SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-273126- -00000-0000
Fecha: 2013-11-20 16:43:43 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE DIACILGLICEROL ACILTRANSFERASA

SOLICITANTE: GLAXOSMITHKLINE INTELLECTUAL PROPERTY (No.2) LIMITED

DIRECCIÓN: 980 Great West Road Brentford, Middlesex TW8 9GS United Kingdom. Gran Bretaña

APODERADO: CARLOS R. OLARTE

BOGOTÁ 20 de noviembre de 2013

P2013/000200

OLARTEMOURE

OLARTE MOURE & ASOC

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-273126- -00000-0000

Fecha: 2013-11-20 16:43:43 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000200**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: GlaxoSmithKline Intellectual Property (No. 2) LIMITED
Nacionalidad o Domicilio: 980 Great West Road Brentford, Middlesex TW8 9GS United Kingdom
Lugar de Constitución: Gran Bretaña
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

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

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2012/038523 Fecha Mayo 18, 2012

Publicación Internacional No. WO 2012/162129 A1 Fecha Noviembre 29,2012

(6) **Título (54)** **COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE DIACILGLICEROL ACILTRANSFERASA**

Clasificación Internacional (51) C07D 498/04

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
IN	Mayo 20, 2011	1452/DEL2011
US	Julio 01,2011	61/503,728

(9) **Comprobante de pago No.** 13- **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. Adjunto copia simple ver expediente No.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Declaraciones. Declaración bajo la regla 4.17 (ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos *tradicionales de las comunidades indígenas*.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [X] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2012/038523

Donghui QUIN
1250 South Collegeville
Road, Collegeville, PA 19426
Estados Unidos de América
Nacionalidad: Estadounidense

Mui CHEUNG
709 Swedeland Road,
King of Prussia, PA 19406
Estados Unidos de América
Nacionalidad: Estadounidense

Hemant JOSHI
One Franklin Plaza,
200 North 16th Street,
Estados Unidos de América
Nacionalidad: India

Raghuram TANGIRALA
709 Swedeland Road,
King of Prussia, PA 19406,
Estados Unidos de América
Nacionalidad: India

Sridhar Reddy BETHI
1250 South Collegeville, Road,
Collegeville, PA 19426,
Estados Unidos de América
Nacionalidad: India

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 113198

Bogotá D.C., Noviembre 07 de 2013 - 13:00:01

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	201243022	06/11/2013	4.770.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	500.000.00	500.000.00
				$500.000.00

SON: **QUINIENTOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-***-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-273126- -00000-0000

Fecha: 2013-11-20 16:43:43 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

Industria y Comercio SUPERINTENDENCIA	PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA *RELACIÓN DE ANEXOS*	
Dependencia: 2020	Fecha: 13 / 11 / 20 AAAA MM DD	Recorrido: - 3
Tipo de Radicación: Entrada: X Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	13-273126-	0	7
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

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

Observaciones:
EL CD ANEXO CONTIENE UN TOTAL DE 7 ARCHIVOS, 7 EN FORMATO P.D.F, LOS CUALES FUERON PROCESADOS

CR.

Industria y Comercio
SUPERINTENDENCIA

ADMISIÓ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-273126- -00000-0000

Fecha: 2013-11-20 16:43:43 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 4

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000200**

SOLICITUD DE:

1

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

[X] Capítulo I. [ ] Capítulo II.

2

SOLICITANTE (71)

Nombre: GlaxoSmithKline Intellectual Property (No. 2) LIMITED
Nacionalidad o Domicilio: 980 Great West Road Brentford, Middlesex TW8 9GS United Kingdom
Lugar de Constitución: Gran Bretaña
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

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

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

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

5

PCT (86)

Solicitud Internacional No. PCT/US2012/038523 Fecha Mayo 18, 2012

Publicación Internacional No. WO 2012/162129 A1 Fecha Noviembre 29,2012

6

Título (54) **COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE DIACILGLICEROL ACILTRANSFERASA**

Clasificación Internacional (51) C07D 498/04

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
IN	Mayo 20, 2011	1452/DEL2011
US	Julio 01,2011	61/503,728

9

Comprobante de pago No. 13- **Fecha** _____

10 **ANEXOS**

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

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2012/038523

Donghui QUIN
1250 South Collegeville
Road, Collegeville, PA 19426
Estados Unidos de América
Nacionalidad: Estadounidense

Mui CHEUNG
709 Swedeland Road,
King of Prussia, PA 19406
Estados Unidos de América
Nacionalidad: Estadounidense

Hemant JOSHI
One Franklin Plaza,
200 North 16th Street,
Estados Unidos de América
Nacionalidad: India

Raghuram TANGIRALA
709 Swedeland Road,
King of Prussia, PA 19406,
Estados Unidos de América
Nacionalidad: India

Sridhar Reddy BETHI
1250 South Collegeville, Road,
Collegeville, PA 19426,
Estados Unidos de América
Nacionalidad: India

Carlos R. Olarte
Juan G. Moure

Alexander Agudelo
Carlos A. Parra
Juan Felipe Acosta
Andrés Rincón
Mónica Guevara
Andrés Alvarado
Ella Ponce
Liliana Galindo
María Clara Calderón
Mauricio Ávila
Laura Escobar
José Jairo Dangond
Gina Cáceres
Isabella Herrera
Zaava Ravid

Medellín
María Clara Múnera

OLARTEMOURE
OLARTE MOURE & ASOCIADOS LTDA.

The undersigned, Los suscritos,

domiciled in GlaxoSmithKline Intellectual Property (NO.2) Limited domiciliados en

980 Great West Road
Brentford, Middlesex
TW8 9GS
United Kingdom

hereby appoint to **Carlos R. Olarte and/or Juan Guillermo Moure** legal representatives with faculties to receive notifications and to appoint judicial or extrajudicial agents in **Patents for Inventions, Utility Models and Industrial Designs,** in the Republic of Colombia, to initiate before said authorities all the necessary actions to accomplish said purposes and to intervene in all instances, grades and procedural levels; to file and prosecute applications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which they may deem fit for the protection of our interests.

nombramos por el presente a **Carlos R. Olarte y/o Juan Guillermo Moure** nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en **Patentes de Invención, Modelos de Utilidad y Diseños Industriales,** en la República de Colombia, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.

Signature/Firma:

Name/Nombre:
Title/Cargo:

Date/Fecha:

City,Country/Ciudad,País:

Signature/Firma: Theodore R. Furman

Name/Nombre: Theodore R. Furman
Title/Cargo:
Authorized Attorney and Official on behalf of GlaxoSmithKline Intellectual Property (NO.2) Limited

Date/Fecha: 06 February 2013

City,Country/Ciudad,País:
King of Prussia, Pennsylvania, USA

NO LEGALIZATION IS REQUIRED

COMMONWEALTH OF PENNSYLVANIA)
) ss
COUNTY OF MONTGOMERY)

Before me, Deborah A. Becker, a Notary Public in and for the Commonwealth and County aforesaid, personally came Theodore R. Furman known to me to be the person whose name is subscribed to the foregoing Power of Attorney and known to me to be an Authorized Attorney and Official for GlaxoSmithKline Intellectual Property (NO.2) Limited and acknowledged to me that he executed said instrument for the purposes and consideration therein expressed and as the act of said Corporation.

Given under my hand and official seal of office this 6th day Of February 2013.

Deborah A. Becker
NOTARY PUBLIC

COMMONWEALTH OF PENNSYLVANIA
NOTARIAL SEAL
DEBORAH A. BECKER, Notary Public
Upper Merion Twp., Montgomery County
My Commission Expires April 6, 2016

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 November 2012 (29.11.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/162129 A1

(51) International Patent Classification:
C07D 498/04 (2006.01)

(21) International Application Number:
PCT/US2012/038523

(22) International Filing Date:
18 May 2012 (18.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1452/DEL/2011 20 May 2011 (20.05.2011) IN
61/503,728 1 July 2011 (01.07.2011) US

(71) Applicant *(for all designated States except US)*: **GLAXOSMITHKLINE LLC** [US/US]; One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **QIN, Donghui** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **CHEUNG, Mui** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **JOSHI, Hemant** [IN/IN]; One Franklin Plaza, 200 North 16th Street, Navimumbai (IN). **TANGIRALA, Raghuram** [IN/IN]; 709 Swedeland Road, Navi-Mumbai (IN). **BETHI, Sridhar, Reddy** [IN/IN]; 1250 South Collegeville Road, Navi-Mumbai (IN).

(74) Agents: **PENG, Tony, W.** et al.; GlaxoSmithKline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2012/162129 A1

(54) Title: NOVEL COMPOUNDS AS DIACYLGLYCEROL ACYLTRANSFERASE INHIBITORS

(57) Abstract: This invention relates to novel compounds which are inhibitors of acyl coenzymeA: diacylglycerol acyltransferase 1 (DGAT-1), to pharmaceutical compositions containing them, to processes for their preparation, and to their use in therapy for the prevention or treatment of diseases related to DGAT-1 dysfunction or where modulation of DGAT-1 activity may have therapeutic benefit including but not limited to obesity, obesity related disorders, hypertriglyceridemia, hyperlipoproteinemia, chylomicronemia, dyslipidemia, non-alcoholic steatohepatitis, diabetes, insulin resistance, metabolic syndrome, hepatitis C virus infection and acne or other skin disorders.

NOVEL COMPOUNDS AS DIACYLGLYCEROL ACYLTRANSFERASE INHIBITORS

FIELD OF INVENTION

This invention relates to novel compounds which are inhibitors of acyl coenzymeA: diacylglycerol acyltransferase 1 (DGAT-1), to pharmaceutical compositions containing them, to processes for their preparation, and to their use in therapy for the prevention or treatment of diseases related to DGAT-1 dysfunction or where modulation of DGAT-1 activity may have therapeutic benefit including but not limited to obesity, obesity related disorders, hypertriglyceridemia, hyperlipoproteinemia, chylomicronemia, dyslipidemia, non-alcoholic steatohepatitis, diabetes, insulin resistance, metabolic syndrome, hepatitis C virus infection and acne or other skin disorders.

BACKGROUND OF THE INVENTION

Obesity is a medical condition that is reaching epidemic proportions among humans in a number of countries throughout the world. It is a condition that is also associated with or induces other diseases or conditions that disrupt life activities and lifestyles. Obesity is recognized as a serious risk factor for other diseases and conditions such as diabetes, hypertension, and arteriosclerosis. It is also known that increased body weight due to obesity can place a burden on joints, such as knee joints, causing arthritis, pain, and stiffness.

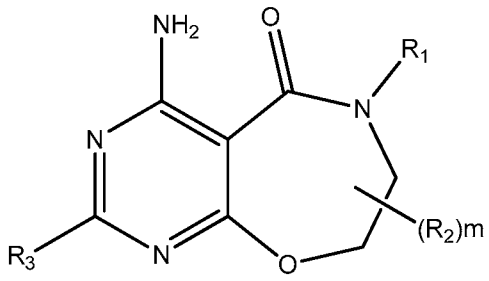
Because overeating and obesity have become such a problem in the general population, many individuals are now interested in losing weight, reducing weight, and maintaining a healthy body weight and desirable lifestyle. One approach to treating obesity is to reduce food intake and/or hyperlipidemia. It has been suggested that molecules which are developed to prevent the accumulation of triglyceride would not only reduce obesity but also have the additional beneficial effect of reducing insulin resistance, a primary factor contributing to the development of diabetes.

Acyl coenzymeA: diacylglycerol acyltransferase 1 (DGAT-1) is one of two known DGAT enzymes that catalyze the final step in mammalian triglyceride synthesis. DGAT-1 is an enzyme that is implicated in the development of both diabetes and insulin resistance. Studies of DGAT-1 deficient mice show that DGAT-1 deficiency protects against insulin resistance and obesity, see Chen, H.C. et al., J Clin Invest., 109(8), 1049-1055 (2002). Therefore, inhibitors of DGAT-1 should be useful for the treatment of metabolic disorders,

e.g. obesity, Type 2 diabetes, and insulin resistance syndrome (or metabolic syndrome) and other associated or related diseases and conditions.

SUMMARY OF THE INVENTION

This invention relates to compounds of Formula (I):



(I)

wherein

R_1 is a bicyclic ring system which contains 9 to 11 ring members including 1 to 4 hetero atoms, in which said bicyclic ring system may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or C_1-C_4alkoxy; and

m is 0-2;

or a pharmaceutically acceptable salt thereof.

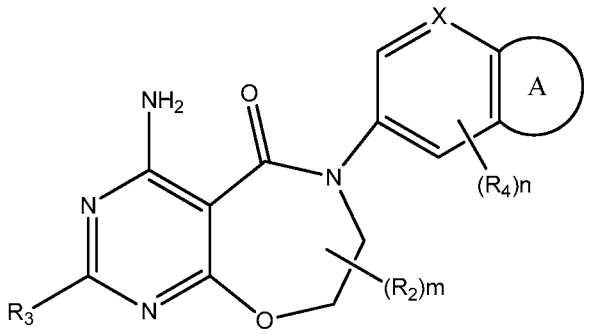
This invention also relates to a pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable carrier.

This invention also relates to a method of treating obesity comprising administering to a human in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in a pharmaceutical composition.

DETAIL DESCRIPTION OF THE INVENTION

This invention relates to compounds of the Formula (I) as defined above.

This invention also relates to compounds of Formula (I)(A):



(I)(A)

wherein A is a 5- or 6-membered heterocyclic ring, which may contain 0 to 3 double bonds and may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -$C(O)R_a$, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or C_1-C_4alkoxy;

R_4 is halo or alkoxy;

X is N or CH; and

m is 0-2;

n is 0-2;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(A), wherein A is a 5-membered heterocyclic ring, which may contain 0-2 double bonds and may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -$C(O)R_a$, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or C_1-C_4alkoxy;

R_4 is halo or alkoxy;

X is N or CH; and

m is 0-2;

n is 0-2;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(A), wherein A is a 6-membered heterocyclic ring, which may contain 0-3 double bonds and may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or C_1-C_4alkoxy;

R_4 is halo or alkoxy;

X is N or CH; and

m is 0-2;

n is 0-2;

or a pharmaceutically acceptable salt thereof.

This invention also relates to any one of the above compounds,

wherein m is 0;

n is 0;

R_3 is hydrogen; and

X is N or CH;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I),

wherein m is 0;

R_3 is hydrogen;

R_1 is a bicyclic ring system selected from the group consisting of tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolyl, dihydroindolyl, indazolyl, dihydroindazolyl, benzothiophenyl, benzodiazolyl, dihydrobenzodiazolyl, benzimidazolyl, indolinyl, benzotriazolyl, pyrrolopyridinyl, benzothiazolyl, benzofuranyl, dihydroquinazolinyl, and pyrrolopyrimidinyl;

wherein said bicyclic ring system may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I),

wherein m is 0;

R_3 is hydrogen;

R_1 is a bicyclic ring system selected from the group consisting of tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolyl, dihydroindolyl, indazolyl, dihydroindazolyl, and pyrrolopyridinyl;

wherein said bicyclic ring system may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I),

wherein m is 0;

R_3 is hydrogen;

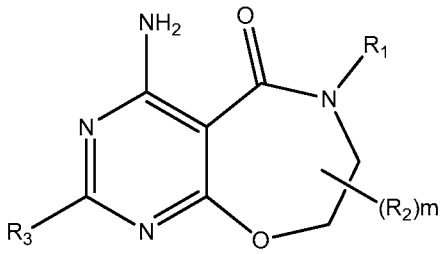
R_1 is a bicyclic ring system selected from the group consisting of tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolyl, dihydroindolyl, indazolyl, dihydroindazolyl, benzothiophenyl, benzodiazolyl, dihydrobenzodiazolyl, benzimidazolyl, indolinyl,

benzotriazolyl, pyrrolopyridinyl, benzothiazolyl, benzofuranyl, dihydroquinazolinyl, and pyrrolopyrimidinyl;

wherein said bicyclic ring system may be substituted by 1 to 3 groups selected from the group consisting of aryl and heteroaryl;

or a pharmaceutically acceptable salt thereof.

This invention relates to compounds of Formula (I)(B):



(I)(B)

wherein

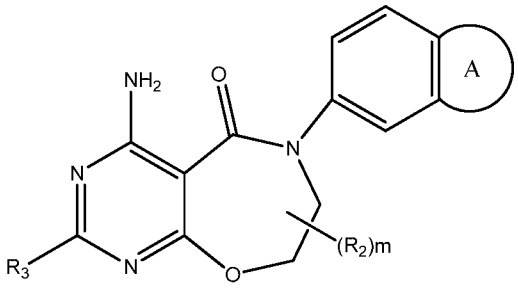
R_1 is a bicyclic ring system which contains 9 to 11 ring members including 1 to 4 hetero atoms, in which said bicyclic ring system may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, oxo, amide, carboxylic acid, and alkoxy;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or alkoxy; and

m is 0-2;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(C):



(I)(C)

wherein A is a 5- or 6-membered heterocyclic ring, which may contain 0 to 3 double bonds and may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, oxo, amide, carboxylic acid, and alkoxy;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or alkoxy; and
m is 0-2;
or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(C), wherein A is a 5-membered heterocyclic ring, which may contain 0 to 3 double bonds and may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, oxo, amide, carboxylic acid, and alkoxy;
each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or alkoxy; and
m is 0-2;
or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B) or (I)(C), wherein m is 0, and R_3 is hydrogen, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds that are exemplified in the Experimental section.

Specific compounds of this invention include:

2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)acetic acid;
ethyl 2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)acetate;
2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)acetic acid;
ethyl 2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)acetate;
6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-methyl-1,2,3,4-tetrahydroquinolin-2-one;
6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-one;
6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-one;

6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-2-propyl-1,2,3,4-tetrahydroisoquinolin-1-one;

6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-propyl-1,2,3,4-tetrahydroquinolin-2-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-2-benzyl-1-(prop-2-en-1-yl)-2,3-dihydro-1H-indazol-3-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-propyl-2,3-dihydro-1H-indazol-3-one;

4-amino-6-(1-propyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-propyl-1H-indazol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-benzothiophen-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1,3-dipropyl-2,3-dihydro-1H-1,3-benzodiazol-2-one;

4-amino-6-(2-propyl-2H-indazol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1,3-benzothiazol-6-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-propyl-2,3-dihydro-1H-indole-2,3-dione;

4-amino-6-(1-benzofuran-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-cyclopropyl-1,2,3,4-tetrahydroquinolin-6-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(2-propyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2,2-difluoroethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-oxepino[2,3-d]pyrimidin-6-yl}-1-(propan-2-yl)-2,3-dihydro-1H-indazol-3-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-oxepino[2,3-d]pyrimidin-6-yl}-1-(2-methoxyethyl)-2,3-dihydro-1H-indazol-3-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-(2,2-difluoroethyl)-2,3-dihydro-1H-indazol-3-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-cyclopropyl-2,3-dihydro-1H-indazol-3-one;

6-amino-4-(1-propyl-1H-1,3-benzodiazol-5-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-one;

4-amino-6-(1-propyl-1H-1,3-benzodiazol-6-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(2-propyl-2H-1,2,3-benzotriazol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-propyl-1H-1,2,3-benzotriazol-6-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(2-methyl-1,3-benzothiazol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(cyclopropylmethyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

3-(5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1H-indol-1-yl)propanoic acid;

4-amino-6-[1-(cyclohexylmethyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(pentan-3-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-[(4-methoxyphenyl)methyl]-1H-indol-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-[(4-fluorophenyl)methyl]-1H-indol-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-[2-(benzyloxy)ethyl]-1H-indol-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-benzyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(3-methoxypropyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2,2-difluoroethyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-methyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2-methoxyethyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(propan-2-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-propyl-2,3-dihydro-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(2,3-dihydro-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2-methoxyethyl)-2,3-dihydro-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1,2-dimethyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-propyl-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2-methoxyethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(cyclohexylmethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-cyclohexyl-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(propan-2-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-methanesulfonyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-cyclopropyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-propyl-1H-indole-2-carboxylic acid;

4-amino-6-[1-propyl-3-(trifluoroacetyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-propyl-3-(1,1,1-trifluoro-2-methoxypropan-2-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-(1-phenyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-[4-(trifluoromethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(3-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(3-chlorophenyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2-methoxyphenyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(3,4-difluorophenyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(2-fluorophenyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-[4-(trifluoromethyl)phenyl]-1H-indol-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-[1-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-[3-(trifluoromethyl)phenyl]-1H-indol-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{1-[3-(trifluoromethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-[1-(1,3-thiazol-2-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-{1-[6-(trifluoromethyl)pyridin-3-yl]-1H-indol-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-[1-(pyridin-2-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-[1-(pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-[1-(pyrazin-2-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-[1-(pyrazin-2-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-{1-[5-(trifluoromethyl)pyridin-2-yl]-1H-indol-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-{1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-[1-(1,3-thiazol-2-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-{1-[6-(trifluoromethyl)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-[1-phenyl-3-(propan-2-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-(2-phenyl-1-propyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-(6-fluoro-1-phenyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-3-benzyl-3,4-dihydroquinazolin-4-one;
6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-3,4-dihydroquinazolin-4-one;
4-amino-6-(1-benzyl-6-fluoro-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;

4-amino-6-{5-propyl-5H-pyrrolo[3,2-d]pyrimidin-2-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one;
4-amino-6-(1-propyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one;
4-amino-6-(1-(6-methylpyridin-3-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one;
4-amino-6-(1-(4-(difluoromethyl)phenyl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one;
4-amino-6-(1-(4-(difluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one;
4-amino-6-(1-(4-(trifluoromethyl)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one;
or a pharmaceutically acceptable salt thereof.

