 1 H), 3.88 - 4.17 (m, 3 H), 3.43 - 3.57 (m, 1 H), 3.11 - 3.24 (m, 1 H), 2.89 - 3.00 (m, 2 H), 2.77 - 2.88 (m, 1 H), 2.22 (s, 3 H), 2.17 (br. s., 3 H), 1.84 - 1.90 (m, 3 H), 1.59 - 1.75 (m, 3 H), 1.52 (d, *J*=4.8 Hz, 3 H), 1.13 - 1.21 (m, 9 H); MS (ESI+) *m/z* 509.4 $(M+H)^+$.
21-AN		4- Ciclopropil- 2- (2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((4S,6R)- 6- metil- 1- oxa- 7- azaspiro[3.5]nonan- 7- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)benzonitrile. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.76 (br. s., 1H), 7.40 (d, *J* = 7.83 Hz, 1H), 7.28 (d, *J* = 8.34 Hz, 1H), 7.17 (d, *J* = 8.84 Hz, 1H), 6.54 - 6.67 (m, 2H), 4.36 - 4.50 (m, 2H), 4.31 (d, *J* = 15.16 Hz, 1H), 4.20 (d, *J* = 15.16 Hz, 1H), 3.91 - 4.02 (m, 1H), 3.71 - 3.81 (m, 1H), 3.61 - 3.71 (m, 1H), 3.44 (td, *J* = 4.71, 13.83 Hz, 1H), 3.12 (ddd, *J* = 3.03, 10.04, 13.45 Hz, 1H), 2.98 - 3.05 (m, 2H), 2.45 - 2.57 (m, 1H), 2.34 - 2.45 (m, 1H), 2.15 (s, 3H), 1.97 - 2.08 (m, 1H), 1.86 - 1.94 (m, 2H), 1.84 (s, 3H), 1.76 - 1.83 (m, 2H), 1.11 (d, *J* = 6.82 Hz, 3H), 0.94 - 1.02 (m, 2H), 0.61 - 0.68 (m, 2H). MS (ESI+) *m/z* 560.3 $(M+H)^+$.

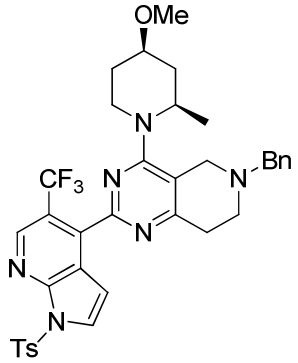
Ejemplo 22

22- A.6- Bencil- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



El producto se preparó como en una manera similar a la descrita en el **Ejemplo 21- b** utilizando 6-bencil-2-cloro-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (190 mg, 0.491 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5-(trifluorometil)-1-(triisopropilsilil)-1H-pirrolo[2,3-b]piridina (460 mg, 0.982 mmol) de $Pd(PPh_3)_4$ (57 mg, 0.049 mmol) y una solución de NaHCO2 M (737 l, 1,47 mmol). El residuo se purificó a través de FCC (0 a 5% MeOH/DCM (1% NH_4OH)) para proporcionar el compuesto del título. MS (ESI+) m/z 537.0 (M+H) +.

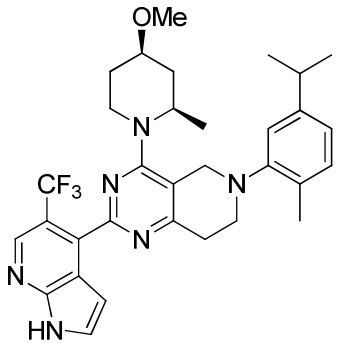
22- B.6- Bencil- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (1- tosil- 5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de 6- bencil- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (214 mg, 0.399 mmol) en THF (4 mL) se añadió NaH 60% en aceite (32 mg, 0.80 mmol) a 0 °C. Después de 20 minutos, se añadió cloruro de p toluenosulfonilo (91 mg, 0.48 mmol) y la reacción se dejó calentar a temperatura ambiente. Después de 2 h, la reacción se apago con una solución saturada de NH_4Cl. La mezcla se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró bajo

presión reducida. El residuo resultante se purificó a través de FCC (0- 70% EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 691.1 (M+H)+.

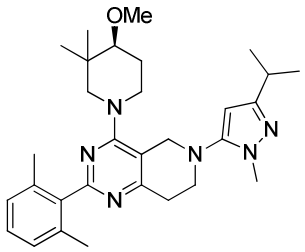
22- C.6- (5- Isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



A una solución de 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (1- tosil- 5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (25 mg, 0.034 mmol), preparado como se describe en los Ejemplos 21- c y 21- d, en EtOH (898 µL) se añadió KOH (17.2 mg, 0.307 mmol) y NH_4OH (202 µL, 5.12 mmol). La reacción se calentó a 100 °C durante 40 min en un reactor de microondas. La reacción se concentró luego y el residuo se disolvió en EtOAc y una solución saturada de NH_4Cl. Las capas se separaron y la fase acuosa se extrajo con EtOAc (2x). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron y se concentraron bajo presión reducida. El residuo resultante se purificó a través de FCC (0- 60% EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 12,24 (br. s., 1 H)., 8,64 (s, 1 H), 7,65 - 7,70 (m, 1 H), 7,11 (d, J = 7,8 Hz, 1 H), 6,94 (s, 1 H), 6,87 (dd, J = 7,7, 1,6 Hz, 1 H), 6,41 (dd, J = 3,5, 1,8 Hz, 1 H), 4,13 (d, J = 15,4 Hz , 1 H), 3,94 - 4,03 (m, 1 H), 3,86 - 3,94 (m, 1 H), 3,44 - 3,50 (m, 1 H), 3,33 - 3,38 (m, 2 H), 3,25 (s, 3 H), 2,92 .3,01 (m, 2 H), 2,84 (dt, J = 13,7, 6,9 Hz, 1 H), 2,43 - 2,47 (m, 1 H), 2,23 (s, 3 H), 1,75 - 1,89 (m, 2 H), 1,61 - 1,72 (m, 2 H), 1,22 (d, J = 6,8 Hz, 4 H), 1,18 (d, J = 6,8 Hz, 6 H), MS (ESI+) m/z 579.1 (M+H)+.

Ejemplo 23

23- A.(*S*)- 2- (2,6- Dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.

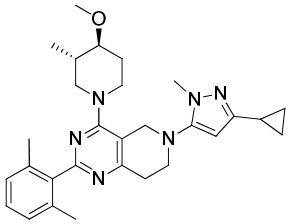
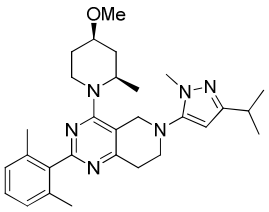
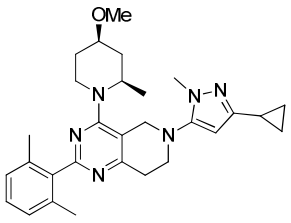


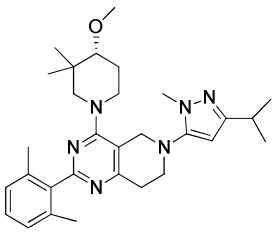
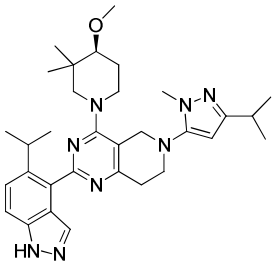
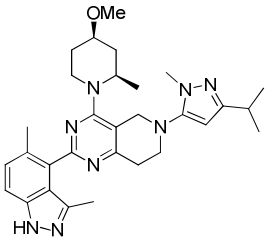
En un vial de reacción de microondas(*S*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (115 mg, 0.302 mmol), preparado por un método similar al descrito en los Ejemplos 21- c y 21- d, se combinó con acetato de metilo isobutirilo (65 mg, 0.45 mmol), tolueno (2 ml) y DMAP (7 mg , 0.060 mmol). El vial se calentó en un reactor de microondas a 150 °C durante 30 min. Luego la mezcla de reacción se diluyó con DCM y agua. Las capas se separaron y la fase acuosa se extrajo dos veces con DCM. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en columna de gel de sílice (0- 100% 10:01 EtOAc: MeOH/heptanos) para proporcionar (*S*)- 1- (2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)- 4- metilpentano- 1,3- dionaMS (ESI+) m/z 493.0 (M+H)+

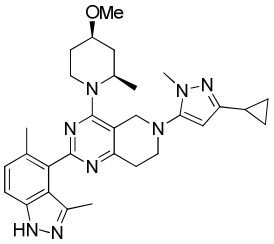
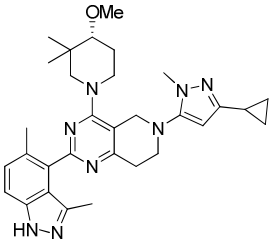
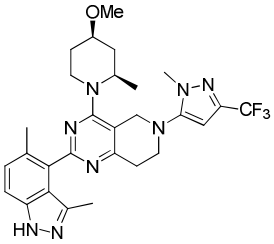
A una solución de reactivo de Lawesson (61 mg, 0.15 mmol) en THF (1 ml) se añadió piridina (0.050 ml) seguido de hidracina de metilo (9.9 l, 0.19 mmol). La mezcla de reacción se agitó durante 35 minutos a temperatura ambiente. Se añadió una solución de(*S*)- 1- (2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)- 4- metilpentano- 1,3- diona (62 mg, 0.13 mmol) en THF (1 ml) y la reacción se selló y se calentó inmediatamente por irradiación de microondas durante 12 minutos a 125 °C. La mezcla de reacción se concentró y el residuo resultante se purificó mediante cromatografíaultrarrápida en columna sobre gel de sílice (0- 5% 10:01 MeOH: NH_4OH/DCM para proporcionar(*S*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,20 (br. s., 1 H), 7,09 (d, J = 7,1 Hz, 2 H), 5,66 (s, 1 H), 3,98 (d, J = 2,3 Hz , 2 H), 3,68 - 3,76 (m, 1 H), 3,66 (s, 3 H), 3,34 (s, 3 H), 3,31 (t, J = 6,1 Hz, 2 H), 3,07 (br. s., 1 H), 2,93 - 3,00 (m, 1 H), 2,84 (spt, J = 6,6 Hz, 1 H), 2,13 (br. s., 6 H), 1,92 - . 2,00 (m, 1 H), 1,64 - 1,74 (m, 1 H), 1,21 (d, J = 7,1 Hz, 6 H), 0,96 (s, 3 H), 0,90 (s, 3 H), MS (ESI+) m/z 503.2 (M+H)+.

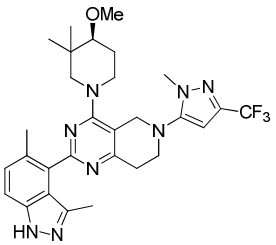
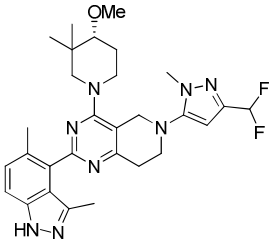
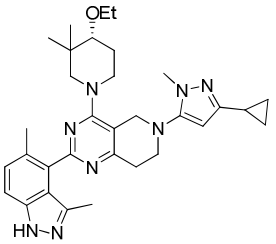
Los siguientes compuestos se prepararon de una manera similar. Para los compuestos que contienen un grupo indazol oindol la síntesis se realizócon los correspondientes intermedios

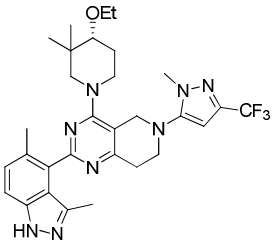
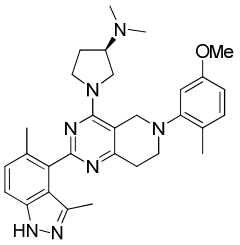
N- tosilo protegidos descritos en los otros ejemplos en este documento y la eliminación del grupo protector tosilo en el último paso se realizócomo se describe en otros ejemplos en este documento.

	Estructura	Nombre Quimico y Datos Analiticos
23- B		6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3-*d*]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 0.51 - 0.63 (m, 2 H) 0.74 - 0.83 (m, 2 H) 0.93 (d, *J*=6.6 Hz, 3 H) 1.29 - 1.42 (m, 1 H) 1.58 - 1.69 (m, 1 H) 1.70 - 1.81 (m, 1 H) 2.01 - 2.10 (m, 1 H) 2.04 (s, 6 H) 2.74 (dd, *J*=13.4, 9.9 Hz, 1 H) 2.88 - 3.06 (m, 4 H) 3.25 - 3.29 (m, 2 H) 3.27 (s, 3 H) 3.56 (s, 3 H) 3.58 - 3.65 (m, 1 H) 3.72 (d, *J*=12.6 Hz, 1 H) 3.96 (s, 2 H) 5.59 (s, 1 H) 7.03 - 7.11 (m, 2 H) 7.12 - 7.22 (m, 1 H); MS (ESI+) *m/z*487.1 $(M+H)^+$.
23- C		2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm7.14 - 7.23 (m, 1 H), 7.04 - 7.11 (m, 2 H), 5.68 (s, 1 H), 4.00 - 4.12 (m, 1 H), 3.89 - 4.00 (m, 1 H), 3.67 - 3.77 (m, 1 H), 3.60 (s, 3 H), 3.37 - 3.48 (m, 1 H), 3.25 (s, 3 H), 3.02 - 3.13 (m, 1 H), 2.95 (t, *J*=5.8 Hz, 2 H), 2.76 (dt, *J*=13.8, 6.9 Hz, 1 H), 2.02 (s, 5 H), 1.78 - 1.91 (m, 2 H), 1.52 - 1.70 (m, 2 H), 1.11 - 1.19 ppm (m, 9 H); MS (ESI+) *m/z*489.3 $(M+H)^+$.
23- D		6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm7.14 - 7.23 (m, 1 H), 7.03 - 7.12 (m, 2 H), 5.59 (s, 1 H), 3.98 - 4.08 (m, 1 H), 3.86 - 3.96 (m, 1 H), 3.68 - 3.80 (m, 1 H), 3.57 (s, 3 H), 3.39 - 3.49 (m, 1 H), 3.25 (s, 4 H), 3.02 - 3.13 (m, 1 H), 2.90 - 2.99 (m, 2 H), 2.02 (s, 6 H), 1.80 -

		1.92 (m, 2 H), 1.71 - 1.80 (m, 1 H), 1.52 - 1.68 (m, 2 H), 1.15 (d, *J*=6.6 Hz, 3 H), 0.73 - 0.83 (m, 2 H), 0.53 - 0.61 (m, 2 H); MS (ESI+) *m/z*487.3 $(M+H)^+$.
23- E		(*R*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina; ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.14 - 7.23 (m, 1 H) 7.07 (d, *J*=7.58 Hz, 2 H) 5.65 (s, 1 H) 3.93 - 4.04 (m, 2 H) 3.70 (d, *J*=8.34 Hz, 1 H) 3.66 (s, 3 H) 3.28 - 3.37 (m, 6 H) 3.12 (br. s., 1 H) 3.04 (br. s., 2 H) 2.95 (dd, *J*=8.59, 3.79 Hz, 1 H) 2.85 (dq, *J*=13.86, 6.92 Hz, 2 H) 2.11 (s, 6 H) 1.92 - 2.01 (m, 1 H) 1.63 - 1.75 (m, 1 H) 1.22 (s, 3 H) 1.20 (s, 3 H) 0.97 (s, 3 H) 0.91 (s, 3 H); MS (ESI+) *m/z*503.4 $(M+H)^+$.
23- F		(*S*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (5- isopropil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.95 (br. s., 1 H), 7.53 (d, *J*=8.8 Hz, 1 H), 7.47 (d, *J*=8.8 Hz, 1 H), 5.73 (s, 1 H), 4.02 (s, 2 H), 3.68 (m, 4 H), 3.42 (s, 2 H), 3.31 - 3.37 (m, 5 H), 3.14 (br. s., 2 H), 2.96 (dd, *J*=8.2, 3.4 Hz, 1 H), 2.86 (spt, *J*=6.8 Hz, 1 H), 1.93 - 2.02 (m, 1 H), 1.65 - 1.76 (m, 1 H), 1.29 (d, *J*=6.8 Hz, 6 H), 1.23 (d, *J*=6.8 Hz, 6 H), 0.98 (s, 3 H), 0.94 (s, 3 H); MS (ESI+) *m/z* 557.1 $(M+H)^+$.
23- G		2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- *d_6*) δ ppm12.58 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.22 (d, *J*=8.3 Hz, 1 H), 5.63 (s, 1 H), 4.07 - 4.14 (m, 1 H), 3.97 - 4.05 (m, 1 H), 3.75 (q, *J*=6.0 Hz, 1 H), 3.61 (s, 3 H), 3.41 - 3.48 (m, 1 H), 3.33 - 3.38 (m, 2 H), 3.25 (s, 3 H), 3.08 - 3.18 (m, 1 H), 2.95 (t, *J*=5.7 Hz, 2 H), 2.76 (dt, *J*=13.8, 6.9 Hz, 1 H), 2.16 (s, 3 H), 1.81 - 1.89 (m, 5 H), 1.54 -

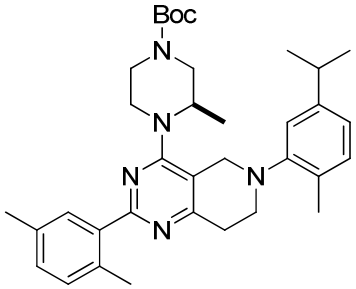
		1.71 (m, 2 H), 1.12 - 1.19 (m, 9 H); MS (ESI+) *m/z*529.4 $(M+H)^+$.
23-H		6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.58 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 5.55 (s, 1 H), 4.04 - 4.15 (m, 1 H), 3.92 - 4.04 (m, 1 H), 3.70 - 3.81 (m, 2 H), 3.58 (s, 3 H), 3.41 - 3.50 (m, 2 H), 3.25 (s, 3 H), 3.07 - 3.20 (m, 1 H), 2.95 (t, *J*=5.8 Hz, 2 H), 2.16 (s, 3 H), 1.85 (s, 6 H), 1.70 - 1.79 (m, 1 H), 1.55 - 1.70 (m, 2 H), 1.17 (d, *J*=6.6 Hz, 3 H), 0.73 - 0.85 (m, 2 H), 0.50 - 0.64 (m, 2 H); MS (ESI+) *m/z* 527.4 $(M+H)^+$.
23- I		(*R*)- 6- (3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.57 (s, 1 H) 7.38 (d, *J*=8.59 Hz, 1 H) 7.21 (d, *J*=8.59 Hz, 1 H) 5.52 (s, 1 H) 4.07 - 4.14 (m, 1 H) 3.96 - 4.03 (m, 1 H) 3.67 (d, *J*=12.38 Hz, 1 H) 3.57 (s, 3 H) 3.33 (br. s., 2 H) 3.27 (s, 3 H) 3.01 - 3.11 (m, 1 H) 2.98 (dd, *J*=8.97, 3.92 Hz, 1 H) 2.92 (t, *J*=6.06 Hz, 2 H) 2.86 (d, *J*=13.14 Hz, 1 H) 2.55 (br. s., 1 H) 2.18 (s, 3 H) 1.94 (d, *J*=3.28 Hz, 1 H) 1.87 (s, 3 H) 1.70 - 1.80 (m, 1 H) 1.49 - 1.62 (m, 1 H) 0.94 (s, 3 H) 0.84 (s, 3 H) 0.76 - 0.82 (m, 2 H) 0.53 - 0.58 (m, 2 H); MS (ESI+) *m/z* 541.3 $(M+H)^+$.
23- J		2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.61 (s, 1 H), 7.40 (d, *J*=8.6 Hz, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 6.35 (s, 1 H), 4.13 - 4.26 (m, 1 H), 4.02 - 4.14 (m, 1 H), 3.73 - 3.89 (m, 4 H), 3.37 -

		3.51 (m, 2 H), 3.25 (s, 3 H), 3.14 - 3.19 (m, , 1 H), 2.98 - 3.00 (m, 2 H), 2.89 (s, 1 H), 2.73 (s, 1 H), 2.16 (s, 3 H), 1.75 - 1.92 (m, 5 H), 1.52 - 1.75 (m, 2 H), 1.18 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 555.5 $(M+H)^+$.
23-K		(*S*)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. 1H NMR (400 MHz, DICLOROMETANO- d_6) δ ppm 7.36 - 7.42 (m, 1 H), 7.24 - 7.29 (m, 1 H), 6.12 (s, 1 H), 4.02 - 4.13 (m, 2 H), 3.81 (s, 3 H), 3.67 - 3.76 (m, 1 H), 3.37 - 3.44 (m, 2 H), 3.33 (s, 4 H), 3.02 - 3.23 (br. m, 3 H), 2.87 - 3.01 (m, 2 H), 2.29 (s, 3 H), 1.91 - 2.04 (m, 5 H), 1.63 - 1.76 (m, 1 H), 0.97 (s, 3 H), 0.91 (s, 3 H); MS (ESI+) *m/z* 569.4 $(M+H)^+$.
23- L		(*R*)- 6- (3- (difluorometil)- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 6.85 (t, *J*=54.8 Hz, 1 H), 6.11 (s, 1 H), 4.21 (d, *J*=14.9 Hz, 1 H), 4.08 (d, *J*=14.9 Hz, 1 H), 3.73 (s, 3 H), 3.66 - 3.71 (m, 1 H), 3.37 - 3.44 (m, 2 H), 3.27 (s, 3 H), 3.02 - 3.10 (m, 1 H), 2.92 - 3.01 (m, 3 H), 2.87 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.88 - 1.96 (m, 1 H), 1.86 (s, 3 H), 1.50 - 1.62 (m, 1 H), 0.94 (s, 3 H), 0.83 (s, 3 H); MS (ESI+) *m/z* 551.5 $(M+H)^+$.
23-M		(*R*)- 6- (3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 5.52 (s, 1 H), 4.08 (s, 1 H), 4.00 (s, 1 H), 3.64 - 3.74 (m, 1 H), 3.59 - 3.64 (m, 1 H), 3.57 (s, 3 H), 3.00 - 3.11 (m, 2 H), 2.92 (t, *J*=5.8 Hz, 2 H),

		2.85 (d, *J*=13.1 Hz, 1 H), 2.17(s, 3 H), 1.82 - 1.92 (m, 4 H), 1.74 (tt, *J*=8.4, 5.0 Hz, 1 H), 1.51 - 1.56 (m, 1 H), 1.09 (t, *J*=6.9 Hz, 3 H), 0.93 (s, 3 H), 0.84 (s, 3 H), 0.75 - 0.81 (m, 2 H), 0.49 - 0.60 (m, 2 H); MS (ESI+) *m/z* 555.5 $(M+H)^+$.
23-N		(*R*)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 6.31 (s, 1 H), 4.15 - 4.32 (m, 1 H), 4.01 - 4.14 (m, 1 H), 3.78 (s, 3 H), 3.70 (d, *J*=13.1 Hz, 1 H), 3.54 - 3.65 (m, 1 H), 3.42 (app q, *J*=6.1 Hz, 2 H), 3.38 (t, *J*=4.0 Hz, 1 H), 3.01 - 3.13 (m, 2 H), 2.96 (br. s., 2 H), 2.88 (d, *J*=13.1 Hz, 1 H), 2.12 - 2.23 (m, 3 H), 1.85 (s, 4 H), 1.47 - 1.66 (m, 1 H), 1.03 - 1.17 (m, 3 H), 0.93 (s, 3 H), 0.75 - 0.87 (m, 3 H); MS(ESI+) *m/z* 583.4 $(M+H)^+$.
23-O		(*R*)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- metoxi- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 12.55 (s, 1 H), 7.36 (d, *J*=8.3 Hz, 1 H), 7.19 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=8.6 Hz, 1 H), 6.68 (d, *J*=2.5 Hz, 1 H), 6.60 (dd, *J*=8.3, 2.5 Hz, 1 H), 4.39 (d, *J*=14.7 Hz, 1 H), 4.18 (d, *J*=14.7 Hz, 1 H), 3.83 (dd, *J*=10.2, 6.7 Hz, 1 H), 3.73 - 3.79 (m, 1 H), 3.72 (s, 3 H), 3.59 - 3.68 (m, 1 H), 3.38 (dd, *J*=10.0, 8.5 Hz, 1 H), 3.26 - 3.29 (m, 1 H), 3.13 - 3.22 (m, 1 H), 2.76 - 2.97 (m, 2 H), 2.62 - 2.66 (m, 1 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 2.15 (s, 6 H), 2.00 - 2.09 (m, 1 H), 1.91 (s, 3 H), 1.64 - 1.76 (m, 1 H); MS (ESI+) *m/z* 512.3 $(M+H)^+$.

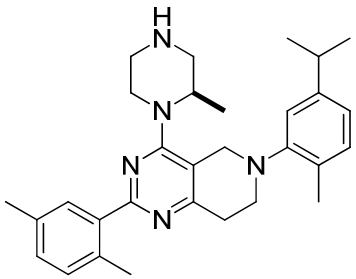
Ejemplo 24

24- A. 4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazina- 1- carboxilato de (R)- terc- butilo



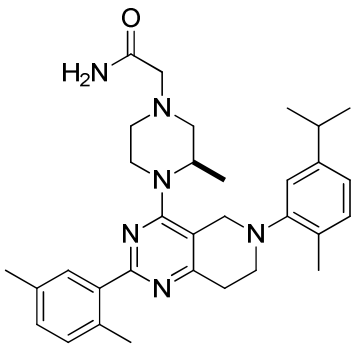
El compuesto del título se preparó de una manera similar a la descrita en el **Ejemplo 21**. MS (ESI+) m/z 570.4 (M+H)+.

24- B.(*R*)- 2- (2,5- Dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



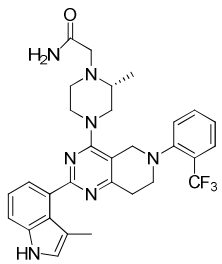
4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazina- 1- carboxilato de (R)- terc- butilo (60 mg, 0.105 mmol) en DCM (1 ml) se trató con TFA (1 ml, 13.0 mmol) a temperatura ambiente durante 15 min. Luego la mezcla se concentró para proporcionar(*R*)- 2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina, el cualse utilizó sin necesidad de purificación adicional. MS (ESI+) m/z 470.4 (M+H)+.

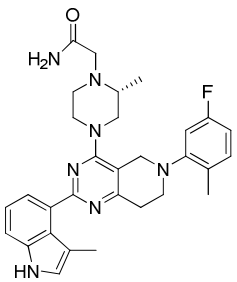
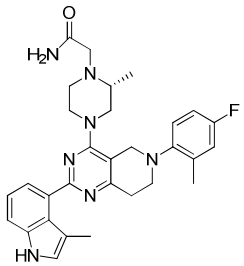
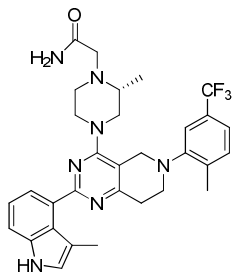
24- C. (*R*)- 2- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida.

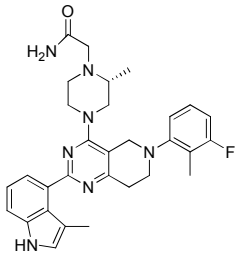
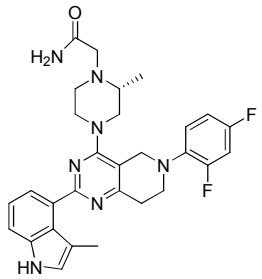
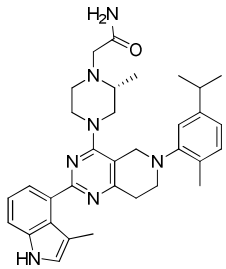


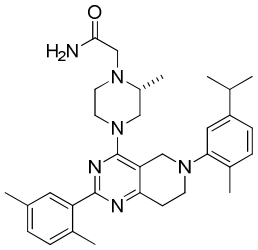
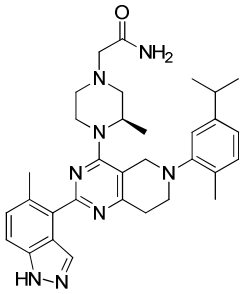
Una mezcla de (*R*)- 2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (43 mg, 0.053 mmol), 2- bromoacetamida (14.6 mg, 0.106 mmol) y DIEA (0.074 ml, 0.424 mmol) en DCM (2 ml) se agitó a temperatura ambiente durante 16 h. Luego la reacción se diluyó con EtOAc, y se lavó sucesivamente con $NaHCO_3$ acuoso saturado, y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro, se filtró y se concentró bajo presión reducida. El residuo resultante se purificó mediante HPLC (C18, acetonitrilo 15- 85% en H_2O con NH_4OH al 0.1%) para proporcionar(*R*)- 2- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida.^{1}H RMN (400 MHz, DMSO- d_6, a 120 °C) δ ppm 7,58 (s, 1 H) 7.8 - 7.18 (m, 5 H) 6,99 (d, J = 1,64 Hz, 1 H) 6,87 (dd, J = 7,71, 1,64 Hz, 1 H) 4.1 - 4.9 (m, 1 H) 3.89 - 4.01 (m, 2 H) 3.48- 3.58 (m, 1 H) 3,37- 3,47 (m, 1 H) 2,97 (t, J = 5,87 Hz, 2 H) 2.81- 2.90 (m, 3 H) 2,78 (d, J = 10,36 Hz, 1 H) 2,61 (dd, J = 11,62, 1,77 Hz, 1 H) 2,47 (s, 3 H) 2,40 (dd, J = 11,31, 3,35 Hz, 1 H) 2,23 a 2,34 (m, 4 H) 2,20 (s, 3 H) 1,28 (d, J = 6,44 Hz, 3 H) 1,19 (dd, J = 6,95, 1,52 Hz, 6 H), MS (ESI+) m/z 527.4 (M+H)+.

Los siguientes compuestos se prepararon de una manera similar.

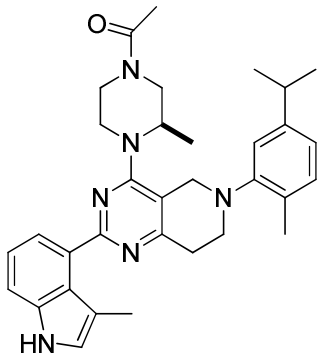
	Estructura	Nombre Quimico y Datos Analiticos
24-D		(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- (trifluorometil)fenil)- 5,6,7,8 tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.93 (br. s., 1 H) 7.68 - 7.82 (m, 3 H) 7.37 - 7.48 (m, 2 H) 7.19 - 7.30 (m, 2 H) 7.05 - 7.18 (m, 3 H) 4.04 (s, 2 H) 3.59 (t, *J*=8.84 Hz, 2 H) 3.05 - 3.24 (m, 3 H) 2.97 (t, *J*=5.56 Hz, 2 H) 2.88 (dd, *J*=12.63, 8.84 Hz, 1 H) 2.72 - 2.82 (m, 2 H) 2.52 - 2.64 (m, 2 H) 2.40 - 2.47 (m, 1 H) 2.02 (s, 3 H) 0.98 (d, *J*=6.06 Hz, 3 H); MS

		(ESI+) *m/z* 564.4 $(M+H)^+$.
24- E		(*R*)- 2- (4- (6- (5- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.92 (d, *J*=1.77 Hz, 1 H) 7.41 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.19 - 7.30 (m, 3 H) 7.08 - 7.16 (m, 3 H) 7.02 (dd, *J*=11.24, 2.65 Hz, 1 H) 6.83 (td, *J*=8.34, 2.53 Hz, 1 H) 4.01 (s, 2 H) 3.62 (t, *J*=11.62 Hz, 2 H) 3.27 - 3.30 (m, 2 H) 3.21 (t, *J*=10.11 Hz, 2 H) 3.13 (d, *J*=16.17 Hz, 1 H) 2.89 - 3.02 (m, 3 H) 2.77 - 2.85 (m, 2 H) 2.59 - 2.65 (m, 1 H) 2.22 (s, 3 H) 2.02 (s, 3 H) 1.02 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 528.4 $(M+H)^+$.
24- F		(*R*)- 2- (4- (6- (4- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.93 (br. s., 1 H) 7.42 (d, *J*=7.83 Hz, 1 H) 7.19 - 7.31 (m, 3 H) 7.00 - 7.18 (m, 5 H) 3.97 (br. s., 2 H) 3.61 (br. s., 2 H) 3.17 - 3.29 (m, 4 H) 3.13 (d, *J*=16.42 Hz, 1 H) 2.99 (br. s., 3 H) 2.80 (d, *J*=14.15 Hz, 2 H) 2.60 (d, *J*=1.77 Hz, 1 H) 2.27 (s, 3 H) 2.03 (s, 3 H) 1.02 (br. s., 3 H); MS (ESI+) *m/z* 528.4 $(M+H)^+$.
24- G		(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.93 (br. s., 1 H) 7.31 - 7.50 (m, 4 H) 7.28 (br. s., 1 H) 7.21 (d, *J*=7.07 Hz, 1 H) 7.06 - 7.18 (m, 3 H) 4.02 - 4.17 (m, 2 H) 3.61 (t, *J*=11.37 Hz, 2 H) 3.17 - 3.30 (m, 3 H) 3.11 (d, *J*=16.17 Hz, 1 H) 2.88 - 3.04 (m, 3 H) 2.81 (d, *J*=15.92 Hz, 2 H) 2.60 - 2.70 (m, 1 H) 2.42 - 2.47 (m, 1 H) 2.34 (s, 3 H) 2.02 (s, 3 H) 1.03 (d, *J*=6.06 Hz, 3 H); MS (ESI+) *m/z* 578.4 $(M+H)^+$.

24-H		(*R*)- 2- (4- (6- (3- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.90 (d, *J*=2.02 Hz, 1 H) 7.39 - 7.44 (m, 1 H) 7.19 - 7.28 (m, 3 H) 7.07 - 7.17 (m, 3 H) 7.02 (d, *J*=8.08 Hz, 1 H) 6.90 (t, *J*=8.84 Hz, 1 H) 4.04 (s, 2 H) 3.58 - 3.66 (m, 2 H) 3.33 - 3.36 (m, 1 H) 3.28 (s, 2 H) 3.17 - 3.25 (m, 1 H) 3.13 (d, *J*=16.17 Hz, 1 H) 2.97 - 3.03 (m, 2 H) 2.92 (dd, *J*=12.76, 8.72 Hz, 1 H) 2.77 - 2.86 (m, 2 H) 2.58 - 2.66 (m, 1 H) 2.16 (d, *J*=2.27 Hz, 3 H) 2.03 (s, 3 H) 1.02 (d, *J*=6.06 Hz, 3 H); MS (ESI+) *m/z* 528.4 $(M+H)^+$.
24- I		(*R*)- 2- (4- (6- (2,4- difluorofenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.90 (s, 1 H) 7.41 (dd, *J*=8.08, 1.01 Hz, 1 H) 7.01 - 7.30 (m, 8 H) 4.13 (s, 2 H) 3.61 (t, *J*=11.62 Hz, 2 H) 3.47 (t, *J*=6.19 Hz, 2 H) 3.36 (br. s., 1 H) 3.18 - 3.25 (m, 1 H) 3.14 (d, *J*=16.17 Hz, 1 H) 2.89 - 2.99 (m, 3 H) 2.78 - 2.85 (m, 2 H) 2.65 (br. s., 1 H) 2.00 (s, 3 H) 1.03 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 532.4 $(M+H)^+$.
24- J		(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.30 (br. s., 1 H) 7.46 (d, *J*=7.83 Hz, 1 H) 7.35 - 7.42 (m, 1 H) 7.22 (t, *J*=7.71 Hz, 1 H) 7.15 (d, *J*=7.58 Hz, 1 H) 7.08 (s, 1 H) 6.98 (d, *J*=1.52 Hz, 1 H) 6.92 (dd, *J*=7.58, 1.52 Hz, 1 H) 5.36 (d, *J*=7.07 Hz, 2 H) 3.97 - 4.08 (m, 2 H) 3.79 (br. s., 2 H) 3.37 (t, *J*=5.43 Hz, 3 H) 3.21 (br. s., 2 H) 3.03 - 3.15 (m, 1 H) 2.81 - 3.03 (m, 3 H) 2.72 (br. s., 1 H) 2.60 (br. s., 1 H) 2.28 (s, 3 H) 2.11 (s, 3 H) 1.25 (m, 7 H) 1.14 (d, *J*=9.35 Hz, 3 H); MS (ESI+) *m/z* 552.4 $(M+H)^+$.

24- K		(*R*)- 2- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, CD_3CN) δ ppm 7.59 (s, 1 H) 7.10 - 7.19 (m, 3 H) 7.03 (d, *J*=1.77 Hz, 2 H) 6.91 (dd, *J*=7.71, 1.64 Hz, 1 H) 5.77 (br. s., 1 H) 3.93 - 4.04 (m, 2 H) 3.64 (dd, *J*=12.63, 2.53 Hz, 2 H) 3.23 - 3.37 (m, 3 H) 3.20 (d, *J*=16.67 Hz, 1 H) 3.02 (t, *J*=6.06 Hz, 2 H) 2.92 - 2.99 (m, 1 H) 2.83 - 2.91 (m, 2 H) 2.78 (d, *J*=16.67 Hz, 1 H) 2.61 - 2.69 (m, 1 H) 2.45 - 2.54 (m, 4 H) 2.35 (s, 3 H) 2.24 (s, 3 H) 1.22 (d, *J*=6.82 Hz, 6 H) 1.07 (d, *J*=6.32 Hz, 3 H); MS (ESI+) *m/z* 527.4 $(M+H)^+$.
24- L		(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida. ^{1}H NMR (400 MHz, DMSO- d_6) δppm 8.09 (s, 1 H) 7.50 (d, *J*=8.34 Hz, 1 H) 7.28 (d, *J*=8.59 Hz, 1 H) 7.10 - 7.18 (m, 2 H) 6.99 (s, 1 H) 6.88 (d, *J*=7.58 Hz, 1 H) 4.07 - 4.15 (m, 1 H) 3.96 - 4.05 (m, 2 H) 3.52 - 3.60 (m, 1 H) 3.45 (t, *J*=11.12 Hz, 1 H) 3.32 - 3.37 (m, 2 H) 3.02 (t, *J*=5.31 Hz, 2 H) 2.75 - 2.91 (m, 4 H) 2.63 (d, *J*=10.36 Hz, 1 H) 2.55 (s, 3 H) 2.38 - 2.46 (m, 1 H) 2.24 - 2.31 (m, 1 H) 2.23 (s, 3 H) 1.31 (d, *J*=6.57 Hz, 3 H) 1.19 (dd, *J*=6.95, 1.64 Hz, 6 H); MS (ESI+) *m/z*553.4 $(M+H)^+$.

<u>Ejemplo 25.</u> 25- A.(*R*)- 1- (4- (6- (5- Isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona.



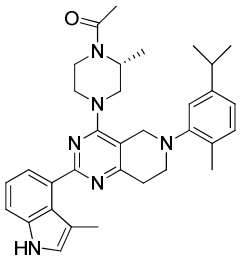
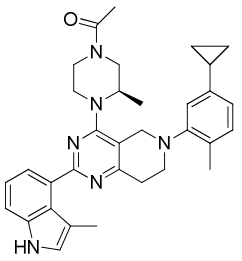
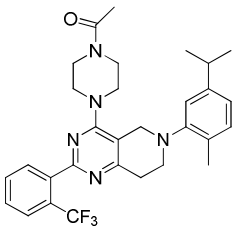
A una solución de 4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazina- 1- carboxilato de (R)- terc- butilo (143 mg, 0.191 mmol), preparado como se describe en el **Ejemplo 17**, en DCM (3 mL), se añadió TFA (2 mL) y la solución se agitó a temperatura ambiente durante 30 min. La reacción se concentró para proporcionar la sal de TFA MS (ESI+) m/z 649.4 (M+H)+.

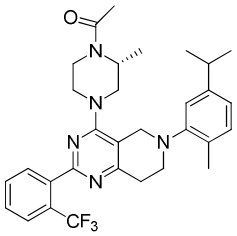
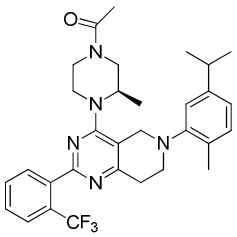
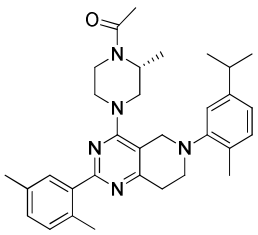
La sal TFA de (*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (2- metilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (62 mg, 0.095 mmol) se disolvió en DCM (5 mL) y anhídrido acético (0.014 ml, 0.143 mmol) y DIEA (0.133 ml, 0.764 mmol). La reacción se agitó a temperatura ambiente durante 45 minutos y se diluyó con EtOAc, y se lavó sucesivamente con $NaHCO_3$saturado y salmuera. La capa orgánica se secó sobre Na_2SO_4 y se filtró. Después de la concentración, el residuo resultante se purificó mediante FCC (60- 90% EtOAc/heptano) para proporcionar (*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona. MS (ESI+) m/z 691.4 (M+H)+.

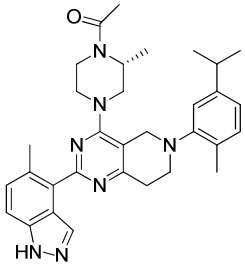
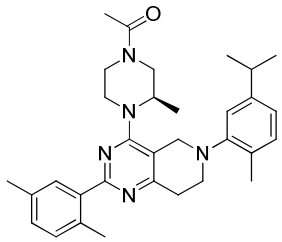
Se disolvió (*R*)- 1- (4- (6- (5- Isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona en EtOH (2 ml), luego se añadió NH_4OH (0.54 ml, 13.7 mmol) seguido por KOH (46 mg, 0.821 mmol). La mezcla se calentó en un reactor de microondas a 100 °C durante 1 h. Luego la reacción se diluyó con EtOAc y se lavó con salmuera. Después de la concentración, el residuo resultante se purificó mediante HPLC (C18, acetonitrilo 15- 85% en H_2O con NH_4OH al 0,1%) para proporcionar (*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona.^{1}H RMN (400 MHz, CD_3CN) δ ppm 9,15 (br. s., 1 H) 7,46 (d, J = 8,08 Hz, 1 H) 7,26 (d, J = 7,33 Hz, 1 H) 7,16 (dd, J = 16,29, 7,96 Hz, 2 H) 7,06 (d, J = 13,64 Hz, 2 H) 6,91 (dd, J = 7,58, 1,52 Hz, 1 H) 3,98- 4,16 (m, 4 H) 3.46- 3.67 (m, 2 H) 3.26- 3.46 (m, 4 H) 2,84- 3,13 (m, 4

H) 2,26 (s, 3 H) 2,00- 2,06 (m, 6 H) 1,23 (d, J = 6,82 Hz, 6 H) 1,11 - 1,21 (m, 3 H), MS (ESI+) m/z 537.4 (M+H)+.

Los siguientes compuestos se prepararon de una manera similar.

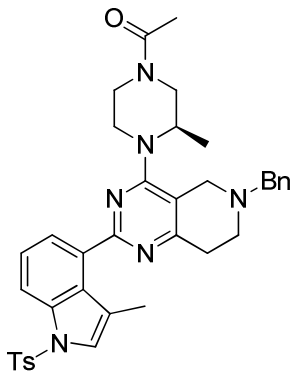
	Estructura	Nombre Quimico y Datos Analiticos
25- B		(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.91 (s, 1 H) 7.40 - 7.43 (m, 1 H) 7.24 (d, *J*=6.57 Hz, 1 H) 7.09 - 7.16 (m, 3 H) 7.03 (br. s., 1 H) 6.87 (dd, *J*=7.71, 1.39 Hz, 1 H) 4.24 - 4.70 (m, 1 H) 4.03 - 4.22 (m, 2 H) 3.70 - 3.86 (m, 3 H) 3.33 - 3.49 (m, 2 H) 3.04 - 3.17 (m, 1 H) 2.78 - 3.04 (m, 5 H) 2.23 (s, 3 H) 1.96 - 2.05 (m, 6 H) 1.31 (d, *J*=7.07 Hz, 1 H) 1.20 (m 8 H); MS (ESI+) *m/z* 537.4 $(M+H)^+$.
25- C		(*R*)- 1- (4- (6- (5- ciclopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.90 (s, 1 H) 7.41 (dd, *J*=7.96, 1.14 Hz, 1 H) 7.22 (d, *J*=6.57 Hz, 1 H) 7.05 - 7.16 (m, 3 H) 6.86 (d, *J*=1.52 Hz, 1 H) 6.69 (dd, *J*=7.83, 1.52 Hz, 1 H) 3.98 - 4.22 (m, 4 H) 3.70 - 3.83 (m, 1 H) 3.45 - 3.70 (m, 2 H) 3.32 - 3.43 (m, 2 H) 3.20 - 3.27 (m, 1 H) 2.88 - 3.07 (m, 3 H) 2.20 (s, 3 H) 1.98 - 2.06 (m, 6 H) 1.83 - 1.93 (m, 1 H) 1.06 - 1.20 (m, 3 H) 0.88 - 0.95 (m, 2 H) 0.59 - 0.65 (m, 2 H); MS (ESI+) *m/z* 535.4 $(M+H)^+$.
25- D		1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.84 (d, *J*=7.83 Hz, 1 H) 7.73 - 7.79 (m, 2 H) 7.64 - 7.70 (m, 1 H) 7.10 (d, *J*=7.83 Hz, 1 H) 7.00 (d, *J*=1.26 Hz, 1 H) 6.88 (dd, *J*=7.58, 1.52 Hz, 1 H) 4.01 (s, 2 H) 3.54 (dd, *J*=6.32, 3.28 Hz, 4 H) 3.42 - 3.48 (m, 2 H) 3.38 (d, *J*=6.06 Hz, 2 H) 2.97 (t, *J*=5.81 Hz, 2 H) 2.85 (dt, *J*=13.83, 6.85 Hz, 1 H) 2.20 (s, 3 H) 2.01 (s, 3 H) 1.19 (d, *J*=6.82 Hz, 6 H); MS (ESI+) *m/z* 538.1 $(M+H)^+$.

25- E		(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.79 (d, *J*=7.58 Hz, 2 H) 7.67 (t, *J*=7.45 Hz, 1 H) 7.59 (t, *J*=7.58 Hz, 1 H) 7.14 (d, *J*=7.58 Hz, 1 H) 6.97 (s, 1 H) 6.92 (dd, *J*=7.83, 1.52 Hz, 1 H) 3.93 - 4.15 (m, 3 H) 3.59 - 3.82 (m, 2 H) 3.43 - 3.59 (m, 1 H) 3.25 - 3.43 (m, 3 H) 3.16 (br. s., 2 H) 2.97 - 3.11 (m, 1 H) 2.84 - 2.97 (m, 1 H) 2.28 (s, 3 H) 2.06 (d, *J*=8.84 Hz, 3 H) 1.20 - 1.35 (m, 10 H); MS (ESI+) *m/z* 552.2 $(M+H)^+$.
25- F		(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 7.84 (d, *J*=7.83 Hz, 1 H) 7.72 - 7.79 (m, 2 H) 7.64 - 7.71 (m, 1 H) 7.10 (d, *J*=7.83 Hz, 1 H) 6.98 (s, 1 H) 6.87 (dd, *J*=7.71, 1.39 Hz, 1 H) 3.94 - 4.18 (m, 4 H) 3.52 - 3.70 (m, 2 H) 3.43 (dd, *J*=13.14, 3.79 Hz, 1 H) 3.37 (br. s., 1 H) 3.17 - 3.27 (m, 1 H) 2.90 - 3.03 (m, 3 H) 2.78 - 2.90 (m, 2 H) 2.20 (s, 3 H) 1.96 - 2.07 (m, 3 H) 1.05 - 1.22 (m, 9 H); MS (ESI+) *m/z* 552.3 $(M+H)^+$.
25- G		(*R*)- 1- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona. ^{1}H NMR (400 MHz, DMSO- d_6, at 100 °C) δ ppm 7.63 (s, 1 H) 7.09 - 7.17 (m, 3 H) 7.00 (s, 1 H) 6.87 (d, *J*=8.08 Hz, 1 H) 4.46 (br. s., 1 H) 3.94 - 4.15 (m, 3 H) 3.83 (d, *J*=12.76 Hz, 1 H) 3.70 (d, *J*=13.64 Hz, 1 H) 3.24 - 3.43 (m, 3 H) 3.18 (dd, *J*=13.20, 3.47 Hz, 1 H) 3.04 (d, *J*=1.77 Hz, 1 H) 2.79 - 2.92 (m, 2 H) 2.34 (s, 3 H) 2.24 (s, 3 H) 2.02 (s, 3 H) 1.16 - 1.31 (m, 9 H); MS (ESI+) *m/z* 512.4 $(M+H)^+$.

25- H		(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 13.02 (br. s., 1 H) 8.13 (s, 1 H) 7.52 (d, *J*=7.07 Hz, 1 H) 7.30 (d, *J*=8.34 Hz, 1 H) 6.99 - 7.21 (m, 2 H) 6.88 (d, *J*=7.58 Hz, 1 H) 4.17 (d, *J*=14.91 Hz, 3 H) 3.85 (br. s., 1 H) 3.77 (d, *J*=12.13 Hz, 2 H) 3.39 - 3.53 (m, 1 H) 3.27 (br. s., 2 H) 3.12 (br. s., 1 H) 3.05 (br. s., 2 H) 2.93 - 3.02 (m, 1 H) 2.87 (dt, *J*=13.64, 6.82 Hz, 1 H) 2.55 (s, 3 H) 2.24 (s, 3 H) 2.03 (d, *J*=17.68 Hz, 3 H) 1.31 (d, *J*=5.31 Hz, 1 H) 1.09 - 1.26 (m, 8 H); MS (ESI+) *m/z* 538.4 $(M+H)^+$.
25- I		(*R*)- 1- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona^{1}H NMR (400 MHz, DMSO- d_6, at 120 °C) δ ppm 7.62 (s, 1 H) 7.09 - 7.17 (m, 3 H) 6.98 (d, *J*=1.89 Hz, 1 H) 6.88 (dd, *J*=7.64, 1.83 Hz, 1 H) 4.00 - 4.21 (m, 3 H) 3.93 (br. s., 1 H) 3.76 (br. s., 1 H) 3.51 - 3.59 (m, 1 H) 3.32 - 3.42 (m, 4 H) 3.24 (br. s., 1 H) 3.01 (t, *J*=6.19 Hz, 2 H) 2.85 - 2.95 (m, 4 H) 2.34 (s, 3 H) 2.25 (s, 3 H) 2.03 (s, 3 H) 1.22 (d, *J*=6.95 Hz, 6 H) 1.17 (d, *J*=6.44 Hz, 3 H); MS (ESI+) *m/z* 512.4 $(M+H)^+$.

<u>Ejemplo 26</u>

26- A.(*R*)- 1- (4- (6- Bencil- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona.

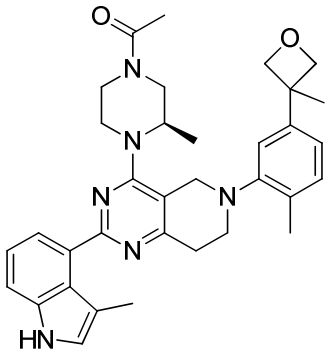


5

Una mezcla de 6- bencil- 2 ,4- dicloro- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (0.655 g, 1.89 mmol), (R) - 1 - (3- metilpiperazin- 1 - il) etanona 2,2,2- trifluoroacetato (1 g, 2.84 mmol) y DIEA (2.65 ml, 15.2 mmol) en i- PrOH (25 mL) se calentó a 80 °C durante 48 h. La mezcla de reacción se diluyó luego con EtOAc, y se lavó sucesivamente con $NaHCO_3$acuoso saturado y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se diluyó con DCM y se filtró para eliminar el sólido. El filtrado se concentró y se purificó mediante FCC (0- 5% MeOH en DCM) para proporcionar(*R*)- 1- (4- (6- bencil- 2- cloro- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona MS (ESI+) m/z 400.3 (M+H)+.

Una mezcla de (*R*)- 1- (4- (6- Bencil- 2- cloro- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona (0.27 g, 0.675 mmol), 3- metil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1- tosil- 1H- indol (0.305 g, 0.743 mmol) y Na_2CO_3 acuoso2 M (1,1 ml, 2,19 mmol) en DME (3 ml) se desgasificó burbujeando con argón. Luego se añadió $Pd(PPh_3P)_4$ (0.117 g, 0.101 mmol) y la mezcla se calentó en un reactor de microondas a 140 °C durante 1.5 h. La reacción se filtró y se diluyó con EtOAc, se lavó sucesivamente con Na_2CO_3 acuoso saturado y salmuera, y luego se secó sobre Na_2SO_4. Después de la concentración, el residuo se purificó mediante FCC (5- 70% EtOAc/heptano) para proporcionar(*R*)- 1- (4- (6- Bencil- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona. MS (ESI+) m/z 649.3 (M+H)+.

26- B. (*R*)- 1- (3- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona.



Una mezcla de(*R*)- 1- (4- (6- bencil- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona (0.35 g, 0.539 mmol), ácido acético (0.154 ml, 2.70 mmol), THF (9 mL) y H_2O (3 mL) se desgasificó a

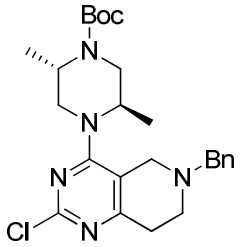
través de vacío y se recarga con gas nitrógeno (2 x). Luego se añadio $Pd(OH)_2$20% molar sobre carbono (0.114 g, 0.162 mmol) y la mezcla se degasificó a través de vacío y se colocó bajo una atmósfera de hidrógeno. La mezcla se agitó a temperatura ambiente bajo atmósfera de H_2 a través de globo durante 2 horas y luego se filtró. Luego la solución se diluyó con EtOAc y se lavó con solución saturada de $NaHCO_3$ acuoso. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar (*R*)- 1- (3- metil- 4- (2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona, el cual se utilizó sin necesidad de purificación adicional. MS (ESI+) m/z 559.3 (M+H)+.

Una mezcla de (*R*)- 1- (3- metil- 4- (2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona (0.155 g, 0.278 mmoles), trifluorometanosulfonato de 2- metil- 5- (3- metiloxetan- 3- il) fenilo(0.086 g, 0.278 mmoles) preparado como se describe en el **Ejemplo 13**, carbonato de cesio (0.272 g, 0.834 mmol) y aducto cloro(2- diciclohexilfosfino- 2'- 4'- 6'- triisopropil- 1,1'- bifenil)[2- (2- aminoetil)fenil]paladio(II)–metil- *t*- butileter (CAS # 1028276- 56- 5) (0.031 g, 0.042 mmol) en THF (4 mL) se calentó en un reactor de microondas a 140 °C durante 3 h. Luego la reacción se filtró y se concentró, el residuo resultante se purificó mediante FCC (60- 100% EtOAc/DCM) para proporcionar (*R*)- 1- (3- metil- 4- (2- (3- metil- 1- tosil- 1H- indol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona MS (ESI+) m/z 719.3 (M+H)+.

Una mezcla de (*R*)- 1- (3- metil- 4- (2- (3- metil- 1- tosil- 1H- indol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona (0.104 g, 0.145 mmol), hidróxido de amonio al 30% (0.854 ml, 21.70 mmoles) y KOH (0.073 g, 1.302 mmol) en EtOH (4 ml) se calentó en un reactor de microondas a 100 °C durante 30 min. La mezcla se concentró y se purificó parcialmente mediante FCC (0- 6% MeOH en DCM). La purificación adicional con HPLC (C18,CH_3CN al 15- 85% en H_2O con NH_4OH al 0,1%) proporcionado(*R*)- 1- (3- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona.^{1}H RMN (400 MHz, DMSO-d_6 a 120 °C)δ ppm 10,50 (br. s., 1 H) 7,42 (d, J = 8,08 Hz, 1 H) 7,25 (d, J = 7,20 Hz, 1 H) 7,19 (d, J = 7,83 Hz, 1 H) 07.07 - 07.15 (m, 2 H) 6,97 (s, 1 H) 6,90 (d, J = 7,96 Hz, 1 H) 4,79 (d, J = 5,43 Hz, 2 H) 4,53 (d, J = 5,05 Hz, 2 H) 4,05 - .. 4,19 (m, 3 H), 3,91 (br. s., 1 H) 3,75 (br. s., 1 H) 3,56 (d, J = 13,26 Hz, 1 H) 3.22 - 3.48 (m, 5 H) 3,00 (t, J = 5,62 Hz, 2 H) 2,29 (s, 3 H) 2,07 (s, 3 H) 1.99 - 2.04 (m, 3 H) 1,65 (s, 3 H) 1,17 (d , J = 6,44 Hz, 3 H), MS (ESI+) m/z 565. 4 (M+H)+.

Ejemplo 27

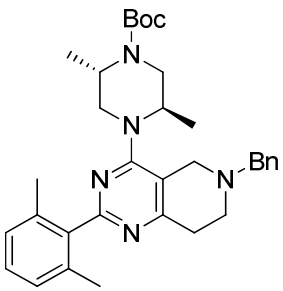
27- A. 4- (6- Bencil- 2- cloro- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato de terc- butilo racémico



Una mezcla de 6- bencil- 2 ,4- dicloro- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (2,0 g, 6.80 mmol), dihidrocloruro de (trans) - 2,5- dimetilpiperazina (7.63 g, 40.8 mmol), DIEA (15.4 ml, 88 mmol) y iPrOH (180 mL) se calentó a 80 °C durante 3.5 días. En ese momento la reacción se diluyó con éter dietílico y el sólido se separó por filtración. Luego el filtrado se lavó con salmuera y la capa orgánica se secó (Na_2SO_4), se filtró y se concentró para proporcionar6- bencil- 2- cloro- 4- (trans) - 2,5- dimetilpiperazin- 1- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidinaracémico crudo, el cual se llevó luego a la siguiente etapa sin purificación adicional. MS (ESI+) m/z 372.2 (M+H)+

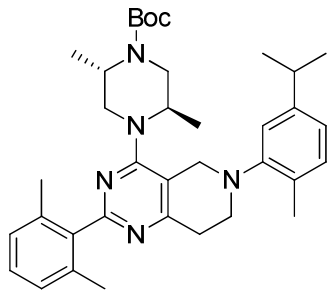
Una solución de 6- bencil- 2- cloro- 4- (trans) - 2,5- dimetilpiperazin- 1- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina *racémica* (2.53 g, 6.80 mmol), Boc_2O (2.26 g, 10.2 mmol), DIEA (3.6 ml, 20.4 mmol) y DCM (30 mL) se agitó a temperatura ambiente durante 30 min. En ese momento la reacción se diluyó con DCM y se lavó con solución de $NaHCO_3$ acuososaturada y salmuera. La capa orgánica se secó(Na_2SO_4), se filtró y se concentró. Luego el residuo se purificó mediante FCC (10- 50% EtOAc/heptano) para proporcionar 4- (6- Bencil- 2- cloro- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilatode terc- butilo racémico MS (ESI+) m/z 472.2 (M+H)+.

27- B. 4- (6- bencil- 2- (2,6- dimetilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato de terc- butilo racémico



A una solución de4- (6- bencil- 2- cloro- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato deterc- butiloracémico (0.54 g, 1.14 mmol) en DME (9 ml) se añadió ácido 2,6- dimetilfenilboronico(0.257 g, 1.72 mmol), $Pd(Ph_3P)_4$ (0.198 g, 0.172 mmol) y una solución acuosa de carbonato de sódio 2 M (1.9 ml). La reacción se calentó a 140 °C en un reactor de microondas durante 1.75 h. La reacción se filtró y se diluyó con EtOAc y salmuera. La capa orgánica se separó y después se secó (Na_2SO_4), se filtró y se concentró. Luego el residuo se purificó mediante FCC (55- 80% EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 542.5 (M+H)+.

27- C. 4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato de terc- butilo racémico

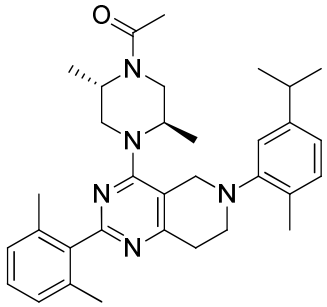


A una solución de4- (6- bencil- 2- (2,6- dimetilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato deterc- butilo*racémico*(0.43 g, 0.794 mmol) en THF (9 ml) y agua (3 ml) se añadió ácido acético (227 µL, 3.97 mmol) y $Pd(OH)_2$ al 20% sobre carbón (50% humedo) (0.167 g, 0.238 mmoles). El matraz fue evacuado y purgado con gas hidrógeno y luego se colocó bajo una atmósfera de hidrógeno. Después de agitar a temperatura ambiente durante 1 h, la mezcla se filtró sobre Celite ®, y la almohadilla de Celite ® se lavó con EtOAc. El filtrado se lavó con $NaHCO_3$ acuoso saturado y luego la capa orgánica se secó sobre sulfato de sodio anhidro, se filtró y se concentró bajo presión reducida para obtener4- (2- (2,6- dimetilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato.terc- butilo*racémico*MS (ESI+) m/z 452.3 (M+H)+.

A una solución de 4- (2- (2,6- dimetilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato deterc- butilo*racémico*(0.187 g, 0.414 mmol) en THF (4 mL) se añadió trifluorometanosulfonato de 5- isopropil- 2- metilfenilo(0.175 g, 0.620 mmol) preparado como se describe en el Ejemplo 15, Cs_2CO_3 (0.404 g, 1.24 mmol) y aducto cloro(2- diciclohexilfosfino- 2'- 4'- 6'- triisopropil-

1,1'- bifenil)[2- (2- aminoetil)fenil]paladio(II)–metil- *t*- butileter(0.046 mg, 0.062 mmol). La reacción se purgó con argón y se calentó a 130 °C durante 3 h en un reactor de microondas. La mezcla se concentró y el residuo se purificó a través de FCC (10- 35% EtOAc/heptano) para proporcionar 4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato*racémica* terc- butilo MS (ESI+) m/z 584.4 (M+H)+.

27- D. 1- (4- (2- (2,6- Dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)etanonaracémico



A una solución de4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazina- 1- carboxilato de terc- butilo*racémico* (0.227 g, 0.389 mmol) y DCM (3 ml) a temperatura ambiente se añadió TFA (1 mL). Después de 25 minutosse añadió una alícuota adicional de 05 mL de TFA. Después de 1 h más la reacción se concentró bajo presión reducida para proporcionar 2- (2,6- dimetilfenil)- 4- ((*trans*)- 2,5- dimetilpiperazin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina como una sal de TFA. MS (ESI+) m/z 484.4 (M+H)+

A una solución de la sal TFA de sal TFA de2- (2,6- dimetilfenil)- 4- ((*trans*)- 2,5- dimetilpiperazin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (0.113 g, 0.233 mmol), DIEA (0.33 ml, 1.87 mmol) y DCM (5 ml) se añadió Ac_2O (0.044 ml, 0.467 mmol). La reacción se agitó a temperatura ambiente durante 1 h antes de ser diluida con EtOAc. La solución se lavó con solución $NaHCO_3$acuoso saturada y luego con salmuera antes de que las capas orgánicas se separaran y luego se secaron (Na_2SO_4), se filtraron y se concentraron. Luego el residuo se purificómediante FCC (35- 45% de EtOAc/heptano) para proporcionar racémica- 1- (4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)etanona^{1}H RMN (400 MHz, DMSO- d_6, a 100 °C) ppm δ 7,14 - 7,19 (m, 1 H) 07.05 - 07.12

(m, 3 H) 6,91 (d, J = 1,39 Hz, 1 H) 6,86 (dd , J = 7,71, 1,52 Hz, 1 H) 4,29 (dt, J = 6,22, 3,27 Hz, 1 H) 4.12 - 4.18 (m, 1 H) 4,00 - 4,07 (m, 1 H) 3.50 - 3.58 (m, 1 H) 3,41 - . 3,47 (m, 1 H) 3,39 (t, J = 6,19 Hz, 2 H) 2,93 (br. s., 4 H) 2,84 (dt, J = 13,80, 6,93 Hz, 1 H) 2,52 (br . s, 1 H) 2,25 (s, 3 H) 2,08 (s, 6 H) 2,01 (s, 3 H) 1,19 (dd, J = 6,95, 2,40 Hz, 6 H) 1,10 - . 1,17 (m, 6 H), MS (ESI+) m/z 526.4 (M+H)+.

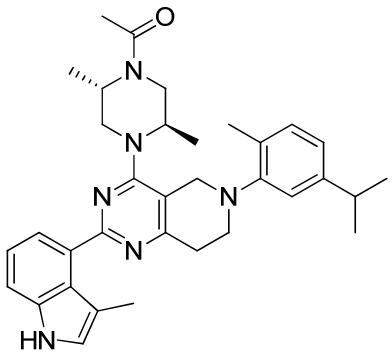
El racémica- 1- (4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)etanona luego se separó mediante HPLC quiral (columna WhelkO; 40% EtOH/heptanos; 1.2 ml/min para proporcionar los dos compuestos siguientes:

27- E.Enantiómero- 1: R_t 9.78 min, (columna WhelkO1 20 X 250 mm, EtOH 50% en heptano). 1H RMN (400 MHz, DMSO- d6, a 120 °) δ ppm 7,14 - 7,19 (m, 1 H) 07.05 - 07.12 (m, 3 H) 6,92 (d, J = 1,52 Hz, 1 H) 6,87 (dd, J = 7,77, 1,58 Hz, 1 H) 4,40 (br. s., 1 H) 4,27 - . 4,34 (m, 1 H) 4.10 - 4.19 (m, 1 H) 04.01 a 04.10 (m, 1 H) 3,52 a 3,58 (m, 1 H) 3.37- 3.48 (m, 4 H) 2,94 (t, J = 6,25 Hz, 2 H) 2,86- 2,89 (m, 1 H) 2,82 (br. s., 1 H). 2,25 (s, 3 H) 2,09 (s, 6 H) 2,01 (s, 3 H) 1,20 (dd, J = 6,95, 2,02 Hz, 6 H) 1,15 (dd, J = 12,82, 6,63 Hz, 6 H), MS (ESI+) m/z 526.4 (M+H)+

27- F. Enantiómero- 2: R_t 14.69 min, (Columna WhelkO1 20 X 250 mm, EtOH al 50% en heptano). ^{1}H RMN (400 MHz, DMSO- d_6, 120 °C) ppm δ 7,14 - 7,19 (m, 1 H) 07.05 - 07.12 (m, 3 H) 6,92 (s, 1 H) 6,87 (dd, J = 7,77, 1,45 Hz, 1 H) 4,34 - 4,49 (m, 1 H) 4,30 (dt, J = 6,76, 3,44 Hz, 1 H) 4.10 - 4.19 (m, 1 H) 04.01 - 04.10 (m, 1 H) 3.52- 3.58 (m, 1 H) 3.37 - 3,48 (m, 4 H) 2,94 (t, J = 6,13 Hz, 2 H) 2.81- 2.84 (m, 2 H) 2,26 (s, 3 H) 2,09 (s, 6 H) 2,01 (s, 3 H) 1,20 (dd, J = 6,88, 1,96 Hz, 6 H) 1,15 (dd, J = 12,82, 6,63 Hz, 6 H), MS (ESI +) m / z 526,4 (M + H) +

El siguiente compuesto se preparó de una manera similar.

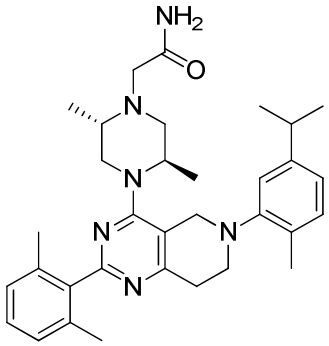
27- G.1- ((*trans*)- 4- (6- (5- Isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,5- dimetilpiperazin- 1- il)etanonade racémico



^{1}H RMN (400 MHz, DMSO- d_6, 100 °C)δ ppm 10,58 (br. s., 1 H). 7,41 (d, J = 8,21 Hz, 1 H) 7.23 - 7.25 (m, 1 H) 7.8 - 7.13 (m, 3 H) 6,97 (s, 1 H) 6.87 (dd, J = 8,08, 1,26 Hz, 1 H) 4,33 (d, J = 4,67 Hz, 1 H) 04.09 - 04.17 (m, 1 H) 4,00 - 4,09 (m, 1 H) 3,54 (br. s., 2 H) 3,39 (t, J = 6,51 Hz, 2 H) 2.97- 3.02 (m, 5 H) 2.81- 2.90 (m, 1 H) 2,25 (s, 3 H) 1,99 - 2,08 (m, 6 H) 1,14 - 1,23 (m, 12 H). MS (ESI+) m/z 551.4 (M+H)+.

Ejemplo 28

28- A. Racémico- 2- (- 4- (2- (2,6- Dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)acetamida.



El compuesto del título se preparó de una manera similar a los descritos en los Ejemplos 24 y 28 anteriores. MS (ESI+) m/z 541.3 (M+H)+. *Racémica*- 2- (- 4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)acetamidaluego se separó mediante HPLC quiral (Columna Cel- LUX2; 30% EtOH/heptanos; 1.2 ml/min) para proporcionar los dos enantiómeros correspondientes:

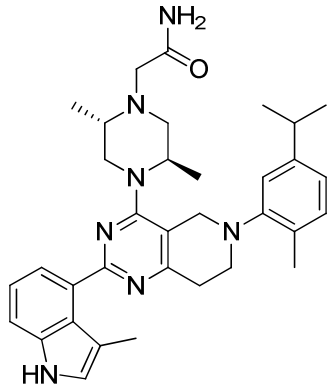
28- B.Enantiómero- 1: R^t 11.83 min, (Columna Cel- LUX2 20 X 250 mm, EtOH al 30% en heptano). ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,14 - 7,21 (m, 2 H) 7,10 (t, J = 7,83 Hz, 4 H) 6,83 - 6,91 (m, 2 H) 4.1 - 4.13 (m, 2 H) 3,88 (br. s., 1 H) 3,32 - . 3,42 (m, 3 H) 2.95- 3.02 (m, 1

H) 2,91 (d, J = 9,09 Hz, 4 H) 2,83 (dt, J = 12,88, 6,19 Hz, 3 H) 2.24 - 2.30 (m, 1 H) 2,22 (s, 3 H) 2,03 (s, 6 H) 1,16 (dd, J = 6,82, 3,28 Hz, 6 H) 1,11 (d, J = 6,32 Hz , 3 H) 0,96 (d, J = 6,32 Hz, 3 H), MS (ESI+) m/z 541.4 (M+H)+.

28- C. Enantiómero- 2: R_t 16.10 min, (Columna Cel- LUX2 20 X 250 mm, EtOH al 30% en heptano). ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,15 - 7,21 (m, 2 H) 7,10 (t, J = 7,83 Hz, 4 H) 6,84- 6,90 (m, 2 H) 04.01 - 04.12 (m, 2 H) 3,88 (br. s., 1 H) 3,33 - . 3,42 (m, 3 H) 2,95- 3,01 (m, 1 H) 2,91 (d, J = 9,09 Hz, 4 H) 2.79- 2.86 (m, 3 H) 2,27 (dd, J = 11,37, 5,81 Hz, 1 H) 2,22 (s, 3 H) 2,03 (s, 6 H) 1,16 (dd, J = 6,82, 3,28 Hz, 6 H) 1,11 (d, J = 6,32 Hz , 3 H) 0,96 (d, J = 6,32 Hz, 3 H), MS (ESI+) m/z 541.4 (M+H)+.

El siguiente compuesto se preparó de una manera similar.

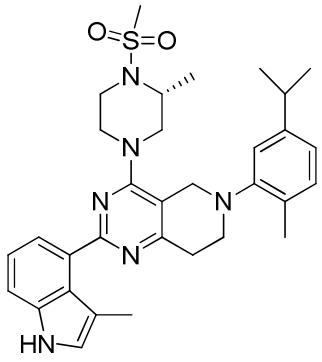
28- D. Racémico- 2- (4- (6- (5- Isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)acetamida.



^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 10,90 (s, 1 H) 7,42 (dd, J = 8,08, 1,01 Hz, 1 H) 7.20 - 7.23 (m, 1 H) 7.10 - 7.19 (m, 5 H) 6,94 (d, J = 1,52 Hz, 1 H) 6,87 (dd, J = 7,83, 1,52 Hz, 1 H) 3.99- 4.12 (m, 2 H) 3,89 - 3,97 (m, 1 H) 3,34- 3,44 (m, 3 H) 3,00- 3,10 (m, 1 H) 2,89 - 3,00 (m, 4 H) 2,79 - 2,88 (m, 3 H) 2,28 (dd, J = 11,75, 5,68 Hz, 1 H) 2,22 (s, 3 H) 2,03 (s, 3 H) 1,18 (dd, J = 6,82, 3,03 Hz, 6 H) 1,14 (d, J = 6,32 Hz, 3 H) 0,98 (d, J = 6,32 Hz, 3 H).MS (ESI+) m/z 566.4 (M+H)+.

Ejemplo 29

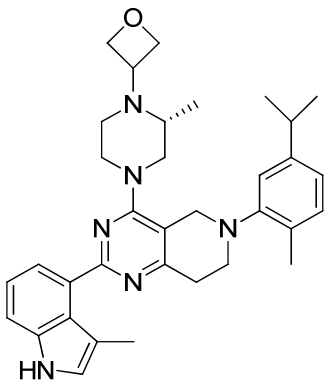
(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (metilsulfonil)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



Una mezcla de(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H-indol- 4- il)- 4- (3- metilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (52 mg, 0.080 mmol), preparada de un modo similar al descrito en el **Ejemplo 25**, cloruro de metanosulfonilo (0.01 ml, 0.096 mmol) y DIEA (0.042 ml, 0.240 mmol) en DCM (3 mL) se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se diluyó con EtOAc, se lavó sucesivamente con $NaHCO_3$ saturado, y salmuera, se secó sobre Na_2SO_4 y se concentró. El residuo resultante se purificó a través de FCC (5- 50% EtOAc/heptano) para proporcionar MS (ESI+) m/z 727.4 (M+H)+.

A una solución de(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H-indol- 4- il)- 4- (3- metil- 4- (metilsulfonil)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3-d]pirimidina (40 mg, 0.055 mmol) en MeOH (4 mL), NH_4OH (0.325 ml, 8.25 mmol) y KOH (27.8 mg, 0.495 mmol). La mezcla se calentó en un reactor de microondas 100 °C durante 1 h. Luego la mezcla se filtró y se concentró. El residuo resultante se purificó a través de FCC (0-45% EtOAc/heptano) para proporcionar ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 10,91 (d, J = 2,02 Hz, 1 H) 7.40- 7.43 (m, 1 H) 7,24 (dd, J = 7,33, 1,01 Hz, 1 H) 7,09 - 7,16 (m, 3 H) 7,02 (d, J = 1,26 Hz, 1 H) 6,87 (dd, J = 7,83, 1,26 Hz, 1 H) 04.03 - 04.16 (m, 3 H) 3,70- 3,84 (m, 2 H) 3,56 (d, J = 12,88 Hz, 1 H) 3.33- 3.42 (m, 2 H) 3.23 - 3.28 (m, 1 H) 3,14 (dd, J = 12,88, 3,54 Hz, 1 H) 2.92- 3.06 (m, 6 H) 2,79 - 2,90 (m, 1 H) 2,22 (s, 3 H) 2,03 (s, 3 H) 1,32 (d, J = 6,82 Hz, 3 H) 1,19 (dd, J = 6,95, 1,89 Hz, 6 H), MS (ESI+) m/z 573.4 (M+H)+.

<u>Ejemplo 30</u> 30- A. (R) - 6 - (5- isopropil- 2- metilfenil) - 2 - (3- metil- 1H- indol- 4- il) - 4 - (3 - metil- 4- (oxetan- 3- il) piperazin- 1- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.

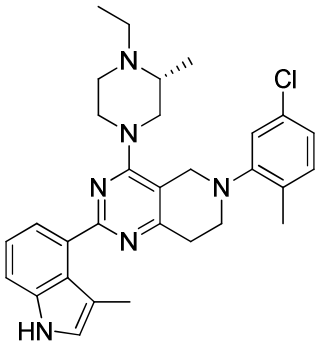


Una mezcla de(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (3- metilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina (53 mg, 0.082 mmol), oxetan- 3- ona (17.6 mg, 0.245 mmol) y $Na(AcO)_3BH$ (51.9 mg, 0.245 mmol) en DCM (3 mL) se agitó a temperatura ambiente durante 3 h. En ese momento quedó material de inicio de manera que se agregó oxetan- 3- ona adicional (17.7 mg, 0.245 mmol) y $Na(AcO)_3BH$ (51.9 mg, 0.245 mmol) y la reacción se agitó durante 16 h. La mezcla se diluyó con EtOAc, se lavó con $NaHCO_3$ saturada y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante FCC (5- 65% EtOAc/heptano) para proporcionar (*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (3- metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.MS (ESI+) m/z 705.5 (M+H)+.

Luego el producto crudo se disolvió en MeOH (4 mL). Se añadió NH_4OH (0.50 ml, 12.8 mmol) y KOH (43.0 mg, 0.766 mmol). Luego la mezcla se calentó en un reactor de microondas a 100 °C durante 45 minutos antes de ser filtrada y concentrada. Luego el residuo se purificó mediante FCC (0- 45% EtOAc/heptano) para proporcionar(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina**.** ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 10,90 (d, J = 1,52 Hz, 1 H) 7,41 (dd, J = 8,08, 1,01 Hz, 1 H) 7,22 (dd, J = 7,33, 1,01 Hz, 1 H) 7.9 - 7.16 (m, 3 H) 6,98 (d, J = 1,26 Hz, 1 H) 6,87 (dd, J = 7,71, 1,39 Hz, 1 H) 4,45- 4,56 (m, 4 H) 3,96- 4,07 (m, 2 H) 3.71 (quin, J = 6,88 Hz, 1 H) 3.42- 3.57 (m, 2 H) 3,36 (s, 1 H) 3.20 - 3.27 (m, 1 H) 3.00- 3.10 (m, 1 H) 2,96 (t, J = 5,81 Hz, 2 H) 2,79- 2,88 (m, 1 H) 2,67 - 2,73 (m, 1 H) 2,55 (d, J = 3,79 Hz, 1 H) 2.43- 2.48 (m, 1 H) 2.16 - 2.25 (m, 4 H) 2,03 (s, 3 H) 1,18 (d, J = 6,82 Hz, 6 H) 0,90 (d, J = 6,32 Hz, 3 H; MS (ESI+) m/z 551.4 (M+H)+.

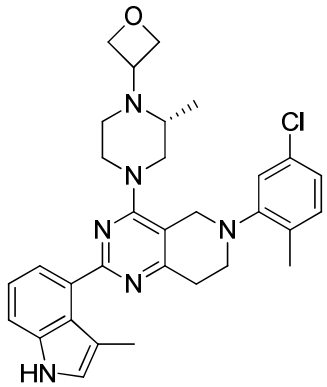
Los siguientes compuestos se prepararon de una manera similar.

30- B.(*R*)- 6- (5- Cloro- 2- metilfenil)- 4- (4- etil- 3- metilpiperazin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.



^{1}H RMN (400 MHz, DMSO- d_6)δ ppm 10,90 (s, 1 H) 7,41 (dd, J = 8,08, 1,01 Hz, 1 H) 7.17 a 7.25 (m, 3 H) 07.04 - 07.16 (m, 3 H) 4,03 (s, 2 H) 3,58 - 3,66 (m, 1 H) 3,55 (d, J = 12,63 Hz, 1 H) 3,31- 3,36 (m, 3 H) 3.12 - 3.22 (m, 1 H) 2.87- 3.02 (m, 3 H) 2,77 - 2,86 (m, 1 H) 2,68- 2,77 (m, 1 H) 2.31- 2.36 (m, 2 H) 2,23 (s, 3 H) 2,02 (s, 3 H) 1,02 (d, J = 6,32 Hz, 3 H) 0,96 (t, J = 7,20 Hz, 3 H), MS (ESI+) m/z 515.3/517.4 (M+H)+.

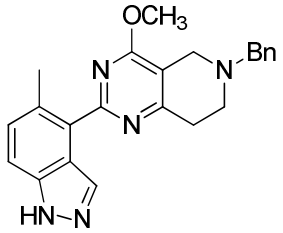
30- C.(*R*)- 6- (5- Cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina



^{1}H RMN (400 MHz, DMSO- d_6)δ ppm 10,90 (s, 1 H) 7,39- 7,42 (m, 1 H) 7.17 - 7.25 (m, 3 H) 07.04 - 07.16 (m, 3 H) 4.44- 4.57 (m, 4 H) 4,02 (s, 2 H) 3,71 (t, J = 6,95 Hz, 1 H) 3.52- 3.58 (m, 1 H) 3,47 (dd, J = 12,00, 1,39 Hz, 1 H) 3.31 - 3.36 (m, 1 H) 3.21 - 3.27 (m, 1 H) 2,95 - 3,08 (m, 3 H) 2.67 - 2.70 (m, 1 H) 2,45 (dd, J = 3,54, 1,52 Hz, 1 H) 2.14 - 2.26 (m, 5 H) 2,03 (d, J = 0,76 Hz, 3 H) 0,88 (d, J = 6,32 Hz, 3 H), MS (ESI+) m/z 543.3/545.3 (M+H)+.

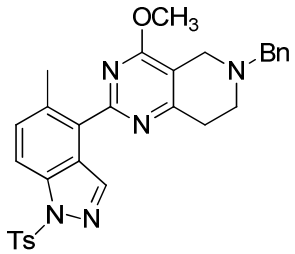
Ejemplo 31

31- A. 6- bencil- 4- metoxi- 2- (5- metil- 1H- indazol- 4- il) - 5,6,7,8- tetrahidropirido [4,3 - d] pirimidina.



Una mezcla de 6- bencil- 2- cloro- 4- metoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (1.09 g, 3.75 mmol), (5- metil- 1H- indazol- 4 - il) ácido bórico (600 mg, 3.41 mmol), $Pd(PPh_3)_4$ (197 mg, 0.170 mmol), y de Na_2CO_3 (2 M, 5.97 ml, 11.9 mmol) en DME (11 ml) se calentó en un reactor de microondas a 140 °C durante 1.5 h. La mezcla de reacción se particionió entre EtOAc y agua. La capa acuosa se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4), y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (20- 100% EtOAc/heptano) para proporcionar 6- bencil- 4- metoxi- 2- (5- metil- 1H- indazol- 4- il) - 5,6,7,8 - tetrahidropirido [4,3- d] pirimidina. MS (ESI+) m/z 386.2 (M+H)+.

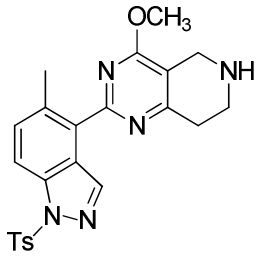
31- B. 6- bencil- 4- metoxi- 2- (5- metil- 1- tosil- 1H- indazol- 4- il) - 5,6,7,8- tetrahidropirido [4,3 - d] pirimidina.



Se añadió 6- bencil- 4- metoxi- 2- (5- metil- 1H- indazol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina (2.00 g, 5.19 mmol) a una suspensión de NaH (60% de dispersión en aceite mineral, 415 mg, 10.4 mmol) en THF (50 ml) a 0 °C. Después de 20 min, se añadió TsCl (1.19 g, 6.23 mmol). La mezcla de reacción se agitó durante 20 min y se añadió solución de NH_4Cl para apagar el exceso de base. La mezcla resultante se extrajo con EtOAc (3x). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron. El residuo se purificó mediante cromatografía de gel de sílice (0- 100% EtOAc/heptano) para proporcionar 6- bencil- 4- metoxi- 2- (5- metil- 1- tosil- 1H- indazol- 4- il) - 5,6 7,8- tetrahidropirido [4,3- d] pirimidina. MS (ESI+) m/z 540.2 (M+H)+.

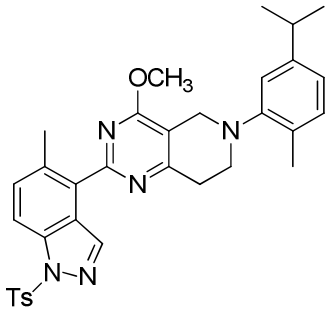
31- C. 4- metoxi- 2- (5- metil- 1- tosil- 1H- indazol- 4- il) - 5,6,7,8- tetrahidropirido [4,3 -

d] pirimidina.



Una mezcla de 6- bencil- 4- metoxi- 2- (5- metil- 1- tosil- 1H- indazol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina (1.85 g, 3.43 mmol) y $Pd(OH)_2$ sobre carbón (húmedo) (10%, 0.722 g, 1.03 mmol) en agua (7.5 ml) y ácido acético (0,59 ml) se agitó bajo 1 atmosfera de hidrógeno a temperatura ambiente durante 2.5 h. La mezcla de reacción se filtró a través de Celite ® y los sólidos se lavaron con EtOAc. Los filtrados combinados se lavaron con solución saturada de $NaHCO_3$. Las capas se separaron y la capa acuosa se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (0- 10% MeOH (NH_4OH al 10%)/DCM) para proporcionar 4- metoxi- 2- (5- metil- 1- tosil- 1H- indazol- 4- il) - 5, 6,7,8- tetrahidropirido [4,3- d] pirimidina. MS (ESI+) m/z 450.1 (M+H)+.

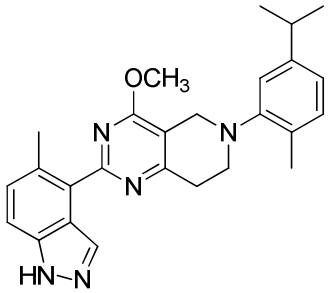
31- D. 6 - (5- isopropil- 2- metilfenil)- 4- metoxi- 2- (5- metil- 1- tosil- 1H- indazol- 4- il) - 5,6,7,8 - tetrahidropirido [4,3- d] pirimidina.



Una mezcla de trifluorometanosulfonato de 4- metoxi- 2- (5- metil- 1- tosil- 1H- indazol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina (250 mg, 0.556 mmol), 5- isopropil- 2- metilfenil (235 mg, 0.834 mmol), X- Phos (53.0 mg, 0.111 mmol), $Pd_2(dba)_3$ (50.9 mg, 0.056 mmol), y Cs_2CO_3 (362 mg, 1.11 mmol) en THF (3 ml) se calentó en un reactor de microondas a 140 °C durante 60 min. La mezcla de reacción se particionió entre EtOAc y agua. La capa orgánica se lavó con salmuera, se secó (Na_2SO_4) y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (0- 50% EtOAc/heptano) para proporcionar 6-(5-

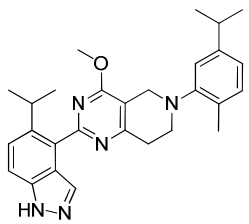
isopropil-2-metilfenil)-4-metoxi-2-(5-metil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.MS (ESI+) m/z 582.1 (M+H)+.