A person of ordinary skills in the art recognizes that compounds of the present invention may have alternative names when different naming software is used.

The following exemplified compounds have alternative chemical names as illustrated in table below.

Ex	Chemical Name	Alternative Chemical Name
1	2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)acetic acid	2-(6-(4-amino-5-oxo-5,6,7,8-tetrahydrooxepino(2,3-*d*)pyrimidin-6-yl)-2-methyl-1-oxo-1,2,3,4-tetrahydronapthalen-2-yl) acetic acid
10	5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-2-benzyl-1-(prop-2-en-1-yl)-2,3-dihydro-1H-indazol-3-one	6-(1-allyl-2-benzyl-3-oxo-2,3-dihydro-1H-indazol-5-yl)-4-amino-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
11	5-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-1-propyl-2,3-dihydro-1H-indazol-3-one	4-amino-6-(3-oxo-1-propyl-2,3-dihydro-1H-indazol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
12	4-amino-6-(1-propyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
33	4-amino-6-[1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridinpyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one

34	4-amino-6-{1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridinpyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
63	4-amino-6-[1-propyl-3-(trifluoroacetyl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(1-propyl-3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
65	4-amino-6-(1-phenyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
66	4-amino-6-{1-[4-(trifluoromethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridinpyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
82	4-amino-6-[1-(1,3-thiazol-2-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(1-(thiazol-2-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
83	4-amino-6-{1-[6-(trifluoromethyl)pyridin-3-yl]-1H-indol-5-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(1-(6-(trifluoromethyl)pyridinpyridin-3-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
94	4-amino-6-[1-phenyl-3-(propan-2-yl)-1H-indol-5-yl]-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(3-isopropyl-1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
95	4-amino-6-(2-phenyl-1-propyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(2-phenyl-1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
96	4-amino-6-(6-fluoro-1-phenyl-1H-indol-5-yl)-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(6-fluoro-1-phenyl-1H-indol-5-yl)-7,8-dihydrooxepino[2,3-d]pyrimidin-5(6H)-one
97	6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-3-benzyl-3,4-dihydroquinazolin-4-one	4-amino-6-(3-benzyl-4-oxo-3,4-dihydroquinazolin-6-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
98	6-{4-amino-5-oxo-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-6-yl}-3,4-dihydroquinazolin-4-one	4-amino-6-(4-oxo-3,4-dihydroquinazolin-6-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
100	4-amino-6-{5-propyl-5H-pyrrolo[3,2-d]pyrimidin-2-yl}-5H,6H,7H,8H-pyrimido[5,4-f][1,4]oxazepin-5-one	4-amino-6-(5-propyl-5H-pyrrolo[3,2-d]pyrimidin-2-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one
101	4-amino-6-(1-propyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one	4-amino-6-(1-propyl-1H-pyrrolo[3,2-b]pyridinpyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), or any of the exemplified compounds, or their pharmaceutically acceptable salts thereof, for use as a medicament.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), or any of the exemplified compounds, or their pharmaceutically acceptable salts thereof, for use in the treatment of obesity.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), or any of the exemplified compounds, or their pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of obesity.

It will be appreciated by those skilled in the art that the compound of the present invention may also be utilized in the form of a pharmaceutically acceptable salt thereof.

Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the disclosed compounds containing a basic amine or other basic functional group may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid or the like. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, phenylacetates, phenylpropionates, phenylbutrates, citrates, lactates, γ-hydroxybutyrates,

glycolates, tartrates mandelates, and sulfonates, such as xylenesulfonates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates and naphthalene-2-sulfonates.

Salts of the disclosed compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine, collidine, choline, quinine, quinoline, and basic amino acid such as lysine and arginine.

Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these should be considered to form a further aspect of the invention. These salts, such as oxalic or trifluoroacetate, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts.

As used herein, the term "a compound of Formula (I)" or "the compound of Formula (I)" refers to one or more compounds according to Formula (I). The compound of Formula (I) may exist in solid or liquid form. In the solid state, it may exist in crystalline or noncrystalline form, or as a mixture thereof. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline or non-crystalline compounds. In crystalline solvates, solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve non-aqueous solvents such as, but not limited to, ethanol, isopropanol, DMSO, acetic acid, ethanolamine, or ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates.

The skilled artisan will further appreciate that certain compounds of the invention that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs." The invention includes all such polymorphs. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

The compound of Formula (I) or a salt thereof may exist in stereoisomeric forms (e.g., it contains one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that a compound or salt of Formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention. It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula (I) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, iodine, and chlorine, such as 2H, 3H, 11C, 13C, 14C, 15N, 17O, 18O, 31P, 32P, 35S, 18F, 36Cl, 123I and 125I.

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as 3H, 14C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H, and carbon-14, i.e., 14C, isotopes are particularly preferred for their ease of preparation and detectability. 11C and 18F isotopes are particularly useful in PET (positron emission tomography), and 125I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

DEFINITIONS

Terms are used within their accepted meanings. The following definitions are meant to clarify, but not limit, the terms defined.

As used herein, unless otherwise defined, the term "alkyl" (or "alkylene") refers to a straight or branched chain alkyl, preferably having from one to twelve carbon atoms, which may be saturated or unsaturated included within the present invention. Examples of "alkyl" as used herein include methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, t-butyl, isopentyl, n-pentyl, and the like, as well as substituted versions thereof.

As used herein, unless otherwise defined, the term "substituted alkyl" (or "alkylene") refers to a straight or branched chain alkyl, preferably having from one to twelve carbon atoms, which may be saturated or unsaturated with multiple degrees of substitution included within the present invention, preferably one, two or three. Suitable substituents are selected from the group consisting of unsubstituted C_3-C_7cycloalkyl, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, difluoromethyl, trifluoromethyl, halo, amino, substituted amino, urea, cyano, hydroxyl, alkoxy, alkylthio, alkylsulfonyl,

sulfonamide, carboxylic acid (eg. COOH), carboxylic ester (eg. methyl ester, ethyl ester, and carboxamide.

As used herein, unless otherwise defined, the term "substituted amino" is meant –NR'R" wherein each R' and R" is independently selected from a group including hydrogen, unsubstituted C_1-C_6alkyl, acyl, unsubstituted C_3-C_7cycloalkyl, wherein at least one of R' and R" is not hydrogen. Examples of substituted amino includes, but are not limited to alkylamino, dialkylaminio, acylamino, and cycloalkylamino.

As used herein, unless otherwise defined, the term "aryloxy" refers to the group –O-C_1-C_6alkylaryl. Examples of –O-C_1-C_6alkylaryl includes, but are not limited to phenylmethoxy, naphthylmethoxy.

As used herein, unless otherwise defined, the term "arylalkyl" refers to the group -C_1-C_6alkylaryl. Examples of –C_1-C_6alkylaryl includes, but are not limited to phenylmethyl, naphthylmethyl.

As used herein, unless otherwise defined, the term "cycloalkyl" refers to an unsubstituted or substituted mono- or polycyclic non-aromatic saturated ring, which optionally includes an alkylene linker through which the cycloalkyl may be attached. Suitable substituents are defined in the definition of 'substituted". Exemplary "cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, as well as unsubstituted and substituted versions thereof.

As used herein, unless otherwise defined, the term "alkoxy" refers to the group -OR^a, where R^a is C_1-C_4alkyl or cycloalkyl as defined above.

As used herein, unless otherwise defined, the term "amide" refers to the group –$C(O)NR^cR^d$, wherein R^c and R^d are each independently H, or C_1-C_6alkyl , or R^c is the remaining portion of a natural or un-natural aminoacid.

As used herein, unless otherwise defined, the term "heterocycle" or "heterocyclyl" or "heterocyclic" refers to unsubstituted and substituted mono- or polycyclic non-aromatic ring system containing one or more heteroatoms. Preferred heteroatoms include N, O, and S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to eight-membered and is either fully saturated or has one or more degrees of unsaturation. Multiple degrees of substitution are included within the present definition. Examples of "heterocyclic" groups include, but are not limited to tetrahydrofuranyl, pyranyl, 1,4-dioxanyl, 1,3-dioxanyl, piperidinyl, pyrrolidinyl, morpholinyl, azetidinyl, piperazinyl, pyrrolidinonyl, piperazinonyl, pyrazolidinyl, and their various tautomers.

As used herein, unless otherwise defined, the term "aryl", unless otherwise defined, is meant aromatic, hydrocarbon, ring system. The ring system may be monocyclic or fused polycyclic (e.g., bicyclic, tricyclic, etc.), substituted or unsubstituted. A C6 ring system, i.e. a phenyl ring, is a suitable aryl group. In various embodiments, the polycyclic ring is a bicyclic aryl group, where suitable bicyclic aryl groups are C8-C12, or C9-C10. A naphthyl ring, which has 10 carbon atoms, is a suitable polycyclic aryl group. Suitable substituents for aryl are described below in the definition of "optionally substituted".

As used herein, unless otherwise defined, the term "heteroaryl",unless otherwise defined, is meant an aromatic ring system containing carbon(s) and at least one heteroatom. Heteroaryl may be monocyclic or polycyclic, substituted or unsubstituted. A monocyclic heteroaryl group may have 1 to 4 heteroatoms in the ring, while a polycyclic heteroaryl may contain 1 to 10 hetero atoms. A polycyclic heteroaryl ring may contain fused, spiro or bridged ring junctions, for example, bicyclic heteroaryl is a polycyclic heteroaryl. Bicyclic heteroaryl rings may contain from 8 to 12 member atoms. Monocyclic heteroaryl rings may contain from 5 to 8 member atoms (carbons and heteroatoms). Exemplary heteroaryl groups include but are not limited to: benzofuran, benzothiophene, furan, imidazole, indole, isothiazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinoline, quinazoline, quinoxaline, thiazole, and thiophene. Suitable substituents for heteroaryl are described below in the definition of "optionally substituted".

As used herein, unless otherwise defined, the term "cyano" refers to the group -CN.

As used herein, unless otherwise defined, the term "acyl" refers to the group -$C(O)R^b$, where R^b is alkyl, cycloalkyl, or heterocyclyl, as each is defined herein.

As used herein, unless otherwise defined, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and event(s) that do not occur.

As used herein, unless otherwise defined, the phrase "substituted" or variations thereof denote an optional substitution, including multiple degrees of substitution, with one or more substitutent group, preferably one, two or three. The phrase should not be interpreted as duplicative of the substitutions herein described and depicted. Suitable optional substituent groups include acyl, C_1-C_6alkyl, substituted C_1-C_6alkyl, unsubstituted C_3-C_7cycloalkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, oxo, and nitro.

PHARMACEUTICAL COMPOSITIONS

The invention further provides a pharmaceutical composition (also referred to as pharmaceutical formulation) comprising a compound of Formula I or pharmaceutically acceptable salt, thereof and one or more excipients (also referred to as carriers and/or diluents in the pharmaceutical arts). The excipients are acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof (i.e., the patient).

In accordance with another aspect of the invention there is provided a process for the preparation of a pharmaceutical composition comprising mixing (or admixing) a compound of Formula I or salt thereof with at least one excipient.

Pharmaceutical compositions may be in unit dose form containing a predetermined amount of active ingredient per unit dose. Such a unit may contain a therapeutically effective dose of the compound of Formula I or salt thereof or a fraction of a therapeutically effective dose such that multiple unit dosage forms might be administered at a given time to achieve the desired therapeutically effective dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well-known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example, by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, or intradermal) routes. Such compositions may be prepared by any method known in the art of pharmacy, for example, by bringing into association the active ingredient with the excipient(s).

When adapted for oral administration, pharmaceutical compositions may be in discrete units such as tablets or capsules; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; oil-in-water liquid emulsions or water-in-oil liquid emulsions. The compound or salt thereof of the invention or the pharmaceutical composition of the invention may also be incorporated into a candy, a wafer, and/or tongue tape formulation for administration as a "quick-dissolve" medicine.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable

inert carrier such as ethanol, glycerol, water, and the like. Powders or granules are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agents can also be present.

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

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars, such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, xanthan gum, and the like.

Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, and aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt, and/or an absorption agent such as bentonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compound or salt of the present invention can also be combined with a free-flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear opaque protective coating consisting of a sealing coat of shellac, a coating of sugar, or

polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different dosages.

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

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

In the present invention, tablets and capsules are preferred for delivery of the pharmaceutical composition.

As used herein, the term “treatment” includes prophylaxis and refers to alleviating the specified condition, eliminating or reducing one or more symptoms of the condition, slowing or eliminating the progression of the condition, and preventing or delaying the reoccurrence of the condition in a previously afflicted or diagnosed patient or subject. Prophylaxis (or prevention or delay of disease onset) is typically accomplished by administering a drug in the same or similar manner as one would to a patient with the developed disease or condition.

The present invention provides a method of treatment in a mammal, especially a human, suffering from obesity, diabetes, hypertension, depression, anxiety, drug addiction, substance addiction, or a combination thereof. Such treatment comprises the step of administering a therapeutically effective amount of a compound of Formula I or salt thereof to said mammal, particularly a human. Treatment can also comprise the step of administering a therapeutically effective amount of a pharmaceutical composition containing a compound of Formula I or salt thereof to said mammal, particularly a human.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician.

The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a compound of Formula I, as well as salts thereof, may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

While it is possible that, for use in therapy, a therapeutically effective amount of a compound of Formula I or salt thereof may be administered as the raw chemical, it is typically presented as the active ingredient of a pharmaceutical composition or formulation.

The precise therapeutically effective amount of a compound or salt thereof of the invention will depend on a number of factors, including, but not limited to, the age and weight of the subject (patient) being treated, the precise disorder requiring treatment and its severity, the nature of the pharmaceutical formulation/composition, and route of administration, and will ultimately be at the discretion of the attending physician or veterinarian. Typically, a compound of Formula I or salt thereof will be given for the treatment in the range of about 0.1 to 100 mg/kg body weight of recipient (patient, mammal) per day and more usually in the range of 0.1 to 10 mg/kg body weight per day. Acceptable daily dosages may be from about 1 to about 1000 mg/day, and preferably from about 1 to about 100 mg/day. This amount may be given in a single dose per day or in a number (such as two, three, four, five, or more) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt thereof may be determined as a proportion of the effective amount of the compound of Formula I per se. Similar dosages should be appropriate for treatment (including prophylaxis) of the other conditions referred herein for treatment. In general, determination of appropriate dosing can be readily arrived at by one skilled in medicine or the pharmacy art.

Additionally, the present invention comprises a compound of Formula I or salt thereof or a pharmaceutical composition thereof with at least one other anti-obesity drug and/or at least one anti-diabetes drug. Such anti-obesity drugs can include, for example, Metformin (or glucophage), CB1 receptor antagonists, GLP-1 agonists, opioid antagonists, and neurotransmitter reuptake inhibitors. When a compound of the invention is employed in combination with another anti-obesity drug or anti-diabetes drug, it is to be appreciated

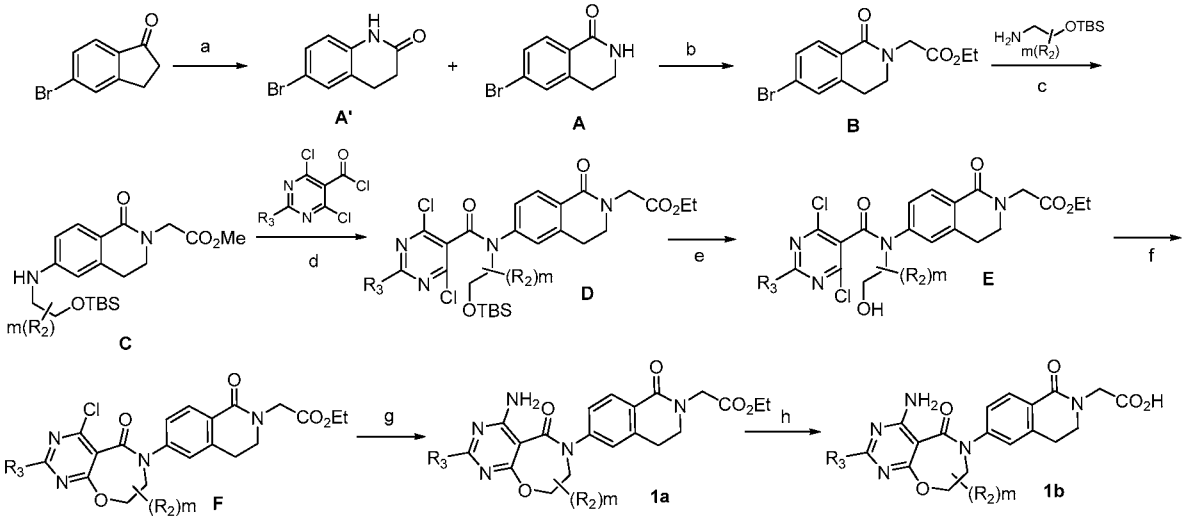
by those skilled in the art that the dose of each compound or drug of the combination may differ from that when the drug or compound is used alone. Appropriate doses will be readily appreciated and determined by those skilled in the art. The appropriate dose of the compound of Formula I or salt thereof and the other therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect, and are with the expertise and discretion of the attending doctor or clinician.

COMPOUNDS PREPARATION

Generic Synthesis Schemes

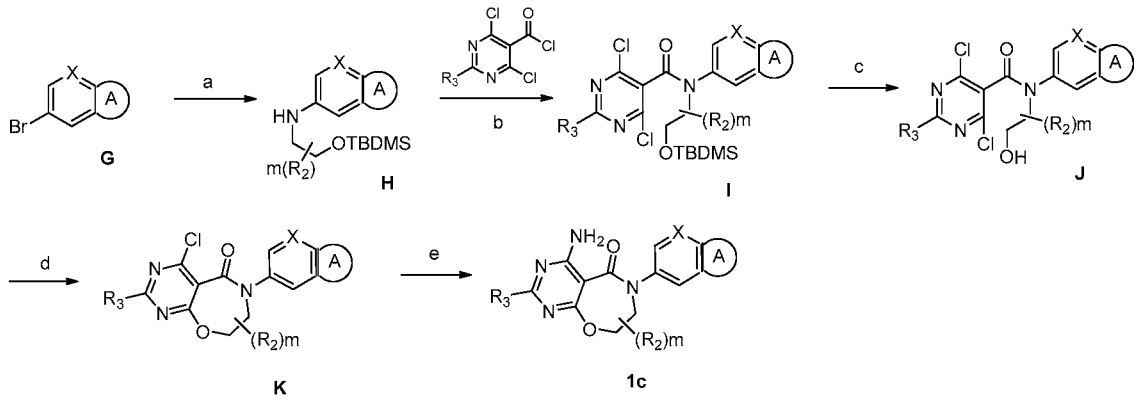
The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working examples. The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. In all of the schemes described below, protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T.W. Green and P.G.M. Wuts, (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons, incorporated by reference with regard to protecting groups). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of the present invention.

The synthesis of the compounds of the general Formula (I) and pharmaceutically acceptable derivatives and salts thereof may be accomplished as outlined below in Schemes 1 – 10 by those skilled in the art. In the following description, the groups are as defined above for compounds of Formula (I) unless otherwise indicated. Starting materials are commercially available or are made from commercially available starting materials using methods known to those skilled in the art.



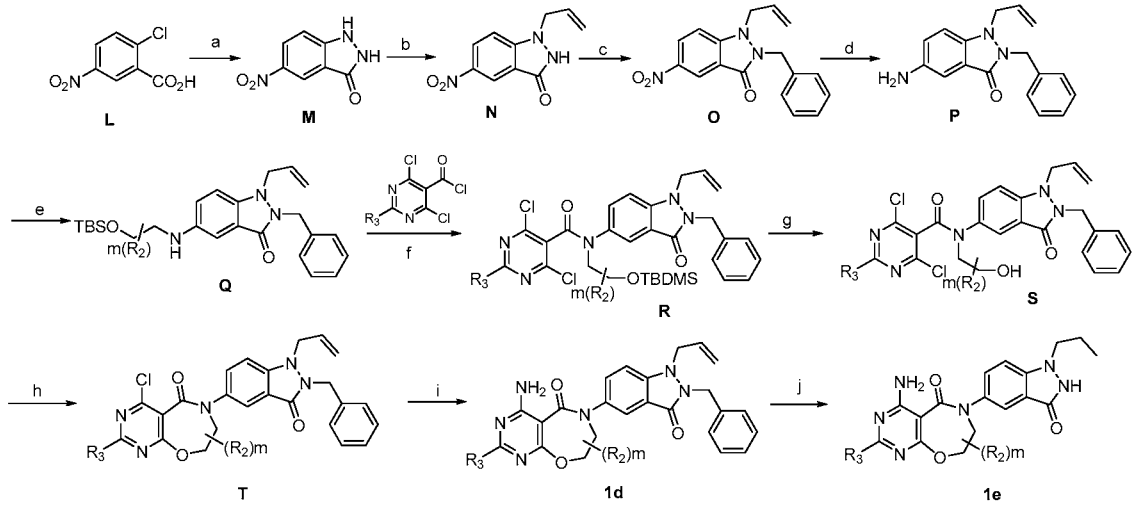
Scheme 1. Reagents and conditions: a) NaN_3, $MeSO_3H$, CH_2Cl_2, RT; b) NaH, $BrCH_2CO_2Et$, THF, RT; c) $Pd(OAc)_2$, Cs_2CO_3, X-Phos, Toluene, 120 °C; d) THF, Et_3N, RT; e) 3%HCl-MeOH, RT; f) CH_3CN, Et_3N, 80 °C; g) NH_3, Dioxane, RT; h) LiOH, Dioxane-H_2O, RT

Compounds of Formula (I) may be prepared as illustrated in Scheme 1. Intermediate **A** can be obtained by rearrangement reaction of 5-bromo-1-indanone with NaN_3 in $MeSO_3H$ in solvents such as CH_2Cl_2. Alkylation of intermediate **A** with an appropriate alkyl halide such as ethyl bromoacetate in the presence of a suitable base such as NaH gives intermediate **B**. Intermediate **A'** can also be similarly alkylated and progressed similar to that of intermediate **A**. Intermediate **B** can then be subjected to amination under Buchwald conditions using an appropriate amine in the presence of reagents such as palladium acetate, ligand such as X-Phos and a base such as cesium carbonate in toluene at 120 °C. Intermediate **C** thus obtained can then be coupled to the appropriately substituted acid chloride to afford **D**. Desilylation of intermediate **D** under standard acidic conditions leads to **E** which is then subjected to ring closure by heating the reaction mixture in acetonitrile at 80 °C in the presence of a base such as triethylamine to give **F**. Substitution of the chloro residue in intermediate **F** with an amino group by treatment with ammonia at room temperature results in compounds of Formula (I) (**1a**). Hydrolysis of the ester group in compound **1a** with base such as LiOH provides another compound of Formula (I) (**1b**).



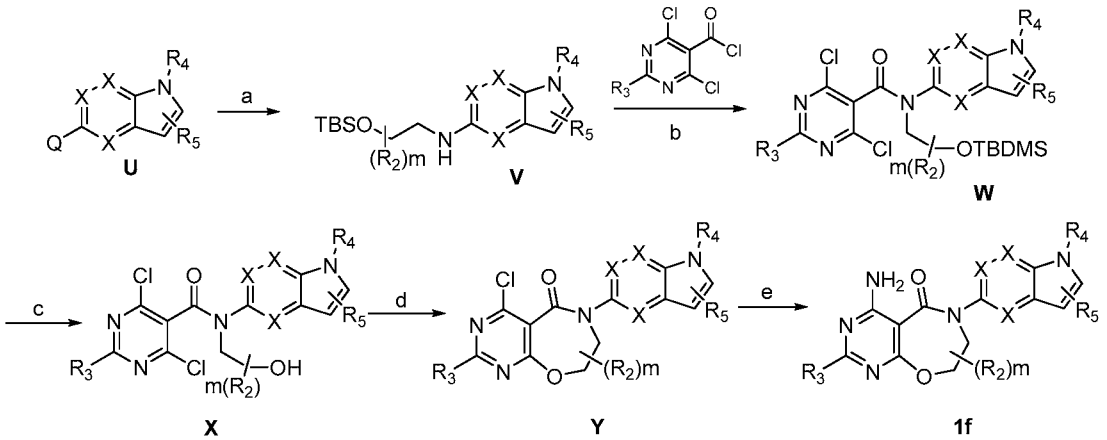
Scheme 2. Reagents and conditions: a) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C; b) THF, Et_3N, RT; c) 3% HCl-MeOH, RT; d) CH_3CN, Et_3N, 80 °C; e) NH_3, Dioxane, RT.

Compounds of Formula (I) may be also prepared as illustrated in Scheme 2. Intermediate **H** can be obtained by the amination of an appropriate bromo substituted heterocyclic compound **G** with a suitably protected amine under the standard Buchwald conditions. Bromide **G** is available either commercially or is synthesized according to standard methods of organic synthesis known to those skilled in the art with or without appropriate protecting groups. Amine intermediate **H** can then be converted to the tertiary amide **I** with an appropriately substituted acid chloride using triethylamine as a base. Desilylation of intermediate **I** followed by ring closure of the resulting alcohol **J** under heating conditions in acetonitrile affords intermediate **K**. Substitution of the chloro residue in intermediate **K** with an amino group by treatment with ammonia at room temperature results in compounds of Formula (I) (**1c**). If necessary, compound **1c** can be subjected to a functional group deprotection reaction under standard conditions to remove the group that was introduced during the preparation of bromide **G**.



Scheme 3. Reagents and conditions: a) $NH_2NH_2.H_2O$, EtOH, 80 °C; b) Allyl bromide, KOH, NaOH, 100 °C; c) Benzyl bromide, NaH, DMF, RT; d) Fe/NH_4Cl, EtOH-H_2O, 85 °C; e) $Br(CH_2)_2OTBDMS$, CH_3CN, K_2CO_3, 80 °C; f)DCM, Et_3N, rt; g) 3% HCl-MeOH, RT; h) CH_3CN, Et_3N, 80 °C; i) NH_3, Dioxane, RT; j) 10% Pd/C, H_2, MeOH, RT.

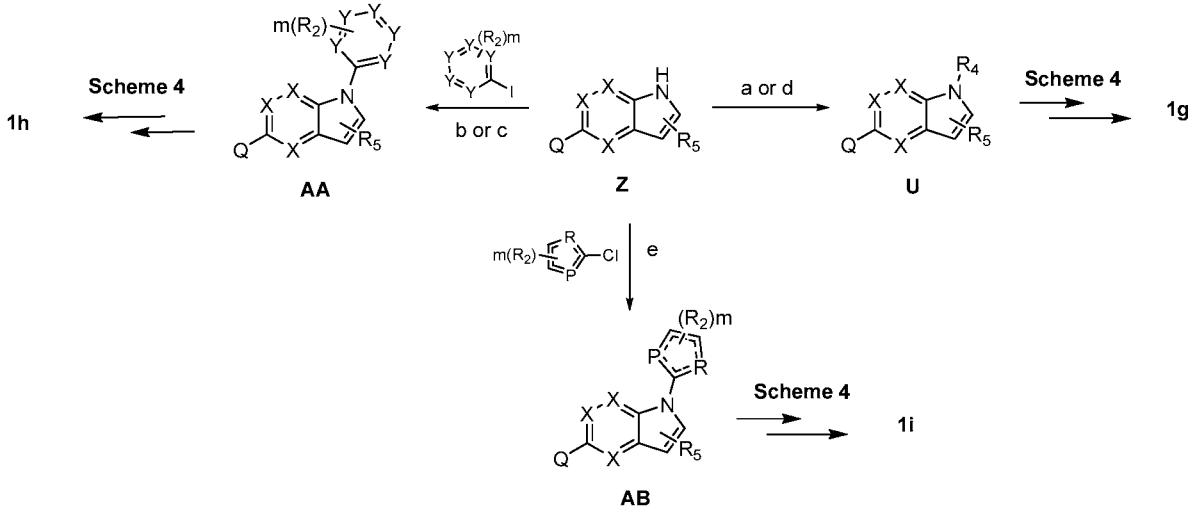
Compounds of Formula (I) may be also prepared as illustrated in Scheme 3. Commercially available 2-chloro-5-nitro benzoic acid **L** was treated with hydrazine hydrate in refluxing ethanol to give the indazolone **M**. Intermediate **M** was then doubly protected first with allyl group on the aniline nitrogen to give **N** and then with a benzyl group on the lactam nitrogen to afford **O**. Intermediate **O** was then reduced to the corresponding amine **P** under standard conditions. Aniline **P** was then alkylated with a suitable alkyl bromide to afford **Q** which was then converted to a tertiary amide **R** using an appropriately substituted acid chloride. Desilylation of intermediate **R** followed by ring closure of the resulting alcohol **S** under heating conditions in acetonitrile affords intermediate **T**. Substitution of the chloro residue in intermediate **T** with an amino group by treatment with ammonia at room temperature results in compounds of Formula (I) (**1d**). Deprotection of benzyl group on the lactam nitrogen of compound **1d** with concomitant reduction of olefin in the allyl moiety provides another compound of Formula (I) (**1e**).



Scheme 4. Reagents and conditions: a) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-Phos, Toluene, 120 °C; b) DCM, Et_3N, RT; c) 3% HCl-MeOH, RT; d) CH_3CN, Et_3N, 80 °C; e) NH_3, Dioxane, RT.

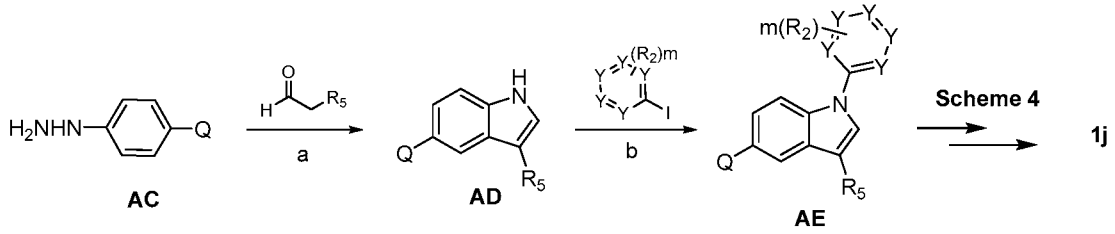
Compounds of Formula (I) may be also prepared as illustrated in Scheme 4. An appropriately substituted indole or a derivative thereof **U**, can be subjected to amination under Buchwald conditions using an appropriate amine in the presence of reagents such as palladium acetate, ligand such as X-Phos and a base such as cesium carbonate in toluene at 120 °C. Intermediate **V** thus obtained can then be coupled to an appropriately

substituted acid chloride to afford **W**. Desilylation of intermediate **W** under standard acidic conditions leads to **X** which is then subjected to ring closure by heating the reaction mixture in acetonitrile at 80 °C in the presence of a base such as triethylamine to give **Y**. Substitution of the chloro residue in intermediate **Y** with an amino group by treatment with ammonia at room temperature results in compounds of Formula (I) (**1f**).



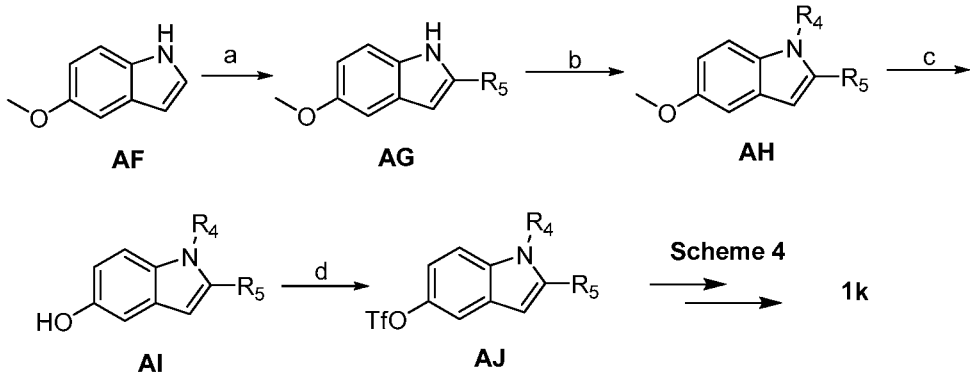
Scheme 5. Reagents and conditions: a) R_4-Br/ R_4-I, Cs_2CO_3, DMF, 100 °C; b) Cu(I)Br, $Cu(OAc)_2$, K_2CO_3, NaOH, 140 °C; c) Cu(I)Br, $Cu(OAc)_2$, K_2CO_3, NaOH, DMF, 110 °C; d) R_4-$B(OH)_2$, 2,2'-bipyridine, Na_2CO_3, $Cu(OAc)_2$, DCE, 110 °C; e) Cs_2CO_3, DMF, 100 °C.

Compounds of Formula (I) may be also prepared via intermediates **U**, **AA** & **AB** as illustrated in Scheme 5. A suitably substituted indole or a derivative thereof **Z** is alkylated or arylated using the appropriate alkyl bromide **R_4-Br** (or iodide **R_4-I**) or aryl/heteroaryl boronic acid **R_4-$B(OH)_2$** respectively under standard conditions to afford the nitrogen-capped intermediate **U**. This can be converted to compounds of formula (I) **1g** by using this intermediate **U** via Scheme 4. Similarly **Z** can also be arylated under copper catalysed conditions with copper (I) bromide and cupric acetate using an appropriately substituted aryl iodide to afford intermediate **AA**. This intermediate can again be transformed into compounds of formula (I) **1h** via Scheme 4. Intermediate **Z** can be treated with 2-chloro substituted heterocycles under heating conditions in the presence of a mild base such as cesium carbonate. The intermediate **AB** thus obtained can be transformed into compounds of Formula (I) **1i** via Scheme 4.



Scheme 6. Reagents and conditions: a) AcOH, 120 °C; b) Cu(I)Br, $Cu(OAc)_2$, K_2CO_3, NaOH, 140 °C.

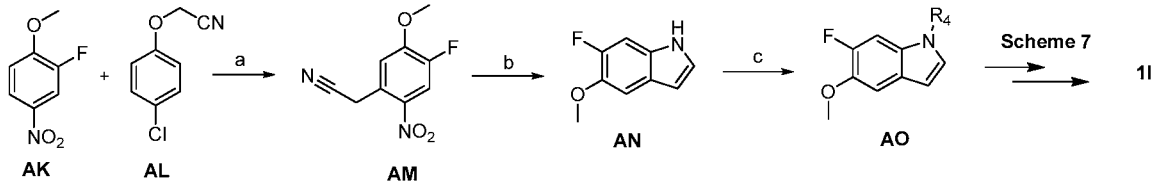
Compounds of Formula (I) may also be synthesized via intermediate **AE** whose synthesis is shown in Scheme 6. An appropriately substituted phenyl hydrazine **AC** is heated with a suitably α-substituted aldehyde in acetic acid at 120 °C to afford the 3-substituted indole **AD**. Intermediate **AD** then is coupled to an appropriately substituted aryl or heteroaryl iodide under copper catalysed conditions (similar to that described for the synthesis of intermediate **AA**) to afford intermediate **AE**. This can then be taken through synthetic sequence similar to that in Scheme 4 to afford compounds of Formula (I) **1j**.



Scheme 7. Reagents and conditions: a) R_5-$B(OH)_2$, AcOH, $Pd(OAc)_2$, copper(II) acetate, 25 °C; b) R_4-Br/ R_4-I, Cs_2CO_3, DMF, 25 °C; c) BBr_3, DCM, 0 °C; d) Triflic anhydride, Py, DCM, 0 °C.