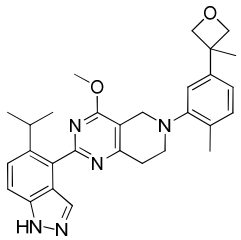
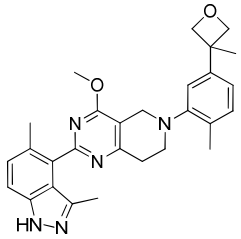
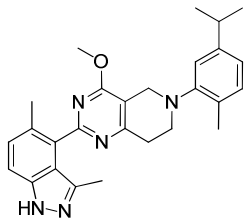
31- E. 6 - (5- isopropil- 2- metilfenil)- 4- metoxi- 2- (5- metil- 1H- indazol- 4- il) - 5,6,7,8 - tetrahidropirido [4,3- d] pirimidina.



Una mezcla de 6-(5-isopropil-2-metilfenil)-4-metoxi-2-(5-metil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (200 mg, 0.344 mmoles), KOH (80 mg, 1.43 mmoles) y solución acuoso concentrada NH_4OH (4 mL) en MeOH (8 ml) se calentó en un reactor de microondas a 80 °C durante 30 min. La mezcla de reacción se particionió entre EtOAc y agua. La capa acuosa se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (0- 100% EtOAc/heptanos) para proporcionar6-(5-isopropil-2-metilfenil)-4-metoxi-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina como un sólido blanco. ^{1}H RMN (400 MHz, CD_2Cl_2)δ ppm 8,31 (s, 1 H) 7,52 (d, J = 8,34 Hz, 1 H) 7,40 (d, J = 8,59 Hz, 1 H) 7,21 (d, J = 7,83 Hz, 1 H) 7,11 (d, J = 1,52 Hz, 1 H) 6,97 (dd, J = 7,71, 1,64 Hz, 1 H) 04.04 - 04.20 (m, 5 H) 3,37 (t, J = 5,68 Hz, 2 H) 3,19 (t, J = 5,56 Hz, 2 H) 2.88 - 3.01 (m, 1 H) 2,70 (s, 3 H) 2,37 (s, 3 H) 1,31 (d, J = 6,82 Hz, 6 H), MS (ESI +) m/z 428.1 (M+H)+.

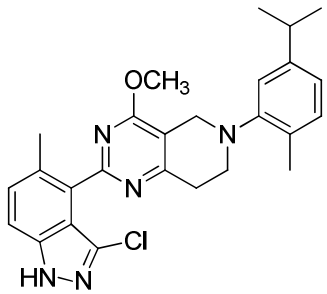
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos
31-F		2-(5-isopropil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.94 (s, 1 H) 7.40-7.46 (m, 2 H) 7.06 (d, J=8.1 Hz, 1 H) 6.97 (d, J=1.5 Hz, 1 H) 6.83 (dd, J=7.6, 1.8 Hz, 1 H) 3.99 (s, 2 H) 3.94 (s, 3 H) 3.48 (quin, J=6.9 Hz, 1 H) 3.23 (t, J=5.68 Hz, 2 H) 3.04 (t, J=5.68 Hz, 2 H) 2.81 (quin,

		J=6.9 Hz, 1 H) 2.24 (s, 3 H) 1.22 (d, J=6.8 Hz, 6 H) 1.17 (d, J=7.1 Hz, 6 H); MS (ESI+) *m/z* 456.1 $(M+H)^+$.
31-G		2-(5-isopropil-1H-indazol-4-il)-4-metoxi-6-(2-metil-5-(3-metiloxetan-3-il)fenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (br. s., 1 H) 7.44 - 7.70 (m, 2 H) 7.27 (d, J=8.3 Hz, 1 H) 7.08 (d, J=1.8 Hz, 1 H) 6.94 (dd, J=7.7, 1.9 Hz, 1 H) 5.04 (d, J=5.6 Hz, 2 H) 4.70 (d, J=5.8 Hz, 2 H) 4.15 (s, 2 H) 4.09 (s, 3 H) 3.60 (quin, J=6.9 Hz, 1 H) 3.39 (t, J=5.7 Hz, 2 H) 3.23 (t, J=5.3 Hz, 2 H) 2.42 (s, 3 H) 1.80 (s, 3 H) 1.37 (d, J=6.8 Hz, 6 H); MS (ESI+) *m/z* 484.0 $(M+H)^+$.
31-H		2-(3,5-dimetil-1H-indazol-4-il)-4-metoxi-6-(2-metil-5-(3-metiloxetan-3-il)fenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. 1H NMR (400 MHz, CD_2Cl_2) δ ppm 9.88 (br. s., 1 H) 7.45 (d, J=8.3 Hz, 1 H) 7.33 (d, J=8.3 Hz, 1 H) 7.27 (d, J=7.8 Hz, 1 H) 7.06 (d, J=1.8 Hz, 1 H) 6.93 (dd, J=7.7, 1.9 Hz, 1 H) 4.99 (d, J=5.3 Hz, 2 H) 4.66 (d, J=5.3 Hz, 2 H) 4.15 (s, 2 H) 4.05 (s, 3 H) 3.38 (t, J=5.7 Hz, 2 H) 3.14 (t, J=5.7 Hz, 2 H) 2.40 (s, 3 H) 2.34 (s, 3 H) 2.05 (s, 3 H) 1.77 (s, 3 H); MS (ESI+) m/z 470.3 $(M+H)^+$.
31-I		2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. 1H NMR (400 MHz, CD_2Cl_2) δ ppm 7.39 - 7.48 (m, 1 H) 7.29 - 7.37 (m, 1 H) 7.21 (d, J=7.8 Hz, 1 H) 7.10 (d, J=1.5 Hz, 1 H) 6.97 (dd, J=7.6, 1.8 Hz, 1 H) 4.15 (s, 2 H) 4.05 (s, 3 H) 3.37 (t, J=5.7 Hz, 2 H) 3.13 (t, J=5.6 Hz, 2 H) 2.87 - 3.02 (m, 1 H) 2.38 (s, 3 H) 2.35 (s, 3 H) 2.08 (s, 3 H) 1.31 (d, J=7.1 Hz, 6 H); MS (ESI+) m/z 442.3 $(M+H)^+$.

Ejemplo 32

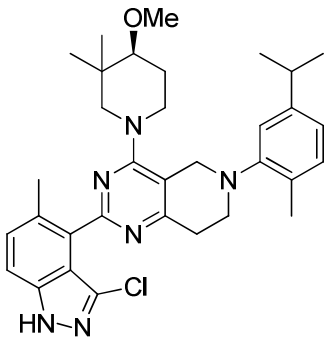
32- A. 2 - (3- Cloro- 5- metil- 1H- indazol- 4- il) - 6 - (5- isopropil- 2- metilfenil)- 4- metoxi- 5, 6,7,8 tetrahidropirido [4,3- d] pirimidina.



Se agregó por goteo blanqueador Elite ® (hipoclorito de sodio al 5.25%) a una solución de 6-(5-isopropil-2-metilfenil)-4-metoxi-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (40 mg, 0.094 mmol) en EtOH (4 ml) a 0 °C. La reacción se monitoreo mediante LC- MS. Después que todo el material de inicio se había consumido, la mezcla de reacción se cargó directamente en HPLC de fase inversa y se purifico (CH_3CN- agua 0- 100%) para proporcionar2-(3-cloro-5-metil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina.^{1}H RMN (400 MHz, CD_3CN) δ ppm 11,23 (br. s., 1 H) 7,55 (d, J = 8,59 Hz, 1 H) 7,41 (d, J = 8,59 Hz, 1 H) 7,18 (d, J = 7,58 Hz, 1 H) 7,10 (d, J = 2,02 Hz, 1 H) 6,95 (dd, J = 7,71, 1,89 Hz, 1 H) 4,11 (s, 2 H) 3,97 (s, 3 H) 3,32 (t, J = 5,68 Hz, 2 H) 3.1 - 3.6 (m, 2 H) 2,92 (ddd, J = 13,83, 6,88, 6,82 Hz, 1 H) 2,33 (s, 3 H) 2,31 (s, 3 H) 1,26 (d , J = 6,82 Hz, 6 H), MS (ESI+) m/z 462.1 (M+H)+.

Los siguientes compuestos se prepararon de una manera similar.

32-B. (*S*)-2-(3-Cloro-5-metil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.

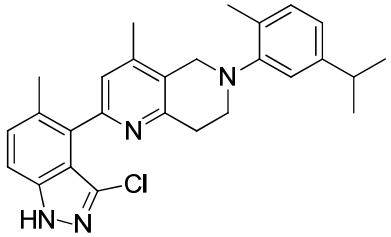


32- B.

^{1}H RMN (400 MHz,CD_3CN) δ ppm 7,50 (d, J = 8,6 Hz, 1 H), 7,36 (d, J = 8,6 Hz, 1 H), 7,13 (d, J = 7,8 Hz, 1 H), 7,01 (d, J = 1,5 Hz, 1 H), 6,90 (dd, J = 7,7, 1,6 Hz, 1 H), 4,02 - 4,14 (m, 2 H),

3,65 - 3,70 (m, 1 H), 3,33 - 3,40 (m, 3 H) , 3,30 (s, 3 H), 3,05 (ddd, J = 13,1, 10,0, 3,2 Hz, 1 H), 2,95 -2,99 (m, 3 H), 2,82 - 2,91 (m, 2 H), 2,25 (s, 6 H), 1,57 - 1,66 (m, 1 H), 1,23 (d, J = 6,6 Hz, 6 H), 0,97 (s, 3 H), 0,91 (s, 3 H), MS (ESI+) m/z 573.0 (M+H)+.

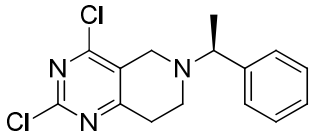
32- C.2-(3-Cloro-5-metil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina.



^{1}H RMN (400 MHz, diclorometano- d_2)δ ppm 10,32 (br. s., 1 H). 7,38 (s, 2 H) 7,21 (d, J = 7,58 Hz, 1 H) 07.08 - 07.13 (m, 2 H) 6,97 (dd, J = 7,58, 1,77 Hz , 1 H) 4,21 (s, 2 H) 3.37- 3.42 (m, 2 H) 3.20 - 3.26 (m, 2 H) 2,95 (dt, J = 13,83, 6,85 Hz, 1 H) 2,40 (s, 3 H) 2,35 (s, 3 H) 2,30 (s, 3 H) 1,31 (d, J = 6,82 Hz, 6 H), MS (ESI+) m/z 445.0 (M+H)+.

Ejemplo 33

33- A. (S) - 2,4- dicloro- 6- (1- feniletil) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.



Una mezcla de amonionitrato cérico (22.6 g, 41.3 mmol), (S)- fenil- etilamina (25 g, 207 mmol) y THF (100 ml) se enfrió a 10 °C y luego se añadió por goteoetilacrilato (51.6 g, 516 mmol). La mezcla de reacción se llevó luego a temperatura ambiente y luego se calentó a 60 °C y se calentó durante 15 h. La mezcla se diluye con agua y EtOAc y luego la capa orgánica se separó, se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó mediante FCC (30% de EtOAc/hexanos) para proporcionar (S)- dietil 3,3 '- ((1- feniletil) azanediil) dipropanoato. MS (ESI+) m/z 322 (M+H)+.

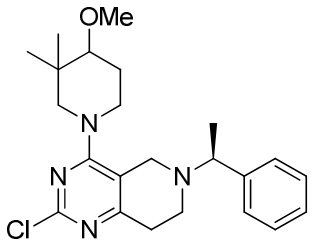
Una suspensión de NaH (2.24 g, 93.4 mmol) en THF (20 ml) se enfrió a 0 °C y luego se añadió por goteo como solución de (S)- dietil 3,3 '- ((1- feniletil) azanediil) dipropanoato (15 g, 46.7 mmol) en THF. La mezcla de reacción se dejó calentar a temperatura ambiente y luego se calentó a 60 °C y se calentó durante 3 h. La mezcla se diluye con agua y EtOAc yluego la capa orgánica se separó, se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó mediante

FCC (EtOAc 5- 7%/hexanos) para proporcionar (S)- etil 4- oxo- 1- ((S)- 1- feniletil) piperidina- 3- carboxilato.

Una combinación de urea (0.37 g, 15.6 mmol), metóxido de sodio (1.47 g, 27.2 mmol) y MeOH (50 mL) se enfrió a 0 °C y luego se añadió una solución de (S)- etil 4- oxo- 1- ((S)- 1- feniletil) piperidina- 3- carboxilato (9.0 g, 7.8 mmol) en THF. La mezcla de reacción se dejó calentar a temperatura ambiente y luego se calentó a 60 °C y se calentó durante 3 h. La mezcla se diluyo con agua y EtOAc y luego la capa orgánica se separó, se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó mediante FCC (8- 10% MeOH/CH_2Cl_2) para proporcionar (S) - 6 - (1- feniletil) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina- 2, 4 - diol.

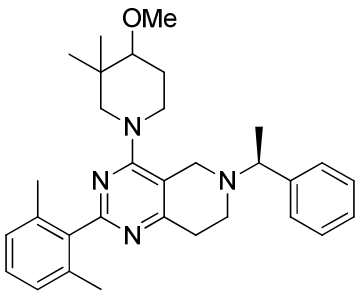
Una combinación de $POCl_3$ (10 mL) y DIEA (2.0 ml) se enfrió a 0 °C y luego se añadió (S) - 6 - (1- feniletil) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina- 2 ,4- diol (2.0 g, 7.38) en THF la mezcla de reacción se dejó calentar a temperatura ambiente y luego se calentó a 60 °C y se calentó durante 3 h. La mezcla se diluyo con agua y EtOAc yluego la capa orgánica se separó, se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó mediante FCC (10% EtOAc/hexanos) para proporcionar (S) - 2,4- dicloro- 6- (1- feniletil) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina . MS (ESI+) m/z 310 (M+2).

33- B. (±)- 2- Cloro- 4- (4- metoxi- 3 ,3- dimetilpiperidin- 1- il) - 6 - ((S)- 1- feniletil) - 5,6,7,8 - tetrahidropirido [4,3- d] pirimidina.



Una mezcla racémica de 4- metoxi- 3 ,3- dimetilpiperidina (0.0 g, 1.95 mmol), (S) - 2,4- dicloro- 6- (1 - feniletil) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina (0.40 g, 1.30 mmol), DIEA (0.50 g, 3.90 mmol) e isopropanol (10 mL) se calentó a 60 °C durante 24 h. La mezcla se diluyo con agua y EtOAc y luego la capa orgánica se separó, se secó (Na_2SO_4), se filtró y se concentró. El residuo fue llevado a la siguiente etapa sin purificación adicional. MS (ESI+) m/z 415.2 (M+H)+.

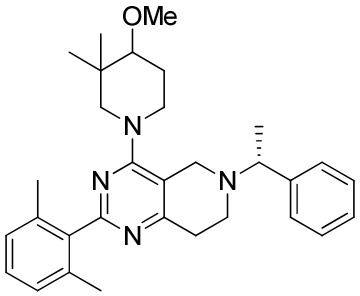
33- C. (±) - 2 - (2,6- dimetilfenil) - 4 - (4- metoxi- 3 ,3- dimetilpiperidin- 1- il) - 6 - ((S) - 1 - feniletil) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.



Una mezcla de 2,6- dimetilfenil ácido borónico (0.081 g, 0.54 mmol), (±)- 2- cloro- 4- (4- metoxi- 3, 3 - dimetilpiperidin- 1- il) - 6 - ((S)- 1- feniletil) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina (0.15 g, 0.36 mmol), $Pd(PPh_3P)_4$ (0.041 g, 0.036 mmol), Na_2CO_3 acuoso saturado (2.0 ml), y DMF (5 ml) se colocó bajo una atmósfera de nitrógeno y se calentó a 120 °C en un reactor de microondas durante 0.5 h. La mezcla se diluyo con agua y EtOAc y luego la capa orgánica se separó, se secó (Na_2SO_4), se filtró y se concentró. Luego el residuo se purificó mediante semi- HPLC preparativa (columna: ZORBAX, XDB, C- 18; A: 10 NH_4OAc mM en agua; B: MeCN; tasa de flujo: 20 ml/min; Gradiente: 0.0 min, 70.0% MeCN, 2,0 min, 80.0% MeCN, 6,0 min, 90.0% MeCN). Después de la liofilización, la mezcla se disolvió en DCM y se lavó con agua para eliminar NH_4OAc, se secó sobre Na_2SO_4 y los disolventes se eliminaron bajo presión reducida. MS (ESI+) m/z 485.3 (M+H)+.

Los siguientes compuestos se prepararon de una manera similar.

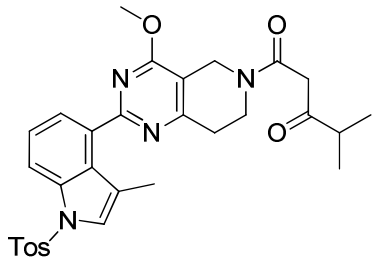
33- B. (±) - 2 - (2,6- dimetilfenil) - 4 - (4- metoxi- 3 ,3- dimetilpiperidin- 1- il) - 6 - ((R) - 1- feniletil) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.



MS (ESI+) m/z 485.4 (M+H)+.

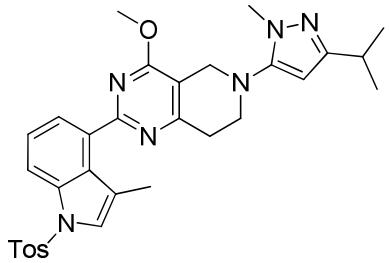
Ejemplo 34

34- A.1-(4-Metoxi-2-(3-metil-1-tosil-1H-indol-4-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-4-metilpentano-1,3-diona.



A una solución de 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina, preparado como se describe en **Ejemplo 17**, (300 mg, 0.67 mmol) en tolueno (3 mL), en un vial de microondas de 2- 5 mL, se añadió 4- metil- 3- oxopentanoato de metilo (0.28 ml, 2 mmoles) seguido de DMAP (25 mg, 0.2 mmol). Luego el recipiente de reacción se selló y se calentó a través de la irradiación de microondas a 150 °C durante 35 min. Luego la mezcla de reacción se enfrió a temperatura ambiente y se diluyó con diclorometano y agua. Las capas se separaron y la capa orgánica se secó al pasar a través de un separador de fases y después se concentró. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (45- 90% acetato de etilo/heptanos) para proporcionar MS (ESI+) m/z 561.3 (M+H)+.

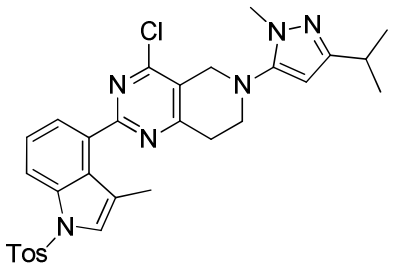
34- B.6-(3-Isopropil-1-metil-1H-pirazol-5-il)-4-metoxi-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



A una solución de (350 mg, 0.624 mmol) en THF (3.3 ml), en un vial de microondas de 2- 5 mL, se añadió reactivo de Lawesson (278 mg, 0.687 mmol) e hidrazina de metilo (0.049 ml, 0.94 mmol). El recipiente se selló y se calentó inmediatamente a través de la irradiación de microondas a 120 °C durante 10 minutos. Luego la reacción se enfrió a temperatura ambiente y se diluyó con diclorometano y agua. Las capas se separaron y la capa acuosa se extrajo dos

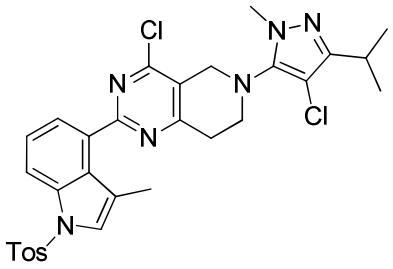
veces más con diclorometano. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (45- 67% acetato de etilo/heptanos) para proporcionar 6-(3-isopropil-1-metil-1H-pirazol-5-il)-4-metoxi-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI+) m/z 571.4 (M+H)+.

34- C.4-Cloro-6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



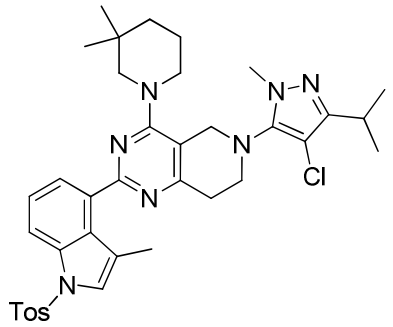
Se añadió etanol (1.8 ml) a 6-(3-isopropil-1-metil-1H-pirazol-5-il)-4-metoxi-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (195 mg, 0.342 mmol) seguido de ácido clorhídrico acuoso 12 N (1.8 ml, 21.8 mmol). Luego la mezcla se calentó a 87 °C durante aproximadamente 15 horas. Luego la mezcla se enfrió a temperatura ambiente, se diluyó con diclorometano, y se neutralizólentamente con bicarbonato de sodio acuoso saturado. Las capas resultantes se separaron y las capas acuosas se extrajeron un tiempo adicional con diclorometano. Las capas orgánicas se combinaron y se secaron al pasar a través de un separador de fases y luego se concentraron. El residuo resultante se diluyó con 1,2- dicloroetano (3.5 ml) y se colocó a 0 °C. Luego se añadió N- clorometileno- cloruro de N, N- dimetil amonio (reactivo de Vilsmeier) (85 mg, 067 mmol). La mezcla resultante se calentó entonces a 35 ºC. Después de 5 minutos a 35 °C la mezcla se diluyó con diclorometano, y se neutralizólentamente con bicarbonato de sodio acuoso saturado. Las capas resultantes se separaron y las capas acuosas se extrajeron un tiempo adicional con diclorometano. Las capas orgánicas se combinaron y se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar4-cloro-6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina sin necesidad de purificación adicional. MS (ESI+) m/z 575.3 (M+H)+.

34- D.4-Cloro-6-(4-cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



A una solución de4-cloro-6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (90 mg, 0.156 mmol) en MeCN (2.0 ml) a 0 °C se añadió N- clorosuccinimida (21 mg, 0.156 mmol). La reacción se permitió agitar durante 2.5 horas a 0 °C, y luego se diluyó con éter dietílico y bicarbonato de sodio acuoso saturado. Las capas se separaron y la capa orgánica se lavó una vez con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar4-cloro-6-(4-cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina sin necesidad de purificación adicional. MS (ESI+) m/z 609.2 (M+H)+.

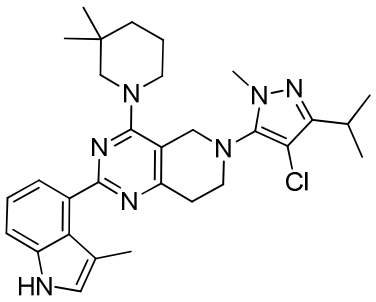
34- E.6-(4-Cloro-3-isopropil-1-metil-1H-pirazol-5-il)-4-(3,3-dimetilpiperidin-1-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



Se añadió isopropanol (2.2 ml) a 4-cloro-6-(4-cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (85 mg, 0.139 mmol) en un vial de microondas. Luego se añadió diisopropiletilamina (0.1 ml, 0.573 mmol) seguido por la sal de HCl de 3,3- dimetilpiperidina (25 mg, 0.167 mmol). El recipiente se selló y se calentó a través de la irradiación de microondas a 120 °C durante 2.5 horas después se enfrió a temperatura ambiente y se diluyó con diclorometano y salmuera. Las capas se separaron y la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (25- 55% acetato de etilo/heptanos) para proporcionar 6-(4-cloro-3-isopropil-1-metil-1H-pirazol-5-il)-4-(3,3-

dimetilpiperidin-1-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.MS (ESI+) m/z 686.4 (M+H)+.

34- F.6-(4-Cloro-3-isopropil-1-metil-1H-pirazol-5-il)-4-(3,3-dimetilpiperidin-1-il)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina.

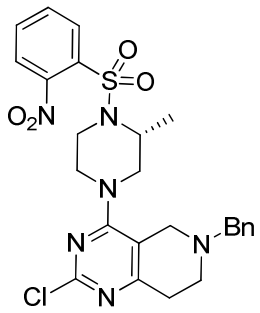


Se añadió etanol (1.8 ml) a6-(4-cloro-3-isopropil-1-metil-1H-pirazol-5-il)-4-(3,3-dimetilpiperidin-1-il)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (74 mg, 0.108 mmol) en un vial de microondas. Luego, se añadió KOH (61 mg, 1.08 mmol) seguido de hidróxido amónico acuoso al 28% (0.6 ml, 4.35 mmol). El recipiente se selló y se calentó a través de la irradiación de microondas a 100 °C durante 75 minutos. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con diclorometano y agua. Las capas se separaron y la capa orgánica se secó al pasar a través de un separador de fases. El eluyente se concentró y el residuo resultante se purificó mediante HPLC de fase inversa (20- 55% MeCN/agua (TFA al 0.1%)). El eluyente de HPLC se neutralizó con bicarbonato de sodio acuoso saturado y se extrajo con diclorometano. El extracto orgánico se secó al pasar a través de un separador de fases y se concentro para proporcionar6-(4-cloro-3-isopropil-1-metil-1H-pirazol-5-il)-4-(3,3-dimetilpiperidin-1-il)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina.

^{1}H NMR(400 MHz, CD_2Cl_2) δ ppm 0,97 (s, 6 H) 1,26 (d, J = 7,1 Hz, 6 H) 1.39- 1.46 (m, 2 H) 1,66- 1,77 (m, 2 H) 2,09 (s, 3 H) 2,99 (dt, J = 13 9, 7,0 Hz, 1 H) 3,04 - . 3,12 (m, 4 H) 3,25 - 3,34 (m, 2 H) 3,53 - 3,59 (m, 2 H) 3,63 (s, 3 H) 4,30 (s, 2 H) 7,04 (br. s., 1 H) 7,20 (t, J = 7,7 Hz, 1 H) 7,32 (d, J = 6,3 Hz, 1 H) 7,41 (d, 1 H) 8,22 (br. s., 1 H).; MS (ESI+) m/z 532.4 (M+H)+.

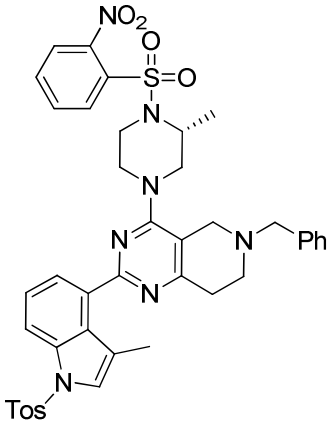
Ejemplo 35

35- A.(*R*)-6-bencil-2-cloro-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



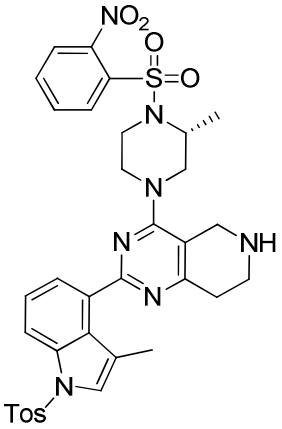
Se añadió isopropanol (80 ml) a 6- bencil- 2 ,4- dicloro- 5 ,6,7,8- tetrahidropirido [4,3-d] pirimidina (CAS# 778574- 06- 4 2.5 g, 8.50 mmol) seguido por trietilamina (3.55 ml, 25.5 mmol) y (R)- 2- metilpiperazina (1.28 g, 12.8 mmol). La mezcla se calentó a 50 °C durante 6.5 horas y luego se enfrió a temperatura ambiente y se diluyó con diclorometano y agua. Las capas se separaron y la capa acuosa se extrajo una vez más con diclorometano. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. Luego una porción del residuo resultante (1.3 g) se disolvió en diclorometano (25 mL) y se cargó con trietilamina (1.2 ml, 8.7 mmol). La mezcla se colocó a 0 °C y luego se añadió 2- nitrobenceno- 1- sulfonilo (0.97 g, 4.4 mmol). La mezcla se agitó a 0 °C durante 30 minutos y luego se calentó a temperatura ambiente y se agitó 1 hora adicional. Luego la mezcla se apagó con bicarbonato de sodio acuoso saturado y se agitó durante 1 hora. Luego la mezcla se diluyo adicionalmente con diclorometano y bicarbonato de sodio acuoso saturado y se separaron las capas. La capa acuosa se extrajo una vez más con diclorometano. Las capas orgánicas fueron combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (50- 85% acetato de etilo/heptanos) para proporcionar:(*R*)-6-Bencil-2-cloro-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI+) m/z 686.4 (M+H)+.

35- B. (*R*)-6-Bencil-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



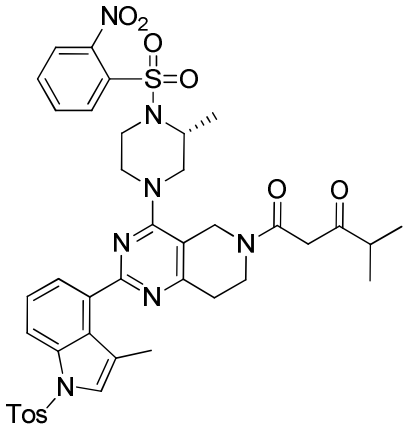
Se añadió 1,2- dimetoxietano (6.75 ml) a un vial de microondas 20 mL que contiene una mezcla de (*R*)-6-Bencil-2-cloro-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (1.1 g, mmol 2.03) y 3- metil- 4- (4,4,5,5- tetrametil- 1 ,3,2-dioxaborolan- 2- il)- 1- tosil- 1H- indol (0.92 g, 2.23 mmoles). Luego se añadió Na_2CO_3acuoso 2M la mezcla de reacción se degasificó a través de tres ciclos de argón/vacío, luego se cargó con $Pd(Ph_3P)_4$ (0.234 g, 0.203 mmol). El vial se cerró herméticamente y se calentó a través de la irradiación de microondas a 140 °C durante 90 minutos. La mezcla se enfrió luego a temperatura ambiente y se diluyó con Et_2O y agua. Las capas se separaron y la capa acuosa se extrajo dos veces más con diclorometano. Las capas orgánicas fueron combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice [55- 75% acetato de etilo (que contenía 2% EtOH /heptanos] para proporcionar (*R*)-6-bencil-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI+) m/z 792.5 (M+H)+.

35- C. (*R*)-2-(3-Metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



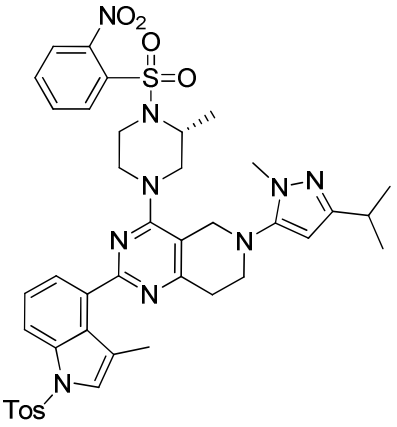
A una solución de (*R*)-6-bencil-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (1.17 g, 1.47 mmol) en MeCN (15 ml) se añadió carbonocloridato de 1- cloroetilo(0.18 ml, 1.62 mmol), y la mezcla se agitó durante 15 minutos momento en el cual la mezcla se concentró al vacío. El residuo resultante se disolvió en una mezcla 2:1 de diclorometano: metanol (15 ml) y se calentó a 40 °C durante 1 hora y luego se colocó a temperatura ambiente durante aproximadmente 15 h. La mezcla se diluyó con diclorometano y bicarbonato sódico acuoso saturado. Las capas se separaron y la capa acuosa se extrajo dos veces más con diclorometano. Las capas orgánicas fueron combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (3- 12% de MeOH/DCM) para proporcionar MS (ESI+) m/z 702.3 (M+H)+.

35- D. (*R*)-4-metil-1-(2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)pentane-1,3-diona.



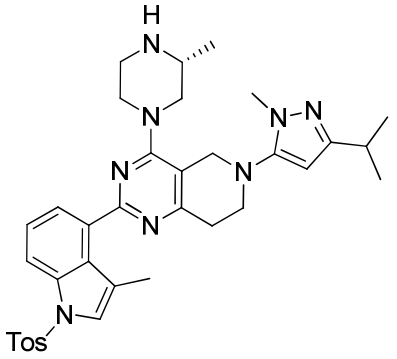
El compuesto del título se preparó a partir de (*R*)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina siguiendo el procedimiento descrito en el **Ejemplo 34**. MS (ESI+) m/z 814.3 (M+H)+.

35- E. (*R*)-6-(3-Isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



El compuesto del título se preparó a partir de (*R*)-4-metil-1-(2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)pentane-1,3-diona siguiendo el procedimiento descrito en el **Ejemplo 34**. MS (ESI+) m/z 824.4 (M+H)+.

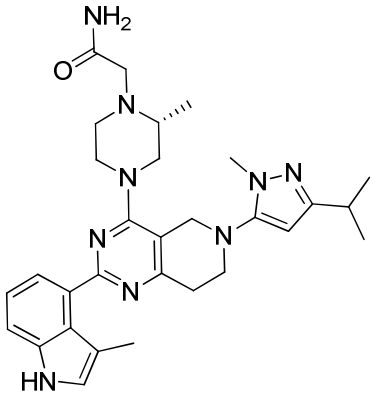
35- F. (*R*)-6-(3-Isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metilpiperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



A una solución de (*R*)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (105 mg, 0.127 mmol) en DMF (3 ml) se añadió DBU (0.1 ml, 0.64 mmol) seguido por ácido 2- mercaptoacético (0.018 ml, 0.255 mmol). La mezcla se agitó durante 3 horas y después se diluyó con agua y diclorometano. Las capas se separaron y la capa acuosa se

extrajo tres veces más con diclorometano. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice [425% (MeOH 2 Men NH_3)/DCM] para proporcionar (*R*)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metilpiperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI+) m/z 639.4 (M+H)+.

35- G. (*R*)-2-(4-(6-(3-Isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida.

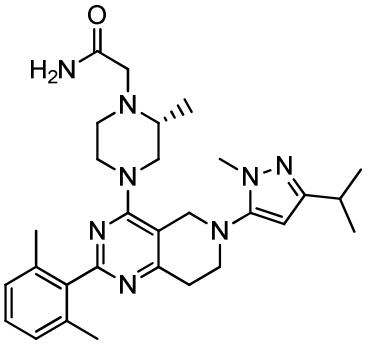


A una solución de (*R*)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metilpiperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (78 mg, 0.122 mmol) en MeCN (2 mL) se añadió diisopropiletilamina (0.064 ml, 0.37 mmol) seguido por 2-bromoacetamida (20 mg, 0.146 mmol). La mezcla se calentó a 55 °C y se agitó durante 105 minutos, luego se enfrió a temperatura ambiente y se apagó con NH_4Cl acuoso saturado. La mezcla se diluyó con diclorometano y bicarbonato sódico acuoso saturado y se separaron las capas. La capa acuosa se extrajo dos veces más con diclorometano y luego las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. Luego el residuo resultante se disolvió entonces en etanol (2.1 ml) y se colocó en un vial de microondas. El frasco se cargó con KOH (69 mg, 1.24 mmol) y hidróxido de amonioacuoso al 28% (0.7 ml, 5.1 mmol), se selló y calentó a través de la irradiación de microondas a 100 °C durante 70 minutos. Luego la mezcla se enfrio a temperatura ambiente, se diluyó con diclorometano y agua y después se neutralizó con $NaHSO_4$ acuosa 1M. Las capas resultantes se separaron y la capa orgánica se secó al pasar a través de un separador de fases. El eluyente se concentró y se purificó mediante HPLC de fase inversa [10- 55% de MeCN/(NH_4OH al 0.1%)agua] para proporcionar(*R*)-2-(4-(6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 1,02 (d, J = 6,3 Hz, 3 H) 1,16 (d, J = 6,8 Hz, 6 H) 2,02 (s, 3 H) 2.59- 2.66

(m, 1 H) 2.72 - 2.85 (m, 3 H) 2,89 - 3,00 (m, 3 H) 3,13 (d, J = 16,2 Hz, 1 H) 3.20 - 3.26 (m, 1 H) 3.27 - 3.30 (m, 3 H) 3,56 - 3,64 (m, 5 H) 4,01 (s, 2 H) 5,73 (s, 1 H) 7.8 - 7.13 (m, 2 H) 7.13 - 7.16 (m, 1 H) 7.18 - 7.22 (m, 1 H) 7,26 (d, J = 2,8 Hz, 1 H) 7,41 (dd, J = 8,1, 1,0 Hz, 1 H) 10,90 (s, 1 H), MS (ESI+) m/z 542.4 (M+H)+.

Ejemplo 36

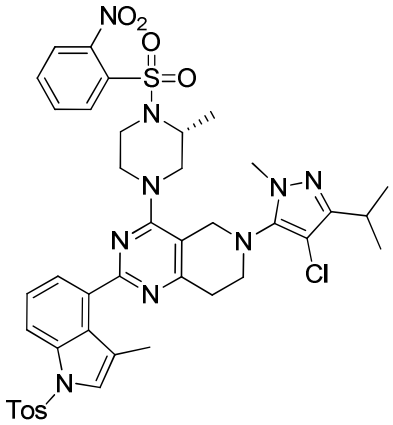
(*R*)-2-(4-(2-(2,6-dimetilfenil)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida.



Se añadió MeCN (2 mL) a4-cloro-2-(2,6-dimetilfenil)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina preparado como se describe en el **Ejemplo 16**, (110 mg, 0.278 mmol) en un vial de microondas. Luego el vial se cargó con diisopropiletilamina (0.24 ml, 1.38 mmol) y (R)- 2- metilpiperazina (56 mg, 0.556 mmol). El vial se cerró herméticamente y se calentó a través de la irradiación de microondas a 100 °C durante 45 minutos. La mezcla se enfrió a temperatura ambiente y después se cargó con 2-bromoacetamida (115 mg, 0.833 mmol), se selló nuevamente y se calentó a través de irradiación de microondas a 100 °C durante 10 minutos. Luego la reacción se enfrió a temperatura ambiente y se adsorbióal vacío sobre sílice y se cargó en una columna decromatografía ultrarrápida de gel de sílice para la purificación [0- 10% (10% NH_4OH)MeOH/DCM]. Luego el material se purificó adicionalmente mediante cromatografía ultrarrápida de gel de sílice adicional {0- 35% [MeOH al 10% (que contenía 1% NH_4OH)/EtOAc]/DCM} para proporcionar(*R*)-2-(4-(2-(2,6-dimetilfenil)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,27 (br. s., 1 H) 7,17 (d, J = 7,58 Hz, 1 H) 7,13 (br. s., 1 H) 7,08 (d, J = 7,58 Hz, 2 H) 5,72 (s, 1 H) 3,98 (s, 2 H) 3,59 (s, 3 H) 3.51- 3.58 (m, 2 H) 3.25- 3.32 (m, 3 H) 3.16 - 3.24 (m , 1 H) 3,11 (d, J = 16,17 Hz, 1 H) 2,94 (br. s., 3 H) 2,71 - . 2,85 (m, 3 H) 2.56- 2.65 (m, 1 H) 2,05 (s, 6 H) 1.11 a 1.19 (m, 6 H) 1,00 (d, J = 6,06 Hz, 3 H), MS (ESI +) m/z 517.34 (M+H)+.

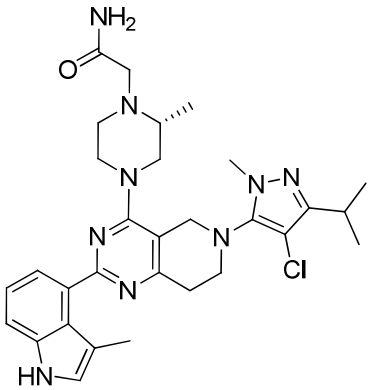
Ejemplo 37

37- A. (*R*)-6-(4-Cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



El compuesto del título se preparó a partir de (*R*)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina siguiendo el procedimiento descrito en el **Ejemplo 34**. MS (ESI+) m/z 858.4 (M+H)+.

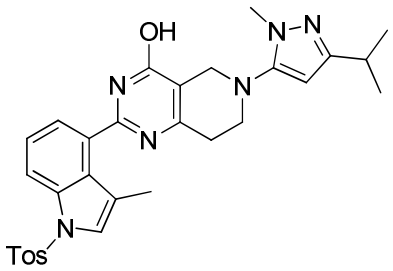
37- B.(*R*)-2-(4-(6-(4-Cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida.



El compuesto del título se preparó a partir de (*R*)-6-(4-cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1-tosil-1H-indol-4-il)-4-(3-metil-4-((2-nitrofenil)sulfonil)piperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina siguiendo los procedimientos descritos en los **Ejemplos 35**. ^{1}H RMN (400 MHz, DMSO- d_6)δ ppm 1,00 (d, J = 6,3 Hz, 3 H) 1,20 (d, J = 6,8 Hz, 6 H) 2,03 (s, 3 H) 2.58- 2.65 (m, 1 H) 2,76- 3,00 (m, 6 H) 3,10 - 3,23 (m, 2 H) 3.27 - 3.30 (m, 1 H) 3,52 (t, J = 6,1 Hz, 2 H) 3,55- 3,64 (m, 5 H) 4.21 - 4.34 (m, 2 H) 7,07 - 7,13 (m, 2 H) 7.13 - 7.16 (m, 1 H) 7,21 (dd, J = 7,3, 1,0 Hz, 1 H) 7.23 - 7.27 (m, 1 H) 7,41 (dd, J = 8,0, 0,9 Hz, 1 H) 10,90 (s, 1 H), MS (ESI+) m/z 576.5 (M+H)+.

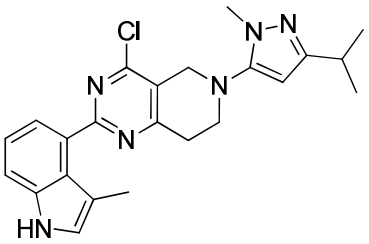
Ejemplo 38

38- A.6-(3-Isopropil-1-metil-1*H*-pirazol-5-il)-2-(3-metil-1-tosil-1*H*-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-ol.



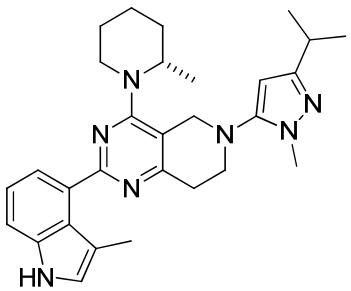
A una solución de6-(3-isopropil-1-metil-1*H*-pirazol-5-il)-4-metoxi-2-(3-metil-1-tosil-1*H*-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina (1.8 g, 3.15 mmol), preparado como se describe en el **Ejemplo 16**, en etanol (10 mL) en un tubosellado de 150 mL, se añadió hidrocloruroconcentrado (10 mL). Después de que el tubo se selló, la reacción se agitó y se calentó a 85 °C durante 18 h. La mezcla de reacción se enfrió a 0 °C y se vertió en agua con hielo. Se añadió $NaHCO_3$ sólido para neutralizar la mezcla de reacción, luego la mezcla se extrajo dos veces con DCM y las capas orgánicas combinadas se secaron sobre Na_2SO_4. El residuo resultante se purificó mediante FCC de gel de sílice (0- 100% EtOAc/heptano) para proporcionar 6-(3-isopropil-1-metil-1*H*-pirazol-5-il)-2-(3-metil-1-tosil-1*H*-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-ol MS (ESI+) m/z 557.2 (M+H)+.

38- B.4-Cloro-6-(3-isopropil-1-metil-1*H*-pirazol-5-il)-2-(3-metil-1*H*-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina.



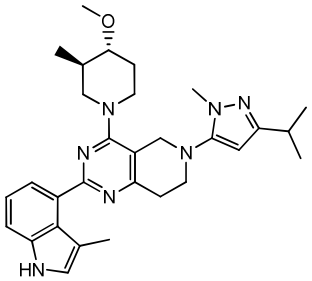
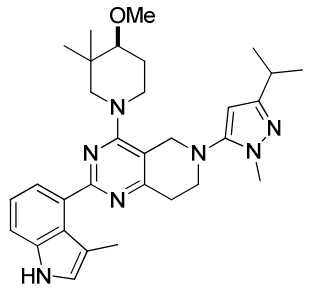
A una solución de6-(3-isopropil-1-metil-1*H*-pirazol-5-il)-2-(3-metil-1-tosil-1*H*-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-ol (550 mg, 0.988 mmol) en metanol (5 mL) en un vial de microondas, se añadió hidróxido de potasio (554 mg, 9.88 mmol) y luego hidróxido amónico al 28% (1 ml, 0.988 mmol). La reacción se calentó a 80 °C a través de irradiación de microondas durante 45 min. La mezcla de reacción se vertió en agua helada, luego se añadió HClacuoso4 N para acidificar la mezcla de reacción a pH = 1, luegose añadió$NaHCO_3$ sólido para neutralizar mezcla de reacción a pH = 7- 8. La mezcla se extrajo dos veces con una solución detrifluoroetanol al 5% en DCM. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se disolvió en dicloroetano (3 ml), y el matraz de reacción se cargó con oxicloruro de fósforo (3.67 ml, 39.5 mmol). El matraz de reacción se tapó yluego se calentóa 80 °C durante 1 h. La mezcla de reacción se enfrió a temperatura ambiente y se vertió en agua con hielo y se diluyó con acetona (10 mL). La mezcla de reacción se agitó durante 30 minutos para proporcionar una solución clara. En ese punto, se añadió $NaHCO_3$ sólido para neutralizar la reacción, y la mezcla se extrajo dos veces con DCM. El residuo resultante se purificó a través de FCC de gel de sílice (0- 100% EtOAc/heptano) para proporcionar 4-cloro-6-(3-isopropil-1-metil-1*H*-pirazol-5-il)-2-(3-metil-1*H*-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina. MS (ESI+) m/z 421.2 (M+H)+.

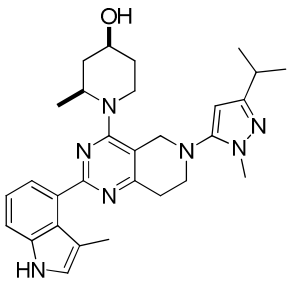
38- C. (*S*)-6-(3-Isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1H-indol-4-il)-4-(2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



A una solución de 4-cloro-6-(3-isopropil-1-metil-1*H*-pirazol-5-il)-2-(3-metil-1*H*-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina (50 mg, 0.123 mmol) en N, N- dimetilacetamida (1,5 ml), se añadió diisopropiletilamina (0.15 ml, 0.86 mmol) y (S)- 2- metilpiperidina (37 mg, 0.37 mmol). La reacción se agitó y se calentó a 125 °C durante 24 h. Después de enfriar, la mezcla se purificó directamente a través de HPLC ((hidróxido amónico al 0.1% en acetonitrilo)/agua = 35% -100%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 8,23 (br. s., 1 H.), 7,42 (d, J = 8,1 Hz, 1 H), 7,33 (d, J = 8,1 Hz, 1 H), 7,16 - 7,26 (m, 1 H), 7,04 (s, 1 H), 5,69 (s, 1 H), 4,06 - 4,16 (m, 1 H), 3,90 - 4,06 (m, 2 H), 3,67 (s, 3 H) , 3,53 (d, J = 13,4 Hz, 1 H), 3,29 - 3,40 (m, 2 H), 3,16 - 3,29 (m, 1 H), 3,10 (d, J = 4,5 Hz, 2 H), 2,85 (dt , J = 13,8, 6,9 Hz, 1 H), 2,10 (s, 3 H), 1,74 - 1,91 (m, 2 H), 1,65 - 1,74 (m, 2 H), 1,48 - 1,65 (m, 2 H), 1,22 (d, J = 6,8 Hz, 6 H), MS (ESI+) m/z 484.4 (M+H)+.

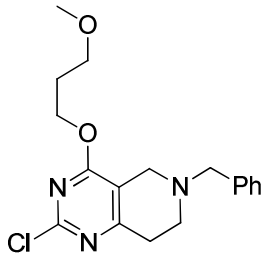
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos
38-D		(6-(3-isopropil-1-metil-1H-pirazol-5-il)-4-((3*R*,4*R*)-4-metoxi-3-metilpiperidin-1-il)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.22 (br. s., 1 H), 7.43 (d, *J*=7.8 Hz, 1 H), 7.34 (d, *J*=7.3 Hz, 1 H), 7.16 - 7.24 (m, 1 H), 7.05 (s, 1 H), 5.68 (s, 1 H), 4.01 (s, 2 H), 3.84 (d, *J*=13.4 Hz, 1 H), 3.73 (d, *J*=14.4 Hz, 1 H), 3.66 (s, 3 H), 3.35 (s, 3 H), 3.31 - 3.35 (m, 2 H), 3.10 (t, *J*=4.9 Hz, 2 H), 2.98 - 3.07 (m, 1 H), 2.94 (td, *J*=9.2, 4.3 Hz, 1 H), 2.81 - 2.89 (m, 1 H), 2.76 (dd, *J*=12.9, 10.4 Hz, 1 H), 2.10 - 2.19 (m, 1 H), 2.09 (s, 3 H), 1.71 - 1.84 (m, 1 H), 1.45 - 1.60 (m, 1 H), 1.22 (d, *J*=6.8 Hz, 6 H), 1.01 (d, *J*=6.6 Hz, 3 H); MS (ESI+) *m/z* 514.4 $(M+H)^+$.
38-E		(*S*)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.28 (br. s., 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.35 (d, *J*=7.1 Hz, 1 H), 7.15 - 7.25 (m, 1 H), 7.06 (s, 1 H), 5.67 (s, 1 H), 4.03 (s, 2 H), 3.73 (d, *J*=11.6 Hz, 1 H), 3.66 (s, 3 H), 3.42 (d, *J*=11.4 Hz, 1 H), 3.35 (s, 3 H), 3.31 - 3.35 (m, 2 H), 3.04 - 3.27 (m, 3 H), 2.97 (dd, *J*=8.5, 3.9 Hz, 2 H), 2.78 - 2.91 (m, 1 H), 2.09 (s, 3 H),

		1.91 - 2.04 (m, 1 H), 1.65 - 1.78 (m, 1 H), 1.21 (d, *J*=6.8 Hz, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H); MS (ESI+) *m/z* 528.4 $(M+H)^+$.
38-F		(±)-1-(6-(3-isopropil-1-metil-1H-pirazol-5-il)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilpiperidin-4-ol. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.25 (br. s., 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.34 (d, *J*=8.1 Hz, 1 H), 7.21 (t, *J*=7.7 Hz, 1 H), 7.06 (s, 1 H), 5.70 (s, 1 H), 4.17 (d, *J*=15.2 Hz, 1 H), 3.96 (d, *J*=15.4 Hz, 1 H), 3.84 - 3.93 (m, 1 H), 3.70 - 3.77 (m, 1 H), 3.68 (s, 3 H), 3.32 - 3.40 (m, 1 H), 3.22 - 3.32 (m, 1 H), 3.06 - 3.13 (m, 2 H), 2.95 - 3.05 (m, 2 H), 2.80 - 2.90 (m, 1 H), 2.51 (br. s., 1 H), 2.09 (s, 3 H), 1.90 - 2.06 (m, 2 H), 1.56 - 1.70 (m, 1 H), 1.42 - 1.55 (m, 1 H), 1.22 (d, *J*=7.1 Hz, 6 H), 1.18 (d, *J*=6.1 Hz, 3 H); MS (ESI+) *m/z* 500.3 $(M+H)^+$.

Ejemplo 39

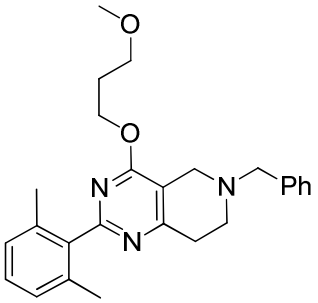
39- A. 6- bencil- 2- cloro- 4- (3- metoxipropoxi) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.



A una solución de 3- metoxipropan- 1- ol (0.500 ml, 5.23 mmol) en t- butanol (5 ml) se añadió una dispersión al 60% de NaH en aceite (70 mg, 1.75 mmol). La suspensión resultante se dejó en agitación durante 30 minutos tiempo en el cual se colocó la reacción a 0 °C y se cargado con 6- bencil- 2 ,4- dicloro- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (CAS# 778574- 06- 4, 300 mg, 1.02 mmol) como una solución en THF (1.5 ml). Después de 20 minutos la mezcla se inactivó con NH4Cl acuosa saturada, y se diluyó con acetato de etilo y agua. Las capas se separaron a continuación y la capa orgánica se lavó con salmuera y se secó sobre Na2SO4, se filtró y se concentró. El residuo resultante se purificó mediante cromatografía

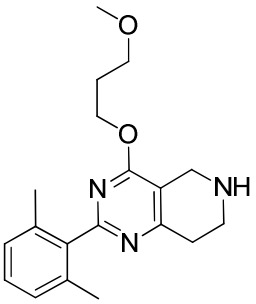
ultrarrápida en gel de sílice para proporcionar 6- bencil- 2- cloro- 4- (3- metoxipropoxi) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina. MS (ESI+) m/z 348.1 (M+H)+.

39- B. 6- Bencil- 2- (2,6- dimetilfenil) - 4 - (3- metoxipropoxi) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.



El compuesto del título se preparó a partir de 6- bencil- 2- cloro- 4- (3- metoxipropoxi) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina proporcionada siguiendo el procedimiento descrito en el **Ejemplo 16**. MS (ESI+) m/z 418.1 (M+H)+.

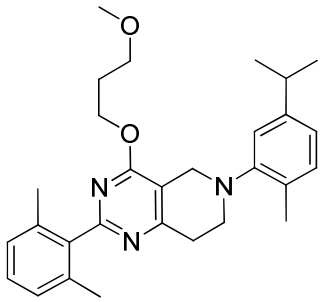
39- C. 2 - (2,6- dimetilfenil) - 4 - (3- metoxipropoxi) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.



A una solución de 6- bencil- 2- (2,6- dimetilfenil) - 4 - (3- metoxipropoxi) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina (170 mg, 0.41 mmol) en THF (3.5 ml) se añadió agua (0.5 ml) y ácido acético (0.070 ml, 1.22 mmol). La mezcla de reacción se colocó bajo atmósfera de argón y después se cargó con $Pd(OH)_2$ 20% molar/carbono (50% húmedo, 114 mg, 0.081 mmol). Luego la atmósfera se reemplazó con gas hidrógeno a través de un globo y se dejóen agitación durante 5 horas. Luegola mezcla se neutralizó con bicarbonato sódico acuoso saturado, se diluyó con diclorometano y se filtró a través de una almohadilla de Celite ®. El eluyente se diluyó adicionalmente con diclorometano y bicarbonato sódico acuoso saturado ylas capas se separaron. La capa acuosa se extrajo dos veces más con diclorometano. Las capas orgánicas se combinan, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo

resultante se purificó mediante cromatografía ultrarrápida en gel de sílice [7- 20% ($NH_3$2 M en MeOH)/DCM] para proporcionar 2 - (2,6- dimetilfenil) - 4 - (3- metoxipropoxi) - 5,6,7 ,8- tetrahidropirido [4,3- d] pirimidina. MS (ESI+) m/z 328.3 (M+H)+.

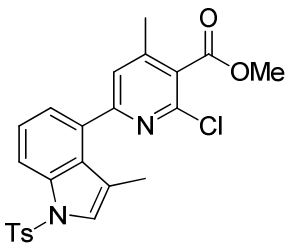
39- D.2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-(3-metoxipropoxi)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina.



A trifluorometanosulfonato de 5- isopropil- 2- metilfenilo, preparado como se describe en el **Ejemplo 15** (153 mg, 0.541 mmol) en un vial de microondas se añadió una solución de 2 - (2,6- dimetilfenil) - 4 - (3- metoxipropoxi) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina en THF (4 ml). Luego, se añadió Cs_2CO_3 (235 mg, 0.721 mmol) y la mezcla de reacción se degasifico a través de una serie deciclos de argón/vacío. Luego la mezcla de reacción se cargó con (CAS # 1028206- 56- 5, 26.6 mg, 0.036 mmol). Luego el recipiente se selló y se calentó a través de irradiación de microondas a 140 °C durante 90 minutos. Luego la reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo y agua. Las capas se separaron y la capa acuosa se extrajo una vez más con acetato de etilo. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4 filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida de gel de sílice (5- 50% acetato de etilo/heptanos) para proporcionar 2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-(3-metoxipropoxi)-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidina.^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 1,25 (d, J = 7,1 Hz, 6 H) 2.08 (quin, J = 6,3 Hz, 2 H) 2,28 (s, 6 H) 2,49 (s, 3 H) 2,92 (dt, J = 13,8, 6,9 Hz, 1 H) 3,28 (s, 3 H) 3,49 (t, J = 5,9 Hz, 2 H) 3,58 (t, J = 5,7 Hz, 2 H) 3,81 (t, J = 5,6 Hz, H 2) 4,37 (s, 2 H) 4,71 (t, J = 6,4 Hz, 2 H) 7,12 (dd, J = 7,7, 1,4 Hz, 1 H) 7,17 (s, 1 H) 7.20 - 7.27 (m , 3 H) 7.36- 7.41 (m, 1 H), MS (ESI+) de m/z 460.4 (M+H)+.

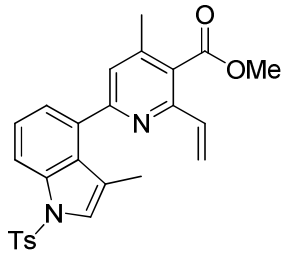
Ejemplo 40

40- A. 2- cloro- 4- metil- 6- (3- metil- 1- tosil- 1H- indol- 4- il) nicotinato de metilo



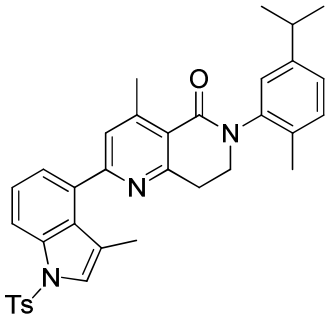
Una mezcla de 2,6- dicloro- 4- metilnicotinato de metilo (0.250 g, 1.14 mmol), 3- metil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il) - 1- tosil- 1H- indol (**Ejemplo 6**) (0.514 g, 1.25 mmol), $Pd(Ph_3P)_4$ (0.131 g, 0.114 mmol), y CsF (0.345 g, 2.27 mmol), en DMF (5 ml) se calentó a 110 °C durante 6 h. En ese momento el recipiente se retiró del baño de aceite y se dejó enfriar a temperatura ambiente. La mezcla se diluyó con salmuera (50 mL) y acetato de etilo (50 mL). Luego las capas se mezclaron y se separaron. La capa acuosa se extrajo adicionalmente con AcOEt (50 mL) y las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. Luego el residuo se purificó a través de FCC (0- 10% EtOAc/heptano) para proporcionar el compuesto del título. MS ESI m/z 469.0 y 470.9 (M H)+.

40- B. 4- metil- 6- (3- metil- 1- tosil- 1H- indol- 4- il)- 2- vinilnicotinato de metilo



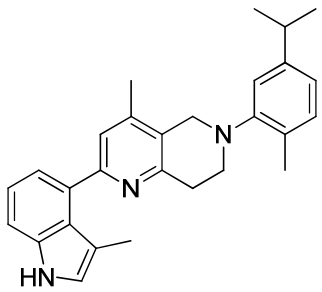
Una solución de 2- cloro- 4- metil- 6- (3- metil- 1- tosil- 1H- indol- 4- il) nicotinato de metilo (0.348 g, 0.742 mmol) en DMF (5 mL) se roció con argón durante 10 min antes de añadir trans- $Pd(PPh_3)_2Cl_2$ (0.052 g, 0.074 mmoles), tri- n- butilo (vinilo) estaño (0,353 g, 1,11 mmol), y BHT (0.016 g, 0.074 mmol). La suspensión resultante se roció con argón durante 5 min y el recipiente se selló y se calentó a 60 °C. Después de 24 h, la reacción se dejó enfriar a temperatura ambiente y se añadió 50% de KF sobre Celite ®. Luego la suspensión resultante se filtró a través de Celite ® eluyendo con EtOAc. Luegola fase orgánica se lavó con KF al 10% en agua y luego se secó (Na_2SO_4), se filtró y se concentró. Luego el residuo se purificómediante FCC (5- 40% EtOAc/heptano) para proporcionar el compuesto del título. MS ESI m/z 461.1 (M+H)+.

40- C. 6-(5-Isopropil-2-metilfenil)-4-metil-2-(3-metil-1-tosil-1H-indol-4-il)-7,8-dihidro-1,6-naftiridin-5(6H)-ona.



Una solución de 4- metil- 6- (3- metil- 1- tosil- 1H- indol- 4- il)- 2- vinilnicotinato de metilo (0.19 g, 0.413 mmol), y 5- isopropil- 2- metilanilina (0.074 g , 0.495 mmol) en AcOH (5 mL) se calentó a 110 °C durante 18 h. En ese momento, la reacción se concentró bajo presión reducida. Luego el residuo se adsorbio en DCM (25 mL) y se lavó con NaOH 1 M acuoso (25 mL). La capa acuosa se extrajo adicionalmente con DCM (2 x 25 mL) y las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. Luego el residuo se purificómediante FCC (20 - 65% EtOAc/heptano) para proporcionar el compuesto del título. MS ESI m/z 578.3 (M+H)+.

40- D. 6-(5-Isopropil-2-metilfenil)-4-metil-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina.

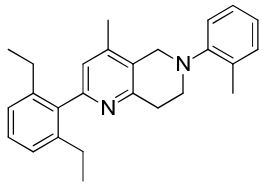
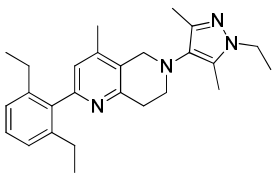
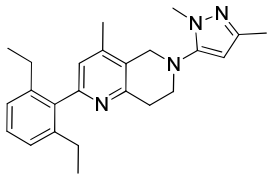


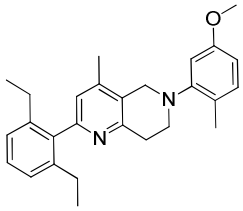
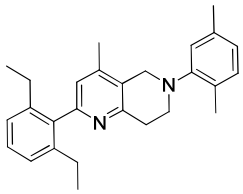
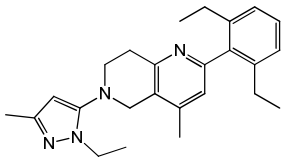
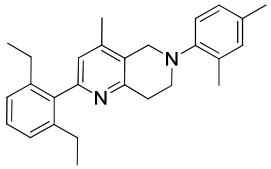
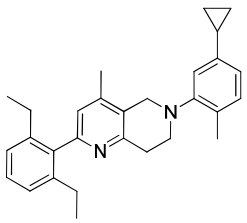
A una solución de 6-(5-isopropil-2-metilfenil)-4-metil-2-(3-metil-1-tosil-1H-indol-4-il)-7,8-dihidro-1,6-naftiridin-5(6H)-ona (0.156 g, 0.270 mmol) en THF (5 mL) a temperatura ambiente se añadió LiAlH4 (5.40 ml, 1 M en THF). La mezcla de reacción se dejó agitar a temperatura ambiente hasta que la conversión se consideró completa según se determinó por LCMS. La reacción se apagó con agua y luego NaOH acuoso1 M. Luego la mezcla se extrajo con DCM. Luego la capa orgánica se secó (Na_2SO_4), se filtró y se concentró. Luego el residuo se purificómediante FCC (10- 60% EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 10,88 (br. s., 1 H.), 7,38 (d, J = 8,1 Hz, 1 H), 7,21 (s, 1

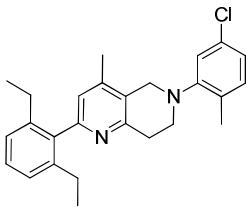
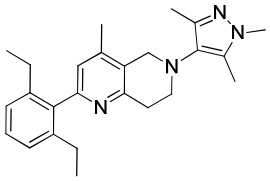
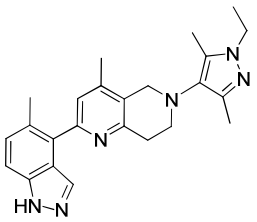
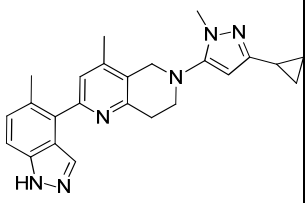
H), 7,05 - 7,17 (m, 4 H), 6,96 (d, J = 6,3 Hz, 1 H), 6,90 (d, J = 8,8 Hz, 1 H), 4,10 (s, 2 H), 3,21 - 3,37 (m, 2 H), 3,01 - 3,09 (m, 2 H), 2,81 - 2,92 (m, 1 H), 2,30 (s, 3 H), 2,28 (s, 3 H), 1,89 (s, 3 H), 1,21 (d, J = 7,1 Hz , 6 H), MS ESI m/z 410.4 (M+H)+.

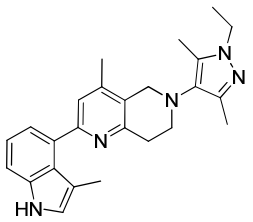
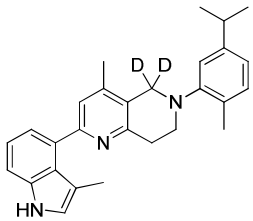
Para la preparación de compuestos deuterados $LiAlD_4$ se utilizó en un método similar en lugar de $LiAlH_4$.

Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos MS (ESI) *m/z*$(M+H)^+$
40-E		2-(2,6-dietilfenil)-4-metil-6-(o-tolil)-5,6,7,8-tetrahidro-1,6-naftiridina. Sal de TFA. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39 – 7.41 (m, 1 H), 7.25 – 7.29 (m, 3 H), 7.18 – 7.21 (m, 3 H), 7.09 – 7.13 (m, 1 H), 4.18 (s, 2 H), 3.56 (br t, *J* = 5.68 Hz, 2 H), 3.34 (br t, *J* = 5.68 Hz, 2 H), 2.52 – 2.41 (m, 5 H), 2.37 (s, 3 H), 2.18 – 2.28 (m, 2 H), 1.11 (t, *J* = 7.58 Hz, 6 H); MS (ESI+) *m/z*371.17 $(M+H)^+$.
40-G		2-(2,6-dietilfenil)-6-(1-etil-3,5-dimetil-1H-pirazol-4-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. 2-(2,6-dietilfenil)-6-(1-etil-3,5-dimetil-1H-pirazol-4-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.31 (m, 1 H) 7.12 (d, *J*=7.58 Hz, 2 H) 6.96 (s, 1 H) 4.06 (s, 2 H) 3.93 (q, *J*=7.16 Hz, 2 H) 3.29 (obs , 2 H,) 2.93 (t, *J*=5.56 Hz, 2 H) 2.25 (q, *J*=7.41 Hz, 4 H) 2.19 (s, 6 H) 2.16 (s, 3 H) 1.26 (t, *J*=7.20 Hz, 3 H) 0.98 (t, *J*=7.45 Hz, 6 H); MS (ESI+) *m/z* 403.3 $(M+H)^+$.
40-H		2-(2,6-dietilfenil)-6-(1,3-dimetil-1H-pirazol-5-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.12 (d, *J*=7.58 Hz, 2 H) 7.00 (s, 1 H) 5.81 (s, 1 H) 4.08 (s, 2 H) 3.63 (s, 3 H) 3.23 (t, *J*=5.81 Hz, 2 H) 3.03 (t, *J*=5.68 Hz, 2 H) 2.22 - 2.28 (m, 7 H) 2.10 (s, 3 H) 0.98 (t, *J*=7.45 Hz, 6 H); MS (ESI+) *m/z* 375.4 $(M+H)^+$.

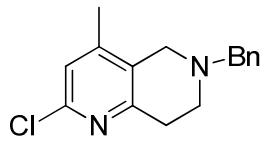
40-I		2-(2,6-dietilfenil)-6-(5-metoxi-2-metilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.25 - 7.29 (m, 1 H) 7.13 (d, *J*=7.58 Hz, 3 H) 6.99 (s, 1 H) 6.80 (d, *J*=2.53 Hz, 1 H) 6.61 (dd, *J*=8.34, 2.53 Hz, 1 H) 4.09 (s, 2 H) 3.74 (s, 3 H) 3.23 (t, *J*=5.68 Hz, 2 H) 3.01 (t, *J*=5.56 Hz, 2 H) 2.22 - 2.30 (m, 10 H) 0.99 (t, *J*=7.58 Hz, 6 H); MS (ESI+) *m/z* 401.3 $(M+H)^+$.
40-J		2-(2,6-dietilfenil)-6-(2,5-dimetilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.25 - 7.30 (m, 1 H) 7.05 - 7.15 (m, 4 H) 6.99 (s, 1 H) 6.83 (d, *J*=7.58 Hz, 1 H) 4.09 (s, 2 H) 3.21 (t, *J*=5.68 Hz, 2 H) 3.02 (t, *J*=5.43 Hz, 2 H) 2.23 - 2.31 (m, 13 H) 0.99 (t, *J*=7.58 Hz, 6 H); MS (ESI+) *m/z* 385.4 $(M+H)^+$.
40-K		2-(2,6-dietilfenil)-6-(1-etil-3-metil-1H-pirazol-5-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.12 (d, *J*=7.58 Hz, 2 H) 7.00 (s, 1 H) 5.83 (s, 1 H) 4.07 (s, 2 H) 3.96 (q, *J*=7.33 Hz, 2 H) 3.21 (t, *J*=5.68 Hz, 2 H) 3.02 (t, *J*=5.81 Hz, 2 H) 2.19 - 2.29 (m, 7 H) 2.12 (s, 3 H) 1.33 (t, *J*=7.20 Hz, 3 H) 0.98 (t, *J*=7.45 Hz, 6 H); MS (ESI+) *m/z* 389.4 $(M+H)^+$.
40-L		2-(2,6-dietilfenil)-6-(2,4-dimetilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.10 - 7.19 (m, 3 H) 6.97 - 7.07 (m, 3 H) 4.05 (s, 2 H) 3.19 (t, *J*=5.68 Hz, 2 H) 3.01 (t, *J*=5.56 Hz, 2 H) 2.22 - 2.31 (m, 13 H) 0.99 (t, *J*=7.58 Hz, 6 H); MS (ESI+) *m/z* 385.4 $(M+H)^+$.
40-M		6-(5-ciclopropil-2-metilfenil)-2-(2,6-dietilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.25 - 7.30 (m, 1 H) 7.07 - 7.16 (m, 3 H) 6.96 - 7.01 (m, 2 H) 6.69 (dd, *J*=7.71, 1.64 Hz, 1 H) 4.10 (s, 2 H) 3.23 (t, *J*=5.68 Hz, 2 H) 2.99 (t, *J*=5.56 Hz, 2 H) 2.22 - 2.31 (m, 10 H) 1.89 (tt, *J*=8.37, 5.02 Hz, 1 H) 0.99 (t, *J*=7.58

		Hz, 6 H) 0.87 - 0.94 (m, 2 H) 0.60 - 0.66 (m, 2 H); MS (ESI+) *m/z* 411.4 $(M+H)^+$.
40-N		6-(5-cloro-2-metilfenil)-2-(2,6-dietilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.23 - 7.30 (m, 3 H) 7.13 (d, *J*=7.58 Hz, 2 H) 7.07 (dd, *J*=8.08, 2.27 Hz, 1 H) 7.00 (s, 1 H) 4.14 (s, 2 H) 3.24 (t, *J*=5.81 Hz, 2 H) 3.03 (t, *J*=5.56 Hz, 2 H) 2.23 - 2.31 (m, 10 H) 0.99 (t, *J*=7.45 Hz, 6 H); MS (ESI+) *m/z* 405.2 $(M+H)^+$.
40-O		2-(2,6-dietilfenil)-4-metil-6-(1,3,5-trimetil-1H-pirazol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.29 (m, 1 H) 7.12 (d, *J*=7.58 Hz, 2 H) 6.96 (s, 1 H) 4.06 (s, 2 H) 3.60 (s, 3 H) 3.29 (s, 2 H) 2.93 (t, *J*=5.56 Hz, 2 H) 2.25 (q, *J*=7.58 Hz, 4 H) 2.19 (d, *J*=4.29 Hz, 6 H) 2.14 (s, 3 H) 0.98 (t, *J*=7.58 Hz, 6 H); MS (ESI+) *m/z* 389.4 $(M+H)^+$.
40-P		6-(1-etil-3,5-dimetil-1H-pirazol-4-il)-4-metil-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.97 (br. s., 1 H) 7.76 (s, 1 H) 7.46 (d, *J*=8.34 Hz, 1 H) 7.28 (d, *J*=8.59 Hz, 1 H) 7.23 (s, 1 H) 4.08 (s, 2 H) 3.94 (q, *J*=7.07 Hz, 2 H) 3.33 - 3.36 (m, 2 H) 3.02 (t, *J*=5.43 Hz, 2 H) 2.36 (s, 3 H) 2.24 (s, 3 H) 2.20 (s, 3 H) 2.18 (s, 3 H) 1.27 (t, *J*=7.20 Hz, 3 H); MS (ESI+) *m/z* 401.3 $(M+H)^+$.
40-Q		6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-4-metil-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.99 (s, 1 H) 7.76 (s, 1 H) 7.47 (d, *J*=8.34 Hz, 1 H) 7.25 - 7.31 (m, 2 H) 5.76 (s, 1 H) 4.09 (s, 2 H) 3.62 (s, 3 H) 3.25 (t, *J*=5.81 Hz, 2 H) 3.10 (t, *J*=5.56 Hz, 2 H) 2.36 (s, 3 H) 2.29 (s, 3 H) 1.74 - 1.83 (m, 1 H) 0.77 - 0.84 (m, 2 H) 0.59 - 0.65 (m, 2 H); MS (ESI+) *m/z* 399.3 $(M+H)^+$.

40-R		6-(1-etil-3,5-dimetil-1H-pirazol-4-il)-4-metil-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.88 (br. s., 1 H) 7.38 (d, *J*=8.08 Hz, 1 H) 7.18 (s, 1 H) 7.08 - 7.13 (m, 2 H) 6.92 - 6.96 (m, 1 H) 4.06 (s, 2 H) 3.93 (q, *J*=7.07 Hz, 2 H) 3.31 - 3.35 (m, 2 H) 2.98 (t, *J*=5.31 Hz, 2 H) 2.22 (s, 3 H) 2.19 (s, 3 H) 2.16 (s, 3 H) 1.89 (s, 3 H) 1.27 (t, *J*=7.33 Hz, 3 H); MS (ESI+) *m/z* 400.4 $(M+H)^+$.
40-S		^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.89 (br. s., 1 H), 7.38 (d, *J*=7.8 Hz, 1 H), 7.21 (s, 1 H), 7.12 (t, *J*=6.9 Hz, 2 H), 7.08 (s, 2 H), 6.96 (d, *J*=7.1 Hz, 1 H), 6.89 (d, *J*=7.6 Hz, 1 H), 3.26 (t, *J*=5.6 Hz, 2 H), 3.04 (t, *J*=5.4 Hz, 2 H), 2.86 (dt, *J*=13.8, 6.9 Hz, 1 H), 2.30 (s, 3 H), 2.27 (s, 3 H), 1.89 (s, 3 H), 1.21 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 412.3 $(M+H)^+$.

Ejemplo 41

41- A. 6- Bencil- 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina.

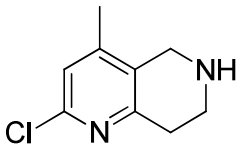


Una mezcla de 1- bencil- 4- piperidona (19.6 ml, 106 mmol), acetoacetamida (11.7 g, 116 mmol) en reactivo de Eaton (40 mL) se dejó en agitación a 110 °C. Después de agitar durante 18 h, la mezcla de reacción se enfrió a temperatura ambiente, y luego ase vertió lentamente en $NaHCO_3$ acuoso agitado (150 g de $NaHCO_3$ en 1000 mL de agua. La mezcla se diluyó con DCM (1000 mL) y H_2O (50 mL), y las dos fases se separaron. Los productos se extrajeron una vez más con DCM (500 mL)a partir de la capa acuosa. La capa orgánica combinada se lavó con salmuera (500 mL), se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. El residuomarrón se trituró con acetona (200 mL) Elprecipitado sólido se recolectó en un embudo, se lavó con acetona (100 mL), y se secó bajo presión reducida para proporcionar 6- bencil- 4- metil- 5, 6,7,8. - tetrahidro- 1 ,6- naftiridin- 2- ol. ^{1}H RMN (400 MHz, $CDCl_3$)δ 12,71 ppm (br. s., 1 H), 7,26 - 7,35 (m, 5 H), 6,22 (s, 1 H), 3,71 (s, 2 H), 3,34 (s, 2 H), 2,70 - 2,73 (m, 2 H), 2,77 - 2,79 (m, 2 H), 2,03 (s, 3 H), MS (ESI+) m/z 255.42 (M+H)+.

Una solución de 6- bencil- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridin- 2- ol (13.6 g, 53.5 mmol), cloruro de benciltrietilamonio (24.4 g, 107 mmol) y $POCl_3$ (100 mL, 1069 mmol)

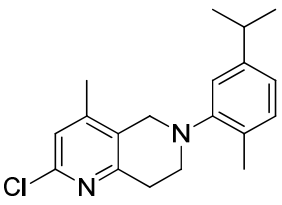
se dejó en agitación a 105 °C. Después de agitar durante 18 h, la mezcla se enfrió a temperatura ambiente, y se diluyó con EtOAc (100 mL). El precipitado se recolectó en un embudo, se lavó con EtOAc (200 ml), y luego se secó bajo presión reducida para proporcionar bencil- 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina como una sal de dihidrocloruro. ^{1}H RMN (400 MHz, DMSO- d_6) δ 12,02 ppm (br. s., 1 H), 7,71 - 7,73 9m, 2 H), 7,48 - 7,49 (m, 3 H), 7,34 (s, 1 H), 4,21 - 4,57 (m, 4 H), 3,60 - 3,62 (m, 1 H), 3,28 - 3,37 (m, 2 H), 3,02 - 3,05 (m, 1 H), 2,19 (s, 3 H), MS (ESI+) m/z 273.33 (M+H)+.

41- B. Hidrocloruro de 2- Cloro- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina.



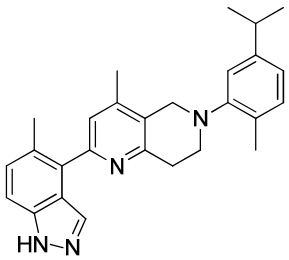
A una suspensión dedihidrocloruro de bencil- 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina cruda(8.00 g, 23.1 mmol) en DCM (100 mL), se añadió 2 M Na_2CO_3 acuoso (50 mL). La mezcla se agitó durante 20 min, y luego se diluyó con salmuera. Los productos se extrajeron dos veces más con DCM, y la capa orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró para proporcionarcrudo (6.14 g). Una solución del residuo y ACECl (5.05 ml, 46.3 mmol) en DCE (100 mL) se dejó en agitación a 70 °C durante 1.5 h bajo nitrógeno. Se añadió MeOH (50 mL) y la mezcla se agitó a la misma temperatura durante 1 h. La mezcla se enfrió a temperatura ambiente y se concentró. El residuo se trituró con MeOH (10 ml) y acetato de etilo (400 mL), y el sólido blanco se recolectó en un embudo, se lavó con EtOAc (200 mL), y se secó bajo presión reducida para proporcionarhidrocloruro de 2- cloro- 4- metil- 5,6,7,8- tetrahidro- 1 ,6- naftiridina (4,54 g): ^{1}H RMN (400 MHz, DMSO- d_6) δ 9,54 ppm (br. s., 2 H), 7,33 (s, 1 H), 4,21 - 4,24 (app t, 2 H), 3,41 - 3,43 (m, 2 H), 3,05 (t, J = 6,57 Hz, 2 H), 2,24 (s, 3 H), MS (ESI+) m/z 183.44 (M+H)+.

41- C. 2- Cloro- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina.



A una suspensión de clorhidrato de 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina (4.03 g, 18.39 mmol) en DCM (100 ml), se añadió Na_2CO_3acuoso 2 M (100 mL). Después de agitar durante 30 min, la mezcla se diluyó con salmuera (200 ml). Los productos se extrajeron dos veces más con DCM. La capa orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. Una suspensión del residuo (3.25 g), trifluorometanosulfonato de 5- isopropil- 2- metilfenilo(11.42 g, 40.5 mmol), aducto de $Pd_2(dba)_3.CHCl_3$(0.762 g, 0.736 mmol), rac- BINAP (0.945 g, 1.471 mmol) y Cs_2CO_3 (17.98 g, 55.2 mmol) en tolueno (17 ml) y t- butanol (3 mL) se dejó en agitación a 90 °C durante 23 h en atmósfera de argón. La reacción se enfrió a temperatura ambiente, y se diluyó con EtOAc y salmuera. Los productos se extrajeron tres veces con EtOAc. La capa orgánica combinada se secó sobre Na_2SO_4, y se filtró. Se añadió el filtrado a 60 g de gel de sílice y luego se concentró. El residuo se lavó con EtOAc en un embudo, y luego el filtrado se concentró. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 330 g de gel de sílice (con 25 g de pre- columna; eluyente: heptano/acetato de etilo = 100:0 a 80:20) para proporcionar el producto deseado, junto con 18% molar de carvacrol (2.97 g). La mezcla se purificó mediante cromatografía ultrarrápida en columna sobre 55 g de gel de sílice de NH- modificado (con 20 g de gel de aminopropil- modificado Silca como pre- columna; eluyente: heptano/acetato de etilo = 100:0 a 90:10) para proporcionar 2 - cloro- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina (2.50 g) como un aceite de color amarillo: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,16 (d, J = 7,83 Hz, 1 H), 6,99 - 7,00 (m, 2 H), 6,92 - 6,95 (m, 1 H), 3,98 (s, 2 H), 3,28 (t, J = 5,81 Hz , 2 H), 3,12 (br. t, J = 5,68 Hz, 2 H), 2,84 - 2,94 (m, 1 H), 2,29 (s, 3 H), 2,20 (s, 3 H), 1,26 (d, J = 6,82 Hz, 6 H), MS (ESI+) m/z 315.34 (M+H)+.

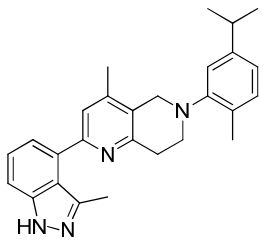
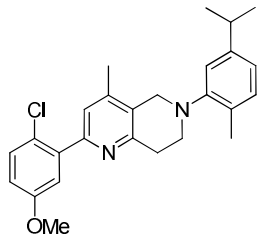
41- D.6-(5-Isopropil-2-metilfenil)-4-metil-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina.

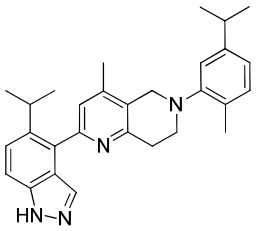
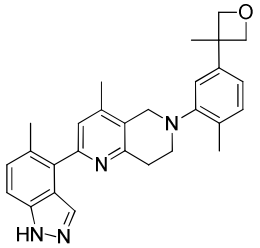
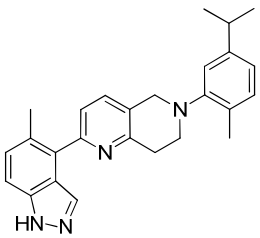


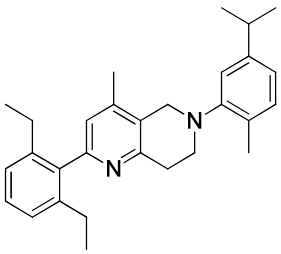
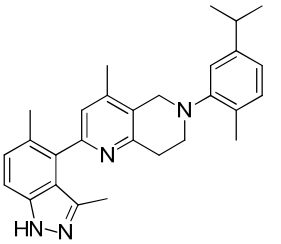
Una mezcla de 2- cloro- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina (2.50 g, 7.94 mmol), ácido 5- metil- 1H- indazol- 4- ilboronico(1.817 g, 10.32 mmol), $Pd(PPh_3)4$ (0.918 g, 0.794 mmol) y K_3PO_4 (3.37 g, 15.88 mmol) en 1,4- dioxano (30 mL) y H_2O (3 ml) se calentó a 130 °C durante 1 h en atmósfera de nitrógeno en un reactor de

microondas. La mezcla se concentró y se diluyó con EtOAc y salmuera. Los productos se extrajeron dos veces con EtOAc. La capa orgánica combinada se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó dos veces mediante cromatografía ultrarrápida en columna sobre 120g de gel de sílice (con 25 g de gel de sílice pre-columna; eluyente: heptano/acetato de etilo = 75:25 a 30:70) para proporcionar un sólido amarillo. El sólido amarillo se suspendió con 25 g de gel de sílice aminopropil- modificado en DCM, y la suspensión se concentró. El residuo se cargó en 55 g de gel de NH- sílice y se purificó mediante cromatografíaultrarrápida en columna (eluyente: heptano/acetato de etilo = 75:25 a 25:75) para proporcionar el producto deseado (2.50 g). El producto se trituró en CH_3CN/H_2O, se recolectó en un embudo y se secó bajo presión reducida para proporcionar 6-(5-isopropil-2-metilfenil)-4-metil-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina (2.23 g) como un sólido blanco: ^{1}H RMN (400 MHz, $CDCl_3$) δ 10,03 ppm (br. s., 1 H), 7,90 (d, J = 0,67 Hz, 1 H), 7,40 (dd, J = 0,67, 8,50 Hz, 1 H), 7,32 (d, J = 8,50 Hz, 1 H) , 7,19 (d, J = 7,75 Hz, 1 H), 7,16 (s, 1 H), 7,08 (d, J = 1,60 Hz, 1 H), 6,94 - 6,97 (dd, J = 1,60, 7,75 Hz, 1 H), 4,14 (s, 2 H), 3,38 (br t, J = 5,68 Hz, 2 H), 3,26 (br t, J = 5,69 Hz, 2 H), 2,87 - 2,98 (m, 1 H), 2,44 (s, 3 H), 2,37 (s, 3 H), 2,31 (s, 3 H), 1,29 (d, J = 6,82 Hz, 6 H), MS (ESI+) m/z 411.33 (M+H)+.

Los siguientes compuestos se prepararon de una manera similar.

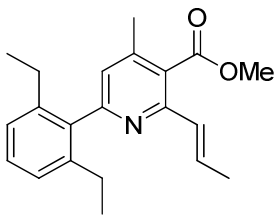
	Estructura	Nombre Quimico y Datos Analiticos MS (ESI) *m/z*$(M+H)^+$
41-E		6-(5-isopropil-2-metilfenil)-4-metil-2-(3-metil-1H-indazol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina. Sal de TFA^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32 – 7.42 (m, 4 H), 7.22 (d, *J* = 7.83 Hz, 1 H), 7.06 (d, *J* = 1.77 Hz, 1 H), 7.00 – 7.02 (m, 1 H), 4.19 (s, 2 H), 3.66 (app t, 2 H), 3.41 (br t, *J* = 5.68 Hz, 2 H), 2.88 – 2.98 (m, 1 H), 2.49 (s, 3 H), 2.35 (s, 3 H), 2.22 (s, 3 H), 1.29 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z*411.26 $(M+H)^+$.
41-F		2-(2-cloro-5-metoxifenil)-6-(5-isopropil-2-metilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35(d, *J* = 8.84 Hz, 1 H), 7.28 (s, 1 H), 7.18 (d, *J* = 7.83 Hz, 1 H), 7.10(d, *J* = 3.28 Hz, 1 H), 7.05 (d, *J* = 1.77 Hz, 1 H), 6.94 (dd, *J* = 1.77, 7.83 Hz, 1 H), 6.86 (dd, *J* = 3.28, 8.84 Hz, 1 H), 4.09 (s, 2 H), 3.83 (s, 3

		H), 3.34 (br t, *J* = 5.68 Hz, 2 H), 3.24 (br t, *J* = 5.68 Hz, 2 H), 2.89 – 2.97 (m, 1 H), 2.34 (s, 3 H), 2.28 (s, 3 H), 1.28 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z*421.30 $(M+H)^+$.
41-G		2-(5-isopropil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79 (s, 1 H), 7.45 – 7.50 (m, 2 H), 7.20(d, *J* = 7.75 Hz, 1 H), 7.11 (s, 1 H), 7.08 (d, *J* = 1.60 Hz, 1 H), 6.96 (dd, *J* = 1.60, 7.75 Hz, 1 H), 4.15 (s, 2 H), 3.38 (br t, *J* = 5.68 Hz, 2 H), 3.18 – 3.26 (m, 3 H), 2.88 – 2.98 (m, 1 H), 2.38 (s, 3 H), 2.31 (s, 3 H), 1.29 (d, *J* = 6.82 Hz, 6 H), 1.26 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z*439.3 $(M+H)^+$.
41-H		4-metil-2-(5-metil-1H-indazol-4-il)-6-(2-metil-5-(3-metiloxetan-3-il)fenil)-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.01 (br s, 1 H), 7.78(app t, 1 H), 7.47 (dd, *J* = 1.01, 8.51 Hz, 1 H), 7.29 (d, *J* = 8.51 Hz, 1 H), 7.27 (s, 1 H), 7.21 (d, *J* = 7.83 Hz, 1 H), 7.08 (d, *J* = 1.94 Hz, 1 H), 6.89 (dd, *J* = 1.94, 7.83 Hz, 1 H), 4.83 (d, *J* = 5.56 Hz, 2 H), 4.55 (d, *J* = 5.56 Hz, 2 H), 4.13 (s, 2 H), 3.30 (br t, *J* = 5.81 Hz, 2 H), 3.10 (br t, *J* = 5.56 Hz, 2 H), 2.37 (s, 3 H), 2.32 (s, 3 H), 2.31 (s, 3 H), 1.65 (s, 3 H); MS (ESI+) *m/z*439.44 $(M+H)^+$.
41-I		6-(5-isopropil-2-metilfenil)-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.98 (br s, 1 H), 7.91(d, *J* = 1.26 Hz, 1 H), 7.53 (d, *J* = 7.83 Hz, 1 H), 7.42 (dd, *J* = 1.01, 8.59 Hz, 1 H), 7.30 – 7.34 (m, 2 H), 7.18(d, *J* = 7.66 Hz, 1 H), 7.03 (d, *J* = 1.94 Hz, 1 H), 6.94 (dd, *J* = 1.94, 7.66 Hz, 1 H), 4.24 (s, 2 H), 3.39 (br t, *J* = 5.94 Hz, 2 H), 3.27 (br t, *J* = 5.68 Hz, 2 H), 2.86 – 2.96 (m, 1 H), 2.44 (s, 3 H), 2.37 (s, 3 H), 1.28 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z*397.3 $(M+H)^+$.

41-J		2-(2,6-dietilfenil)-6-(5-isopropil-2-metilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.31 (m, 1 H) 7.10 - 7.16 (m, 3 H) 7.07 (d, *J*=1.52 Hz, 1 H) 7.00 (s, 1 H) 6.89 (dd, *J*=7.58, 1.52 Hz, 1 H) 4.11 (s, 2 H) 3.21 - 3.28 (m, 2 H) 2.99 (app t, *J*=5.56 Hz, 2 H) 2.86 (spt, *J*=6.86 Hz, 1 H) 2.27 (s, 6 H) 2.22 - 2.31 (obs m, 4 H) 1.20 (d, *J*=6.82 Hz, 6 H) 0.99 (t, *J*=7.45 Hz, 6 H)MS (ESI+) *m/z* 413.3 $(M+H)^+$.
41-K		2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.55 (br. s., 1 H) 7.38 (d, *J*=8.34 Hz, 1 H) 7.23 (d, *J*=8.34 Hz, 1 H) 7.08 - 7.17 (m, 3 H) 6.90 (d, *J*=7.83 Hz, 1 H) 4.14 (s, 2 H) 3.25 - 3.30 (m, 2 H) 3.00 - 3.07 (m, 2 H) 2.82 - 2.90 (m, 1 H) 2.31 (s, 3 H) 2.28 (s, 3 H) 2.16 (s, 3 H) 1.78 (s, 3 H) 1.21 (d, *J*=6.82 Hz, 6 H); MS (ESI+) *m/z* 426.4 $(M+H)^+$.

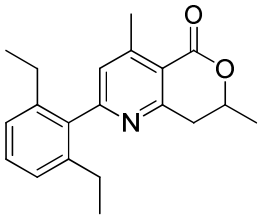
Ejemplo 42

42- A. 6 - (2,6- dietilfenil)- 4- metil- 2- (prop- 1- en- 1- il) nicotinato de (E)- metilo



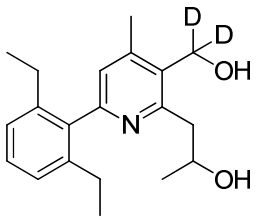
El compuesto del título se preparó por el método similar al descrito en el **Ejemplo 41** utilizando ácido (E)- prop- 1- en- 1- ilboronico. MS (ESI+) m/z 324.3 (M+H)+.

42- B. 2 - (2,6- dietilfenil) - 4,7- dimetil- 7 ,8- dihidro- 5H- pirano [4,3- b] piridin- 5- ona.



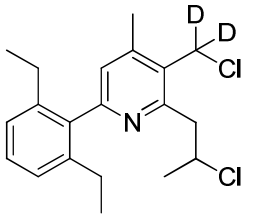
Una mezcla de 6 - (2,6- dietilfenil)- 4- metil- 2- (prop- 1- enil) nicotinato de (E)- metilo (150 mg, 0.464 mmol), H_2O (0.17 ml, 9.28 mmol) y TFA (2.9 ml, 37.1 mmol) se calentó en un reactor de microondas a 160 °C durante 30 min. Se observó material de inicio. Se añadió adicional TFA (0.5 ml) y H_2O (0.05 ml) y se continuó el calentamiento a 160 °C durante 45 min y luego a 140 °C durante 2 h. La reacción se vertió entonces en $NaHCO_3$saturado y se extrajo con EtOAc. La capa orgánica se lavó con salmuera y después se secó sobre Na_2SO_4 y se concentró. Luego el residuo se purificó con FCC (0- 50% EtOAc/heptano) para proporcionar 2 - (2,6- dietilfenil) - 4,7- dimetil- 7 ,8- dihidro- 5H- pirano [4,3- b] piridin- 5- ona. MS (ESI+) m/z 310.3 (M+H)+.

42- C. 1 - (6 - (2,6- dietilfenil) - 3 - (hidroxi ($^2H_2$) metil)- 4- metilpiridina- 2- il) propan- 2- ol.



Una mezcla de 2 - (2,6- dietilfenil) - 4,7- dimetil- 7 ,8- dihidro- 5H- pirano [4,3- b] piridin- 5- ona (118 mg, 0.381 mmoles), borodeuterido de sodio (63.9 mg, 1.53 mmol) en THF/EtOH (2:1) (6 mL) se calentó a 60 °C durante 3 h. La reacción se diluyó con EtOAc y se filtró. El filtrado se concentró y se purificó con FCC (5- 60% EtOAc/heptano) para proporcionar 1 - (6 - (2,6- dietilfenil) - 3 - (hidroxilo (2H2) metil)- 4- metilpiridina- 2- il) propan- 2- ol. MS (ESI+) m/z 316.4 (M+H)+.

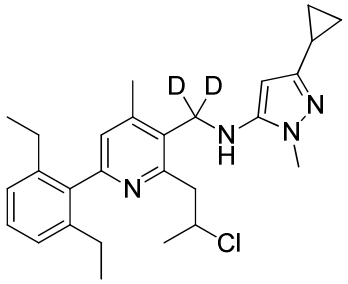
42 - D. 3 - (cloro (2H2) metil) - 2 - (2- cloropropil) - 6 - (2,6- dietilfenil)- 4- metilpiridina.



Una mezcla de 1 - (6 - (2,6- dietilfenil) - 3 - (hidroxi ($^2H_2$) metil)- 4- metilpiridina- 2- il) propan- 2- ol (99 mg, 0.314 mmol) y $SOCl_2$ (0.14 ml, 1.88 mmol) en DCM (5 mL) se agitó a temperatura ambiente durante 3 h. La reacción se vertiócuidadosamente en $NaHCO_3$ acuoso saturadoy se diluyó con EtOAc. Las capas se mezclaron y luego se separó. La capa orgánica se

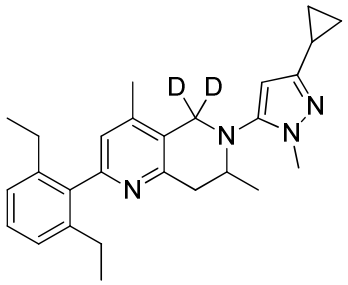
lavó con salmuera, se secó sobre Na_2SO_4, y se filtró. Luego el residuo, seguido de concentración, proporcionó 3 - (cloro (2H2) metil) - 2 - (2- cloropropil) - 6 - (2,6- dietilfenil)- 4- metilpiridinacrudo. MS (ESI+) m/z 352.2 (M+H)+.

42- E. N-((2-(2-Cloropropil)-6-(2,6-dietilfenil)-4-metilpiridin-3-il)($^2H_2$)metil)-3-ciclopropil-1-metil-1H-pirazol-5-amina.



Una mezcla de 3 - (cloro ($^2H_2$) metil) - 2 - (2- cloropropil) - 6 - (2,6- dietilfenil)- 4- metilpiridina (29.6 mg, 0.084 mmol), 3- ciclopropil- 1- metil- 1H- pirazol- 5- amina (57.6 mg, 0.420 mmol), NaI (37.8 mg, 0.252 mmol) y DIEA (0.044 ml, 0.252 mmol) en THF (3 ml) se agitó a temperatura ambiente durante 1 h. Luego la mezcla de reacción se calentó a 60 °C durante 4 h. Luego la reacción se diluyó con EtOAc, se lavó con soluciónacuoso saturada de $NaHCO_3$ y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante FCC (5- 100% EtOAc/heptano seguido por 0- 10% MeOH/DCM) para proporcionar N-((2-(2-cloropropil)-6-(2,6-dietilfenil)-4-metilpiridin-3-il)($^2H_2$)metil)-3-ciclopropil-1-metil-1H-pirazol-5-amina.MS (ESI+) m/z 453.3 (M+H)+.

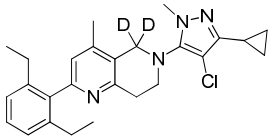
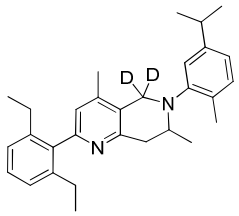
42- F. 6-(3-Ciclopropil-1-metil-1H-pirazol-5-il)-2-(2,6-dietilfenil)-4,7-dimetil-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina.



A una solución de N-((2-(2-cloropropil)-6-(2,6-dietilfenil)-4-metilpiridin-3-il)($^2H_2$)metil)-3-ciclopropil-1-metil-1H-pirazol-5-amina (14.2 mg, 0.031 mmol) en acetonitrilo (2 ml), se añadió DIEA (0.016 ml, 0.094 mmol) seguido de NaI (9.4 mg, 0.063 mmol). La mezcla se calentó en un reactor de microondas a 160 °C durante 30 min. En ese momento la reacción se diluyó con EtOAc y se lavó con solución $NaHCO_3$acuoso saturado y después con

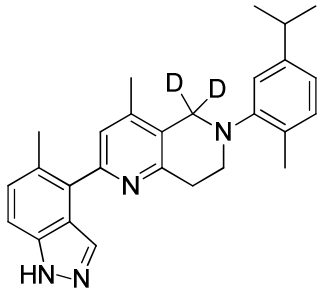
salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. Luego el residuo se purificó con FCC (5- 50% EtOAc/heptano) para proporcionar6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(2,6-dietilfenil)-4,7-dimetil-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina. racémico^{1}H RMN (400 MHz, CD_2Cl_2)δ ppm 7,23 - 7,32 (m, 1 H) 7,13 (d, J = 7,58 Hz, 2 H) 6,91 (s, 1 H) 5,67 (s, 1 H) 3,68 (s, 3 H) 3,41- 3,53 (m, 1 H) 3.15 - 3,29 (m, 1 H) 2,87 (dd, J = 17,05, 6,44 Hz, 1 H) 2.33 (q, J = 7,49 Hz, 4 H) 2,22 (s, 3 H) 1,84 (tt, J = 8,46, 5,05 Hz, 1 H) 1.1 - 1.8 (m, 9 H) .82 - 0,89 (m, 2 H), 0.63 - 0.69 (m, 2 H). MS (ESI+) m/z 417.4 (M+H)+. Dos enantimeros se obtuvieron por separación quiral (Columna OD 4.6 X 250 mm, EtOH al 5% en heptano). 42- G enanatiomero 1: R_t 9,26 min, MS (ESI+) m/z 417.3 (M+H)+; 42- H enanatiomero 1: R_t 12.62 min, MS (ESI+) m/z 417.3 (M+H)+.

Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos
42-I		6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(2,6-dietilfenil)-4-metil-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.45 (t, *J*=7.71 Hz, 1 H) 7.37 (s, 1 H) 7.23 (d, *J*=7.83 Hz, 2 H) 3.67 (s, 3 H) 3.53 - 3.60 (m, 2 H) 3.48 (t, *J*=5.56 Hz, 2 H) 2.37 - 2.50 (m, 5 H) 2.18 - 2.31 (m, 2 H) 1.79 - 1.91 (m, *J*=8.15, 8.15, 5.43, 5.31 Hz, 1 H) 1.10 (t, *J*=7.45 Hz, 6 H) 0.84 - 0.93 (m, 4 H). MS (ESI+) *m/z* 437.3 $(M+H)^+$.
42-J		**43-J** -2-(2,6-dietilfenil)-6-(5-isopropil-2-metilfenil)-4,7-dimetil-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina racémico.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 - 7.30 (m, 1 H) 7.09 - 7.17 (m, 4 H) 6.99 (s, 1 H) 6.91 (dd, *J*=7.71, 1.64 Hz, 1 H) 3.53 - 3.60 (m, 1 H) 3.13 (dd, *J*=16.93, 4.80 Hz, 1 H) 2.85 (dt, *J*=13.71, 6.92 Hz, 1 H) 2.67 - 2.75 (m, 1 H) 2.22 - 2.32 (m, 10 H) 1.16 - 1.23 (m, 6 H) 0.93 - 1.03 (m, 9 H); MS (ESI+) *m/z* 429.4 $(M+H)^+$. **43-K** ent-1 R_t 5.38 min, (Columna OD 4.6 X 250 mm, 5% EtOH en heptano). MS (ESI+) *m/z* 429.4 $(M+H)^+$ **43-L** ent-2R_t 6.50 min, Columna OD 4.6 X 250 mm, 5% EtOH en heptano). MS (ESI+) *m/z* 429.4 (M+H)

Ejemplo 43

43- A. . 6 - (5- isopropil- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- indazol- 4- il) - 5,6,7,8- tetrahidro (5,5- 2H2) - 1,6- naftiridina.



Una solución declorhidrato de 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina (3.10 g, 12.7 mmol), Boc_2O (3.06 g, 14.0 mmol) y DIPEA (3.34 ml, 19.1 mmol) en DCM (30 ml) se dejó en agitación a temperatura ambiente durante 45 min. La mezcla se diluyó con solución acuosa de ácido cítrico al 5% y DCM. La capa orgánica se separó en un embudo de separación, y se concentró. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 80 g de gel de sílice (con 25 g de gel de sílice pre- columna; eluyente: heptano/acetato de etilo = 100:0 a 50:50) para proporcionar2- cloro- 4- metil- 7,8- dihidro- 1 ,6- naftiridina- 6 (5H)- carboxilato de terc- butilo^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,02 (s, 1 H), 4,47 (s, 2 H), 3,71 (t, J = 5,81 Hz, 2 H), 2,95 (br. t, J = 5,68 Hz, 2 H), 2,23 (s, 3 H), 1,50 (s, 9 H), MS (ESI+) m/z 283.30 (M+H)+.

A una suspensión de tricloruro de rutenio (0.141 g, 0.681 mmol) y NaIO4 (8.32 g, 38.9 mmol) en H_2O (30 ml) a 0 °C,se añadió una solución de 2- cloro- 4- metil- 7, 8 - dihidro- 1 ,6- naftiridina- 6 (5H)- carboxilato de terc- butilo (2.75 g, 9.73 mmol) en EtOAc (30 ml). Después de agitar durante 5 min., La mezcla de reacción se calentó hasta temperatura ambiente y se agitó. Después de agitar durante 21.5 horas, la mezcla se diluyó con EtOAc y salmuera. La capa orgánica se separó, se secó sobre Na_2SO_4, se filtró y se concentró. El crudo se purificó mediante cromatografíaultrarrápida en columna sobre 80 g de gel de sílice (con 25 g de pre- columna de gel de sílice; eluyente: heptano/acetato de etilo = 100:0 a 70:30) para proporcionar2- cloro- 4- metil - 5- oxo- 7 ,8- dihidro- 1 ,6- naftiridina- 6 (5H)- carboxilato de terc- butilo (2.10 g) como un sólido blanco: ^{1}H RMN (400 MHz, $CDCl_3$)δ ppm 7,15 (s, 1 H), 3,98 (t, J = 6,32 Hz, 2 H), 3,13 (t, J = 6,32 Hz, 2 H), 2,70 (s, 3 H), 1,58 (s, 9 H) .

Una solución compleja 2- cloro- 4- metil- 5- oxo- 7 ,8- dihidro- 1 ,6- naftiridina- 6 (5H)- carboxilato de de terc- butilo (2.08 g, 7.01 mmol) y borano- d_3-THF (21.0 ml, 21.0 mmol) se dejó en agitación a 60 °C durante 17 h bajo nitrógeno. La mezcla de reacción se enfrió a temperatura ambiente, y se apagó con MeOH (2 mL). La mezcla se diluyó conNH_4Cl acuoso saturado, salmuera, y EtOAc. Los productos se extrajeron dos veces con EtOAc. La capa

orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar2- cloro- 4- metil- 5 ,6,7,8- tetrahidro (5,5- $^2H_2$) - 1,6 - naftiridina- 6- carboxilato de terc- butilo junto con una impureza como un aceite incoloro (incorporación de deuterio de 94%). El material obtenido se utilizó sin purificación adicional: MS (ESI+) m/z 285.30 (M+H)+.

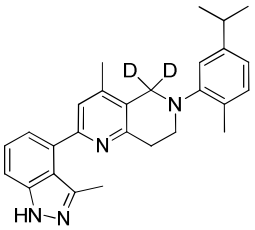
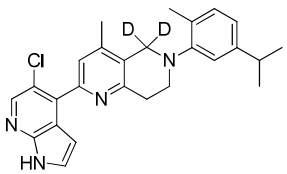
A una solución de 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro (5,5- 2H2) - 1,6- naftiridina- 6- carboxilato de terc- butilo (1.59 g, 5.58 mmol) en EtOAc (8 ml), se añadió HCl 4 M en 1,4- dioxano (6.98 ml, 27.9 mmol) yse precipitó un sólido blanco. Después de agitar durante 1 h, se añadio HCl 4 M adicional en 1,4- dioxano (6.98 ml, 27.9 mmol). Después de agitar durante 1 hora adicional, se añadió MeOH (10 mL) a la mezcla de reacción, seguido por la adición de EtOAc (400 ml). El sólido precipitado se recolectó en un embudo, se lavó con EtOAc (100 mL), y se secó bajo presión reducida para proporcionar el producto deseado como una sal de hidrocloruro (1.29 g). El sólido se neutralizó con $Na_2CO_3$2 M acuoso (10 mL) en DCM (10 ml). La mezcla se dejó en agitación durante 1 h. La mezcla se diluyó con salmuera y DCM. La capa orgánica se separó y se concentró para proporcionar 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro (5,5- $^2H_2$) - 1,6- naftiridina (93% D): ^{1}H RMN (400 MHz , $CDCl_3$) δ ppm 6,96 (s, 1 H), 3,17 (t, J = 5,94 Hz, 2 H), 2,91 (t, J = 5,94 Hz, 2 H), 2,17 (s, 3 H).

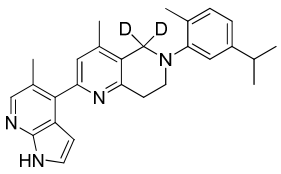
Una suspensión de 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro (5,5- 2H2) - 1,6- naftiridina (0.92 g, 4.98 mmol), trifluorometanosulfonato de 5- isopropil- 2- metilfenilo (4.22 g, 14.95 mmol), aducto $Pd_2(dba)_3$.$CHCl_3$(0.206 g, 0.199 mmol), rac- BINAP (0.248 g, 0.399 mmol) y Cs_2CO_3 (4.87 g, 14.95 mmol) en tolueno (4 ml) y terc - butanol (0.7 ml) se dejó en agitación a 90 °C durante 17 h bajo nitrógeno. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con EtOAc y salmuera. Los productos se extrajeron tres veces con EtOAc. La capa orgánica se secó sobre Na_2SO_4, y se filtró. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 80 g de gel de sílice (con 15 g de pre- columna de gel de sílice; eluyente: heptano/acetato de etilo = 100:0 a 80:20), seguido mediante cromatografía ultrarrápida en columna sobre 20 g de NH -modificado con gel de sílice (con 15 g de pre-columna de gel de sílice NH- modificado; eluyente: heptano/acetato de etilo = 100:0 a 90:10) para proporcionar 2- cloro- 6- (5- isopropil- 2- metilfenil) - 4- metil- 5 ,6,7,8- tetrahidro (5,5- $^2H_2$) - 1,6- naftiridina (94% D) como un sólido naranja pálido: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,16 (d, J = 7,83 Hz, 1 H), 6,99 - 7,00 (m, 2 H), 6,92 - 6,95 (m, 1 H), 3,28 (t, J = 5,81 Hz, 2 H), 3,12 (t , J = 5,81 Hz, 2 H), 2,84 - 2,94 (m, 1 H), 2,29 (s, 3 H), 2,20 (s, 3 H), 1,26 (d, J = 6,82 Hz, 6 H), MS (ESI+) m/z 317.40 (M+H)+.

Una mezcla de 2- cloro- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5 ,6,7,8- tetrahidro (5,5- $^2H_2$) - 1,6- naftiridina (120 mg, 0.379 mmol), ácido de 5- metil- 1H- indazol- 4-

ilboronico(87 mg, 0.492 mmol), $Pd(PPh_3)_4$ (43.8 mg, 0.038 mmol) y K_3PO_4 (161 mg, 0.757 mmol) en 1,4- dioxano (1.3 ml) y H_2O (0.13 ml) a 130 °C durante 1 h en atmósfera de nitrógeno en un reactor de microondas. La mezcla se concentró y se diluyó con EtOAc y salmuera. Los productos se extrajeron dos veces con EtOAc, y la capa orgánica combinada se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó dos veces mediante cromatografía ultrarrápida en columna sobre 12 g de gel de sílice (eluyente: heptano/acetato de etilo = 75:25 a 30:70), seguido mediante cromatografía ultrarrápida en columna sobre 12 g de gel de sílice de NH- modificado (eluyente: heptano / EtOAc = 75:25 a 25:75) para proporcionar 6 - (5- isopropil- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- indazol- 4- il) - 5,6,7,8- tetrahidro (5,5- $^2H_2$) - 1,6- naftiridina. ^{1}H RMN (400 MHz, $CDCl_3$)δ 10,06 ppm (br. s., 1 H), 7,90 (d, J = 1,01 Hz, 1 H), 7,37 - 7,40 (m, 1 H), 7,31 (d, J = 8,59 Hz, 1H), 7,19 (d, J = 7,66 Hz, 1H), 7,16 (s, 1 H), 7,07 (d, J = 1,85 Hz, 1 H), 6,95 (dd, J = 1,85, 7,66 Hz, 1 H), 3,37 (br. t, J = 5,81 Hz, 2 H), 3,26 (br. t, J = 5,81 Hz, 2 H), 2,87 - 2,97 (m, 1 H), 2,44 (s, 3 H), 2,37 (s, 3 H), 2,31 (s , 3 H), 1,28 (d, J = 6,82 Hz, 6 H), MS (ESI+) m/z 413.27 (M+H)+.

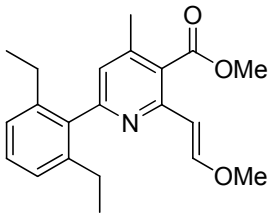
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos MS (ESI) *m/z*$(M+H)^+$
43-B		6-(5-isopropil-2-metilfenil)-4-metil-2-(3-metil-1H-indazol-4-il)-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.78 (br s, 1 H), 7.51(d, *J* = 7.83 Hz, 1 H), 7.35 – 7.39 (m, 1 H), 7.34 (s, 1 H), 7.10 – 7.15 (m, 2 H), 7.09 (d, *J* = 1.94 Hz, 1 H), 6.90 (dd, *J* = 1.94, 7.58 Hz, 1 H), 3.27 (br t, *J* = 5.68 Hz, 2 H), 3.07 (br t, *J* = 5.68 Hz, 2 H), 2.82 – 2.92 (m, 1 H), 2.32 (s, 3 H), 2.27 (s, 3 H), 2.23 (s, 3 H), 1.21 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z*413.4 $(M+H)^+$.
43-C		2-(5-cloro-1H-pirrolo[2,3-b]piridin-4-il)-6-(5-isopropil-2-metilfenil)-4-metil-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.95 (br s, 1 H), 8.32 (s, 1 H), 7.55 (d, *J* = 3.54 Hz, 1 H), 7.35 (s, 1 H), 7.14 (d, *J* = 7.66 Hz, 1H), 7.10 (d, *J* = 1.60 Hz, 1H), 6.89 (dd, *J* = 1.60, 7.66 Hz, 1 H), 6.30 (d, *J* = 3.54 Hz, 1H), 3.27 (br t, *J* = 5.68 Hz, 2 H), 3.09 (br t, *J* = 5.68 Hz, 2 H), 2.83 – 2.93

		(m, 1 H), 2.32 (s, 3 H), 2.28 (s, 3 H), 1.22 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z*433.13 $(M+H)^+$.
43-D		6-(5-isopropil-2-metilfenil)-4-metil-2-(5-metil-1H-pirrolo[2,3-b]piridin-4-il)-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.55 (br s, 1 H), 8.15 (s, 1 H), 7.40 – 7.41 (m, 1 H), 7.27 (m, 1 H), 7.14 (d, *J* = 7.83 Hz, 1 H), 7.10 – 7.10 (m, 1 H), 6.89 – 6.91 (m, 1 H), 6.22 – 6.23 (m, 1 H), 3.27 (br t, J = 5.81 Hz, 2 H), 3.08 (br t, *J* = 5.68 Hz, 2 H), 2.84 – 2.91 (m, 1 H), 2.33 (s, 3 H), 2.32 (s, 3 H), 2.28 (s, 3 H), 1.22 (d, *J* = 6.82 Hz, 6 H); MS (ESI+) *m/z*413.3 $(M+H)^+$.

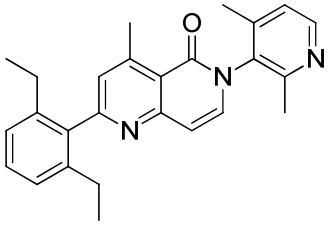
Ejemplo 44

44- A. 6 - (2,6- dietilfenil) - 2 - (2- metoxivinil)- 4- metilnicotinato de (E)- metilo



El compuesto del título se preparó de una manera similar a la descrita en el **Ejemplo 41**. MS (ESI+) m/z 354.4 (M+H)+.

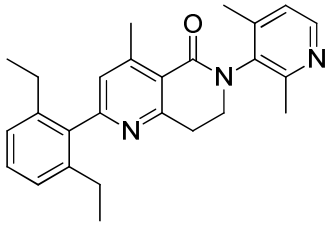
44- B. 2 - (2,6- dietilfenil) - 6 - (2,4- dimetilpiridin- 3- il)- 4- metil- 1 ,6- naftiridin- 5 (6H)- ona.



A una solución de 6 - (2,6- dietilfenil) - 2 - (2- metoxivinil)- 4- metilnicotinato de (E)- metilo (82 mg, 0.23 mmol) en tolueno (2.8 ml) y ácido acético (1.9 ml) Se añadió 2,4- dimetilpiridin- 3- amina (425 mg, 3.48 mmol). La reacción se calentó a 115 °C durante 6 h. La mezcla se concentró bajo presión reducida. El residuo se purificó a través de FCC (40- 80% de

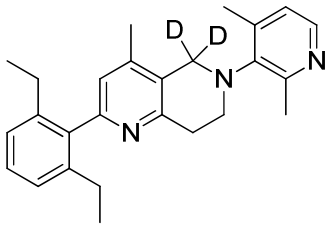
EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6)δ ppm 8,43 (d, J = 4,8 Hz, 1 H), 7,58 (d, J = 7,6 Hz, 1 H), 7,31 - 7,36 (m, 3 H), 7,19 (d, J = 7,6 Hz, 2 H), 6,78 (d, J = 7,6 Hz, 1 H), 2,84 (s, 3 H), 2,24 - 2,35 (m, 7 H), 2,11 (s, 3 H), 1,02 (t, J = 7,6 Hz, 6 H), MS (ESI+) m/z 398.3 (M+H)+.

44- C. 2 - (2,6- dietilfenil) - 6 - (2,4- dimetilpiridin- 3- il)- 4- metil- 7 ,8- dihidro- 1 ,6- naftiridin- 5 (6H)- ona.



A una solución de 2 - (2,6- dietilfenil) - 6 - (2,4- dimetilpiridin- 3- il)- 4- metil- 1 ,6- naftiridin- 5 (6H)- ona (44 mg, 0.11 mmol) y formiato de amonio (70 mg, 1.1 mmol) se añadió Pd/C (118 mg, 5%). La reacción se selló y se calentó a 80 °C durante 2 h. La reacción se filtró. El residuo se purificó a través de FCC (40- 80% de EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 400.4 (M+H)+.

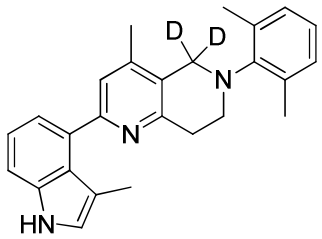
44- D.2-(2,6-Dietilfenil)-6-(2,4-dimetilpiridin-3-il)-4-metil-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina.



A 2 - (2,6- dietilfenil) - 6 - (2,4- dimetilpiridin- 3- il)- 4- metil- 7 ,8- dihidro- 1 ,6- naftiridin- 5 (6H)- ona (32 mg , 0.08 mmol) se añadió una solución 1M de deuteruro de aluminio de litio (1.60 ml). Después de 16 h, la solución se enfrió a 0 °C yse añadió lentamente hidrato de sulfato de sodio. La mezcla se filtró y se concentró bajo presión reducida. El residuo se purificó a través de FCC (0- 70% EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d6) δ ppm 8,13 (d, 1 H), 7,24 - 7,30 (m, 1 H), 7,13 (d, J = 7,6 Hz, 2 H), 7,06 - 7,11 (m, 1 H), 6,96 - 7,01 (m, 1 H), 3,41 (t, J = 5,6 Hz, 2 H), 2,99 (t, J = 5,4 Hz, 2 H), 2,34 (s, 3 H), 2,27 (q, J = 7,6 Hz, 4 H), 2,21 (s, 3 H), 1,00 (t, 6 H), MS (ESI+) m/z 388.3 (M+H)+.

Los siguientes compuestos se prepararon de una manera similar.

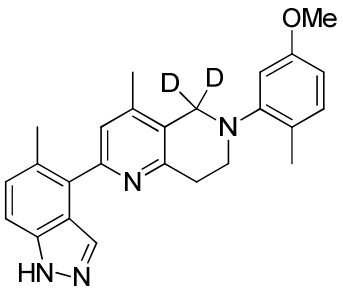
44- B. 6-(2,6-dimetilfenil)-4-metil-2-(3-metil-1H-indol-4-il)-5,6,7,8-(5,5-$^2H_2$)tetrahidro-1,6-naftiridina.



^{1}H RMN (400 MHz, DMSO- d_6) δ ppm10,88 (br. s., 1 H), 7,38 (dd, J = 7,9, 0,9 Hz, 1 H), 7,20 (s, 1 H), 7,12 (s, 1 H), 7,10 (d, J = 8,1 Hz , 1 H), 7,03 - 7,08 (m, 2 H), 6,99 - 7,03 (m, 1 H), 6,94 - 6,99 (m, 1 H), 3,44 (t, J = 5,6 Hz, 2 H), 3,02 (t, J = 5,4 Hz, 2 H), 2,31 (s, 6 H), 2,23 (s, 3 H), 1,90 (s, 3 H), MS (ESI+) m/z 384.3 (M+H)+.

Ejemplo 45

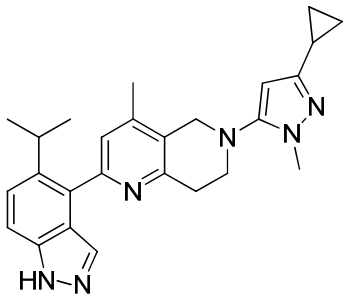
6-(5-metoxi-2-metilfenil)-4-metil-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina.



A una solución de 6-(5-metoxi-2-metilfenil)-4-metil-2-(5-metil-1H-indazol-4-il)-7,8-dihidro-1,6-naftiridin-5(6H)-ona (48 mg, 0.085 mmol), preparado como en el **Ejemplo 40**, en THF (170 µL) se añadió una solución 1M de deuteruro de alumínio delitio (424 µL). Después de 2.5 h, la solución se enfrió a 0 °C yse añadió lentamente hidrato de sulfato de sodio. La mezcla se filtró y se concentró bajo presión reducida. El residuo se purificó a través de FCC (50- 80% de EtOAc/heptano) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 12,99 (s, 1 H), 7,77 (s, 1 H), 7,47 (d, J = 8,6 Hz, 1 H), 7,20 - 7,35 (m, 2 H), 7,14 (d, J = 8,3 Hz, 1 H), 6,80 (d, J = 2,5 Hz, 1 H), 6,62 (dd, J = 8,2, 2,7 Hz, 1 H), 3,75 (s, 3 H), 3,21 - 3,29 (m, 2 H), 3,09 (t, J = 5,8 Hz, 2 H), 2,37 (s, 3 H), 2,32 (s, 3 H), 2,25 (s, 3 H), MS (ESI+) m/z 401,3 (M+H)+ .

Ejemplo 46

46- A. 6-(3-Ciclopropil-1-metil-1H-pirazol-5-il)-2-(5-isopropil-1H-indazol-4-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina.



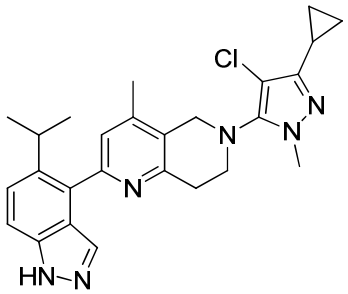
Se utilizó un microondas para irradiar una suspensión de hidrocloruro de 2- cloro- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina (1.00 g, 4.56 mmol), 3- ciclopropil-3-oxopropanoato de metilo (1.298 g, 9.13 mmol), 4- pirrolidinopiridina (0.068 g, 0.456 mmol) y DIPEA (1.20 ml, 6.85 mmol) en tolueno (10 ml) a 150 °C durante 45 min. La mezcla se enfrió a temperatura ambiente y se diluyó con HCl1 M acuoso (10 mL) y EtOAc. Los productos se extrajeron dos veces con EtOAc. La capa orgánica combinada se lavó con una solución mixta de 1M HCl acuoso/salmuera (1 mL/2 mL), se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar crudo. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 12 g de gel de sílice (eluyente: DCM/EtOAc = 90:10 a 0:100) para proporcionar 1 - (2-cloro- 4- metil- 7 ,8- dihidro- 1 ,6- naftiridin- 6 (5H)- il)- 3- ciclopropilpropano- 1 ,3- diona crudo (0.70 g): MS (ESI+) m/z 293.31 (M+H)+. El material obtenido se utilizó sin purificación adicional.

Se utilizó un microondas para irradiar una solución de crudo proporcionando 1 - (2-cloro- 4- metil- 7 ,8- dihidro- 1 ,6- naftiridin- 6 (5H)- il)- 3- ciclopropilpropano- 1, 3 - diona crudo (0.70 g), piridina (1.5 ml, 19.1 mmol), reactivo de Lawesson (1.064 g, 2.63 mmol) e hidracina de metilo (0.151 ml, 2.87 mmol) en THF (9 ml) a 120 °C durante 20 min. La mezcla se diluyó con EtOAc y salmuera. La capa orgánica se extrajo con EtOAc, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 80 g de gel de sílice (eluyente: heptano/acetato de etilo = 80:20 a 0:100) para proporcionar 2- cloro- 6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina (110 mg): ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,02 (s, 1 H), 5,56 (s, 1 H), 3,96 (s, 2 H), 3,69 (s, 3 H), 3,08 - 3,23 (m, 4 H), 2,19 (s, 3 H) , 1,83 - 1,90 (m, 1 H), 0,86 - 0,91 (m, 2 H), 0,68 - 0,72 (m, 2 H), MS (ESI+) m/z 303.28 (M+H)+.

Se utilizó microondas para irradiar una solución de 2- cloro- 6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 4- metil- 5 ,6,7,8- tetrahidro- 1, 6 - naftiridina (30 mg, 0.099 mmol), 5-isopropil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il)- 1H- indazol crudo (38.2 mg, 0.119

mmol) , $Pd(PPh_3)_4$ (11.45 mg, 9.91 µmol) y K_3PO_4 (42.1 mg, 0.198 mmol) en 1,4- dioxano (0.5 ml) y H_2O (0.05 ml) a 130 °C durante 1 h bajo nitrógeno. Se añadió $Pd(PPh_3)_4$ adicional (22.90 mg, 0.020 mmol) a la mezcla. En un microondas se irradió la mezcla a 130 °C durante 2 horas más bajo atmósfera de nitrógeno. La mezcla se diluyó con salmuera y EtOAc. La capa orgánica se separó, se secó sobre Na_2SO_4, se filtró y se concentró.El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 12 g de gel de sílice (eluyente: DCM/MeOH = 100:0 a 10:1) para proporcionar 6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(5-isopropil-1H-indazol-4-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina:^{1}H RMN (400 MHz, $CDCl_3$)δ 9,98 ppm (br. s., 1 H), 7,76 (d, J = 0,76 Hz, 1 H), 7,45 - 7,51 (m, 2 H), 7,12 (s, 1 H), 5,65 (s, 1 H), 4,11 (s, 2 H), 3,75 (s, 3 H), 3,30 -3,33 (app t, 2 H), 3,15 a 3,24 (m, 3 H), 2,30 (s, 3 H), 1,87 a 1,94 (m, 1 H), 1,25 (d, J = 7,07 Hz, 6 H), 0,89 - 0,94 (m, 2 H), 0,72 - 0,76 (m, 2 H), MS (ESI+) m/z 427.33 (M+H)+.

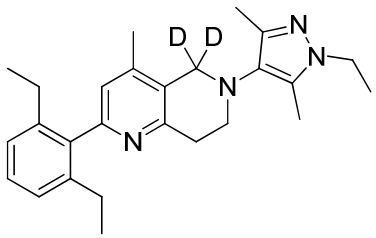
46- B. 6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(5-isopropil-1H-indazol-4-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina.



A una solución de 6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(5-isopropil-1H-indazol-4-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridina (20 mg, 0.047 mmol) en THF (0.5 ml), se añadió NCS (6.26 mg, 0.047 mmol) a temperatura ambiente. Después de agitar durante 2,5 h, la mezcla de reacción se diluyó con H_2O y DCM. La capa orgánica se separó y se concentró. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 12 g de gel de sílice NH- modificado (eluyente: DCM/MeOH = 100:0 a 10:1) para proporcionar el producto deseado, junto con una pequeña cantidad de pinacol (10 mg). El crudo se purificó mediante HPLC (C18, H_2O (0,1% NH_4OH)/CH_3CN) para proporcionar 6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(5-isopropil-1H-indazol-4-il)-4-metil-5,6,7,8-tetrahidro-1,6-naftiridino (2.6 mg) como un sólido de color rosa: ^{1}H RMN (400 MHz, $CDCl_3$) δ 10,02 ppm (br. s., 1 H), 7,77 (s, 1 H), 7,46 - 7,51 (m, 2 H), 7,13 (s, 1 H), 4,36 (s, 2 H), 3,72 (s, 3 H), 3,58 (t, J = 5,81 Hz, 2 H), 3,16 - 3,23 (m, 3 H), 2,28 (s, 3 H), 1,85 - 1,92 (m, 1 H), 1,26 (d, J = 6,82 Hz, 6 H), 0,93 (s, 2 H), 0,90 - 0,92 (m, 2 H), MS (ESI+) m/z 461.14 (M+H)+.

Ejemplo 47

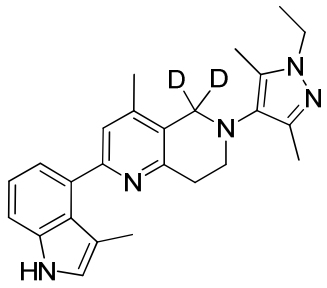
47- A. 2-(2,6-Dietilfenil)-6-(1-etil-3,5-dimetil-1H-pirazol-4-il)-4-metil-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina.



Una mezcla de2-(2,6-dietilfenil)-6-(1-etil-3,5-dimetil-1H-pirazol-4-il)-4-metil-7,8-dihidro-1,6-naftiridin-5(6H)-ona (88 mg, 0.211 mmol), preparado con el método similar al descrito en el **Ejemplo 41**, y deuteruro de aluminio de litio 1M (2.11 ml, 2.11 mmol) se agitó a temperatura ambiente durante 1 h. Luego la reacción se apagó con $Na_2SO_4 \cdot 10H_2O$ y después se diluyó con THF y se filtró. El filtrado se concentró y el residuo resultante se purificó mediante HPLC (XB C18 acetonitrilo 15- 85% en H_2O con 0.1% NH_4OH) para proporcionar de 2-(2,6-dietilfenil)-6-(1-etil-3,5-dimetil-1H-pirazol-4-il)-4-metil-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,24 - 7,30 (m, 1 H) 7,12 (d, J = 7,83 Hz, 2 H) 6,96 (s, 1 H), 3,93 (q, J = 7,07 Hz, 2 H) 3,29 (d, J = 5,56 Hz, 2 H) 2,93 (t, J = 5,56 Hz, 2 H) 2,25 (q, J = 7,49 Hz, 4 H) 2,17 (d, J = 13,89 Hz, 9 H) 1,26 (t, J = 7,20 Hz, 3 H) 0,98 (t, J = 7,58 Hz, 6 H). MS (ESI+) m/z 405.3 (M+H)+.

Los siguientes compuestos se prepararon de una manera similar.

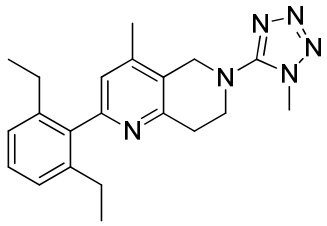
47- B.6-(1-etil-3,5-dimetil-1H-pirazol-4-il)-4-metil-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidro(5,5-$^2H_2$)-1,6-naftiridina.



^{1}H RMN (400 MHz, DMSO- d_6)δ ppm 10,88 (br. s., 1 H). 7,38 (d, J = 7,33 Hz, 1 H) 7,18 (s, 1 H) 7.7 - 7.14 (m, 2 H) 6,94 (d, J = 6,32 Hz, 1 H) 3,93 (q, J = 7,33 Hz, 2 H) 3,33 (br. s., 1 H)

3,28 (s, 1 H) 2,98 (t, J = 5,68 Hz, 2 H) 2,12 - . 2,25 (m, 9 H) 1,89 (s, 3 H) 1,27 (t, J = 7,20 Hz, 3 H), MS (ESI +) m/z 402.3 (M+H)+.

<u>Ejemplo 48</u> 2 - (2,6- dietilfenil)- 4- metil- 6- (1- metil- 1H- tetrazol- 5- il) - 5,6,7,8- tetrahidro- 1 ,6- naftiridina.



Una solución de 6 - (2,6- dietilfenil)- 4- metil- 2- vinilnicotinato de metilo (0.50 g, 1.62 mmol) y acetato de amonio (1.25 g, 16.2 mmol) en AcOH (9 ml) se dejó en agitación a 120 °C en un tubo sellado. Después de agitar durante 14 h, la mezcla de reacción se enfrió a temperatura ambiente, y se concentró. El residuo se particionió entre DCM y 2 M Na_2CO_3 acuoso, y se extrajo con DCM. La capa orgánica separada se concentró. El residuo se purificó mediante cromatografía ultrarrápida en columna sobre 40 g de gel de sílice (eluyente: DCM/EtOAc = 80:20 a 0:100) para proporcionar 2 - (2,6- dietilfenil)- 4- metil- 7 ,8- dihidro - 1,6- naftiridin- 5 (6H)- ona. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,29 (t, J = 7,75 Hz, 1 H), 7,14 (d, J = 7,75 Hz, 1 H), 7,06 (s, 1 H), 6,01 (br. s., 1 H), 3,58 - 3,62 (m, 2 H), 3,20 (t, J = 6,57 Hz, 2 H), 2,76 (s, 3 H), 2,31 - 2,37 (m, 4 H), 1,06 (t, J = 7,58 Hz, 2 H), MS (ESI+) m/z 295.32 (M+H)+.

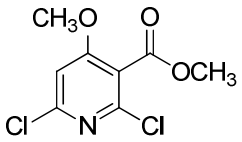
En un matraz dondese colocó 2 - (2,6- dietilfenil)- 4- metil- 7 ,8- dihidro- 1 ,6- naftiridin- 5 (6H)- ona (299 mg, 1.016 mmol), se añadió LAH en THF (5.0 ml, 5.08 mmol). Después de agitar durante 45 min, se añadió LAH adicional en THF (5.0 ml, 5.08 mmol). Después de agitar durante 2.5 h adicionales, la mezcla de reacción se diluyó con H_2O y luego con NaOH 1 M acuoso. Los productos se extrajeron con DCM. La solución orgánica separada se concentró para proporcionar crudo. El crudo se disolvió en 1.25 M de HCl/MeOH (3 ml), y se agitó durante 5 min. La solución se concentró para proporcionar crudo como aceite amarillo. El crudo se disolvió en acetato de isopropilo, y se concentró para proporcionar el producto deseado como su sal de hidrocloruro. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7,25 - 7,27 (m, 1 H), 7,13 (d, J = 7,83 Hz, 1 H), 6,96 (s, 1 H), 4,27 (s, 2 H), 3,50 (br. t, J = 6,06 Hz 2 H), 3,25 (br. t, J = 6,06 Hz, 2 H), 2,30 . 2,35 (m, 4 H), 2,27 (s, 3 H), 1,05 (t, J = 7,58 Hz, 2 H), MS (ESI+) m/z 281.35 (M+H)+.

A una solución dedihidrocloruro de 2 - (2,6- dietilfenil)- 4- metil- 5 ,6,7,8- tetrahidro- 1 ,6- naftiridina (21.7 mg, 0.061 mmol) en THF (0.5 ml), 1.6 M n- BuLi en hexanos (0.119 ml,

0.190 mmol) a - 78 °C bajo nitrógeno. Después de agitar durante 10 min. a la misma temperatura, se añadió1- metil- 5- (metilsulfonil)- 1H- tetrazol (24.90 mg, 0.154 mmol). La mezcla se calentó hasta temperatura ambiente y se agitó durante 19 h. La mezcla se diluyó con salmuera y EtOAc. Los productos se extrajeron con EtOAc, y la capa orgánica se concentró. El producto crudo se purificó mediante RP- HPLC (X-Bridge Fenil®, H_2O (0,1% NH_4OH)/CH_3CN), luego las fracciones, incluyendo el producto deseado se liofilizó para proporcionar el producto deseado. ^1H RMN (400 MHz, $CDCl_3$) δ ppm 7,26 - 7,30 (m, 2 H), 7,14 (d, J = 7,58 Hz, 1 H), 6,98 (s, 1 H), 4,58 (s, 2 H), 4,01 (s, 3 H), 3,68 (t, J = 5,94 Hz, 2 H), 3,25 (br. t, J = 5,94 Hz, 2 H), 2,30 - 2,37 (m, 7 H), 1,06 (t, J = 7,58 Hz, 6 H), MS (ESI+) m/z 363.27 (M+H)+.

Ejemplo 49

49- A. 2,6- dicloro- 4- metoxinicotinato de metilo



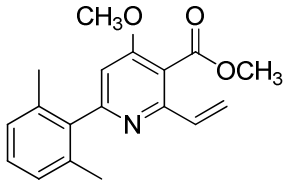
A una solución de 2,4,6- tricloronicotinato de metilo [(5.04 g, 20.96 mmol), preparado como se describe en WO2010/31589] en metanol (52 mL) se añadió metóxido de sodio (25% por peso en metanol, 5.04 ml, 22.0 mmol) a temperatura ambiente. La mezcla blanca turbia se agitó durante 17 h, después se particionió entre EtOAc y agua. Las capas se separaron y la capa acuosa se extrajo adicionalmente con EtOAc (2x). Las capas orgánicas combinadas se secaron sobre sulfato sódico, se filtró y se concentró. El residuo se purificó mediante FCC (0- 20% EtOAc: heptano) para proporcionar 2,6- dicloro- 4- metoxinicotinato de metilo MS (ESI+) m/z 236.1 (M+H)+.

2,6- dicloro- 4- metoxinicotinato de metilo también se preparó mediante el método alternativo descrito a continuación:

Una solución 1,0 M de TMPMgCl·LiCl en THF y tolueno [(15.6 ml, 15.6 mmol) se añadió a 2,6- dicloro- 4- metoxipiridina (2.32 g, 13.0 mmol), preparado como se describe en WO2007/21710] y la mezcla de reacción clarade color naranja- marrón se agitó a temperatura ambiente. Después de 20 min, la solución de Grignard resultante se añadió por goteo a una solución de cloroformiato de metilo (3.08 ml, 39.1 mmol) en tolueno (52 ml). Después de agitar durante 15 min, la mezcla de reacción se particionió entre EtOAc y solución acuosa saturada de bicarbonato sódico. La capa acuosa se extrajo con EtOAc (2x) y las capas orgánicas combinadas se lavaron con salmuera, después se secaron sobre sulfato de sodio, se filtraron y se

concentraron. El residuo se purificó mediante FCC (0- 25% EtOAc: heptanos) para proporcionar 2,6- dicloro- 4- metoxinicotinato de metilo.

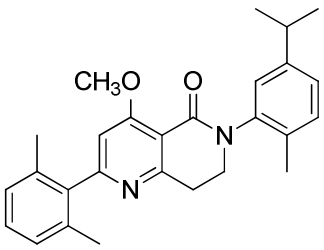
49- B. 6 - (2,6- dimetilfenil)- 4- metoxi- 2- vinilnicotinato de metilo



Una mezcla de 2,6- dicloro- 4- metoxinicotinato de metilo (2.3 g, 9.74 mmol), ácido 2,6- dimetilfenilboronico (1.75 g, 11.7 mmol), $Pd(PPh_3)$ 4 (1.13 g, 0.974 mmol), y solución de bicarbonato de sodio acuosa 2.0 M (14.6 ml, 29.2 mmol) en DMF (97 ml) se degasificó por evacuación y se llenó nuevamente con nitrógeno (5 ciclos). Luego la mezcla de reacción se calentó a 110 °C y se agitó a esa temperatura. Después de 16.5 horas, se añadió 4,4,5,5- tetrametil- 2- vinil- 1 ,3,2- dioxaborolano (4.17 ml, 24.36 mmol) a la mezcla de reacción, seguido por $Pd(PPh_3)$ 4 (500 mg, 0.417 mmol) y solución de carbonato de sodio acuoso 2.0 M (7 ml, 13.98 mmol). La mezcla resultante se agitó adicionalmente a 110 °C.

Después de 4.5 h, la mezcla de reacciónse filtró en caliente, enjuagandocon EtOAc, y el filtrado se concentró en el rotavapor para eliminar una porción de DMF. El concentrado residual se particionió entre EtOAc y agua con salmuera. La capa acuosa se extrajo con EtOAc (2x), y las capas orgánicas combinadas se lavaron con salmuera (3x), luego se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó mediante FCC (0- 25% EtOAc/heptano) para proporcionar 6 - (2,6- dimetilfenil)- 4- metoxi- 2- vinilnicotinato.MS (ESI+) m/z 298.2 (M+H)+.

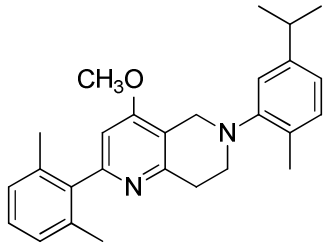
49- C. 2-(2,6-Dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-metoxi-7,8-dihidro-1,6-naftiridin-5(6H)-ona.



Una solución de 6 - (2,6- dimetilfenil)- 4- metoxi- 2- vinilnicotinato (1.77 g, 5.95 mmol) y 5- isopropil- 2- metilanilina (4.44 g, 29.8 mmol) en tolueno (26.5 ml) y ácido acético

(13.2 ml) se calentó a 110 °C y se agitó a esa temperatura. Después de 12 h, la mezcla de reacción se retiró del calor y se concentró en el rotavapor para eliminar el volumen del solvente. El residuo se particionió entre EtOAc ysolución de hidróxido de sodio 1N acuosoagregando salmuera. Las capas se separaron y la capa acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, después se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó mediante FCC (0- 15% EtOAc/DCM) para proporcionar2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-metoxi-7,8-dihidro-1,6-naftiridin-5(6H)-ona.El producto contenía algo de 5- isopropil- 2- metilanilina y se utilizó en la siguiente etapa sin purificación adicional. MS (ESI+) m/z 415.2 (M+H)+.

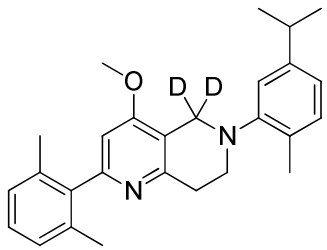
49- D. 2 - (2,6- dimetilfenil) - 6 - (5- isopropil- 2- metilfenil)- 4- metoxi 5,6,7,8- tetrahidro- 1 ,6- naftiridina.



Una solución 1.0 M de hidruro de aluminio de litioen THF (405 µL.0,405 mmol) se añadió a un recipiente que contiena 2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-metoxi-7,8-dihidro-1,6-naftiridin-5(6H)-ona (42 mg, 0.101 mmol). La mezcla de reacción, la cual se burbujeó y se tornó de color naranja claro, se agitó a temperatura ambiente. Después de 1 h, la mezcla de reacción se diluyó con 1 ml de THF y se enfrió a 0 °C con un baño de hielo. Se añadió por goteo 150µL de una mezcla 09:01 THF/H_2O, seguido por la adición lenta de 100 µL de NaOH acuoso 1N. Después de agitar durante 5 minutos, el baño de hielo se retiró y se añadió en secuencia100 µL de H_2O y 1 mL deTHF. La mezcla se agitó durante 10 min, luego se añadió, 150 mg de sulfato de magnesio y el matraz se agitó y se agitó suavemente. Luego la mezcla se filtró a través de Celite ® y la torta del filtro se lavó con EtOAc. El filtrado se concentró y el residuo se purificó mediante FCC (0- 20% EtOA/heptano) para proporcionar 2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-metoxi-5,6,7,8-tetrahidro-1,6-naftiridina.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,19 (dd, J = 8,4, 6,8 Hz, 1 H) 7.9 - 7.14 (m, 3 H) 7,03 (d, J = 1,5 Hz, 1 H) 6,89 (dd , J = 7,7, 1,6 Hz, 1 H) 6,81 (s, 1 H) 4,00 - 4,03 (m, 2 H), 3,86 (s, 3 H) 3,22 (t, J = 5,7 Hz, 2 H) 2,97 (t, J = 5,6 Hz, 2 H) 2,86 (spt, J = 6,8 Hz, 1 H) 2,25 (s, 3 H) 2,03 (s, 6 H) 1,19 (d, J = 7,1 Hz, 6 H), MS (ESI+) m/z 401.3 (M+H)+.

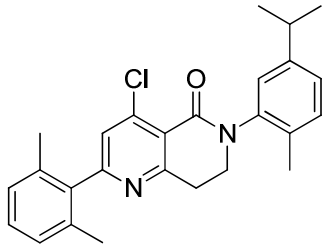
Los siguientes compuestos se prepararon de una manera similar.

49- E. 2 - (2,6- dimetilfenil) - 6 - (5- isopropil- 2- metilfenil)- 4- metoxi 5,6,7,8- tetrahidro (5,5- 2H2) - 1,6- naftiridina.



^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,16 - 7,22 (m, 1 H) 07.08 - 07.14 (m, 3 H) 7,02 (d, *J = 1,8* Hz, 1 H) 6,88 (dd, J = 7,7, 1,6 Hz, 1 H) 6,81 (s, 1 H), 3,86 (s, 3 H) 3,21 (t, J = 5,7 Hz, 2 H) 2,96 (t, J = 5,7 Hz, 2 H) 2,85 (spt, J = 6,9 Hz, 1 H) 2,24 (s, 3 H) 2,03 (s, 6 H) 1,19 (d, J = 7,1 Hz, 6 H), MS (ESI+)m/z 403.3 (M+H)+.

<u>Ejemplo 50</u> 50- A.4-Cloro-2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-7,8-dihidro-1,6-naftiridin-5(6H)-ona.

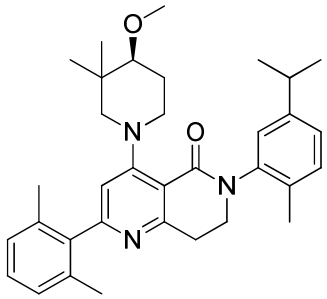


A una solución de2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-metoxi-7,8-dihidro-1,6-naftiridin-5(6H)-ona (1.49 g, 3.59 mmol) en dioxano (23,96 ml) se añadió trimetilsilanolato de potasio (2.306 g, 17.97 mmol) como un sólido en una porción. El recipiente de presión de 75- ml se selló y la mezcla de reacción se calentó a 140 °C durante 3 h. La mezcla de reacción se dejó enfriar a temperatura ambiente antes de abrir el recipiente. La mezcla de reacción se vertió entonces en agua y DCM y el pH acuosa se ajustó a pH 7 con HCl 1 N. Las capas acuosas se extrajo de nuevo con DCM (2x) y las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron. El crudo2-(2,6-dimetilfenil)-4-hidroxi-6-(5-isopropil-2-metilfenil)-7,8-dihidro-1,6-naftiridin-5(6H)-ona se usó directamente en la siguiente etapa sin purificación adicional.

A una solución de2-(2,6-dimetilfenil)-4-hidroxi-6-(5-isopropil-2-metilfenil)-7,8-dihidro-1,6-naftiridin-5(6H)-ona crudo (1,4 g, 3.50 mmol) en DCM (35.0 ml) se añadió reactivo de Vilsmeier (0.895 g, 6.99 mmol) como un sólido en una porción y la mezcla de reacción se agitó

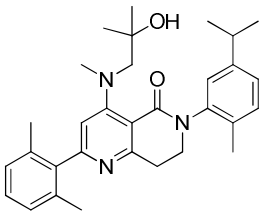
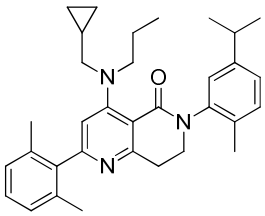
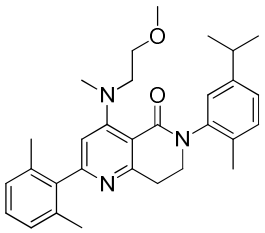
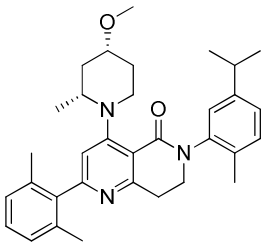
a temperatura ambiente. Después de 2 hse añadió 500 mg de reactivo de Vilsmeier y continuó la agitación. Después de 35 minutos se añadió una porción adicional de 200 mg de reactivo de Vilsmeier y continuó la agitación. Después de 15 minutos la mezcla de reacción se diluyó con DCM y se vertió en solución acuosa saturada de bicarbonato de sodio que contenía NaOH 1**N**. Las capas se separaron y la capa acuosa se extrajo con DCM (2x). Las capas orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. El residuo se purificó mediante FCC (0- 20% EtOAc/heptano) para proporcionar4-cloro-2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-7,8-dihidro-1,6-naftiridin-5(6H)-ona.MS (ESI+) m/z 419.2 (M+H)+.

50- B. (S) - 2 - (2,6- dimetilfenil) - 6 - (5- isopropil- 2- metilfenil) - 4 - (4- metoxi- 3, 3 - dimetilpiperidin- 1- il) - 7,8- dihidro- 1 ,6- naftiridin- 5 (6H)- ona.



Un matraz de reacción de 10- ml que contiena una solución de color naranja de4-cloro-2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-7,8-dihidro-1,6-naftiridin-5(6H)-ona (100 mg, 0.239 mmol), sal HCl de (S)- 4- metoxi- 3 ,3- dimetilpiperidina (129 mg, 0.716 mmol) y DIEA (208 µl, 1.193 mmol) en DMA (1.2 ml) se colocó en un baño de arena precalentado a 110 °C y se agitó a esa temperatura. Después de 4 h, la mezcla de reacción se dejó enfriar a temperatura ambiente, luego se diluyó con DCM y se vierti en la mezcla de solución acuosa saturada de bicarbonato sódico y salmuera. La capa acuosa se extrajo con DCM (3x), y las capas orgánicas combinadas se lavaaron con salmuera, después se secaron sobre sulfato de sodio, se filtraron y se concentró. El residuo se purificó mediante FCC (0- 100% EtOAc/heptano) para proporcionar(*S*)-2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidro-1,6-naftiridin-5(6H)-ona.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,07 - 7,25 (m, 6 H) 6,73 (s, 1 H) 3,80 - 3,96 (m, 1 H) 3.63- 3.79 (m, 1 H) 3,27 (s, 3 H) 03.09 - 03.24 (m, 2 H) 2.93- 3.07 (m, 3 H) 2,79- 2,92 (m, 2 H) 2.18 - 2.22 (m, 3 H) 2,06 (s, 6 H) 1.79- 1.94 (m, 1 H) 1,48 - 1,65 (m, 1 H) 1,21 (d, J = 6,8 Hz, 6 H) 01.14 - 01.19 (m, 1 H) 0,90 (s, 3 H) 0,83 (s, 1 H) * 0,78 (s, 2 H) *; MS (ESI+) m/z 526.3 (M+H)+. (* Indica un grupo metilo que aparece como dos picos debido a la rotación restringida).

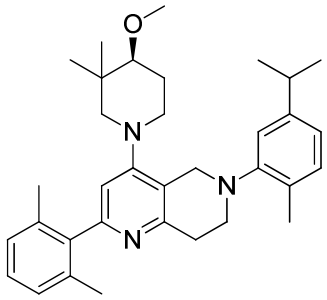
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos
50-C		2-(2,6-dimetilfenil)-4-((2-hidroxi-2-metilpropil)(metil)amino)-6-(5-isopropil-2-metilfenil)-7,8-dihidro-1,6-naftiridin-5(6H)-ona. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.05 - 7.26 (m, 6 H) 6.91 (s, 1 H) 4.32 (s, 1 H) 3.86 - 4.00 (m, 1 H) 3.63 - 3.75 (m, 2 H) 3.17 - 3.29 (m, 2 H) 3.03 (s, 3 H) 2.94 - 3.02 (m, 1 H) 2.88 (quin, *J*=6.9 Hz, 1 H) 2.19 (s, 3 H) 2.04 (s, 6 H) 1.21 (d, *J*=6.8 Hz, 6 H) 1.04 (s, 6 H); MS (ESI+) *m/z*486.3 $(M+H)^+$.
50-D		4-((ciclopropilmetil)(propil)amino)-2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-7,8-dihidro-1,6-naftiridin-5(6H)-ona. 1H NMR (400 MHz, DMSO-d_6) δ ppm 7.06 - 7.26 (m, 6 H) 6.68 (s, 1 H) 3.82 - 3.93 (m, 1 H) 3.63 - 3.73 (m, 1 H) 3.35 - 3.51 (m, 2 H) 3.07 - 3.31 (m, 3 H) 2.93 - 3.04 (m, 1 H) 2.87 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.20 (s, 3 H) 2.06 (s, 6 H) 1.49 - 1.59 (m, 2 H) 1.21 (d, *J*=6.8 Hz, 6 H) 1.01 - 1.08 (m, 1 H) 0.82 (t, *J*=7.3 Hz, 3 H) 0.43 - 0.50 (m, 2 H) 0.10 - 0.16 (m, 2 H); MS (ESI+) *m/z*496.3 $(M+H)^+$.
50-E		2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-((2-metoxietil)(metil)amino)-7,8-dihidro-1,6-naftiridin-5(6H)-ona. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.07 - 7.24 (m, 6 H) 6.67 (s, 1 H) 3.83 - 3.93 (m, 1 H) 3.67 - 3.77 (m, 1 H) 3.53 - 3.56 (m, 2 H) 3.47 - 3.53 (m, 2 H) 3.23 (dd, *J*=9.5, 4.2 Hz, 1 H) 3.20 (s, 3 H) 2.95 - 3.05 (m, 1 H) 2.93 (s, 3 H) 2.87 (dt, *J*=13.9, 6.9 Hz, 1 H) 2.18 (s, 3 H) 2.06 (s, 6 H) 1.20 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 472.3 $(M+H)^+$.
50-F		2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-7,8-dihidro-1,6-naftiridin-5(6H)-ona. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.08 - 7.24 (m, 6 H) 6.69 (s, 0.5 H)* 6.64 (s, 0.5 H)* 3.87 - 3.99 (m, 2 H) 3.65 - 3.85 (m, 1 H) 3.52 (qd, 1 H) 3.35 - 3.44 (m, 1 H) 3.24 (d, *J*=1.8 Hz, 3 H) 3.11 - 3.22 (m, 1 H) 2.94 - 3.10 (m, 1 H) 2.88 (quin, *J*=6.9 Hz, 1 H) 2.18 (d, *J*=4.3 Hz, 3 H) 2.06 (s, 6 H) 1.65 - 1.96 (m, 4 H) 1.25 (d, *J*=6.8 Hz, 2 H)*

		1.21 (d, *J*=7.1 Hz, 6 H) 1.18 (d, *J*=6.8 Hz, 1 H)*, * indica picos adicionales debido a rotación restringida;MS (ESI+) *m/z* 512.3 $(M+H)^+$.

Ejemplo 51

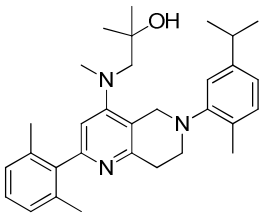
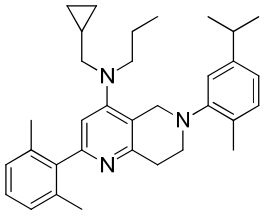
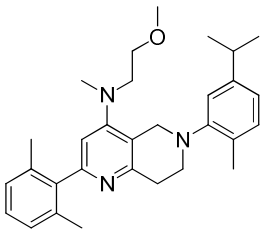
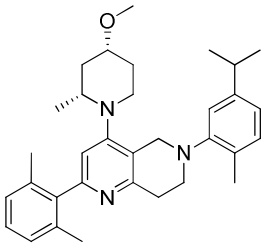
51- A.(*S*)-2-(2,6-Dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidro-1,6-naftiridina.



Se añadió una solución 1.0 M de hidruro de aluminio de litioen THF (23.0 ml, 3.00 mmol) a un recipiente que contenia (*S*)-2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidro-1,6-naftiridin-5(6H)-ona (63 mg, 0.120 mmol). El matraz de reacción se tapó y la mezcla de reacción de color rosa se calentó a 55 °C y se agitó a esa temperatura. Después de 1.5 h, el baño de aceite se separó, la mezcla de reacción se diluyó con 6 mL de THF, y el matraz de reacción se enfrió a 0 °C. Luego se añadió 0.9 ml de una mezcla 09:01 THF/H_2O por goteo, seguido por 3 ml de THF, y se añadió lentamente 0.3 mL de NaOH 2 N. Después de agitar durante 5 minutos, el baño de hielo se retiró y se añadió 600 µL de H_2O y 6 mL de THF. La mezcla se agitó durante 10 min, luego se añadió 900 mg de sulfato de magnesio y la mezcla se agitó aún más. La mezcla se filtró entonces a través de Celite ® y la torta del filtro se lavó con EtOAc. El filtrado se concentró y el residuo se purificó mediante FCC (0- 50% EtOAc/heptanos) para proporcionar (*S*)-2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidro-1,6-naftiridina.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,14 - 7,19 (m, 1 H) 07.06 - 07.12 (m, 3 H) 6,94 (d, J = 1,5 Hz, 1 H) 6,83 (dd, J = 7,8, 1,5 Hz, 1 H) 6,68 (s, 1 H) 4.10 - 4.22 (m, 2 H) 3,28 (s, 3 H) 03.07 - 03.18 (m, 1 H) 2.73- 3.04 (m, 6 H) 2,23 (s , 3 H) 2,00 (s, 6 H) 1,91 - 2,03 (m, 2 H) 1,58 (d, J = 9,3 Hz, 1 H) 1,20 - 1,28 (m, 1 H) 1,16 (d, J = 6,8 Hz, 6 H) 1,01 (d, J = 10,4 Hz, 6 H), MS (ESI +) m / z 512,4 (M + H) +.

Los siguientes compuestos se prepararon de una manera similar.

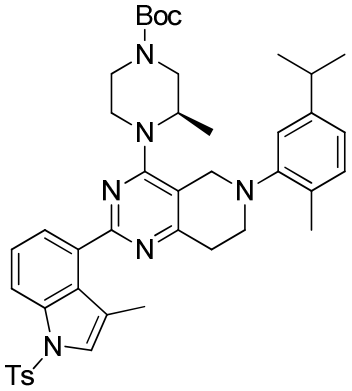
	Estructura	Nombre Quimico y Datos Analiticos MS (ESI) *m/z*$(M+H)^+$

51-B		1-((2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidro-1,6-naftiridin-4-il)(metil)amino)-2-metilpropan-2-ol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.13 - 7.19 (m, 1 H) 7.06 - 7.12 (m, 3 H) 6.92 (d, *J*=1.5 Hz, 1 H) 6.86 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.75 (s, 1 H) 4.37 (s, 1 H) 4.05 - 4.10 (m, 2 H) 3.11 (s, 2 H) 2.91 (s, 3 H) 2.89 - 2.96 (m, 2 H) 2.80 (dt, *J*=13.6, 6.8 Hz, 0 H) 2.23 (s, 3 H) 2.01 (s, 6 H) 1.16 (d, *J*=6.8 Hz, 6 H) 1.06 (s, 6 H); MS (ESI+) *m/z*472.3 $(M+H)^+$.
51-C		N-(ciclopropilmetil)-2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-N-propil-5,6,7,8-tetrahidro-1,6-naftiridin-4-amina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.22 (m, 1 H) 7.07 - 7.12 (m, 3 H) 6.90 (d, *J*=1.5 Hz, 1 H) 6.85 (dd, *J*=7.6, 1.5 Hz, 1 H) 6.79 (s, 1 H) 4.03 - 4.09 (m, 2 H) 3.14 (t, *J*=7.1 Hz, 2 H) 2.89 - 2.98 (m, 4 H) 2.80 (dt, *J*=13.8, 6.9 Hz, 1 H) 2.23 (s, 3 H) 2.01 (s, 6 H) 1.45 (m, 2 H) 1.15 (d, *J*=6.8 Hz, 6 H) 0.87 - 0.94 (m, 1 H) 0.83 (t, *J*=7.3 Hz, 3 H) 0.35 - 0.42 (m, 2 H) 0.04 - 0.10 (m, 2 H); MS (ESI+) *m/z*482.3 $(M+H)^+$.
51-D		2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-N-(2-metoxietil)-N-metil-5,6,7,8-tetrahidro-1,6-naftiridin-4-amina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.13 - 7.19 (m, 1 H) 7.06 - 7.12 (m, 3 H) 6.95 (d, *J*=1.5 Hz, 1 H) 6.85 (dd, *J*=7.7, 1.6 Hz, 1 H) 6.68 (s, 1 H) 4.04 - 4.08 (m, 2 H) 3.52 (t, *J*=5.6 Hz, 2 H) 3.29 (t, *J*=6.2 Hz, 2 H) 3.20 (s, 3 H) 3.19 - 3.24 (m, 2 H) 2.96 (t, *J*=5.9 Hz, 2 H) 2.75 - 2.88 (m, 4 H) 2.23 (s, 3 H) 2.02 (s, 6 H) 1.18 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 458.3 $(M+H)^+$.
51-E		2-(2,6-dimetilfenil)-6-(5-isopropil-2-metilfenil)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidro-1,6-naftiridina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.15 - 7.21 (m, 1 H) 7.08 - 7.13 (m, 3 H) 6.90 - 6.94 (m, 2 H) 6.86 (dd, *J*=7.7, 1.6 Hz, 1 H) 4.23 (d, *J*=15.7 Hz, 1 H) 4.02 (d, *J*=15.7 Hz, 1 H) 3.34 - 3.42 (m, 1 H) 3.26 - 3.30 (m, 2 H) 3.25 (s, 3 H) 3.15 - 3.22 (m, 1 H) 2.89 - 3.09 (m, 3 H) 2.82 (dt, *J*=13.7, 6.9 Hz, 1 H) 2.24 (s, 3 H) 2.00 (s, 6 H) 1.97 -

		2.11 (m, 2 H) 1.34 - 1.44 (m, 1 H) 1.19 - 1.25 (m, 1 H) 1.17 (d, *J*=6.8, Hz, 3 H)* 1.15 (d, *J*=6.8, Hz, 3 H)* 0.91 (d, 3 H), * indica picos adicionales debido a rotación restringida;MS (ESI+) *m/z* 498.4 $(M+H)^+$.

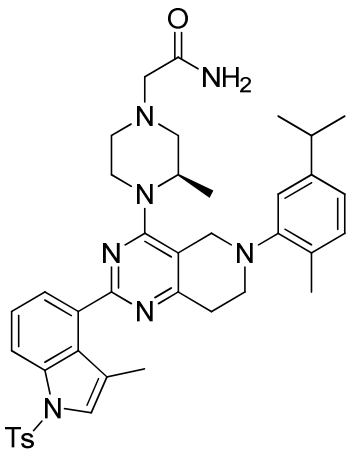
Ejemplo 52

52- A. 4-(6-(5-isopropil-2-metilfenil)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilpiperazina-1-carboxilatode (R)- terc- butilo



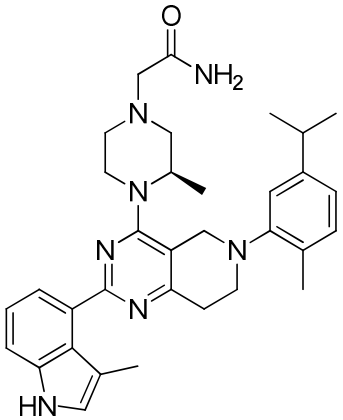
Una mezcla de 4-cloro-6-(5-isopropil-2-metilfenil)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (**Ejemplo 17- E**) (0.274 g, 0.468 mmol), 3-metilpiperazina-1-carboxilatode (R)- terc- butilo (0.375 g, 1.87 mmol) y DIEA (0.33 ml, 1.87 mmol) en N, N- dimetilacetamida (3 mL) se calentó a 125 °C durante 15 h. La mezcla de reacción se diluyó con EtOAc, se lavó con solución acuosa saturada de $NaHCO_3$ y salmuera. La capa orgánica se secó sobre Na_2SO_4, se concentró, se purificó a través de FCC (0- 40% EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 749.4(M+H)+.

52- B.(*R*)-2-(4-(6-(5-Isopropil-2-metilfenil)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilpiperazin-1-il)acetamida



Una solución de4-(6-(5-isopropil-2-metilfenil)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilpiperazina-1-carboxilato de (R)- terc- butilo (0.143 g, 0.191 mmol), TFA (2 ml) y DCM (3 mL) se agitó a temperatura ambiente durante 30 minutos antes de ser concentrada. Al residuo resultante en DCM (3 ml) se añadió DIEA (0.133 ml, 0.764 mmol), 2- bromoacetamida (0.040 g, 0.287 mmol) y yoduro de sodio (0.043 g, 0.287 mmol). La mezcla se agitó a temperatura ambiente durante 20 horas y después se diluyó con EtOAc. La mezcla se lavó con solución acuoso saturada de $NaHCO_3$ y después con salmuera. La capa orgánica se secó sobre Na_2SO_4. Después de la concentración, el residuo se purificó a través de FCC (60- 90% EtOAc/heptano) para proporcionar el compuesto del título.MS (ESI+) m/z 706.4 (M+H)+.

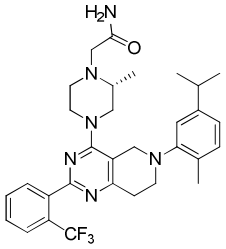
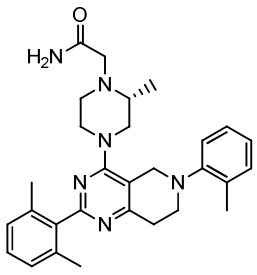
52- C.(*R*)-2-(4-(6-(5-Isopropil-2-metilfenil)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilpiperazin-1-il)acetamida.

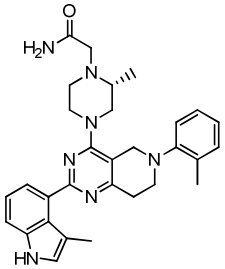
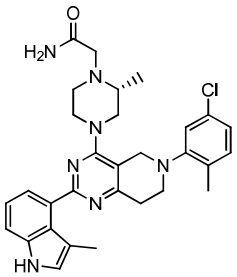
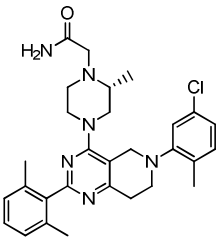


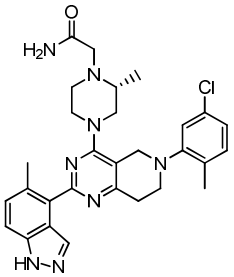
Una mezcla de(*R*)-2-(4-(6-(5-isopropil-2-metilfenil)-2-(3-metil-1-tosil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilpiperazin-1-il)acetamida (0.075 mg, 0.106

mmol), hidróxido de amonio al 30% (0,63 ml 15.94 mmol) e hidróxido de potasio (0,054 g, 0,956 mmol) en etanol (3 ml) se calentó en un reactor de microondas a 100 °C durante 1 h. La mezcla de reacción se concentró y luego se filtró, antes de ser purificado a través de HPLC (C18 RP, 15- 85% CH_3CN en H_2O con NH_4OH al 0.1% para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, CD3CN) delta ppm 9,16 (br. s., 1 H) 7,45 (d, J = 8,08 Hz, 1 H) 7,25 (dd, J = 7,20, 1,14 Hz, 1 H) 7,15 (dd, J = 15,28, 7,71 Hz, 2 H) 7.1 - 7.9 (m, 2 H) 6.82- 6.94 (m, 2 H) 5,80 (br. s., 1 H) 3,94 - . 4,13 (m, 3 H) 3.51- 3.60 (m, 1 H) 3.41- 3.50 (m, 1 H) 3,28 - 3,41 (m, 2 H) 2,95- 3,12 (m, 2 H) 2.82- 2.95 (m, 3 H) 2,78 (d, J = 10,86 Hz, 1 H) 2.57- 2.66 (m, 1 H) 2,47 a 2,56 (m, 1 H) 2,37 (td, J = 10,74, 3,03 Hz, 1 H) 2,26 (s, 3 H) 2,05 (s, 3 H) 1,30 (d, J = 6,82 Hz, 3 H) 1,23 (dd, J = 6,82, 1,01 Hz, 6 H), MS (ESI+) m/z 552.4 (M+H)+.

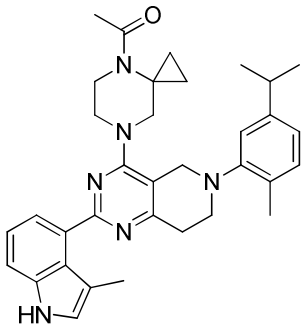
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos MS (ESI) *m/z*$(M+H)^+$
52-D		(*R*)-2-(4-(6-(5-isopropil-2-metilfenil)-2-(2-(trifluorometil)fenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 7.75 - 7.80 (m, 2 H) 7.65 (t, *J*=7.45 Hz, 1 H) 7.56 (t, *J*=7.71 Hz, 1 H) 7.14 (d, *J*=7.58 Hz, 1 H) 7.06 (br. s., 1 H) 6.96 (d, *J*=1.52 Hz, 1 H) 6.91 (dd, *J*=7.71, 1.64 Hz, 1 H) 3.92 - 4.04 (m, 2 H) 3.67 (d, *J*=12.38 Hz, 2 H) 3.21 - 3.40 (m, 4 H) 3.08 (t, *J*=5.81 Hz, 2 H) 2.77 - 2.98 (m, 4 H) 2.60 - 2.74 (m, 1 H) 2.47 - 2.60 (m, 1 H) 2.27 (s, 3 H) 1.24 (d, *J*=6.82 Hz, 6 H) 1.09 (d, *J* 5.81 Hz, 3 H); MS (ESI+) *m/z* 567.4 $(M+H)^+$.
52-E		(*R*)-2-(4-(2-(2,6-dimetilfenil)-6-(o-tolil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.14 - 7.27 (m, 4 H), 7.05 - 7.12 (m, 2 H), 6.97 - 7.04 (m, 1 H), 3.98 (s, 2 H), 3.57 (t, *J*=12.4 Hz, 2 H), 3.24 - 3.29 (m, 2 H), 3.15 - 3.23 (m, 1 H), 3.11 (app. d, *J*=16.2 Hz, 1 H), 2.96 (t, *J*=5.7 Hz, 2 H), 2.90 (dd, *J*=12.8, 8.7 Hz, 1 H), 2.81 (s, 1 H), 2.75 - 2.79 (m, 1 H), 2.59 (t, *J*=6.1 Hz, 1 H), 2.43 - 2.48 (m, 1 H), 2.26 (s, 3 H), 2.06 (s, 6 H), 1.00 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 485.2 $(M+H)^+$.

52-F		(*R*)-2-(2-metil-4-(2-(3-metil-1H-indol-4-il)-6-(o-tolil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)piperazin-1-il)acetamida. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.23 (br. s., 1 H), 7.44 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.35 (dd, *J*=7.2, 0.9 Hz, 1 H), 7.19 - 7.25 (m, 3 H), 7.11 - 7.15 (m, 1 H), 7.05 - 7.08 (m, 1 H), 7.03 (dd, *J*=7.3, 1.3 Hz, 1 H), 4.01 (s, 2 H), 3.68 (d, *J*=12.1 Hz, 2 H), 3.23 - 3.39 (m, 4 H), 3.13 (t, *J*=5.7 Hz, 2 H), 2.89 - 3.02 (m, 2 H), 2.84 (app. d, *J*=16.9 Hz, 1 H), 2.64 - 2.73 (m, 1 H), 2.59 (t, *J*=9.9 Hz, 1 H), 2.33 (s, 3 H), 2.10 (d, *J*=1.0 Hz, 3 H), 1.11 (d, *J*=6.1 Hz, 3 H); MS (ESI+) *m/z* 510.3 $(M+H)^+$.
52-G		(*R*)-2-(4-(6-(5-cloro-2-metilfenil)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 8.25 (br. s., 1 H), 7.44 (dd, *J*=8.1, 1.0 Hz, 1 H), 7.35 (dd, *J*=7.3, 1.0 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.17 (dd, *J*=8.1, 0.5 Hz, 1 H), 7.10 (d, *J*=2.3 Hz, 1 H), 7.05 - 7.07 (m, 1 H), 7.03 (dd, *J*=8.1, 2.0 Hz, 1 H), 3.98 (s, 2 H), 3.66 (app. d, *J*=11.9 Hz, 2 H), 3.24 - 3.38 (m, 4 H), 3.14 (t, *J*=5.9 Hz, 2 H), 2.90 - 3.03 (m, 2 H), 2.85 (app. d, *J*=16.9 Hz, 1 H), 2.64 - 2.75 (m, 1 H), 2.60 (t, *J*=9.9 Hz, 1 H), 2.29 (s, 3 H), 2.10 (d, *J*=0.8 Hz, 3 H), 1.11 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 544.3 $(M+H)^+$.
52-H		(*R*)-2-(4-(6-(5-cloro-2-metilfenil)-2-(2,6-dimetilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.26 (d, *J*=2.8 Hz, 1 H), 7.23 (d, *J*=8.3 Hz, 1 H), 7.15 - 7.20 (m, 2 H), 7.12 (d, *J*=2.8 Hz, 1 H), 7.09 (s, 1 H), 7.07 (m, *J*=1.8 Hz, 1 H), 7.05 (d, *J*=2.0 Hz, 1 H), 4.01 (br. s., 2 H), 3.53 - 3.62 (m, 2 H), 3.31 (br. s, 2 H), 3.26 - 3.29 (m, 1 H), 3.17 - 3.25 (m, 1 H), 3.11 (app. d, *J*=16.2 Hz, 1 H), 2.88 - 2.99 (m, 3 H), 2.76 – 2.82 (m, 2 H), 2.57 - 2.65 (m, 1 H), 2.23 (s, 3 H), 2.05 (s, 6 H), 1.01 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 519.2 $(M+H)^+$.