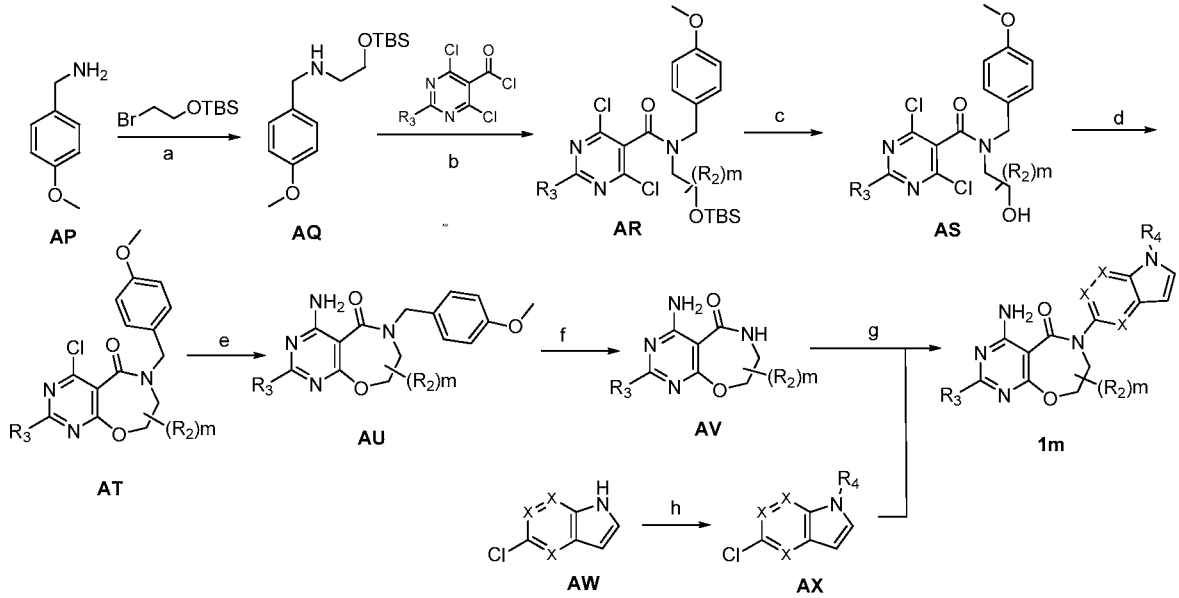
Compounds of Formula (I) may also be synthesized via intermediate **AJ** whose synthesis is described in Scheme 7. Commercially available 5-methoxy indole **AF** was substituted suitably with R_5 moiety using R_5-substituted boronic acid under palladium catalysed conditions to afford 2-substituted indole derivative **AG**. Intermediate **AG** in turn is alkylated (or arylated) under standard conditions using a suitable alkylating agent such as R_4-bromide (or the corresponding iodide) to afford **AH**. Demethylation of the methoxy group with boron tribromide and triflation of the resulting intermediate **AI** gives the

appropriately susbstituted indole derivative **AJ**. This intermediate can then be taken through the various synthetic steps of Scheme 4 to produce compounds of Formula (I) **1k**.



Scheme 8. Reagents and conditions: a) K^{t}OBu, DMF, -20 °C; b) 10% Pd/C, Ethanol, 27 °C; c) R_4-Br/ R_4-I, $Cu(OAc)_2$, CuBr, K_2CO_3, NaOH, DMF, 80 °C

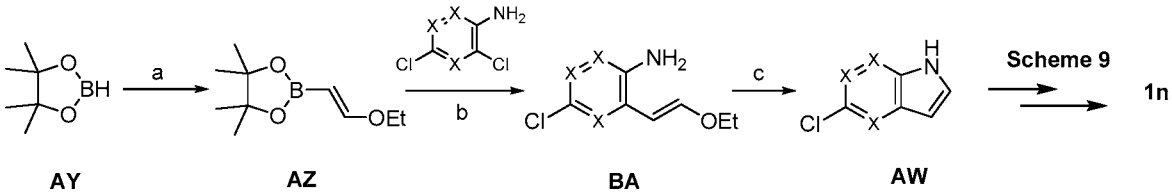
Compounds of Formula (I) may also be synthesized via intermediate **AO** whose synthesis is described in Scheme 8. Intermediate **AM** can be prepared by a cyanomethyl transfer reacton using an agent such as **AL** when treated with the substrate **AK** in the presence of a strong base such as potassium *tert*-butoxide. Nitro arene **AM** can then be subjected to a reduction using palladium on carbon and the resulting transient aniline condenses internally to cyclise to form indole **AN** thereby losing an equivalent of ammonia. Indole **AN** can then be suitably alkylated (or arylated) under standard conditions to afford **AO**. Fluoro indole **AO** can be taken through steps similar to those described in Scheme 7 for intermediate **AH,** followed by those in Scheme 4 eventually leading to the synthesis of compounds of Formula (I) **1l**.



Scheme 9. Reagents and conditions: a) $Br(CH_2)_2OTBDMS$, K_2CO_3, ACN, 80 °C; b) DCM, Et_3N, RT; c) 3% HCl-MeOH, RT; d) CH_3CN, Et_3N, 80 °C; e) NH_3, Dioxane, RT; f)

TFA, anisole, 90 °C; g) K_3PO_4 dibasic, CuI, (1*S*,2*S*)-cyclohexane-1,2-diamine, 1,4-dioxane, 110 °C; h) R_4-Br, Cs_2CO_3, DMF, 25 °C.

An alternative methodology is described in Scheme 9 towards the synthesis of compounds of Formula (I). *p*-Methoxy benzylamine is alkylated with TBS-protected bromoethanol in acetonitrile using a mild base such as potassium carbonate under heating conditions to afford secondary amine **AQ**. Intermediate **AQ** was converted to the tertiary amide **AR** upon treatment with an appropriately substituted acid chloride under standard conditions. Desilylation of **AR** under acidic conditions followed by ring closure of the resultant alcohol **AS** by heating in acetonitrile afforded PMB-substituted oxazepinone **AT**. Conversion of the chloro group in **AT** to an amine was effected by treatment with ammonia in dioxane to afford **AU**. Removal of the PMB group under TFA conditions in the presence of a scavenger anisole at 90 °C afforded the key intermediate **AV**. Oxazepinone **AV** was then coupled to appropriately substituted 5-chloro indole **AX** under copper catalysed conditions to afford compounds of Formula (I) **1m**. Intermediate **AX** can itself be prepared by alkylation of 5-chloro indole **AW** with a suitable bromide (or iodide) under standard conditions.



Scheme 10. Reagents and conditions: a) di(cyclopenta-2,4-dien-1-yl)zirconium(IV) chloride, ethoxyethyne, DCM, RT, b) K_3PO_4 dibasic, $Pd(OAc)_2$,,dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine, ACN, water, 80 °C ; c), AcOH, 140 °C.

Compounds of Formula (I) can also be synthesized via intermediates such as **AW** as described in Scheme 10. Various substituted indoles represented by **AW** can be synthesized starting from ethoxy vinyl boronate **AZ** which itself is prepared by treatment of pinacolate borane **AY** with ethoxyethyne in the presence of a zirconium catalyst at room temperature. Intermediate **AZ** is then treated with 2, 4-dichloro substituted aniline under palladium catalysed conditions using a suitable ligand and base such as potassium phosphate dibasic to afford aniline **BA**. Intermediate **BA** is then heated in acetic acid at 140 °C to give indole **AW**. Intermediate **AW** can then be carried over through appropriate synthetic steps described in Scheme 9 to finally afford compounds of Formula (I) **1n**.

EXPERIMENTALS

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention. Unless otherwise noted, reagents are commercially available or are prepared according to procedures in the literature. The symbols and conventions used in the descriptions of processes, schemes, and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry.

In the Examples:

Chemical shifts are expressed in parts per million (ppm) units. Coupling constants (J) are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), m (multiplet), br (broad).

Flash column chromatography was performed on silica gel.

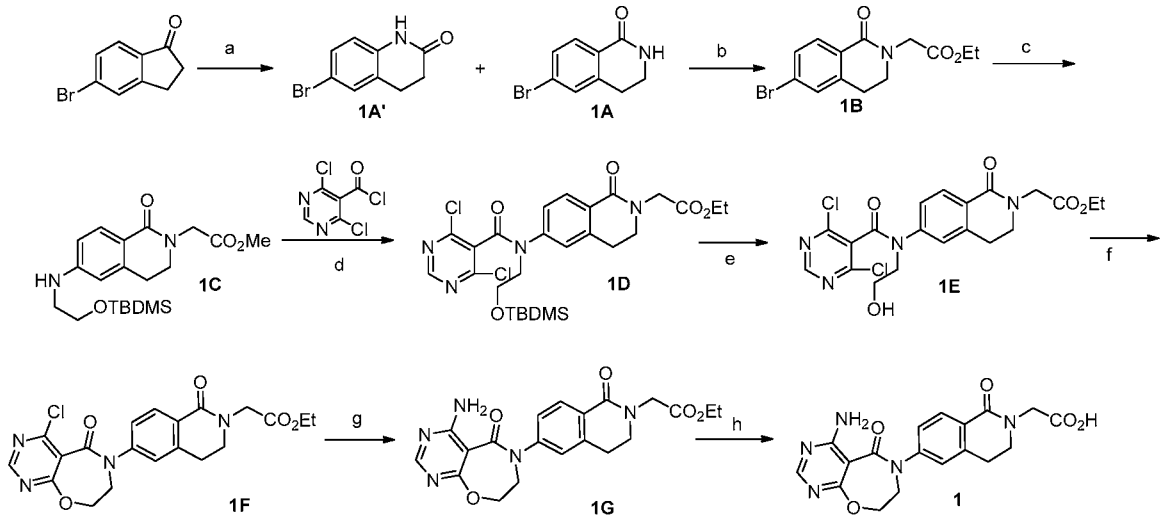
The naming programs used are ACDLABs 11.0 Namebatch, ACD IUPAC or Chem Draw.

Abbreviations:

Ac	acetyl
ACN	acetonitrile
AcOH	acetic acid
BBr_3	boron tribromide
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
Cs_2CO_3	cesium carbonate
Cu(I)Br	copper (I) bromide

$Cu(OAc)_2$	copper (II) acetate
DCE	dichloroethane
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et_3N	triethylamine
g	grams
h	hours
LiOH	lithium hydroxide
K_2CO_3	potassium carbonate
K^tOBu	potassium tert-butoxide
KOH	potassium hydroxide
m/z	mass to charge ratio
MeOH	methanol
$MeSO_3H$	methyl sulfonic acid
mmol	millimoles
Na_2CO_3	sodium carbonate
NaH	sodium hydride
NaN_3	sodium azide
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
Pd	palladium
Pd/C	palladium on carbon
$Pd(OAc)_2$	palladium (II) acetate
Py	pyridine
rt	room temperature
TBAF	tetrabutyl ammonium fluoride
TBDMS (TBS)	*tert*-butyl dimethylsilyl
Tf_2O	triflic anhydride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Example 1: 2-(6-(4-Amino-5-oxo-5,6,7,8-tetrahydrooxepino(2,3-*d*)pyrimidin-6-yl)-2-methyl-1-oxo-1,2,3,4-tetrahydronapthalen-2-yl) acetic acid:

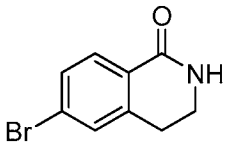


Reagents and conditions: a) NaN_3, $MeSO_3H$, CH_2Cl_2, RT, 8h; b) NaH, $BrCH_2CO_2Et$, THF, RT, 5h; c) $NH_2(CH_2)_2OTBDMS$, $Pd(OAC)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C, 24h; d) THF, Et_3N, RT, 16h; e) 3%HCl-MeOH, RT, 4h; f) CH_3CN, Et_3N, 80 °C, 16h; g) NH_3, Dioxane, RT, 16h; h) LiOH, Dioxane-H_2O, RT, 16h.

Procedures:

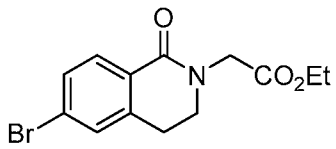
2-(6-(4-Amino-5-oxo-5,6,7,8-tetrahydrooxepino(2,3-*d*)pyrimidin-6-yl)-2-methyl-1-oxo-1,2,3,4-tetrahydronapthalen-2-yl) acetic acid:

6-Bromo-3,4-dihydroisoquinolin-1(2H)-one (1A):



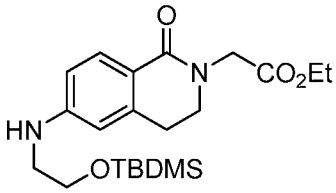
NaN_3 (6.2 g, 94.78 mmol) was added to a solution of 5-bromo-1-indanone (10 g, 47.39 mmol) in 40 mL mixture of methane sulphonic acid and dichloromethane (1:1) in portion wise at 0 °C-5 °C. The resulting mixture was stirred for 8 h at room temperature. The reaction mixture was cooled to 0 °C in ice bath, neutralized with 5 % aq. NaOH solution, and the aqueous layer with extracted with ethyl acetate (2x100 mL). The combined organic layer was washed with water and brine solution, dried over sodium sulphate, filtered and concentrated under vacuum. The residue was purified by silica gel flash column chromatography by eluting with 30 % ethyl acetate in hexane to afford title compound (6.4 g, 60%) as solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.4 Hz, 1H), 7.5 (d, J = 8.4 Hz, 1H), 7.4 (s, 1H), 6.1 (bs, 1H), 3.6 (t, J = 6.8 Hz, 2H), 3.0 (t, J = 6.4 Hz, 2H).

Ethyl 2-(6-bromo-2-oxo-3,4-dihydroquinolin-1(2H)-yl) acetate (1B):



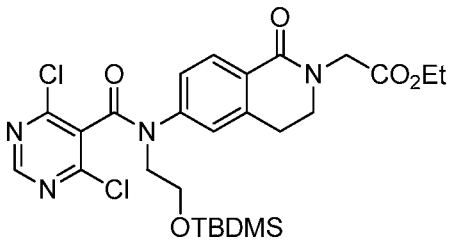
Sodium hydride (0.63 g, 26.25 mmol) was added portion wise to an ice cold solution of product of Example 1A (3 g, 13.3 mmol) in THF (40 mL), and the mixture was stirred for 30 min. Ethyl bromo acetate (3.3 g, 19.9 mmol) was now added slowly, and the mixture was stirred at room temperature for 5 h. The reaction was then cooled to 0 °C, excess NaH quenched with ice water, and the aqueous layer was extracted twice with ethyl acetate (2x50 mL). The combined organic layers were washed with water followed by brine solution, dried over sodium sulphate, filtered and concentrated under vacuum. The residue was purified using flash column chromatography by eluting with 15% ethyl acetate in hexane to afford title compound (2 g, 48%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4 (m, 2H), 6.6 (m, 1H), 4.6 (s, 2H), 4.2 (q, J = 6.9 Hz, 2H), 2.9 (m, 2H), 2.7 (m, 2H), 1.2 (t, J = 6.9 Hz, 3H).

Ethyl 2-(6-(2-(tert-butyldimethylsilyloxy)ethylamino)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1C):



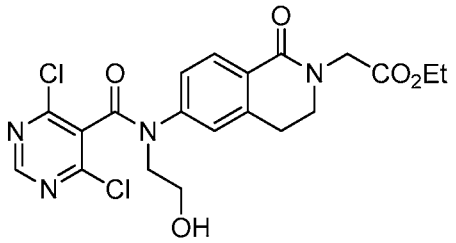
A mixture of product of Example 1B (1.5 g, 4.8 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (1.0 g, 5.71 mmol), cesium carbonate (1.87 g, 5.73 mmol), palladium acetate (0.11 g, 0.47 mmol) and X-PHOS (0.23 g, 0.47 mmol) in toluene (15 mL) under argon was refluxed at 120 °C for 24 h. The reaction was cooled, the mixture was diluted into ethyl acetate and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.95 g, 48%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 8.4 Hz, 1H), 6.51 (m, 1H), 6.32 (s, 1H), 4.4 (m, 1H), 4.29 (s, 2H), 4.2 (q, J = 6.9 Hz, 2H), 3.81 (t, J = 5.1 Hz, 2H), 3.59 (t, J = 6.3 Hz, 2H), 3.25 (q, J = 5.7 Hz, 2H), 2.94 (t, J = 6.9 Hz, 2H), 1.27 (t, J = 6.9 Hz, 3H), 0.9 (s, 9H), 0.06 (s, 6H); ESI-MS m/z = 407 $(M+H)^+$.

Ethyl 2-(6-(N-(2-(tert-butyldimethylsilyloxy)ethyl)-4,6-dichloropyrimidine-5-carboxamido)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1D):



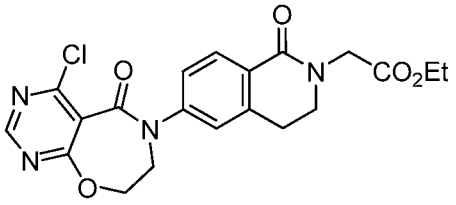
To a stirred, cooled (0 °C) solution of product of Example 1C (0.95 g, 2.33 mmol) and TEA (1.18 g, 11.67 mmol) in THF (15 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.74 g, 3.5 mmol) in THF (5 mL). After 16 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 12% ethyl acetate in hexane as eluent to afford title compound (0.75 g, 55%) as an solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.6 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.34 (dd, J_1 = 1.2 Hz, J_2 = 7.5 Hz, 1H), 7.29 (s, 1H), 4.34 (s, 2H), 4.21 (q, J = 6.9 Hz, 2H), 4.03 (t, J = 5.7 Hz, 2H), 3.93 (t, J = 4.8 Hz, 2H), 3.6 (t, J = 6.3 Hz, 2H), 2.94 (t, J = 7.2 Hz, 2H), 1.27 (t, J = 7.8 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ESI-MS m/z = 581 $(M+H)^+$.

Ethyl 2-(6-(4,6-dichloro-N-(2-hydroxyethyl)pyrimidine-5-carboxamido)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1E):



A solution of product of Example 1D (0.75 g, 1.29 mmol), in a methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 4 h. Methanol was removed in vacuo. The residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.45 g, 75%) as solid, which was carried on to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.36 (m, 1H), 7.31 (s, 1H), 4.28 (s, 2H), 4.2 (q, J = 7.2 Hz, 2H), 4.1 (m, 2H), 3.96 (m, 2H), 3.62 (t, J = 6.4 Hz, 2H), 3.0 (t, J = 6.4 Hz, 2H), 2.1 (t, J = 5.6 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 467 $(M+H)^+$.

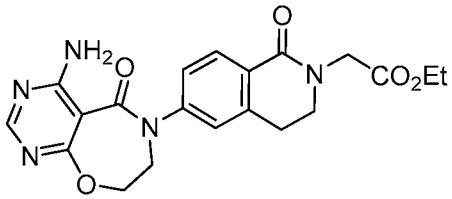
Ethyl 2-(6-(4-chloro-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1F):



A slurry of product of Example 1E (0.4 g, 0.85 mmol) and TEA (0.43 g, 4.28 mmol) in acetonitrile (10 mL) was stirred at 80 °C for 16 h. The reaction was cooled, concentrated in vacuo, and diluted with ethyl acetate. The mixture was washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.35 g, 95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.29 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 4.78 (t, J = 4.8 Hz, 2H), 4.34 (s, 2H), 4.23 (q, J =7.6 Hz, 2H),

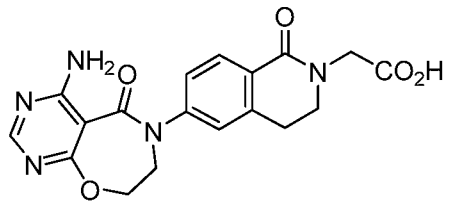
4.1 (t, J = 4.8 Hz, 2H), 3.7 (t, J = 6.8 Hz, 2H), 3.1 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 431 $(M+H)^+$.

Ethyl 2-(6-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1G):



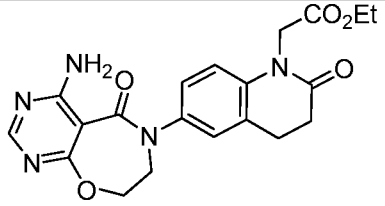
A solution of product of Example 1F (0.3 g, 0.697 mmol) in 0.5M ammonia in p-dioxane (10 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated in vacuo and diluted with ethyl acetate. The organic layer was washed with water, saturated aqueous brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.22 g, 70%) as an white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.3 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.2 (m, 2H), 4.71 (t, J = 4.2 Hz, 2H), 4.34 (s, 2H), 4.23 (q, J = 6.9 Hz, 2H), 4.04 (t, J = 4.8 Hz, 2H), 3.69 (m, 2H), 3.1 (t, J = 6.3 Hz, 2H), 1.29 (t, J = 6.9 Hz, 3H); LC-MS: 91% pure, m/z = 412 $(M+H)^+$.