52-I		(*R*)-2-(4-(6-(5-cloro-2-metilfenil)-2-(5-metil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilpiperazin-1-il)acetamida. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.13 (s, 1 H), 7.50 (d, *J*=7.8 Hz, 1 H), 7.22 - 7.31 (m, 3 H), 7.11 - 7.15 (m, 1 H), 7.08 (dd, *J*=7.8, 1.8 Hz, 1 H), 3.97 - 4.08 (m, 2 H), 3.60 - 3.68 (m, 2 H), 3.13 (app. d, *J*=16.2 Hz, 1 H), 3.06 (t, *J*=5.7 Hz, 1 H), 2.92 - 3.00 (m, 1 H), 2.77 - 2.86 (m, 2 H), 2.54 - 2.57 (m, 3 H), 2.23 - 2.26 (m, 3 H), 1.03 (d, *J*=6.3 Hz, 3 H); MS (ESI+) *m/z* 545.2 $(M+H)^+$.

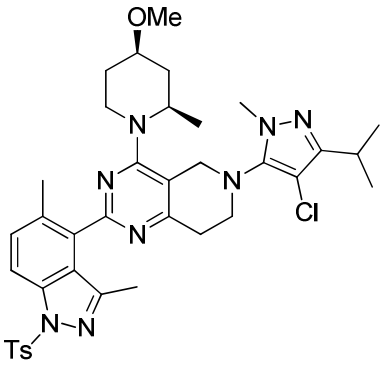
<u>Ejemplo 53</u> 1-(7-(6-(5-Isopropil-2-metilfenil)-2-(3-metil-1H-indol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-4,7-diazaspiro[2.5]octan-4-il)etanona.



Preparado de una manera similar a la descrita en el **Ejemplo 52** usandodihidrocloruro 4,7-diazaspiro [2,5] octano. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 10,89 (s, 1 H) 7,41 (dd, J = 7,83, 1,01 Hz, 1 H) 7,21 (dd, J = 7,33, 1,01 Hz, 1 H) 7,07 a 7,16 (m, 3 H) 6,99 (d, J = 1,26 Hz, 1 H) 6,87 (dd, J = 7,71, 1,39 Hz, 1 H) 4,01 (s, 2 H) 3.61- 3.83 (m, 2 H) 3,36 - 3,52 (m, 2 H) 3,32 (br. s., 4 H) 2,97 (t, J = 5,81 Hz, 2 H) 2.85 (quin, J = 6,82 Hz, 1 H) 2,21 (s, 3 H) 2,12 (s, 3 H) 2,01 (s, 3 H) 1,20 (d, J = 7,07 Hz, 6 H) 0.94 - 1.09 (m, 4 H), MS (ESI +) m / z 549,4 (M + H) +.

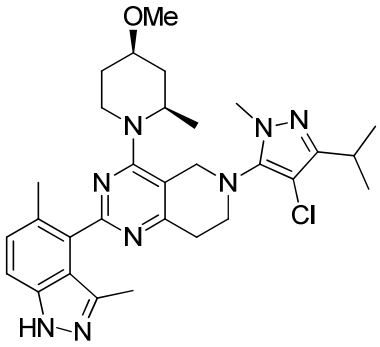
<u>Ejemplo 54</u>

54- A.6-(4-Cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



El compuesto del título se preparó de una manera similar a la descrita en el **Ejemplo 34-D** utilizando2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-6-(3-isopropil-1-metil-1H-pirazol-5-il)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI +) m/z 717.3 (M+H)+.

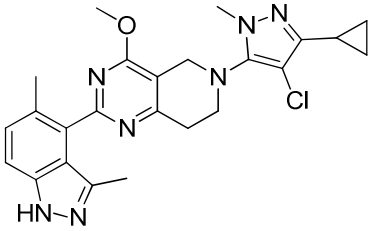
54- B. 6-(4-Cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



El compuesto del título se preparó de una manera similar a la descrita en el **Ejemplo 19- F** usando 6-(4-cloro-3-isopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 12,58 (s, 1 H), 7,40 (d, J = 8,6 Hz, 1 H), 7,22 (d, J = 8,6 Hz, 1 H), 4,23 - 4,39 (m, 2 H), 3,62 (s, 3 H), 3,46 - 3,58 (m, 1 H), 3,38 - 3,46 (m, 1 H), 3,02 - 3,12 (m, 1 H), 2,92 - 2,99 (m, 4 H), 2,84 - 2,92 (m, 1 H), 2,16 (s, 3 H), 1,96 (s, 1 H), 1,89 (br. s., 1 H), 1,85 (s, 6 H), 1,49. - 1,67 (m, 3 H), 1,20 (d, J = 6,8 Hz, 6 H), 1,14 (d, J = 6,3 Hz, 3 H), MS (ESI+) m/z 563.3 (M+H)+.

El siguiente compuesto se preparó de una manera similar.

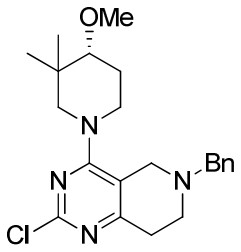
54- B. 6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



^{1}H NMR(400 MHz, CD_2Cl_2) δ ppm 9,85 (br. s., 1 H). 7,39- 7,52 (m, 1 H) 7,33 (d, J = 8,3 Hz, 1 H) 4,33 (s, 2 H) 4,04 (s, 3 H) 3,70 (s, 3 H) 3,59 (t, J = 5,8 Hz, 2 H) 3,08 (t, J = 5,7 Hz, 2 H) 2,33 (s, 3 H) 2,059 (s, 3 H) 1,89 (quin, J = 6,8 Hz, 1H) 0.83 - 0,97 (m, 4 H), MS (ESI+) m/z 464.2 (M+H)+.

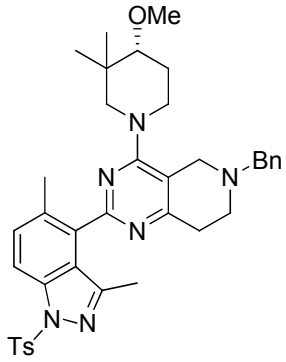
Ejemplo 55

55- A.(*R*)-6-bencil-2-cloro-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



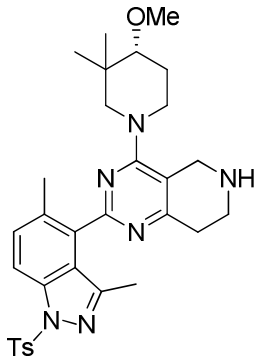
A una solución de 6- bencil- 2 ,4- dicloro- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (5.55 g, 18.8 mmol) en iPrOH (170 ml) se añadiócloruro de (R) - 4- metoxi- 3 ,3-dimetilpiperidin- 1- io,**Ejemplo 7- D** (3.08 g, 17.1 mmol) y TEA (7.2 ml, 51.4 mmol). Luego la mezcla de reacción se calentó durante la noche a 50 °C. En ese punto se eliminó el disolvente al vacío y el residuo se purificó a través de FCC (0- 50% EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 401.3 (M+H)+.

55- B. (*R*)-6-Bencil-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



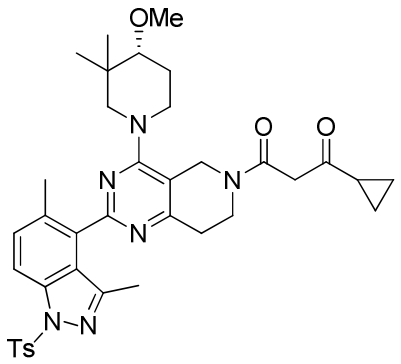
A una solución de(*R*)-6-bencil-2-cloro-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (5.04 g, 12.6 mmol) en 1,4-dioxano (100 mL) se añadió 3,5-dimetil- 4- (4,4,5,5- tetrametil- 1 ,3,2- dioxaborolan- 2- il) - 1- tosil- 1H- indazol, **Ejemplo 3**, (6,16 g, 12.6 mmol), $Pd(Ph_3P)_4$ (2.18 g, 1.89 mmol) y una solución 2M de carbonato de sodio (18.9 ml, 37.7 mmol). La mezcla de reacción se calentó a 100 °C bajo una atmósfera de nitrógeno durante 16 h. Luego la mezcla de reacción se dejó enfriar a temperatura ambiente y se diluyó con EtOAc y agua. Luego las capas se mezclaron y se separaron. La capa orgánica se lavó con agua y luego salmuera. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró. Luego el residuo se purificó a través de FCC (0- 70% EtOAc/heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 665.6 (M+H)+.

55- C. (*R*)-2-(3,5-Dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



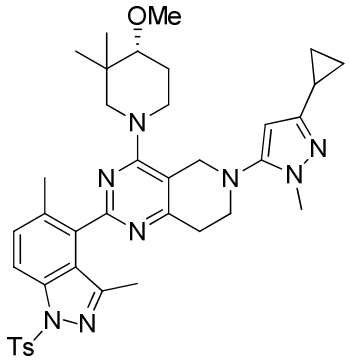
A una solución de(*R*)-6-Bencil-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (3.0 g, 4.51 mmol) en THF (24 mL) y agua (6 mL) se añadió ácido acético (1.30 ml, 22.6 mmol). La solución se calentó a 40 °C y $Pd(OH)_2$ 20% sobre carbóno (0.792 mg, 1.13 mmol). Luego lamezcla se agitó bajo una atmósfera de hidrógeno durante 2,25 h. Luego la mezcla se dejó enfriar a temperatura ambiente y se filtró sobre Celite ®, lavando con acetato de etilo y MeOH. Luego el filtrado se alcalinizó con NaOH acuoso 1 N y se extrajo con AcOEt (3 x). Las capas orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron bajo presión reducir. Luego el residuo se purificó a través de FCC (0- 15% MeOH/DCM; con 10% NH_4OH en DCM) para obtener el compuesto del título. MS (ESI+) m/z 575.5 (M+H)+.

55- D.(*R*)-1-Ciclopropil-3-(2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5*H*)-il)propano-1,3-diona.



Una solución de (*R*)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (0.200 g, 0.35 mmol), 4- DMAP (0.013 g, 0.10 mmol) y 3- metil- 3- ciclopropil oxopropanoato de metilo (0.13 ml, 1.04 mmol) en tolueno (3 mL) se calentó a 150 °C en un reactor de microondas durante 35 min. La reacción se diluyó con EtOAc y agua. La fase acuosa se extrajo adicionalmente con acetato de etilo (3x) y las capas orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron bajo presión reducida. Luego el residuo se purificó a través de FCC (0- 10% MeOH/DCM) para obtener el compuesto del título. MS (ESI+) m z 685.6 (M+H)+.

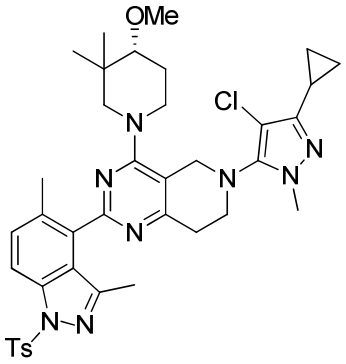
55- E. (*R*)-6-(3-Ciclopropil-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



Un vial de microondas se cargó con (*R*)-1-ciclopropil-3-(2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5*H*)-il)propano-1,3-diona (0.563 g, 0.82 mmol) y THF (5 ml) y se colocó bajo una atmósfera de nitrógeno. Luego se añadió en secuencia metilhidrazina (87 l, 1.64 mmol), piridina (0.25 ml) y reactivo de Lawesson (0,366 g, 0,90 mmol). El recipiente se selló y se calentó a 125 °C en un reactor de microondas durante 12 min. En ese punto la mezcla de reacción se concentró y el residuo se purificó a través de FCC (0- 10% MeOH/DCM; 10% NH_4OH en DCM) para

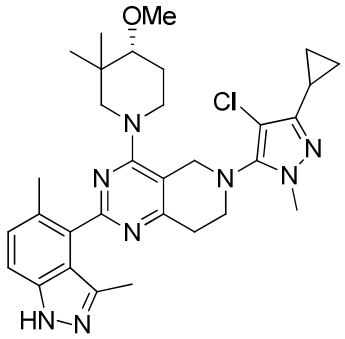
obtener el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 8.56 – 8.61 (m, 1 H), 8.05 (d, *J* = 8,6 Hz, 1 H), 7,79 (d, J = 8,3 Hz, 2 H), 7,56 (d, J = 8,8 Hz, 1 H), 7,38 (d, J = 8,6 Hz, 2 H), 5,52 (s, 1 H), 4,08 (d, J = 13,4 Hz, 1 H), 3,96 (d, J = 15,4 Hz, 1 H), 3,61 - 3,69 (m, 1 H), 3,55 (s, 3 H), 3,28 - 3,31 (m, 2 H), 3,26 (s, 3 H), 3,04 (t, J = 10,2 Hz, 1 H), 2,94 - 2,99 (m, 1 H), 2,82 - 2,92 (m, 2 H), 2,33 (s, 3 H), 2,19 (s, 3 H), 1,86 - 1,94 (m, 1 H), 1,83 (s, 3 H), 1,67 - 1,78 (m, 1 H), 1,45 - 1,58 (m, 1 H), 0,91 (s, 3 H), 0,74 - 0,83 (m, 5H), 0,50 - 0,58 (m, 2 H), MS (ESI+) m/z 695.6 (M+H)+.

55- F. (*R*)-6-(4-Cloro-3-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



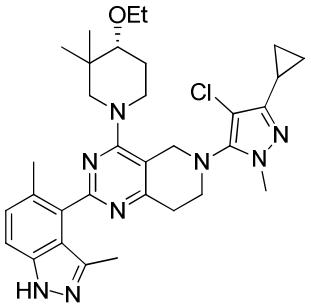
A una solución de (*R*)-6-(3-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (0.062 g, 0.089 mmol) en DCM (2 mL) bajo una atmósfera de nitrógeno se añadió N- clorosuccinimida (0.012 g, 0.089 mmol). La mezcla se dejó en agitación durante 1 hora a temperatura ambiente. Luego la mezcla de reacción se purificó directamente mediante FCC (40- 75% EtOAc/heptanos) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, diclorometano- d_2) δ ppm 8.08 (d, J = 8,3 Hz, 1 H), 7,79 (d, J = 8,3 Hz, 2 H), 7,45 (d , J = 8,8 Hz, 1 H), 7,25 (d, J = 8,3 Hz, 2 H), 4,32 (d, J = 14,7 Hz, 1 H), 4,22 (d, J = 14,4 Hz, 1 H), 3,67 (d, J = 11,6 Hz, 1 H), 3,58 (s, 3 H), 3,52 (dq, J = 12,8, 6,3 Hz, 2 H), 3,28 a 3,36 (m, 4 H), 3,09 (br. s ., 1 H), 2,99 (br. s., 2 H), 2,92 (dd, J = 8,6, 3,8 Hz, 1 H), 2,86 (d, J = 11,6 Hz, 1 H), 2,72 (s, 2 H), 2,36 (s, 3 H), 2,25 (s, 3 H), 1,88 - 1,96 (m, 4 H), 1,78 - 1,88 (m, 1 H), 1,52 - 1,69 (m, 3 H), 0,94 (s, 3 H), 0,81 - 0,90 (m, 8 H), MS (ESI+) mz 729.4 (M+H)+.

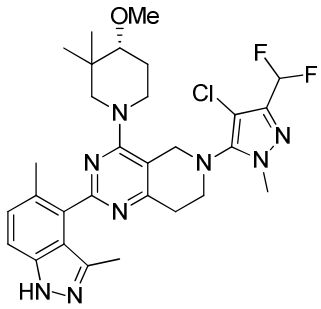
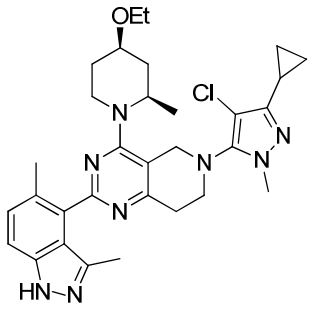
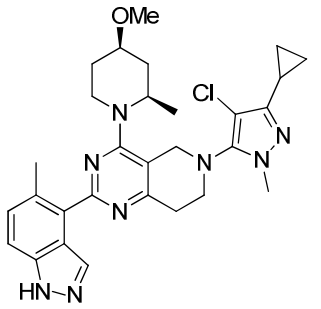
55- G.(*R*)-6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.

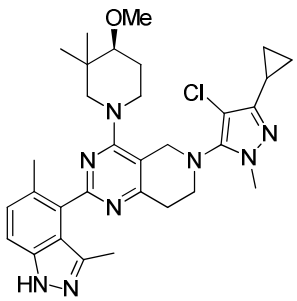
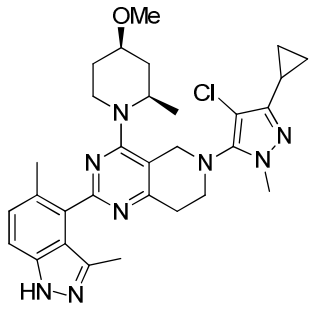
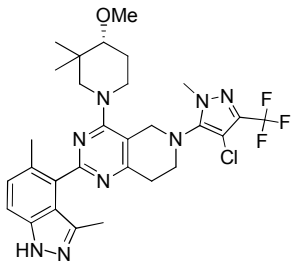


A una solución de (*R*)-6-(4-cloro-3-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (0.050 g, 0.068 mmol) en MeOH (3 mL) se añadió K_2CO_3 (0.057 g, 0.410 mmol). La mezcla se calentó a 55 °C bajo una atmósfera de nitrógeno durante 2 h. En ese momento la mezcla se diluyó con EtOAc y se lavó con solución saturada acuosa de NH_4Cl y después con salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se purificó mediante FCC (0- 10% MeOH/DCM) para proporcionar el compuesto del título.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 12,59 (s, 1 H), 7,39 (d,J = 8,3 Hz, 1 H), 7,21 (d, J = 8,8 Hz, 1 H), 4,39 (d, J = 14,9 Hz, 1 H), 4,25 (d, J = 14,7 Hz, 1 H), 3,62 - 3,78 (m, 1 H), 3,56 (s, 3 H), 3,46 - 3,55 (m, 2 H), 3,30 (d, J = 3,5 Hz, 1 H), 3,26 (s, 3 H), 2,99 - 3,08 (m, 1 H), 2,97 (dd, J = 9,1, 4,0 Hz, 1 H), 2,92 (aprox. t, J = 5,9 Hz, 2 H), 2,85 (d, J = 12,9 Hz, 1 H),2,18 (s, 3 H), 1,85 - 1,96 (m, 4 H), 1,74 a 1,82 (m, 1 H), 1,49 - 1,60 (m, 1 H), 0,92 (s, 3 H), (m traslapado, 2 H), 0,81 (s, 3H), 0,72 a 0,77 (m, 2 H); MS (ESI +) m / z 575,5 (M + H) +.

Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos
55-H		(*R*)-6-(4-cloro-3-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1*H*-indazol-4-il)-4-(4-etoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.08 - 7.30 (m, 1 H), 4.33 - 4.48 (m, 1 H), 4.16 - 4.31 (m, 1 H), 3.64 - 3.75 (m, 1 H), 3.58 - 3.63 (m, 1 H), 3.54 - 3.57 (m, 3 H), 3.46 - 3.54 (m, 2 H), 2.99 - 3.10 (m, 2 H), 2.92 (t, *J*=5.8 Hz, 2 H), 2.84 (d, *J*=13.1 Hz, 1 H), 2.15 - 2.22 (m, 3 H), 1.83 - 1.91 (m, 4 H), 1.74 - 1.82 (m, 1 H), 1.50 - 1.63 (m, 1 H), 1.09 (t, *J*=6.9 Hz, 3 H), 0.90 - 0.94 (m, 3 H), 0.82 - 0.88

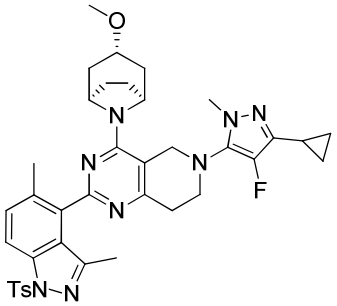
		(m, 5 H), 0.71 - 0.77 (m, 2 H); MS(ESI+) *m/z* 590.4 $(M+H)^+$
55-I		(*R*)-6-(4-cloro-3-(difluorometil)-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.8 Hz, 1 H), 6.93 (t, *J*=53.1 Hz, 1 H), 4.45 (d, *J*=14.7 Hz, 1 H), 4.31 (d, *J*=14.9 Hz, 1 H), 3.71 (s, 3 H), 3.64 - 3.69 (m, 1 H), 3.53 - 3.62 (m, 2 H), 3.26 (s, 3 H), 3.00 - 3.09 (m, 1 H), 2.91 - 3.00 (m, 3 H), 2.85 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.85 - 1.97 (m, 4 H), 1.50 - 1.63 (m, 1 H), 0.92 (s, 3 H), 0.83 (s, 3 H); MS (ESI+) *m/z* 585.5 $(M+H)^+$.
55-J		6-(4-cloro-3-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1*H*-indazol-4-il)-4-((2*R*,4*R*)-4-etoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 12.61 (s, 1 H) 7.40 (d, *J*=8.34 Hz, 1 H) 7.22 (d, *J*=8.59 Hz, 1 H) 4.31 - 4.38 (m, 1 H) 4.23 - 4.31 (m, 1 H) 3.65 - 3.78 (m, 1 H) 3.58 (s, 3 H) 3.48 - 3.56 (m, 3 H) 3.39 - 3.48 (m, 2 H) 3.24 - 3.29 (m, 1 H) 3.03 - 3.15 (m, 1 H) 2.93 (t, *J*=5.81 Hz, 2 H) 2.16 (s, 3 H) 1.82 - 1.92 (m, 5 H) 1.78 (tt, *J*=8.34, 5.05 Hz, 1 H) 1.50 - 1.65 (m, 2 H) 1.15 (d, *J*=6.32 Hz, 3 H) 1.10 (t, *J*=6.95 Hz, 3 H) 0.82 - 0.88 (m, 2 H) 0.71 - 0.77 (m, 2 H); MS (ESI+) *m/z* 575.4 $(M+H)^+$.
55-K		6-(4-cloro-3-ciclopropil-1-metil-1*H*-pirazol-5-il)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-2-(5-metil-1*H*-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 13.00 (s, 1 H), 8.06 - 8.10 (m, 1 H), 7.51 (dd, *J*=8.5, 0.6 Hz, 1 H), 7.29 (d, *J*=8.6 Hz, 1 H), 4.20 - 4.41 (m, 2 H), 3.72 - 3.87 (m, 1 H), 3.58 (s, 3 H), 3.49 - 3.56 (m, 2 H), 3.42 - 3.49 (m, 1 H), 3.26 (s, 3 H), 3.11 - 3.19 (m, 1 H), 3.03 (app. t, *J*=5.7 Hz, 2 H), 2.54 (s, 3 H), 1.84 - 1.97 (m, 2 H), 1.79 (tt,

		J=8.3, 5.1 Hz, 1 H), 1.56 - 1.71 (m, 2 H), 1.19 (d, *J*=6.6 Hz, 3 H), 0.82 - 0.89 (m, 2 H), 0.72 - 0.77 (m, 2 H); MS (ESI+) *m/z* 547.5 $(M+H)^+$.
55-L		(*S*)-6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, acetona-*d*6) δ ppm 11.71 (br. s., 1 H), 7.42 (d, *J*=8.3 Hz, 1 H), 7.23 (d, *J*=8.6 Hz, 1 H), 4.48 (d, *J*=14.9 Hz, 1 H), 4.39 (d, *J*=14.9 Hz, 1 H), 3.72 - 3.81 (m, 1 H), 3.53 - 3.67 (m, 5 H), 3.41 (dd, *J*=13.1, 1.8 Hz, 1 H), 3.32 (s, 3 H), 3.10 - 3.19 (m, 1 H), 2.98 - 3.07 (m, 3 H), 2.92 (d, *J*=12.9 Hz, 1 H), 2.78 - 2.81 (m, 2 H), 2.26 (s, 3 H), 1.96 - 1.98 (m, 3 H), 1.79 - 1.88 (m, 1 H), 1.62 - 1.73 (m, 1 H), 0.98 (s, 3 H), 0.92 (s, 3 H), 0.71 - 0.90 (m, 5 H); MS (ESI+) *m/z* 575.4 $(M+H)^+$.
55-M		6-(4-cloro-3-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1*H*-indazol-4-il)-4-((2*R*,4*R*)-4-metoxi-2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.58 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 4.21 - 4.41 (m, 2H), 3.65 - 3.76 (m, 1H), 3.58 (s, 3H), 3.47 - 3.56 (m, 2H), 3.37 - 3.45 (m, 1H), 3.20 - 3.26 (m, 3H), 3.02 - 3.14 (m, 1H), 2.94 (t, *J* = 6.1 Hz, 2H), 2.16 (s, 3H), 1.83 - 1.92 (m, 5H), 1.73 - 1.82 (m, 1H), 1.51 - 1.66 (m, 2H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.81 - 0.90 (m, 2H), 0.70 - 0.78 (m, 2H); MS(ESI+) *m/z* 561.3 $(M+H)^+$.
55-N		(*R*)-6-(4-cloro-1-metil-3-(trifluorometil)-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.1 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 4.47 (d, *J*=15.2 Hz, 1 H), 4.33 (d, *J*=14.9 Hz, 1 H),

		3.76 (s, 3 H), 3.63 - 3.72 (m, 1 H), 3.57 - 3.63 (m, 2 H), 3.26 (s, 3 H), 3.00 - 3.09 (m, 1 H), 2.91 - 3.00 (m, 3 H), 2.86 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.90 - 1.96 (m, 1 H), 1.88 (s, 3 H), 1.51 - 1.62 (m, 1 H), 0.92 (s, 3 H), 0.83 (s, 3 H); MS (ESI+) *m/z* 603.5 $(M+H)^+$.

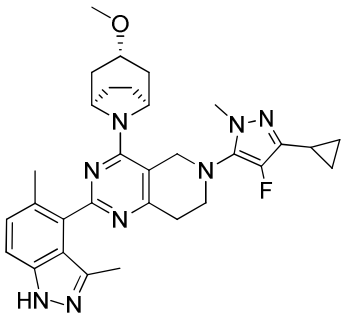
Ejemplo 56

56- A. 6-(3-Ciclopropil-4-fluoro-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-((3-*endo*)-3-metoxi-8-azabiciclo[3.2.1]octan-8-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



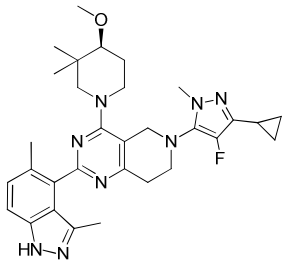
A una solución de6-(3-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-((3-*endo*)-3-metoxi-8-azabiciclo[3.2.1]octan-8-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (45 mg, 0.13 mmol), preparado en un método similar al descrito en el **Ejemplo 55-E**, en acetonitrilo (1 mL) se añadió selectflúor ® (88 mg, 0.13 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante una noche. La mezcla de reacción se concentró y el residuo se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 100% acetato de etilo/heptanos) para proporcionar 6-(3-ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-((3-*endo*)-3-metoxi-8-azabiciclo[3.2.1]octan-8-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina MS (ESI+) m/z 711.7 (M+H)+.

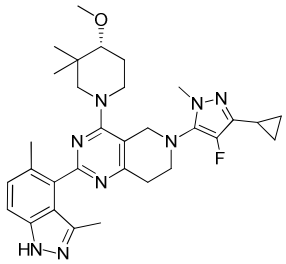
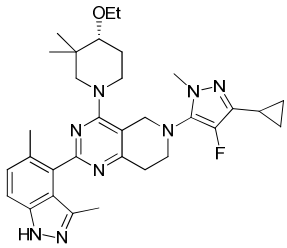
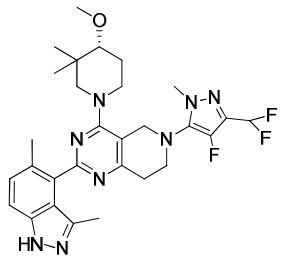
56- B.6-(3-ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-((3-*endo*)-3-metoxi-8-azabiciclo[3.2.1]octan-8-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.

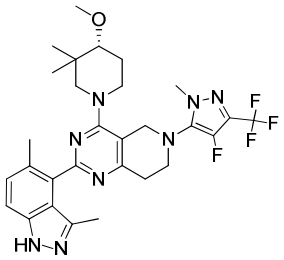


Se preparó 6-(3-ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-((3-*endo*)-3-metoxi-8-azabiciclo[3.2.1]octan-8-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina en un método similar al descrito en el Ejemplo **55- G.** ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 12,57 (s, 1 H), 7,37 (d,J = 8,3 Hz, 1 H), 7,20 (d, J = 8,6 Hz, 1 H), 4,37 (br. s., 2 H), 4,21 (s, 2 H), 3,55(S, 3 H), 3,40 - 3,46 (m, 4 H), 3,20 (s, 3 H), 2,89 (t, J = 5,8 Hz, 2 H), 2,18 (s, 3 H), 1,93 - 2,04 (m, 4 H), 1,82 - 1,88 (m, 6 H), 1,74 - 1,81 (m, 1 H), 0,80 - 0,87 (m, 2 H), 0,70 - 0,75 (m, 2 H); MS (ESI+) m/z 557.6 (M+H)+.

Los siguientes compuestos se prepararon con un método similar.

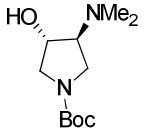
	Estructura	Nombre Quimico y Datos Analiticos
56-C		*(S)*-6-(3-ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (br. s., 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.3 Hz, 1 H), 4.29 (d, *J*=13.4 Hz, 1 H), 4.17 (d, *J*=14.1 Hz, 1 H), 3.64 - 3.74 (m, 1 H), 3.54 (s, 3 H), 3.42 - 3.50 (m, 2 H), 3.27 (s, 3 H), 2.95 - 3.10 (m, 2 H), 2.89 - 2.96 (m, 2 H), 2.80 - 2.89 (m, 1 H), 2.58 - 2.63 (m, 1 H), 2.18 (s, 3 H), 1.83 - 1.96 (m, 4 H), 1.71 - 1.81 (m, 1 H), 1.49 - 1.60 (m, 1 H), 0.92 (s, 3 H), 0.78 - 0.87 (m, 5 H), 0.66 - 0.75 (m, 2 H); MS (ESI+) *m/z* 559.4 $(M+H)^+$.

56-D		*(R)*-6-(3-ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.6 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 4.29 (d, *J*=14.9 Hz, 1 H), 4.16 (d, *J*=15.2 Hz, 1 H), 3.64 - 3.72 (m, 1 H), 3.53 (s, 3 H), 3.46 (t, *J*=6.2 Hz, 2 H), 3.27 (s, 3 H), 3.00 - 3.08 (m, 1 H), 2.97 (dd, *J*=9.0, 3.9 Hz, 1 H), 2.91 (app. t, *J*=6.1 Hz, 2 H), 2.84 (d, *J*=12.9 Hz, 1 H), 2.18 (s, 3 H), 1.88 - 1.95 (m, 1 H), 1.87 (s, 3 H), 1.72 - 1.81 (m, 1 H), 1.49 - 1.60 (m, 1 H), 0.92 (s, 3 H), 0.80 - 0.86 (m, 5 H), 0.68 - 0.74 (m, 2 H); MS (ESI+) *m/z* 559.5 $(M+H)^+$.
56-E		*(R)*-6-(3-ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-etoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. 1H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 4.22 - 4.34 (m, 1 H), 4.10 - 4.20 (m, 1 H), 3.65 - 3.75 (m, 1 H), 3.55 - 3.64 (m, 1 H), 3.53 (s, 3 H), 3.46 (t, *J*=6.1 Hz, 2 H), 2.99 - 3.10 (m, 2 H), 2.88 - 2.95 (m, 2 H), 2.84 (d, *J*=12.9 Hz, 1 H), 2.18 (s, 3 H), 2.00 (s, 1 H), 1.87 (s, 4 H), 1.72 - 1.81 (m, 1 H), 1.55 (d, *J*=10.1 Hz, 1 H), 1.23 (s, 1 H), 1.09 (t, *J*=6.9 Hz, 3 H), 0.91 (s, 3 H), 0.79 - 0.87 (m, 5 H), 0.67 - 0.74 (m, 2 H); MS(ESI+) *m/z* 573.5 $(M+H)^+$.
56-F		(*R*)-6-(3-(difluorometil)-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.1 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 6.95 (t, *J*=53.3 Hz, 1 H), 4.36 (d, *J*=14.7 Hz, 1 H), 4.23 (d, *J*=15.2 Hz, 1 H), 3.63 - 3.75 (m, 4 H), 3.53 (t, *J*=6.2 Hz, 2 H), 3.27 (s, 3 H), 3.01 - 3.10 (m, 1 H), 2.90 - 3.00 (m, 3 H), 2.86 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.88 - 1.96 (m, 1 H), 1.87 (s, 3 H), 1.50 - 1.61 (m, 1 H), 0.92 (s, 3 H), 0.82 (s, 3 H); MS (ESI+) m/z 569.6 $(M+H)^+$.

56-G		(*R*)-2-(3,5-dimetil-1H-indazol-4-il)-6-(4-fluoro-1-metil-3-(trifluorometil)-1H-pirazol-5-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.59 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.8 Hz, 1 H), 4.40 (d, *J*=15.2 Hz, 1 H), 4.25 (d, *J*=15.2 Hz, 1 H), 3.75 (s, 3 H), 3.65 - 3.72 (m, 1 H), 3.55 (t, *J*=6.3 Hz, 2 H), 3.27 (s, 3 H), 3.01 - 3.10 (m, 1 H), 2.91 - 3.00 (m, 3 H), 2.86 (d, *J*=13.1 Hz, 1 H), 2.18 (s, 3 H), 1.88 - 1.95 (m, 1 H), 1.86 (s, 3 H), 1.50 - 1.62 (m, 1 H), 0.92 (s, 3 H), 0.82 (s, 3 H); MS (ESI+) *m/z* 587.5 $(M+H)^+$.

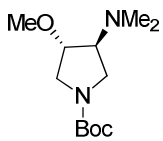
Ejemplo 57

57- A. 3 - (dimetilamino)- 4- hidroxipirrolidina- 1- carboxilato de (trans)- terc- butilo racémico



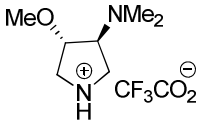
A una solución dedihidrocloruro de (trans) - 4 - (dimetilamino)- pirrolidin- 3- ol racémico(0.87 g, 4.28 mmol) en DCM (10 ml) se añadió trietilamina (2.39 ml, 17.1 mmol) y dicarbonato de di- terc- butilo (0.99 ml, 4.28 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó entonces con agua y se extrajo tres veces con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar 3 - (dimetilamino)- 4-hidroxipirrolidina- 1- carboxilato de (trans)- terc- butilo racémico.^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 5.09 (d, *J* = 4,8 Hz, 1 H), 4,09 (br. s., 1 H), 3,42 (m, 2 H), 3,08 - . 3,18 (m, 1 H), 2,95 - 3,04 (m, 1 H), 2,17 (s, 6 H), 1,39 (s, 9 H).

57- B. (trans)- terc- butil- 3- (dimetilamino)- 4- metoxipirrolidina- 1- carboxilato racémico.



A una solución de 3 - (dimetilamino)- 4- hidroxipirrolidina- 1- carboxilato de (trans)- terc- butilo racémico (0.96 g, 4.17 mmol) en THF (40 ml) a 0 °C se añadió NaH (0.25 g, 6.25 mmoles, dispersión al 60% en aceite mineral), y la mezcla de reacción se agitó a 0 °C durante 10 min. Luego, se añadió por goteoyodometano (0.29 ml, 4.6 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se apagó con NH_4Cl acuoso saturado y se extrae tres veces con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar racémica- (trans)- terc- butil- 3- (dimetilamino)- 4- metoxipirrolidina- 1- carboxilato. ^{1}H RMN (400 MHz, DMSO- d_6) ppm δ 3,84 (br. s., 1 H)., 3,46 - 3,54 (m, 1 H), 3,25 (s, 3 H), 3,12 - 3,22 (br. s., m, 3 H), 2,72 (br. s., 1 H), 2,16 (s, 6 H), 1,39 (s, 9 H).

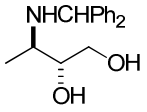
57- C. 2,2,2- trifluoroacetato de (trans) - 3 - (dimetilamino)- 4- metoxipirrolidin- 1- io racémico



A una solución de (trans)- terc- butil- 3- (dimetilamino)- 4- metoxipirrolidina- 1- carboxilato racémico (0.68 g, 2.8 mmol) en DCM (4.0 ml) se añadió TFA (2.1 ml, 28 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 18 h. Luego, la mezcla de reacción se concentró bajo presión reducida para proporcionar de2,2,2- trifluoroacetato de (trans) - 3 - (dimetilamino)- 4- metoxipirrolidin- 1- io. ^{1}H RMN (400 MHz, OXIDO DE DEUTERIO) δ ppm 4.42 – 4.48 (m, 1 H), 3.96 – 4.05 (m, 2H), 3.60 (d, *J* = 5,4 Hz, 2 H), 3,48 - 3,55 (m, 1 H), 3,39 (s, 3 H), 2,97 (s, 6 H).

Ejemplo 58

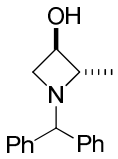
58- A. Racémica- (2R *, 3R *) - 3 - (bencidrilamino) butano- 1 ,2- diol.



A una suspensión agitada de (E)- but- 2- en- 1- ol (825 l, 9,32 mmol) en DCM (23 ml) se añadió m- CPBA (2.19 g, 9.79 mmol) a 0 °C. La reacción se dejó calentar a temperatura ambiente y se agitó durante 16 h. Después, la mezcla de reacción se enfría a 0 °C y la solución se filtró y el sólido se lavó con DCM frío. El filtrado se concentró y se llevó al siguiente paso.

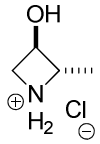
A una solución de 3 - (metiloxiran- 2- il) metanol (0.826 g, 9.38 mmol) en DCM se añadió α- aminodifenilmetano (1.50 ml, 8.44 mmol) y titanio (IV) isopropóxido (5.5 ml, 18,7 mmol), y la mezcla de reacción se calentó a 60 °C durante 16 h. Se añadió una solución acuosa saturada de sal de Rochelle a la mezcla seguido por una solución de NaOH 3 N. La mezcla reacción se agitó durante la noche. Luego la fase acuosa se extrajo con DCM (3 x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron y se concentraron bajo presión reducida. El residuo se purificó a través de FCC (30- 60% EtOAc/heptanos) para proporcionar el compuesto del título. MS (ESI+) m/z 272.4 (M+H)+.

58- B.Racémica- (trans)- 1- benzhidril- 2- metilazetidin- 3- ol.



Preparación de racémica- (trans)- 1- benzhidril- 2- metilazetidin- 3- ol se realizó como se describe en Tetrahedron Letters, 1991, 32, 6935- 6938; en este caso el material de inicio utilizado fue racémico. ^{1}H RMN (400MHz, $CDCl_3$) δ ppm 7,47 - 7,38 (m, 5 H), 7,35 - 7,24 (m, 5 H), 4,36 (s, 1 H), 3,95 (quin, J = 6,4 Hz, 1 H), 3,69 (ddd, J = 1,0, 6,4, 7,7 Hz, 1 H), 3,03 (quin, J = 6,1 Hz, 1 H), 2,61 - 2,54 (m, 1 H), 1,79 - 1,71 (m, 1 H), 0,77 (d, J = 6,3 Hz, 3 H).

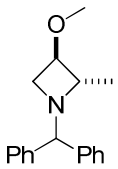
58- C. Cloruro de racémica- (trans)- 3- hidroxi- 2- metilazetidin- 1- io.



A una solución de racémica- (trans)- 1- benzhidril- 2- metilazetidin- 3- ol (0,137 g, 0.541 mmol) en MeOH (5,41 ml) se añadió Pd/C al 10% (57 mg, 0.027 mmol) y HCl4 M en dioxano (406 l, 1.62 mmol). H_2 se burbujeó a través de la solución durante 15 minutos, y la mezcla de reacción se agitó durante la noche. La mezcla se filtró a través de una almohadilla de Celite ® y se enjuagó con DCM. El filtrado se concentró para proporcionar el compuesto del título.

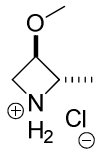
Ejemplo 59

59- A.Racémica- (trans)- 1- benzhidril- 3- metoxi- 2- metilazetidina.



A una solución de racémica- (trans)- 1- benzhidril- 2- metilazetidin- 3- ol (0.198 g, 0.782 mmol) en THF (16 ml) se añadió yodometano (98 µl, 1,6 mmol) e hidruro de sodio (0.035 g , 0.86 mmoles, 60% en aceite mineral). Después de 1.5 h, se añadió agua y la mezcla se extrajo con EtOAc (3x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron y se concentró bajo presión reducida. El residuo se purificó a través de FCC (0- 15% EtOAc/n- heptano) para proporcionar el compuesto del título. MS (ESI+) m/z 268.2 (M+H)+.

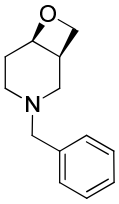
59- B.Cloruro de (trans)- 3- metoxi- 2- metilazetidin- 1- io racémico



La preparación decloruro de (trans)- 3- metoxi- 2- metilazetidin- 1- io racémico se realizó como se describe en el **Ejemplo 58- C.**

Ejemplo 60

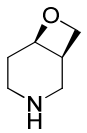
60- A. (cis)- 3- bencil- 7- oxa- 3- azabiciclo [4.2.0] octano racémico.



Paso 1: A una solución de sal de hidrocloruro de 1- bencil- 4- oxopiperidina- 3- carboxilato de etilo(5.2 g, 17.5 mmol) en EtOH (80 ml) se añadió $NaBH_4$ (5.29 g, 140 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h, después se filtró a través de celite y se concentró bajo presión reducida. El residuo se disolvió en DCM, se lavó con agua, se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar una mezcla de cis y trans diastereómeros de 1- bencil- 3- (hidroximetil) piperidin- 4- ol, que se utilizó para la siguiente etapa sin purificación adicional.

Paso 2: A una solución de cis crudo anterior y la mezcla de trans de 1- bencil- 3- (hidroximetil) piperidin- 4- ol (2.69 g, 12.16 mmol) en DCM (60 ml) se añadió DIPEA (3.39 ml, 24.31 mmoles) y MsCl (0.947 ml, 12.2 mmol) por goteo a 0 °C. La mezcla de reacción se agitó adicionalmente durante 1.5 horas a 0- 5 °C y después se apagó con solución acuosa saturada de $NaHCO_3$. La fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraronpara proporcionar una mezcla decompuestos mono ybi- mesilado. Luego el producto crudo se disolvió en THF (250 ml) y se añadió NaH (1.05 g, 43.8 mmol, 60% en aceite mineral) en porciones a temperatura ambiente. Después de agitar durante 40 min a temperatura ambiente, la mezcla de reacción se calentó luego a 65 °C durante 4.5 h. La mezcla de reacción se enfrió a temperatura ambiente, después se apagó con agua y se concentró al vacío. El residuo se disolvió en EtOAc, se lavó con solución acuosa saturada de NH_4Cl, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 100% EtOAc/heptanos) para proporcionar (cis)- 3- bencil- 7- oxa- 3- azabiciclo [4.2.0] octano racémico como un aceite incoloro. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,32 - 7,41 (m, 5H), 4,97 (ddd, J = 3,03, 4,42, 6,19 Hz, 1H), 4,68 (t, J = 5,68 Hz, 1H), 4,07 - 4,13 (m, 1H), 3,53 - 3,60 (m, 2H), 2,90 - 2,98 (m, 1H), 2,82 - 2,90 (m, 1H), 2,52 - 2,59 (m, 2H), 2,49 (dd, J = 6,32, 11,37 Hz, 1H), 1,83 - 1,87 (m, 2H).

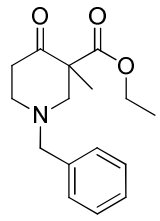
60- B. (cis)- 7- oxa- 3- azabiciclo [4.2.0] octano racémico



A una solución de (cis)- 3- bencil- 7- oxa- 3- azabiciclo [4.2.0] octano racémico (440 mg, 2.165 mmol) y HOAc (200 µl, 3,49 mmol) en MeOH (40 ml) se añadió Pd/C (5%, 461 mg, 0.216 mmol) a temperatura ambiente bajo atmósfera de nitrógeno. El recipiente fue evacuado y se llenó nuevamente con hidrógeno 3 veces y luego se dejó agitar bajo una atmósfera de hidrógeno durante 3 horas. La mezcla se filtró a través de Celite y el Celite se lavó con MeOH y EtOAc. Los filtrados se combinaron y se concentraron bajo presión reducida (temperatura del baño < 30 °C) para proporcionar (cis)- 7- oxa- 3- azabiciclo [4.2.0] octano racémico como una sal de ácido acético. ^{1}H RMN (400 MHz, CD_3OD) δ ppm 5,11 (td, J = 3,32, 6,76 Hz, 1H), 4,84 (t, J = 6,57 Hz, 1H), 4,24 (dd, J = 3,92, 6,44 Hz, 1H), 3,46 (dd, J = 6,95, 13,52 Hz, 1H), 3,33 - 3,40 (m, 1H), 3,04 -3,14 (m, 3H), 1,95 -2,02 (m, 2H).

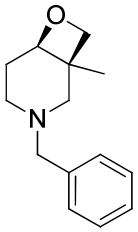
Ejemplo 61

61- A. 1- bencil- 3- metil- 4- oxopiperidina- 3- carboxilato de etilo



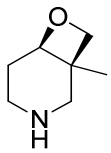
A una suspensión dehidrocloruro de 1- bencil- 4- oxopiperidina- 3- carboxilato de etilo (20 g, 67.2 mmol) en THF (130 ml)/DMF (130 ml) se añadió KOH (polvo, 7.64 g, 136 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 5- 10 minutos, luego añadió yodometano (4.62 ml, 73.9 mmol) por goteo. La mezcla de reacción se agitó adicionalmente durante 3 horas a temperatura ambiente y después se apagó con agua. La fase acuosa se extrajo dos veces con éter dietílico. Las fases orgánicas se combinaron y se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 20% EtOAc/heptanos) para proporcionar 1- bencil- 3- metil- 4- oxopiperidina- 3- carboxilato de etilo.^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7,15 - 7,45 (m, 5H), 4,00 - 4,21 (m, 2H), 3,66 (d, J = 13,39 Hz, 1H), 3,47 (d, J = 13,39 Hz , 1H), 3,30 (dd, J = 2,78, 11,62 Hz, 1H), 2,96 - 3,08 (m, 1H), 2,77 (ddd, J = 6,69, 11,68, 14,46 Hz, 1H), 2,36 - 2,45 (m, 1H), 2,27 - 2,35 (m, 1H), 2,14 (d, J = 11,37 Hz, 1H), 1,15 (t, J = 7,07 Hz, 3H), 1,09 (s, 3H).

61- B. (cis)- 3- bencil- 1- metil- 7- oxa- 3- azabiciclo [4.2.0] octano racémico



El compuesto anterior se sintetizó en una manera similar al **Ejemplo 60- A** para proporcionar (cis)- 3- bencil- 1- metil- 7- oxa- 3- azabiciclo [4.2.0] octano racémico. ^{1}H RMN (400 MHz, $CDCl_2$) δ ppm 7,17 - 7,47 (m, 5H), 4,49 - 4,65 (m, 1H), 4,27 (d, J = 5,05 Hz, 1H), 4,12 (d, J = 5,05 Hz, 1H), 3,57 (br. s., 2H), 2,47 - . 2,62 (m, 4H), 1,73 - 1,95 (m, 2H), 1,17 (s, 3H).

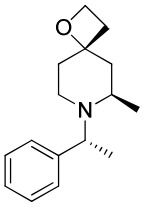
61- C. (cis)- 1- metil- 7- oxa- 3- azabiciclo [4.2.0] octano racémico.



El compuesto anterior se sintetizó en una manera similar al **Ejemplo 60- B** para proporcionar (cis)- 1- metil- 7- oxa- 3- azabiciclo [4.2.0] octano racémico como una sal de ácido acético. ^{1}H RMN (400 MHz, CD_3OD) ppm δ 4,74 (t, J = 2,91 Hz, 1H), 4,44 (d, J = 6,32 Hz, 1H), 4,39 (d, J = 6,57 Hz, 1H), 3,32 - 3,39 (m, 1H), 3,18 - 3,29 (m, 2H), 3,10 (d, J = 13,39 Hz, 1H), 1,95 a 2,10 (m, 2H), 1,28 (s, 3H).

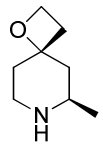
Ejemplo 62

62- A. (6R 4S,)- 6- metil- 7- ((R)- 1- feniletil)- 1- oxa- 7- azaespiro [3,5] nonano.



A una solución de yoduro de trimetilsulfoxonio (10.1 g, 46.0 mmol) en t- BuOH (anhidro, 10 ml) se añadió tBuOK (1M en t- BuOH, 36.8 ml, 36.8 mmol) y la mezcla resultante se agitó a 60 °C durante 1 h. Luego se añadió lentamente una solución de (R)- 2- metil- 1- ((R)- 1- feniletil) piperidin- 4- ona (2 g, 9.20 mmol) en t- BuOH (6 mL). La mezcla de reacción se calentó a 60 °C durante 72 h, después se enfrió a temperatura ambiente y se vertió en agua. La fase acuosa se extrajo con EtOAc (2x). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo resultante se purificó mediante cromatografía ultrarrápida en gel de sílice (0- 30% EtOAc/heptanos) para proporcionar el isómero deseado (4S, 6R)- 6- metil- 7- ((R)- 1- feniletil)- 1- oxa- 7- azaespiro [3,5] nonano como un aceite incoloro (0.67 g, 30%). ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 7,48 (d, J = 7,83 Hz, 2H), 7,34 (t, J = 7,58 Hz, 2H), 7,24 (t, J = 6,82 Hz, 1H), 4,39 - 4,51 (m, 2H), 4,25 (q, J = 6,74 Hz, 1H), 2,78 - 3,01 (m, 1H), 2,30 - 2,45 (m, 3H), 2,21 - 2,30 (m, 1H), 2,13 (td, J = 2,56, 13,07 Hz, 1H), 1,85 a 1,95 (m, 1H), 1,44 - 1,62 (m, 2H), 1,28 (d, J = 6,82 Hz, 3H), 1,20 (d, J = 6,32 Hz, 3H).

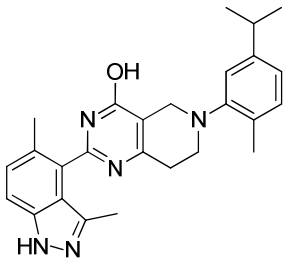
62- B. (4S, 6R)- 6- metil- 1- oxa- 7- azaespiro [3,5] nonano.



El compuesto anterior se sintetizó en una manera similar al **Ejemplo 60- B** para proporcionar (4S, 6R)- 6- metil- 1- oxa- 7- azaespiro [3,5] nonano como una sal de ácido acético. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 4,53 (t, J = 7,83 Hz, 2H), 3,19 - 3,30 (m, 2H), 3,01 (dt, J = 3,03, 13,14 Hz, 1H), 2,45 (dt, J = 1,26, 7,83 Hz, 2H), 2,15 - 2,28 (m, 2H), 1,93 (dt, J = 4,80, 13,77 Hz, 1H), 1,77 (dd, J = 12,51, 13,77 Hz, 1H), 1,34 (d, J = 6,57 Hz, 3H).

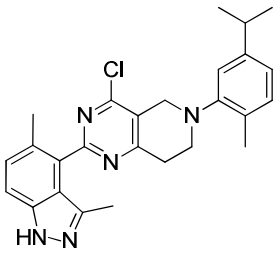
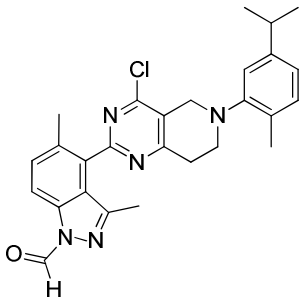
Ejemplo 63

63- A.2-(3,5-Dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-ol.



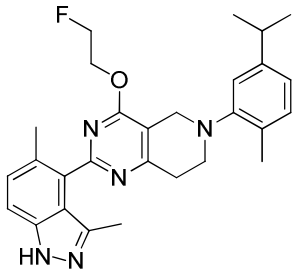
Se añadió etanol (12 ml) a 2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (2.07 g, 3.47 mmol), seguido de ácido clorhídrico acuoso 12 N de (12 ml). Luego la mezcla se calentó a 85 °C durante 18 h. La mezcla se enfrió a temperatura ambiente, se diluyó con diclorometano y se neutralizólentamente con bicarbonato de sodio acuoso saturado. Las capas resultantes se separaron y las capas acuosas se extrajeron con diclorometano. Las capas orgánicas se combinaron. Los extractos orgánicos combinados se secaron y se concentraron. El residuo se purificó mediante FCC (0- 100% EtOAc/heptano) para proporcionar2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-ol. MS (ESI+) m/z428.3 (M+H)+.

63- B. 4-Cloro-2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina y 63- C.4-(4-Cloro-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-il)-3,5-dimetil-1H-indazol-1-carbaldehido.

A una suspensión de2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-ol (1.3 g, 3.04 mmol) en DCE (50 ml) se añadió reactivo de Vilsmeier (1.95 g, 15.2 mmol).La mezcla se calentó a 50 °C durante 2 h. LC- MS mostró una reacción completa. La mezcla de reacción se vertió en agua, ylas capas se separaron. La capa acuosa se extrajo con DCM. Los extractos orgánicos se combinaron y se concentraron. El residuo se purificó mediante FCC (0- 100% EtOAc/heptano) para proporcionar4-cloro-2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidinaMS (ESI+) m/z 446.3 (M+H)+ y 4-(4-cloro-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-il)-3,5-dimetil-1H-indazol-1-carbaldehidoMS (ESI+) m/z 474.3 (M+H)+.

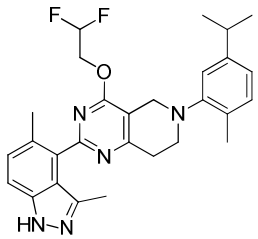
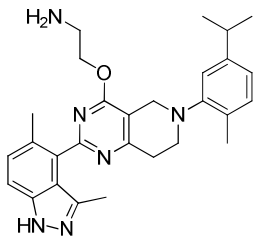
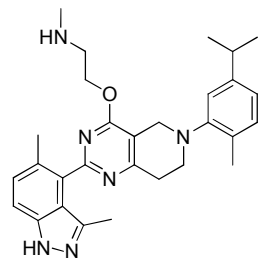
63- D.2-(3,5-Dimetil-1H-indazol-4-il)-4-(2-fluoroetoxi)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.

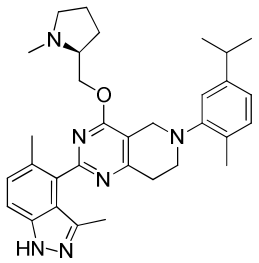
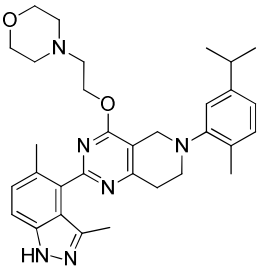
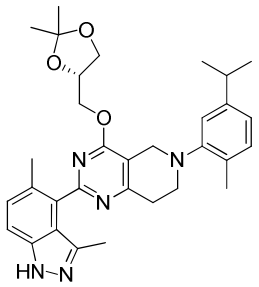


A una solución de 4-(4-cloro-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-il)-3,5-dimetil-1H-indazol-1-carbaldehido (30 mg, 0.063 mmol) en THF (3 ml) se añadió 2- fluoroethanol (16.2 mg, 0.25 mmol) y NaH (15.1 mg, 0.63 mmol, 60% en aceite mineral). La mezcla se agitó a temperatura ambiente durante 4 h. LC- MS mostró una reacción completa. La mezcla de reacción se concentró y el residuo se particionió entresoluciónde NH_4Clacuosa saturada y DCM. Se separaron las capas y la capa acuosa se extrajo de nuevo con DCM. Los extractos orgánicos se combinaron y se concentraron. El residuo se purificó mediante FCC (0- 100% EtOAc/heptano) para proporcionar2-(3,5-dimetil-1H-indazol-4-il)-4-

(2-fluoroetoxi)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina**.** ^{1}H RMN (400 MHz,METANOL- d_4) δ ppm7,47 (d, J = 8,59 Hz, 1H), 7,34 (s, 1H), 7,15 (d, J = 7,71 Hz, 1H), 7,06 (d, J = 1,39 Hz, 1H), 6,92 (dd, J = 1,52 , 7,71 Hz, 1H), 4,71 a 4,81 (m, 2H), 4,67 (s, 2H), 4,13 (s, 2H), 3,33 - 3,39 (m, 2H), 3,05 (t, J = 5,56 Hz, 2H), 2,88 (td, J = 6,93, 13,80 Hz, 1H), 2,32 (s, 3H), 2,27 (s, 3H), 1,98 (s, 3H), 1,25 (d, J = 6,82 Hz, 6H); MS (ESI+) m/z 474.4 (M+H)+.

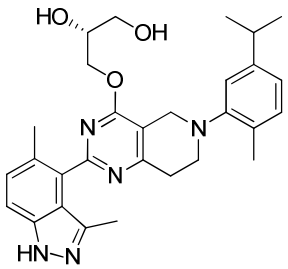
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos
63-E		4-(2,2-difluoroetoxi)-2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm7.47 (d, J = 8.59 Hz, 1H), 7.33 (d, J = 8.59 Hz, 1H), 7.14 (d, J = 7.71 Hz, 1H), 7.06 (d, J = 1.52 Hz, 1H), 6.92 (dd, J = 1.52, 7.71 Hz, 1H), 6.03 - 6.38 (m, 1H), 4.71 (dt, J = 3.66, 14.21 Hz, 2H), 4.14 (s, 2H), 3.36 (t, J = 5.68 Hz, 2H), 3.07 (t, J = 5.62 Hz, 2H), 2.88 (td, J = 6.93, 13.80 Hz, 1H), 2.32 (s, 1H), 2.28 (s, 3H), 1.98 (s, 3H), 1.25 (d, J = 6.82 Hz, 6H); MS (ESI$^+$) m/z 492.5 (M+H)$^+$.
63-F		2-((2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)oxi)etanamina. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm7.46 (d, J = 8.59 Hz, 1H), 7.32 (d, J = 8.84 Hz, 1H), 7.14 (d, J = 7.83 Hz, 1H), 7.08 (d, J = 1.64 Hz, 1H), 6.92 (dd, J = 1.71, 7.77 Hz, 1H), 4.44 - 4.52 (m, 2H), 4.16 (s, 2H), 3.33 - 3.37 (m, 2H), 2.99 - 3.09 (m, 4H), 2.88 (td, J = 6.90, 13.86 Hz, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 1.99 (s, 3H), 1.25 (d, J = 6.95 Hz, 6H); MS (ESI$^+$) *m/z*471.5 (M+H)$^+$.
63-G		2-((2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)oxi)-N-metiletanamina. ^{1}H NMR (400 MHz, METHANOL-d_4) δppm 7.46 (d, J = 8.59 Hz, 1H), 7.32 (d, J = 8.59 Hz, 1H), 7.14 (d, J = 7.96 Hz, 1H), 7.08 (d, J = 1.64 Hz, 1H), 6.92 (dd, J = 1.64, 7.71 Hz, 1H), 4.52 - 4.59 (m, 2H), 4.15 (s, 2H), 3.32 - 3.37 (m, 2H), 3.04 (t, J = 5.62 Hz, 2H), 2.93 - 2.99 (m,

		2H), 2.88 (td, J = 6.90, 13.86 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 1.98 (s, 3H), 1.25 (d, J = 6.95 Hz, 6H); MS (ESI^+) *m/z*485.6 $(M+H)^+$.
63-H		(*S*)-2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-((1-metilpirrolidin-2-il)metoxi)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm7.46 (d, J = 8.46 Hz, 1H), 7.32 (d, J = 8.59 Hz, 1H), 7.14 (d, J = 7.96 Hz, 1H), 7.05 (d, J = 1.52 Hz, 1H), 6.91 (dd, J = 1.71, 7.77 Hz, 1H), 4.47 - 4.55 (m, 1H), 4.40 (dd, J = 6.32, 11.24 Hz, 1H), 4.07 - 4.20 (m, 2H), 3.33 - 3.39 (m, 2H), 3.00 - 3.09 (m, 3H), 2.87 (td, J = 6.93, 13.80 Hz, 1H), 2.76 (dtd, J = 4.55, 6.62, 8.61 Hz, 1H), 2.44 (s, 3H), 2.29 - 2.38 (m, 4H), 2.27 (s, 3H), 2.00 - 2.10 (m, 1H), 1.99 (s, 3H), 1.73 - 1.83 (m, 2H), 1.62 - 1.73 (m, 1H), 1.20 - 1.28 (m, 6H); MS (ESI^+) m/z 525.5 $(M+H)^+$.
63-I		4-(2-((2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)oxi)etil)morfolina. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm7.46 (d, J = 8.46 Hz, 1H), 7.32 (d, J = 8.59 Hz, 1H), 7.14 (d, J = 7.83 Hz, 1H), 7.05 (d, J = 1.64 Hz, 1H), 6.92 (dd, J = 1.71, 7.77 Hz, 1H), 4.62 (t, J = 5.56 Hz, 2H), 4.12 (s, 2H), 3.60 - 3.68 (m, 4H), 3.35 (t, J = 5.68 Hz, 2H), 3.04 (t, J = 5.62 Hz, 2H), 2.83 - 2.93 (m, 1H), 2.81 (t, J = 5.62 Hz, 2H), 2.50 - 2.59 (m, 4H), 2.32 (s, 3H), 2.27 (s, 3H), 1.99 (s, 3H), 1.25 (d, J = 6.95 Hz, 6H); MS (ESI^+) m/z 541.5 $(M+H)^+$.
63-J		(*S*)-4-((2,2-dimetil-1,3-dioxolan-4-il)metoxi)-2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI^+) m/z 542.5 $(M+H)^+$.

Ejemplo 64

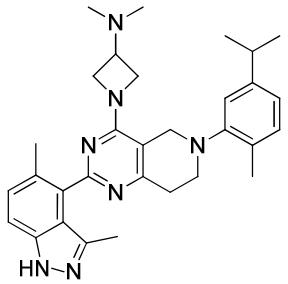
(*R*)-3-((2-(3,5-Dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)oxi)propano-1,2-diol.



A solución de (*S*)-4-((2,2-dimetil-1,3-dioxolan-4-il)metoxi)-2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (20 mg, 0,037 mmol) en TFA (0,9 ml) y H_2O (0,1 ml) se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se concentró y el residuo se particionió entre DCM y NaHCO3 acuoso saturado. Las capasse separaron y la capa acuosa se extrajo con DCM. Los extractos orgánicos se combinaron y se concentraron. El residuo se purificó por HPLC de fase inversa (C18, acetonitrilo al 10-100% en H_2O con NH_4OH al 0,1%) para proporcionar (*R*)-3-((2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)oxi)propano-1,2-diol.^{1}H RMN (400 MHz,CD2Cl2) ppm δ 7,33 (d, J = 8,46 Hz, 1H), 7,21 (d, J = 8,59 Hz, 1H), 7,08 (d, J = 7,96 Hz, 1H), 6,97 (d, J = 1,52 Hz, 1H), 6,86 (dd, J = 1,71, 7,77 Hz, 1H), 4,36 a 4,47 (m, 2H), 4,06 (s, 2H), 3,88 a 3,95 (m, 1H), 3,53 a 3,60 (m, 1H), 3,46 a 3,52 (m, 1H), 3,26 (t, J = 5,68 Hz, 2H), 3,02 a 3,10 (m, 2H), 2,76 a 2,86 (m, 1H), 2,26 (s, 3H), 2,20 (s, 3H), 1,92 (s, 3H), 1,17 (d, J = 6,95 Hz, 6H);MS (ESI +) m/z502,5 $(M + H)^+$.

Ejemplo 65

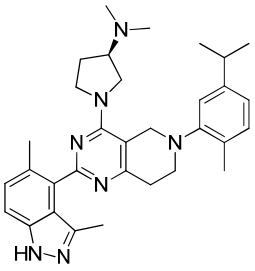
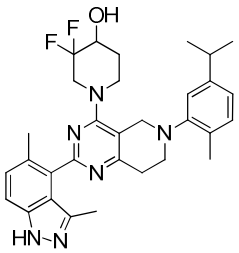
65- A. 1-(2-(3,5-Dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-N,N-dimetilazetidin-3-amina.

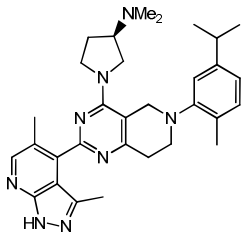
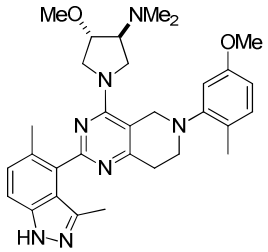


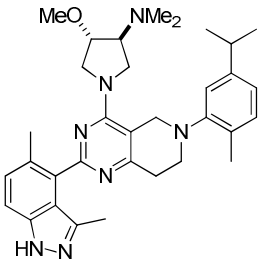
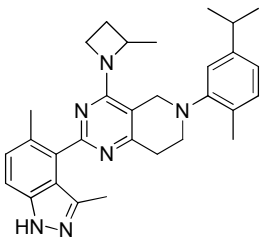
Una solución de 4-cloro-2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (30 mg, 0,07 mmol), sal de bistrifluoroacetato de N,

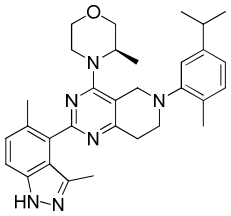
N- dimetilazetidin- 3- amina (20,0 mg, 0,2 mmol) y DIEA (0,06 ml, 0,35 mmol) en DMA (1,5 ml) se calentó a 180 ° C durante 3 min en un reactor de microondas. La mezcla de reacción se filtró a través de un filtro PTFE 0.45 mM y el filtrado se purificó mediante HPLC de fase inversa (C18, acetonitrilo al 10- 100% - H_2O con NH4OH al 0.1%) para proporcionar 1-(2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-N,N-dimetilazetidin-3-amina.^{1}H RMN (400 MHz, metanol- d4) delta ppm 7,43 (d, J = 8,46 Hz, 1H), 7,30 (d, J = 8,59 Hz, 1H), 7,13 (d, J = 7,83 Hz, 1H), 7,04 (d, J = 1,39 Hz, 1H), 6,91 (dd, J = 1,52, 7,71 Hz, 1H), 4,36 (t, J = 8,21 Hz, 2H), 4,08 a 4,20 (m, 4H), 3,32 a 3,38 (m, 2H), 3,18 a 3,27 (m, 1H) , 2,79 a 2,97 (m, 3H), 2,31 (s, 3H), 2,27 (s, 3H), 2,18 (s, 6H), 2,04 (s, 3H), 1,24 (d, J = 6,95 Hz, 6H); MS (ESI +) m/z510,5 (M + H) +.

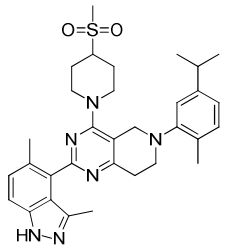
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos
65-B		(*R*)-1-(2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-N,N-dimetilpirrolidin-3-amina. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm7.42 (d, J = 8.46 Hz, 1H), 7.30 (d, J = 8.72 Hz, 1H), 7.13 (d, J = 7.96 Hz, 1H), 7.04 (d, J = 1.52 Hz, 1H), 6.90 (dd, J = 1.58, 7.77 Hz, 1H), 4.36 - 4.45 (m, 1H), 4.24 (d, J = 14.6 Hz, 1H), 3.88 - 4.01 (m, 2H), 3.76 (dt, J = 6.57, 10.55 Hz, 1H), 3.54 (dd, J = 8.59, 10.61 Hz, 1H), 3.41-3.25 (m, 2H traslapado con el solvente), 2.96 - 3.08 (m, 1H), 2.78 - 2.95 (m, 3H), 2.29 (m, 12H), 2.15 - 2.26 (m, 1H), 2.03 (s, 3H), 1.83 (quin, J = 10.26 Hz, 1H), 1.24 (d, J = 6.95 Hz, 6H);MS (ESI$^+$) *m/z*524.5 (M+H)$^+$.
65-C		1-(2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3,3-difluoropiperidin-4-ol. ^{1}H NMR (400 MHz, DICLOROMETANO-d_2) δ ppm 7.39 (d, *J*=8.3 Hz, 1 H), 7.27 (d, *J*=8.6 Hz, 1 H), 7.14 (d, *J*=7.8 Hz, 1 H), 6.98 (d, *J*=1.5 Hz, 1 H), 6.92 (dd, *J*=7.7, 1.6 Hz, 1 H), 3.93 - 4.13 (m, 3 H), 3.71 - 3.91 (m, 1 H), 3.49 - 3.68 (m, 2 H), 3.40 (td, *J*=6.1, 1.5 Hz, 3 H), 3.12 (t, *J*=5.7 Hz, 2 H), 2.89 (spt, *J*=6.8 Hz, 1 H), 2.28 (s, 6 H), 2.04 - 2.19 (m, 1 H), 1.98 (s, 3 H), 1.86 - 1.96 (m, 1 H), 1.25 (d, *J*=6.8 Hz, 6 H); MS (ESI+) m/z

		547.5 (M+H)+.
65-D		(*R*)-1-(2-(3,5-dimetil-1H-pirazolo[3,4-b]piridin-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-N,N-dimetilpirrolidin-3-amina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.14 (s, 1 H), 8.41 (s, 1 H), 7.12 (d, *J*=7.8 Hz, 1 H), 7.01 (d, *J*=1.5 Hz, 1 H), 6.88 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.43 (d, *J*=15.2 Hz, 1 H), 4.20 (d, *J*=14.9 Hz, 1 H), 3.89 (dd, *J*=10.4, 7.1 Hz, 1 H), 3.74 - 3.82 (m, 1 H), 3.58 - 3.69 (m, 1 H), 3.38 - 3.45 (m, 1 H), 3.13 - 3.23 (m, 1 H), 2.90 - 3.00 (m, 1 H), 2.79 - 2.88 (m, 2 H), 2.28 (s, 3 H), 2.23 (s, 3 H), 2.16 (s, 6 H), 2.05 - 2.09 (m, 1 H), 2.04 (s, 3 H), 1.64 - 1.76 (m, 1 H), 1.19 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 525.3 $(M+H)^+$.
65-E **65-F**		La (*trans)*-1-(2-(3,5-dimetil-1H-indazol-4-il)-6-(5-metoxi-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-4-metoxi-N,N-dimetilpirrolidin-3-aminaracémica se separó mediante HPLC quiral (columna AD-H; 20%IPA (5mM NH_4OH) en CO_2; 75g/min) para proporcionar los siguienes dos compuestos: **Enantiómero-1 (65-E)**:$[\alpha]_D^{20}$ −6.8; R_t 5.4 min, (AD-H 20 X 250 mm column; 20%IPA (5mM NH_4OH) en CO_2; 75g/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=8.8 Hz, 1 H), 6.71 (d, *J*=2.5 Hz, 1 H), 6.60 (dd, *J*=8.2, 2.7 Hz, 1 H), 4.31 (d, *J*=14.9 Hz, 1 H), 4.25 (d, *J*=14.7 Hz, 1 H), 3.89 - 3.96 (m, 2 H), 3.71 - 3.78 (m, 4 H), 3.54 - 3.65 (m, 2 H), 3.23 - 3.29 (m, 5 H), 2.84 - 2.90 (m, 2 H), 2.75 - 2.82 (m, 1 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 2.19 (s, 6 H), 1.90 (s, 3 H); MS (ESI+) *m/z* 542.3 $(M+H)^+$. **Enantiómero-2 (65-F)**: $[\alpha]_D^{20}$ +4.6; R_t 6.8 min, (columna AD-H 20 X 250 mm; 20%IPA (5mM NH_4OH) en CO_2; 75g/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 7.11 (d, *J*=8.3 Hz, 1 H), 6.71 (d, *J*=2.5 Hz, 1 H), 6.60 (dd, *J*=8.2, 2.7 Hz, 1 H), 4.31 (d, *J*=14.7 Hz, 1 H), 4.25 (d, *J*=14.7 Hz, 1 H), 3.90 - 3.95 (m, 2 H), 3.71 - 3.79 (m, 4 H), 3.54 - 3.63 (m, 2

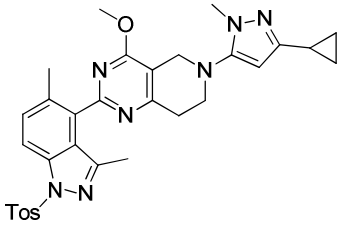
		H), 3.23 - 3.28 (m, 5 H), 2.87 (t, *J*=5.8 Hz, 2 H), 2.76 - 2.81 (m, 1 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 2.19 (s, 6 H), 1.90 (s, 3 H); MS (ESI+) *m/z* 542.3 $(M+H)^+$.
65-G **65-H**		La (*trans)*-1-(2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-4-metoxi-N,N-dimetilpirrolidin-3-aminaracémica se separó mediante HPLC quiral (columna AD-H; 20%IPA (5mM NH_4OH) en CO_2; 80g/min) para proporcionar los siguientes dos compuestos: **Enantiómero-1 (65-G)**:$[\alpha]_D^{20}$ +8.0; R_t 3.5 min, (columna AD-H 20 X 250 mm column; 20%IPA (5mM NH_4OH) en CO_2; 80g/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 7.12 (d, *J*=8.1 Hz, 1 H), 6.99 - 7.02 (m, 1 H), 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.29 (s, 2 H), 3.89 - 3.96 (m, 2 H), 3.73 - 3.81 (m, 1 H), 3.53 - 3.64 (m, 2 H), 3.26 - 3.28 (m, 4H), 2.77 - 2.91 (m, 2 H), 2.23 (s, 3 H), 2.22 (s, 3 H), 2.19 (s, 6 H), 1.91 (s, 3 H), 1.19 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 554.4 $(M+H)^+$.**Enantiómero-2 (65-H)**:$[\alpha]_D^{20}$ −10.5; R_t 4.5 min (columna AD-H 20 X 250 mm column; 20%IPA (5mM NH_4OH) en CO_2; 80g/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.57 (br. s, 1 H), 7.38 (d, *J*=8.3 Hz, 1 H), 7.21 (d, *J*=8.6 Hz, 1 H), 7.12 (d, *J*=7.8 Hz, 1 H), 7.01 (br. s, 1 H), 6.89 (d, *J*=7.8 Hz, 1 H), 4.29 (br. s., 2 H), 3.92 (br. s., 2 H), 3.71 - 3.82 (m, 1 H), 3.58 (br. s., 2 H), 3.25 - 3.30 (m, 4 H), 2.78 - 2.93 (m, 4 H), 2.23 (s, 3 H), 2.22 (s, 3 H), 2.19 (br. s., 6 H), 1.91 (s, 3 H), 1.19 (d, *J*=7.1 Hz, 6 H); MS (ESI+) *m/z* 554.4 $(M+H)^+$.
65-I **65-J**		La 2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-(2-metilazetidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidinaracémica se separó mediante HPLC quiral (columna IB; 40%IPA (10mM NH4OH) en CO2; 75g/min) para proporcionar los siguientes dos compuestos: **Enantiómero-1** (**65-I**): R_t 2.1 min, (columna IB 20 X 250 mm; 40%IPA (10mM NH_4OH) en CO_2; 75g/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56

		(s, 1 H), 7.37 (d, *J*=8.6 Hz, 1 H), 7.20 (d, *J*=8.3 Hz, 1 H), 7.12 (d, *J*=7.8 Hz, 1 H), 6.99 (s, 1 H), 6.88 (dd, *J*=7.8, 1.5 Hz, 1 H), 4.47 - 4.59 (m, 1 H), 4.25 - 4.33 (m, 1 H), 4.12 - 4.25 (m, 2 H), 3.95 (d, *J*=15.2 Hz, 1 H), 3.24 - 3.29 (m, 1 H), 3.15 - 3.23 (m, 1 H), 2.74 - 2.92 (m, 3 H), 2.35 - 2.43 (obs m, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 1.91 (s, 3 H), 1.87 - 1.98 (obs m, 1 H), 1.34 (d, *J*=6.1 Hz, 3 H), 1.20 (d, *J*=1.0 Hz, 3 H), 1.18 (d, *J*=0.8 Hz, 3 H) ; MS (ESI+) *m/z* 481.4 $(M+H)^+$.**Enantiómero-2** (**65-J**): R_t 2.5 min (columna IB 20 X 250 mm; 40%IPA (10mM NH_4OH) en CO_2; 75g/min). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 7.12 (d, *J*=8.1 Hz, 1 H), 6.99 (s, 1 H), 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.47 - 4.61 (m, 1 H), 4.25 - 4.34 (m, 1 H), 4.11 - 4.25 (m, 2 H), 3.95 (d, *J*=15.4 Hz, 1 H), 3.24 - 3.29 (m, 1 H), 3.15 - 3.24 (m, 1 H), 2.76 - 2.91 (m, 3 H), 2.36 - 2.43 (obs m, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 1.91 (s, 3 H), 1.87 - 1.98 (obs m, 1 H), 1.34 (d, *J*=6.1 Hz, 3 H), 1.20 (d, *J*=1.0 Hz, 3 H), 1.18 (d, *J*=1.0 Hz, 3 H) ; MS (ESI+) *m/z* 481.4 $(M+H)^+$.
65-K		(*R*)-4-(2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.22 (d, *J*=8.8 Hz, 1 H), 7.11 (d, *J*=8.1 Hz, 1 H), 6.95 (d, *J*=1.5 Hz, 1 H), 6.87 (dd, *J*=7.6, 1.5 Hz, 1 H), 4.04 (s, 2 H), 3.86 - 3.97 (m, 1 H), 3.80 (d, *J*=11.1 Hz, 1 H), 3.62 - 3.71 (m, 1 H), 3.48 - 3.61 (m, 2 H), 3.35 - 3.41 (m, , 4 H), 2.95 (t, *J*=5.8 Hz, 2 H), 2.76 - 2.89 (m, 1 H), 2.22 (s, 3 H), 2.18(s, 3 H), 1.88 (s, 3 H), 1.17 - 1.19 (m, 9 H); MS (ESI+) *m/z* 511.5 (M+H); MS (ESI+) *m/z* 511.5 $(M+H)^+$.

65-L		2-(3,5-dimetil-1H-indazol-4-il)-6-(5-isopropil-2-metilfenil)-4-(4-(metilsulfonil)piperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.6 (s, 1H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.22 (d, *J*=8.8 Hz, 1 H), 7.11 (d, *J*=8.1 Hz, 1 H), 6.96 (d, *J*=1.5 Hz, 1 H), 6.88 (dd, *J*=7.7, 1.6 Hz, 1 H), 4.05 (s, 2 H), 3.99 (d, *J*=13.4 Hz, 2 H), 3.37 (t, *J*=5.9 Hz, 2 H), 2.98 - 3.05 (m, 2H), 2.92 (s, 3 H), 2.79 - 2.88 (m, 1 H), 2.78 (s, 2 H), 2.20 (d, *J*=9.3 Hz, 6 H), 2.06 (d, *J*=12.1 Hz, 2 H), 1.87 (s, 3 H), 1.67 (qd, *J*=12.4, 3.7 Hz, 2 H), 1.19 (d, *J*=6.8 Hz, 6 H); MS (ESI+) *m/z* 573.3 $(M+H)^+$.

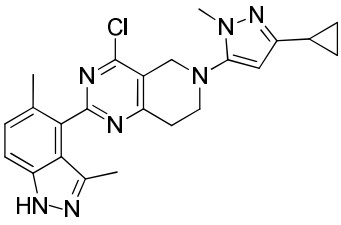
Ejemplo 66

66- A.66-A. 6-(3-Ciclopropil-1-metil-1H-pirazol-5-yl)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



Este compuesto se preparó de una manera similar a la descrita en el **Ejemplo 34- B**. MS (ESI +) m/z 584,4 (M + H) +.

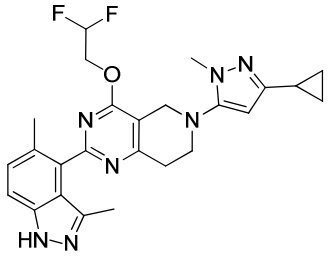
66- B. 4-Cloro-6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



Este compuesto se preparó de una manera similar a la descrita en el Ejemplo 63 a partir de 6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI +) m/z 434,3 (M + H) +.

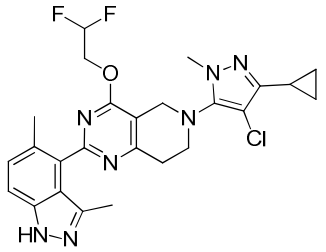
Ejemplo 67

67- A. 6-(3-Ciclopropil-1-metil-1H-pirazol-5-il)-4-(2,2-difluoroetoxi)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



Compuesto del título se preparó de una manera similar a la descrita en el **Ejemplo 63- D** a partir de 4-cloro-6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI +) m/z 480,3 (M + H) +.

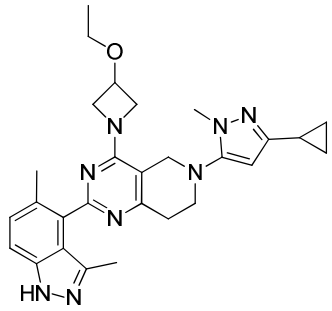
67- B. 6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-4-(2,2-difluoroetoxi)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



El compuesto del título se preparó de una manera similar a la descrita en el **Ejemplo 68-B** a partir de 6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-4-(2,2-difluoroetoxi)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.^{1}H RMN (400 MHz, METANOL- d4) δ ppm7,47 (d, J = 8,59 Hz, 1H), 7,33 (d, J = 8,72 Hz, 1H), 6,02 a 6,36 (m, 1H), 4,69 (dt, J = 3,66, 14,21 Hz, 2H), 4,38 (s , 2H), 3,68 (s, 3H), 3,59 (t, J = 5,68 Hz, 2H), 3,03 (t, J = 5,68 Hz, 2H), 2,26 (s, 3H), 1,97 (s, 3H), 1,80 - 1,91 (m, 1H), 0,80 a 0,94 (m, 4H), MS (ESI +) m/z514,4 (M + H) +.

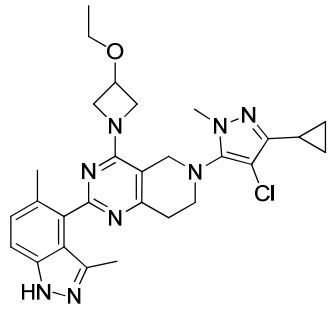
Ejemplo 68

68- A. 6-(3-Ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(3-etoxiazetidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



Este compuesto se preparó de una manera similar a la descrita en el **Ejemplo 65- A** a partir de 4-cloro-6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. MS (ESI +) m/z 499,5 $(M + H)^+$.

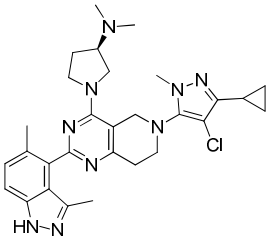
68- B. 6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(3-etoxiazetidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



A una solución de 6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(3-etoxiazetidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (30 mg, 0,060 mmol) en DCM (2 ml) se añadió N- clorosuccinimida (9,64 mg, 0,072 mmol) a temperatura ambiente. La mezcla se agitó durante 30 minutos ya continuación se concentró. El residuo se purificó por HPLC en fase inversa (C18, 10- 100% de acetonitrilo- H2O con 0,1% NH4OH) para proporcionar ^{1}H RMN (400 MHz, METANOL- D4) delta ppm7,43 (d, J = 8,46 Hz, 1H), 7,30 (d, J = 8,59 Hz, 1H), 4,49 (dd, J = 6,63, 9,41 Hz, 2H), 4,35 a 4,45 (m, 3H), 4,14 (dd , J = 4,04, 10,36 Hz, 2H), 3,66 (s, 3H), 3,46 a 3,55 (m, 4H), 2,89 (t, J = 5,68 Hz, 2H), 2,27 (s, 3H), 2,04 (s, 3H), 1.81 a 1.88 (m, 1H), 1,19 (t, J = 7,01 Hz, 3H), 0,76 a 0,93 (m, 4H), MS (ESI +) m/z 533,4 (M + H) +.

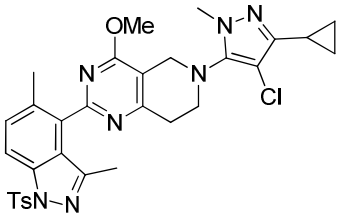
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos

68-C		(*R*)-1-(6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-N,N-dimetilpirrolidin-3-amina. ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ ppm7.42 (d, J = 8.59 Hz, 1H), 7.29 (d, J = 8.59 Hz, 1H), 4.42 (d, J = 14.91 Hz, 1H), 3.86 - 3.98 (m, 2H), 3.75 (dt, J = 6.69, 10.55 Hz, 1H), 3.65 (s, 3H), 3.43 - 3.64 (m, 4H), 2.94 - 3.06 (m, 1H), 2.78 - 2.94 (m, 2H), 2.30 (s, 6H), 2.27 (s, 3H), 2.16 - 2.25 (m, 1H), 2.04 (s, 3H), 1.77 - 1.91 (m, 2H), 0.78 - 0.92 (m, 4H);MS (ESI$^+$) *m/z*546.5 (M+H)$^+$.

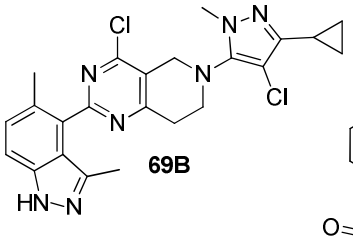
Ejemplo 69

69- A. 6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.

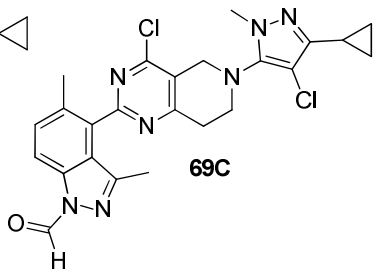


A una solución de 6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (7,0 g, 11,99 mmol) en DCM (120 ml) se añadió N- clorosuccinimida (1,76 g, 13,19 mmol) a temperatura ambiente, y la mezcla de reacción se agitó durante la noche. La mezcla se concentró y el residuo se purificó directamente mediante FCC (20- 100% EtOAc/heptano) para proporcionar MS (ESI +) *m/z* 619,9 (M+H)$^+$.

69- B.4-Cloro-6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina y **65-C. 4-(4-Cloro-6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-il)-3,5-dimetil-1H-indazol-1-carbaldehido.**



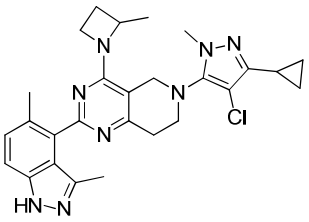
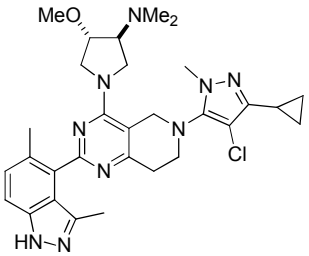
69B

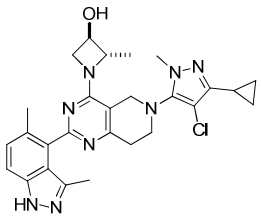
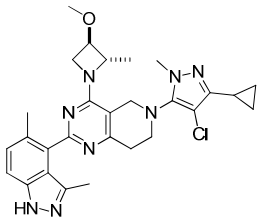


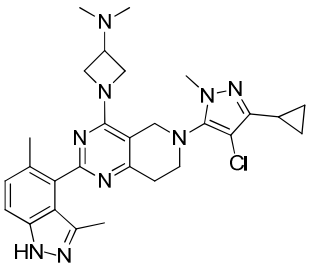
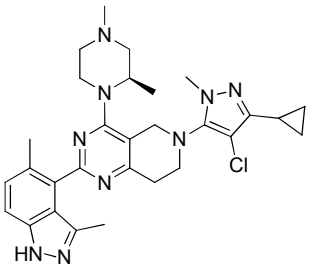
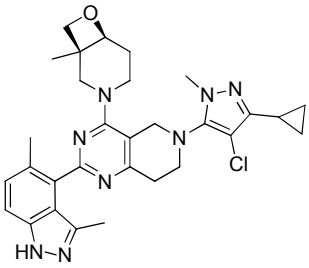
69C

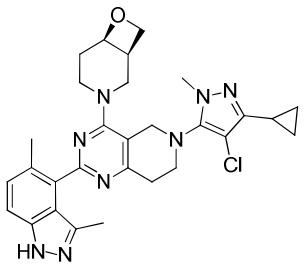
A una solución de 6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-metoxi-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (5,4 g, 8,74 mmol) en EtOH (50 ml) se añadió HCl concentrado (21,2 ml, 699 mmol) a temperatura ambiente, y la mezcla de reacción se calentó después a 100 °C durante 24 h. Luego la mezcla se enfrió a temperatura ambiente y se agregó 200 mL de agua. A continuación, se añadió NaOH sólido hasta que el pH de la solución alcanzó un pH de 10. Se agregó EtOAc a la mezcla de reacción y las capas resultantes se separaron y las capas acuosas se extrajeron con EtOAc(3x). Las capas orgánicas se combinaron y los extractos orgánicos combinados se secaron (Na2SO4), se filtraron y se concentraron a un sólido amarillo claro y se utilizaron sin purificación adicional. El sólido amarillo (2,47 g, 5,49 mmol) se disolvió en DMF (55 ml) y se agregó reactivo de Vilsmeier (3,51 g, 27,4 mmol) a la mezcla a temperatura ambiente, y la mezcla de reacción se agitó durante 15 min. A continuación, la mezcla de reacción se vertió en agua, y se añadió Et2O. Las capas se separaron y la capa acuosa se extrajo con Et2O. Los extractos orgánicos se combinaron y se lavaron con LiCl acuoso al 5%. Luego, los extractos orgánicos se secaron (Na2SO4), se filtraron y se concentraron a un aceite de color amarillo. El residuo se purificó mediante FCC (20- 100% EtOAc/heptano) para proporcionar4-cloro-6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina*and* 4-(4-cloro-6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-il)-3,5-dimetil-1H-indazol-1-carbaldehido, MS (ESI +) m/z 468,1 $(M+H)^+$ y MS (ESI^+) m/z 496,1 $(M+H)^+$, respectivamente.

Los siguientes compuestos se prepararon a partir de 4-cloro-6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina ó 4-(4-cloro-6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-il)-3,5-dimetil-1H-indazol-1-carbaldehido en una manera similar al **Ejemplo 65-A.**

69-D **69-E**		La 6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(2-metilazetidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina racémica se separó mediante HPLC quiral (columna LUX-2; 30% EtOH/heptanos; 1.0 mL/min) para proporcionar los siguientes dos compuestos:**Enantiómero-1** (**69-D**): R_t 11.52 min, (LUX-2 4.6 X 250 mm column, 30% EtOH en heptano). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.54 (s, 1 H), 7.36 (d, *J*=8.5 Hz, 1 H), 7.19 (d, *J*=8.8 Hz, 1 H), 4.49 - 4.58 (m, 1 H), 4.45 (d, *J*=15.4 Hz, 1 H), 4.22 - 4.31 (m, 1 H), 4.09 - 4.22 (m, 2 H), 3.60 (s, 3 H), 3.43 - 3.52 (m, 1 H), 2.74 - 2.91 (m, 2 H), 2.34 - 2.44 (m, 1 H), 2.19 (s, 3 H), 1.92 (s, 3 H), 1.85 - 1.90 (m, 1 H), 1.74 - 1.83 (m, 1 H), 1.33 (d, *J*=6.2 Hz, 3 H), 0.82 - 0.90 (m, 2 H), 0.72 - 0.78 (m, 2 H); MS (ESI+) *m/z* 503.3 $(M+H)^+$. **Enantiómero-2** (**69-E**): R_t 15.86 min, (columna LUX-2 4.6 X 250 mm, 30% EtOH en heptano). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.53 (s, 1 H), 7.36 (d, *J*=8.5 Hz, 1 H), 7.19 (d, *J*=8.6 Hz, 1 H), 4.49 - 4.57 (m, 1 H), 4.45 (d, *J*=15.0 Hz, 1 H), 4.23 - 4.30 (m, 1 H), 4.10 - 4.22 (m, 2 H), 3.60 (s, 3 H), 3.43 - 3.52 (m, 1 H), 3.34 - 3.41 (m, 1 H), 2.75 - 2.90 (m, 2 H), 2.35 - 2.44 (m, 1 H), 2.19 (s, 3 H), 1.92 (s, 3 H), 1.84 - 1.90 (m, 1 H), 1.74 - 1.82 (m, 1 H), 1.33 (d, *J*=6.1 Hz, 3 H), 0.81 - 0.88 (m, 2 H), 0.72 - 0.78 (m, 2 H); MS (ESI+) *m/z* 503.3 $(M+H)^+$
69-F **69-G**		La (*trans*)-1-(6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-4-metoxi-N,N-dimetilpirrolidin-3-amina racémica se separó mediante HPLC quiral (columna WhelkOD-H; 15% EtOH (DEA)/heptanos; 1.0 mL/min) para proporcionar los siguientes dos compuestos: **Enantiómero-1** (**69-F**): R_t 10.05 min, (columna WhelkOD-H 4.6 X 250 mm, 15% EtOH (DEA) en heptano). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d,

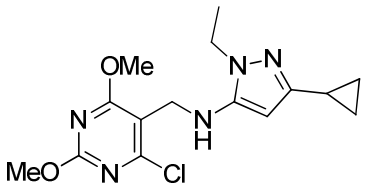
		J=8.8 Hz, 1 H), 4.49 - 4.61 (m, 2 H), 3.87 - 3.94 (m, 2 H), 3.69 - 3.76 (m, 1 H), 3.52 - 3.63 (m, 5 H), 3.41 - 3.49 (m, 2 H), 3.26 (s, 3 H), 2.86 (t, *J*=5.4 Hz, 2 H), 2.74 - 2.81 (m, 1 H), 2.20 (s, 3 H), 2.18 (s, 6 H), 1.92 (s, 3 H), 1.74 - 1.83 (m, 1 H), 0.82 - 0.88 (m, 2 H), 0.73 - 0.78 (m, 2 H); MS (ESI+) *m/z* 576.3 $(M+H)^+$. **Enantiómero-2 (69-G)**: R_t 14.69 min, (columna WhelkOD-H 4.6 X 250 mm, 15% EtOH (DEA) en heptano). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 4.48 - 4.59 (m, 2 H), 3.87 - 3.94 (m, 2 H), 3.69 - 3.76 (m, 1 H), 3.53 - 3.63 (m, 5 H), 3.42 - 3.48 (m, 2 H), 3.26 (s, 3 H), 2.83 - 2.90 (m, 2 H), 2.74 - 2.81 (m, 1 H), 2.20 (s, 3 H), 2.18 (s, 6 H), 1.92 (s, 3 H), 1.73 - 1.83 (m, 1 H), 0.81 - 0.89 (m, 1 H), 0.70 - 0.78 (m, 1 H); MS (ESI+) *m/z* 576.3 $(M+H)^+$.
69-H		*(trans)*-1-(6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-2-metilazetidin-3-ol racémico. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 12.57 (s, 1 H), 7.38 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 5.64 (d, *J*=6.3 Hz, 1 H), 4.51 - 4.39 (m, 2 H), 4.20 - 3.99 (m, 3 H), 3.84 (dd, *J*=5.3, 8.1 Hz, 1 H), 3.60 (s, 3 H), 3.53 - 3.42 (m, 1 H), 3.41 - 3.35 (m, 1 H), 2.92 - 2.74 (m, 2 H), 2.19 (s, 3 H), 1.91 (s, 3 H), 1.83 - 1.73 (m, 1 H), 1.29 (d, *J*=6.3 Hz, 3 H), 0.89 - 0.81 (m, 2 H), 0.78 - 0.71 (m, 2 H); MS (ESI+) *m/z* 519.1 $(M+H)^+$.
69-I		6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-((*trans)*-3-metoxi-2-metilazetidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina racémico. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 12.57 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=8.6 Hz, 1 H), 4.52 - 4.41 (m, 2 H), 4.31 - 4.22 (m, 1 H), 4.10 (d, *J*=15.2 Hz, 1 H), 3.96 (dd, *J*=4.7, 8.5 Hz, 1 H), 3.84 (td, *J*=4.5, 6.2 Hz, 1 H), 3.60 (s, 3 H), 3.53 - 3.44 (m, 1 H), 3.43 - 3.36 (m, 1 H), 3.23 - 3.18 (s, 3 H),

		2.92 - 2.75 (m, 2 H), 2.19 (s, 3 H), 1.90 (s, 3 H), 1.75-1.82 (m, 1 H), 1.34 (d, *J*=6.3 Hz, 3 H), 0.89 - 0.82 (m, 2 H), 0.78 - 0.71 (m, 2 H); MS (ESI+) *m/z* 533.1 (M+H).
69-J		1-(6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-N,N-dimetilazetidin-3-amina. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 12.56 (s, 1 H) 7.37 (d, *J*=8.59 Hz, 1 H) 7.19 (d, *J*=8.59 Hz, 1 H) 4.33 (s, 2 H) 4.18 (t, *J*=7.96 Hz, 2 H) 3.98 (dd, *J*=8.84, 5.31 Hz, 2 H) 3.60 (s, 3 H) 3.40 - 3.49 (m, 2 H) 3.00 - 3.13 (m, 1 H) 2.81 (t, *J*=5.43 Hz, 2 H) 2.19 (s, 3 H) 2.05 (s, 6 H) 1.92 (s, 3 H) 1.78 (tt, *J*=8.34, 5.05 Hz, 1 H) 0.82 - 0.90 (m, 2 H) 0.72 - 0.79 (m, 2 H), MH (ESI+) *m/z* 532.5 (M+H)$^+$.
69-K		(*R*)-6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(2,4-dimetilpiperazin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 12.60 (s, 1 H), 7.39 (d, *J*=8.34 Hz, 1 H), 7.21 (d, *J*=8.59 Hz, 1 H), 4.27 - 4.36 (m, 1 H), 4.17 - 4.27 (m, 1 H), 3.95 (d, *J*=6.32 Hz, 1 H), 3.57 (s, 3 H), 3.45 - 3.55 (m, 2 H), 3.39 - 3.44 (m, 1 H), 3.21 - 3.30 (m, 2 H), 2.93 (t, *J*=5.94 Hz, 2 H), 2.18 - 2.25 (m, 2 H), 2.17 (s, 3 H), 2.14 (s, 3 H), 2.02 - 2.09 (m, 1 H), 1.89 (s, 3 H), 1.73 - 1.82 (m, 1 H), 1.18 (d, *J*=6.57 Hz, 3 H), 0.82 - 0.88 (m, 2 H), 0.72 - 0.77 (m, 2 H); MS (ESI+) m/z 546.5 (M+H).
69-L		(1*S**,6*S**)-3-(6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-1-metil-7-oxa-3-azabiciclo[4.2.0]octano racémico. ^{1}H NMR (400 MHz, CD$_3$CN) δ ppm 10.72 (br. s., 1 H), 7.40 (d, *J*=8.34 Hz, 1 H), 7.24 (d, *J*=8.59 Hz, 1 H), 4.59 (t, *J*=3.16 Hz, 1 H), 4.55 (d, *J*=14.91 Hz, 1 H), 4.44 (d, *J*=6.06 Hz, 1 H), 4.28 (d, *J*=14.91 Hz, 1 H), 4.23 (d, *J*=5.81 Hz, 1 H), 3.92 (td, *J*=11.81, 4.42 Hz, 1 H), 3.65 (d, *J*=13.64 Hz, 1 H), 3.57 -

		3.63 (m, 4 H), 3.57 (s, 3 H), 3.45 - 3.53 (m, 2 H), 3.30 (d, *J*=13.39 Hz, 1 H), 2.89 - 3.06 (m, 2 H), 2.24 (s, 3 H),1.98 - 2.06 (m, 1 H), 1.80 - 1.87 (m, 2 H), 1.21 (s, 3 H), 0.83 - 0.89 (m, 2 H), 0.75 - 0.80 (m, 2 H). MS (ESI+) *m/z* 559.5 $(M+H)^+$.
69-M		(*cis*)-3-(6-(4-cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-7-oxa-3-azabiciclo[4.2.0]octano racémico. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 9.48 (br. s, 1H), 7.26 (d, *J* = 8.59 Hz, 1H), 7.16 (d, *J* = 9.09 Hz, 1H), 4.93 - 5.00 (m, 1H), 4.63 (dd, *J* = 6.32, 7.58 Hz, 1H), 4.47 (d, *J* = 14.65 Hz, 1H), 4.35 (t, *J* = 5.68 Hz, 1H), 4.14 (d, *J* = 14.65 Hz, 1H), 3.91 - 4.01 (m, 1H), 3.54 - 3.71 (m, 3H), 3.52 (s, 3H), 3.47 - 3.51 (m, 1H), 3.35 - 3.44 (m, 1H), 3.07 - 3.17 (m, 1H), 2.85 - 3.07 (m, 2H), 2.20 (s, 3H), 1.92 (s, 3H), 1.86 - 1.91 (m, 2H), 1.75 (tt, *J* = 5.34, 8.18 Hz, 1H), 0.73 - 0.80 (m, 4H); MS (ESI+) *m/z* 545.3 $(M+H)^+$.

Ejemplo 70

70- A. N ((4- cloro- 2 ,6- dimetoxipirimidin- 5- il) metil)- 3- ciclopropil- 1- etil- 1H- pirazol- 5- amina.

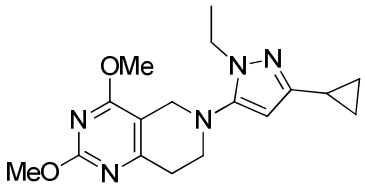


A una solución preenfriada (- 78 ° C) de 4- cloro- 2 ,6- dimetoxipirimidina (7,0 g, 40,1 mmol) en THF (125 ml) bajo una atmósfera de nitrógeno se añadió n- BuLi (17,6 ml, 44,1 mmol, 2,5 M en heptano). La solución resultante se mantuvo a - 78 ° C durante 0.5 h antes de agregar DMF (7,45 ml, 96 mmol). La solución resultante se agitó a - 78 °C durante 20 minutos y luego se retiró del baño de hielo seco y se dejó en agitación durante 30 min. En ese momento la solución se volvió al baño de hielo seco y se agitó durante 20 min antes de apagar mediante

la adición lenta de 30 ml de HCl 6 N. El matraz se retiró del baño de hielo seco y se dejó calentar a temperatura ambiente donde se dejó en agitación durante 2 h. La mezcla se concentró parcialmente bajo presión reducida y luego se diluyó con EtOAc y se lavó con NaHCO3 acuoso saturado. La capa acuosa se extrajo adicionalmente con EtOAc (2 x 300 ml) y las capas orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Después del secado en alto vacío el producto 4- cloro- 2 ,6- dimetoxipirimidina- 5- carbaldehído fue llevado a la siguiente etapa sin purificación adicional.MS (ESI +) m/z 202,9 (M+H) +.

Una solución de 4- cloro- 2 ,6- dimetoxipirimidina- 5- carbaldehído (2,4 g, 11,8 mmol), y 3- ciclopropil- 1- etil- 1H- pirazol- 5- amina (2,15 g, 14,2 mmol) en THF se calentó a 50 ° C durante 3 h. Luego el matraz se retiró del baño de calentamiento y se enfrió en un baño de hielo y EtOH (13 ml), seguido por NaBH4 (0,896 g, 23,7 mmol). La mezcla resultante se dejó calentar gradualmente a temperatura ambiente y se agitó durante 18 h. El exceso de NaBH4 se apagó lentamente con NH4Cl acuoso saturado y se diluyó con EtOAc. La capa acuosa se extrajo adicionalmente con EtOAc (2 x 250 ml) y las capas orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. El residuo se purificó luego a través de la FCC (20- 75% EtOAc/heptano) para proporcionar el compuesto del título N ((4- cloro- 2 ,6- dimetoxipirimidin- 5- il) metil)- 3- ciclopropil- 1- etil- 1H- pirazol- 5- amina. MS (ESI +) m/z 338,0 $(M+H)^+$.

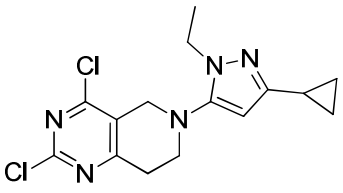
70- B. 6 - (3- ciclopropil- 1- etil- 1H- pirazol- 5- il) - 2,4- dimetoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina.



A una solución de N- ((4- cloro- 2 ,6- dimetoxipirimidin- 5- il) metil)- 3- ciclopropil- 1- etil- 1H- pirazol- 5- amina (2,42 g, 7,16 mmol) en DME (50 ml) y agua (15 ml) se añadió 4,4,5,5- tetrametil- 2- vinil- 1 ,3,2- dioxaborolano (2,5 ml, 14,3 mmol), Pd (Ph3P) 4 (0,828 g, 0,716 mmol) y carbonato de sodio (2,47 g, 23,3 mmol). La mezcla se roció con argón durante 15 minutos y luego se calentó a reflujo durante 18 h. Luego la mezcla se absorbió sobre gel de sílice y se secó bajo presión reducida. Después de cargar en seco, el producto se purificó mediante FCC (10 a 75% EtOAc/heptano) para proporcionar 3- ciclopropil- N- ((2,4- dimetoxi- 6- vinilpirimidin- 5- il) metil)- 1- etil- 1H- pirazol- 5- amina. MS (ESI^+) m/z 330,1 $(M+H)^+$.

3- ciclopropil- N- ((2,4- dimetoxi- 6- vinilpirimidin- 5- il) metil)- 1- etil- 1H- pirazol- 5- amina (2,10 g, 6,38 mmoles) se recolectó en AcOH (40 ml) y se calentó a 100 ° C durante 5 horas. El disolvente se eliminó a presión reducida y el residuo se recolectó en EtOAc (150 ml) y se lavó con solución acuosa saturada de NaHCO3 (150 ml). La capa acuosa se extrajo de nuevo con AcOEt (3 x 150 ml) y las capas orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. El residuo se purificó luego mediante FCC (40- 80% EtOAc/heptano) para proporcionar el compuesto del título 6 - (3- ciclopropil- 1- etil- 1H- pirazol- 5- il) - 2,4- dimetoxi- 5, 6 7,8- tetrahidropirido [4,3- d] pirimidina. MS (ESI +) m/z 330,2 $(M+H)^+$.

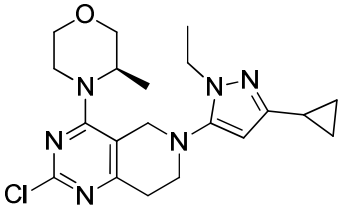
70- C. 2,4- dicloro- 6- (3- ciclopropil- 1- etil- 1H- pirazol- 5- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina.



Una solución de 6 - (3- ciclopropil- 1- etil- 1H- pirazol- 5- il) - 2,4- dimetoxi- 5 ,6,7,8- tetrahidropirido [4,3- d] pirimidina (1.20 g, 3,64 mmol) en 12 N HCl (15 ml) y EtOH (15 ml) se calentó a reflujo durante 8 h. El disolvente se eliminó luego a presión reducida y el producto 6 - (3- ciclopropil- 1- etil- 1H- pirazol- 5- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina- 2 ,4- diol se llevó a la siguiente etapa sin purificación adicional. MS (ESI +) m/z 302,1 (M+H) +.

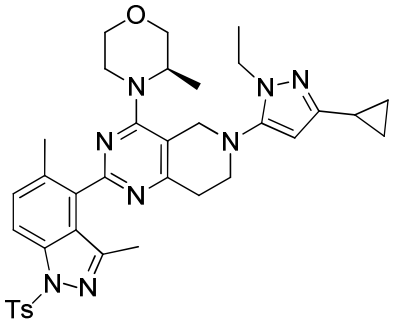
A 6 - (3- ciclopropil- 1- etil- 1H- pirazol- 5- il) - 5,6,7,8- tetrahidropirido [4,3- d] pirimidina- 2 ,4- diol (1,10 g, 3,64 mmol) se añadió $POCl_3$ (11,4 ml) y esta mezcla se calentó a reflujo. Después de 3,5 h, el exceso de $POCl_3$ se eliminó por destilación. El residuo se enfrió a 0 °C y se añadió lentamente a una solución de MeOH (50 ml) y Et_3N (12 ml). La solución se agitó a temperatura ambiente durante 15 min y se evaporó. El residuo se disolvió en DCM y se lavó con una solución de $NaHCO_3$ acuoso saturado. La capa acuosa se extrajo adicionalmente con DCM (2x). Las capas orgánicas combinadas se secaron con sulfato de sodio, se filtraron y se concentraron. El residuo se purificó mediante FCC (0- 50% EtOAc/heptano) para proporcionar el compuesto del título 2,4- dicloro- 6- (3- ciclopropil- 1- etil- 1H- pirazol- 5- il) - 5,6, 7,8- tetrahidropirido [4,3- d] pirimidina. MS (ESI +) m/z 338,0 $(M+H)^+$.

70- D. (*R*)-4-(2-Cloro-6-(3-ciclopropil-1-etil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina.



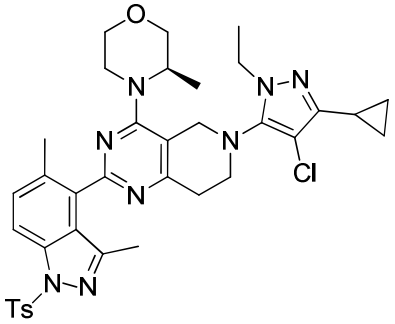
A una solución de 2,4- dicloro- 6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il) - 5,6,7,8-tetrahidropirido [4,3- d] pirimidina (0,110 g , 0,325 mmol) en DMA (2,2 ml) se añadió (R)- 3-metilmorfolina (49,3 mg, 0,488 mmol) y DIPEA (284 l, 1,63 mmol). La mezcla se calentó a 110 ° C durante 2 h. Se añadió agua y la fase acuosa se extrajo con EtOAc (3x). Las fases orgánicas se combinaron, se lavaron con salmuera (3x), se secaron con sulfato de sodio, se filtraron y se concentraron bajo presión reducida. La purificación por FCC (0- 60% EtOAc/heptano) proporcionó el compuesto del título MS (ESI^+) m/z 403,1 $(M+H)^+$.

70- E. (*R*)-4-(6-(3-Ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina.



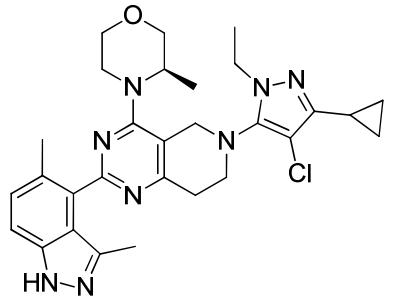
A una solución de (*R*)-4-(2-cloro-6-(3-ciclopropil-1-etil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina (0.116 g, 0.288 mmol) en DME (1.4 mL) se agregó 3,5-dimetil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1-tosil-1H-indazol (0.129 g, 0.302 mmol), $Pd(Ph_3P)_4$ (0.033 g, 0.029 mmol) y Na_2CO_3 acuoso (0.43 mL, 2 M). La mezcla se roció con argón y se calentó en un reactor de microondas a 130 ° C durante 1 h 20 min. La mezcla se filtró y se concentró bajo presión reducida. La purificación por FCC (40-100% EtOAc/heptano) proporcionó el compuesto del título (*R*)-4-(6-(3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina. MS (ESI^+) m/z 667.2 $(M+H)^+$.

70- F. (*R*)-4-(6-(4-Cloro-3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina.



A una solución de (*R*)-4-(6-(3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina (0,075 g, 0,112 mmol) en DCM (2,2 ml) se añadió NCS (0,016 g, 0,124 mmol). Después de 1 h, el disolvente se eliminó a presión reducida y el residuo se purificó directamente mediante FCC (20- 80% EtOAc /heptanos) para proporcionar el compuesto del título (*R*)-4-(6-(4-cloro-3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina. MS (ESI$^+$) m/z 701.1 $(M+H)^+$.

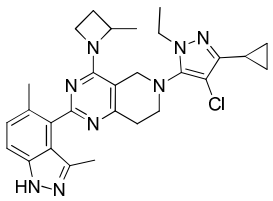
70- G. (*R*)-4-(6-(4-Cloro-3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina.

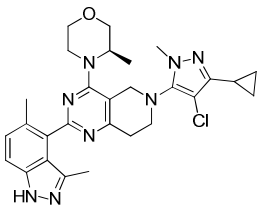
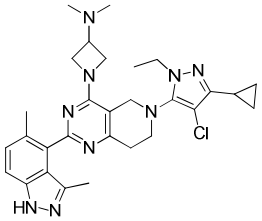


A una solución de (*R*)-4-(6-(4-cloro-3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina (0,081 g, 0,116 mmol) en MeOH (3 ml) se añadió K_2CO_3 (0,080 g, 0,578 mmol). La mezcla fue calentada a 55 ° C durante 1 h 30 min. El metanol se eliminó a presión reducida y el residuo se recolectó en agua y la fase acuosa se neutralizó a pH = 6 (con HCl 3N) y después se extrajo con EtOAc (3x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron y se concentraron bajo presión reducida. La purificación por FCC (MeOH al 0- 4%/DCM) proporcionó el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d6) δ ppm

12,58 (s, 1H), 7,39 (d, J = 8,4 Hz, 1H), 7,21 (d, J = 8,5 Hz, 1H), 4,33 (d, J = 14,9 Hz, 1H), 4,18 (d, J = 15,0 Hz, 1H), 3,90 (q, J = 7,2 Hz, 2H), 3,87 a 3,82 (m, 1H), 3,81 a 3,74 (m, 1H), 3,67 (dd , J = 11,2, 2,9 Hz, 1H), 3,63 a 3,42 (m, 4H), 3,39 a 3,31 (m, 1H), 3,00 a 2,93 (m, 2H), 2,18 (s, 3H), 1,88 (s, 3H), 1,84 a 1,73 (m, 1H), 1,29 a 1,21 (m, 3H), 1,14 (d, J = 6,6 Hz, 3H), 0,89 a 0,81 (m, 4H), 0,80 a 0,73 (m, 1H); MS (ESI +) m/z 547,2 (M+H) +.

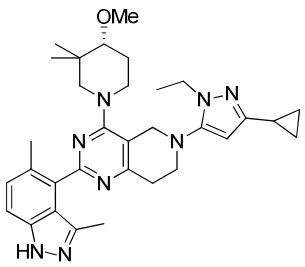
Los siguientes compuestos se prepararon de una manera similar.

	Estructura	Nombre Quimico y Datos Analiticos
70-H **70-I**		La6-(4-cloro-3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(2-metilazetidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina racémica se preparó medianteSFC MS-100; fase móvil: 5-55% MeOH + 5 mM NH_4OH en CO_2, 5 ml/min; columna: CelLUX2, 5µm, 4.6 x 100 mm) para proporcionar los enantiomeros correspondientes. **Enantiómero-1 (70-H):** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.54 (s, 1 H) 7.36 (d, *J*=8.46 Hz, 1 H) 7.19 (d, *J*=8.59 Hz, 1 H) 4.48 - 4.56 (m, 1 H) 4.45 (d, *J*=15.41 Hz, 1 H) 4.22 - 4.28 (m, 1 H) 4.17 (q, *J*=7.58 Hz, 1 H) 4.09 (d, *J*=15.41 Hz, 1 H) 3.91 - 3.98 (m, 2 H) 3.42 - 3.52 (m, 1 H) 3.36 (d, *J*=7.20 Hz, 1 H) 2.75 - 2.92 (m, 2 H) 2.35 - 2.41 (m, 1 H) 2.19 (s, 3 H) 1.92 (s, 3 H) 1.84 - 1.90 (m, 1 H) 1.80 (tt, *J*=8.32, 5.07 Hz, 1 H) 1.33 (d, *J*=6.06 Hz, 3 H) 1.26 (t, *J*=7.20 Hz, 3 H) 0.83 - 0.88 (m, 2 H) 0.74 - 0.79 (m, 2 H); MS (ESI$^+$) *m/z* 517.5 (M+H)$^+$; 98.6%ee (R_t 3.67 min, instrumento: SFC MS-100; fase movil: 5-55% MeOH + 5 mM NH_4OH en CO_2, 5 ml/min; columna: CelLUX2, 5µm, 4.6 x 100 mm) **Enantiómero-2 (70-I):** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.54 (s, 1 H) 7.36 (d, *J*=8.46 Hz, 1 H) 7.19 (d, *J*=8.46 Hz, 1 H) 4.42 - 4.55 (m, 2 H) 4.22 - 4.29 (m, 1 H) 4.16 (q, *J*=7.87 Hz, 1 H) 4.09 (d, *J*=15.16 Hz, 1 H) 3.90 - 3.99 (m, 2 H) 3.43 - 3.51 (m, 1 H) 3.33 - 3.39 (m, 1 H) 2.74 - 2.92 (m, 2 H) 2.35 - 2.43 (m, 1 H) 2.19 (s, 3 H) 1.92 (s, 3 H) 1.85 - 1.90 (m, 1 H) 1.74 - 1.85 (m, 1 H) 1.33 (d, *J*=6.19 Hz, 3 H) 1.26 (t, *J*=7.20 Hz, 3 H) 0.82 - 0.90 (m, 2 H) 0.73 - 0.80 (m, 2 H); MS (ESI$^+$) *m/z*517.4 (M+H)$^+$; 98%ee (R_t 3.97

		min, instrumento: SFC MS-100; fase móvil: 5-55% MeOH + 5 mM NH_4OH en CO_2, 5 ml/min; columna: CelLUX2, 5 □ 5 ml/min;
70-J		(*R*)-4-(6-(4-cloro-3-ciclopropil-1-metill-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-yl)-3-metilmorfolina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.61 (br. s., 1 H), 7.46 - 7.33 (m, 1 H), 7.22 (d, *J*=8.6 Hz, 1 H), 4.42 - 4.29 (m, 1 H), 4.29 - 4.13 (m, 1 H), 3.85 (br. s., 1 H), 3.79 (d, *J*=11.1 Hz, 1 H), 3.72 - 3.64 (m, 1 H), 3.62 - 3.52 (m, 6 H), 3.53 - 3.46 (m, 2 H), 2.95 (br. s., 2 H), 2.18 (s, 3 H), 1.89 (s, 3 H), 1.83 - 1.69 (m, 1 H), 1.15 (d, *J*=6.3 Hz, 3 H), 0.90 - 0.81 (m, 2 H), 0.78 - 0.67 (m, 2 H); MS (ESI+) *m/z* 533.2 $(M+H)^+$.
70-K		1-(6-(4-cloro-3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-N,N-dimetilazetidin-3-amina. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.19 (d, *J*=8.6 Hz, 1 H), 4.32 (s, 2 H), 4.18 (t, *J*=8.0 Hz, 2 H), 4.03 - 3.88 (m, 4 H), 3.42 (t, *J*=5.6 Hz, 2 H), 3.13 - 2.98 (m, 1 H), 2.82 (t, *J*=5.4 Hz, 2 H), 2.19 (s, 3 H), 2.11 - 2.00 (m, 6 H), 1.92 (s, 3 H), 1.80 (tt, *J*=5.1, 8.3 Hz, 1 H), 1.27 (t, *J*=7.2 Hz, 3 H), 0.91 - 0.81 (m, 2 H), 0.81 - 0.70 (m, 2 H); MS (ESI+) *m/z* 546.2 $(M+H)^+$.

Ejemplo 71

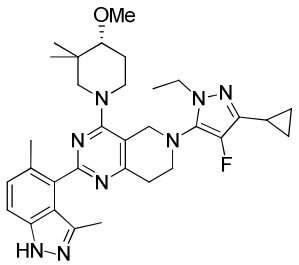
71- A. (*R*)-6-(3-Ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



(*R*)-6-(3-Ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina, preparada en un

método similar al descrito en el **Ejemplo 70- E**, se trató en un método similar al descrito en el **Ejemplo 70- G**. El residuo se purificó mediante FCC (3- 6% de MeOH/DCM) para proporcionar el compuesto del título. 1H RMN (400 MHz, DMSO- d6)delta 12,60 ppm (s, 1 H), 7,39 (d, J = 8,3 Hz, 1 H), 7,21 (d, J = 8,6 Hz, 1 H), 5,54 (s, 1 H), 4,16 a 4,04 (m, 1 H), 4,00 a 3,94 (m, 1 H), 3,89 (q, J = 7,1 Hz, 2 H), 3,66 (d, J = 13,6 Hz, 1 H), 3,27 (s, 3 H), 3,11 a 2,76 (m, 5 H), 2,18 (s, 3 H), 1,91 (dd, J = 4,5, 9,1 Hz, 1 H), 1,87 (s, 3 H), 1,77 (tt, J = 5,0, 8,4 Hz, 1 H), 1,54 (q, J = 9,3 Hz, 1 H), 1,30 (t, J = 7,2 Hz, 3 H), 0,93 (s, 3 H), 0,83 (s, 3 H), 0,82 a 0,77 (m , 2 H), 0,59 - 0,52 (m, 2 H), MS (ESI +) m/z 555,2 (M+H) +.

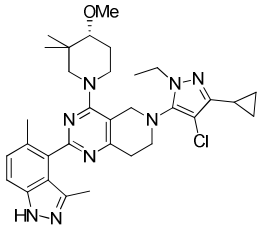
71- B. (*R*)-6-(3-Ciclopropil-1-etil-4-fluoro-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



(*R*)-6-(3-Ciclopropil-1-etil-4-fluoro-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina se preparó en un método similar al descrito en el **Ejemplo 56- A**. El residuo se purificó mediante FCC (3- 6% de MeOH/DCM) para proporcionar el compuesto del título. 1H RMN (400 MHz, DMSO- d6) δ ppm 12,59 (s, 1 H), 7,39 (d, J = 8,6 Hz, 1 H), 7,21 (d, J = 8,6 Hz, 1 H), 4,32 a 4,20 (m, 1 H), 4,19 a 4,07 (m, 1 H), 3,85 (q, J = 7,1 Hz, 2 H), 3,67 (d, J = 13,9 Hz, 1 H), 3,54 a 3,39 (m, 2 H), 3,28 (br. s., 3 H), 3,11 - . 2,89 (m, 3 H), 2,84 (d, J = 13,1 Hz, 1 H), 2,63 a 2,54 (m, 1 H), 2,23 a 2,13 (m, 3 H), 1,96 a 1,84 (m, 1 H), 1,83 a 1,72 (m, 1 H), 1,53 (d, J = 9,6 Hz, 1 H), 1,25 (t, J = 7,2 Hz, 3 H), 0,91 (s, 3 H), 0,87 - 0,82 (m, 2H), 0,82 (s, 3H), 0,76 a 0,68 (m, 2 H), MS (ESI +) m/z 573,5 (M+H)+.

Ejemplo 72

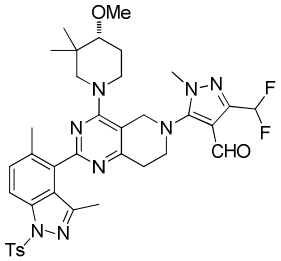
(*R*)-6-(4-Cloro-3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



El compuesto del título se preparó a partir de (*R*)-6-(3-ciclopropil-1-etil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina mediante la eliminación del grupo protector tosilo como en el **Ejemplo 70- G** seguido por cloración del pirazol de una manera similar a la descrita en el **Ejemplo 70- F**. El residuo se purificó mediante FCC (MeOH/DCM al 2- 6%) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 12,59 (s, 1 H), 7,39 (d, J = 8,3 Hz, 1 H), 7,21 (d, J = 8,8 Hz, 1 H), 4,44 a 4,30 (m, 1 H), 4,21 (d, J = 14,7 Hz, 1 H), 3,89 (q, J = 7,1 Hz, 2 H), 3,67 (d, J = 12,9 Hz, 1 H), 3,58 a 3,40 (m , 2 H), 3,28 (br. s., 3 H), 3,13 - . 2,78 (m, 5 H), 2,18 (s, 3 H), 1,89- 1,93 (m obs 1 H), 1,87 (s, 3. H), 1,76- 1,83 (m, 1 H), 1.48- 1.58 (m, 1 H), 1,23 (t, J = 7,2 Hz, 3 H), 0,91 (s, 3 H), 0,89 a 0,83 (m , 2 H), 0,82 (s, 3 H), 0,80 a 0,71 (m, 2 H), MS (ESI +) m/z 589,2 (M+H).

Ejemplo 73

73- A. (*R*)-3-(Difluorometil)-5-(2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-1-metil-1H-pirazole-4-carbaldehido.

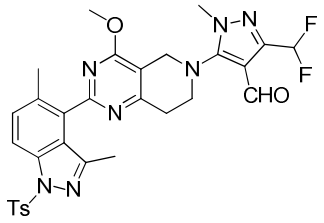


Una mezcla de(*R*)-2-(3,5-dimetil-1-tosil-1*H*-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (320 mg, 0,557 mmol), 5- cloro-3- (difluorometil)- 1- metil- 1H- pirazol- 4- carbaldehído (217 mg, 1.114 mmol) y fluoruro de cesio (169 mg, 1.114 mmol) en DMA (2.2 mL) se calentó a 140 ° C durante 1,5 h. La mezcla de reacción se particionió entre EtOAc y agua. La capa acuosa se extrajo con EtOAc (2x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó mediante FCC (EtOAc- heptano 10- 100%)

para proporcionar (*R*)-3-(difluorometil)-5-(2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-1-metil-1H-pirazole-4-carbaldehido. MS (ESI +) m/z 733,4 (M+H) +.

El siguiente compuesto se preparó de una manera similar.

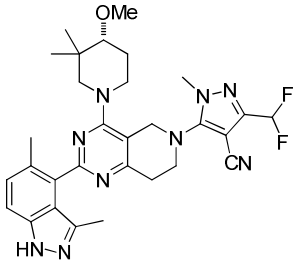
73- B. 73-B. 3-(difluorometil)-5-(2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-metoxi-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-1-metil-1H-pirazol-4-carbaldehido



MS (ESI +) m/z 622,2 (H+H) +.

Ejemplo 74

74- A. (*R*)-3-(Difluorometil)-5-(2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-1-metil-1H-pirazol-4-carbonitrilo.

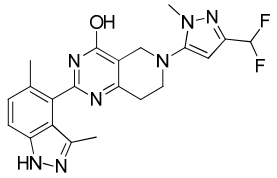


Un recipiente se cargó con (*R*)-3-(difluorometil)-5-(2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-1-metil-1H-pirazole-4-carbaldehido (54 mg, 0,074 mmol), hidrocloruro de hidroxilamina (77 mg, 1,105 mmol), y DMSO (49 µL). El recipiente se tapó y se colocó en un baño de arena precalentado a 100 ° C y la mezcla de reacción se agitó a esa temperatura. Después de 2 h, la mezcla se diluyó con metanol y se transfirió a un matraz de fondo redondo. Se agregó carbonato de potasio, y la mezcla se agitó durante 2 horas a 60 ° C, luego se dejó enfriar a temperatura ambiente. Luego la mezcla se filtró a través de Celite y se concentró, se disolvió nuevamente en metanol, se filtró a través de un filtro de jeringa, y se purificó por HPLC (15- 100 %CH_3CN en agua con NH_4OH al 0.1%) para proporcionar (*R*)-3-(difluorometil)-5-(2-(3,5-dimetil-1H-indazol-4-il)-4-(4-metoxi-3,3-dimetilpiperidin-1-il)-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-1-metil-1H-pirazol-4-carbonitrilo.^{1}H RMN (400 MHz, CD_3OD) δ ppm 7,44 (d, J = 8,6 Hz, 1 H), 7,31 (d, J

= 8,6 Hz, 1 H), 6,54 a 6,92 (m, 1 H), 4,64 (d, J = 14,8 Hz, 1 H), 4,53 (d, J = 14,8 Hz, 1 H), 3,85 a 3,95 (m, 1 H), 3,80 (s, 3 H), 3,67 a 3,75 (m, 2 H), 3,52 (dd, J = 13,4, 1,3 Hz, 1 H), 3,37 (s, 3 H), 3,01 a 3,10 (m, 4 H), 2,26 (s, 3 H), 2,01 (s, 3 H), 1,97 - 2,06 (m, 1 H), 1,67 a 1,79 (m, 1 H), 1,01 (s, 3 H), 0,93 (s, 3 H), MS (ESI +) m/z 576,4 $(M+H)^+$.

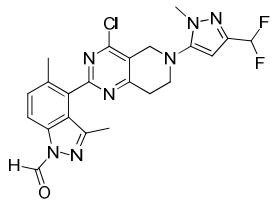
Ejemplo 75

75- A. 6-(3-(Difluorometil)-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-ol.



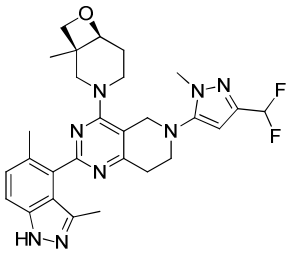
A una solución de 3-(difluorometil)-5-(2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-metoxi-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-1-metil-1H-pirazol-4-carbaldehido (0.8 g, 1.287 mmol) en etanol (10.7 mL) se agregó HCl concentrado (2,1 mL). El recipiente de microondas se selló y la mezcla se irradió a 125 ° C durante 1 h 20 min. Luego la mezcla de reacción se enfrió a 0 ° C y se vertió en agua con hielo. Se agregó lentamente bicarbonato de sodio sólido para neutralizar la mezcla de reacción a pH = 7, luego el producto bruto se extrajo con DCM (3x) y las capas orgánicas combinadas se secaron sobre sulfato de sodio para proporcionar 6-(3-(difluorometil)-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-ol, MS (ESI +) m/z 426,4 $(M+H)^+$.

75- B. 4-(4-Cloro-6-(3-(difluorometil)-1-metil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-il)-3,5-dimetil-1H-indazol-1-carbaldehido.



Este compuesto se preparó de una manera similar al **Ejemplo 69- C**. MS (ESI +) m/z 472,1 $(M+H)^+$.

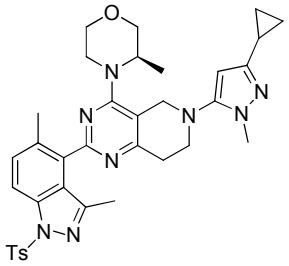
75- C.(1*S,6*S**)-3-(6-(3-(Difluorometil)-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-1-metil-7-oxa-3-azabiciclo[4.2.0]octano racémico**



Este compuesto se preparó de una manera similar al **Ejemplo 65- A**. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 12.58 (s, 1H), 7.38 (d, *J* = 8,59 Hz, 1 H), 7,20 (d, J = 8,84 Hz, 1 H), 6,85 (t, J = 55,00 Hz , 1 H), 6,17 (s, 1 H), 4,57 (t, J = 3,03 Hz, 1 H), 4,30 a 4,39 (m, 2 H), 4,14 a 4,22 (m, 2 H), 3,92 (td, J = 12,00, 4,29 Hz, 1 H), 3,73 (s, 3 H), 3,67 (d, J = 13,39 Hz, 1 H), 3,49 a 3,57 (m, 1 H), 3,38 a 3,46 (m, 1 H), 3,29 a 3,36 (m, 2 H), 2,86 a 3,05 (m, 2 H), 2,19 (s, 3 H), 1,96 a 2,07 (m, 1 H), 1,89 (s, 3 H), 1,85 - 1,92 (m, 1 H), 1,20 (s, 3 H), MS (ESI +) m/z 535,2 $(M+H)^+$.

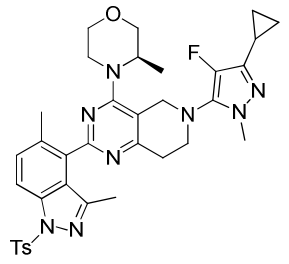
Ejemplo 76

76-A. (*R*)-4-(6-(3-Ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina.



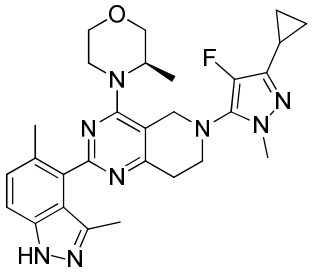
El compuesto del título se preparó a partir de (*R*)-4-(2-cloro-6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina en una manera similar al **Ejemplo 70- E**. MS (ESI +) m/z 653,4 $(M+H)^+$.

76-B.(*R*)-4-(6-(3-Ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina.



El compuesto del título se preparó a partir de (*R*)-4-(6-(3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina como se describió en el **Ejemplo 56- A**. MS (ESI +) m/z 671,2 $(M+H)^+$.

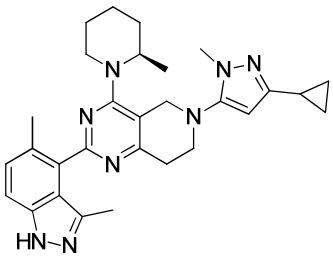
76-C. (*R*)-4-(6-(3-Ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina.



El compuesto del título se preparó a partir de (*R*)-4-(6-(3-ciclopropil-4-fluoro-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-il)-3-metilmorfolina como se describe en el **Ejemplo 55- G**. ^{1}H RMN (400 MHz, CD_2Cl_2) δ ppm 9,70 (br. s., 1H), 7,29 (d, J = 8,59 Hz, 1H), 7,18 (d, J = 8,34 Hz, 1H), 4,08 (td, J = 13,89, 15,41 Hz, 2H), 3,71 a 3,82 (m, 2H), 3,67 (dd, J = 2,91, 11,24 Hz, 1H), 3,52 a 3,60 (m, 2H), 3,51 (s, 3H), 3,25 a 3,47 (m, 4H), 2,87 a 3,12 (m, 2H), 2,15 (. br. s., 3H), 1,87 (. br. s., 3H), 1,72 (tt, J = 5,40, 8,24 Hz, 1H), 1,15 (d, J = 6,57 Hz, 3H), 0,63 a 0.85 (m, 4H). MS (ESI +) m/z 517,3 $(M+H)^+$.

Ejemplo 77

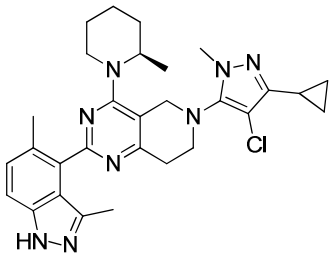
77-A. (*R*)-6-(3-Ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.



(*R*)-6-(3-Ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1-tosil-1H-indazol-4-il)-4-(2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina, se preparó en un método similar al descrito en el **Ejemplo 55- E**, se trató en un método similar al descrito en el **Ejemplo 55- G**. El residuo se purificó mediante FCC (MeOH/DCM al 1- 7%) para proporcionar el

compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ 12,59 ppm (s, 1 H), 7,45 a 7,31 (m, 1 H), 7,21 (d, J = 8,8 Hz, 1 H), 5,55 (s, 1 H), 4,10 a 3,88 (m, 3 H), 3,57 (s, 3 H), 3,51 a 3,40 (m, 1 H), 3,14 (t, J = 11,2 Hz, 1 H), 2,93 (t, J = 5,9 Hz, 2 H), 2,17 (s, 3 H), 1,87 (s, 3 H), 1,80 a 1,45 (m, 8 H), 1,16 (d, J = 6,8 Hz, 3 H), 0,84 a 0,73 (m, 2 H), 0,61 a 0,50 (m, 2 H)); MS (ESI +) m/z 497,3 (M+H).

77- B.(*R*)-6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina.

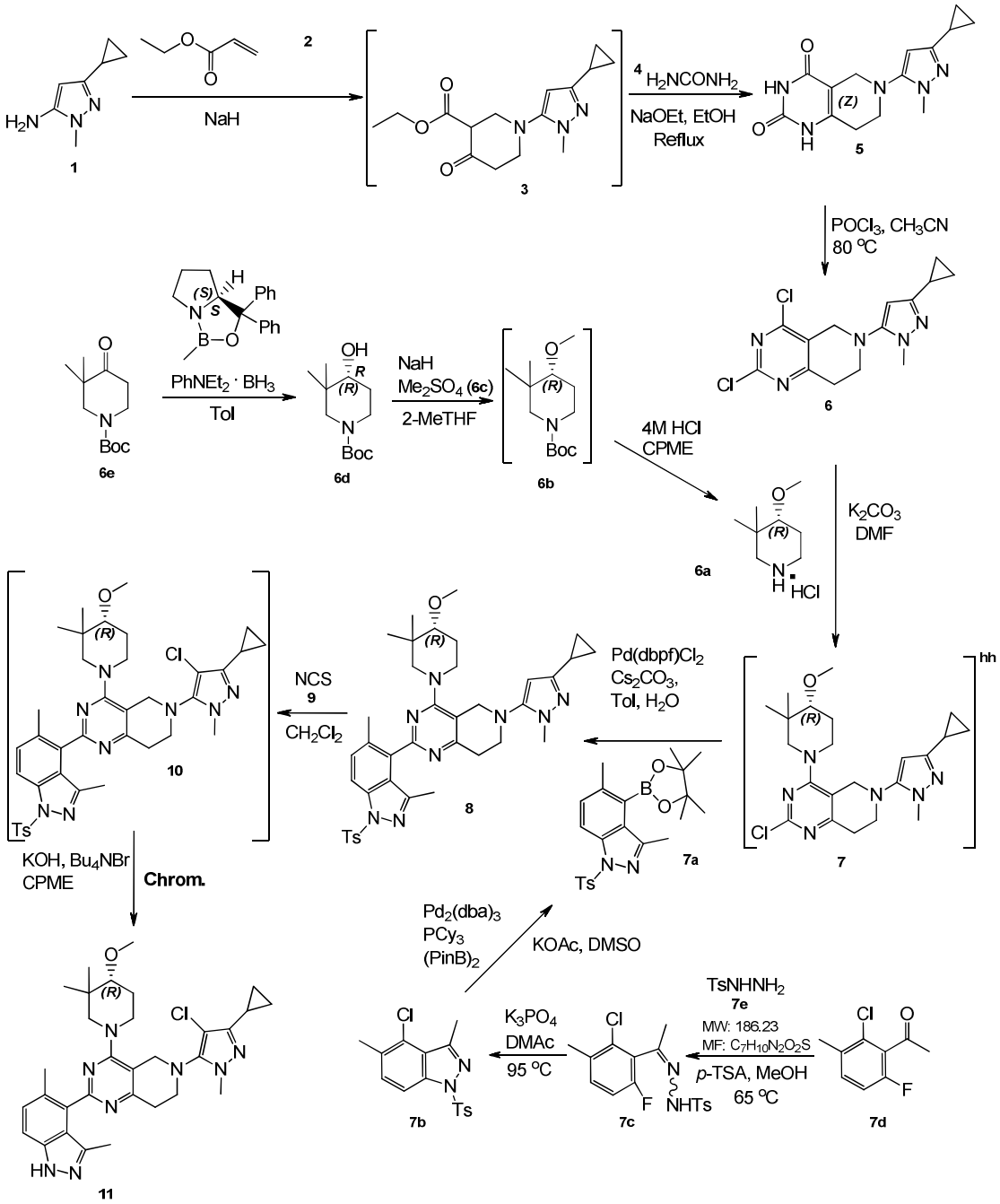


Se preparó (*R*)-6-(4-Cloro-3-ciclopropil-1-metil-1H-pirazol-5-il)-2-(3,5-dimetil-1H-indazol-4-il)-4-(2-metilpiperidin-1-il)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina en un método similar al descrito en el **Ejemplo 55- F**. El residuo se purificó mediante FCC (MeOH/DCM al 1- 7%) para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 12,59 (s, 1 H), 7,39 (d, J = 8,6 Hz, 1 H), 7,21 (d, J = 8,6 Hz, 1 H), 4,38 a 4,16 (m, 2 H), 3,99 (d, J = 6,6 Hz, 1 H), 3,57 (s, 3 H), 3,54 a 3,49 (m, 2 H), 3,45 a 3,37 (m, 1 H), 3,14 (t , J = 10,7 Hz, 1 H), 2,93 (t, J = 5,8 Hz, 2 H), 2,17 (s, 3 H), 1,89 (s, 3 H), 1,83 a 1,74 (m, 1 H), 1,44 - 1,73 (m, 6 H), 1,15 (d, J = 6,6 Hz, 3 H), 0,88 a 0,82 (m, 2 H), 0,78 - 0,72 (m, 2 H), MS (ESI +) m/z 531,3 (M+H).

<u>Ejemplo 78</u>

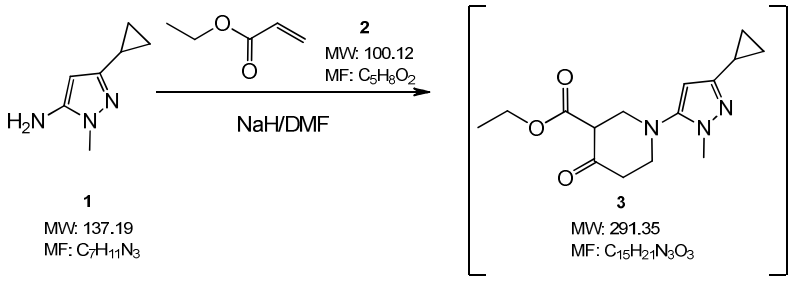
Síntesis alternativa del Ejemplo 55- G

Esquema sintético general:


NaH
PhNEt2 · BH3
Tol
NaH
Me2SO4 (6c)
2-MeTHF
4M HCl
CPME
POCl3, CH3CN
80 °C
K2CO3
DMF
Pd(dbpf)Cl2
Cs2CO3,
Tol, H2O
NCS
9
CH2Cl2
KOH, Bu4NBr
CPME
Chrom.
Pd2(dba)3
PCy3
(PinB)2
KOAc, DMSO
K3PO4
DMAc
95 °C
TsNHNH2
7e
MW: 186.23
MF: C7H10N2O2S
p-TSA, MeOH
65 °C

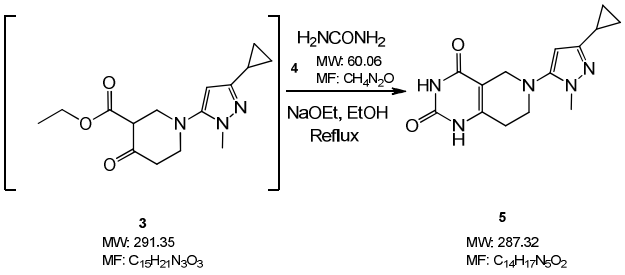
Paso 1+2 → [3]

5



En un matraz de fondo redondo de 4 cuellos de 22 L purgado con nitrógeno, se agregó 500 g de 5- aminopirazol **1**, 3500 mL de DMF y se enfrió a 2 ° C. Se agregó en porciones 160 g de NaH al 60% en aceite mineral (1.1 eq). La reacción se agitó a 0- 5 ° C durante 60 minutos y se formó una suspensión. Se agregó 870 ml de acrilato de etilo (2,2 eq) a 5- 20 ° C a la reacción durante 20 minutos. La reacción se agitó a 0- 20 ° C durante 1,5 horas seguido por la adición de 260 g de HOAc, 5000 ml de EtOAc, 5000 ml de solución de Na_2CO_3 al 5%, y 5000 ml de agua. Se formaron dos capas, se separaron y la capa acuosa se extrajo dos veces con 2000 ml de EtOAc. Todas las capas de EtOAc se combinaron y se mantuvieron a temperatura ambiente durante la noche. Las capas combinadas de EtOAc se pasaron a través de una almohadilla de gel de sílice y se lavaron con 1500 mL de EtOAc. El filtrado y el lavado se combinaron, se concentraron a un volumen mínimo como un residuo oleoso de color marrón y se purgaron con nitrógeno a temperatura ambiente durante la noche. Se obtuvo 1268 g de producto oleoso espeso con una pureza por HPLC (254 nm): 35.08%. Rendimiento: 119,7% (sin corrección de la pureza).

Paso [3]+4 → 5

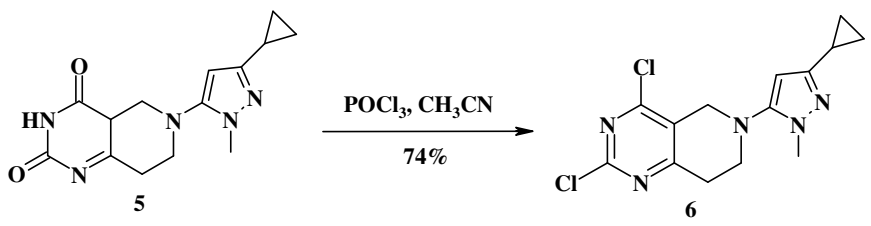


En un matraz de fondo redondo de 4 cuellos de 22 L de 498 g de urea **4**, se agregó 1268 g de cetoéster **3** crudo, 5000 ml de EtOH absoluto y 3800 g de solución de NaOEt/EtOH al 21%. La mezcla se calentó a 80 ° C y se agitó a 80 ° C durante 30 h. Luego la mezcla se dejó enfriar a temperatura ambiente y se agitó durante la noche. Luego la mezcla se enfrió a 0- 5 ° C y se agregó 733 g de HOAc a través de un embudo de adición durante 40 minutos a 0- 10 ° C.

Luego la mezcla se dividió en 4 partes iguales. Cada parte se concentró a 50 ºC/30 mbar a una pasta aguada espesa. A cada parte se agregó 1000 mL de agua y 500 ml de DCM. Las cuatro partes se combinaron nuevamente y el pH de la capa acuosa se ajustó a 8.8 mediante la adición de solución de NaOH al 50%. Se formaron sólidos y se agregó 2.0 L de agua y 1,0 L de DCM. El lote entero se filtró y se lavó con 500 ml de EtOAc. El material de filtrado se secó a 55 mbar ºC/30 durante el fin de semana. Se obtuvo 65.3 g de sólido de color beige. Pureza por HPLC (254 nm): 95.58%. ^{1}H RMN (DMSO- d_6): consistente con la estructura molecular. LC- MS: ES+288.0.

El filtrado se filtró nuevamente, se lavó con agua y se eliminó la capa acuosa. Se aisló 3.0 g de sólido de color beige sobre el filtro. Se concentraron el filtrado DCM y el lavado EtOAc al vacío y el residuo se disolvió en 1.2 L de solución de HCl 2,0 M. Se agregó 1.0 L TBME y se ajustó el pH a 8,8 mediante la adición de 200 g de solución de NaOH al 50%. La mezcla se dejó agitar durante 60 minutos a 38 ° C y luego se filtró. El pH de la capa acuosa se ajustó a 3.0 mediante la adición de solución de HCl concentrada. El pH se ajustó a – 0.24 con solución de HCl concentrada y se agregó 500 mL de TBME. Se separaron las capas y se lavó la capa acuosa con 1.0 L de TBME. El pH se ajustó a 7.5 con solución de NaOH al 50% y se mantuvo a temperatura ambiente durante la noche. Luego la capa acuosa (pH 7,0 - 7.5) se extrajo luego tres veces con 1.0 L de 2- Me THF. La capa acuosa se desechó y las capas 2- ME THF se combinaron y luego se concentraron a 40 ° C/30 mbar. El THF 2- Se me removió azeotrópicamente con iPOAc. El fondo es espeso, el sobrenadante tiene una cantidad insignificante de producto. El sobrenadante se decantó y el residuo se lavó con iPOAc. El sobrenadante de iPOAc se eliminó. Al residuo, se agregó 500 mL de THF. Al calentarse se formó una suspensión. Se agregó 500 mL de iPOAc. Se concentró a 800 mL. Se enfrió a temperatura ambiente y se agitó a temperatura ambiente durante la noche. Se filtró, se lavó con iPOAc. Se secó a 65 ° C/30 mbar durante la noche. Se obtuvo 58,0 g de sólido de color beige. HPLC (254 nm): 95.1%. ^{1}H RMN (DMSO- d_6): consistente con la estructura molecular. Rendimiento combinado a partir de la amina **1** (dos cosechas): 12,6%.

Paso 5 → 6



5

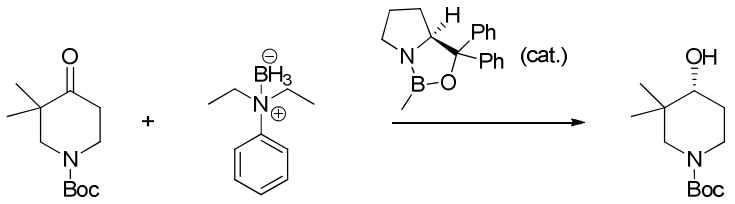
MW: 287.32
MF: $C_{14}H_{17}N_5O_2$

6

MW: 324.22
MF: $C_{14}H_{15}Cl_2N_5$

Se agregó $POCl_3$ (176 ml) lentamente a una suspensión de **5** (200 g, pureza al 97.7%) y MeCN (1.05 L) en un matraz de 5- L a 77 a 80 ºC durante 30 minutos (reacción ligeramente exotérmica, evolución de gas de HCl). Los contenidos se calentaron suavemente a reflujo a 80- 81 ° C durante 16 h para obtener una suspensión de color naranja- marrón y luego se comprobó CPS (por HPLC, SM <2%). Se agrególentamente H_2O (600 ml) en el matraz a 5- 10 ° C durante 30 min (reacción exotérmica) y luego los contenidos se agitaron a 5- 10 ° C durante 2 h. se agregó i- ProAc (3,47 L) en un recipiente durante 2 min, y luego se agregó lentamente una solución de Na_2CO_3 (504 g) en H_2O (6,2 l) a la mezcla a 5- 10 ° C durante 1 h (evolución de gas CO_2). La mezcla se mantuvo a 10 - 20 ºC durante la noche (pH final de 5.5- 6.0). La capa acuosa inferior se eliminó. La capa orgánica superior se lavó una vez con H_2O (1.2 L) y una vez con solución saturada de NaCl (1.2 L), se secó sobre $MgSO_4$ anhidro, se filtró, y luego se concentró (55 ° C, 35 mbar) a una suspensión espesa. Se agregó TBME (800 ml) en el matraz y la suspensión se calentó a 45 ° C durante 30 min y luego se agregó heptanos (800 ml). Los contenidos se enfriaron a 15 ° C durante 30 minutos y luego se filtraron los sólidos (filtración rápida). La torta del filtro se secó en un horno de vacío (55- 60 ° C, 35 mbar) durante 16 h para proporcionar **6** (164 g) como un sólido amarillo. Pureza por HPLC (254 nm) de **6**: 99.53% ^1H Análisis RMN ($CDCl_3$): consistente con la estructura. Rendimiento teórico = [(200x0.977)/287.32] = 220,6 g x324.22. Rendimiento real = (164x0.9953)/220,6 = 74,0%

Paso 6e → 6d



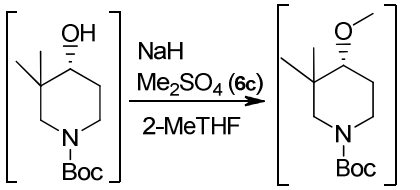
A un matraz de fondo redondo de 4 cuellos de 12 L purgado con nitrógeno, se agregó 38.9 g de catalizador S- Me CBS, 2.35 L de tolueno anhidro y 471 g de complejo BH_3.dietilanilina (DEAB). Se preparó una solución de 649.2 g de cetona en 3.90 L de tolueno anhidro en un matraz de fondo redondo de 5 L mediante agitación a temperatura ambiente. La mezcla en el matraz de fondo redondo de 12 L se calentó a 35 ° C y la solución de cetona se añadió a 35- 42 ° C en 55 minutos. La mezcla se agitó durante 30 minutos a 40- 30 ° C. La mezcla clara se enfrió a 10- 15 ° C y se agregó 4.06 L de solución de HCl 1,0 M durante 10 minutos mientras se controlaba la temperatura a 15- 25 ° C. La mezcla se agita durante 30 minutos a 20 ° C durante

30 min. Las capas se separaron y la fase orgánica se lavó con 4.0 L de solución de HCl 1,0 M, 2.0 L de solución 1,0 N de NaHCO3 y dos veces con 2.0 L de agua. Las capas orgánicas combinadas se concentraron a 50 ° C/30 mbar para proporcionar 657 g de un producto oleoso. A 657g de producto crudo oleoso se agregó 1.0 L de heptano a 50 ºC. La mezcla se enfrió a 0- 10 ° C, se sembró y se agitó a 0- 10 ° C durante 1 h. La mezcla se filtró y se lavó con 500 ml de heptano frío. Los sólidos aislados se secaron a 35 ° C/30 mbar durante el fin de semana. Se obtuvo 542.1 g de sólido blanco. Pureza por HPLC (210 nm): 94,7%. HPLC quiral (205 nm): 99,8% ee. ^{1}H RMN (DMSO- d_6): limpia y consistente con la estructura molecular. HPLC quiral ML (205 nm): 90,8% ee.

El agua madre se concentró para eliminar todos los volátiles a 50 ° C/30 mbar. Se agregó 350 g de heptano y la mezcla se enfrió a 0- 5 ° C, se sembró y se agitó a 0- 5 ° C durante 2 h. La mezcla se filtró y los sólidos se lavaron con heptano frío. Los sólidos recogidos se secaron a 35 ° durante la noche C/30 mbar. Se obtuvo 39.8 g de sólido blanco. Pureza por HPLC (210 nm): 96.4%. HPLC quiral (205 nm): 98,8% ee. ^{1}H RMN (DMSO- d_6): limpio y consistente con la estructura molecular.

Se eliminó ML por HPLC quiral (205 nm): 73,6% ee. Rendimiento total: 90,4%

Paso 6d 6c+→ [6b]

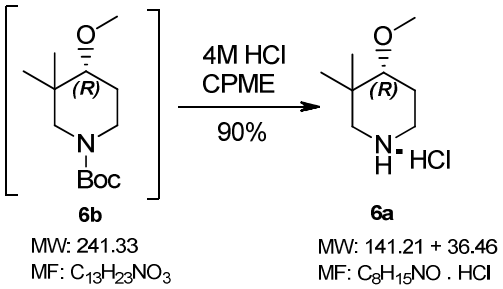


6d
MW: 229.32
MF: $C_{12}H_{23}NO_3$

6b
MW: 241.33
MF: $C_{13}H_{23}NO_3$

A un matraz de fondo redondo de 12 L purgado con nitrógeno se agregó 572 g de alcohol quiral **6d** y 4900 ml de 2- Me THF. La mezcla se enfrió a 0- 10 ° C y se agregó 199,5 g de NaH al 60% en aceite mineral en porciones. La mezcla se agitó a 0- 10 ° C durante 30 minutos y se agregó 566,3 g de Me_2SO_4 en porciones a 0- 10 ° C. Se agregó 5.3 mL de agua y la suspensión se agitó a 5- 20 ° C durante 16 horas. La mezcla se enfrió a 0- 5 ° C y se agregó por goteo 570 mL de agua y 1140 ml de solución de K_2CO_3 al 20%. Se agitó a temperatura ambiente durante 2 h. Al sentar las capas se separaron y la capa orgánica se lavó dos veces con 1100 mL de solución de NaCl al 20% y una vez con 1000 mL de agua. La capa orgánica se concentró a 50 ºC/30 mbar 858.7 g de rendimiento de un residuo oleoso. Rendimiento total: 121%.

Paso [6B] → 6 bis

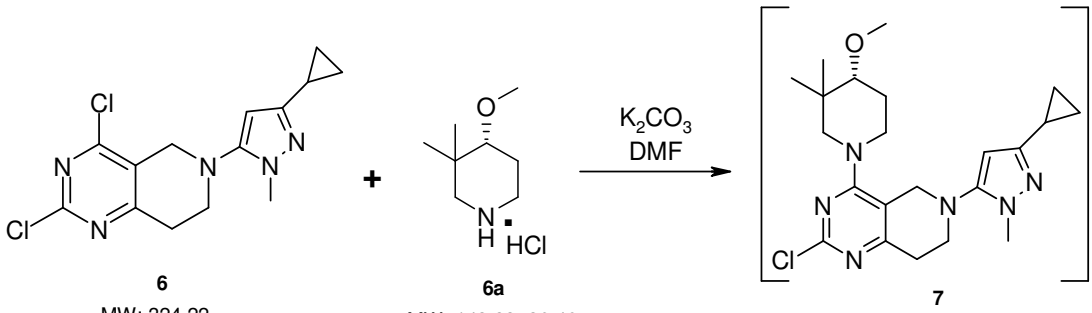


6b
MW: 241.33
MF: $C_{13}H_{23}NO_3$

6a
MW: 141.21 + 36.46
MF: $C_8H_{15}NO$. HCl

A un matraz de fondo redondo de L 12 purgado con nitrógeno, se agregó 848,7 g de Boc- amina **6b** y 800 ml de CPME. A temperatura ambiente se agregó 2.66 L de 4,0 M de HCl/CPME y la mezcla se dejó agitar a temperatura ambiente durante 18 horas. Se agregó 4000 ml de heptano y la mezcla se dejó agitar a temperatura ambiente durante 2 horas. La mezcla se filtró y se lavó con 1000 mL de heptanos. El sólido aislado se secó a 35 ° C/30 mbar durante el fin de semana. Se obtuvo 514.6 g de sólido blanco **6a**. Rendimiento: 82,1%.
^{1}H RMN (D_2O): consistente con la estructura molecular.

Paso 6+6 bis → [7]



6
MW: 324.22
MF: $C_{14}H_{15}Cl_2N_5$

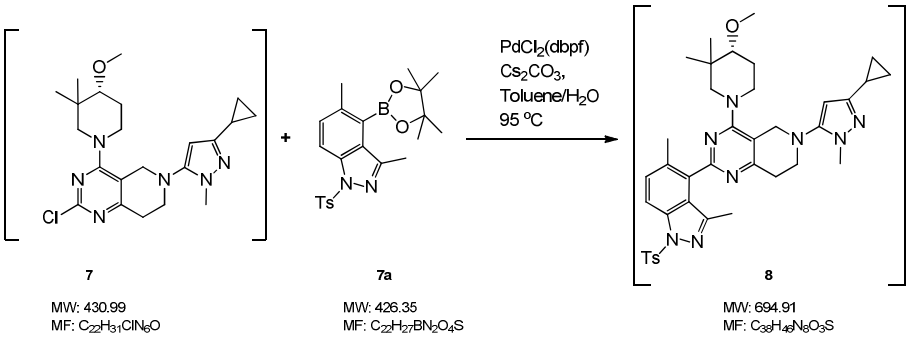
6a
MW: 143.23+36.46
MF: $C_8H_{17}NO$. HCl

7
MW: 430.99
MF: $C_{22}H_{31}ClN_6O$

Un matraz de fondo redondo de 4- cuellos de 12- L, se cargó con **6** (404.4 g, 1.247 mol), **6a** (261,9 g, 1,457 mol) y DMF (2.5 L) a temperatura ambiente. Se agitó a temperatura ambiente para proporcionar una pasta aguada. Se enfrió a 0- 5 ° C. Se agregó K_2CO_3 (518,6 g, 3,752 mol) en porción racional en 30 minutos mientras se mantenía la temperatura a 0- 5 ° C. Se agitó la pasta aguada resultante buena en 0- 5 ° C durante 6 horas. Se calentó lentamente a temperatura ambiente. Después de 8 horas (desde la terminación de la adición de K_2CO_3), se detuvo la agitación y se dejó reposar durante la noche. Se agitó a temperatura ambiente y se agregó MTBE (3,0 L) a una pasta aguada. Se agregó H_2O (3.0 L), exotérmica (Tmáx ~ 31 º C). Una

solución bifásica con una pequeña cantidad de sólidos. La mezcla de reacción se transfirió a un matraz de 22- L con una válvula inferior. El matraz de fondo redondo de 12- L se enjuagó con MTBE (4.09 L) y H_2O (2.67 L), y se transfirió al matraz de 22- L. Se agitó a temperatura ambiente durante ~ 1 h. Se dejó reposar. Aún quedó una cantidad pequeña de sólidos entre las capas. Se agregó MTBE (0.79 L, total 7.88 L) y H_2O (0.63 L, total 6.30 L). Aún algunos sólidos no se disolvieron (sólidos solubles en H_2O). La capa acuosa se separó. La fase con sólidos se mantuvo con la capa orgánica. La capa orgánica se lavó con H_2O (250 mL) para disolver los sólidos. La capa acuosa se eliminó. La capa acuosa de 250 ml se extrajo con MTBE (1,0 L). La capa de MTBE se guardo y la capa acuosa se eliminó. La primera capa acuosa se extrajo con la capa de MTBE de 1.0 L y 1.66 L de MTBE fresco (total: 2.66 L). La capa de MTBE se separó (HPLC indicó que no había **7** en la capa acuosa, eliminada). La capa de MTBE se combinó en la primera capa orgánica. Se extrajo con H_2O (1.77 L), seguido por salmuera al 20% (1.77 L). La capa orgánica se separó. Se concentró sobre rotovapor para proporcionar un residuo oleoso espumoso para proporcionar **7**. Peso: 605 g. se dejo sentar a temperatura ambiente durante la noche. HPLC: 91.03%, **6**: nd, regio- isómero de **7**: 6,11% (254 nm).LC- MS (M +1: 431,0, 432,8) confirmó la estructura. Se agregó tolueno (500 mL). Se concentró sobre rotavapor a un residuo oleoso espumoso. Se agregó tolueno (500 mL). Se concentró sobre rotavapor a un residuo oleoso espumoso. Peso: 661,2 g. Se utilizó directamente en el siguiente paso.

Paso [7]+7a → [8]



7
MW: 430.99
MF: $C_{22}H_{31}ClN_6O$

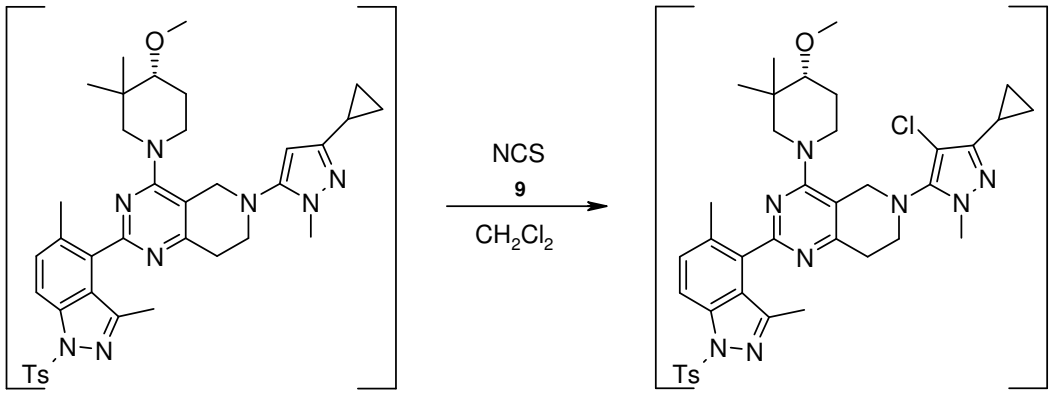
7a
MW: 426.35
MF: $C_{22}H_{27}BN_2O_4S$

8
MW: 694.91
MF: $C_{38}H_{46}N_8O_3S$

Un matraz de fondo redondo de 4 cuellos de 12 L se cargó con 584,1 g de 7 crudo/solución de tolueno, 273,3 g de 7a, 30,8 g de Pd (dbpf) Cl2, y 3,3 L de tolueno. Se burbujeó nitrógeno a través de la mezcla durante 30 minutos y luego se calentó a 60 °C mientras el burbujeo con nitrógeno continuó. En un matraz Erlenmeyer de 1000 mL se cargó 520,8 g de carbonato de cesio y 374 ml de agua. Se burbujeó nitrógeno a través de la solución a 60 °C durante 30 minutos. A 60 °C, la solución de carbonato de cesio se cargó a la mezcla. Luego la mezcla se calentó a reflujo a 93- 95 ° C durante 17.5 horas y después se enfrió. A 30 ° C se agregó 2.5 L de agua y se formaron 2 capas oscuras. La capa orgánica se aisló y se filtró a través de un lecho

de Celite. La capa orgánica se extrajo con 1,9 L de solución 2,0 M de HCl dos veces. Las capas acuosas se combinaron y se lavaron con 1.9 L de tolueno. Se agregó 446 ml de solución de NaOH al 50% y 3,9 L de EtOAc a 40 ° C a la capa acuosa y se utilizó 100 ml de solución de NaOH 4,0 N para ajustar el pH a 9. Las capas se separaron y la capa orgánica se mantuvo a temperatura ambiente durante la noche. La capa orgánica se lavó con 3.9 L de solución de NaCl al 20%. La capa orgánica se concentró proporcionando 600 g de un residuo. El residuo se recolectó en 1000 ml de MTBE a 40 ° C y 22 g de pica 120 se añadió y se mezcló. La mezcla se filtró a través de una almohadilla de gel de sílice con 1,0 L de TBME a temperatura ambiente durante la noche por la gravedad. La solución de TBME se cargó en un matraz de fondo redondo de 22 L y se agregó 500 ml de HCl 6-5 N en iPA y se agitó a temperatura ambiente durante 40 minutos. La mezcla se filtró y la torta del filtro se lavó tres veces con 1.0 L de EtOAc. La torta de filtro húmeda se transfirió a un matraz de fondo redondo de 22 L utilizando 6.0 L de solución de Na2CO3 al 5% y 6.0 L de EtOAc. Las capas se separaron y la capa orgánica se lavó con 2.0 L de solución de NaCl al 20% . La capa orgánica se mantuvo a temperatura ambiente durante la noche y después se concentró a sequedad a 40 °C/30 mbar. El residuo se recolectó en 1.0 L de DCM a 30- 40 °C y se filtró a través de un lecho de Celite en un embudo de vidrio sinterizado lavado con 500 ml de DCM y se concentró a 40 ° C/30 mbar a sequedad. Se utilizó otros 1000 ml de DCM para disolver el residuo y se concentró a 40 °C/30 mbar de nuevo hasta sequedad. Se obtuvo 538.1 g de un sólido negro espumoso. 1H NMR (CDCl3): HPLC consistente (210 nm): 95,8% del producto. LC- MS: ES+695.2. Rendimiento total: 95,1% a partir de dicloropirimidina (sin corrección de la pureza).

Paso [8]+9 → [10]



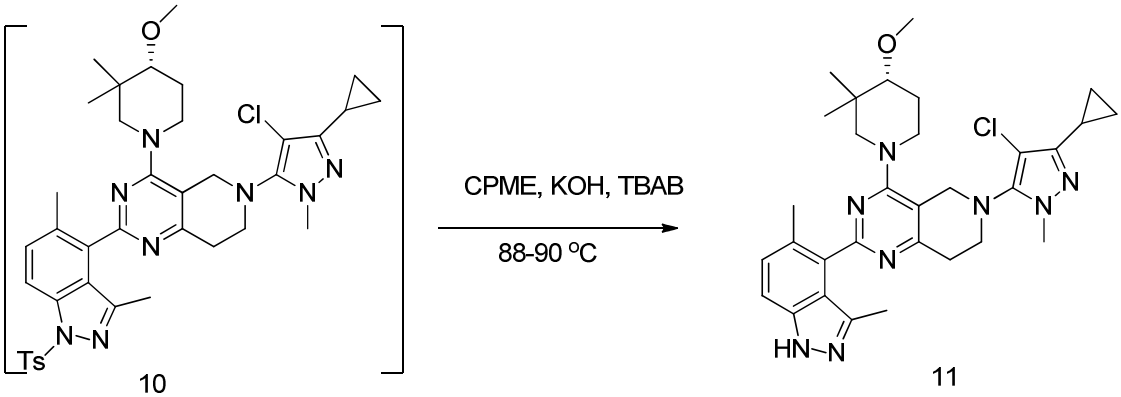
8
MW: 694.91
MF: $C_{38}H_{46}N_8O_3S$

10
MW: 729.35
MF: $C_{38}H_{45}ClN_8O_3S$

Se disolvió **8** (534 g, 768,5 mmol) en CH_2Cl_2 (2.00 L). Se observó un poco de los sólidos y una pequeña cantidad de H_2O. Se agregó 60 g de MgSO4 anhidro. Se filtró y se enjuagó con CH_2Cl_2 (1.0 L) (la filtración fue lenta) y se añadió a la mezcla de reacción. Se cargó en un matraz de fondo redondo de 4 cuellos de 12 L a temperatura ambiente bajo N_2. Se enjuagó con CH_2Cl_2 (0.5 L) y se añadió a la mezcla de reacción. Se cargó NCS (102,6 g, 768,5 mmol) a temperatura ambiente en 5- 10 minutos (levemente exotérmica, temperatura ambiente entre 14 ºC y 20 ºC). Se enjuagó con CH_2Cl_2 (0.5 L, total 4.0 L) y se agregó en la mezcla de reacción (20 ºC). Una solución de color pardo, se agitó a temperatura ambiente bajo N_2 durante la noche.

Se agregó H_2O (2.00 L) y se agitó a temperatura ambiente durante 30- 60 minutos. Se dejó sentar durante 2 h. Se separó la capa orgánica y se lavó con H_2O (2.00 L). Se separó la capa orgánica y se lavó con NaHCO3 acuoso saturado (2.00 L). Se separó la capa orgánica, se secó con MgSO4 anhidro (100 g) y la mezcla se dejo sentar a temperatura ambiente durante la noche. Se filtró MgSO4 y la mezcla de reacción se concentró en rotavapor al vacío a sequedad para proporcionar un residuo de aceite espumante (peso: 470 g). Se agregó CPME (350 ml) y se concentró al vacío hasta sequedad para proporcionar un residuo de aceite espumante. Se repitió dos veces más para obtener **10** como un residuo de aceite espumante. Peso: 470 g (rendimiento crudo: 83%). HPLC: 91.6%, **11**: 1.26%, 7,2 min, impurezas: 4.67% y varias otras impurezas pequeñas (210 nm). LC- MS (M +1: 729.1, 731.1) confirmó la estructura.

Paso 10 → 11



10 11

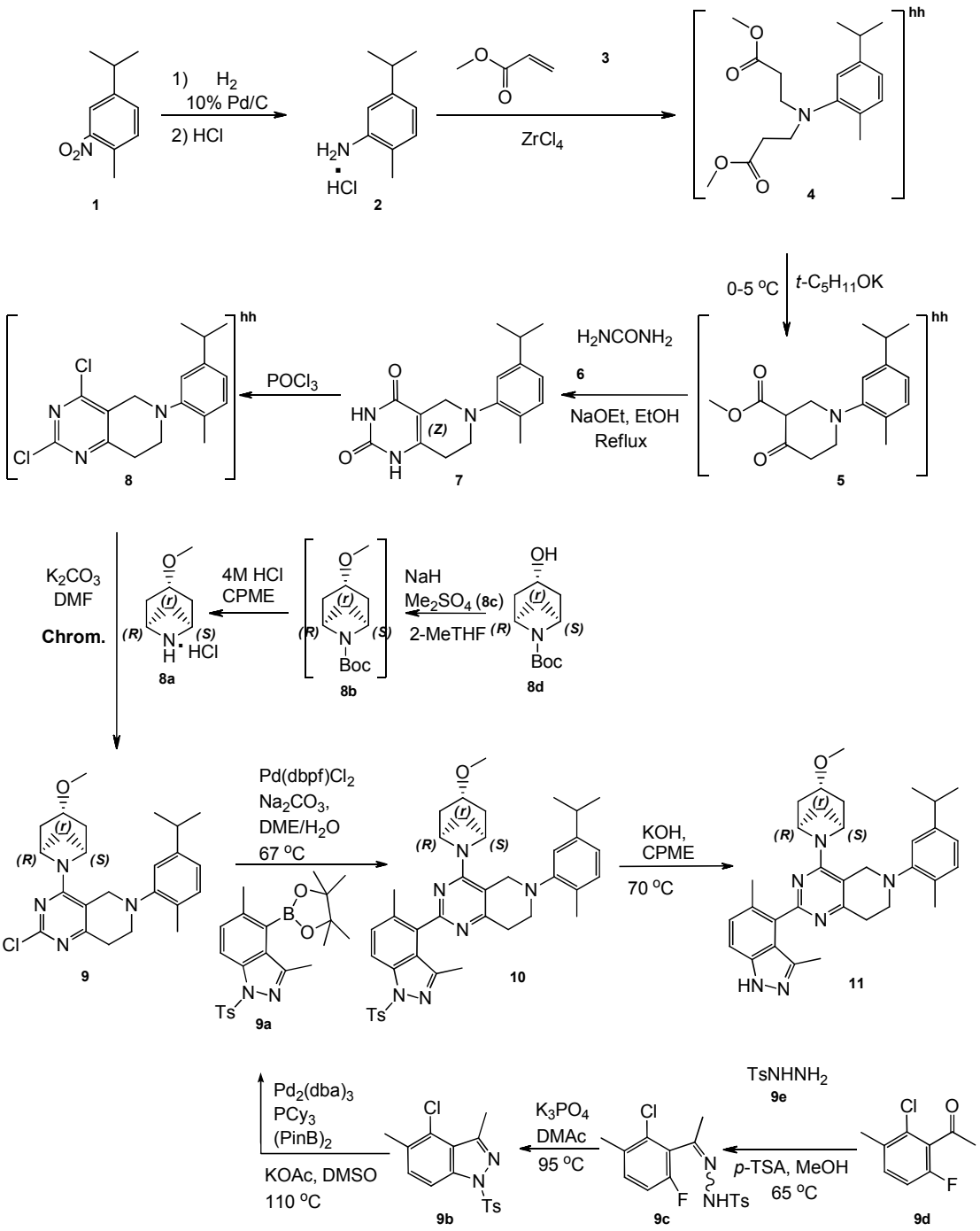
Se cargó un matraz de 5- L con 235 g del compuesto crudo **10**, 2300 ml de CPME, y 36 g de KOH. Se calentó a 90 ° C, se agregó 23.5 g de TBAB. Se mantuvo a 90.6 º C durante 3 horas. Se enfrió a 20 ºC, se agregó 600 ml de agua, se agitó durante 30 minutos. Las dos capas

se separaron. La capa orgánica se lavó con 400 ml de agua dos veces y 500 ml de salmuera. La capa orgánica se concentró a sequedad para proporcionar 175 g del producto deseado con un rendimiento del 95%. El producto se purificó mediante cromatografía en columna. Un matraz de 5- L se cargó con 1600 mL de agua, luego se agregó lentamente una solución de 170 g del producto en 400 mL de metanol. Se agitó a 20 °C durante 1 h después de la adición. Los sólidos se filtraron y la torta húmeda se lavó con MeOH al 20% en agua. Se secó a 45 °C durante 16 h para proporcionar 160 g del producto deseado con rendimiento del 94%. LC- MS y RMN confirmaron la estructura. HPLC: 98,6%; disolventes residuales cumplen las especificaciones.