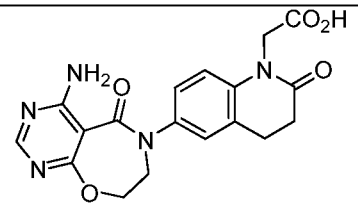
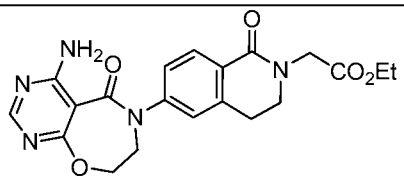
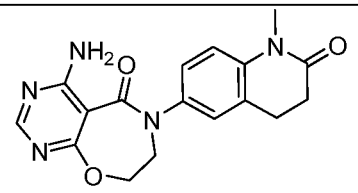
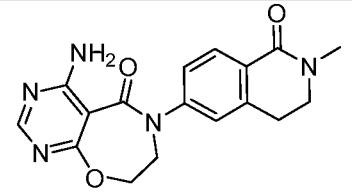
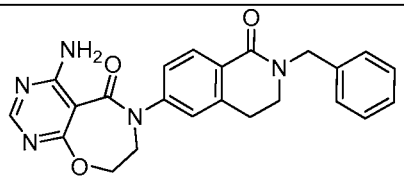
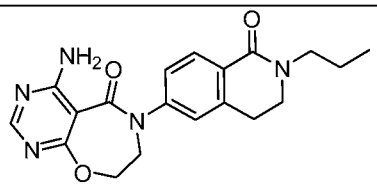
2-(6-(4-Amino-5-oxo-5,6,7,8-tetrahydrooxepino(2,3-*d*)pyrimidin-6-yl)-2-methyl-1-oxo-1,2,3,4-tetrahydronapthalen-2-yl) acetic acid (1):

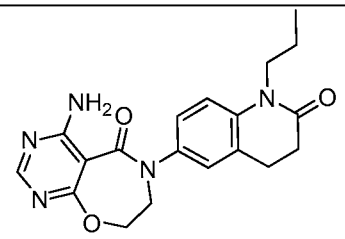


A solution of product of Example 1G (0.18 g, 0.43 mmol) and lithium hydroxide (0.055 g, 1.309 mmol) in 5 mL of p-dioxane-water (4:1) mixture was stirred at room temperature for 16 h. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified using 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and resulting solids were filtered off and dried in vacuo to afford title compound (0.12 g, 72%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.8 (bs, 1H), 8.45 (bs, 2H), 8.36 (s, 1H), 7.9 (d, J = 9.0 Hz, 1H), 7.4 (m, 2H), 4.7 (m, 2H), 4.21 (m, 2H), 4.13 (m, 2H), 3.64 (t, J = 6.3 Hz, 2H), 3.03 (t, J = 5.7 Hz, 2H); HPLC purity: 99%, m/z = 384 $(M+H)^+$.

Examples 2 - 9 were prepared by the method described above for Example 1 or routine variations thereof starting from the requisite halo-quinolinone.

Ex	Structure	Analytical Data	Mass/Purity
2		^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.29 (m, 1H), 7.23 (dd, J_1 = 2.1 Hz, J_2 = 8.1 Hz, 1H), 7.0 (d, J = 9.0 Hz, 1H), 4.67 (s, 2H), 4.6 (t, J = 4.2 Hz, 2H), 4.15 (q, J = 7.8 Hz, 2H),	ESI-MS m/z = 412 $(M+H)^+$; LC-MS purity: 97%.

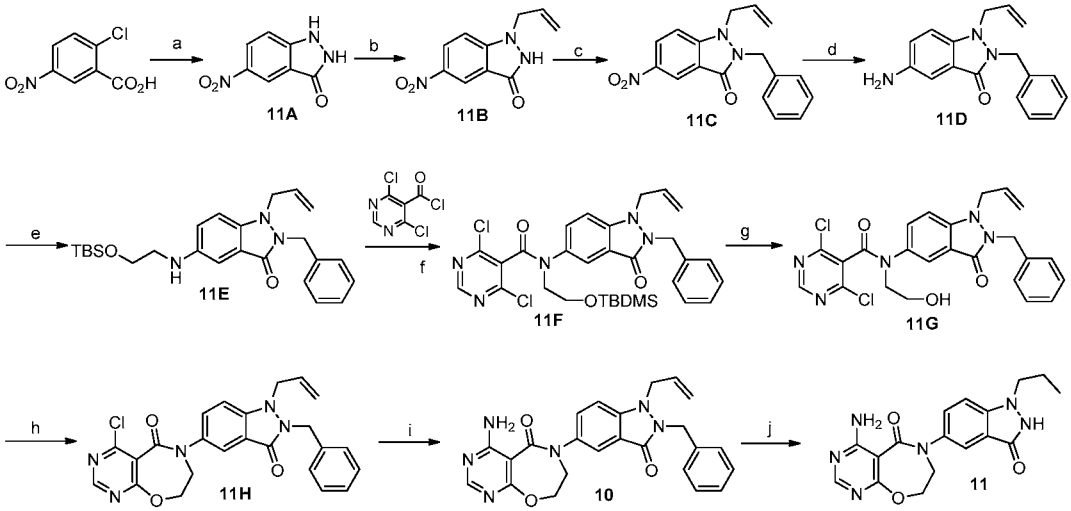
		3.96 (t, J = 4.2 Hz, 2H), 2.91 (t, J = 6.9 Hz, 2H), 2.6 (t, J = 7.8 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H).	
3		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.0 (bs, 1H), 8.17 (s, 1H), 7.61 (bs, 2H), 7.28 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.6 (m, 4H), 3.96 (m, 2H), 2.9 (t, J = 6.8 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H).	ESI-MS m/z = 384 $(M+H)^+$; LC-MS purity: 99%.
4		^{1}H NMR (300 MHz, $CDCl_3$): δ 8.3 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.2 (m, 2H), 4.71 (t, J = 4.2 Hz, 2H), 4.34 (s, 2H), 4.23 (q, J = 6.9 Hz, 2H), 4.04 (t, J = 4.8 Hz, 2H), 3.69 (m, 2H), 3.1 (t, J = 6.3 Hz, 2H), 1.29 (t, J = 6.9 Hz, 3H).	ESI-MS m/z = 412 $(M+H)^+$;LC-MS purity: 91%.
5		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.62 (bs, 2H), 7.25 (m, 1H), 7.12 (m, 1H), 4.6 (t, J = 4.0 Hz, 2H), 3.95 (t, J = 4.4 Hz, 2H), 3.27 (s, 3H), 2.88 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 8.4 Hz, 2H).	ESI-MS m/z = 340 $(M+H)^+$;HPLC purity: 96%.
6		^{1}H NMR (300 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.9 (d, J = 9.0 Hz, 1H), 7.62 (bs, 2H), 7.35 (m, 2H), 4.6 (t, J = 4.2 Hz, 2H), 4.02 (t, J = 4.8 Hz, 2H), 3.56 (t, J = 6.3 Hz, 2H), 2.99 (m, 5H).	ESI-MS m/z = 340 $(M+H)^+$; LC-MS purity: 96.6 %.
7		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.62 (bs, 2H), 7.41-7.27 (m, 6H), 7.15 (s, 1H), 4.72 (s, 2H), 4.61 (t, J = 4.4 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H), 3.5 (t, J = 6.4 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H).	ESI-MS m/z = 416 $(M+H)^+$; HPLC purity: 97%.
8		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.9 (d, J = 9.2 Hz, 1H), 7.62 (bs, 2H), 7.35 (m, 2H), 4.6 (t, J = 4.0 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H), 3.55 (m, 2H), 3.44 (t, J = 6.8 Hz, 2H), 2.97 (t, J = 6.4 Hz, 2H), 1.58 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H).	ESI-MS m/z = 368 $(M+H)^+$; HPLC purity: 97%.

9		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.21 (m, 3H), 4.6 (t, J = 4.4 Hz, 2H), 3.96 (t, J = 4.4 Hz, 2H), 3.8 (t, J = 7.6 Hz, 2H), 2.86 (t, J = 6.8 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H), 1.55 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 368 $(M+H)^+$; HPLC purity: 99%.

Example 10: 6-(1-Allyl-2-benzyl-3-oxo-2,3-dihydro-1H-indazol-5-yl)-4-amino-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one

and

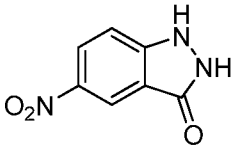
Example 11: 4-Amino-6-(3-oxo-1-propyl-2,3-dihydro-1H-indazol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:



Reagents and conditions: a) $NH_2NH_2.H_2O$, EtOH, 80 °C, 16h; b) Allyl bromide, KOH, NaOH, 100 °C, 3h; c) Benzyl bromide, NaH, DMF, RT, 16h; d) Fe/NH_4Cl, EtOH-H_2O, 85 °C, 3h; e) $Br(CH_2)_2OTBDMS$, CH_3CN, K_2CO_3, 80 °C, 24h; f) DCM, Et_3N, rt, 6h; g) 3%HCl-MeOH, RT, 1h; h) CH_3CN, Et_3N, 80 °C, 16h; i) NH_3, Dioxane, RT, 2h; j) 10% Pd/C, H_2, MeOH, RT, 2h.

Procedures:

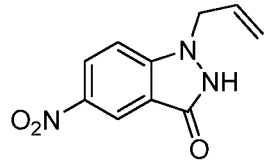
5-nitro-1H-indazol-3(2H)-one (11A):



Hydrazine hydrate (4 mL, 124 mmol) was added to a solution of 2-chloro-5-nitro benzoic acid (5 g, 24.8 mmol) in absolute ethanol (30 mL), and the resulting mixture was refluxed for 16 h. The reaction mixture was concentrated under reduced pressure. Residue was

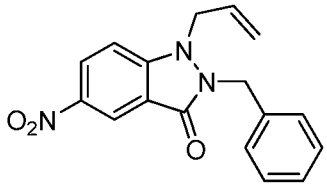
trituated with methanol to give 6.5 g of crude intermediate. 2N aq. HCl (40 mL) was added to the crude product, and the mixture was refluxed for 8 h. Reaction mixture was cooled to 0 °C, solids were collected via filtration, washed with cold water and dried under vacuum. Residue was purified by flash chromatography using 1% methanol in chloroform as eluent to afford title compound (2 g, 27%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 11.3 (bs, 1H), 8.67 (s, 1H), 8.12 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 7.5 (d, J = 9.0 Hz, 1H); ESI-MS *m/z*: 179 (M+H)$^+$.

1-Allyl-5-nitro-1H-indazol-3(2H)-one (11B):



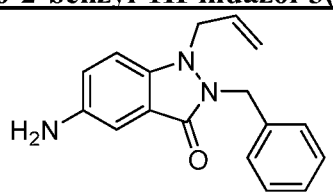
Allyl bromide (2.7 g, 22.34 mmol) was added to a mixture of product of Example 11A (4 g, 22.34 mmol) and 1N aqueous KOH solution (25 mL), and the mixture was refluxed for 2h. 15% NaOH (2 mL) and allyl bromide (0.54 mg, 0.04 mmol) were added, and again the mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and neutralized using 3N aqueous HCl solution. Resulting solids were collected via filtration, washed with water and dried under vacuum to afford title product (4.5 g, 92%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.5 (bs, 1H), 8.67 (s, 1H), 8.15 (dd, J_1 = 2.1 Hz, J_2 = 9.9 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 5.96 (m, 1H), 5.13 (m, 2H), 4.93 (d, J = 5.7 Hz, 2H).

1-Allyl-2-benzyl-5-nitro-1H-indazol-3(2H)-one (11C):



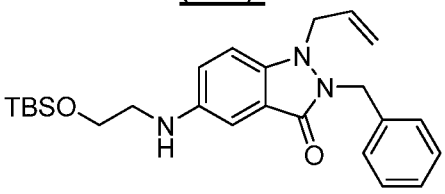
Sodium hydride (0.55 g, 13.68 mmol) was added portion wise to an ice cold solution of product of Example 11B (2.5 g, 11.4 mmol) in DMF (20 mL), and the mixture was stirred for 30 min. Benzyl bromide (3.9 g, 22.8 mmol) was now added slowly, and the mixture was stirred at room temperature for 16 h. The reaction was then cooled to 0 °C and quenched with ice water. The aqueous layer was extracted twice with ethyl acetate (2x50 mL). The combined organic layers were washed with water followed by brine solution, dried over sodium sulphate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography using 5% ethyl acetate in hexane as eluent to afford title compound (2.2 g, 62%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (d, J = 2.0 Hz, 1H), 8.23 (dd, J_1 = 2.0 Hz, J_2 = 9.2 Hz, 1H), 7.7 (d, J = 9.2 Hz, 1H), 7.5 (d, J = 5.7 Hz, 2H), 7.4 (m, 3H), 5.98 (m, 1H), 5.44 (s, 2H), 5.2 – 5.07 (m, 2H), 4.98 (d, J = 5.2 Hz, 2H).

1-Allyl-5-amino-2-benzyl-1H-indazol-3(2H)-one (11D):



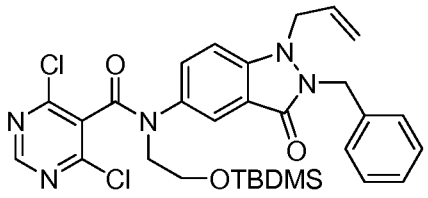
Iron powder (0.77 g, 14.22 mmol) was added to a solution of product of Example 11C (2.2 g, 7.11 mmol) in 80 mL of ethanol-water mixture (4:1) followed by NH_4Cl (0.19 g, 3.55 mmol), and the mixture was refluxed for 4 h. The solvent was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, filtered and removed in vacuo. Residue was purified by flash chromatography using 20% ethyl acetated in hexane as eluent to afford title compound as solid (1.6 g, 66%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.5 (m, 2H), 7.39 (m, 3H), 7.19 (d, J = 8.4 Hz, 1H), 6.81 (dd, J_1 = 2.1 Hz, J_2 = 9.3 Hz, 1H), 6.64 (m, 1H), 5.9 (m, 1H), 5.3 (s, 2H), 5.06 (m ,2H), 4.73 (m, 2H); ESI-MS m/z = 280 $(M+H)^+$.

1-Allyl-2-benzyl-5-(2-(tert-butyldimethylsilyloxy)ethylamino)-1H-indazol-3(2H)-one (11E):



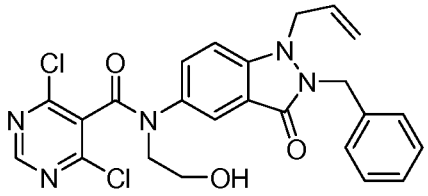
Potassium carbonate (2.6 g, 19.32 mmol) was added to a mixture of (2-bromoethoxy)(tert-butyl)dimethylsilane (0.92 g, 3.87 mmol) and product of Example 11D (0.9 g, 3.22 mmol) in acetonitrile (70 mL), and the mixture was refluxed for 24 h. Reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. Separated organic layer was washed with brine solution, dried over sodium sulfate, filtered and concentrated under vacuum. Residue was purified by flash chromatography using 15% ethyl acetate in hexane as eluent to afford title compound (0.35 g, 25%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (m, 2H), 7.34 (m, 3H), 7.21 (d, J = 8.8 Hz, 1H), 6.84 (dd, J_1 = 2.0 Hz, J_2 = 9.6 Hz, 1H), 6.49 (d, J = 1.6 Hz, 1H), 5.86 (m, 1H), 5.28 (s, 2H), 5.21 (t, J = 6.0 Hz, 1H), 5.05 (m, 2H), 4.72 (d, J = 5.2 Hz, 2H), 3.69 (t, J = 6.4 Hz, 2H), 3.11 (q, J = 5.6 Hz, 2H), 0.82 (s, 9H), 0.03 (s ,6H).

N-(1-Allyl-2-benzyl-3-oxo-2,3-dihydro-1H-indazol-5-yl)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-4,6-dichloropyrimidine-5-carboxamide (11F):



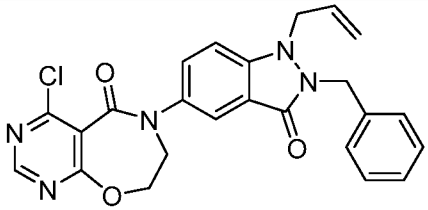
To a stirred, cooled (0 °C) solution of product of 11E (0.55 g, 1.23 mmol) and TEA (0.5 g, 5.0 mmol) in DCM (12 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.26 g, 1.23 mmol) in DCM (5 mL). After 6 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 12% ethyl acetate in hexane as eluent to afford title compound (0.35 g, 46%) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.75 (s, 1H), 7.75 (s, 1H), 7.46 (m, 3H), 7.36 (m, 4H), 5.94 (m, 1H), 5.34 (s, 2H), 5.08 (m, 1H), 4.96 (m ,1H), 4.82 (m, 2H), 4.0 (m, 2H), 3.77 (t, J = 4.8 Hz, 2H), 0.8 (s, 9H), 0.01 (s, 6H); ESI-MS m/z = 611 $(M+H)^+$.

N-(1-Allyl-2-benzyl-3-oxo-2,3-dihydro-1H-indazol-5-yl)-4,6-dichloro-N-(2-hydroxyethyl)pyrimidine-5-carboxamide (11G):



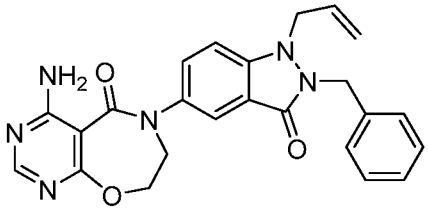
A solution of product of Example 11F (0.35 g, 0.57 mmol) in a methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 1 h. Methanol was removed in vacuo. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.25 g, 88%) as an oil, which was carried on to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.75 (s, 1H), 7.75 (s, 1H), 7.46 (m, 3H), 7.36 (m, 4H), 5.94 (m, 1H), 5.34 (s, 2H), 5.12 (m, 1H), 5.03 (m ,1H), 4.86 (m, 2H), 3.9 (t, J = 6.0 Hz, 2H), 3.77 (t, J = 4.8 Hz, 2H); ESI-MS m/z = 498 $(M+H)^+$.

6-(1-Allyl-2-benzyl-3-oxo-2,3-dihydro-1H-indazol-5-yl)-4-chloro-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (11H):



A slurry of product of Example 11G (0.25 g, 0.5 mmol) and TEA (0.22 g, 2.2 mmol) in acetonitrile (20 mL) was stirred at 80 °C for 16 h. The reaction was cooled, concentrated in vacuo, and diluted with ethyl acetate. The organic layer was washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.22 g, 94%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.8 (s, 1H), 7.68 (s, 1H), 7.55 (m, 3H), 7.38 (m, 4H), 5.94 (m, 1H), 5.4 (s, 2H), 5.17 (m, 1H), 5.05 (m, 1H), 4.93 (d, J = 4.8 Hz, 2H), 4.76 (t, J = 4.0 Hz, 2H), 4.15 (t, J = 4.8 Hz, 2H); ESI-MS m/z = 462 $(M+H)^+$.