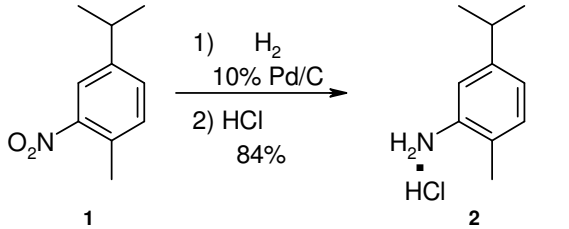
Ejemplo 79

Síntesis alternativa del Ejemplo 19- F

Esquema Sintético general:


1) H2
10% Pd/C
2) HCl
ZrCl4
0-5 °C
t-C5H11OK
H2NCONH2
NaOEt, EtOH
Reflux
POCl3
4M HCl
CPME
NaH
Me2SO4 (8c)
2-MeTHF
K2CO3
DMF
Chrom.
Pd(dbpf)Cl2
Na2CO3,
DME/H2O
67 °C
KOH,
CPME
70 °C
TsNHNH2
p-TSA, MeOH
65 °C
K3PO4
DMAc
95 °C
Pd2(dba)3
PCy3
(PinB)2
KOAc, DMSO
110 °C

5 **Paso 1 → 2**



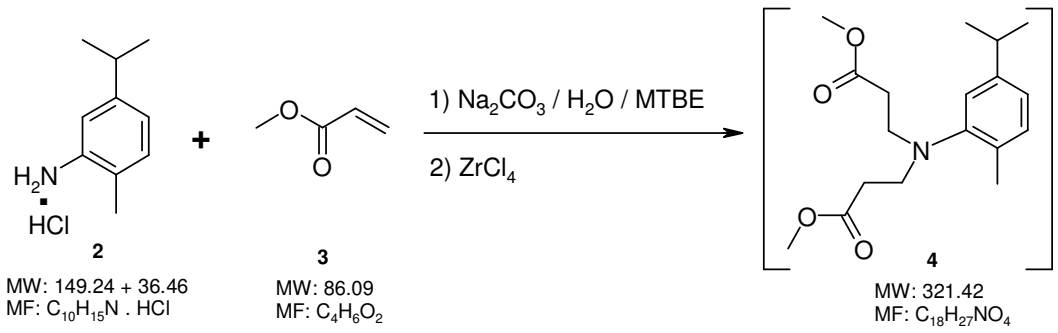
1
MW: 179.22
MF: $C_{10}H_{13}NO_2$

2
MW: 149.24 + 36.46
MF: $C_{10}H_{15}N$. HCl

Un hidrogenador de 5- L fue cargadocon Pd / C al 10% (50% húmedo, 12.0 g) y se purgó con N_2 5 veces. EtOH cargado (2.0 L), luego **1** (426.6 g). Se enjuagó con EtOH (1.2 L, total 3.2 L) y se agregó a la mezcla de reacción. Se purgó con N_2 5 veces, luego con H_2 5 veces. Se hidrogenóa 15 pisg de H_2, se agitó a 325 rpm y 25 ° C durante 6 h. No se obtuvo recaptación de H_2 después de 3.5 h. La mezcla de reacción se almacenó en el reactor a temperatura ambiente bajo N_2 durante la noche. La mezcla de reacción se filtró a través de una almohadilla de Celite. El reactor se enjuagó con EtOH (110 g). La almohadilla de Celitese enjuagó con el enjuague de EtOH, luego, con EtOH fresco (150 ml). La mezcla de reacción y los enjuaguesse combinaron para proporcionar una solución de color azul oscuro. Se concentró sobre rotavapor hasta sequedad para obtener la base libre cruda**2** como un líquido de color azul oscuro. Peso: 360 g. HPLC: 81.3% (254 nm). ^{1}H y ^{13}C-RMN confirmó la estructura con algunas impurezas.

Se agrególa base libre cruda **2**con CPME (150 mL) para proporcionar una solución. Se concentró hasta sequedad (peso: 408 g) sobre rotavapor. El residuo se disolvió en CPME (2.0 L)para proporcionar una solución de color azul oscuro. Se agregó 4M HCl en CPME (650 mL) lentamente (1 h). Los sólidos se comenzaron a formar después de que se agregó 200 mL de HCl. Se enjuagaron con CPME (850 mL, total 3.55 L, incluyendo desde el residuo **2**) y se agregaron a la mezcla de reacción. Una buena pasta aguada de color rosáceo (T 36 ° C). Se enfrió lentamente a temperatura ambiente. Se agitó a temperatura ambiente durante la noche. Los sólidos se filtraron a través de una almohadilla de polipropilenoy se lavaron con CPME (3,0 L). El sólido se secóen el horno de vacío a 40 ºCdurante el fin de semana(No se observó mucho cambio después de un par de horas) para proporcionar un sólido de color rosa. Peso: 374.5 g (húmedo: 419.6 g), rendimiento: 84.7%.HPLC: 99.0% (254 nm). HPLC: 94.2%, ~ 1% regio- isómero (210 nm, 254 nm), ~ 3.8% des- isopropil **2** (254 nm).RMN y LC- MS (M +1: 150,1) confirmó la estructura.

Paso 2 + 3 → [4]

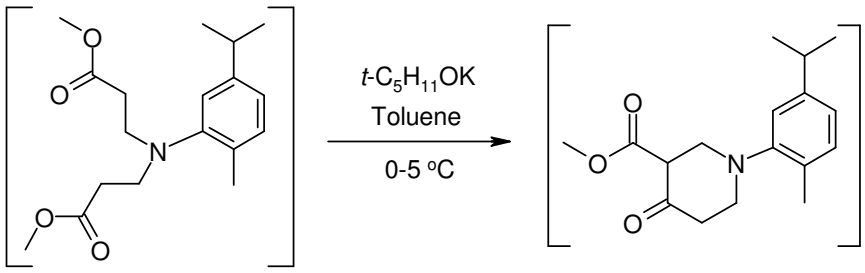


Se mezcló 4.1 L de solución de Na_2CO_3al 10%, 370 g de sal deanilina HCl (**2**), y 4.0 L de TBME a temperatura ambiente durante 30 min. Se formaron dos capas claras. La fase orgánica se separó y se lavó dos veces con 1,0 L de NaCl al 20%. HPLC de la capa orgánica (210 nm): 93,7% de anilina (5,34 m), 5,66% 2,7 min, 0,6% 5,2 min. La capa orgánica se secó con 80 g de sulfato de magnesio anhidro. Los sólidos se filtraron, se lavaron con TBME. La solución de TBME combinada se concentró a 45 ºC/30 mbar hasta sequedad. Se purgó con nitrógeno durante 2 h. se obtuvo 295 g de base libre de anilina oleosa. HPLC (210 nm): 94,4% de anilina (5,34 m), 5,2% 2,7 min, 0,4% 5,2 min. ^{1}H RMN (DMSO- d_6): consistente con la estructura molecular.

Se mezcló 295g de base libre de anilina y 700 g (700 mL) de acrilato (**3**). El lote se enfrióa 0 a 5 ° C con un baño de hielo/agua. Luego se agregó a través de un embudo de adición de sólidos 69,1 g de $ZrCl_4$en polvo durante 2 horas a 6 ± 3 ° C. Se agitó a 0 a 5 ° C durante 30 minutos. El baño de hielo se removió, el lote se dejó calentara temperatura ambiente. Se agitó a 10- 20 º C durante 3 horas. HPLC: 79,3% del producto **4** (8.89 min), 1,3% de producto demono-adición (7,93 min), un 5,6% 6,71 min, 7,5% 14.1 min del total excepto el acrilato.

A temperatura ambiente, se agregó a l lote 2.0 L de tolueno y 1,36 L de solución de Na_2CO_3al 10%, mientras se controlóla temperatura del lote a temperatura ambiente. El lote se filtró a través de un lecho de Celite y se lavó con 300 mL de tolueno. La capa de tolueno se separó y se lavó con 500 mL de solución de $NaHCO_3$ 1.0 M (pH 10acuoso) y se lavó dos veces con 500 mL de solución de NaCl al20% (pH 8, 6.5 acuoso). La capa orgánica se secó con 50 g de $MgSO_4$. El sólido se filtró y se lavó con tolueno. El filtrado de tolueno combinado se concentró a 45 ºC/30mbar, luego a 60 ° C/30 mbar hasta sequedad. El producto **4** se purgó con nitrógeno durante el fin de semana. Se obtuvo 644,9 g de líquido de color naranja. Este producto **4**oleoso se utilizódirectamente en el siguiente paso sin purificación adicional. Rendimiento: 100,7% (sen COrrección de pureza). Pureza por HPLC (210 nm): 81,7%. Impurezasprincipales: 5,0% 6,7 min, 1,4% de producto mono-adición (7,9 min), 0,6% 9,4 min, 1,2% 11,0 min, 6,8% 14,1 min. ^{1}H RMN (DMSO- d_6): consistente con la estructura molecular.

Paso [4] → [5]

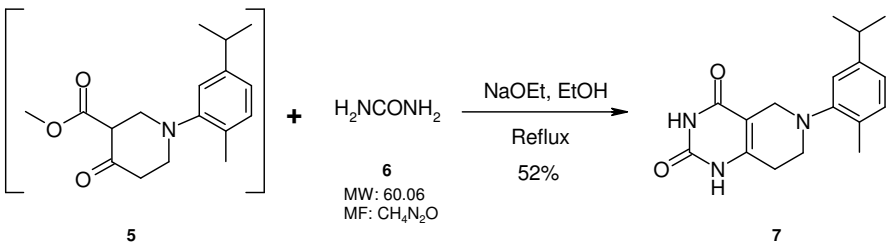


4
MW: 321.42
MF: $C_{18}H_{27}NO_4$

5
MW: 289.38
MF: $C_{17}H_{23}NO_3$

A una solución de 630,7 g de diéster en 6,3 L de tolueno pre- enfriado a 0 ~ 5 ° C con un baño de hielo/agua, se agregó a través de un embudo de adición 2,475 kg de solución de amilatode potasio al 25% en tolueno a 0 a 5 ° C por goteó durante 60 min. El lote se convirtió en una suspensión amarilla al final de la adición. El lote se agitó a 0 a 5 ° C durante 30 min. A 0- 15 ° C, se agregó 294,6 g de HOAc por goteóen 15 min y 5,5 L de solución de $NaHCO_3$1,0 M. El lote se mezcló a temperatura ambiente y la capa acuosa se separó. La fase orgánica se lavó dos veces con 2 L de solución de NaCl al 20%. La capa orgánica se secó con 100 g de $MgSO_4$ anhidro. El sólido se filtró, se lavó con tolueno. La solución de tolueno combinadase mantuvo a temperatura ambiente durante la noche. La solución de tolueno se concentró a 55 ° C/30 mbar hasta sequedad y se purgó con nitrógeno durante 2 h. se obtuvo 622,1 g de aceite de color amarillo. Este producto oleoso se utilizó directamente en el siguiente paso sin purificación adicional. Rendimiento: 101,8%. HPLC (210 nm): 41,2% 11,3 min, 49,6% 12,5 min (probablemente tautomerización de ceto- enol), impurezasprincipales: 2,3% 7,6 min, 0,7% 15,6 min. ^{1}H RMN (DMSO- d_6): consistente con la estructura molecular.

Paso [5] + 6 → 7



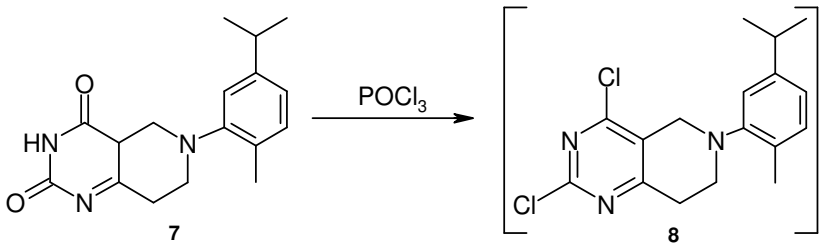
5
MW: 289.38
MF: $C_{17}H_{23}NO_3$

6
MW: 60.06
MF: CH_4N_2O

7
MW: 299.38
MF: $C_{17}H_{21}N_3O_2$

A una mezcla de 271,1 g de urea (**6**) y 622,1 g de cetoéster (**5**) en 3,75 L de EtOH (fresco), se agregó 2.117 kg de 21% NaOEt / EtOH en porciones a 15 ° C. El lote se calentó y se agitó a 80 ° C durante 20 h bajo agitación uniforme. El lote se dejó enfriar a temperatura ambiente durante la noche. El lote se enfrió a 12 ° C con un baño de hielo, se agregó 392,3 g de HOAc en el lote lentamente a12 - 16 ° C durante 20 min. El lote se concentró en porciones de 1,5 L a 50 ° C/30 mbar hasta casi sequedad. El residuo sólido se agitó en 6,0 L de agua a temperatura ambiente durante 1 h. La torta se secó y se lavó con 1,0 L de agua. La torta húmeda de filtro se agitó con 1,7 L de *i*- POAC, y se calentó a reflujo. Se agitó y se enfrió a temperatura ambiente, y se agitó durante la noche. El lote se filtró y la tortase lavó con 600 mL de i- POAC. La torta de filtro se secó a 60 oC/30 mbar durante la noche para obtener 335,7 g de **7** como polvo de color beige. Rendimiento: 52,2%. HPLC (210 nm): 95,5% ^{1}H RMN (DMSO- d_6): consistente con la estructura molecular.

Paso 7 → [8]



7
MW: 299.38
MF: $C_{17}H_{21}N_3O_2$

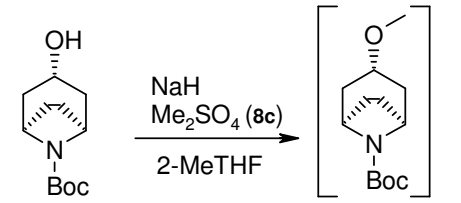
8
MW: 336.27
MF: $C_{17}H_{19}Cl_2N_3$

A un matraz de 3- cuellos de fondo redondo de 5- L, equipado con un agitador mecánico, un termómetro, un condensador de reflujo, unmanto de calefacción, y una entrada de nitrógeno secargócon, 106g (354mmol) del material de inicio, uracilo, **7** y 1.0L de toluenoa temperatura ambiente. La pasta aguada de color beige amarillo se agitó a 23 ° C durante 10 minutos. Se agregóen una porción, 1.040kg (6.78mol) de oxicloruro de fósforo. La mezcla se calentó a una temperatura interna a 105 ° C durante 30 minutos. Se mantuvo a esta temperatura durante 6 horas. La mezcla de reacción con el tiempo se convertirá en una solución oscura transparente, lo cual es una indicación de que la reacción de cloración está completa. HPLC no muestró más uracilo, solo quedó **7**. La solución se enfrió a 23 ° C y se mantuvo durante la noche.

El exceso de oxicloruro de fósforo se destiló al vacío, mientras el lote de temperatura se mantuvo por debajo de 45 ° C. El $POCl_3$ restante se elimina azeotrópicamente mediante la adición de dos adiciones de 300 mL de tolueno. La mezcla de reacción se diluyó en 1,0 L de

tolueno. La solución oscura se enfrió a una temperatura interna a 15 ° C. La solución de tolueno se basificó con una solución acuosa de 200 g de carbonato de sodio en 1,5 L de agua. Seaseguro que el pH final fuera 9. La suspensión de color canela resultante se agitó a temperatura ambiente durante 1 h. las capas se separaron. La capa acuosa se extrajo con 500 mL de tolueno. Las capas orgánicas combinadas se lavaron con 400 mL de salmuera y 100 mL de agua. Las capas se separaron. La capa orgánica se concetró a un peso constante de, T: 156g de **8** como un aceite oscuro con un rendimiento> 100%. HPLC, TLC y ^{1}H- RMN: consistente con la estructura molecular.

Paso 8d 8c + → [8b]

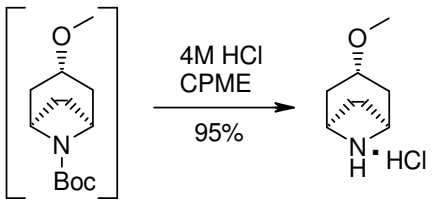


8d
MW: 227.31
MF: $C_{12}H_{21}NO_3$

8b
MW: 241.33
MF: $C_{13}H_{23}NO_3$

Se agitó N- BOC- Nortropin **8d** (106,5 g) con 2- MeTHF (450 mL) a temperatura ambiente para proporcionar una pasta aguada. Se enfrió a 12 º C. Se agregó con NaH (60% en aceite mineral, 37,48 g) a esta temperatura y se enjuagó con 2- MeTHF (50 mL). Algunas burbujas se observaron alinicio, pero no tan exotérmicas. Se agitaron a 10 ° C durante 30 minutos para obtener una pasta aguada. Se agregó $(CH_3)_2SO_4$ (106,4 g). Se enjuagó con 2- MeTHF (100 mL, total 600 mL) y se agregó a la mezcla de reacción para obtener una pasta aguada. Se agregó H_2O (1 mL). Se calentó a temperatura ambiente (lentamenteexotérmica, la temperatura se elevó a ~ 30 º C, luego se enfrió). Se agitó a temperatura ambiente durante la noche. La mezcla de reacción se enfrió a ~ 10 º C. Se agregó H_2O (100 mL). Se agregó solución acuosa de K_2CO_3al 20% (200 mL) para proporcionaruna solución bifásica (pH 14). Se agitó a temperatura ambiente durante 2 horas. Se transfirió a un embudo separador. Se enjuagó con TBME (300 mL) y se agregó a la mezcla de reacción. La capa acuosa se separó y se desechó. La capa orgánica se extrajo con H_2O dos veces (300 mL cada una). La capa orgánica se concentró hasta sequedad sobre rotavapor. CPME (100 mL) se agregó y se concentró hasta sequedad sobre rotavapor para obtener **8b** como un residuo de aceite. Peso: 139,3 g. Utilizado directamente en el siguiente paso sin purificación adicional.

Paso [8b] → 8a

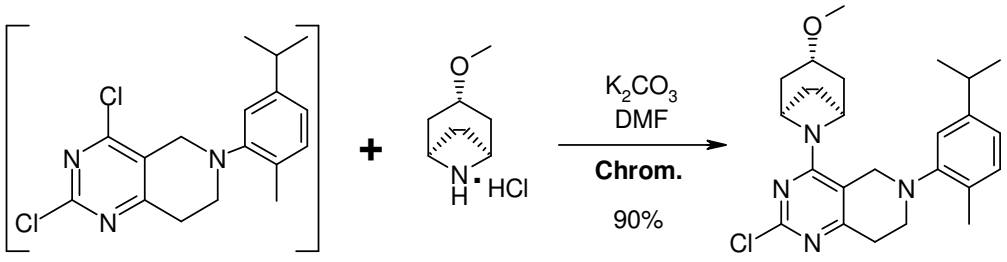


8b
MW: 241.33
MF: $C_{13}H_{23}NO_3$

8a
MW: 141.21 + 36.46
MF: $C_8H_{15}NO$. HCl

Se transfirió **8b** (139,3 g, de 468,53 mmol de BOC- nortropin) a un matraz de fondo redondo de 4- cuellos de 2- L. Se enjuagó con CPME (50 mL) y se agregó a la mezcla de reacción. Se enfrió a 5- 10 º C. Siendo aún una solución. Se agregó con HCl 4M en CPME (340 mL) a esta temperatura. Se agitó y se calentó lentamente a temperatura ambiente. Se agitó a temperatura ambiente durante la noche para obtener una pasta aguada. Se agregó heptanos (400 mL) para proporcionar una pasta aguada blanca. Se agitó a temperatura ambiente durante 2 h. Los sólidos se filtraron a través de una almohadilla polipropileno y se lavó con heptanos (50 mL) bajo flujo de N_2. El sólido se secó en el horno de vacío a 40 ºC durante el fin de semana para proporcionar unsólido blanco. Peso: 81,3 g (húmedo: 84,2 g), rendimiento: 97,6% (a partir de**8d**).RMN(D_2O)confirmó la estructura.

Paso [8] + 8a → 9



8
MW: 336.27
MF: $C_{17}H_{19}Cl_2N_3$

8a
MW: 141.21 + 36.46
MF: $C_8H_{15}NO$. HCl

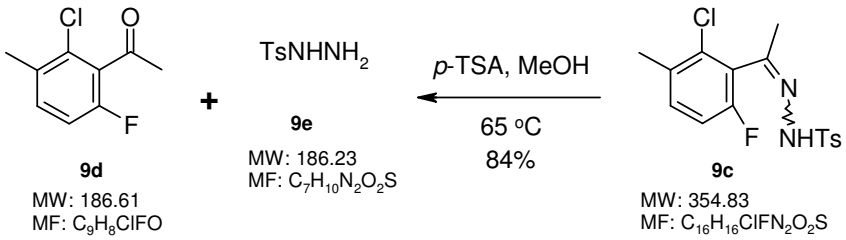
9
MW: 441.02
MF: $C_{25}H_{33}ClN_4O$

Un matraz de fondo redondo de 3- cuellos de 3- L, equipado con un agitador mecánico, un termómetro, una entrada de nitrógeno y un embudo de adición, y un baño de enfriamiento, se cargó a 20 ° C, con 105 g (760mmol) de carbonato de potasio, 66g (372mmol) de sal HCl de **8a** y 5 g (35mmol) de forma de base libre de **8a** y 500 mL de DMF. La suspensiónse agitómecánicamente a 20 ° C durante 10 minutos y se enfrió a una temperatura interna por debajo de 5 º C durante 30 minutos. Se agregó a la suspensión fría, una solución de 112 g (333mmol) (conteniendo tolueno al 18%) del dicloruro, **8** en 300 mL de DMF durante 15 minutos a través de un embudo de adición. El embudo se lavó dos veces con 50 mL de DMF.

Se mantuvo a esta temperatura durante 10 h. La mezcla de reacción se calentó gradualmente a temperatura ambiente durante la noche. La mezcla de reacción se enfrió a una temperatura interna a 15 ° C. Se diluyó con 800 mL de acetato de etilo. Se diluyó con 1.02L de agua en porciones, mientras se mantuvo la temperatura interna por debajo de 22ºC. La solución de color naranja se agitó con precipitados a 20 ° C durante 30 minutos. Las capas se separaron. El pH de la capa acuosa se comprobó y se aseguró de su valor en 10. La capa orgánica oscurase lavó con 750ml de agua. Se lavó con 500 mL de una solución de ácido cítrico al 10%. El pH comprobó ser 2. Finalmente, la capa orgánica se lavó con 400 mL de salmuera. La capa orgánica se concentró a una temperatura de 45 ° C aun peso constante de, T: 164g de **9** como un aceite de color canela con un rendimiento> 100%, el cualse solidificó a un sólido amarillo ceroso al sentarse. HPLC indica que no hay signos de DMF disolvente. TLC muestra sólo una cantidad de traza del material de inicio de dicloruro, **8**.

El producto crudo**9** se pasó a través de una almohadilla de gel de sílice para eliminar el aductode des- isopropilo al 4%. Simplemente, se disolvió 182g de aducto nortropina crudo**9** en 50 mL de diclorometano y 200 mL de tolueno. La solución se colocó sobre un lecho de 328g de gel de sílice (60- 230mesh). [1,8 g de sílice a 1 g de **9**crudo]. Se eluyó con 100% de tolueno. El producto deseado **9**se eluyó en primer lugar, dejando todos los demás atrás incluyendo el sub producto de des- isopropilo. Después de combinar las fracciones y concentrarlas a un peso constante, el rendimiento es 148g de un aceite amarillo pálido, el cual se solidificó con el tiempo a un sólido de color amarillo brillante de **9**. La pureza es de ~ 98% por HPLC a 210nm.

Paso 9d 9c + 9e →



9d
MW: 186.61
MF: C_9H_8ClFO

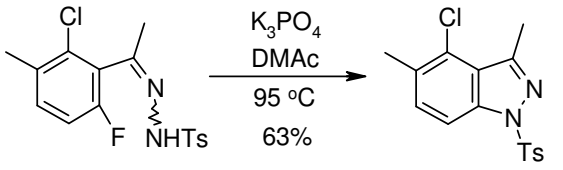
9e
MW: 186.23
MF: $C_7H_{10}N_2O_2S$

9c
MW: 354.83
MF: $C_{16}H_{16}ClFN_2O_2S$

Un matraz de fondo redondo de 4 cuellos de 5- L, cargado con**9d** (498,3 g), **9e** (621,6 g, 1,25 eq), monohidrato de p- TSA (50,8 g, 0,1 eq) y MeOH (2,5 l) para proporcionar una pasta aguada blanca. Se agitó a temperatura ambiente. La mezcla de reacción se calentó a 65 ºCdurante 45 min. La mezcla de reacción se agitó a 65 ºCdurante ~ 8 h. La mezcla de reacción se enfrió lentamente a temperatura ambiente y se agitó a temperatura ambiente durante la noche para obtener una pasta aguada blanca. La mezcla de reacción se enfrió adicionalmente a 5 ° C y se agitó durante 3- 4 h. Los sólidos se filtraron a través de una almohadilla de polipropilenoy se lavaron tres veces con MeOH frío (333 mL). El sólido se secó en el horno de vacío a

50ºCdurante la noche para proporcionar un sólido blanco. Peso: 824 g (húmedo: 873,6 g), rendimiento: 87%.HPLC (mezcla E / Z): 100% (210 nm), 99,61% (254 nm).RMN (tasa de isómerosE / Z: 4.6/1.0 ~) y LC- MS (M +1: 354,9, 356,7), confirmó la estructura.

Paso 9c 9b →



9c

MW: 354.83
MF: $C_{16}H_{16}ClFN_2O_2S$

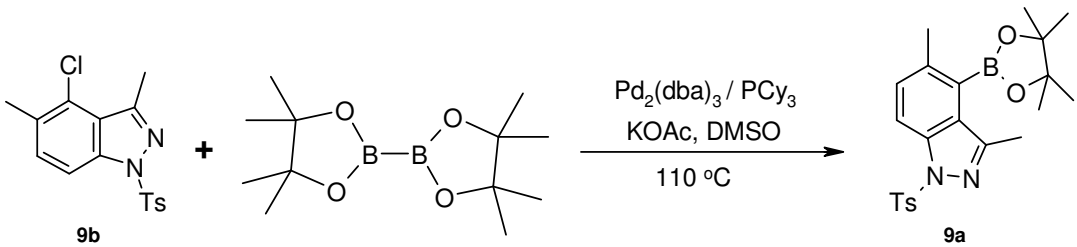
9b

MW: 334.83
MF: $C_{16}H_{15}ClN_2O_2S$

Un matraz de fondo redondode 4-cuellos de 12- L, se cargó con **9c** (819 g), K_3PO_4 (979,9 g, 2,0 eq) y DMAc (3,28 L) a temperatura ambiente para proporcionar una pasta aguada blanca. La mezcla de reacción se calentó a 95 ± 3 ºCdurante 45 min. Se agitó a 95 ± 3 ºC durante 10 horas. Se enfrió lentamente a temperatura ambiente y se agitó a temperatura ambiente durante la noche. Se agregó H_2O (6,56 L) en 1,5 horas, mientras se mantuvo la temperatura <35 ºC con un baño de hielo. La mezcla de reacción se enfrió a 20 ° C y se agitó durante 1 h. Los sólidos se filtraron a través de una almohadilla de polipropilenoy se lavaron con H_2O (4 L). El sólido se secó en el horno de vacío a 50- 60 ºCdurante la noche a 593 g. El secado continuó a 50- 60 ºCdurante el fin de semana para proporcionar un sólido de color marrón claro.Peso: 583,1 g (húmedo: 698,4 g), rendimiento: 75,4%. HPLC:97,0% (254 nm).

Un matraz de fondo redondo de 4 cuellos de 5- L, se cargó con **9b** (402,0 g) y 2- propanol (4,02 L) para obtener una pasta aguada. La mezcla de reacción se agitó a temperatura ambiente. Se calentó a 82 ºCdurante 45 min. La mezcla de reacción se agitó a 82 ºCdurante 1 h. Se enfrió a temperatura ambiente. La mezcla de reacción se enfrió lentamente a 5 ºC y se agitó a esta temperatura durante 1 h. Los sólidos se filtraron a través de una almohadilla de polipropileno y se lavaron con 2- propanolfrío (1,35 L). El sólido se secóen el horno de vacío a 50- 60 ºC durante la noche para proporcionar un sólido arenoso de color crema.Peso: 339,9 g (húmedo: 341,7 g), rendimiento: 84,6% (total 63,7%). HPLC:99,0% (254 nm).RMN y LC- MS (M +1: 334,9, 336,8) confirmó la estructura.

Paso 9b 9a →



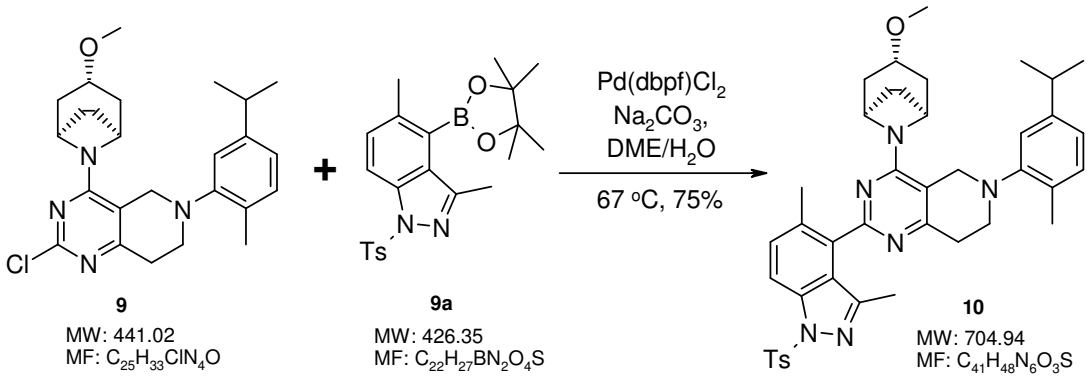
9b
MW: 334.83
MF: $C_{16}H_{15}ClN_2O_2S$

MW: 253.94
MF: $C_{12}H_{24}B_2O_4$

9a
MW: 426.35
MF: $C_{22}H_{27}BN_2O_4S$

A un matraz de fondo redondode 4 cuellos de 5-Lpurgado con nitrógeno, se agregó 45,1 g de Pd_2 (dba) $_3$, 66,4 g de PCy_3, y se burbujeó 1.0 L- de nitrógeno DMSO.Se agitó a temperatura ambiente mientras se burbujeó el nitrógeno durante 60 min en un matraz de fondo redondode 4- cuellosde 12- L con nitrógeno durante 30 minutos, luegose agregó 660,2 g de tosilo indazolo, 1.502 g de pinacol diboro (3,0 eq), 580,6 g de KOAc (3,0 eq), y 5,5 L de DMSO. Se burbujeó nitrógeno y se purgóa espacio de cabeza del lote durante 10 minutos, luego se calentó a 70 ° C durante 60 minutos manteniendoel burbujeado y purga de nitrógeno. A 70 º C, se agrego todo el catalizador preformado /suspensión fina de DMSO como se preparó anteriormente. El lote se calentó a 110 ° C y se agitó a 110 º C durante 15 horas manteniendo el burbujeado y purga de nitrógeno. El lote se enfrió a temperatura ambiente y se mantuvoduranteel fin de semana. El lote se calentó a 50 ° C para hacer el lote de una suspensión espesa a una suspensión menos espesa, se transfirió todo el contenido a un matraz de fondo redondode 4- cuellos de 22- L con 5.500 mL de 2- MeTHF, 5.000 mL de agua, y 160 g de Celite . El lote se agitó a 40- 50 ° C durante 30 min. La capa orgánica se separó. La capa acuosa se extrajo nuevamente con 1.0 L de 2- MeTHF y 1.5 L de agua. La capa orgánica combinada y la capa acuosa conteniendoCelitese filtraron a través de unaalmohadilla de celite, se lavaron con 2.000 mL de 2- MeTHF. La capa orgánica se separó. La solución se mantuvo a temperatura ambiente durante la noche. La capa orgánica se lavócon 3.0 L de solución de NaCl al 20%, y 4.0 L de solución de NaCl al 6%. La capa orgánica se dividió en 3 partes, cada una se concentró a 40 ° C/30 mbar hasta casi sequedad, a cada una se agregó 600 mL de heptano, se concentró a 40 ° C/30 mbar hasta casi sequedad. A cada una se agregó 600 mL de heptano. Se agitó a 45 ° C para hacer una suspensiónde fluido libre. Se combinó en un matraz de fondo redondode 12- L, se agregó 5.3 L más heptano. Se agitó a 45 ° C durante 2 h, se enfrió a temperatura ambiente y se agitó durante la noche. El lote se filtró, la torta se lavó con 2.0 L de heptano. La torta húmeda se secó a 55 °C/30 mbar durante la noche. Se obtuvo 596,8 g de un sólido de color rosa claro. Rendimiento: 71.0%. Pureza por HPLC (254 nm): 98,2%. LC- MS: ES + 426.9. RMN ($CDCl_3$): consistente con la estructura molecular.

Paso 9 + 9 bis → 10

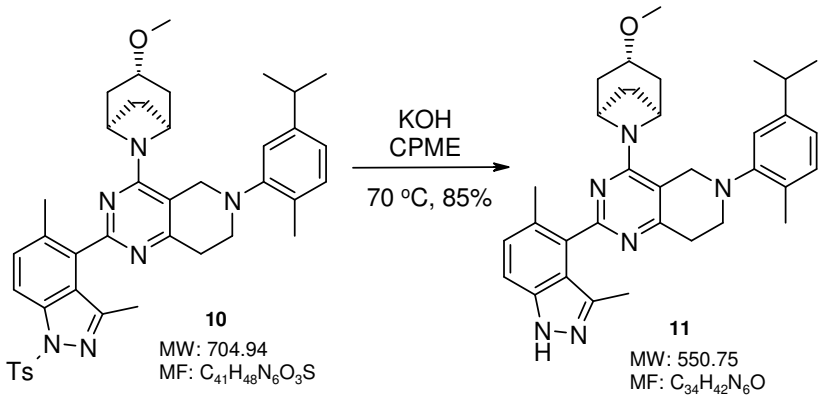


A un matraz de fondo redondo de 3- cuellosde 2- L, se equipó con un agitador mecánico, un condensador de reflujo, un manto de calefacción, un termómetro y una entrada de nitrógeno se carga a 20 ° C, 40 g (90.7mmol) de aducto de nortropina, **9**, 46.3g (108.6mmol) de boronato de indazol, **9a** y 600 mL de dimetoxietano para proporcionar una solución de color marrón brillante. Se agitóvigorosamente durante 10 minutos a 20 º C para asegurar visualmente que todos los trozos de sólidos se hayan disuelto. Una solución acuosa de 30 g (283mmol) de carbonato de sodio se agitó en 330 mL de agua. Se agregó 2,0 g (3.07mmol) del catalizador de Pd (3.4mol%) y se enjuagó con 50 mL de dimetoxietano. La mezcla tipo solución se calentó a una temperatura interna de 67ºC rápidamente en menos de 15 minutos. Se agitó y se mantuvo a esta temperatura durante 2 h. se enfrió a temperatura ambiente. Se filtraron La mezcla de reacción, una pasta aguadacolor canela a través de un embudo Buchner al vacío sobre una almohadilla de polipropileno. La tortade filtro se lavó dos veces con 100 mL de MTBE, dos veces con 100 mL de agua y una vez con 50 mL de dimetoxietano. La torta de filtro se secó en un horno a una temperatura de 48ºC al vacío con una purga ligera de nitrógeno durante 20h para obtener T: 61g del producto crudode Suzukideseado **10** con rendimiento del 95 ~%.

161g del producto crudo de Suzuki se disolvió en 650 mL de diclorometano. La solución clara de color amarillo pálido se lavó dos veces con 160 mL de agua y 276g de salmuera. La solución orgánica se pasó a través de una almohadilla corta de 228g de gel de sílice (malla 60-230). Se eluyó con 100% de diclorometano y seguido por acetato de etilo/diclorometano al 30%. Las fracciones se combinaron y se concentraron. Diclorometano residual se elimino con 400 mL de MTBE para obtener 360 g de torta húmeda. La torta húmeda de **10** se agitó mecánicamente en 1.4L de MTBE a una temperatura interna de 45 ° C. La pasta aguada se agitó a temperatura ambiente durante la noche y se filtró al vacío sobre un embudo Buchner sobre una almohadilla de polipropileno. La torta de filtrado se lavó con MTBE y se secó al aire a temperatura ambiente durante 30 minutos. Luego los sólidos se secaron en un horno a una temperatura de 48ºC al vacío con una purga ligera de nitrógeno durante 18h para proporcionar:

135g de producto Suzukipurificado **10**con recuperación del ~ 84%. La pureza es> 99% por HPLC a 210nm. La estructura es consistente por ^{1}H- RMN y LC / MS (MH $^{+}$ = 705).

Paso 10 → 11



Un matraz de fondo redondo de 3- cuellosde 3- L, se equipó con un agitador mecánico, un manto de calefacción, un condensador de reflujo, y una entrada de nitrógeno, se cargó a 20 ° C, 100 g (142mmol) de **10**, 20 g (357mmol) de hidróxido de potasio pulverizadoy 1 litro de éterciclopentil metílico. La pasta aguadase mezcló mecánicamente a 20 ° C durante 10 minutos. Se calentó gradualmente a una temperatura interna de 68ºC. Se agitó y se mantuvo a esta temperatura durante 7 h.La mezcla de reacción se enfrió a 20 ° C. Se agitódurante la noche. Se agregó 500 mL de agua, 500 mL de éterciclopentil metílico y 500 mL de salmuera. Las capas se separaron. La capa orgánica se lavó con 500 mL de agua y 500 mL de salmuera. Las capas se separaron. La capa orgánica se diluyó con 500 mL de acetato de isopropilo. La capa orgánica se lavó con 700 mL de agua. Las capas se separaron. La capa orgánica se pasó a través de un embudo de vidrio sinterizado grueso al vacío sobre un papel de filtro de fibra de vidrio. La capa orgánica se concentró a una temperatura de 40 ° C aún peso constante para obtener T: 221g de crudo **11** como un aceite gomoso.

El producto crudo de **11**, la forma de base libre de la sustancia farmacológica, LKP581 tendrán que ser solidificados. Inicialmente, los sólidos de **11**se obtuvieronal rascara partir de heptano. Sin embargo, tanto como 2% de retención de disolvente con base en^{1}H- RMNhizo este proceso inaceptable. Después de muchos esfuerzos de desarrollo de procesos yentradas desdeel grupo de cristalización, se ideó una condición posible, permitiendo la liberación del lote de CSP de LKP581 como un sólido, conel rendimiento del nivel de pureza correcto. Por lo tanto, se cumplió con AUDD. Simplemente, el aceite crudode **11**se disolvió en metanol. Cuidadosamente, se agregóeste en agua. Se filtró y se secó.

Ejemplo 80

Solvato MTBE del Ejemplo 19- F

A 100 mg de la forma libreamorfa del Ejemplo 19- F se agregó 100µL de MTBE. Con agitación se formó una solución clara. La solución se agitó a - 20 ° C y durante aproximadamente60 minutos se formó un precipitado. El sólido resultante se recolectómediante filtración y se secó a 40 ° C al vacío durante 72 horas.

La forma sólida se hizó cristalina mediante XRPD, con un punto de fusión de 102,8 ° C y una pérdida de peso concurrente del 4,9%. El XRPD se muestra en la Figura 1. La DSC y TGA se muestran en la Figura 2.

Picos de difracción de rayos X de polvos del Ejemplo 19- F a partir de MTBE

Ángulo 2θ	d valor Å	Intensidad Relativa %
3,433	25,74	29,9
6,369	13,88	40,3
7,058	12,52	50,3
9,306	9,50	49,6
10.522	8,41	42,5
11.908	7,43	54,2
12.511	7,08	36,7
13.434	6,59	69,3
15.527	5,71	54,8
16.385	5,41	60,6
17,39	5,10	100
18.883	4,70	78,1
20.285	4,38	52,9
22.351	3,98	34,1
23.297	3,82	38,5

Ejemplo 81

Solvato Me- THF del Ejemplo 19- F

A 100 mg de la forma libreamorfa se agregó 100µL (o 200 µL) de Me- THF. Con agitación se formó una solución clara. La solución se agitó a - 20 ° C y duranteaprox. 2 horas se formó un precipitado. El sólido resultante se recolectó por filtración y se secó a 40 ° C al vacío durante 72 horas.

Se encontró que el material recolectado y analizado sin secar tenía un patrón XRPD diferente que el material secadolo que sugiere una conversión de formas cristalinas. La conversión podría ser seguidamediante XPRD durante ~ 30 minutos bajo condiciones ambientales.

La forma sólida se hizo cristalina mediante XRPD, con un punto de fusión de 126,8 ° C y una pérdida de peso concurrente del 1,5%. El XRPD se muestra en la Figura 3 y la Figura 5. La DSC y TGA se muestran en la Figura 4.

Picos de difracción de rayos X de Polvos del precipitado inicial del Ejemplo 19- F a partir de Me- THF

Ángulo 2θ	d valor Å	Intensidad Relativa %
4,394	20,11	93,1
6,959	12,70	41,8
8,629	10,24	38,1
11,31	7,82	30,8
13.387	6,61	40,3
16.778	5,28	100
17.287	5,12	75,3
17.865	4,96	73,2
18.849	4,70	63,7
19.452	4,56	56,4
22.353	3,97	44,6
22,83	3,89	38
26.312	3,38	26,2

Picos de difracción de rayos X de polvos del material seco del Ejemplo 19- F a partir de Me-THF

Ángulo 2θ	d valor Å	Intensidad Relativa %
5,148	17,16	100
7,37	11,99	40,2
9,908	8,92	29,1
10.807	8,18	20
11.489	7,70	24

13.904	6,36	17,9
14.434	6,13	18,3
15.273	5,80	19,7
15.879	5,58	28,6
17.164	5,16	56,6
19.318	4,59	21,4

Ejemplo 82

Solvato de tolueno del Ejemplo 19- F

A 100 mg de la forma libre amorfa, se agregó 150µL de tolueno. Con agitación se formó una solución clara. La solución se agitó a - 20 ° C y duranteaprox. 12 horas se formó un precipitado. El sólido resultante se recolectómediante filtración y se secó a 40 °C al vacío durante 72 horas.

La forma sólida se hizo cristalina mediante XRPD, con un punto de fusión de 117,4 ° C y una pérdida de pesoconcurrente del 3,2%. El XRPD se muestra en la Figura 6. La DSC y TGA se muestran en la Figura 7.

Picos de difracción de rayos X de polvos del Ejemplo 19- F a partir de tolueno

Ángulo	d valor	Intensidad Relativa
2θ	Å	%
5,134	17,21	35,9
7,431	11,90	35,9
9,97	8,87	35,8
10.975	8,06	37,2
11.562	7,65	33,4
12.209	7,25	26,4
13.632	6,50	28,8
14.448	6,13	46,1
15.032	5,89	32,5
15.865	5,59	37,3
16.974	5,22	100
17,28	5,13	68,2
18.829	4,71	65,6
22.402	3,97	25

23.165	3,84	29,4

Ejemplo 83

Solvato de EtOAc del Ejemplo 19- F

A 100 mg de la forma libre amorfa, se agregó150µL de EtOAc. Con agitación se formó una solución clara. La solución se agitó a - 20 ° C y duranteaprox. 4 horas se formó un precipitado. El sólido resultante se recolectómediante filtración y se secó a 40 ° C al vacío durante 72 horas.

La forma sólida sehizo cristalina mediante XRPD, con un punto de fusión de 117,4 ° C y una pérdida de pesoconcurrente del 3,2%. El XRPD se muestra en la Figura 8. La DSC y TGA se muestran en la Figura 9.

Picos de difracción de rayos X de polvos del Ejemplo 19- F a partir de EtOAc

Ángulo 2θ	d valor Å	Intensidad Relativa %
5,188	17,03	64,2
7,43	11,90	70,2
9,171	9,64	18,7
10.048	8,80	42,2
11,07	7,99	61,8
11.555	7,66	66
12.318	7,19	27,1
13.778	6,43	33,8
14,49	6,11	52,1
15.972	5,55	37,9
17.394	5,10	100
19.025	4,66	68,4
23.283	3,82	38,3

Ejemplo 84

Forma de Clorhidrato A del Ejemplo 19- F

La forma de Clorhidrato A del Ejemplo 19- F se preparó en una escala de 100 mg. Al material de base libredel Ejemplo 19- F, se agregó una solución de HCl 0,1 N en IPA a una tasa molar de 1:1,1 creando un exceso leve de HCl. Tras la adición del ácido, la solución se volvió transparente después de <1 min de agitación. La solución se protegió de la luz y se dejó agitar a temperatura ambiente. Se observóopacidad después de pocas horas, pero la mezcla de reacción

se dejó en agitación durante 48 horas. El material se recolectómediante filtración al vacío, se enjuagó con IPA, y se secó pasando aire a través de la muestra en una configuración de filtración de vacío durante 1 hora. El rendimiento fue de 85%aproximadamente.

Mediante el análisis elemental y Karl Fisher, el Clorhidrato del 19- F Ejemplo se determinó como una sal de monocloruro sin un hidrato estequiométrico. Es cristalina y experimenta una pérdida de agua a 127 ° C (endoterma DSC amplia) seguido por una fusión a 190 ° C. se observó la pérdida de masa de una manera gradualmediante TGA: 5,4% en peso a 138 ° C y un 2,8% de peso adicional a 186 ° C. El XRPD se muestra en la Figura 11. La TGA se muestra en la Figura 12. La DSC no hermética se muestra en la Figura 13. La DSC hermética se muestra en la Figura 14.

Picos XRPD de la forma de clorhidrato A del Ejemplo 19- F

Ángulo 2θ	d valor Å	Intensidad Relativa %
4,666	18,94	28,9
6,928	12,76	32,5
7,63	11,59	100
9,394	9,41	55,6
10.875	8,14	21,1
12.252	7,22	21,7
14.263	6,21	26,2
15.378	5,76	41
17.227	5,15	31,1
18.146	4,89	54,6
19.187	4,63	52,4
26.521	3,36	29,8

Ejemplo 85

Forma de Clorhidrato B del Ejemplo 19- F

La forma de Clorhidrato B del Ejemplo 19- F estuvo en una escala de 500 mg. Su síntesis es similar a aquella de la Forma A, excepto que se utilizó tiempo de secado adicional. Al material de base libre del Ejemplo 19- F, se agregó una solución de HCl 0,1 N en IPA en una tasa molar de 1:1,1 creando un exceso leve de HCl. Tras la adición del ácido, la solución se volvió transparente después de <1 min de agitación. La solución se protegió de la luz y se dejó agitar a temperatura ambiente. Se observó opacidad después de pocas horas, pero la mezcla de

reacción se dejó agitar durante 48 horas. El material se recolectó mediante filtración al vacío, se enjuagó con IPA, se secó pasando aire a través de la muestra en una configuración de filtración de vacío durante 1 hora y luego se colocó en un horno de vacío (40 ° C) durante 72 horas. La forma B resultó después de este período. El rendimiento fue de aproximadamente el 85%.

Se prepararon las suspensiones acuosas de la forma de clorhidrato A del Ejemplo 19- F y la forma de Clorhidrato B del Ejemplo 19- F. La forma A se volvióamorfa en 24 horas; la forma B parece retener una pequeña cantidad de la cristalinidad Forma B, pero se vuelve significativamente amorfa.

Mediante cromatografía iónica, la Formade Clorhidrato B del ejemplo 19- Fse determinó como una sal de monocloruro. Es cristalina y experimenta una pérdida de agua a 127 ° C (endoterma DSC amplia) seguido por una fusión a 199 ° C. A 167 ° C, se pierde 5,5% por peso mediante TGA. El XRPD se muestra en la Figura 15. La TGA se muestra en la Figura 16. La DSC no hermética se muestra en la Figura 17.

Picos XRPD de la forma de Clorhidrato B del Ejemplo 19- F

Ángulo 2θ	d valor Å	Intensidad Relativa %
4,916	17,98	27,1
7,407	11,94	44,1
8,041	11,00	85
8,368	10,57	100
9,681	9,14	41,3
9,983	8,86	39,7
13.252	6,68	30,2
15.006	5,90	45
15.554	5,70	39,2
19.271	4,61	47,2
20.137	4,41	35,4

Ejemplo 86

Forma de fosfato Adel Ejemplo 19- F

La forma de fosfato A del Ejemplo 19- F se produjo sobre una escala de 25 mg. La base libre del Ejemplo 19- f se disolvió en acetona a 42mg/mL. Luego se agregó una solución de ácido fosfórico 0,1 M en acetona a una tasa molar de 1:1,5 generando un exceso de ácido. La concentración de la solución de base libre fue por lo tanto 19.6mg/mL. Se observó alguna

turbidez inmediata. La solución se dejó en agitación durante 48 horas a temperatura ambiente produciendo una suspensión opaca. El material se recolectómediante filtración al vacío, se lavó con acetona y se secó en una horno de vacío (40 ° C) durante 24 horas.

La forma de Fosfato A del Ejemplo 19- F es cristalina y se funde a 128 ° C. El XRPD se muestra en la Figura 18. La DSC hermética se muestra en la Figura 19.

Picos XRPD de la forma de Fosfato A del Ejemplo 19- F

Ángulo 2θ	d valor Å	Intensidad Relativa %
4,73	18,68	100
7,956	11,11	12
9,584	9,23	19
10.644	8,31	15,1
13.588	6,52	13,1
14.548	6,09	15,5
16.287	5,44	25,9
17.266	5,14	21,1
11.835	7,48	14
18.948	4,68	19,1

Ejemplo 87

Forma de fosfato B del Ejemplo 19- F

La Forma de fosfato B del Ejemplo 19- F se produjo sobre una escala de 25 mg. El material de la base libre del Ejemplo 19- F se disolvió en acetona a 9.2mg/mL. Luego,se agregó una solución de ácido fosfórico 0,1 M en acetona a una tasa molar de 1:1,4 generando un exceso de ácido. La concentración de la solución de la base libre fue por lo tanto 7.45mg/mL. La solución fueaclaróal adicionar el ácido fosfórico. La solución se dejó agitar durante 72 horas a temperatura ambiente produciendo una suspensión opaca. El material se recolectómediante filtración al vacío, se lavó con acetona y se secó pasando aire a través del aparato de filtración de vacío durante aproximadamente 30 minutos.

Mediante cromatografía iónica, la forma de Fosfato B del Ejemplo 19- F se determinó como una sal de monofosfato. Es cristalina y tiene varios endotermas según se determinó mediante DSC hermética: 119 ° C, 131 ° C y 164 ° C. El XRPD se muestra en la Figura 20. La DSC hermética se muestra en la Figura 21.

Picos de XRPD de la forma de fosfato B del Ejemplo 19- F

Ángulo 2θ	d valor Å	Intensidad Relativa %
4,428	19,95	100
5,873	15,05	16,4
7,086	12,47	20,8
7,993	11,06	57,6
10.188	8,68	23,1
11.865	7,46	25,8
13.382	6,62	54,8
14.434	6,14	29,6
16.946	5,23	32,1
18.742	4,73	58,7
20.709	4,29	29,3
21.718	4,09	29,1
22.728	3,91	38,7

Ejemplo 88

Forma de fosfato C del Ejemplo 19- F

Después de 2 ciclos de DVS a partir de 0- 85% de humedad relativa, se encontró que la forma de Fosfato B del Ejemplo 19- F se convirtióen la forma de Fosfato C del Ejemplo 19- F.

Mediante análisis elemental y Karl Fisher, se determinó la forma C del Ejemplo 19- F como una sal de monofosfato con un dihidrato estequiométrico. Es cristalina y experimenta una pérdida de agua a 70 ° C (endoterma DSC amplia) seguido mediante una fusión a 165 ° C. A 119 ° C, se pierde 1,2% por peso mediante TGA. El XRPD se muestra en la Figura 22. La DSC no hermética se muestra en la Figura 23. El TGA se muestra en la Figura 24.

Picos de XRPD delaforma de fosfato C del Ejemplo 19- F

Ángulo 2θ	d valor Å	Intensidad Relativa %
4,50	19,65	100
7,93	11,15	11,6
8,65	10,22	13,9
10,63	8,32	10,3
12,00	7,38	15,8

13,85	6,39	21,9
15,35	5,77	14
16,06	5,52	15,4
17,65	5,03	18
18,82	4,72	18,7

Ejemplo 89.

Solubilidad del Ejemplo 19- F, la forma de clorhidrato A del Ejemplo19- F, y la forma de fosfato C del Ejemplo 19- F

	Solubilidad de equilibrio de 24 horas (mg / mL) [pH]		
	Ejemplo 19- F	Formade clorhidrato A del Ejemplo 19- F	Forma de fosfato Cdel Ejemplo 19- F
Forma Física	Amorfo	Cristalino	Cristalino
pH 1	<0,0005 [1,32]	0,14 [1,41]	0,83 [1,22]
pH 4,5	<0,0005 [4,28]	<0,001 [4,54]	0.006 [3.70]
pH 6,8	<0,0005 [6,62]	<0,001 [6,86]	0.001 [5.83]
SGF	<0,0005 [1,3]	0,13 [2,20]	0,55 [1,84]
SIF	*	<0,001 [6,60]	0.001 [6.56]
FeSSIF pH 5,5	<0,0005 [7]	1,01 [5,78]	0,65 [5,22]
FaSSIF pH 6,5	<0,0005 [6,47]	0,01 [6,58]	0,02 [6,09]
Agua	<0,0005 [6,09]	<0,001 [4,68]	0,04 [3,33]
CAPMUL MCM	> 26,5	24,97	4,21
Glicérido de aceite de maíz	> 26,1	23,08	13,14
HPBCD al 20%	0,003	0,03	0,77
PG	3,426	13,89	15,48
PEG300	8,260	10,19	13,89
PEG300 al 50%	0,016	8,01	5,23
Solutol al 10%	0,078	7,77	8,96
Cremophor al 10%	*	5,14	8,76
Tween80 al 1%	0,006	0,52	0,71
SLS al 1%	0,005	0,48	0,53
MEPC5	*	16,45	22,07
MEPC4	*	11,57	25,96

* Datos no disponibles

Ejemplo 90

Datos importantes in vivo que demuestran desempeño biofarmacéutico avanzado

La forma de Clorhidrato B del Ejemplo 19- F (30 y 100mpk) y la forma de Fosfato C del Ejemplo 19- F (100mpk) se han dosificadas en una formulación de suspensión (0,1% Tween80/0.5% CH) a 100mpk en ratas Sprague Dawley. A 30mpk la sal de HCl tiene niveles de exposición plasmática similares a aquellos observados después de una dosis de microemulsión. La exposición a 100mpk fue menor a partir de las formas de sal en comparación con la microemulsión. La exposición plasmática después de una dosis de 300mpk de sal de HCl es aproximadamente la misma que después de la dosis de 100mpk. Los datos de este experimento se resumen en la Figura 25.

El tamaño de la partícula de suspensión de la forma de Clorhidrato B del Ejemplo 19- F fue d (0,5) y d (0,9) fueron 4.3µm y 13.8µm respectivamente. El tamaño de la partícula de suspensión de la forma de fosfato C del Ejemplo 19- F fue d (0,5) y d (0,9) fueron 8.5µm y 37.0µm respectivamente. Después de 24 horas, los sólidos en suspensión se han convertido en su mayor parte amorfos.

Ejemplo 91

Solvato del Ejemplo 55- G

A 100 mg de una Ejemplo 55- G de base libre,se agregó 1000µL de EtOAc al 10% en heptano. Con agitación se formó una suspensión fina. La suspensión se calentó a 50 ° C a 1 ° C / min y se mantuvo durante 30 minutos en cuyo punto se enfrió a 0,5 ° C / min a 5 ° C donde se mantuvo durante 30 minutos. El sólido resultante se recolectómediante filtración, se lavó con 1000µL de heptano frío y se secó a 40 ° C al vacío durante 72 horas.

Esta forma sehizo cristalina mediante XRPD con un punto de fusión de 134,8 ° C y una pérdida de peso concurrente del 4,3%. El vXRPD se muestra en la Figura 26. La DSC y el TGA se muestran en la Figura 27.

Picos de difracción de rayos X de polvos del Ejemplo 55- Ga partir de EtOAc al 10%en heptano

Ángulo 2θ	d valor Å	Intensidad Relativa %

6,805	12,99	13,7
7,752	11,41	18,4
8,75	10,11	17,7
10.211	8,66	19,6
10.909	8,11	14
11.635	7,61	24,6
12.485	7,09	26,9
12.972	6,82	18,6
14.159	6,26	79,2
14.831	5,97	29,2
15.714	5,64	21,8
16.227	5,46	45,3
17.249	5,14	100
17.899	4,96	35
18.411	4,82	35,4
19.351	4,59	28,1
20.094	4,42	31,3
22.443	3,96	21,7
23.089	3,85	49,9
23.813	3,74	30,7
24.303	3,66	22,8
25.326	3,52	25,9
25.809	3,45	30,2
27.193	3,28	24,3
27.973	3,19	25,3
28.863	3,09	20

Ejemplo 92

Tri- hidrato del Ejemplo 55- G

A 600mg del Ejemplo 55- G de base libre,se agregó 7500µL de MeOH al 50% en agua. Con agitación se formó una suspensión fina la cual es de naturaleza amorfa. La suspensión se calentó a 50 ° C a 1 ° C / min y se mantuvo durante 30 minutos en cuyo punto se enfrió a 0,5 ° C / min a 5 ° C donde se mantuvo durante 30 minutos. El sólido resultante se recolectómediante filtración,luego se secó a 40 ° C al vacío durante 72 horas. El rendimiento fue de aproximadamente el 92%.

Esta forma sehizo cristalina mediante XRPD con un punto de fusión de 123,7 ° C y una pérdida de peso al calentar de 6,6%. El contenido de agua es de 7,5% mediante Karl Fischer. El XRPD se muestra en la Figura 28. La DSC y TGA se muestran en la Figura 29. La DSC en recipiente sellado se muestra en la Figura 30.

Picos de difracción de rayos X de polvos de la Figura 55- Ga partir de MeOH al 50% en agua

Ángulo 2θ	d valor Å	Intensidad Relativa %
6,602	13,39	17,9
8,161	10,83	100
9,746	9,08	19,2
12.689	6,98	62,2
13.109	6,75	39,9
13,91	6,37	20,2
14.544	6,09	29,1
16.441	5,39	20,9
16.999	5,22	27,9
17.517	5,06	22,9
19.318	4,59	29,4
21.222	4,19	34,3
22,71	3,92	37,8
23.065	3,86	29,5
24.253	3,67	23,4
25.351	3,51	31,9
27.787	3,21	30,8

Ejemplo 93

Sulfato del Ejemplo 55- G

A 100 mg de base libre del Ejemplo 55- G, se agregó 1 M equivalente de ácido sulfúrico y 1000µL de acetona. Con agitación se formó una solución clara. Esta solución se calentó a 50 ° C a 1 ° C / min y se mantuvo durante 30 minutos en cuyo tiempo se enfrió a 0,5 ° C / min hasta 5 ° C donde se mantuvo durante 30 minutos. El sólido resultante se recolectómediante filtración en frío luego se secó a 40 ° C al vacío durante 72 horas.

Esta forma es hemisulfato débilmente cristalino con un punto de fusión de 131,4 ° C y una pérdida de peso concurrente del 1,8% a 200 ° C. El XRPD se muestra en la Figura 31. La DSC y TGA se muestran en la Figura 32.

Picos de difracción de rayos X de polvos desulfato del Ejemplo 55- G

Ángulo 2θ	d valor Å	Intensidad Relativa %
5,227	16,91	100
6,198	14,26	29,4
8,648	10,23	42,1
10.047	8,80	82,2
11.452	7,73	42,6
12.769	6,93	63,4
14.551	6,09	68,4
16.203	5,47	63,1
17.059	5,20	56,1
17.827	4,98	56,1
19.214	4,62	55,9
19.952	4,45	55,1

Ejemplo 94

Tosilato del ejemplo 55- G

A 600 mg del Ejemplo 55- Gde base libre, se agregó equivalente 1M de ácido p-toluensulfónico hidratado y 7500µL de acetona. Con agitación se formó una solución clara. Esta solución se calentó a 50 ° C a 1 ° C / min y se mantuvo durante 30 minutos en cuyo tiempo se enfrió a 0,5 ° C / min a 5 ° C donde se mantuvo durante 30 minutos. El sólido resultante se recolectómediante filtración,luego se secó a 40 ° C al vacío durante 72 horas. El rendimiento fue de aproximadamente el 75%.

Esta forma es sal de tosilato 1:1débilmente cristalina con un punto de fusión de 143,8 ° C y una pérdida de peso concurrente del 1,2% a 200 ° C. El XRPD se muestra en la Figura 33. La DSC y TGA se muestran en la Figura 34.

Picos de difracción de rayos X de polvos detosilatodel Ejemplo 55- G

Ángulo	d valor	Intensidad

2θ	Å	Relativa %
4,157	21,25	64,4
6,405	13,80	47,6
8,264	10,70	51,4
9,769	9,05	47,3
12.366	7,16	57,6
13.724	6,45	72,2
14.639	6,05	87,5
16.026	5,53	77,1
18.069	4,91	100
18.889	4,70	82,4

Ejemplo 95

Besilato del Ejemplo 55- G

A100 mg del Ejemplo 55- G de base libre, se agregó equivalente 1M de ácido benceno sulfónico y 1000µL de acetona. Con agitación se formó una solución clara. Esta solución se calentó a 50 ° C a 1 ° C / min y se mantuvo durante 30 minutos en cuyo tiempo se enfrió a 0,5 ° C / min a 5 ° C donde se mantuvo durante 30 minutos. El sólido resultante se recolectó por filtración y se secó a 40 ° C al vacío durante 72 horas.

Esta forma es solvato de acetona de sal de besilato 1:1cristalino con un punto de fusión de 155,7 ° C. Hay un endoterma de baja temperatura a 85,9 ° C con una pérdida de peso concurrente del 5,4%, lo cual probablemente corresponde a la pérdida de acetona. El XRPD se muestra en la Figura 35. La DSC y TGA se muestran en la Figura 36.

Picos de difracción de rayos X de polvos debesilato del Ejemplo 55- G

Ángulo 2θ	d valor Å	Intensidad Relativa %
6,799	13,00	22,1
7,624	11,60	14,9
8,215	10,76	26
9,196	9,62	40,7
10.674	8,29	22,8
11.177	7,92	11,3

11.715	7,55	11,3
13.324	6,65	28,5
13,71	6,46	100
14.352	6,17	24,9
14.912	5,94	49,6
15.358	5,77	35
16.169	5,48	54,2
16.706	5,31	21,8
17,16	5,17	27,6
17.465	5,08	52,4
17.737	5,00	33,1
18.952	4,68	14
19.915	4,46	46,3
21.568	4,12	17,1
22.119	4,02	69
22.422	3,97	35,4
23.656	3,76	18
24,45	3,64	76,1
25.535	3,49	17,3
27.668	3,22	19,9
28.393	3,14	32,3
29.209	3,06	18,5
29.832	2,99	18,1
30.595	2,92	18,5
33.143	2,70	17,7

Ejemplo 96

Solvato MTBE del Ejemplo 55- G

A 100 mg del Ejemplo 55- G de base libre,se agregó 1000µL de MTBE al 10% en heptano (o también se puede utilizar MTBE puro). Con agitación se formó una suspensión fina. La suspensión se calentó a 50 ° C a 1 ° C / min y se mantuvo durante 30 minutos en cuyo tiempo se enfrió a 0,5 ° C / min a 5 ° C donde se mantuvo durante 30 minutos. El sólido resultante se recolectó por filtración y se secó a 40 ° C al vacío durante 72 horas.

Esta forma es cristalina con un punto de fusión de 134,2 ° C con una pérdida de peso concurrente del 6,9% correspondiente a la pérdida de MTBE. El XRPD se muestra en la Figura 37. La DSC y TGA se muestran en la Figura 38.

Picos de difracción de rayos X de polvos de solvato MTBE del Ejemplo 55- G

Ángulo 2θ	d valor Å	Intensidad Relativa %
4,074	21,69	13,9
6,728	13,14	22,3
7,659	11,54	36,3
8,627	10,25	26,8
10.148	8,72	27
10.853	8,15	19,4
11.418	7,75	39,3
12.313	7,19	31,9
12.889	6,87	27,3
14.043	6,31	88,8
14.684	6,03	27,6
15.969	5,55	61,2
16.689	5,31	50,7
17.149	5,17	100
17.842	4,97	39,2
18.338	4,84	43,1
19.119	4,64	33,9
19.752	4,49	32
23.113	3,85	37,6
24.397	3,65	22,2
25.187	3,54	22
25.794	3,45	24,9
27.159	3,28	20,3

Ejemplo 97

Propiedades de absorción de humedad de las diferentes formas cristalinas del Ejemplo 55-G en comparación con la forma libre amorfa

	amorphous	Di-hydrate	Sulfate	tosylate	Besylate (acetone solvate)	Hydrate
DVS % Weight gain						
40% RH	1.9	-1	3.5	2.2	-3.5	7.1
90% RH	3.3	-0.2 *	9	5.3	-2 *	9.3

Solubilidad de diferentes formas cristalinas del Ejemplo 55- G en comparación con la forma libre amorfa

mg/mL (pH)	amorphous	Di-hydrate	tosylate	Besylate (acetone solvate)	hydrate
pH 1.2	> 10 [1.2]	5.698 (1.59)	1.618 (1.47)	3.161 (1.44)	4.402 (1.7)
pH 4.5	0.01 [4.8]	< 0.0005 (4.46)	< 0.0005 (4.54)	< 0.0005 (4.39)	< 0.0005 (4.54)
pH 6.8	< 0.0005 [6.8]	0.041 (3.82)	0.257 (2.97)	0.075 (3.57)	< 0.0005 (6.63)
SGF	> 10 [1.6]	6.603 (1.33)	2.034 (1.31)	3.179 (1.31)	7.061 (1.4)
FeSSIF (pH 5.5)	1.2 [5.6]	< 0.0005 (4.51)	< 0.0005 (5.1)	< 0.0005 (5.5)	0.001 (5.75)
FaSSIF (pH 6.5)	0.07 [6.9]	0.081 (3.54)	< 0.0005 (5.7)	< 0.0005 (5.98)	< 0.0005 (6.56)
Water	< 0.0005 [6.2]	0.451 (2.64)	0.495 (2.42)	0.457 (2.57)	< 0.0005 (6.12)

Ejemplo 98

Datos in vivo

El Hidrato del Ejemplo 55- G se dosificó en una formulación de suspensión (0,1% Tween80/0.5% CH) a 30 y 100mpk a ratas Sprague Dawley. A 30mpk el hidrato tiene niveles de exposición plasmáticos similares a con aquellos observados después de una dosis de microemulsión o suspensión amorfa. La exposición a 100mpk fue ligeramente inferior a partir de hidrato cristalino en comparación con la microemulsión o la suspensión amorfa. Sin embargo, el aumento en exposición fue proporcional en la dosis para el hidrato indicando que la forma sería adecuada para utilizar en operaciones in vivo con mayores dosis. Los resultados de este experimento se resumen en la Figura 39.

Ejemplo 99

Ensayo FLIPR

Los compuestos se probaron para determinar su capacidad para inhibir movilización de calcio mediadapor C5a utilizando una línea celular estable que sobre expresala C5aR humana y la proteína Gα15 sobre el sistema Tetra FLIPR (Lector de Placas de imágenes fluorescente). Las células se mantuvieron en medios de cultivo que contienen DMEM (Medio EagleModificado de Dulbecco) con 4,5 g / L de glucosa, suero fetal de bovino al 10%, 100 U / mL, aminoácido no esencial1x, y 250 mg / mL de G418 (Geneticina). Antes de la prueba de los compuestos, las células se sembraron a 10.000 células/pozo en una placa negrade 384- pozos

defondo claro, y se incubaron durante la noche a 37 ° C con CO_2 al 5%. En el día del experimento, los medios de cultivo se eliminaron, y se reemplazaron con un buffer de ensayo HBSS (Solución Salina Equilibrada de Hanks) con HEPES 20 mM (ácido 4 - (2- hidroxietil)- 1-piperazinaetanosulfonico) y BSA al 0,1% (albúmina de suero bovino) BSA conteniendotinte de calcio **5** (Molecular Devices) y probenecid 2,5 mM. Después de 1 hora de incubación a 37 ° C, CO_2 al 5% durante 60 min, las células se pre- incubaron con compuestos durante 30 minutos a temperatura ambiente, en DMSO al 1% (dimetilsulfóxido). Luego se agrego la C5a humanaa la concentración de CE50 (0,1 - 0,25 nM) y se detectaron cambios en la movilización de calcio utilizando FLIPR.

Ejemplo número	FLIPR IC^{50} (nM)
23- I	0.5
17- M	30
29	2
19- F	4
16- I	48
20- D	164
21- AJ	6
21- R	1
24- G	7
17- S	160
21- AF	4
54- B	2
17- AM	2
17- R	10
43- A	56
23- T	2
16- V	338
17- AI	19
21- AG	1
24- D	91

Ejemplo número	FLIPR IC_{50} (nM)
23- H	1
30- A	16
17- T	54
19- AE	4
17- AP	10
17- H	10
22- C	2
21- AH	1
24- I	464
17- AN	31
31- I	9
24- E	75
44- D	131
17- AY	9
16- S	90
17- AQ	16
19- AF	1
17- AJ	94
43- D	802
17- BK	163

Ejemplo número	FLIPR IC^{50} (nM)
42- K	217
19- AD	2
44- E	38
19- N	29
21- D	0.5
40- L	180
47- B	56
21- AK	5
42- H	58
17- G	4
42- I	14
23- F	5
50- E	790
24- L	6
40- Q	868
19- AB	17
31- H	77
28- D	4
41- F	550
21- S	30
41- E	21
21- E	23
19- AK	31
24- C	31
25- C	5
19- L	746
32- B	2
53	18

Ejemplo número	FLIPR IC_{50} (nM)
46- B	42
46- A	20
19- AI	2
40- S	78
42- L	4
21- Q	1
40- M	11
21- X	308
23- D	8
40- D	132
45	27
19- CA	4
21- M	56
33- C	79
40- P	37
21- P	7
19- AH	4
41- T	3
41- D	49
21- AB	4
21- AE	9
21- AI	1
41- J	22
26- B	20
17- P	13
19- K	65
19- X	47
52- C	1

Ejemplo número	FLIPR IC^{50} (nM)
17- AS	46
25- F	23
55- I	1
23- K	64
55- T	2
19- Q	112
17- BG	15
17- BE	415
55- L	3
48	198
28- B	3
56- C	1
56- B	2
21- N	2
21- K	2
63- E	23
56- F	1
21- AM	1
55- N	6
55- T	4
68- C	16
69- M	8
46- C	25
69- H	4
70- T	9
65- H	4

Ejemplo número	FLIPR IC_{50} (nM)
17- AZ	39
17- AV	12
55- H	4
23- J	8
55- J	5
24- J	8
39- D	74
32- A	6
55- M	1
51- D	197
23- C	40
21- AL	1
56- E	2
68- B	2
65- B	2
65- K	2
63- T	31
63- I	32
65- A	1
70- J	12
69- L	1
65- I	1
69- J	67
69- I	4
70- K	20
71- B	2

Ejemplo 100

Ensayo de Regulación Positiva de CD11b en Sangre Entera Humana

Se recolectó sangre entera en tubos de heparina de sodio y el ensayo comenzó dentro de 2 horas de la extracción de sangre. La sangre se incubó con compuestos en DMSO al 1% (dimetilsulfóxido) a temperatura ambiente durante 10 minutos agitación suave. Luego se agregó 2 nM de C5a humana durante 15 minutos a temperatura ambiente con agitación suave. Después del periodo de incubación de C5a las células se lavaron una vez con buffer FACS frio (citofluorimetría de flujo), (solución salina amortiguada con fosfato + albúmina de suero bovino al 5%). Los anticuerpos FITC (fluoresceína isotiocianato) de ratón anti-humano CD15 y PE-Cy5 (ficoeritrina-cianina 5) de ratón anti-humano CD11b (de Becton Dickinson) se mezclaron suavemente con las células y se dejaron incubar durante 30 minutos en hielo protegidos de la luz. Las células fueron lavadas tres veces con buffer FACS frío. Los glóbulos rojos (RBC) se lisaron mediante la incubación con buffer FACS de lisis BD (Becton Dickinson) durante 10 minutos a temperatura ambiente. Las células se peletizaron y el procedimiento de lisis se repitió hasta que todos los glóbulos rojos se lisaron. Los leucocitos restantes se resuspendieron en un buffer de lisis BD. Las muestras fueron adquiridas en el citómetro de flujo LSRII y 10.000 eventos de la población de granulocitos CD15 + se recogieron. La intensidad de fluorescencia media de CD11b de la población de células CD15 + se evaluó utilizando el software FACSDiVa (Becton Dickinson).

EJEMPLO N º	hCD11b IC50 (nM)
23-I	22
19-F	13
29	300
17-AN	423
31-I	18
24-E	385
21-AJ	15
21-R	15
24-G	670
55-T	23
21-AF	28
54-B	19

EJEMPLO N º	hCD11b IC50 (nM)
23-H	24
30-A	5785
17-T	451
19-AE	22
17-AP	513
17-H	300
22-C	17
21-AH	6
17-AY	45
55-H	4
16-S	2250
17-AQ	277

EJEMPLO N º	hCD11b IC50 (nM)
17-R	42
43-A	178
56-C	6
23-T	25
21-AG	22
24-D	1500
19-AD	26
44-E	188
21-D	7
47-B	1420
21-AK	51
17-G	114
42-I	2120
23-F	28
24-L	391
19-AB	26
31-H	72
28-D	58
21-S	180
21-E	422
19-AK	30
25-C	183
32-B	24
17-AS	67
55-L	36
28-B	107
21-N	8
21-K	11

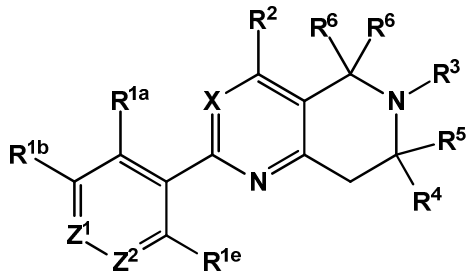
EJEMPLO N º	hCD11b IC50 (nM)
19-AF	6
17-BK	40
56-B	45
46-B	224
46-A	1987
19-AI	7
40-S	793
21-Q	7
40-M	69
23-D	18
40-D	264
45	583
19-CA	50
21-M	181
33-C	238
21-P	26
19-AH	17
41-T	70
41-D	153
21-AB	11
21-AE	93
21-AI	8
41-J	302
26-B	907
23-K	11
17-P	70
52-C	178
24-J	423

EJEMPLO N º	hCD11b IC50 (nM)
23-C	95
23-J	38
21-AL	19
63-E	29
56-F	11
21-AM	7
55-N	12
55-T	5
68-C	69
69-M	45
76-C	46
69-H	196
70-T	19
68-B	17
71-B	10

EJEMPLO N º	hCD11b IC50 (nM)
32-A	63
55-M	15
65-K	26
63-T	197
63-I	60
65-A	30
70-J	39
69-L	54
65-I	19
69-J	112
69-I	25
70-K	37
65-H	56
65-B	16
70-H	41
70-I	38

Reivindicaciones

1. Un compuesto de la fórmula (I) o una sal del mismo:



(I)

en donde

X es N o CH;

Z^1 es N o CR^{1c};

Z^2 es N o CR^{1d}, en donde al menos uno de Z^1 y Z^2 no es N;

R^{1a} se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, C_1- C_6alcoxilo, haloC_1 - C_6alquilo, haloC_1 - C_6alcoxilo, ciano o halógeno;

R^{1b} se selecciona del grupo que consta de hidrógeno, amino, hidroxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y mono y di C_1- C_4alquilamino;

R^{1c} es hidrógeno, halógeno o C_1- C_6alquilo;

R^{1d} se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6alquilo, y C_1- C_6alcoxilo;

R^{1e} se selecciona entre hidrógeno, halógeno, ciano, C_1- C_6alquilo, haloC_1 - C_6alquilo, C_1- C_6alcoxilo y haloC_1- C_6alcoxilo, sulfona, C_3- C_7cicloalquilo; o

R^{1a} y R^{1b} tomados en combinación forman un anillo heterocíclico saturado o insaturado de 5 miembros que tiene uno o dos heteroátomos de anillo seleccionados entre N, O o S, dicho anillo heterocíclico es sustituido por 0, 1, o 2 sustituyentes de C1- C6alquilo o halógeno independientemente seleccionados;

en donde al menos uno de R^{1a} y R^{1e} no es hidrógeno;

R^2 se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, C_1 - C_6alcoxilo, C_1- C_6alquiltio, C_3- C_7cicloalquilo, C_3- C_7cicloalquilC_1- C_4alquilo y $(CH_2)_pNR^{2a}R^{2b}$, en donde cada grupo alquilo y alcoxilo es sustituido por 0 o 2 sustituyentes seleccionados del grupo que consta de hidroxilo, halógeno, y C_1- C_4alcoxilo, amino, mono y di C_1- C_4- alquilamino;

p es 0 o 1;

R^{2a} es hidrógeno, C_1- C_6alquilo o hidroxiC_1 - C_6alquilo;

R^{2b} es hidrógeno, C_1- C_6alquilo, C_3- C_7cicloalquilo o C_3- C_7cicloalquilC_1 - C_4alquilo, en donde cada alquilo es sustituido o no sustituido con hidroxilo, C_1 - C_4alcoxilo, C_1- C_4alcoxicarbonilo, o heterociclo en donde el heterociclo es un saturado, insaturado o un anillo aromático de cinco o seis miembros que tiene 1 o 2 heteroátomos de anillo seleccionados entre N, O o S y es sustituido o no sustituido con 1 ó 2 sustituyentes de C_1- C_4alquilo independientemente seleccionados; o

$NR^{2a}R^{2b}$ tomados en combinación forman un sistema de anillo heterocíclico saturado de 4 a 8 miembros que tiene 1 ó 2 anillos y 0 o 1 heteroátomos de anillo adicionales seleccionados entre N, O o S, el sistema de anillo heterocíclico saturado es sustituido o no sustituido con 1- 4 sustituyentes seleccionados independientemente del grupo que consta de C_1- C_4alquilo, hidroxilo, C_1- C_4alcoxilo, C_1- C_4alcoxiC_1 - C_4alquilo, hidroxiC_1 - C_4alquilo, halógeno, amino, mono y di C_1- C_4alquilamino, C_1 - C_4alcoxicarbonilo, C_1- C_4alcanoilo, S (O) $_2C_1$- C_4alquilo, CH_2C (O) (C_1- C_4alcoxilo) y CH_2C (O) NH_2;

R^3 se selecciona del grupo que consta de fenilo sustituido, heteroarilo sustituido, y fenilC_1- C_3alquilo, en donde el heteroarilo se selecciona de piridilo, pirazolilo, imidazolilo, tetrazolilo, oxazolilo, y isoxazolilo, y en donde cada grupo fenilo o heteroarilo es sustituido por 1, o 2 3 sustituyentes que son independientemente seleccionados del grupo que consta de C_1- C_4alquilo, C_1- C_4alcoxilo, halógeno, ciano, haloC_1 - C_4alquilo, haloC_1 - C_4alcoxilo, hidroxiC_1 - C_4alquilo, C_1- C_4alcoxiC_1 - C_4alquilo, C_3- C_6cicloalquilo, y oxaciclo saturado que tiene 4, 5, o 6 átomos de anillo y un oxígeno de anillo, dicho oxaciclo es sustituido o no sustituido con 1 ó 2 sustituyentes de C_1- C_4alquilo independientemente seleccionados, y en donde cada fenilo o heteroarilo comprende al menos un sustituyente *orto* no- hidrógeno al punto de fijación al resto del compuesto de la fórmula (I);

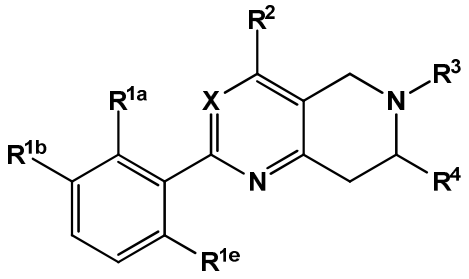
R^4 es hidrógeno o C_1- C_4alquilo;

R^5 es hidrógeno; o

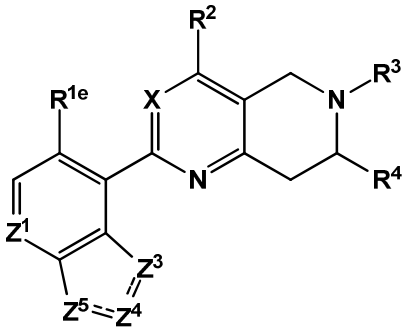
R^4 y R^5 tomados en combinación son oxo; y

R^6 es hidrógeno en cada ocurrencia o CR^6_2, tomada en combinación, forma un carbonilo divalente.

2. Un compuesto de la reivindicación 1, el cual es un compuesto de la fórmula (II) o la fórmula (III), o una sal del mismo:



(II)



(III)

en donde

Z^1 es N o CH;

Z^3 es N (H), N (C_1- C_4alquilo), o C (R^{1f});

Z^4 es N o CH;

Z^5 es N (H), N (C_1- C_4alquilo) o C (R^{1g}), en donde uno o dos de Z^3, Z^4 y Z^5 es nitrógeno;

R^{1f} es hidrógeno, C_1- C_4alquilo o halógeno; y

R^{1g} es hidrógeno o C_1- C_4alquilo.

3. Un compuesto de la reivindicación 1 o la reivindicación 2, en donde R^3 es fenilo o 1H- pirazolilo, cada uno de los cuales es sustituido por 1 ó 2 grupos de C_1- C_4alquilo independientemente seleccionados y 0, 1 o 2 sustituyentes adicionales seleccionados entre el grupo que consta de halógeno, ciano, C_1- C_4alquilo, haloC_1- C_4alquilo, C_1- C_4alcoxilo, ciclopropilo, oxetanilo o 1- metil- oxetanilo.

4. El compuesto de la reivindicación 2 o la reivindicación 3, en el cual R^{1a} es hidrógeno o metilo;

R^{1e} es hidrógeno, halógeno, ciano, metilo o trifluorometilo, en donde al menos uno de R^{1a} y R^{1e} no es hidrógeno;

Z^3 es C (R^{1f});

Z^4 es N o CH;

Z^5 es N (H), y

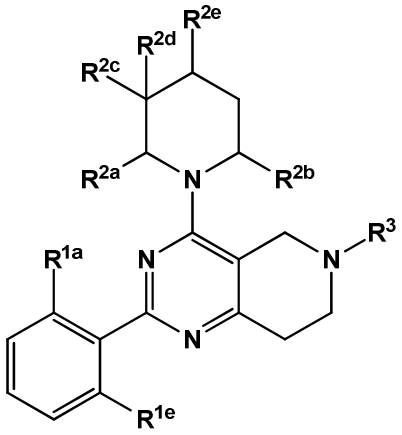
R^{1f} es hidrógeno o metilo.

5. El compuesto de cualquiera de las reivindicaciones 1 a 3, en el cual R^1 es 2,6- dimetilfenilo, 2,6- dietilfenilo, 3,5- dimetil- 1H- indazol- 4- ilo, 3,5- dimetil- 1H indol- 4- ilo, 3,5- dimetil- 1H- indol- 4- ilo, 3,5- dimetil- 1H- pirazolo [3,4- b] piridin- 4- ilo, o 5- trifluorometil- 3H pirrolo [2,3- b] piridin- 4- ilo.

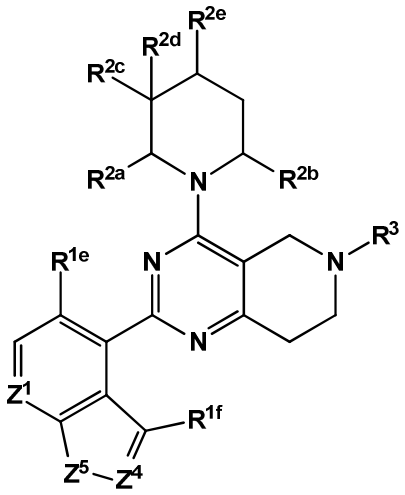
6. El compuesto de cualquiera de las reivindicaciones 1 a 5, en el cual R^4 es hidrógeno.

7. El compuesto de cualquiera de las reivindicaciones 1 a 5, en el cual X es N.

8. Un compuesto de cualquiera de las reivindicaciones 1 a 7, el cual es un compuesto de la fórmula (IV) o (V), o una sal del mismo:



(IV)



(V)

en donde

R^{2a}, R^{2b}, R^{2c}, y R^{2d} se seleccionan independientemente entre hidrógeno y C_1- C_4alquilo; o

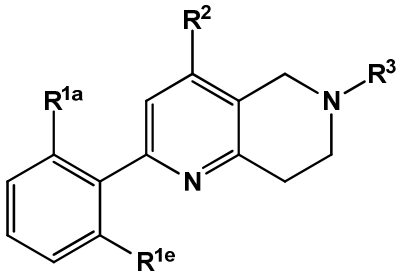
R^{2a} y R^{2b}, tomados en combinación, forman un grupo de C_1- C_3alquileno divalente; y

R^{2e} es hidroxilo o C_1- C_4alcoxilo.

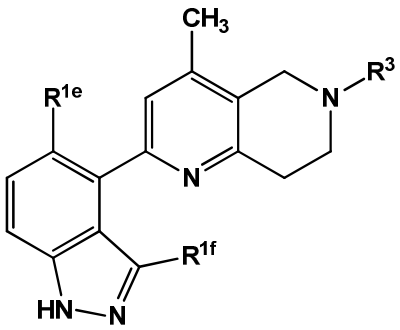
9. El compuesto de cualquiera de las reivindicaciones 1 a 5, en el cual X es CH.

10. El compuesto de cualquiera de las reivindicaciones 1 a 5 o 9, en el cual R^2 es hidrógeno o metilo.

11. Un compuesto de cualquiera de las reivindicaciones 1 a 5, 9 o 10, el cual es un compuesto de la fórmula (VI) o (VII), o una sal del mismo:



(VI)



(VII)

en donde

en la fórmula (VI), R^{1a} y R^{1e} son metilo o etilo; o

en la fórmula (VII), R^{1e} y R^{1f} son hidrógeno o metilo, en donde al menos un R^{1f} o R^{1e} es metilo.

12. Un compuesto de la reivindicación 1, o una sal del mismo, en el que R^6 es deuterio.

13. Un compuesto de la reivindicación 1, o una sal del mismo, dicho compuesto se selecciona del grupo formado por:

1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperidin- 4- ol racémico;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina *racémica*;

1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidin- 4- ol *racemico*;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (3- metoxiazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (1,3- dimetil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- N- (2- metoxietil)- N- metil- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

1- ((2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (3- (2- metoxietil)- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (tetrahidrofuran- 2- il)- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

N- ciclopentil- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- *N*- metil- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- amina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol *racémico*;

(*R*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (2- metilpirrolidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- *N*- metil- *N*- ((tetrahidrofuran- 2- il)metil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- amina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (3- (metoximetil)piperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina *racémica*;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- (4- (metoximetil)piperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*S*)- 1- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.;

1- ((2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol;

1- (2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidina- 3- carboxilato de etilo;

2,2'- ((2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)azanediil)dietanol;

2- (2,6- dimetilfenil)- N- propil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

2- ((2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)acetato de metilo;

(*R*)- 2- ((6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)amino)- 3- metilbutan- 1- ol;

4- (3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2R,4S)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*S*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1*H*- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3- metilpiperidin- 3- ol;

6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2*S*,4*S*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- N,N- dimetil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

2- (2,6- dimetilfenil)- N- (2- metoxietil)- N- metil- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- (4- metoxipiperidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- (3,3- dimetilpirrolidin- 1- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,2- dimetilmorfolina;

4- (azetidin- 1- il)- 2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (4- metoxipiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- cloro- 2- metilfenil)- 4- (4- metoxipiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- metil- 1- (metil(2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)amino)propan- 2- ol;

1- ((6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)(metil)amino)- 2- metilpropan- 2- ol;

6- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,2- dimetilmorfolina;

6- (5- isopropil- 2- metilfenil)- N,N- dimetil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3,3- dimetilpiperidin- 4- ol;

6- (5- isopropil- 2- metilfenil)- N- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

N- isopropil- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

4- (azetidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperidin- 4- ol racémico;

6- (5- isopropil- 2- metilfenil)- N- (2- metoxietil)- N- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- amina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)azetidin- 3- ol;

6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémica;

4- (3- fluoroazetidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3,3- dimetilpiperidin- 4- ol;

(*S*)- 4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 3- metilmorfolina;

(*S*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperidin- 3- ol;

(*R*)- 1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperidin- 3- ol;

6- (5- isopropil- 2- metilfenil)- 4- ((3*R*,4*R*)- 4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((*3S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- (1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)pirrolidin- 2- il)metanol;

(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- (3- metoxi- 3- metilazetidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilazetidin- 3- ol;

6- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- oxa- 6- azaspiro[3.3]heptano;

6- (5- isopropil- 2- metilfenil)- 4- (3- metoxiazetidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina;

(3- *endo*)- 8- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 8- azabiciclo[3.2.1]octan- 3- ol;

(*S*)- 2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*S*)- 6- (5- cloro- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- metoxi- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.;

2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (1- metil- 1H- indazol- 7- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (1- metil- 1H- indazol- 7- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (2- metoxifenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- cloro- 2- metoxifenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- cloro- 2- metilfenil)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 2- (5- fluoro- 2- metilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- isopropil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1*H*- pirrolo[2,3- *b*]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- Ciclopropil- 1H- pirrolo[2,3- b]piridin- 4- il)- 4- (3,3- dimetilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- Dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,5- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,6- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*R*)- 2- (2,4- dimetilpiridin- 3- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,5- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (3,5- dimetilpiridin- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (5- metoxi- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- cloro- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,4- dimetilpiridin- 3- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (5- fluoro- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (4- fluoro- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- ciclopropil- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (5- ciclopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- (trifluorometil)- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- ((3*S*,4*S*)- 4- metoxi- 3- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dimetilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (4- (2- (2,5- Dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (2- (2,6- dimetilfenil)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)piperazin- 1- il)acetamida;

(*R*)- 2- (4- (2- (2,6- dimetilfenil)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (o- tolil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- cloro- 2- metilfenil)- 2- (2,6- dimetilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- cloro- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- (trifluorometil)fenil)- 5,6,7,8 tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (4- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (2- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)acetamida.;

(*R*)- 2- (4- (6- (3- fluoro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (2,4- difluorofenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)acetamida;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- ciclopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona;

1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (2- (trifluorometil)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (6- (5- isopropil- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)etanona;

(*R*)- 1- (4- (2- (2,5- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilpiperazin- 1- il)etanona;

(*R*)- 1- (3- metil- 4- (2- (3- metil- 1H- indol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)piperazin- 1- il)etanona;

1- (4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)etanona racémica;

1- ((*trans*)- 4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2,5- dimetilpiperazin- 1- il)etanona racémica;

2- (- 4- (2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)acetamida racémica;

2- (4- (6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- (*trans*)- 2,5- dimetilpiperazin- 1- il)acetamida racémica;

(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (metilsulfonil)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- isopropil- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- ; metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 4- (4- etil- 3- metilpiperazin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (5- cloro- 2- metilfenil)- 2- (3- metil- 1H- indol- 4- il)- 4- (3- metil- 4- (oxetan- 3- il)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- metoxi- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- ; tetrahidropirido[4,3- d]pirimidina;

2- (5- isopropil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metoxi- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (5- isopropil- 1H- indazol- 4- il)- 4- metoxi- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3- cloro- 5- metil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metoxi- 5,6,7,8 tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (3- cloro- 5- metil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- ((*S*)- 1- feniletil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémica;

2- (2,6- dimetilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- ((R) 1- feniletil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémica;

6- (4- cloro- 3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

(*R)*- 4- metil- 1- (2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (3- metil- 4- ((2- nitrofenil)sulfonil)piperazin- 1- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)pentano- 1,3- diona;

(*R*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (3- metil- 4- ((2- nitrofenil)sulfonil)piperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1- tosil- 1H- indol- 4- il)- 4- (3- metilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (4- (6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (2- (2,6- dimetilfenil)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*R*)- 2- (4- (6- (4- cloro- 3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidin- 4- il)- 2- metilpiperazin- 1- il)acetamida;

(*S*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1H- indol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- ((3R,4R)- 4- metoxi- 3- metilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

1- (6- (3- isopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilpiperidin- 4- ol racémico;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (3- metoxipropoxi)- 5,6,7,8- tetrahidropirido[4,3- *d*]pirimidina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 4- metil- 6- (o- tolil)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina2- (2,6- dietilfenil)- 6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 5,6,7,8-

tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (1,3- dimetil- 1H- pirazol- 5- il)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (5- metoxi- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (2,5- dimetilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (1- etil- 3- metil- 1H- pirazol- 5- il)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (2,4- dimetilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (5- ciclopropil- 2- metilfenil)- 2- (2,6- dietilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (5- cloro- 2- metilfenil)- 2- (2,6- dietilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 4- metil- 6- (1,3,5- trimetil- 1H- pirazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 2- (3- metil- 1H- indol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (5- fluoro- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (3- metil- 1H- indol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro($^2H_2$)- 1,6- naftiridina.;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (3- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2- cloro- 5- metoxifenil)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (5- isopropil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

4- metil- 2- (5- metil- 1H- indazol- 4- il)- 6- (2- metil- 5- (3- metiloxetan- 3- il)fenil)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dietilfenil)- 4,7- dimetil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (2,6- dietilfenil)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (5- isopropil- 2- metilfenil)- 4,7- dimetil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (3- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (5- cloro- 1H- pirrolo[2,3- b]piridin- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

6- (5- isopropil- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- pirrolo[2,3- b]piridin- 4- il)- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (2,4- dimetilpiridin- 3- il)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina;

2- (3- metil- 1H- indol- 4- il)- 6- (2,6- dimetilfenil)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^2H_2$)- 1,6- naftiridina ;

6- (5- metoxi- 2- metilfenil)- 4- metil- 2- (5- metil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidro(5,5- $^{2}H_{2}$)- 1,6- naftiridina;

6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (5- isopropil- 1H- indazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (5- isopropil- 1H- indazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dietilfenil)- 6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^{2}H_{2}$)- 1,6- naftiridina;

2- (3- metil- 1H- indol- 4- il)- 6- (1- etil- 3,5- dimetil- 1H- pirazol- 4- il)- 4- metil- 5,6,7,8- tetrahidro(5,5- $^{2}H_{2}$)- 1,6- naftiridina;

2- (2,6- dietilfenil)- 4- metil- 6- (1- metil- 1H- tetrazol- 5- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- metoxi- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- metoxi- 5,6,7,8- tetrahidro(5,5- ^{2}- 1,6- naftiridina;

(*S*)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

2- (2,6- dimetilfenil)- 4- ((2- hidroxi- 2- metilpropil)(metil)amino)- 6- (5- isopropil- 2- metilfenil)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

4- ((ciclopropilmetil)(propil)amino)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2- metoxietil)(metil)amino)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 7,8- dihidro- 1,6- naftiridin- 5(6H)- ona;

(*S*)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

1- ((2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidro- 1,6- naftiridin- 4- il)(metil)amino)- 2- metilpropan- 2- ol;

N- (ciclopropilmetil)- 2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- N- propil- 5,6,7,8- tetrahidro- 1,6- naftiridin- 4- amina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- N- (2- metoxietil)- N- metil- 5,6,7,8- tetrahidro- 1,6- naftiridin- 4- amina;

2- (2,6- dimetilfenil)- 6- (5- isopropil- 2- metilfenil)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidro- 1,6- naftiridina;

2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- etoxi- 2- metilpiperidin- 1- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- (difluorometil)- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (4- cloro- 3- (difluorometil)- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- etoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 2- (5- metil- 1*H*- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1*H*- pirazol- 5- il)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- ((2*R*,4*R*)- 4- metoxi- 2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 2- (3,5- dimetil- 1*H*- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 6- (1- metil- 3- (trifluorometil)- 1*H*- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((3- *endo*)- 3- metoxi- 8- azabiciclo[3.2.1]octan- 8- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(S)- 6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(R)- 6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina; y

(R)- 6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- etoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(S)- 6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(cis)- 3- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (1- metil- 3- (trifluorometil)- 1H- pirazol- 5- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 1- metil- 7- oxa- 3- azabiciclo[4.2.0]octano racémico;

(R)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- ciclopropil- 2- (2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((4*S*,6*R*)- 6- metil- 1- oxa- 7- azaspiro[3.5]nonan- 7- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)benzonitrilo;

(R)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- metoxi- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina;

(R)- 6- (4- cloro- 1- metil- 3- (trifluorometil)- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(R)- 6- (3- (difluorometil)- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(R)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (4- fluoro- 1- metil- 3- (trifluorometil)- 1H- pirazol- 5- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- fluoroetoxi)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (2,2- difluoroetoxi)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

2- ((2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)oxi)etanamina;

2- ((2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)oxi)- N- metiletanamina;

(S)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- ((1- metilpirrolidin- 2- il)metoxi)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

4- (2- ((2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)oxi)etil)morfolina;

(*R*)- 3- ((2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)oxi)propano- 1,2- diol;

1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina;

(*R*)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina;

1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3,3- difluoropiperidin- 4- ol;

(*R*)- 1- (2- (3,5- dimetil- 1H- pirazolo[3,4- b]piridin- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina;

(3S,4S)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- metoxi- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(3R,4R)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- metoxi- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(3R,4R)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(3S,4S)- 1- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(*R*)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 4- (2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilmorfolina;

2- (3,5- dimetil- 1H- indazol- 4- il)- 6- (5- isopropil- 2- metilfenil)- 4- (4- (metilsulfonil)piperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 4- (2,2- difluoroetoxi)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (3- etoxiazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilpirrolidin- 3- amina;

(R)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(S)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(3R,4R)- 1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(3S,4S)- 1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 4- metoxi- N,N- dimetilpirrolidin- 3- amina;

(trans)- 1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 2- metilazetidin- 3- ol racémico;

6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- ((*trans)*- 3- metoxi- 2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina racémico;

1- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2,4- dimetilpiperazin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(1*S**,6*S**)- 3- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 1- metil- 7- oxa- 3- azabiciclo[4.2.0]octano racémico;

(*cis*)- 3- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 7- oxa- 3- azabiciclo[4.2.0]octano racémico;

(*R*)- 4- (6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilmorfolina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*S*)- 6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilazetidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 4- (6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilmorfolina;

1- (6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- N,N- dimetilazetidin- 3- amina;

(*R*)- 6- (3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (3- ciclopropil- 1- etil- 4- fluoro- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- etil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina;

(*R*)- 3- (difluorometil)- 5- (2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (4- metoxi- 3,3- dimetilpiperidin- 1- il)- 7,8- dihidropirido[4,3- d]pirimidin- 6(5H)- il)- 1- metil- 1H- pirazol- 4- carbonitrilo

(1*S**,6*S**)- 3- (6- (3- (difluorometil)- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 1- metil- 7- oxa- 3- azabiciclo[4.2.0]octano racémico;

(*R*)- 4- (6- (3- ciclopropil- 4- fluoro- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidin- 4- il)- 3- metilmorfolina;

(R)- 6- (3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina; y

(*R*)- 6- (4- cloro- 3- ciclopropil- 1- metil- 1H- pirazol- 5- il)- 2- (3,5- dimetil- 1H- indazol- 4- il)- 4- (2- metilpiperidin- 1- il)- 5,6,7,8- tetrahidropirido[4,3- d]pirimidina.

14. Una composición farmacéutica que comprende uno o más vehículos farmacéuticamente aceptables y una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las reivindicaciones 1 a 13.

15. Una combinación, en particular una combinación farmacéutica, que comprende una cantidad terapéuticamente efectiva del compuesto según cualquiera de las reivindicaciones 1 a 13 y un segundo agente terapéuticamente activo.

16. Se proporciona un método para inhibir anafilaxia inducida por C5a en un sujeto, el método comprende administrar al sujeto una cantidad terapéuticamente eficaz del compuesto según cualquiera de las reivindicaciones 1 a 13.

17. Un método para tratar en un sujeto un trastorno o enfermedad mediada por la activación del complemento, el método comprende administrar al sujeto una cantidad terapéuticamente eficaz del compuesto según cualquiera de las reivindicaciones 1 a 13.

18. El método de la reivindicación 17, en el que la enfermedad o trastorno se selecciona del grupo que consta de degeneración macular relacionada con la edad, atrofia geográfica, retinopatía diabética, uveítis, retinitis pigmentosa, edema macular, uveítis de Behcet, coroiditis multifocal, síndrome de Vogt-Koyanagi-Harada, uveítis intermedia, retino-coroiditis perdigonada, oftalmía simpática, penfigoide cicatricial ocular, pénfigo ocular, neuropatía óptica isquémica no arterítica, inflamación post-operatoria, oclusión venosa de la retina, alteraciones neurológicas, esclerosis múltiple, accidente cerebro vascular, síndrome de Guillain Barre, lesión cerebral traumática, enfermedad de Parkinson, trastornos de la activación del complemento inadecuados o indeseables, complicaciones en hemodiálisis, rechazo del aloinjerto hiperagudo, rechazo de xenoinjertos, toxicidad inducida por interleucina-2 durante terapia con IL-2, enfermedades inflamatorias, inflamación de enfermedades autoinmunes, enfermedad de Crohn, síndrome de distrés respiratorio agudo del adulto (SDRA), miocarditis, condiciones de reperfusión post-isquémicas, infarto de miocardio, angioplastia con balón, síndrome pos-perfusión en bypass renal o bypass cardiopulmonar, aterosclerosis, hemodiálisis, isquemia renal, reperfusión de la arteria mesentérica después de la reconstrucción aórtica, enfermedad infecciosa o sepsis, transtornos complejos inmunes y trastornos autoinmunes, artritis reumatoide, lupus eritematoso sistémico (LES), nefritis por lupus, nefritis proliferativa, fibrosis hepática, anemia hemolítica, miastenia gravis, regeneración de tejidos, regeneración neuronal, disnea, hemoptisis, SDRA, asma, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, embolia pulmonar e infartos, neumonía, enfermedades originadas por polvo fibrogénico, fibrosis pulmonar, asma, alergia, broncoconstricción, neumonitis por hipersensibilidad, enfermedades parasitarias, síndrome de Goodpasture, vasculitis pulmonar, vasculitis pauci-inmune, inflamación asociada con complejos inmunes, síndrome antifosfolípido, glomerulonefritis y la obesidad.

19. Un método de tratamiento de degeneración macular relacionada con la edad que comprende administrar a un sujeto que lo necesita una cantidad eficaz de una composición que comprende un compuesto de cualquiera de las reivindicaciones 1 a 14.

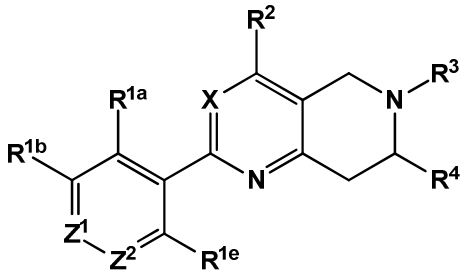
20. Un compuesto según cualquiera de las reivindicaciones 1 a 13, para su uso como un medicamento.

21. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 13 en la fabricación de un medicamento para el tratamiento en un sujeto de un trastorno o enfermedad mediada por la activación del complemento.

22. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 13, para el tratamiento de la degeneración macular relacionada con la edad.

Resumen

La presente invención proporciona un compuesto de la fórmula I:



(I)

un método para fabricar los compuestos de la invención, y sus usos terapéuticos. La presente invención además proporciona una combinación de agentes farmacológicamente activos y una composición farmacéutica.

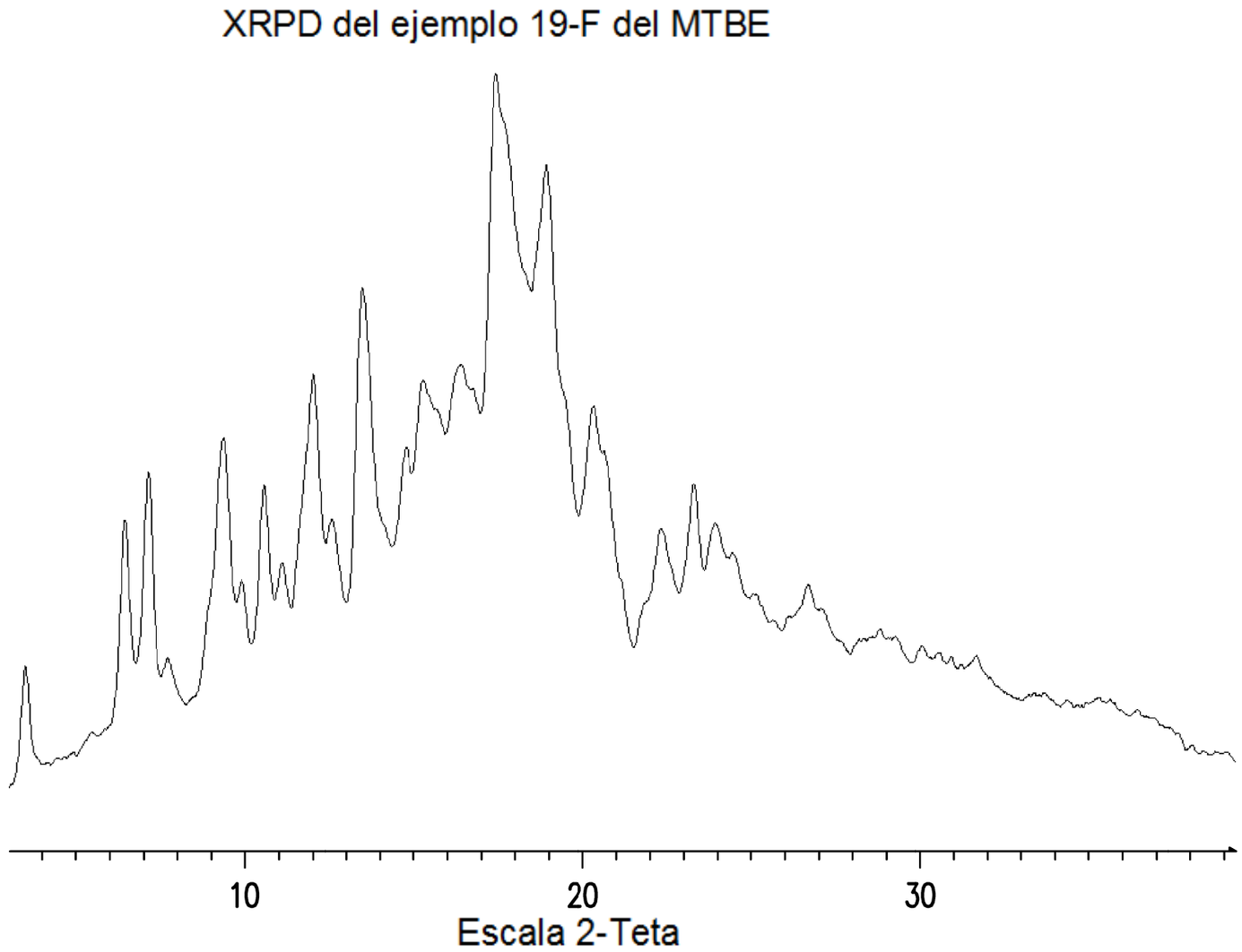


FIG. 1

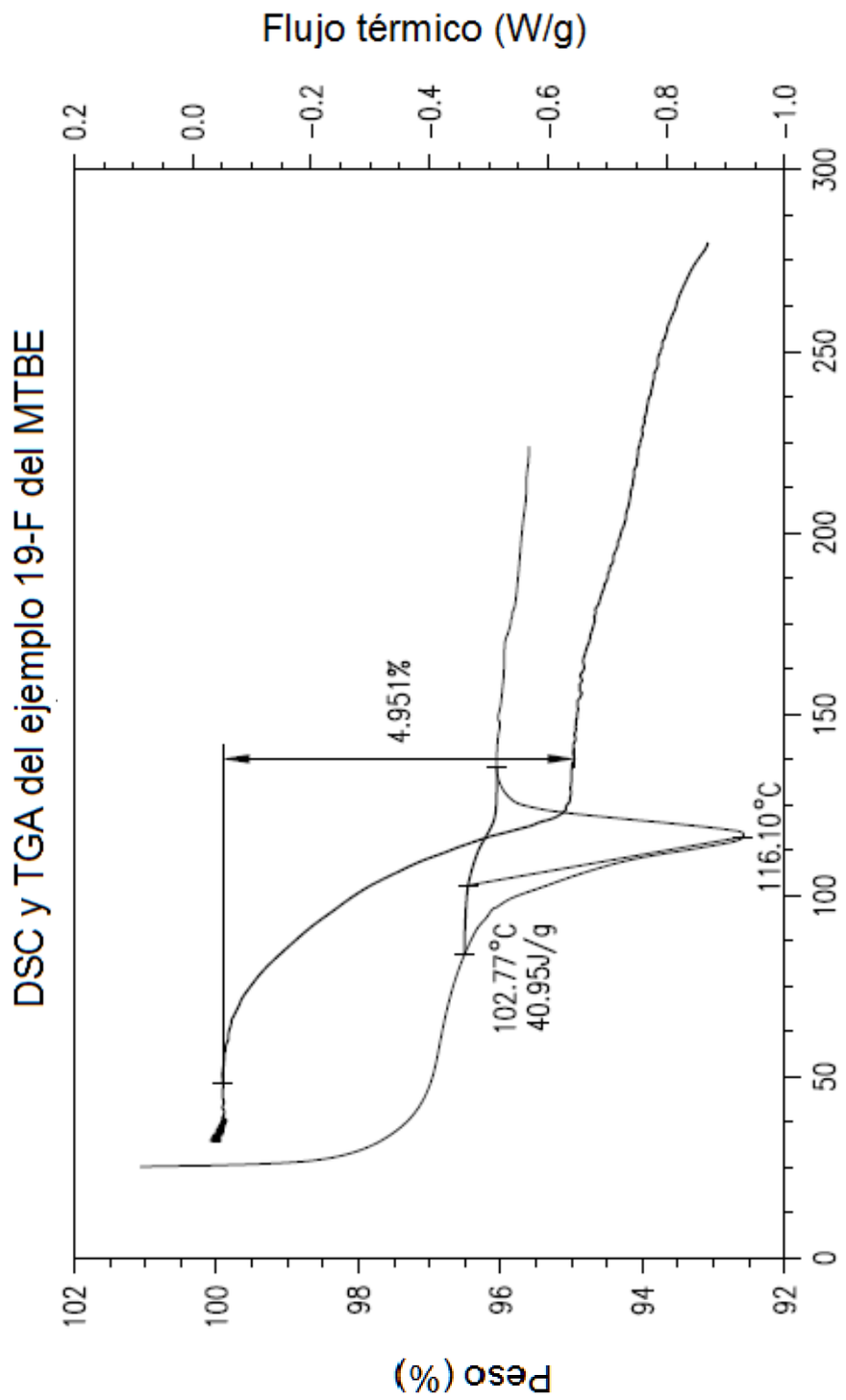

DSC y TGA del ejemplo 19-F del MTBE
Flujo térmico (W/g)
0.2
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
Peso (%)
102
100
98
96
94
92
Temperatura (°C)
0
50
100
150
200
250
300
4.951%
102.77°C
40.95J/g
116.10°C

FIG. 2

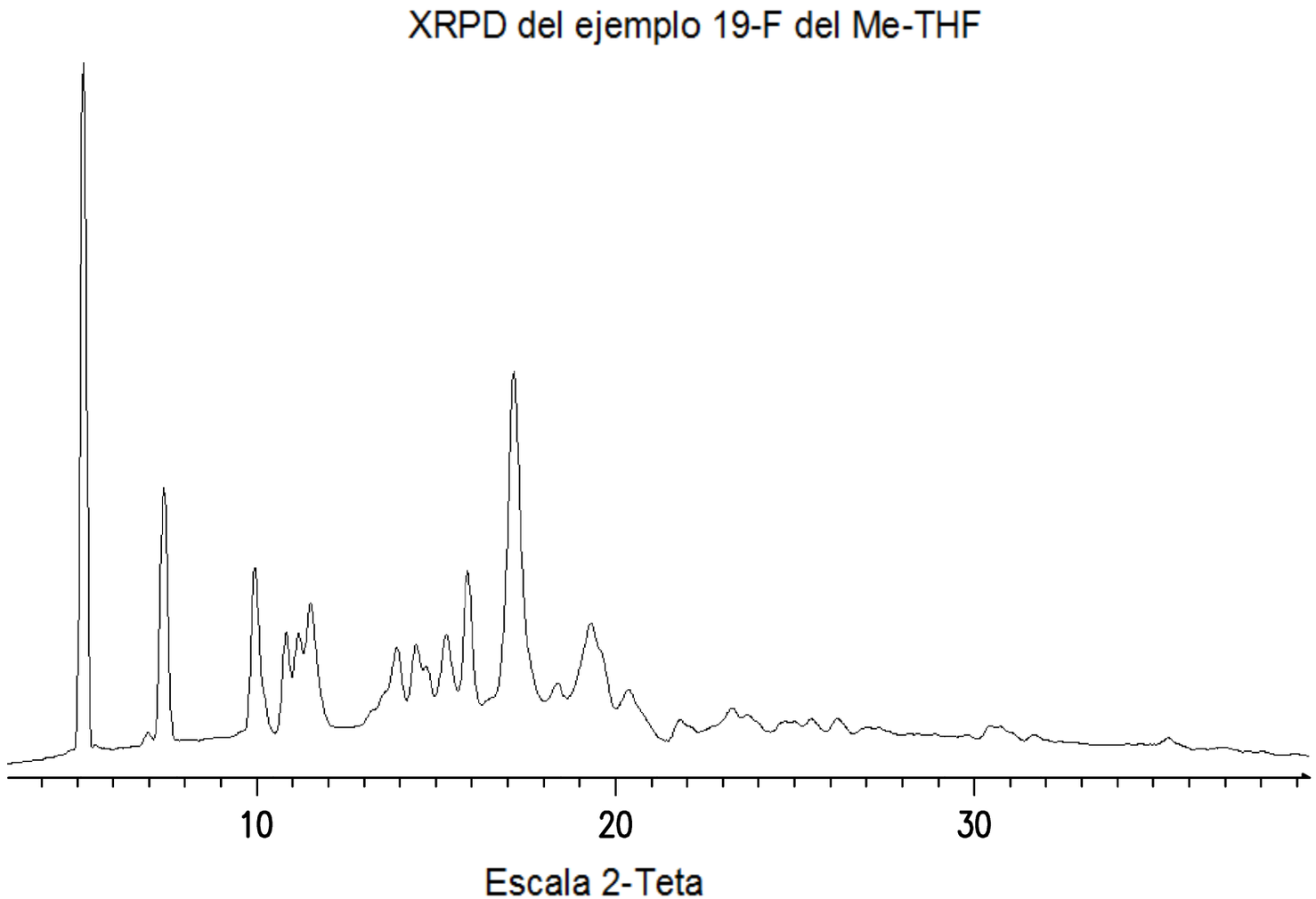


FIG. 3

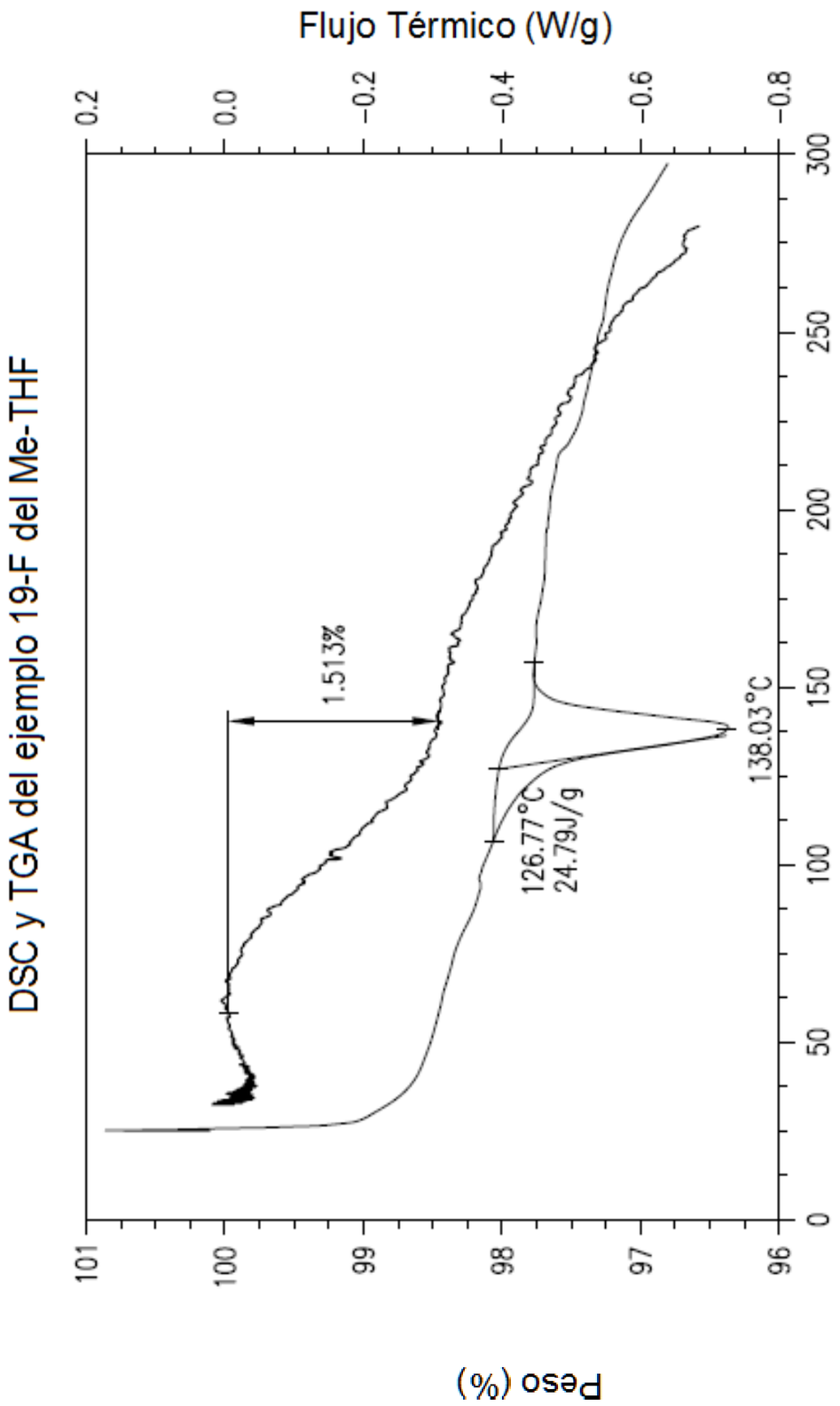

DSC y TGA del ejemplo 19-F del Me-THF
Flujo Térmico (W/g)
0.2
0.0
−0.2
−0.4
−0.6
−0.8
Peso (%)
101
100
99
98
97
96
Temperatura (°C)
0
50
100
150
200
250
300
1.513%
126.77°C
24.79J/g
138.03°C

FIG. 4

XRPD del ejemplo 19-F del precipitado inicial (patrón superior) y material seco (patrón inferior) del Me-THF

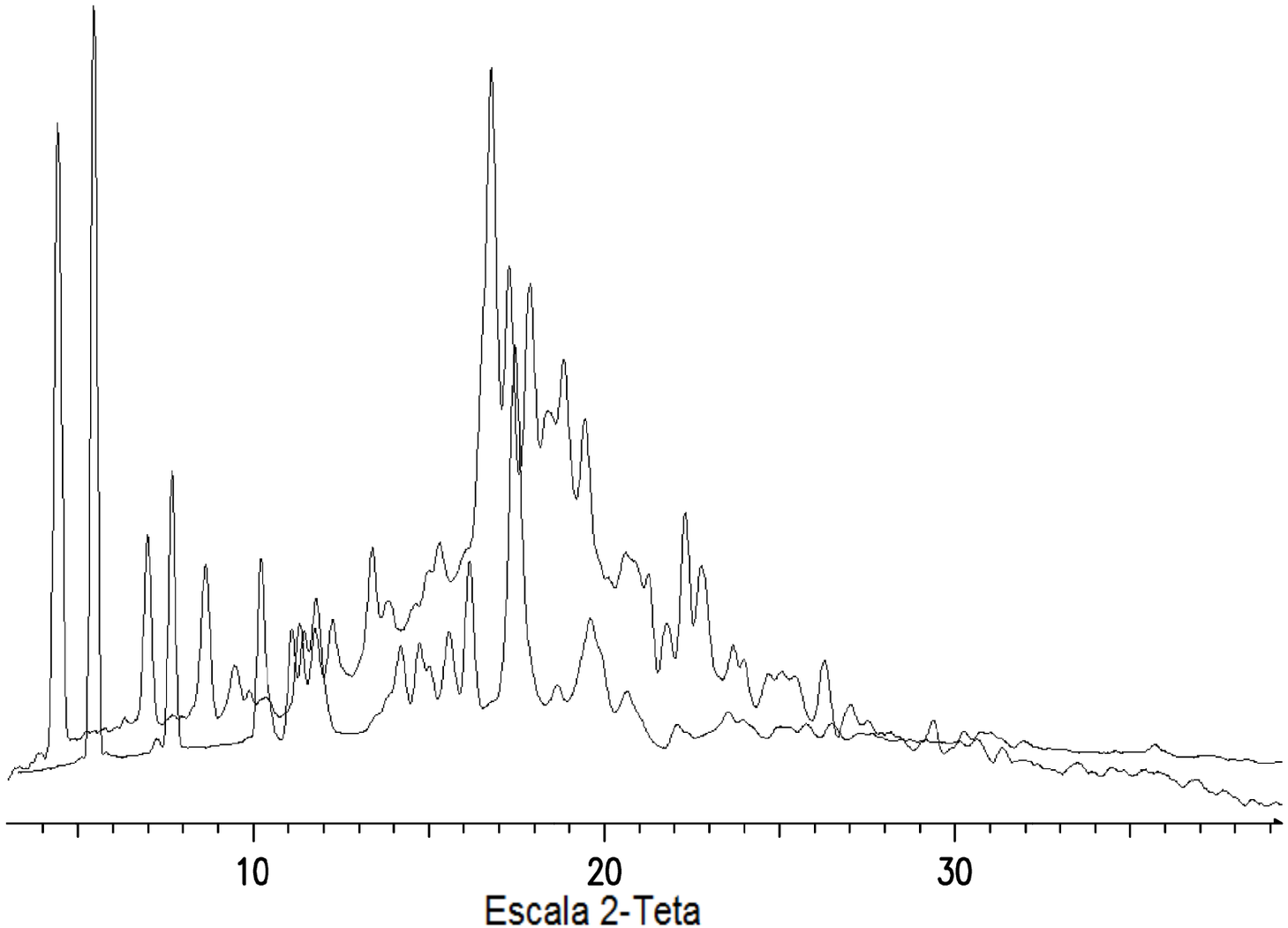


FIG. 5

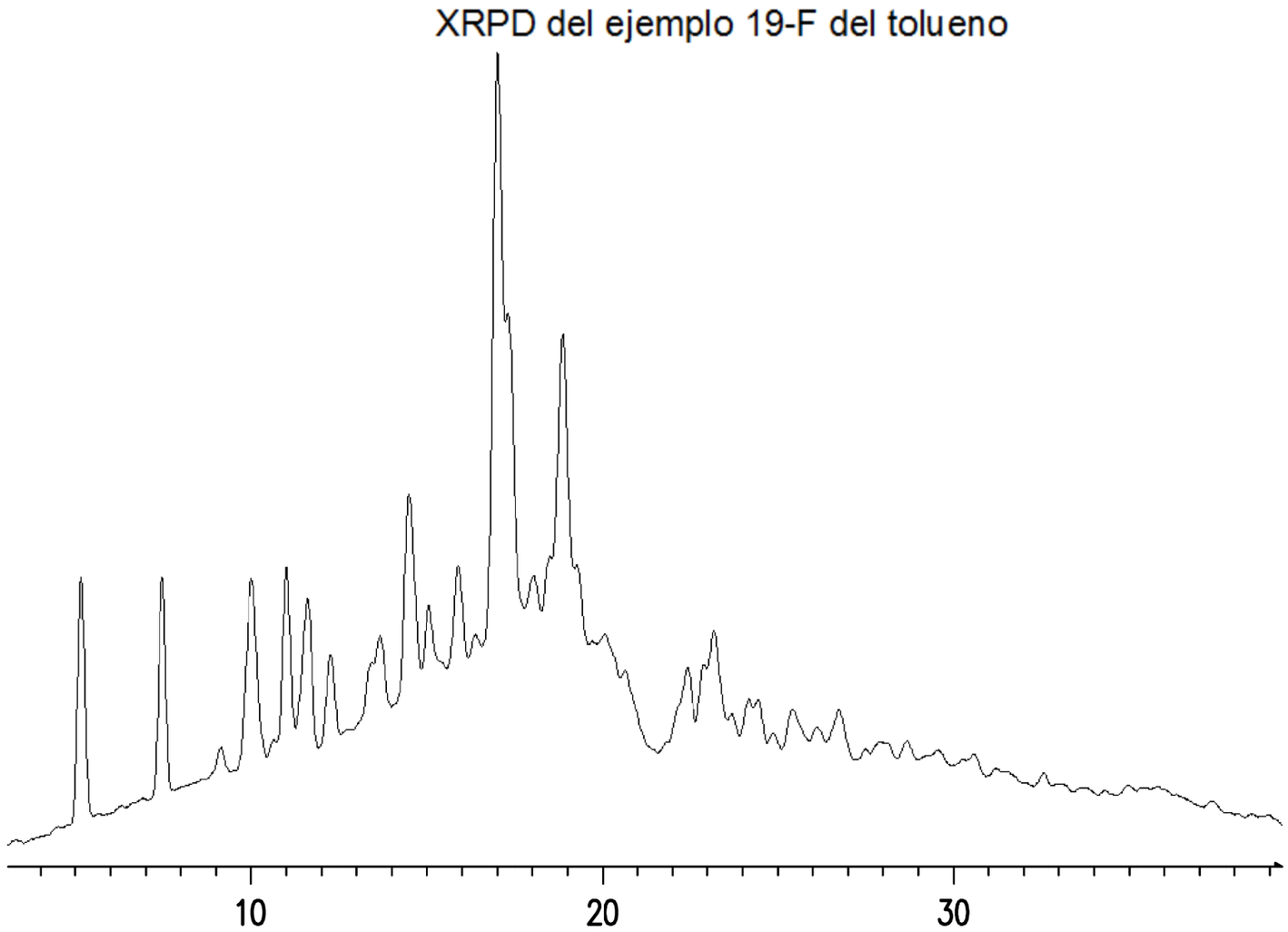


FIG. 6

DSC y TGA del ejemplo 19-Fdel tolueno

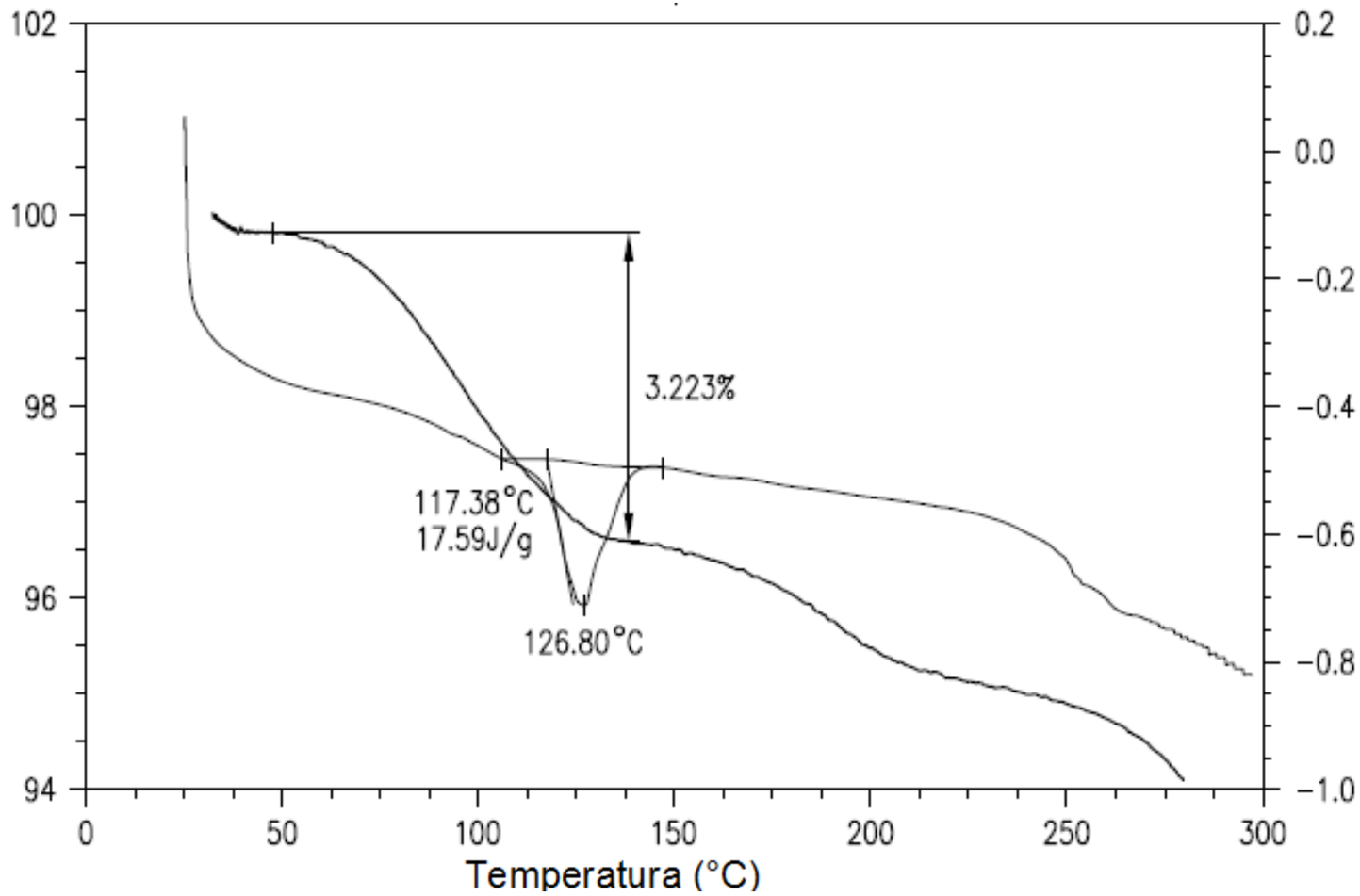


FIG. 7

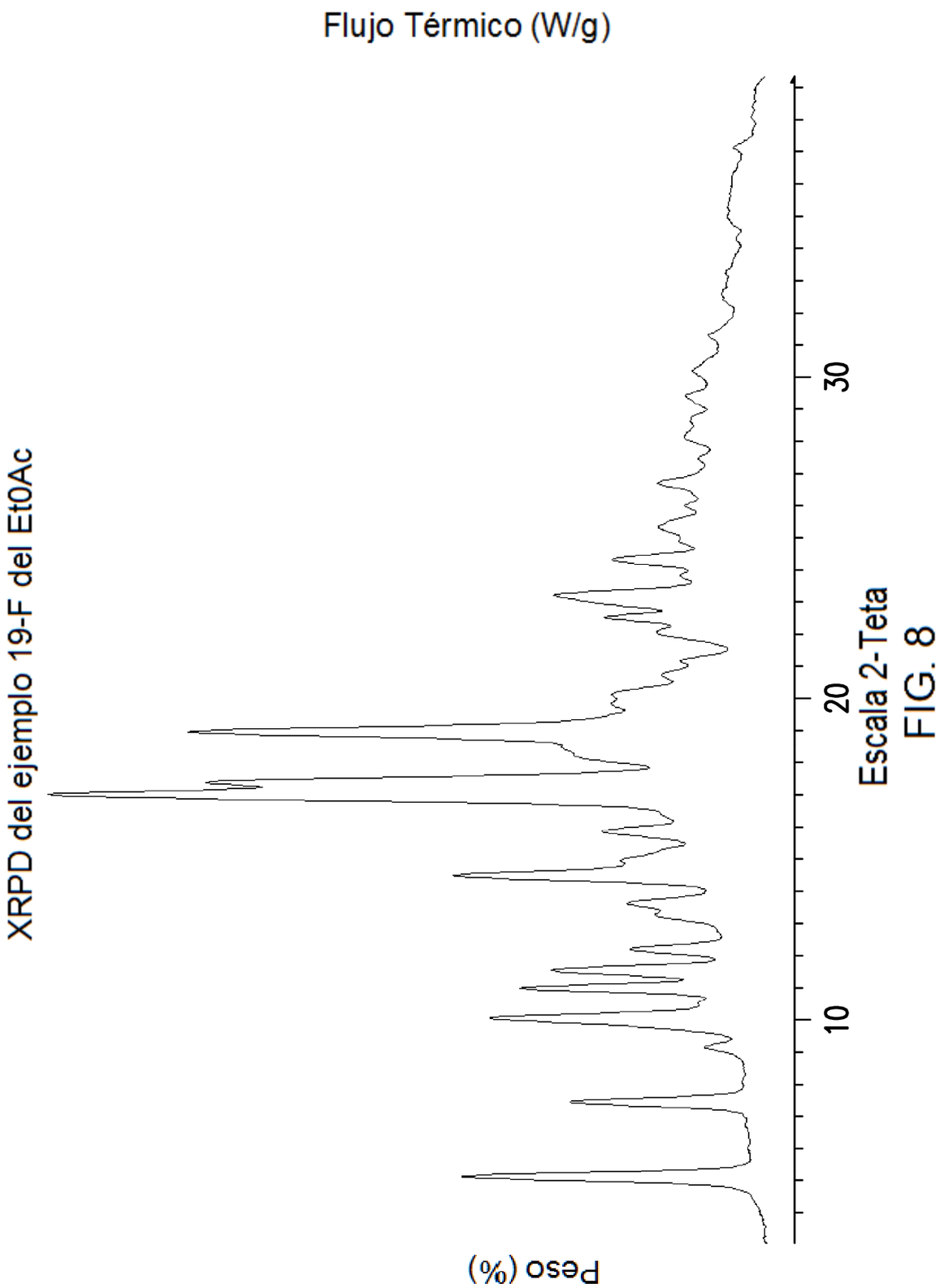

Flujo Térmico (W/g)
XRPD del ejemplo 19-F del EtOAc
Peso (%)
10
20
30
Escala 2-Teta

FIG. 8

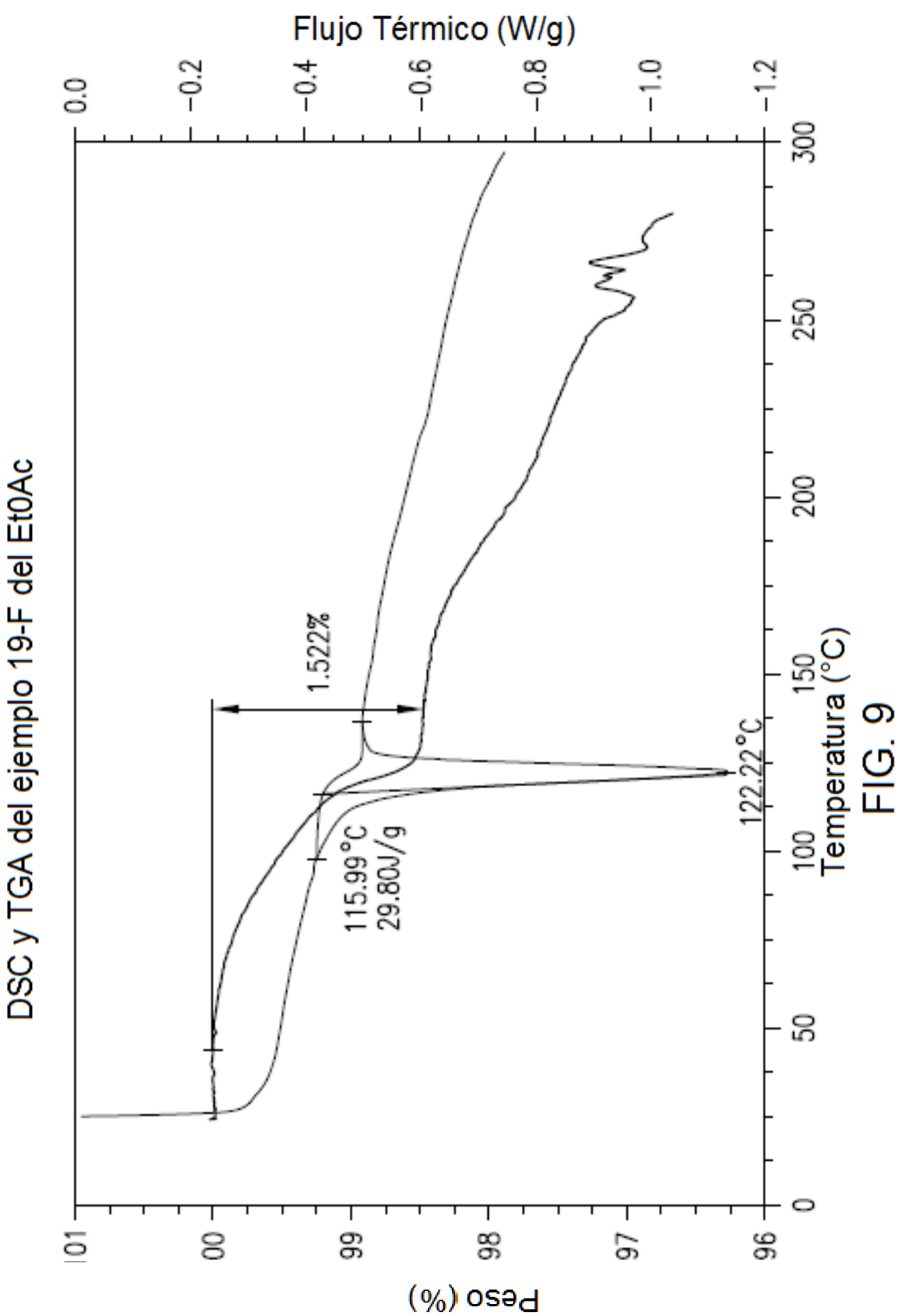

DSC y TGA del ejemplo 19-F del Et0Ac
Flujo Térmico (W/g)
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
1.522%
115.99 °C
29.80J/g
122.22°C
Peso (%)
101
00
99
98
97
96
0
50
100
150
200
250
300
Temperatura (°C)

FIG. 9

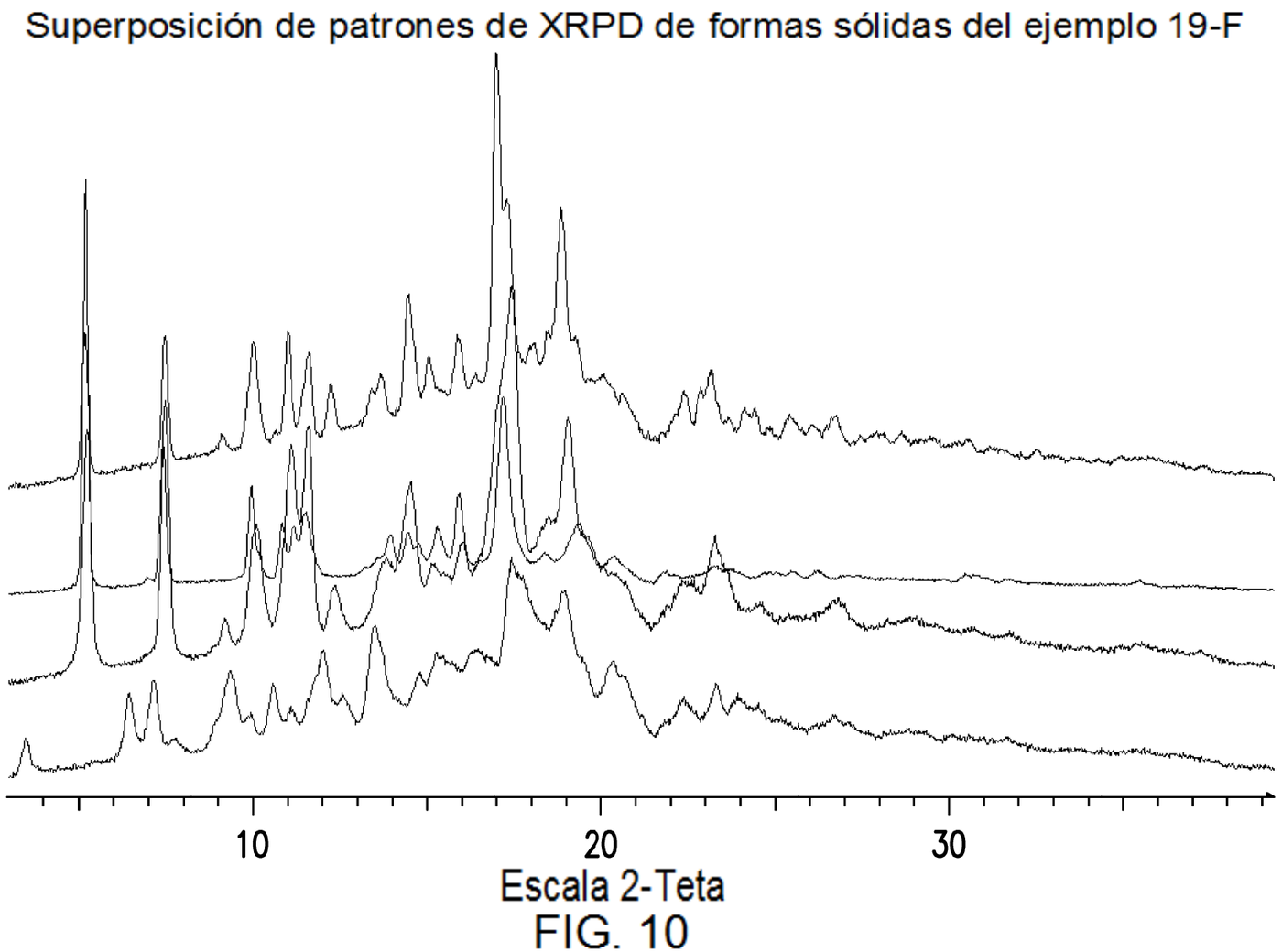

Superposición de patrones de XRPD de formas sólidas del ejemplo 19-F
10
20
30
Escala 2-Teta

FIG. 10

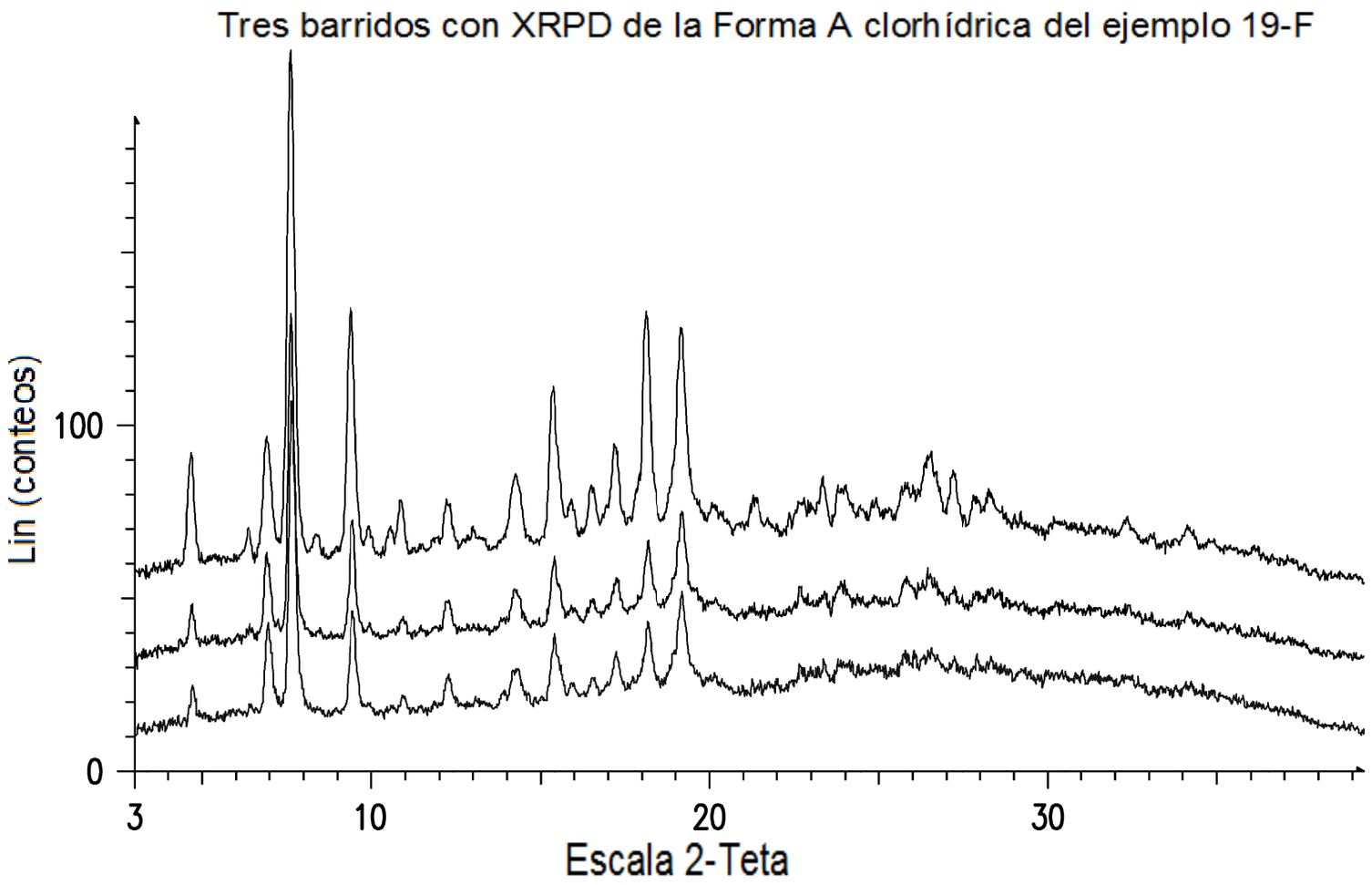

Tres barridos con XRPD de la Forma A clorhídrica del ejemplo 19-F
Lin (conteos)
100
0
3
10
20
30
Escala 2-Teta

FIG. 11

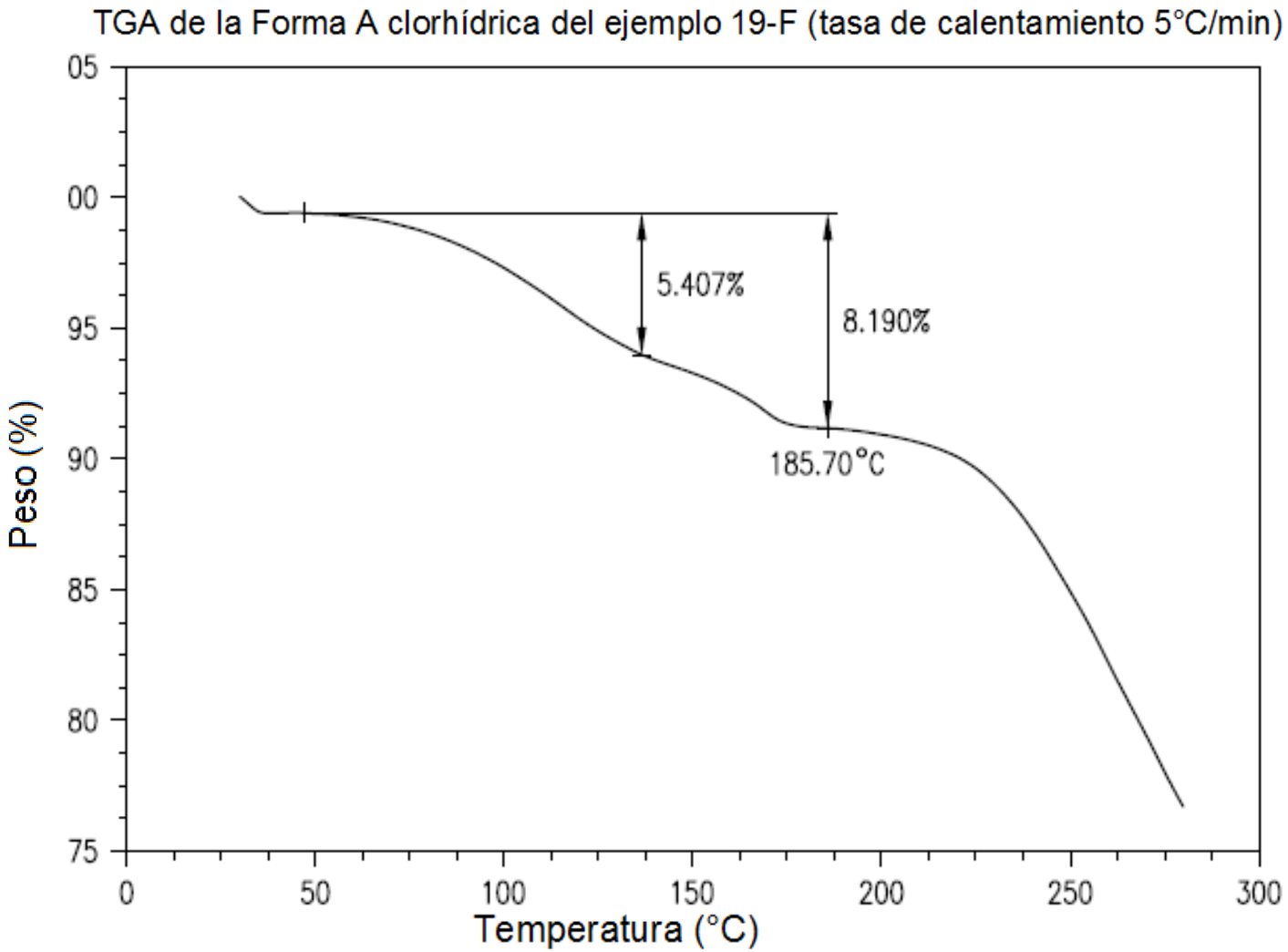

TGA de la Forma A clorhídrica del ejemplo 19-F (tasa de calentamiento 5°C/min)
05
00
95
90
85
80
75
Peso (%)
5.407%
8.190%
185.70°C
0
50
100
150
200
250
300
Temperatura (°C)

FIG. 12

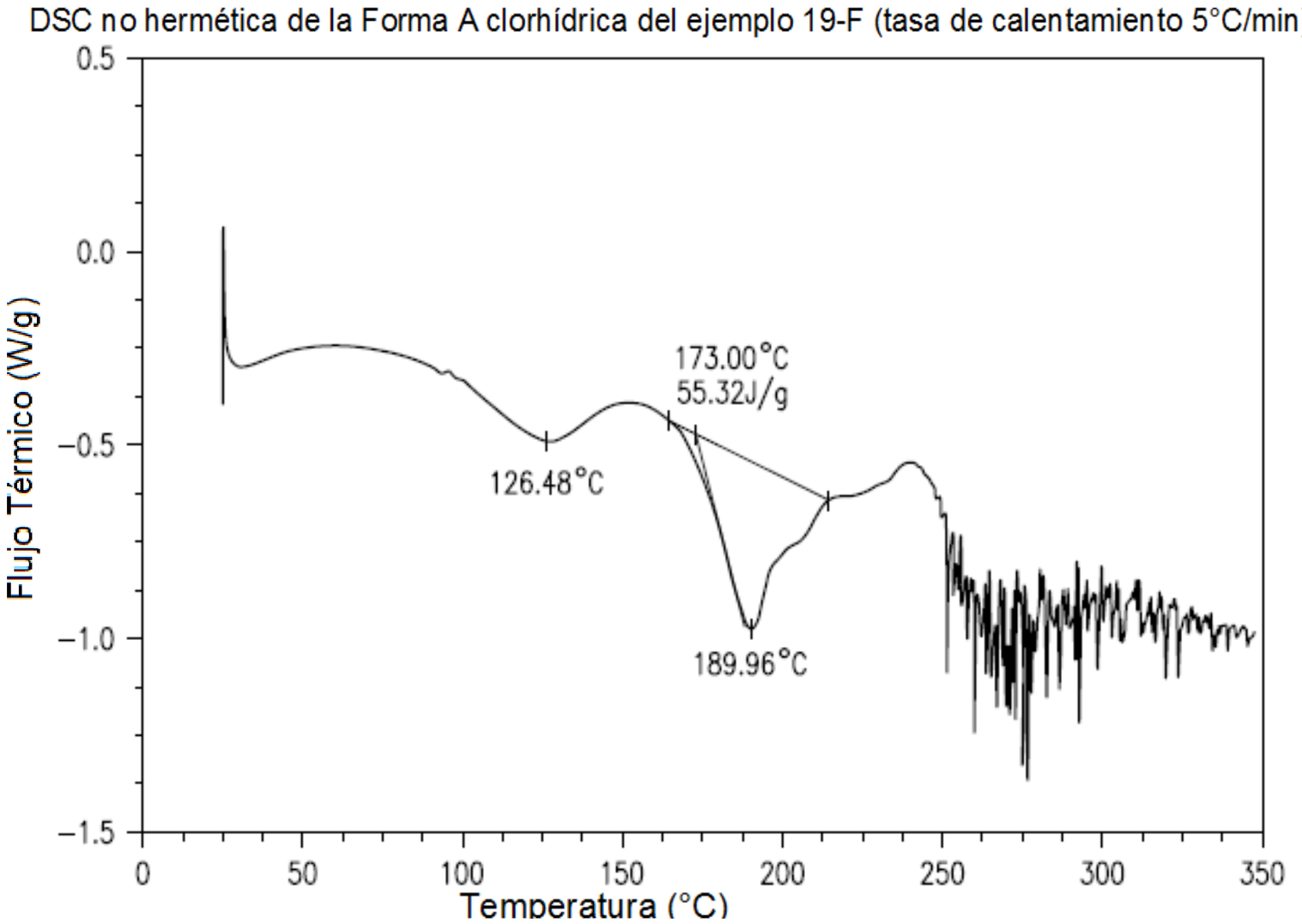

DSC no hermética de la Forma A clorhídrica del ejemplo 19-F (tasa de calentamiento 5°C/min)
Flujo Térmico (W/g)
0.5
0.0
−0.5
−1.0
−1.5
0
50
100
150
200
250
300
350
Temperatura (°C)
173.00°C
55.32J/g
126.48°C
189.96°C

FIG. 13

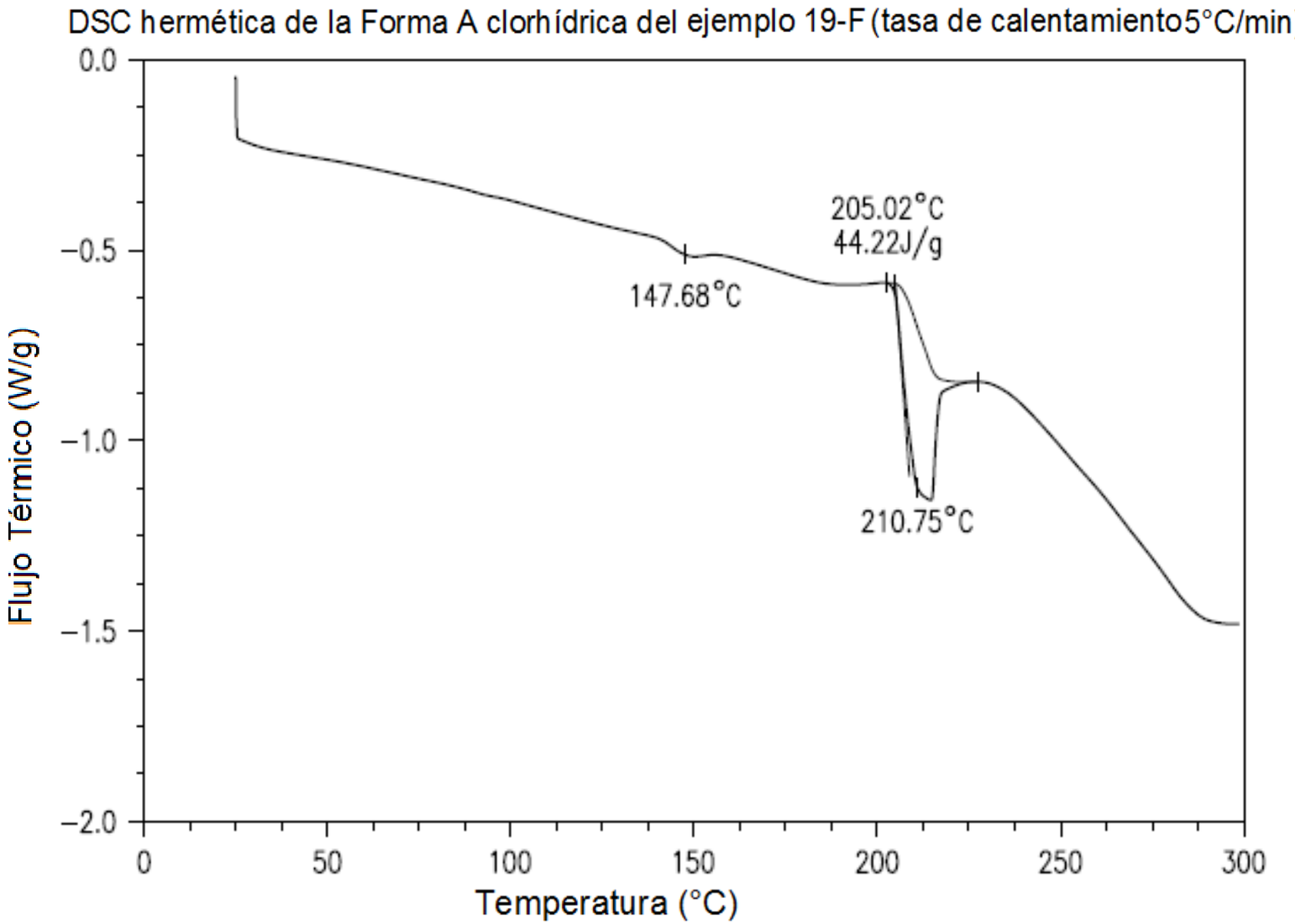

DSC hermética de la Forma A clorhídrica del ejemplo 19-F (tasa de calentamiento5°C/min)
Flujo Térmico (W/g)
0.0
−0.5
−1.0
−1.5
−2.0
205.02°C
44.22J/g
147.68°C
210.75°C
0
50
100
150
200
250
300
Temperatura (°C)

FIG. 14

Dos barridos XRPD de la Forma B clorhídrica del ejemplo 19-F en comparación con un barrido de la forma A

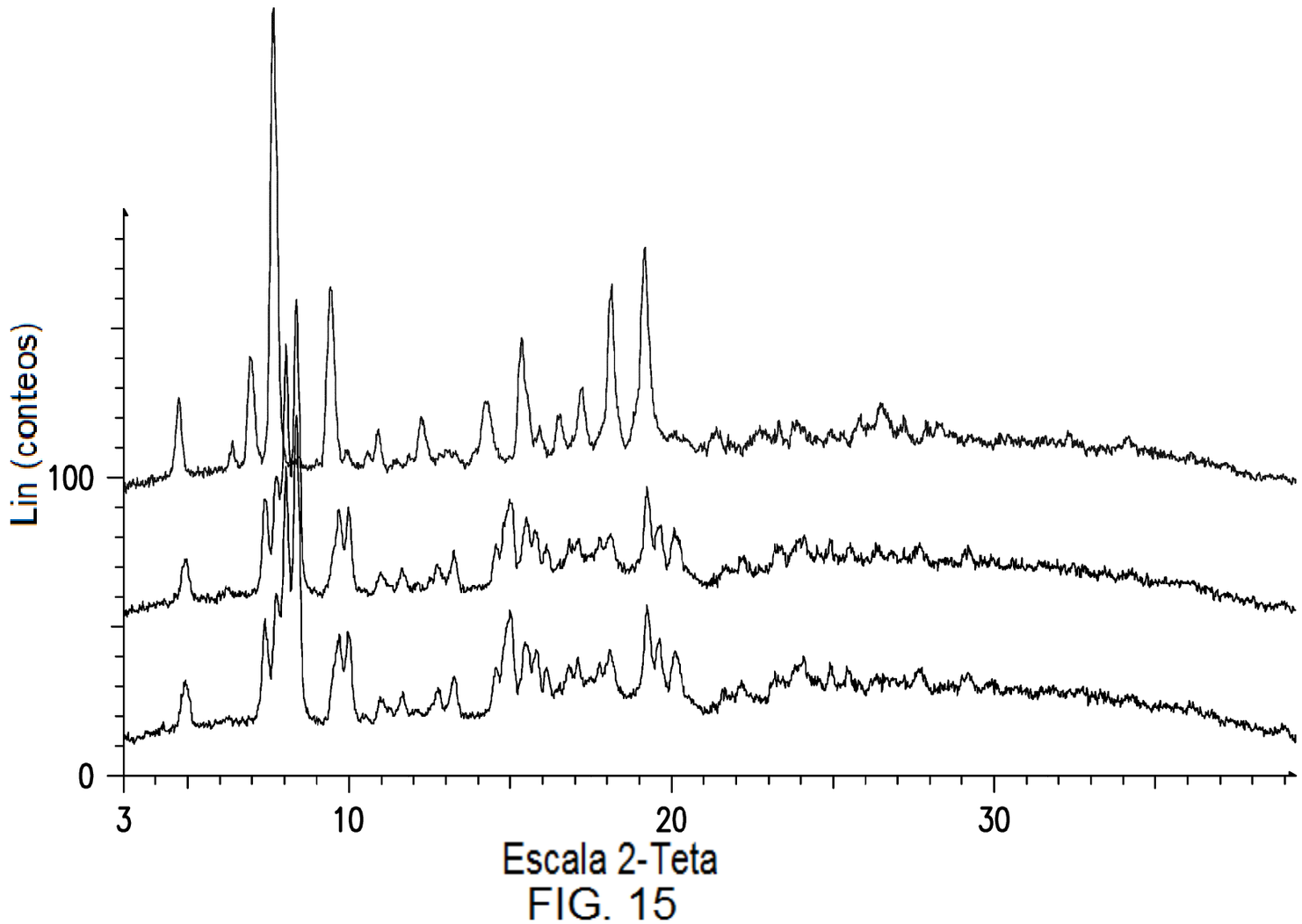


FIG. 15

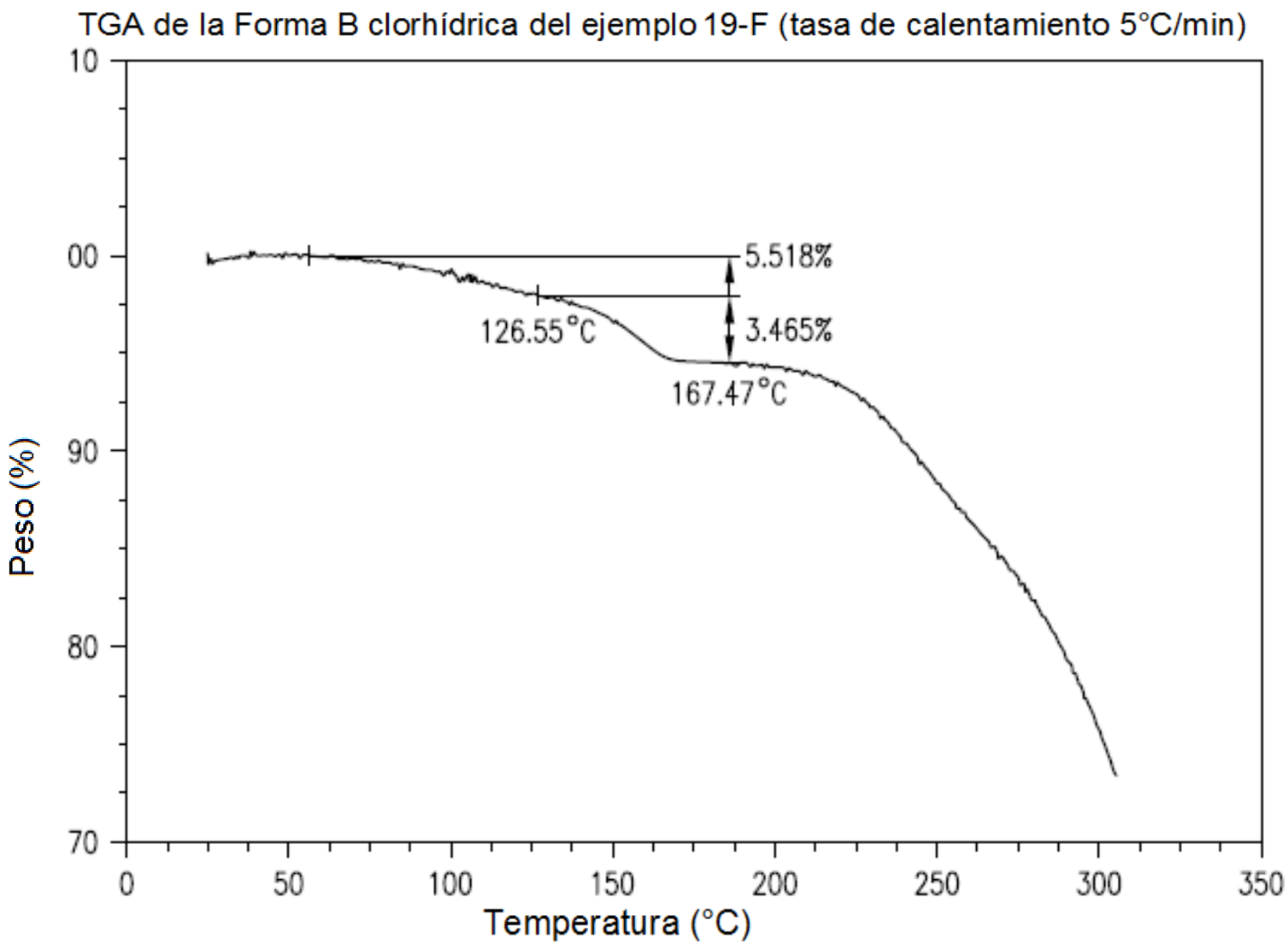

TGA de la Forma B clorhídrica del ejemplo 19-F (tasa de calentamiento 5°C/min)
10
00
90
80
70
Peso (%)
5.518%
3.465%
126.55°C
167.47°C
0
50
100
150
200
250
300
350
Temperatura (°C)

FIG. 16

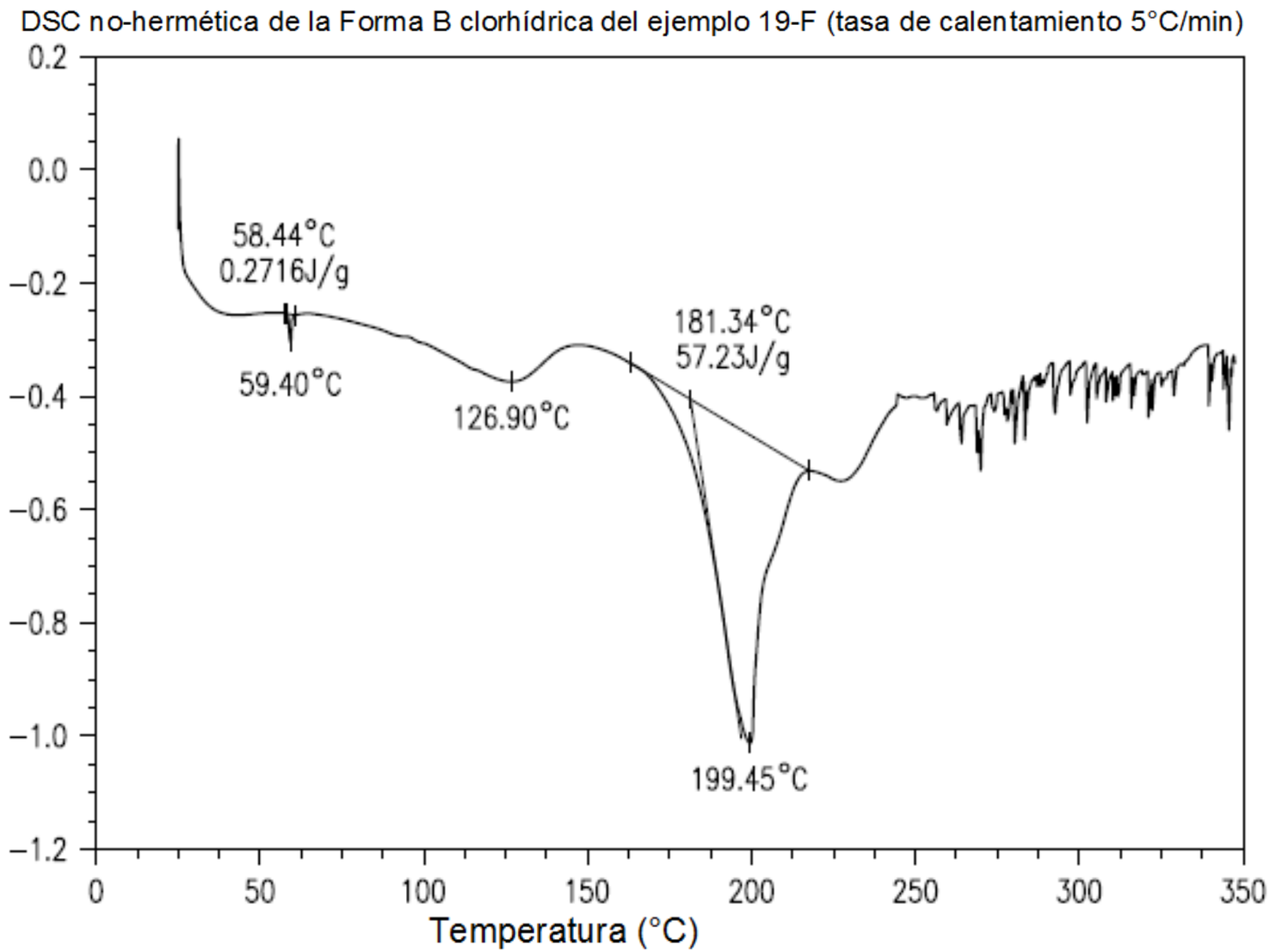

DSC no-hermética de la Forma B clorhídrica del ejemplo 19-F (tasa de calentamiento 5°C/min)
0.2
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
58.44°C
0.2716J/g
59.40°C
126.90°C
181.34°C
57.23J/g
199.45°C
0
50
100
150
200
250
300
350
Temperatura (°C)