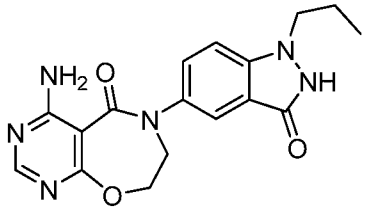
6-(1-Allyl-2-benzyl-3-oxo-2,3-dihydro-1H-indazol-5-yl)-4-amino-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (10):



A solution of product of Example 11H (0.22 g, 0.46 mmol) in 0.5M ammonia in p-dioxane (40 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo and diluted with ethyl acetate. The organic layer was washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.17 g, 82%) as an white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.62 (s, 1H), 7.55 (m, 3H), 7.38 (m, 4H), 7.19 (bs,

2H), 5.97 (m, 1H), 5.39 (s, 2H), 5.16 (m, 1H), 5.09 (m, 1H), 4.91 (d, J = 5.6 Hz, 2H), 4.65 (t, J = 4.4 Hz, 2H), 3.98 (t, J = 4.4 Hz, 2H); LC-MS purity: 94%, m/z = 443 $(M+H)^+$.

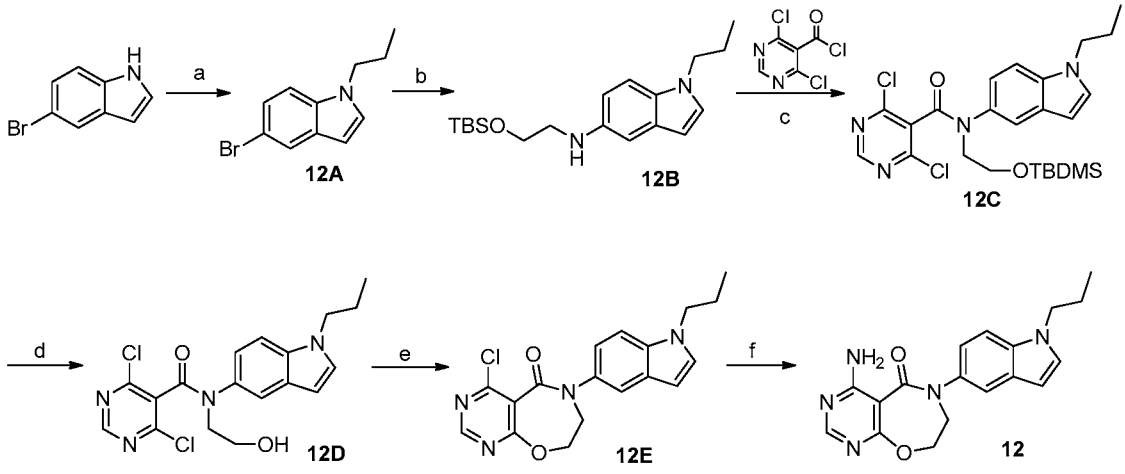
4-Amino-6-(3-oxo-1-propyl-2,3-dihydro-1H-indazol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (11):



Excess 10% Pd/C (0.15 g) was added to a solution of product of Example 10 (0.15 g, 0.226 mmol) in 120 mL of methanol, and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered over celite bed, filtrate was concentrated under reduced pressure, and the residue partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was triturated with ethyl acetate to afford title compound (0.09 g, 75%) as brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.5 (bs, 1H), 8.17 (s, 1H), 7.63 (bs, 2H), 7.56 (m, 1H), 7.51 (d, J = 9.3 Hz, 1H), 7.3 (dd, J_1 = 1.2 Hz, J_2= 9.0 Hz, 1H), 4.63 (t, J = 4.2 Hz, 2H), 4.1 (t, J = 7.2 Hz, 2H), 3.98 (t, J = 4.2 Hz, 2H), 1.76 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H); HPLC purity: 95%, ESI-MS m/z = 355 $(M+H)^+$.

–

Example 12: 4-Amino-6-(1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

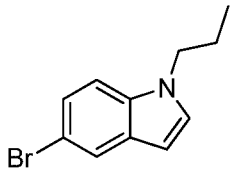


Reagents and conditions: a) n-propyl bromide, Cs_2CO_3, DMF, 100 °C, 2h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C, 2.5h; c) DCM, Et_3N, RT, 1h; d) 3%HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxane, RT, 2h.

Procedures:

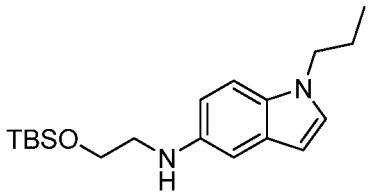
4-Amino-6-(1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

5-bromo-1-propyl-1H-indole (12A):



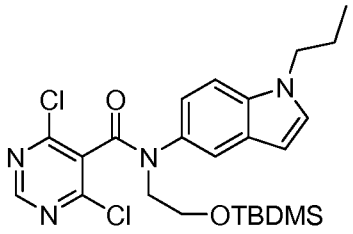
1-Bromopropane (1.25 g, 10.2 mmol) was added to a solution of 5-bromo indole (2 g, 10.2 mmol) in DMF (30 mL) followed by cesium carbonate (6.63 g, 20.4 mmol), and the mixture was stirred at 100 °C for 2 h. Insoluble solids were filtered off, and filtrate was concentrated. Residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 5% ethyl acetate in hexane as eluent to afford title compound (1.8 g, 74%) as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 1.6 Hz, 1H), 7.28 (m, 1H), 7.20 (m, 1H), 7.09 (d, J = 3.2 Hz, 1H), 6.41 (d, J = 2.4 Hz, 1H), 4.05 (t, J = 7.2 Hz, 2H), 1.87 (m, 2H), 0.9 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 238 $(M+H)^+$.

N-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-propyl-1H-indol-5-amine (12B):



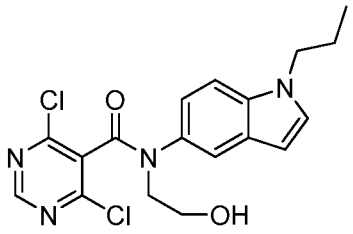
A mixture of product of Example 12A (2 g, 8.4 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (1.5 g, 8.4 mmol), cesium carbonate (4.09 g, 12.6 mmol), palladium acetate (0.18 g, 0.84 mmol) and X-PHOS (0.4 g, 0.84 mmol) in Toluene (25 mL) under Argon was refluxed at 120 °C for 2.5 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (1.5 g, 53%) as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J = 8.8 Hz, 1H), 7.0 (d, J = 2.8 Hz, 1H), 6.86 (d, J = 2.08 Hz, 1H), 6.68-6.65 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.30 (d, J = 3.2 Hz, 1H), 4.01 (t, J = 7.2 Hz, 2H), 3.85 (t, J = 5.6 Hz, 2H), 3.25 (t, J = 5.2 Hz, 2H), 1.86-1.81 (m, 2H), 0.93 (t, J = 5.6 Hz, 3H), 0.91 (s, 9H), 0.07(s, 6H); ESI-MS m/z = 333 $(M+H)^+$.

N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(1-propyl-1H-indol-5-yl)pyrimidine-5-carboxamide (12C):



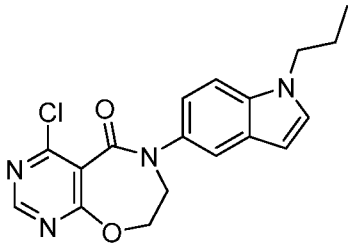
To a stirred, cooled (0 °C) solution of product of Example 12B (1.5 g, 4.51 mmol) and TEA (1.82 g, 18 mmol) in DCM (30 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.95 g, 4.5 mmol) in DCM (5 mL). After 1 h, the reaction was concentrated in vacuo, diluted into ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 12% ethyl acetate in hexane as eluent to afford title compound (1 g, 43%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.66 (m, 1H), 7.21-7.13 (m, 2H), 7.09 (d, J = 3.6 Hz, 1H), 6.39 (d, J = 3.2 Hz, 1H), 4.06 (t, J = 6.4 Hz, 2H), 4.01 (t, J = 7.2 Hz, 2H), 3.91 (t, J = 5.6 Hz, 2H), 1.84-1.78 (m, 2H), 0.94 (t, J = 8.0 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ESI-MS m/z = 507 $(M+H)^+$.

4,6-Dichloro-N-(2-hydroxyethyl)-N-(1-propyl-1H-indol-5-yl)pyrimidine-5-carboxamide (12D):



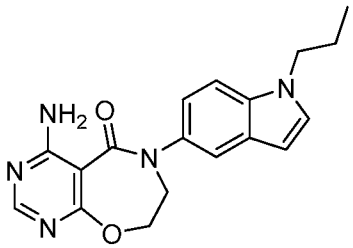
A solution of product of Example 12C (1 g, 1.97 mmol), in 15 mL of methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 1 h. Methanol was removed in vacuo, the residue dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.6 g, 77%) as solid, which was carried on to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 (s, 1H), 7.65 (s, 1H), 7.17 (m, 2H), 7.11 (d, J = 2.8 Hz, 1H), 6.42 (d, J = 2.8 Hz, 1H), 4.15 (t, J = 5.2 Hz, 2H), 4.02 (t, J = 6.8 Hz, 2H), 3.93 (q, J = 4.8 Hz, 2H), 1.84-1.77 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H); ESI-MS m/z = 393 $(M+H)^+$.

4-Chloro-6-(1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (12E):



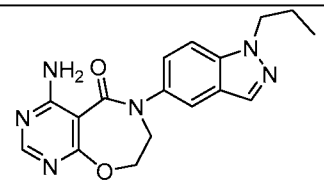
A slurry of product of Example 12D (0.6 g, 1.68 mmol) and TEA (1.36 g, 13.44 mmol) in acetonitrile (25 mL) was stirred at 80 °C for 16 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.3 g, 55%) as a white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.82 (s, 1H), 7.57 (m, 2H), 7.46 (d, J = 3.0 Hz, 1H), 7.13 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 6.48 (d, J = 3.0 Hz, 1H), 4.75 (t, J = 4.5 Hz, 2H), 4.16 (m, 4H), 1.82 (m, 2H), 0.84 (t, J = 7.5 Hz, 3H); ESI-MS m/z = 357 $(M+H)^+$.

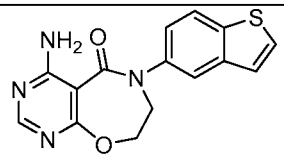
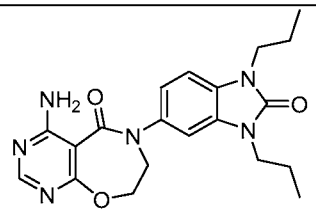
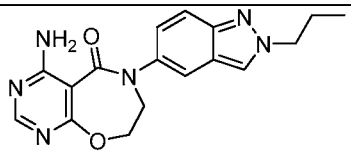
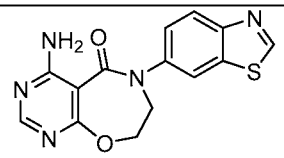
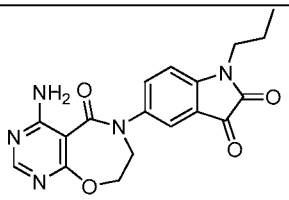
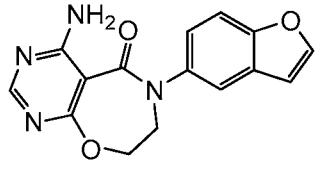
4-Amino-6-(1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (12):

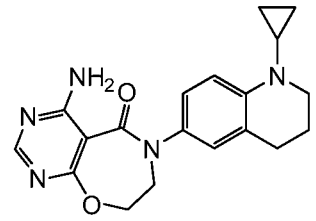
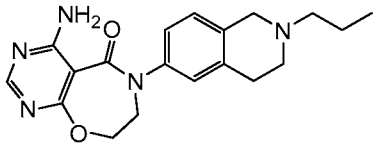
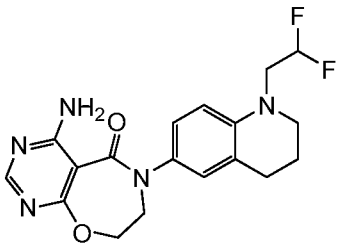
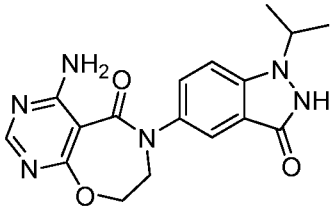
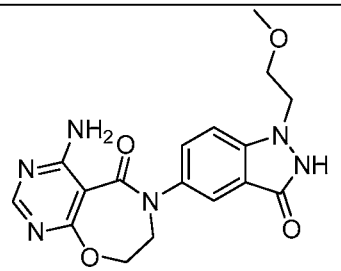


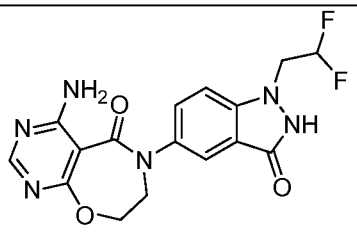
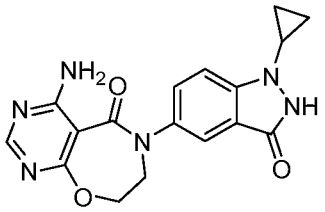
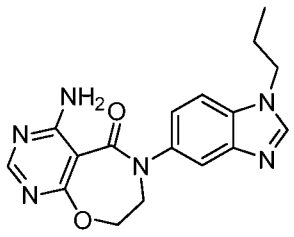
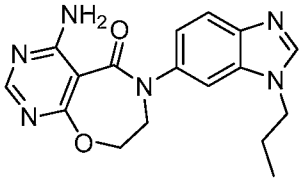
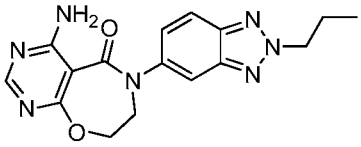
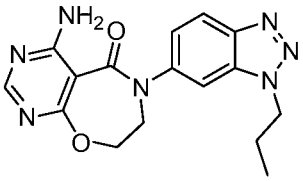
A solution of product of Example 12E (0.3 g, .84 mmol) in 0.5M ammonia in p-dioxane (15 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.2 g, 71%) as an white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.52 (s, 1H), 7.5 (m, 1H), 7.42 (d, J = 3.2 Hz, 1H), 7.09 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 4.63 (t, J = 3.6 Hz, 2H), 4.15 (t, J = 6.8 Hz, 2H), 3.98 (t, J = 4.4 Hz, 2H), 1.76 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 338 $(M+H)^+$; HPLC purity: 92.5%.

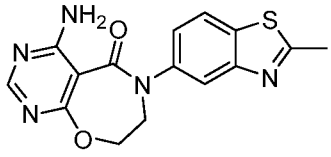
Examples 13 – 31 were prepared by the method described above for Example 12 or routine variations thereof using appropriately substituted starting materials.

Ex	Structure	Analytical Data	Mass/Purity
13		^{1}H NMR (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.08 (s, 1H), 7.74 (m, 2H), 7.6 (bs, 2H), 7.38 (d, J = 1.8 Hz, 1H), 4.65 (t, J = 4.2 Hz, 2H), 4.39 (t, J = 6.9 Hz, 2H), 4.01 (t, J = 4.5 Hz, 2H),	ESI-MS m/z = 339 $(M+H)^+$; HPLC purity: 99%.

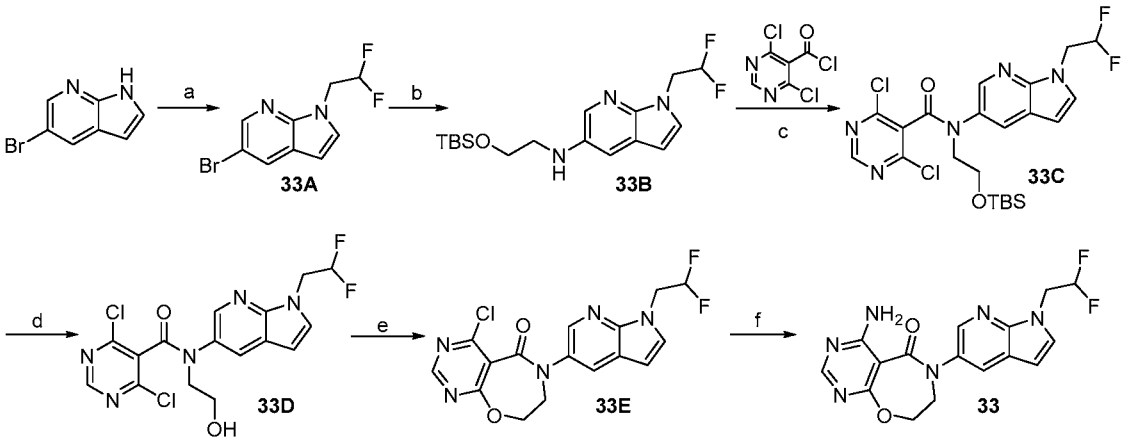
		1.9-1.83 (m, 2H), 0.82 (t, J = 7.5 Hz, 3H).	
14		^{1}H NMR (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.9 (m, 1H), 7.84 (d, J = 5.7 Hz, 1H), 7.64 (bs, 2H), 7.47 (d, J = 5.4 Hz, 1H), 7.38 (dd, J_1 = 2.1 Hz, J_2= 8.7 Hz, 1H), 4.65 (t, J = 4.2 Hz, 2H), 4.04 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 313 $(M+H)^+$. HPLC purity: 94%,
15		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.62 (bs, 2H), 7.24 (m, 2H), 7.02 (d, J = 7.6 Hz, 1H), 4.63 (m, 2H), 3.97 (m, 2H), 3.83-3.56 (q, J = 7.2 Hz, 4H), 1.68-1.65 (m, 4H), 0.86 (t, J = 6.8 Hz, 6H).	ESI-MS m/z = 397 $(M+H)^+$; LCMS purity: 98%.
16		^{1}H NMR (300MHz, DMSO-d_6): δ 8.4 (s, 1H), 8.17 (s, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.19 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 7.15 (bs, 2H), 4.64 (t, J = 4.2 Hz, 2H), 4.39 (t, J = 7.2 Hz, 2H), 4.0 (t, J = 4.2 Hz, 2H), 2.0 (m, 2H), 0.83 (t, J = 7.5 Hz, 3H).	ESI-MS m/z = 339 $(M+H)^+$; HPLC purity: 96%.
17		^{1}H NMR (300MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.23 (d, J = 1.5 Hz, 1H), 8.19 (s, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.9 (bs, 2H), 7.57 (dd, J_1 = 1.8 Hz, J_2= 8.7 Hz, 1H), 4.66 (t, J = 4.5 Hz, 2H), 4.07 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 314 $(M+H)^+$; HPLC purity: 96%.
18		^{1}H NMR (300MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.66 (bs, 2H), 7.63 (m, 2H), 7.26 (d, J = 8.1 Hz, 1H), 4.64 (t, J = 4.5 Hz, 2H), 3.97 (t, J = 4.5 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 1.64 (m, 2H), 0.92 (t, J = 7.2 Hz, 2H).	ESI-MS m/z = 368 $(M+H)^+$; HPLC purity: 93%.
19		^{1}H NMR (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.66-7.63 (m, 3H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.4Hz, 1H), 7.1 (bs, 2H), 4.65 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 4.8 Hz, 2H).	ESI-MS m/z: 297 $(M+H)^+$; HPLC purity: 97%.