FIG. 17

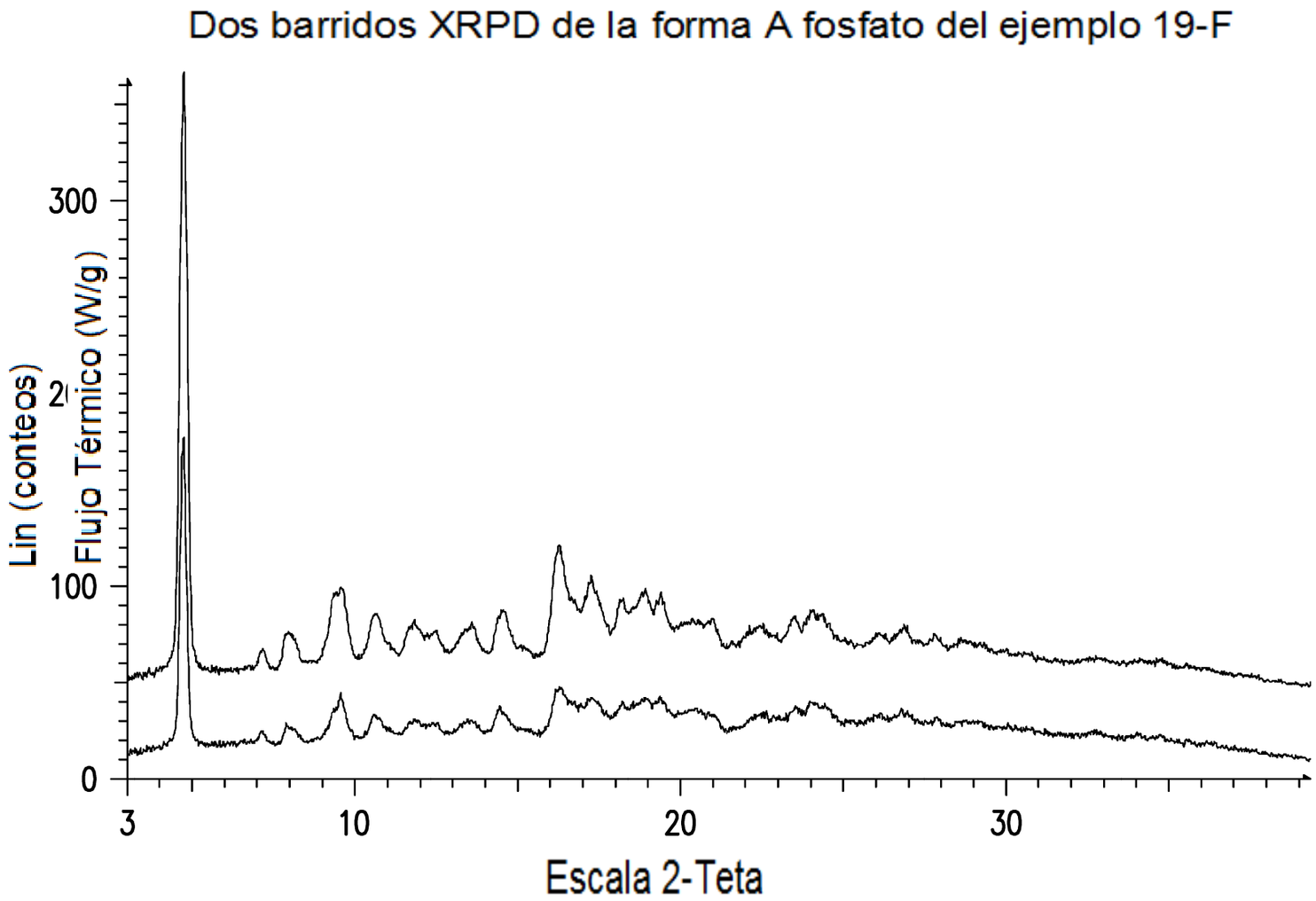

Dos barridos XRPD de la forma A fosfato del ejemplo 19-F
Lin (conteos)
Flujo Térmico (W/g)
300
200
100
0
3
10
20
30
Escala 2-Teta

FIG. 18

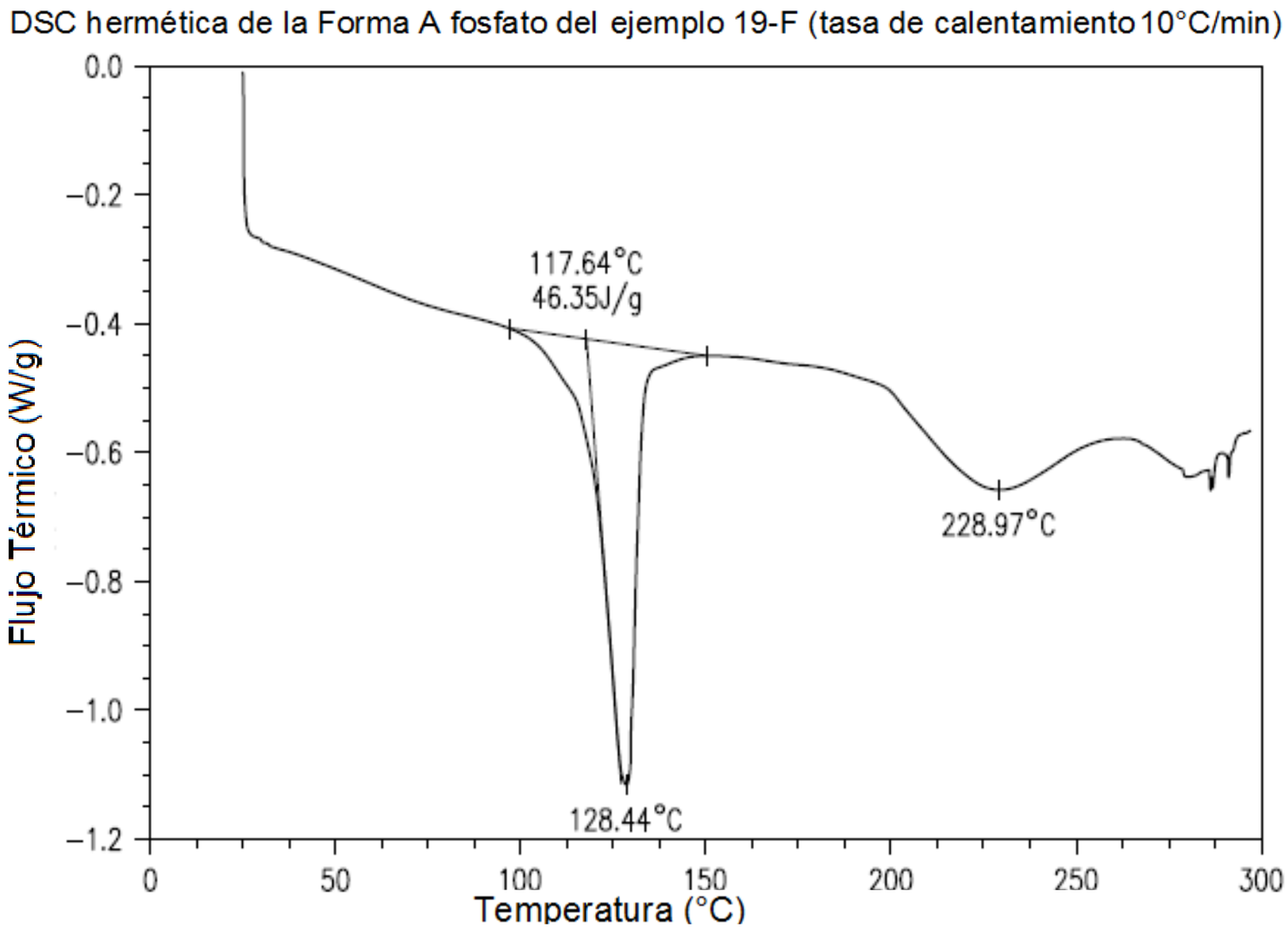

DSC hermética de la Forma A fosfato del ejemplo 19-F (tasa de calentamiento 10°C/min)
Flujo Térmico (W/g)
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
117.64°C
46.35J/g
128.44°C
228.97°C
0
50
100
150
200
250
300
Temperatura (°C)

FIG. 19

Dos barridos XRPD de la Forma B fosfato del ejemplo 19-F con la Forma A fosfato del ejemplo 19-F para comparación

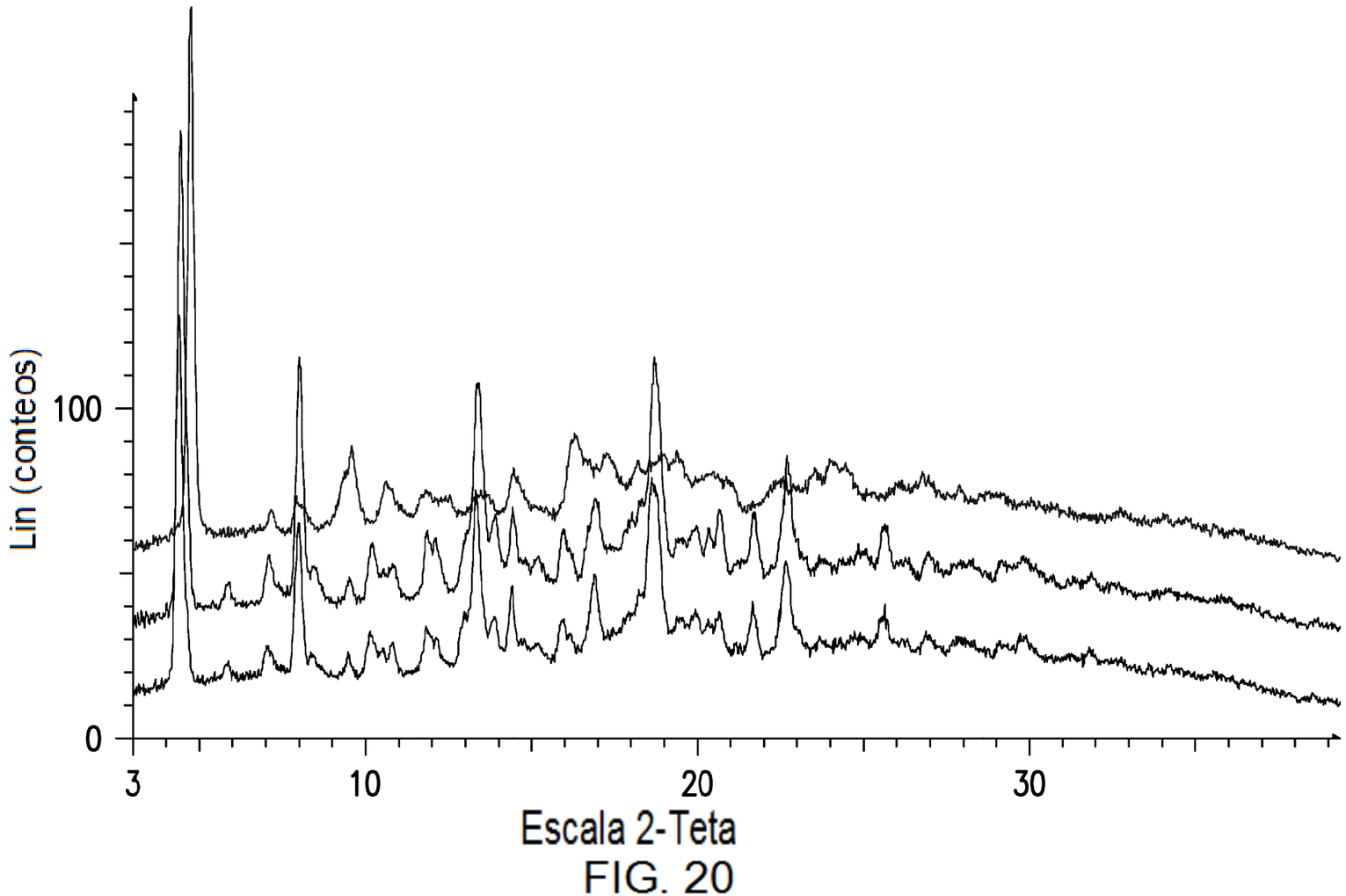


FIG. 20

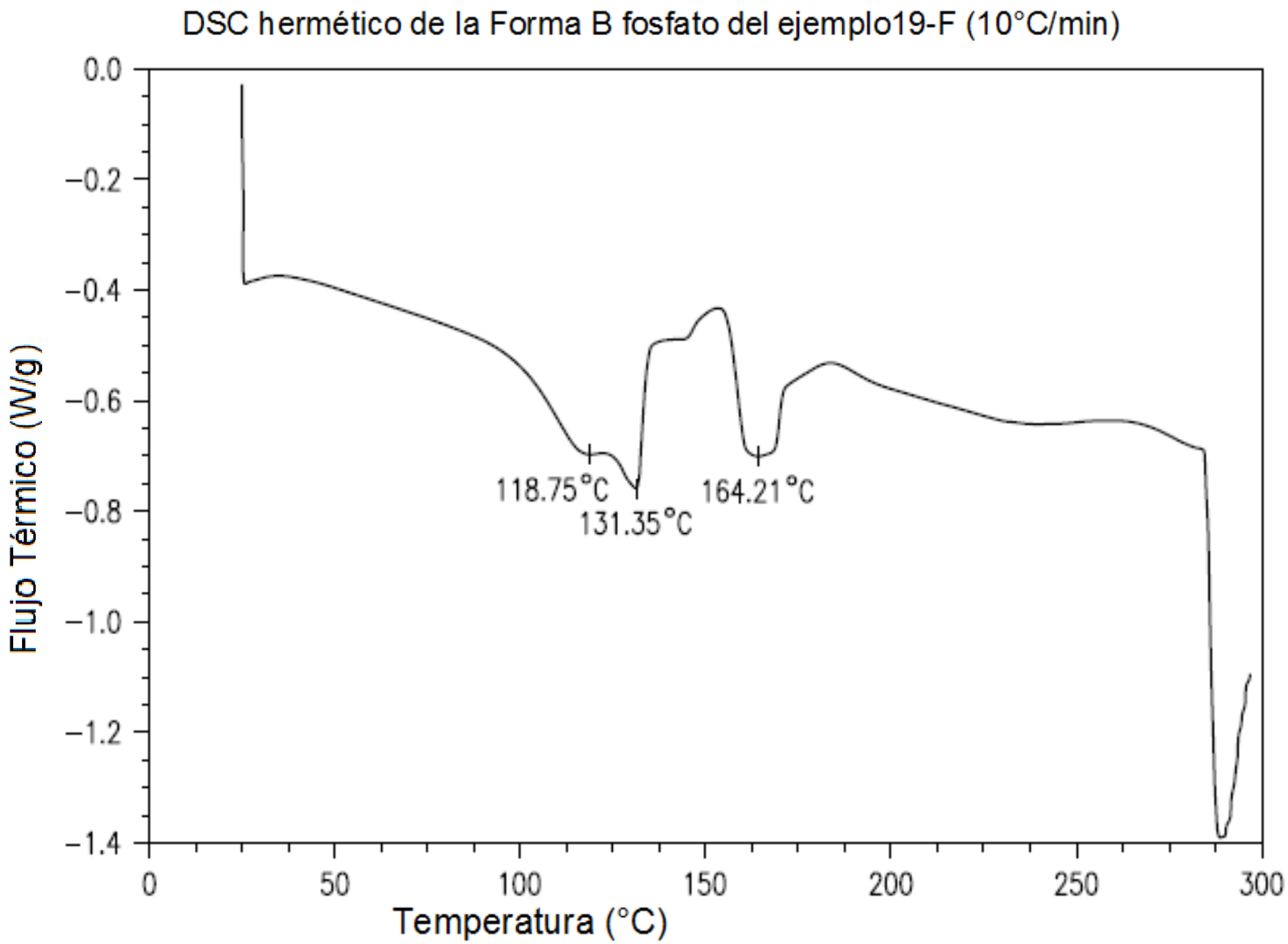

DSC hermético de la Forma B fosfato del ejemplo19-F (10°C/min)
Flujo Térmico (W/g)
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
118.75°C
131.35°C
164.21°C
0
50
100
150
200
250
300
Temperatura (°C)

FIG. 21

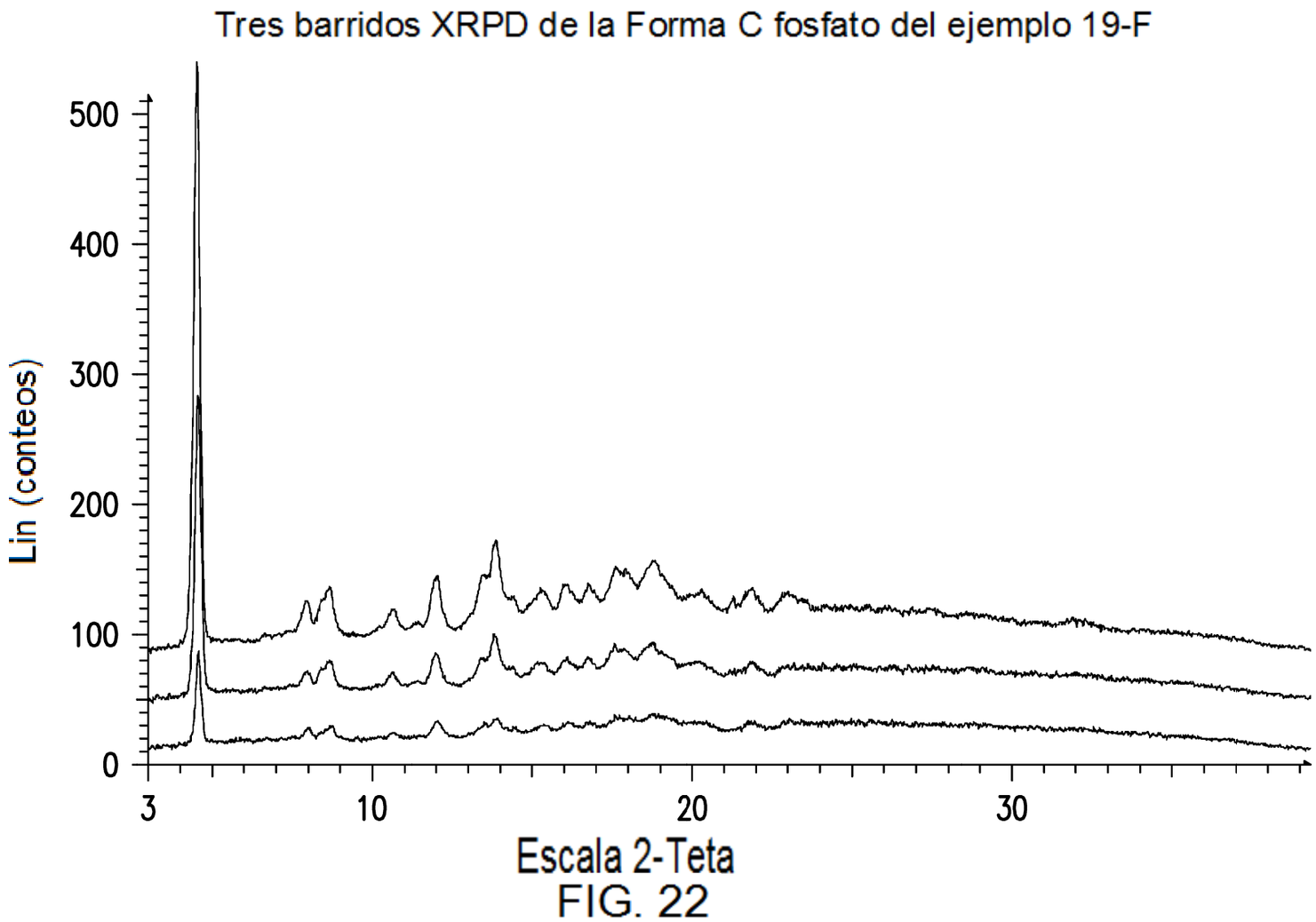

Tres barridos XRPD de la Forma C fosfato del ejemplo 19-F
Lin (conteos)
500
400
300
200
100
0
3
10
20
30
Escala 2-Teta

FIG. 22

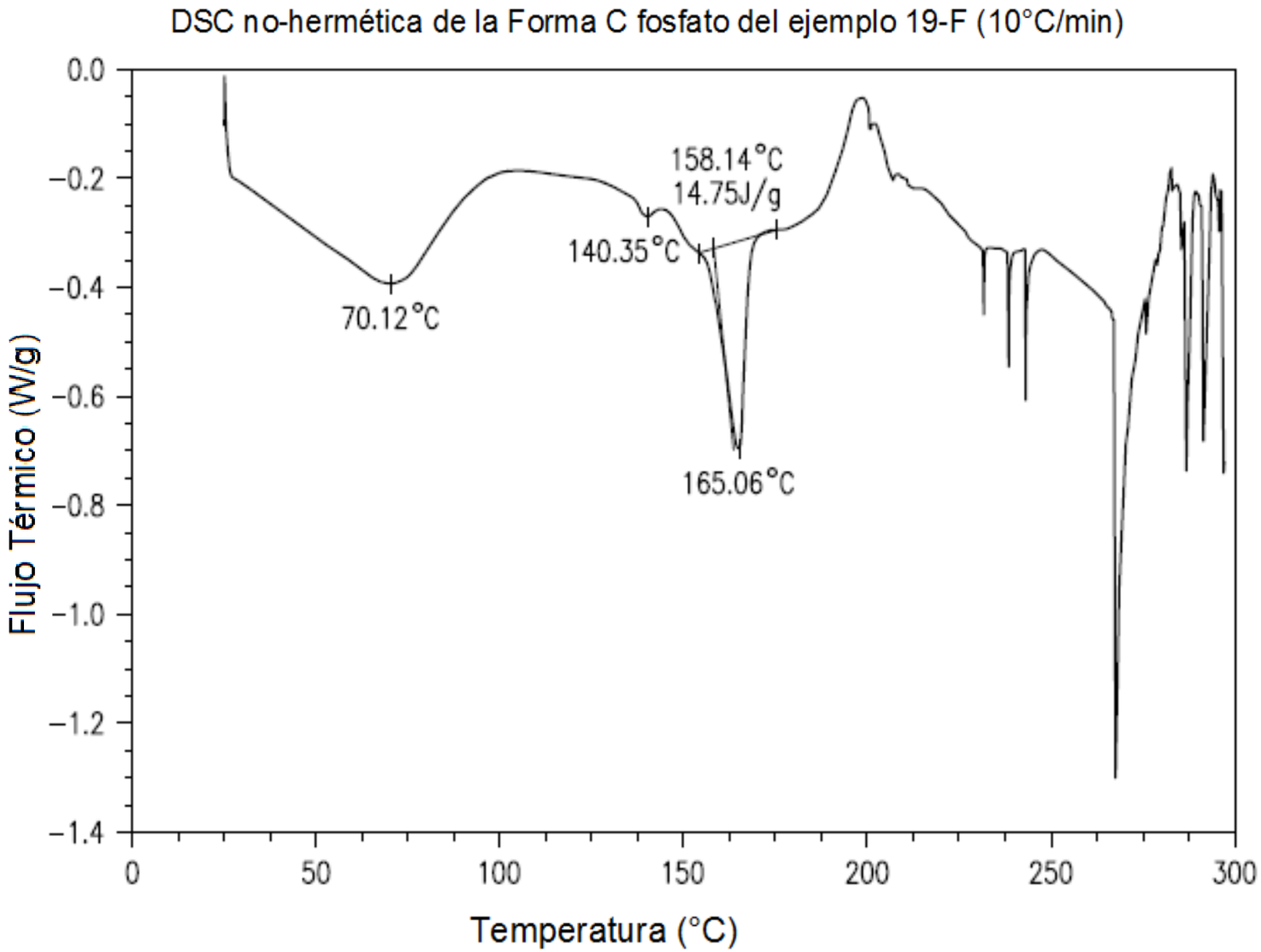

DSC no-hermética de la Forma C fosfato del ejemplo 19-F (10°C/min)
Flujo Térmico (W/g)
Temperatura (°C)
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
0
50
100
150
200
250
300
158.14°C
14.75J/g
140.35°C
70.12°C
165.06°C

FIG. 23

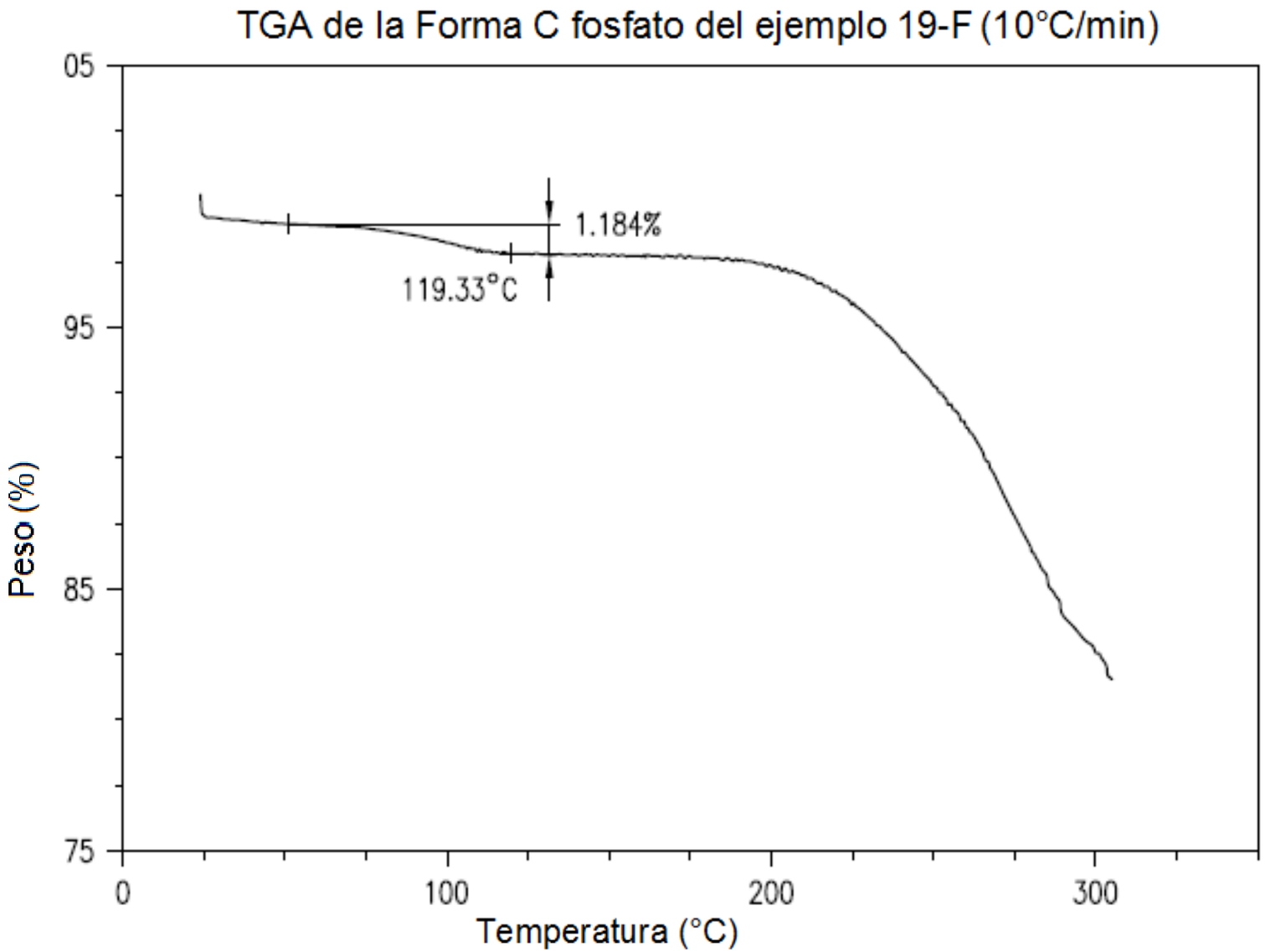

TGA de la Forma C fosfato del ejemplo 19-F (10°C/min)
05
95
85
75
Peso (%)
1.184%
119.33°C
0
100
200
300
Temperatura (°C)

FIG. 24

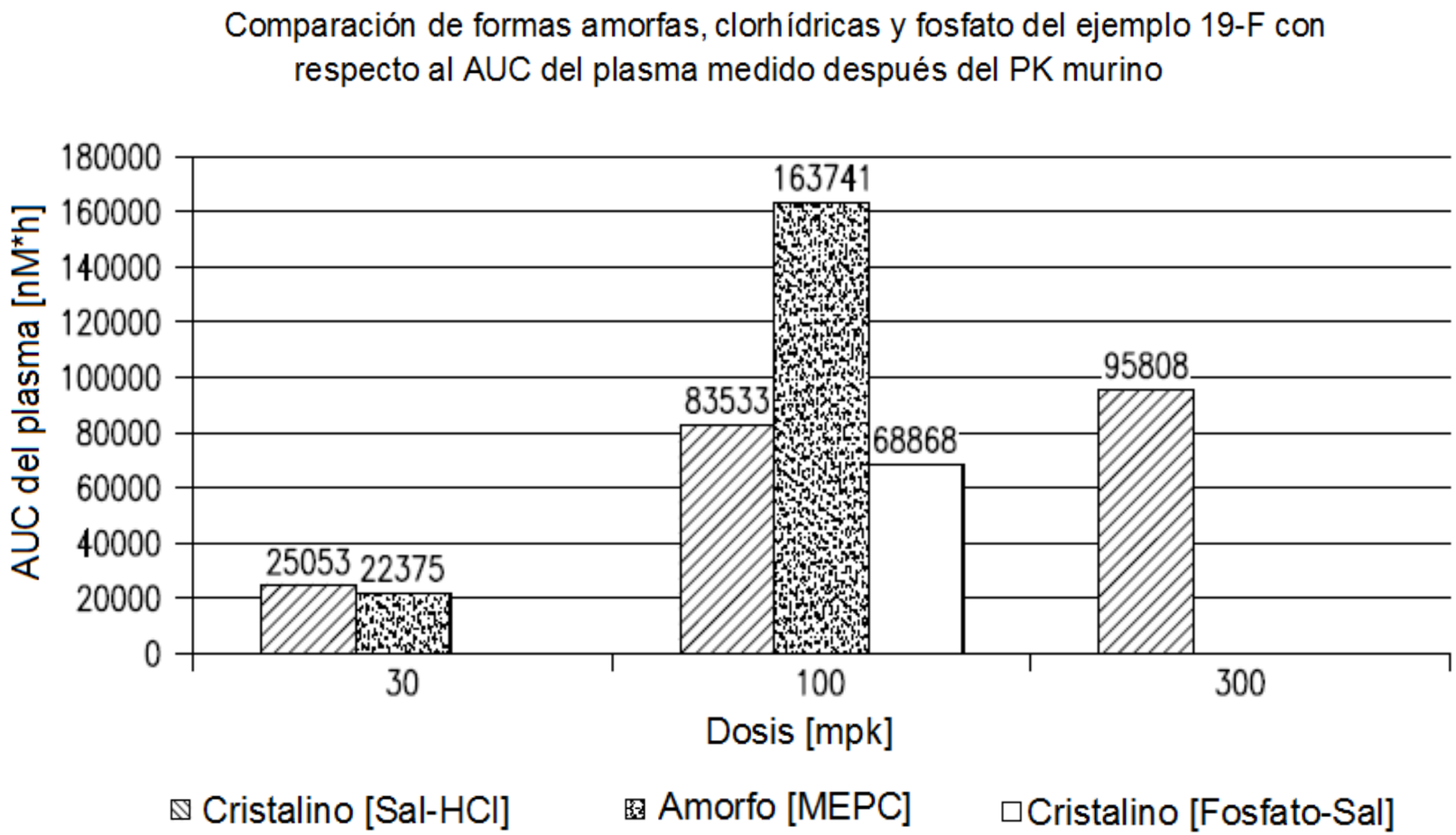

Comparación de formas amorfas, clorhídricas y fosfato del ejemplo 19-F con respecto al AUC del plasma medido después del PK murino
AUC del plasma [nM*h]
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
25053
22375
83533
163741
68868
95808
30
100
300
Dosis [mpk]
Cristalino [Sal-HCl]
Amorfo [MEPC]
Cristalino [Fosfato-Sal]

FIG. 25

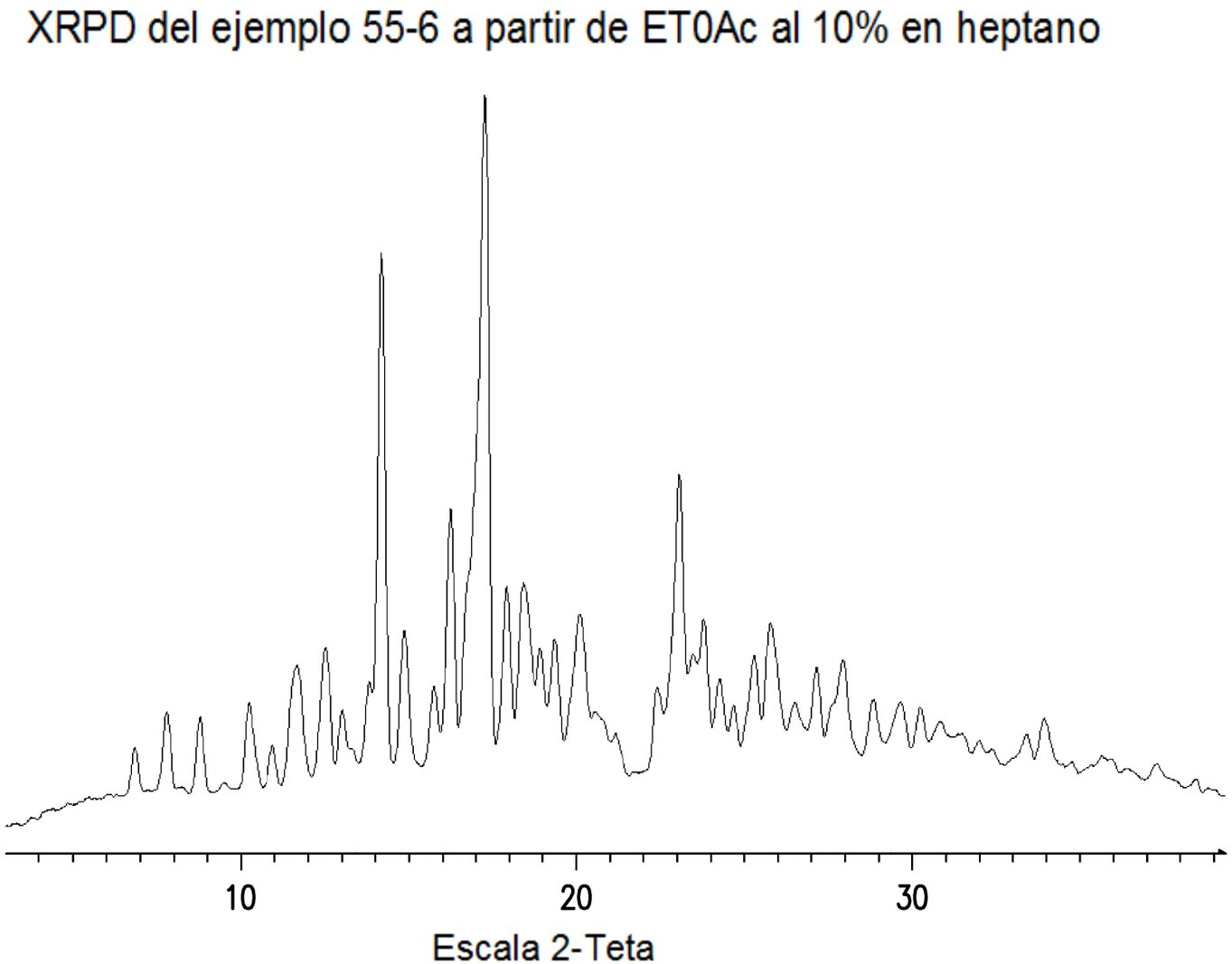

XRPD del ejemplo 55-6 a partir de ET0Ac al 10% en heptano
10
20
30
Escala 2-Teta

FIG. 26

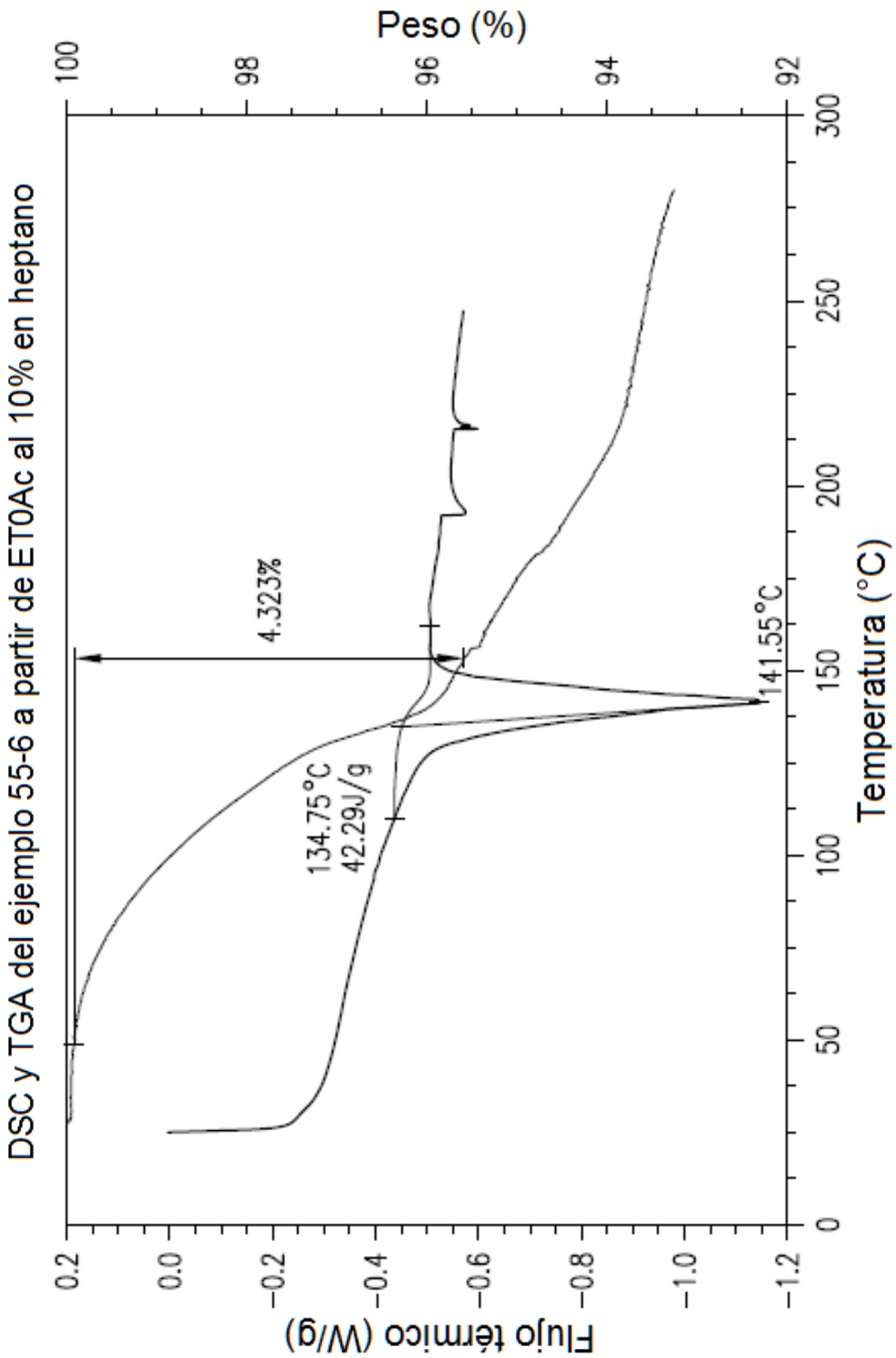

DSC y TGA del ejemplo 55-6 a partir de ET0Ac al 10% en heptano
Peso (%)
100
98
96
94
92
4.323%
134.75°C
42.29J/g
141.55°C
Flujo térmico (W/g)
0.2
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
0
50
100
150
200
250
300
Temperatura (°C)

FIG. 27

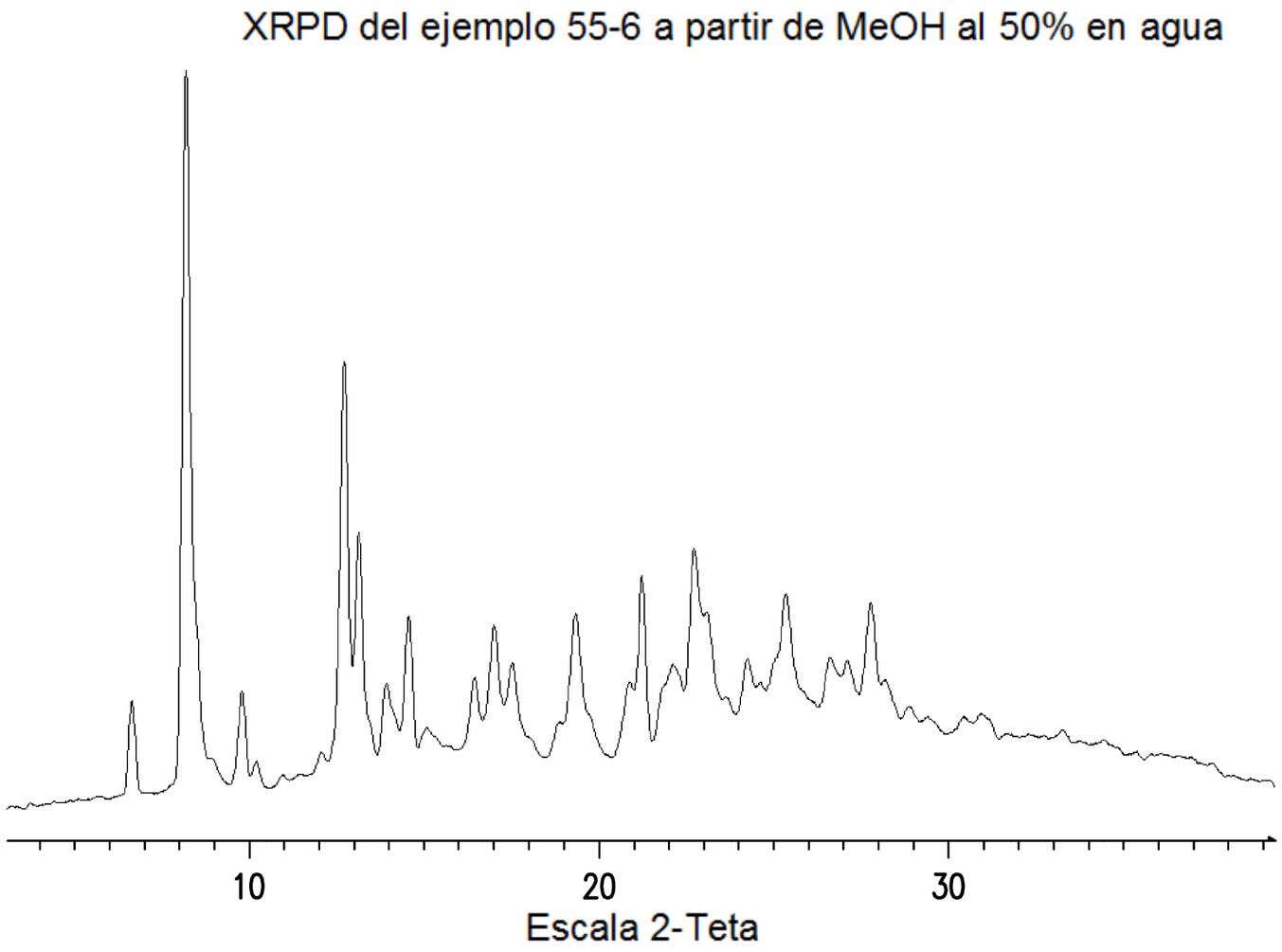

XRPD del ejemplo 55-6 a partir de MeOH al 50% en agua
10
20
30
Escala 2-Teta

FIG. 28

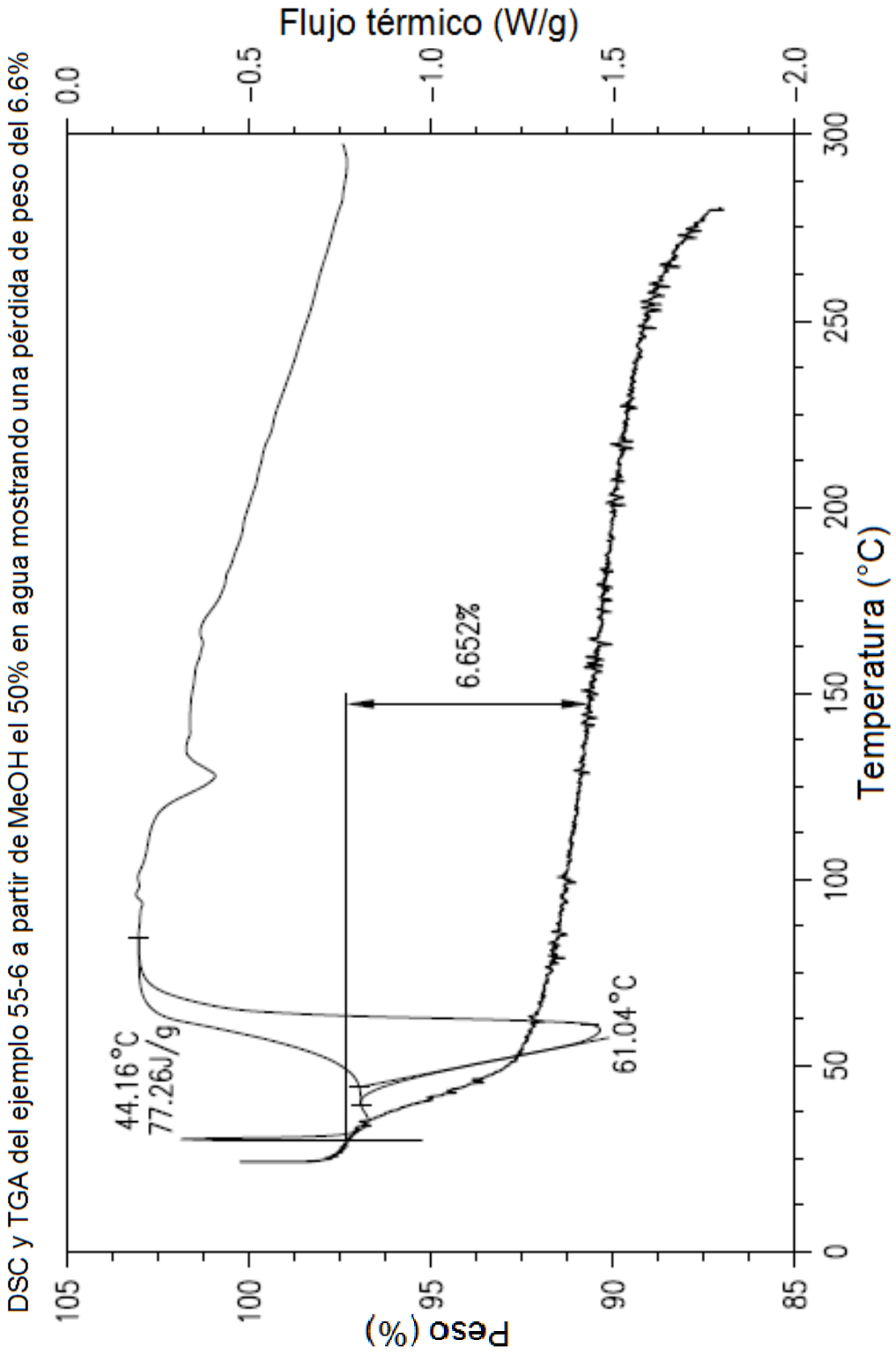

DSC y TGA del ejemplo 55-6 a partir de MeOH el 50% en agua mostrando una pérdida de peso del 6.6%
Flujo térmico (W/g)
0.0
−0.5
−1.0
−1.5
−2.0
Peso (%)
105
100
95
90
85
Temperatura (°C)
0
50
100
150
200
250
300
6.652%
44.16°C
77.26J/g
61.04°C

FIG. 29

DSC en recipiente sellado del ejemplo 55-6 a partir de MeOH al 50% en agua mostrando un punto de fusión verdadero

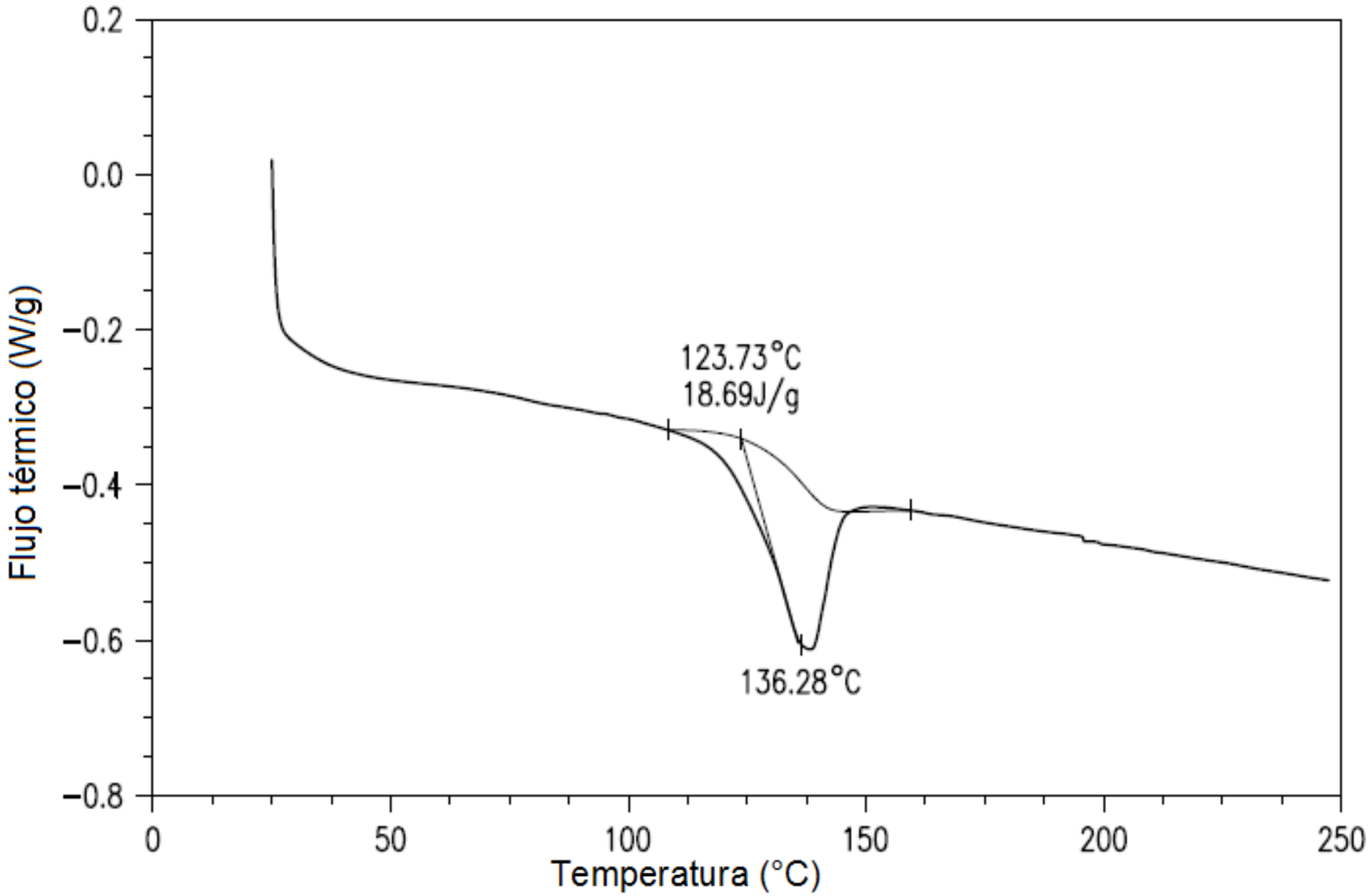


FIG. 30

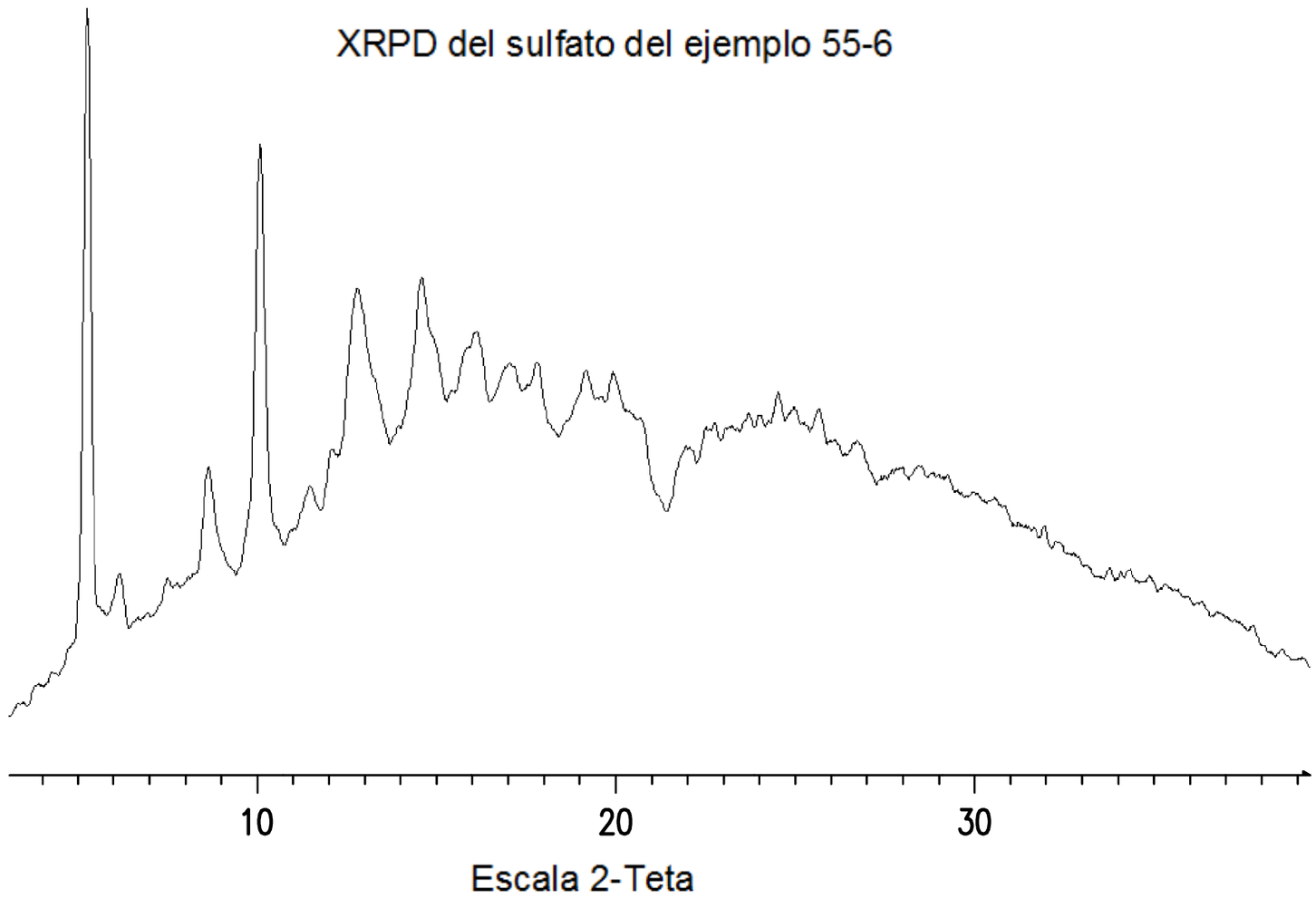


FIG. 31

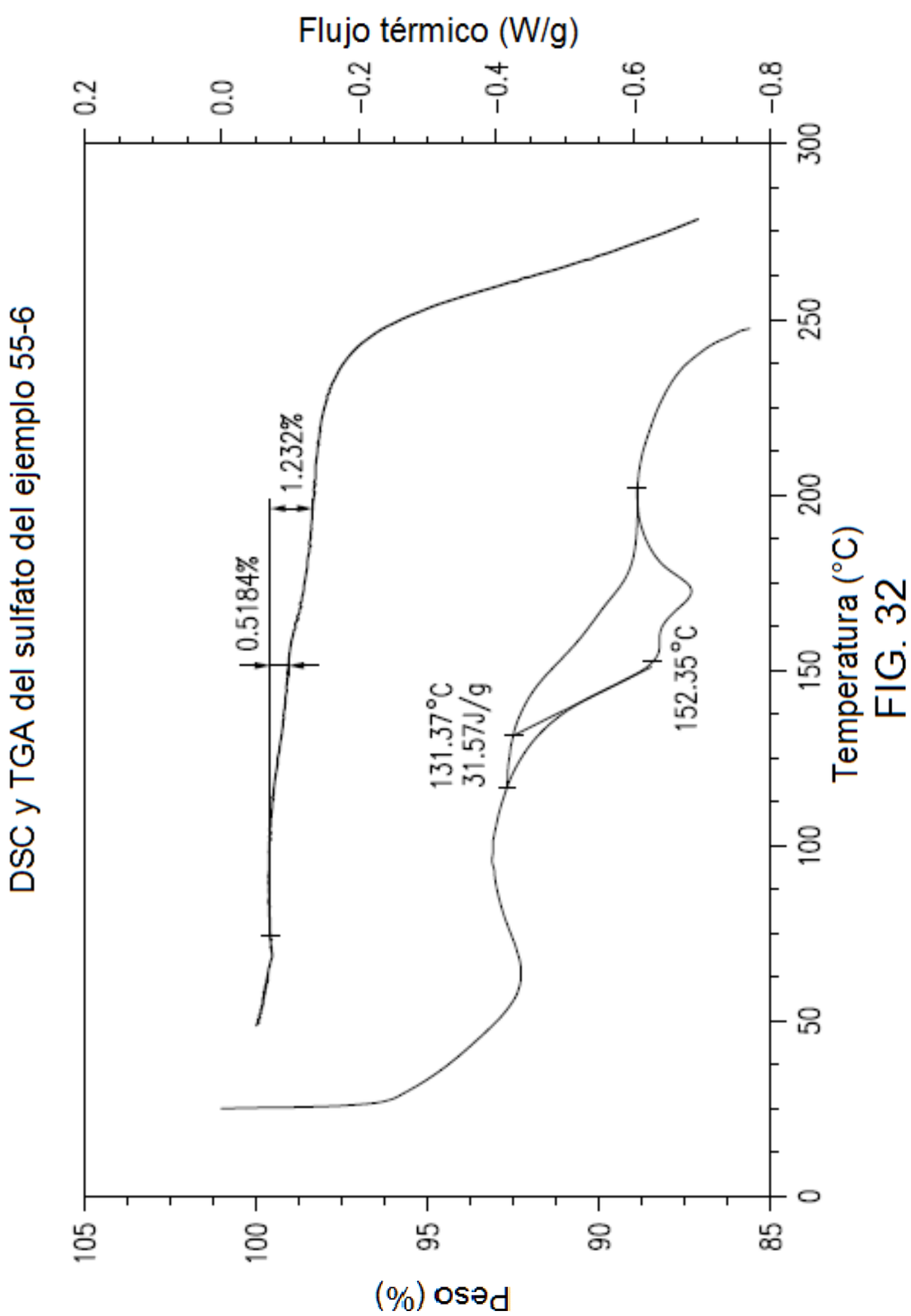

DSC y TGA del sulfato del ejemplo 55-6
Flujo térmico (W/g)
0.2
0.0
−0.2
−0.4
−0.6
−0.8
0.5184%
1.232%
131.37°C
31.57J/g
152.35°C
Peso (%)
105
100
95
90
85
0
50
100
150
200
250
300
Temperatura (°C)

FIG. 32

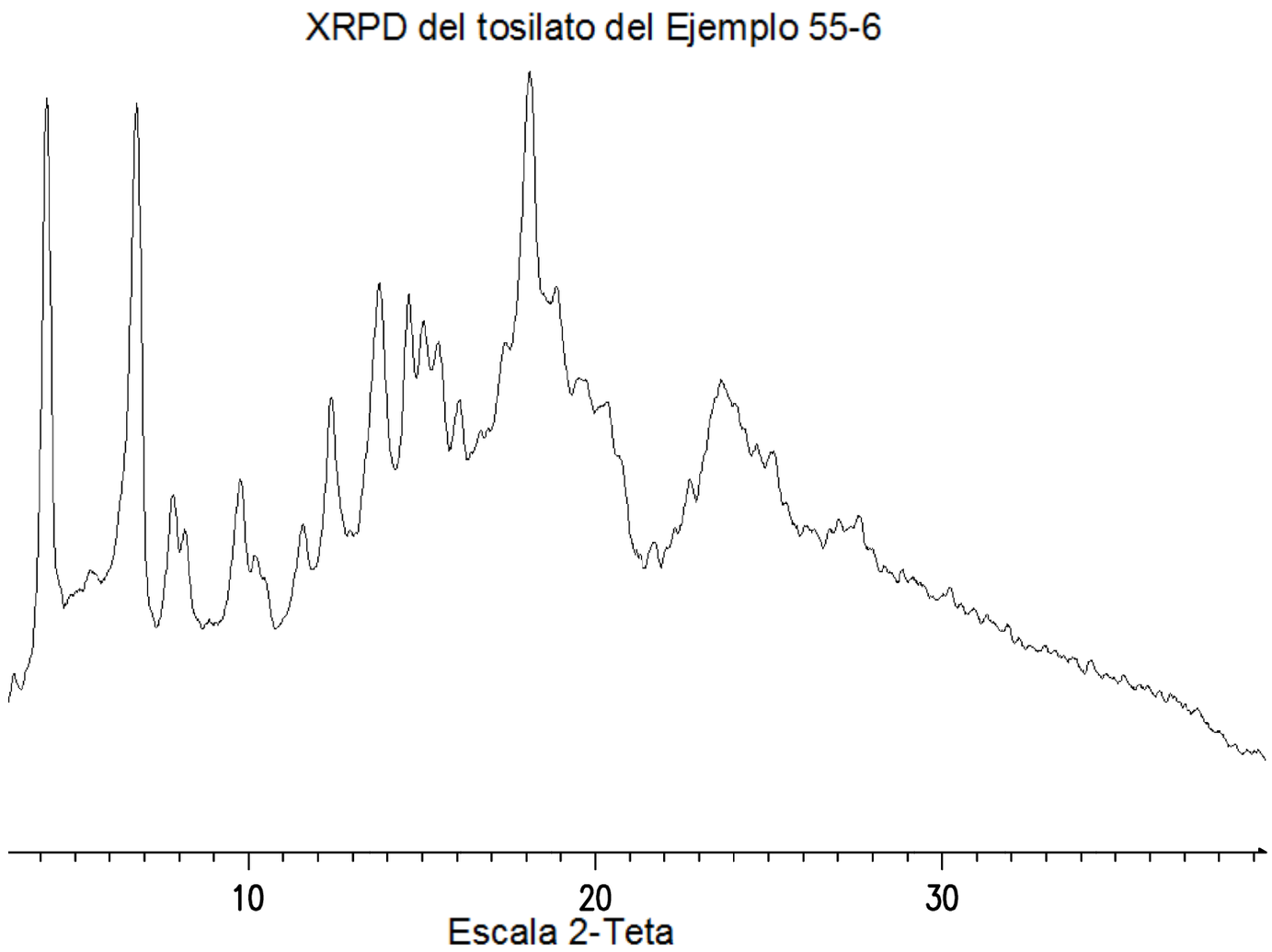


FIG. 33

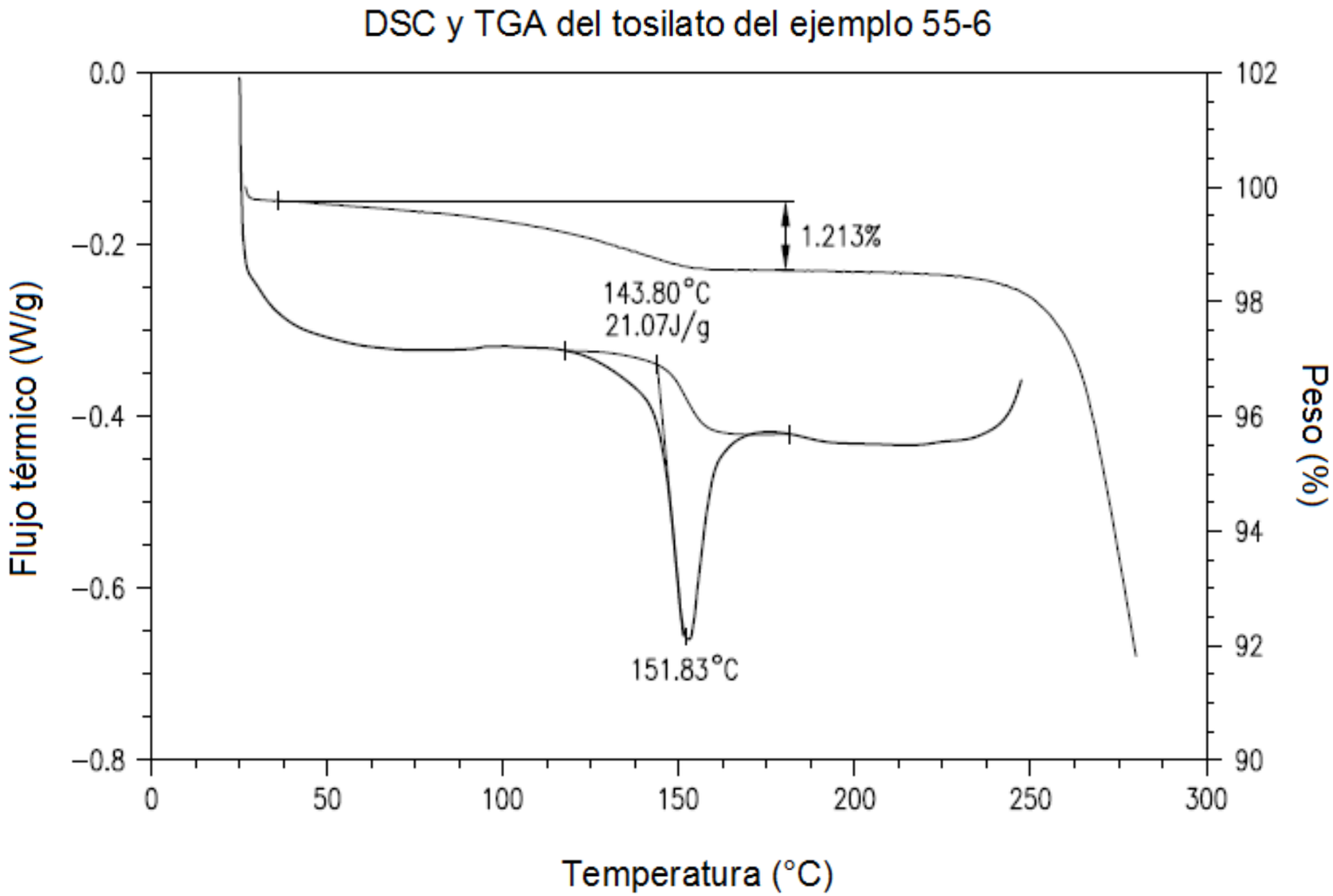

DSC y TGA del tosilato del ejemplo 55-6
Flujo térmico (W/g)
Peso (%)
Temperatura (°C)
0.0
−0.2
−0.4
−0.6
−0.8
102
100
98
96
94
92
90
0
50
100
150
200
250
300
1.213%
143.80°C
21.07J/g
151.83°C

FIG. 34

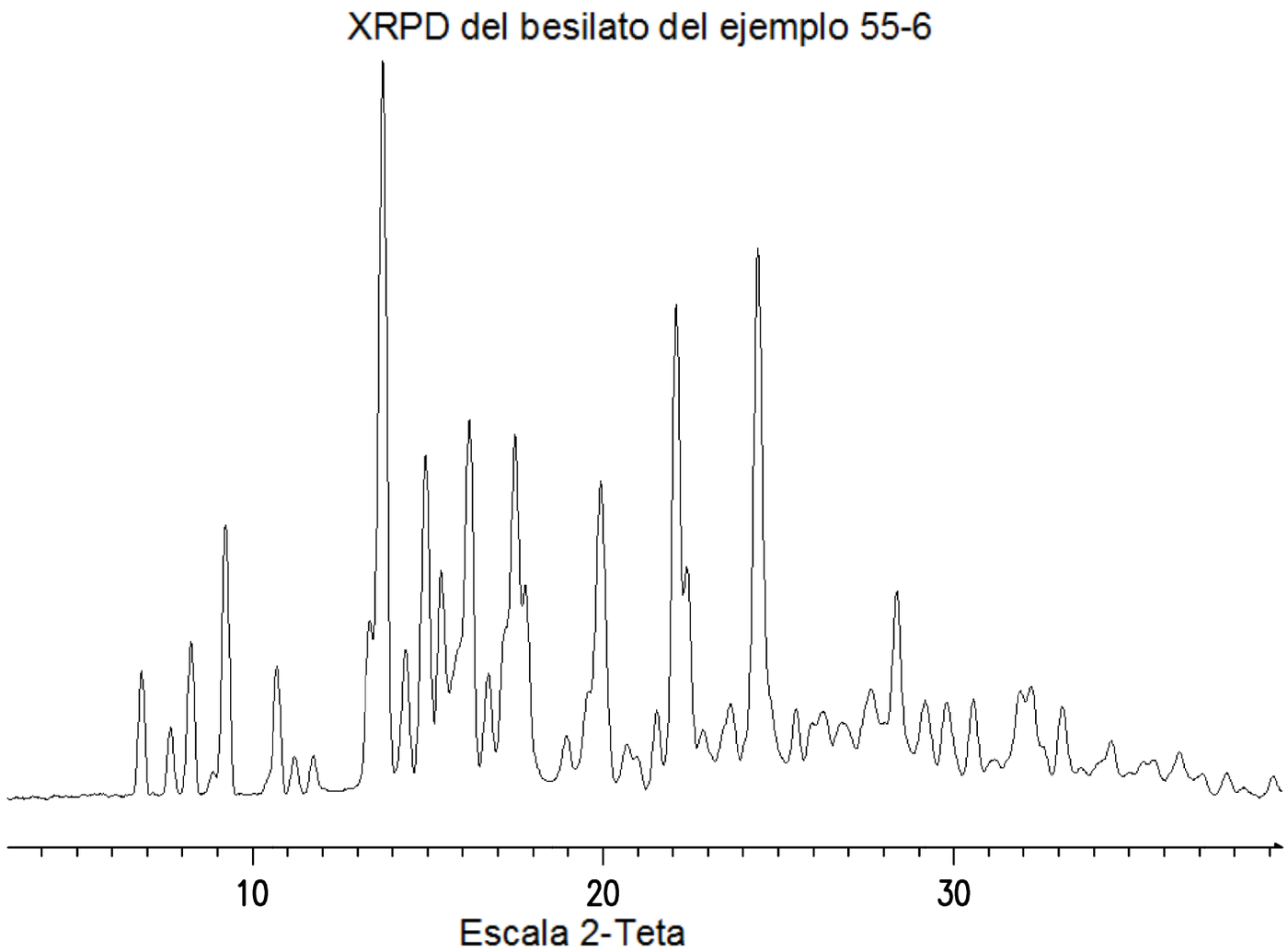


FIG. 35

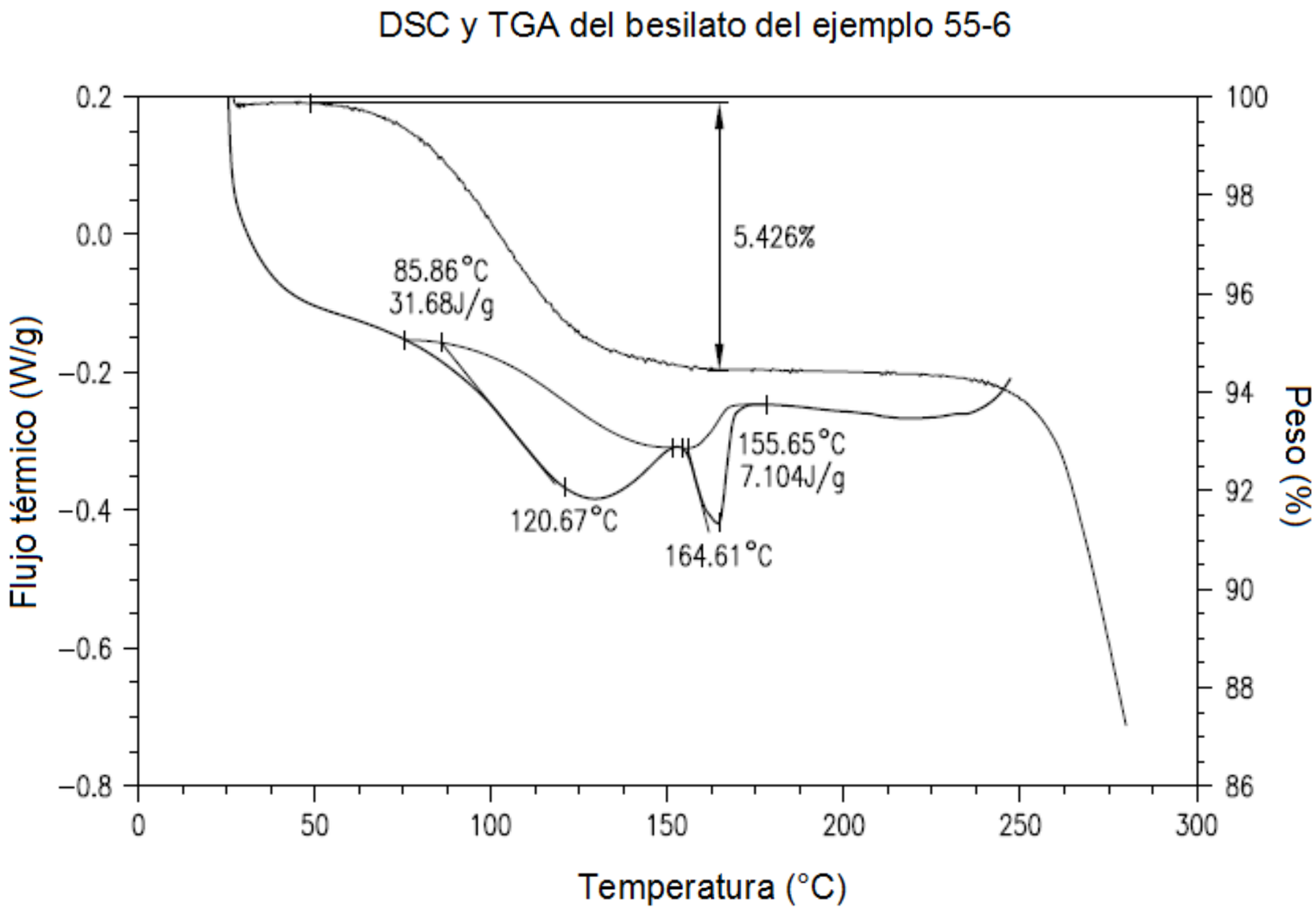

DSC y TGA del besilato del ejemplo 55-6
Flujo térmico (W/g)
Peso (%)
Temperatura (°C)
0.2
0.0
−0.2
−0.4
−0.6
−0.8
100
98
96
94
92
90
88
86
0
50
100
150
200
250
300
5.426%
85.86°C
31.68J/g
120.67°C
155.65°C
7.104J/g
164.61°C

FIG. 36

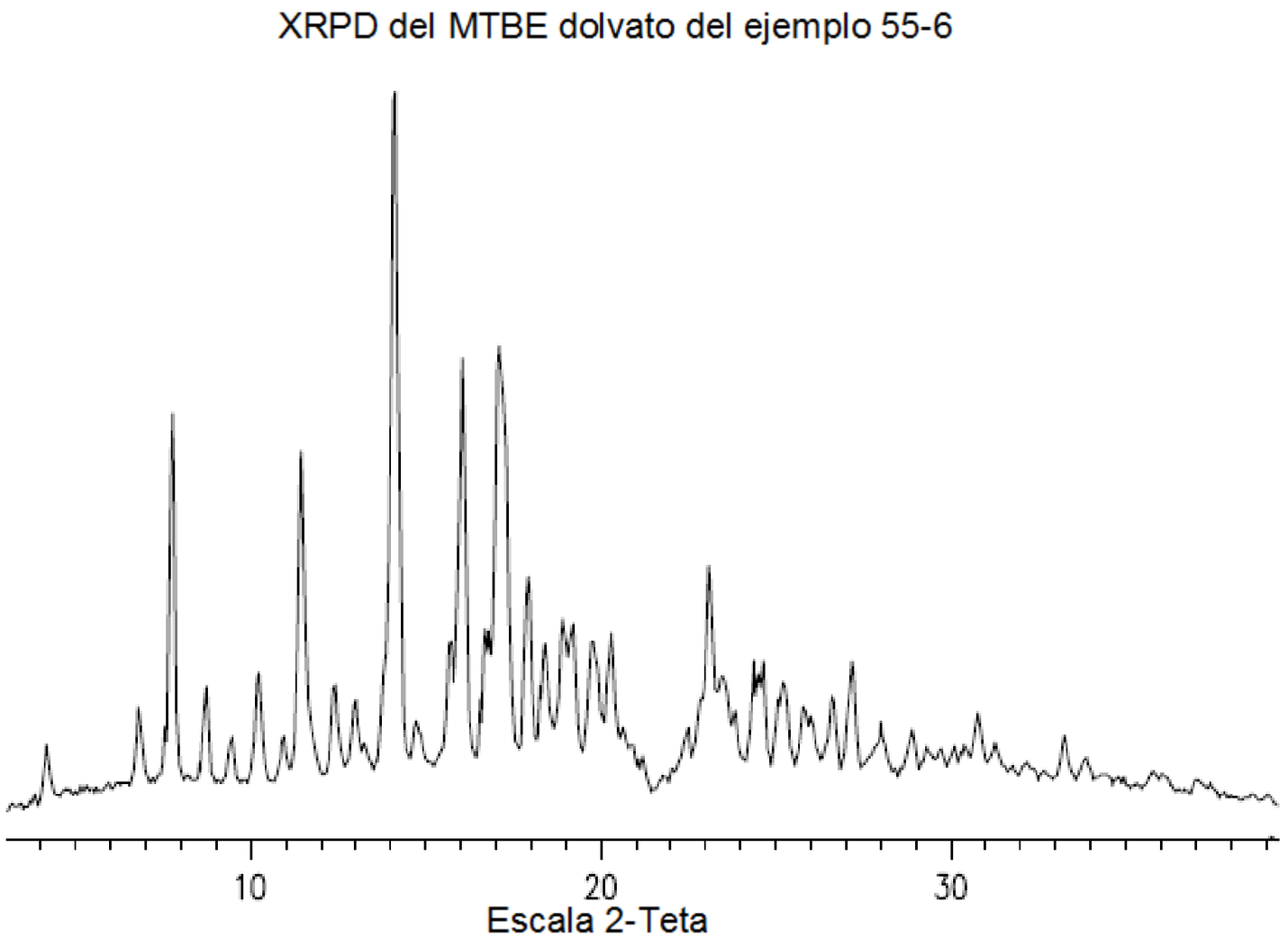


FIG. 37

DSC y TGA del MTBE solvato del Ejemplo 55-6

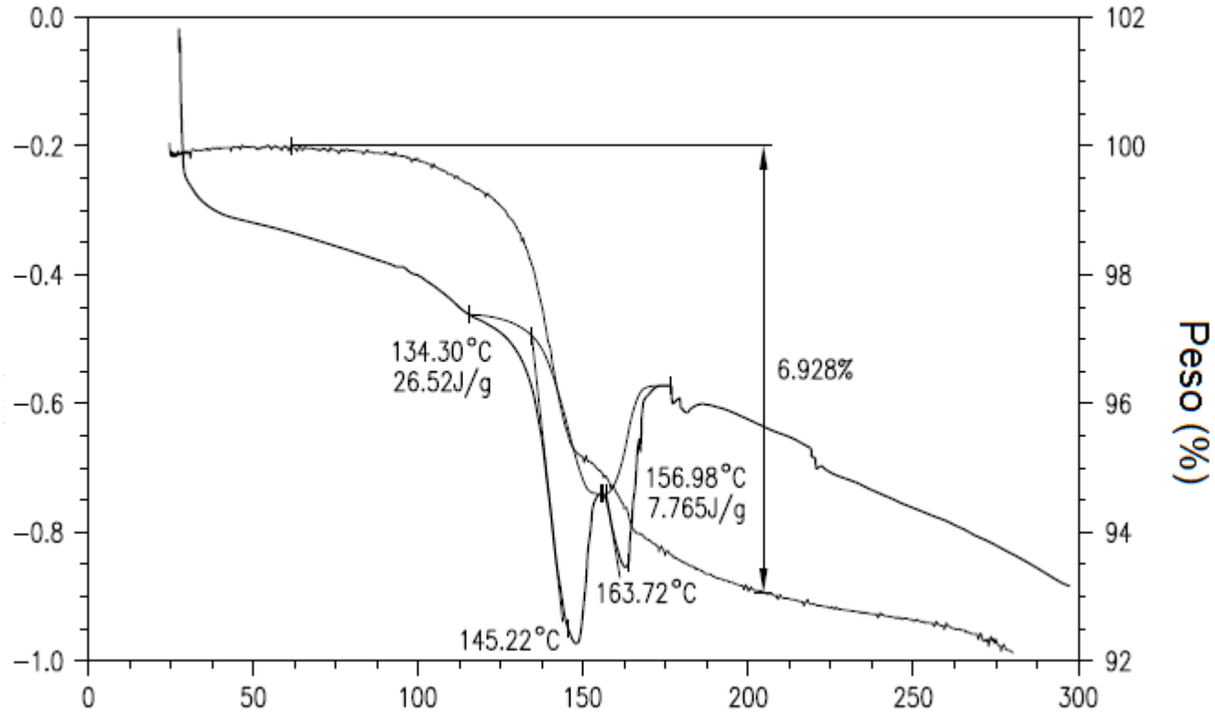


FIG. 38

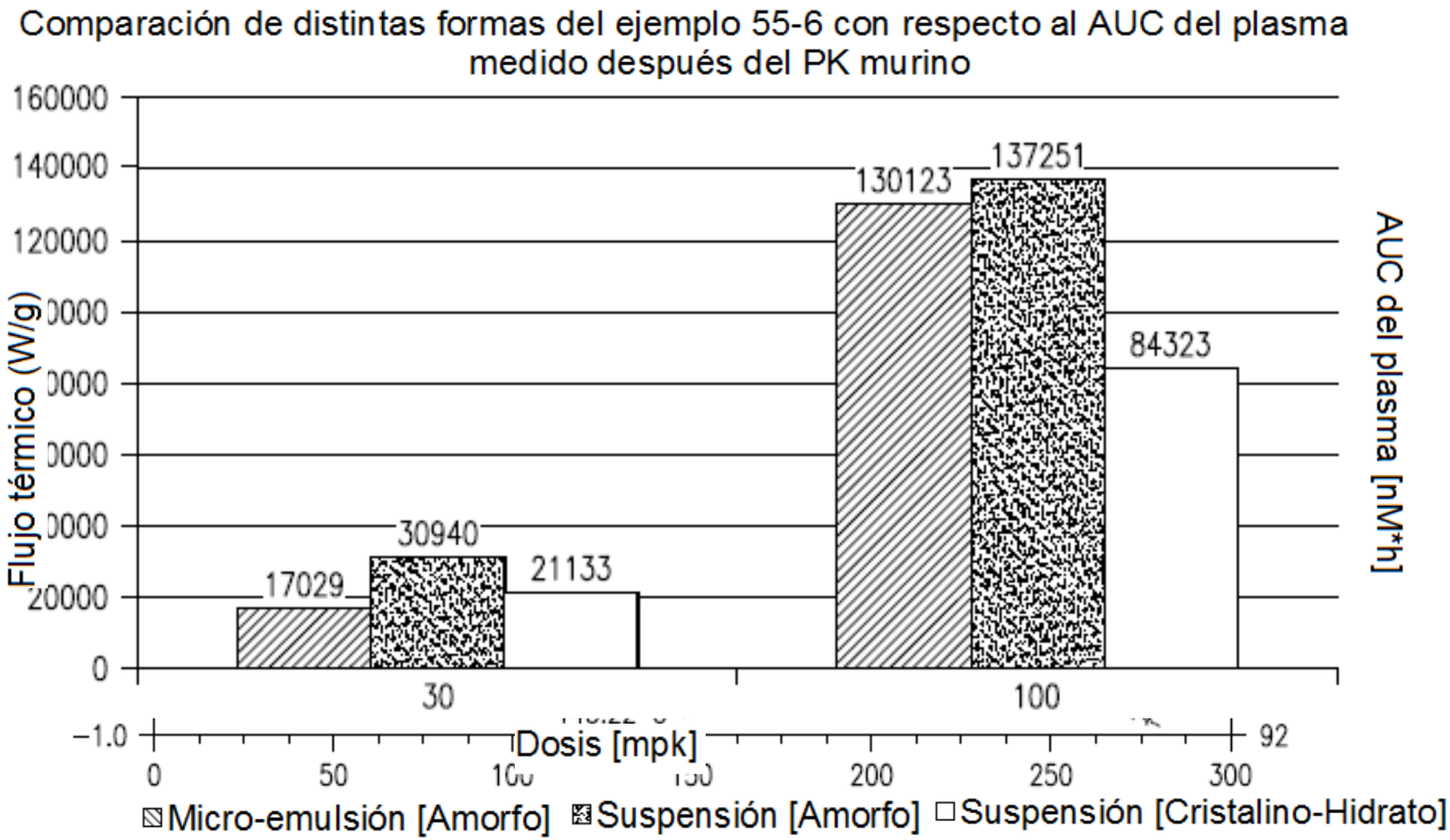

Comparación de distintas formas del ejemplo 55-6 con respecto al AUC del plasma medido después del PK murino
Flujo térmico (W/g)
AUC del plasma [nM*h]
160000
140000
120000
0
17029
30940
21133
130123
137251
84323
30
100
92
−1.0
Dosis [mpk]
0
50
200
250
300
Micro-emulsión [Amorfo]
Suspensión [Amorfo]
Suspensión [Cristalino-Hidrato]

FIG. 39

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 54683-WO-PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2012/047617	International filing date *(day/month/year)* 20/07/2012	(Earliest) Priority Date *(day/month/year)* 22/07/2011
Applicant NOVARTIS AG		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/047617

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/4375 A61K31/519 A61P27/02 A61P37/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/110416 A2 (NEUROGEN CORP [US]; MAYNARD GEORGE D [US]; GHOSH MANUKA [US]; YUAN JUN) 24 November 2005 (2005-11-24) claims 1,109	1-22
A	WO 2005/014558 A1 (VERTEX PHARMA [US]; WILSON DEAN M [US]; TERMIN ANDREAS P [US]; NEUBERT) 17 February 2005 (2005-02-17) claim 89; table 2; compounds 64,71	1-15
A	WO 2010/014939 A1 (GENENTECH INC [US]; BERGERON PHILIPPE [US]; COHEN FREDERICK [US]; ESTR) 4 February 2010 (2010-02-04) claim 6	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2012	19/09/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gettins, Marc

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/047617

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		WO 2010014939 A1	04-02-2010