20		^{1}H NMR (300MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.57 (bs, 2H), 7.04 (d, J = 8.7 Hz, 1H), 7.0 (dd, J_1 = 2.4 Hz, J_2 = 8.7 Hz, 1H), 6.89 (d, J = 2.7 Hz, 1H), 4.57 (t, J = 4.8 Hz, 2H), 3.88 (t, J = 4.5 Hz, 2H), 3.20 (t, J = 5.4 Hz, 2H), 2.67 (t, J = 6.3 Hz, 2H), 2.28 (m, 1H), 1.84 (m, 2H), 0.80 (m, 2H), 0.53 (m, 2H).	ESI-MS m/z = 352 $(M+H)^+$; HPLC purity: 99.2%.
21		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.24 (m, 3H), 4.60 (m, 2H), 4.12 (s, 2H), 3.97 (m, 2H), 3.31-3.25 (m, 2H), 3.0 (m, 2H), 2.82 (m, 2H), 1.73 (m, 2H), 0.84 (t, J = 6.8 Hz, 3H).	ESI-MS m/z = 354 $(M+H)^+$; HPLC purity: 95%.
22		^{1}H NMR (400MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.58 (bs, 2H), 6.94 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.21 (tt, J_1 = 4.0 Hz, J_2 = 55.2 Hz, 1H), 4.56 (t, J = 4.8 Hz, 2H), 3.87 (t, J = 4.4 Hz, 2H), 3.70 (dt, J_1 = 3.6 Hz, J_2 = 15.6 Hz, 2H), 3.37 (m, 2H), 2.70 (t, J = 6.0 Hz, 2H), 1.85 (m, 2H).	ESI-MS m/z = 376 $(M+H)^+$; HPLC purity: 98.24%.
23		^{1}H NMR (400MHz, DMSO-D_2O): δ 8.18 (s, 1H), 7.56 (d, J = 1.2 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.28 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 4.76 (m, 1H), 4.64 (t, J = 4.8 Hz, 2H), 3.99 (t, J = 4.4 Hz, 2H), 1.38 (d, J = 6.8 Hz, 6H).	ESI-MS m/z = 354 $(M+H)^+$; HPLC purity: 96.4%.
24		^{1}H NMR (300MHz, DMSO-d_6): δ 10.65 (bs, 1H), 8.17 (s, 1H), 7.64 (bs, 2H), 7.55 (s, 1H), 7.49 (d, J = 9.3 Hz, 1H), 7.29 (m, 1H), 4.63 (m, 2H), 4.30 (m, 2H), 3.99 (m, 2H), 3.66 (m, 2H), 3.19 (s, 3H).	ESI-MS m/z = 370 $(M+H)^+$; HPLC purity: 95.2%.

25		^{1}H NMR (300MHz, DMSO-d_6): δ 10.85 (bs, 1H), 8.17 (s, 1H), 7.64 (bs, 2H), 7.6-7.56 (m, 2H), 7.37 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 6.50 (tt, J_1 = 3.3 Hz, J_2 = 54.9 Hz, 1H), 4.74-4.58 (m, 4H), 4.0 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 377 $(M+H)^+$; HPLC purity: 97%.
26		^{1}H NMR (300MHz, DMSO-d_6): δ 10.85 (bs, 1H), 8.17 (s, 1H), 7.63 (bs, 2H), 7.58 (d, J = 1.5 Hz, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.32 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 4.61 (t, J = 3.9 Hz, 2H), 3.96 (t, J = 4.2 Hz, 2H), 3.38 (m, 1H), 0.99 (d, J = 5.4 Hz, 4H).	ESI-MS m/z = 353 $(M+H)^+$, HPLC purity: 93%.
27		^{1}H NMR (400MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.18 (s, 1H), 7.7-7.6 (m, 4H), 7.23 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 4.66 (t, J = 4.4 Hz, 2H), 4.20 (t, J = 6.8 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H), 1.81 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 337 $(M+H)^+$; LCMS purity: 95%.
28		^{1}H NMR (400MHz, DMSO-d_6): δ 8.28 (s, 1H), 8.18 (s, 1H), 7.7-7.6 (m, 4H), 7.18 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 4.66 (t, J = 4.4 Hz, 2H), 4.2 (t, J = 6.8 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H), 1.81 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 339 $(M+H)^+$; LCMS purity: 99%.
29		^{1}H NMR (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.97-7.93 (m, 2H), 7.67 (bs, 2H), 7.44 (dd, J_1 = 1.8 Hz, J_2 = 9.3 Hz, 1H), 4.72 (t, J = 6.9 Hz, 2H), 4.66 (t, J = 4.2 Hz, 2H), 4.06 (t, J = 4.5 Hz, 2H), 2.04 (m, 2H), 0.86 (t, J = 7.5 Hz, 3H).	ESI-MS m/z = 340 $(M+H)^{+-}$; HPLC Purity: 98%.
30		^{1}H NMR (400MHz, DMSO-d_6): δ 8.19 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.66 (bs, 2H), 7.43 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 4.67 (m, 4H), 4.09 (t, J = 4.4 Hz, 2H), 1.95 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H).	ESI-MS m/z = 340 $(M+H)^{+-}$; HPLC Purity: 97%.

31		^{1}H NMR (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.65 (bs, 2H), 7.42 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 4.66 (t, J = 4.4 Hz, 2H), 4.05 (t, J = 4.4 Hz, 2H), 2.82 (s, 3H).	ESI-MS m/z = 328 $(M+H)^+$; HPLC purity: 92%.

Example 33: 4-Amino-6-(1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

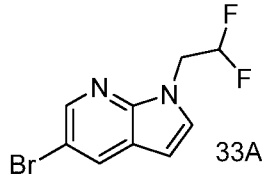


Reagents and conditions: a) 1,1-Difluoro-2-iodoethane, Cs_2CO_3, DMF, 70 °C, 1h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 110 °C, 3h; c) DCM, Et_3N, RT, 1h; d) 3% HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 70 °C, 4h; f) NH_3, Dioxane, RT, 2h.

Procedures:

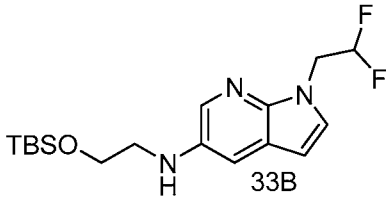
4-Amino-6-(1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

5-Bromo-1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridine (33A):



1,1-Difluoro-2-iodoethane (2.19 g, 11.42 mmol) was added to a solution of 5-bromo,7-azaindole (1.5 g, 7.61 mmol) in DMF (30 mL) followed by cesium carbonate (4.96 g, 15.2 mmol), and the mixture was stirred at 70 °C for 1 h. Insoluble solids were filtered off, and filtrate was concentrated. Residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in reduced pressure and purified by flash chromatography using 5% ethyl acetate in hexane to afford title compound (1.3 g, 65%) as oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, J = 2.1 Hz, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 2.1 Hz, 1H), 6.46 (d, J = 3.6 Hz, 1H), 6.28-5.88 (tt, J_1 = 3.9 Hz, J_2 = 55.8 Hz, 1H), 4.60 (dt, J_1 = 4.2 Hz, J_2 = 14.1 Hz, 2H).

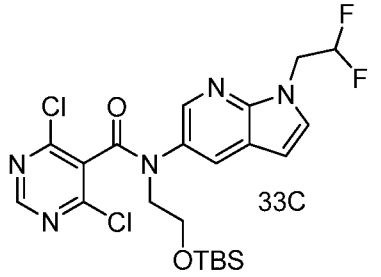
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-amine (33B):



33B

A mixture of product of Example 33A (1.3 g, 8.4 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (1.0 g, 5.98 mmol), cesium carbonate (3.24 g, 9.96 mmol), palladium acetate (0.11 g, 0.49 mmol) and X-PHOS (0.23 g, 0.49 mmol) in toluene (25 mL) under Argon was refluxed at 110 °C for 3 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.61 g, 34.5%) as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 3.2 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 6.23-5.92 (tt, J_1 = 4.4 Hz, J_2 = 55.6 Hz, 1H), 4.54 (dt, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 2H), 3.94 (bs, 1H), 3.85 (t, J = 5.6 Hz, 2H), 3.25 (t, J = 4.8 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 6H).

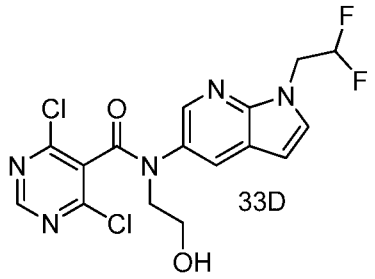
N-**(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidine-5-carboxamide (33C):**



33C

To a stirred, cooled (0 °C) solution of product of Example 33B (0.61 g, 1.71 mmol) and TEA (0.52 g, 5.15 mmol) in DCM (25 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.43 g, 2.05 mmol) in DCM (5 mL). After 1 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 12% ethyl acetate in hexane as eluent to afford title compound (0.67 g, 73%) as a syrup. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 6.45 (d, J = 3.9 Hz, 1H), 6.24-5.84 (tt, J_1 = 4.2 Hz, J_2 = 55.5 Hz, 1H), 4.55 (dt, J_1 = 4.2 Hz, J_2 = 14.1 Hz, 2H), 4.06 (t, J = 5.1 Hz, 2H), 3.94 (t, J = 4.8 Hz, 2H), 0.86 (s, 9H), 0.058 (s, 6H).

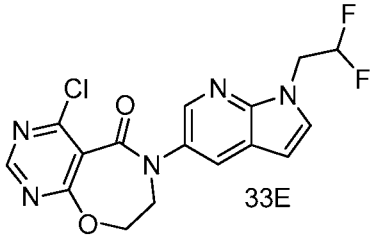
4,6-Dichloro-N-(1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-hydroxyethyl)pyrimidine-5-carboxamide (33D):



33D

A solution of product of Example 33C (0.67 g, 1.26 mmol), in 20 mL of methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 1 h. Methanol was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in reduced pressure to afford title compound (0.4 g, 76%) as solid, which was carried to the next step without further purification. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 6.49 (d, J = 3.6 Hz, 1H), 6.25-5.85 (tt, J_1 = 4.2 Hz, J_2 = 55.5 Hz, 1H), 4.56 (dt, J_1 = 4.2 Hz, J_2 = 14.1 Hz, 2H), 4.14 (t, J = 4.8 Hz, 2H), 3.96 (t, J = 4.8 Hz, 2H).

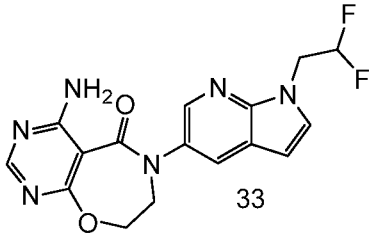
4-Chloro-6-(1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (33E):



33E

A slurry of product of Example 33D (0.4 g, 0.96 mmol) and TEA (0.19 g, 1.92 mmol) in acetonitrile (20 mL) was stirred at 70 °C for 4 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in reduced pressure to afford title compound (0.3 g, 82%) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.33 (d, J = 2.4 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 3.9 Hz, 1H), 6.57 (d, J = 3.6 Hz, 1H), 6.31-5.91 (tt, J_1 = 3.9 Hz, J_2 = 56.1 Hz, 1H), 4.81 (t, J = 4.5 Hz, 2H), 4.66 (dt, J_1 = 3.9 Hz, J_2 = 13.8 Hz, 2H), 4.10 (t, J = 4.8 Hz, 2H).

4-Amino-6-(1-(2,2-difluoroethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (33):

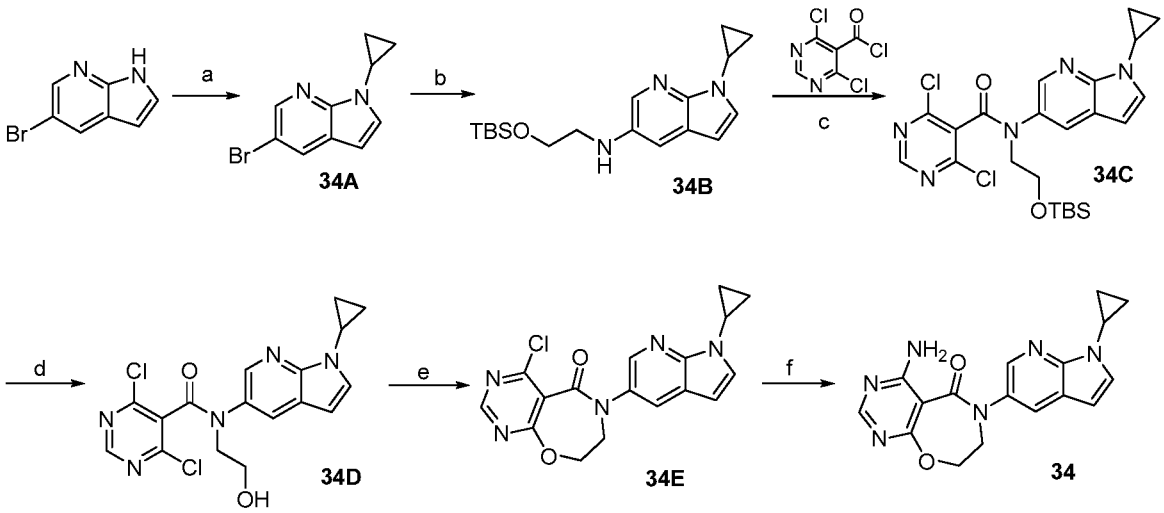


33

A solution of product of Example 33E (0.3 g, 0.79 mmol) in 0.5M ammonia in p-dioxane (15 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in

vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in reduced pressure to afford title compound (0.25 g, 86%) as an off-white solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.20 (bs, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 3.3 Hz, 1H), 6.55 (d, J = 3.6 Hz, 1H), 6.31-5.91 (tt, J_1 = 4.5 Hz , J_2 = 55.8 Hz, 1H), 5.67 (bs, 1H), 4.75 (t, J = 4.5 Hz, 2H), 4.65 (dt, J_1 = 3.9 Hz, J_2 = 13.8 Hz, 2H), 4.07 (t, J = 4.5 Hz, 2H) ; ESI-MS m/z = 361 $(M+H)^+$. HPLC purity: 98.14%.

Example 34: 4-Amino-6-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

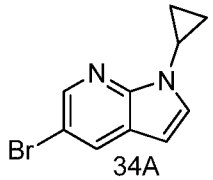


Reagents and conditions: a) Cyclopropyl boronic acid, 2,2'-bipyridine, Na_2CO_3, $Cu(OAc)_2$, DCE, 110 °C, 8h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C, 2.5h; c) DCM, Et_3N, RT, 1h; d) TBAF, THF, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxane, RT, 2h.

Procedures:

4-Amino-6-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

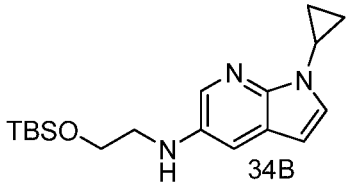
5-Bromo-1-cyclopropyl-1H-pyrrolo[2,3-b]pyridine (34A):



Cyclopropylboronic acid (0.872 g, 10.15 mmol) was added to a solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine (1 g, 5.08 mmol), Na_2CO_3 (1.076 g, 10.15 mmol), copper(II)acetate (0.922 g, 5.08 mmol) and 2,2'-bipyridine (0.793 g, 5.08 mmol) in dichloroethane (20 mL), and the mixture was stirred at 110 °C for 8h. The reaction mixture was concentrated, and then diluted with ethyl acetate and water. Organic layer was separated, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in reduced pressure and purified by flash chromatography using 10% ethyl acetate in pet ether to afford title compound (0.38 g, 31.3%) as oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (d, J = 2.1 Hz, 1H),

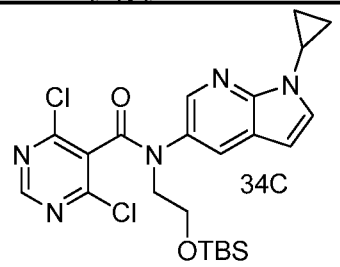
7.99 (d, J = 2.1 Hz, 1H), 7.20 (d, J = 3.3 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 3.5 (m, 1H), 1.15 (m, 2H), 1.03 (m, 2H).

N-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-amine (34B):



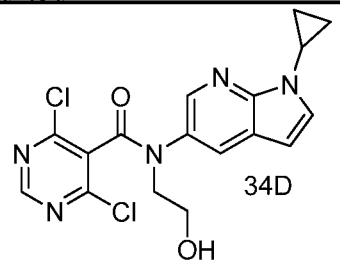
A mixture of product of Example 34A (0.38 mg, 1.603 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.337 g, 1.923 mmol), cesium carbonate (0.783 g, 2404 mmol), palladium acetate (0.036 g, 0.160 mmol) and X-PHOS (0.076 g, 0.160 mmol) in Toluene (15 mL) under Argon was refluxed at 120 °C for 12 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x5 mL) and saturated aqueous brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in reduced pressure and purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.25 g, 40.5%) as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.8 Hz, 1H), 7.10 (d, J = 3.6 Hz, 1H), 6.22 (d, J = 3.2 Hz, 1H), 3.84 (t, J = 5.2 Hz, 2H), 3.46 (m, 1H), 3.24 (t, J = 5.2 Hz, 2H), 1.1 (m, 2H), 1.01 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H).

N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidine-5-carboxamide (34C):



To a stirred, cooled (0 °C) solution of product of Example 34B (0.25 g, 0.754 mmol) and TEA (0.315 mL, 2.262 mmol) in DCM (10 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.191 g, 0.905 mmol) in DCM (5 mL). After 1 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x5 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 12% ethyl acetate in pet ether to afford title compound (0.25 g, 60.2%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.37 (s, 1H), 8.0 (s, 1H), 7.22 (d, J = 3.6 Hz, 1H), 6.33 (d, J = 3.2 Hz, 1H), 4.05 (t, J = 5.6 Hz, 2H), 3.92 (t, J = 5.2 Hz, 2H), 3.45 (m, 1H), 1.13 (m, 2H), 1.0 (m, 2H), 0.86 (s, 9H), 0.05 (s, 6H).

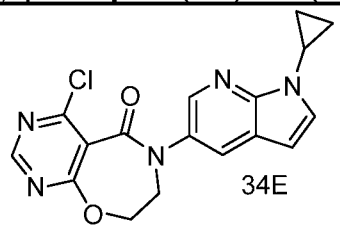
4,6-Dichloro-N-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(2-hydroxyethyl)pyrimidine-5-carboxamide (34D):



34D

TBAF (0.387 g, 1.481 mmol) was added to a solution of Example 34C (0.25 g, 0.494 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 1 h. THF was removed in vacuo, the residue dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.19 g, 91%) as solid, which was carried on to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.42 (s, 1H), 7.97 (s, 1H), 7.24 (d, J = 3.2 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.15 (m, 2H), 3.97 (q, J = 4.8 Hz, 2H), 3.45 (m, 1H), 2.11 (t, J = 5.2 Hz, 1H), 1.12 (m, 2H), 1.01 (m, 2H).

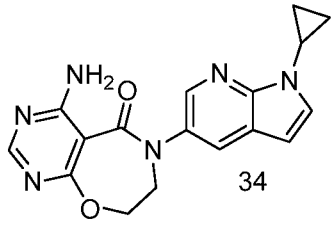
4-Chloro-6-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (34E):



34E

A slurry of product of Example 34D (0.19 g, 0.484 mmol) and TEA (0.203 mL, 1.453 mmol) in acetonitrile (15 mL) was stirred at 80 °C for 6 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.17 g, 98%) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.36 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 3.9 Hz, 1H), 6.45 (d, J = 3.3 Hz, 1H), 4.8 (t, J = 4.8 Hz, 2H), 4.09 (t, J = 4.5 Hz, 2H), 3.56 (m, 1H), 1.16 (m, 2H), 1.08 (m, 2H).

4-Amino-6-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (34):

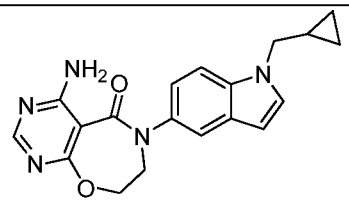
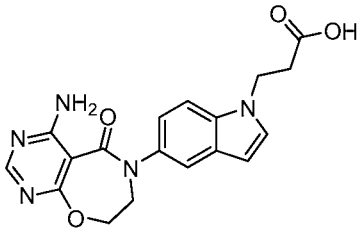
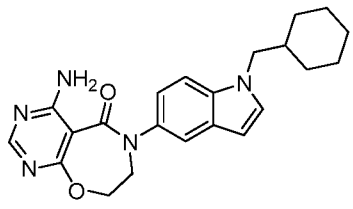
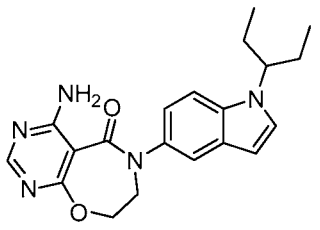


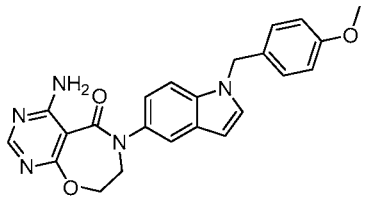
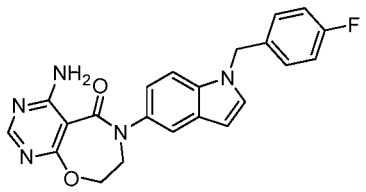
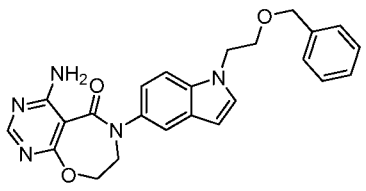
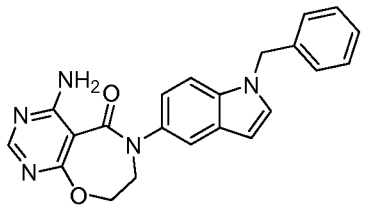
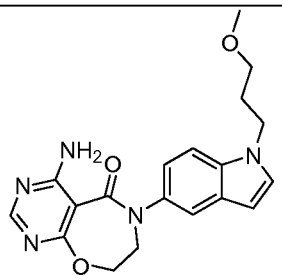
34

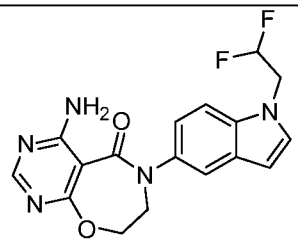
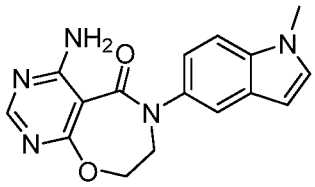
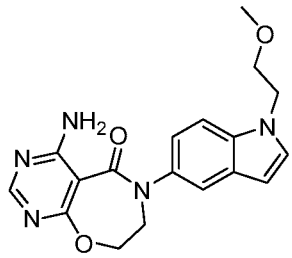
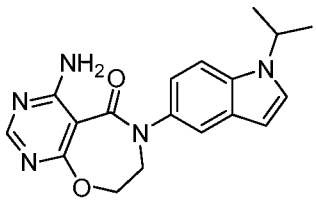
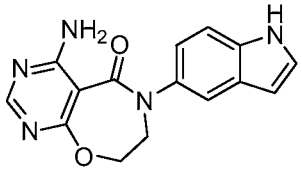
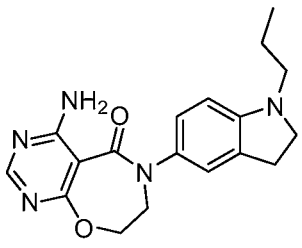
A solution of product of Example 34E (0.17 g, 0.478 mmol) in 0.5M ammonia in p-dioxane (15 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated

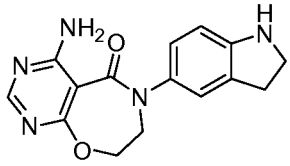
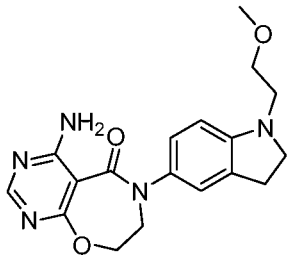
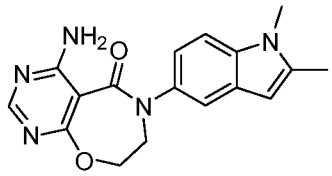
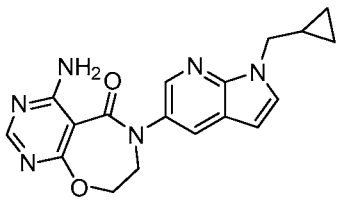
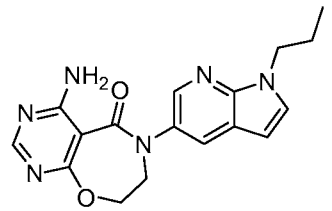
in vacuo to afford title compound (0.1 g, 60.4%) as an white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.26 (d, J = 2.1 Hz, 1H), 8.18 (s, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.65 (bs, 2H), 7.54 (d, J = 3.6 Hz, 1H), 6.46 (d, J = 3.3 Hz, 1H), 4.67 (t, J = 3.6 Hz, 2H), 4.02 (t, J = 4.2 Hz, 2H), 3.62 (m, 1H), 1.1-1.0 (m, 4H); ESI-MS m/z = 337 $(M+H)^+$; HPLC purity: 97%.

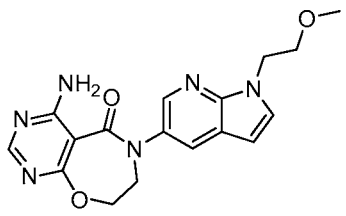
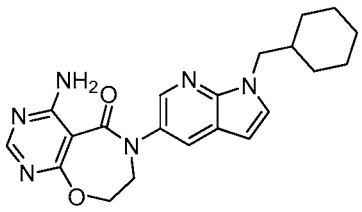
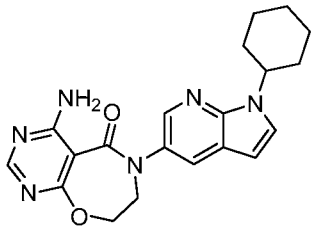
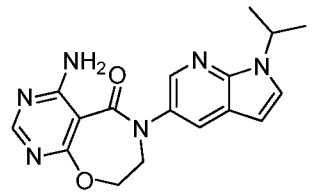
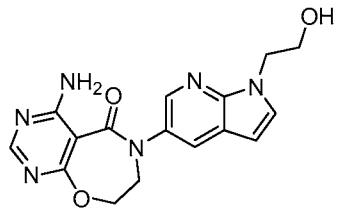
Examples 35 – 62 were prepared by the procedures analogous to those described in Example 33 or Example 34 using appropriately substituted starting materials.

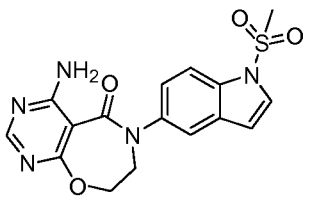
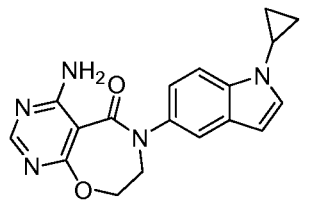
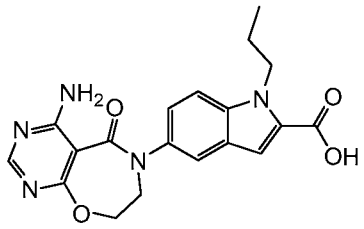
Ex	Structure	Analytical Data	Mass/Purity
35		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.49 (m, 2H), 7.08 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 2H), 6.52 (d, J = 3.2 Hz, 1H), 4.64 (t, J = 4.4 Hz, 2H), 4.06 (d, J = 6.8 Hz, 2H), 3.98 (t, J = 4.8 Hz, 2H), 1.25 (m, 1H), 0.52 (m, 2H), 0.38 (m, 2H).	ESI-MS m/z = 350 $(M+H)^+$; HPLC purity: 98.7%.
36		^{1}H NMR (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 8.17 (s, 1H), 7.61 (bs, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 3.6 Hz, 1H), 7.09 (dd, J_1 = 1.6 Hz, J_2 = 10.8 Hz, 1H), 6.44 (d, J = 3.6 Hz, 1H), 4.63 (t, J = 4.4 Hz, 2H), 4.41 (t, J = 6.8 Hz, 2H), 3.98 (t, J = 4.4 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H)	ESI-MS m/z = 366 (M-H)-; HPLC purity: 97.7%.
37		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.52 (m, 2H), 7.38 (d, J = 3.3 Hz, 1H), 7.06 (dd, J_1 = 2.1 Hz, J_2 = 10.8 Hz, 1H), 6.44 (d, J = 2.7 Hz, 1H), 4.63 (t, J = 3.9 Hz, 2H), 4.04 (m, 4H), 1.79 (m, 1H), 1.7-1.45 (m, 5H), 1.2-0.9 (m, 5H).	ESI-MS m/z = 392 $(M+H)^+$; HPLC purity: 97%.
38		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.60 (bs, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.49 (m, 2H), 7.05 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 4.63 (t, J = 4.0 Hz, 2H), 4.27 (m, 1H), 4.0 (t, J = 3.6 Hz, 2H), 1.86 (m, 4H), 0.66 (t, J = 7.2 Hz, 6H).	ESI-MS m/z = 366 $(M+H)^+$; HPLC purity: 96%.

39		^{1}H NMR (300MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.60 (bs, 2H), 7.55 (d, J = 3.3 Hz, 1H), 7.49 (m, 2H), 7.2 (d, J = 8.4 Hz, 2H), 7.04 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 3.0 Hz, 1H), 5.35 (s, 2H), 4.61 (t, J = 3.9 Hz, 2H), 3.96 (t, J = 4.5 Hz, 2H), 3.69 (s, 3H).	ESI-MS m/z = 416 $(M+H)^+$; HPLC purity: 96%.
40		^{1}H NMR (300MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.58 (m, 3H), 7.52 (m, 2H), 7.28-7.25 (m, 2H), 7.22-7.0 (m, 3H), 6.51 (d, J = 3.3 Hz, 1H), 5.43 (s, 2H), 4.62 (t, J = 4.5 Hz, 2H), 3.97 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 404 $(M+H)^+$; HPLC purity: 97%.
41		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.56-7.5 (m, 2H), 7.44 (d, J = 2.8 Hz, 1H), 7.32-7.16 (m, 4H), 7.09 (d, J = 8.8 Hz, 1H), 6.46 (d, J =2.8 Hz, 1H), 4.64 (t, J = 4.0 Hz, 2H), 4.45 (s, 2H), 4.41 (t, J = 4.8 Hz, 2H), 3.98 (t, J = 4.4 Hz, 2H), 3.75 (t, J = 4.8 Hz, 2H).	ESI-MS m/z = 430 $(M+H)^+$; HPLC purity: 99 %.
42		^{1}H NMR (400MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.60 (bs, 2H), 7.58 (d, J = 2.8 Hz, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.33-7.29 (m, 1H), 7.26-7.20 (m, 4H), 7.06 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.51 (d, J = 3.2 Hz, 1H), 5.44 (s, 2H), 4.61 (t, J = 4.4 Hz, 2H), 3.97 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 386 $(M+H)^+$; HPLC purity: 98%.
43		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.50 (m, 2H), 7.40 (d, J = 2.8 Hz, 1H), 7.1 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 4.63 (m, 2H), 4.24 (t, J = 6.8 Hz, 2H), 3.98 (m, 2H), 3.24 (m, 5H), 1.97 (m, 2H).	ESI-MS m/z = 368 $(M+H)^+$; HPLC purity: 99%.

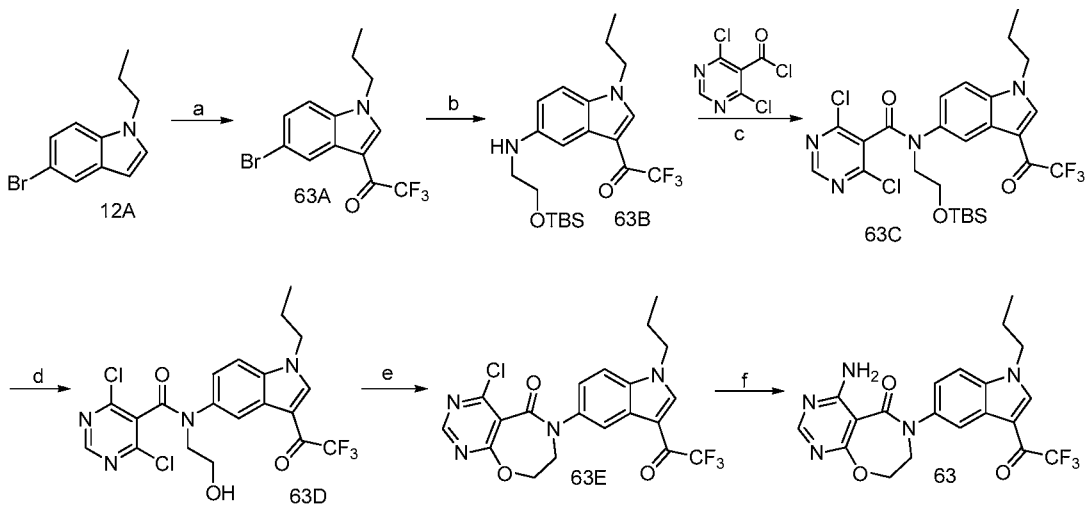
44		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.60 (bs, 2H), 7.58-7.53 (m, 2H), 7.43 (d, J = 2.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 3.2 Hz, 1H), 6.5-6.2 (m, 1H), 4.76-4.6 (m, 4H), 4.0 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 360 $(M+H)^+$; HPLC purity: 95%.
45		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.51 (d, J = 1.8 Hz, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 3.0 Hz, 1H), 7.12 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 6.44 (d, J = 3.0 Hz, 1H), 4.64 (t, J = 4.2 Hz, 2H), 3.98 (t, J = 4.5 Hz, 2H), 3.8 (s, 3H).	ESI-MS m/z = 310 $(M+H)^+$; HPLC purity: 92%.
46		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.50 (m, 2H), 7.41 (d, J = 2.8 Hz, 1H), 7.08 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.44 (d, J = 2.8 Hz, 1H), 4.64 (t, J = 4.4 Hz, 2H), 4.35 (t, J = 5.2 Hz, 2H), 3.98 (t, J = 4.4 Hz, 2H), 3.65 (t, J = 5.2 Hz, 2H), 3.22 (s, 3H)	ESI-MS m/z = 354 $(M+H)^+$; HPLC purity: 99%.
47		^{1}H NMR (300MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.56-7.49 (m, 2H), 7.5 (d, J = 1.8 Hz, 1H), 7.08 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 6.48 (d, J = 3.0 Hz, 1H), 4.77 (m, 1H), 4.63 (t, J = 4.2 Hz, 2H), 3.98 (t, J = 4.5 Hz, 2H), 1.46 (d, J = 6.9 Hz, 6H).	ESI-MS m/z = 338 $(M+H)^+$; HPLC purity: 96%.
48		^{1}H NMR (400MHz, DMSO-d_6): δ 11.2 (bs, 1H), 8.17 (s, 1H), 7.60 (bs, 2H), 7.49 (d, J = 1.6 Hz, 1H), 7.40 (m, 2H), 7.04 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.44 (m, 1H), 4.63 (t, J = 4.4 Hz, 2H), 3.97 (t, J = 4.8 Hz, 2H).	ESI-MS m/z = 296 $(M+H)^+$; HPLC purity: 93%.
49		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.57 (bs, 2H), 6.98 (s, 1H), 6.92 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 4.57 (t, J = 4.4 Hz, 2H), 3.86 (t, J = 4.8 Hz, 2H), 3.33 (t, J = 8.0 Hz, 2H), 3.0 (t, J = 7.6 Hz, 2H), 2.89 (t, J = 8.4	ESI-MS m/z = 340 $(M+H)^{+-}$; LCMS Purity: 99%.

		Hz, 2H), 1.55 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).	
50		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.57 (bs, 2H), 6.98 (s, 1H), 6.84 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 5.58 (bs, 1H), 4.57 (t, J = 4.4 Hz, 2H), 3.86 (t, J = 4.4 Hz, 2H), 3.44 (t, J = 8.4 Hz, 2H), 2.91 (t, J = 8.0 Hz, 2H).	ESI-MS m/z = 298 $(M+H)^{+-}$; HPLC Purity: 94%.
51		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.58 (bs, 2H), 6.98 (s, 1H), 6.92 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 4.57 (t, J = 4.4 Hz, 2H), 3.87 (t, J = 4.4 Hz, 2H), 3.53 (t, J = 6.0 Hz, 2H), 3.41 (t, J = 8.0 Hz, 2H), 3.28 (s, 3H), 3.23 (t, J = 5.6 Hz, 2H), 2.89 (t, J = 8.4 Hz, 2H).	ESI-MS m/z = 356 $(M+H)^{+-}$; HPLC Purity: 97%.
52		^{1}H NMR (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.02-6.98 (m, 2H), 7.01 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.23 (s, 1H), 4.63 (t, J = 4.0 Hz, 2H), 3.96 (t, J = 4.4 Hz, 2H), 3.67 (s, 3H), 2.87 (s, 3H).	ESI-MS m/z = 324 $(M+H)^{+}$; HPLC purity: 96%.
53		^{1}H NMR (400MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 3.2 Hz, 1H), 6.50 (d, J = 3.6 Hz, 1H), 5.64 (bs, 1H), 4.75 (t, J = 4.0 Hz, 2H), 4.17 (d, J = 6.8 Hz, 2H), 4.07 (t, J = 4.4 Hz, 2H), 1.29 (m, 1H), 0.61 (q, J = 6.0 Hz, 2H), 0.42 (q, J = 4.8 Hz, 2H).	ESI-MS m/z = 351 $(M+H)^{+}$; HPLC purity: 96%.
54		^{1}H NMR (400MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 6.48 (d, J = 3.6 Hz, 1H), 5.64 (bs, 1H), 4.75 (t, J = 4.4 Hz, 2H), 4.26 (t, J = 6.8 Hz, 2H), 4.07 (t, J = 4.4 Hz, 2H), 1.91 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H);	ESI-MS m/z = 339 $(M+H)^{+}$; HPLC purity: 93.5%.

55		^{1}H NMR (400MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 3.6 Hz, 1H), 6.48 (d, *J* = 3.6 Hz, 1H), 5.71 (bs, 1H), 4.75 (t, *J* = 4.4 Hz, 2H), 4.48 (t, *J* = 5.2 Hz, 2H), 4.06 (t, *J* = 4.4 Hz, 2H), 3.74 (t, *J* = 4.8 Hz, 2H), 3.33 (s, 3H);	ESI-MS *m/z* = 355 $(M+H)^+$; HPLC purity: 91.63%.
56		^{1}H NMR (400MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 5.65 (bs, 1H), 4.75 (t, *J* = 4.4 Hz, 2H), 4.12 (d, *J* = 7.2 Hz, 2H) 4.07 (t, *J* = 4.4 Hz, 2H), 1.93 (m, 1H), 1.7-1.6 (m, 4H), 1.25-1.14 (m, 3H), 1.03 (m, 2H).	ESI-MS *m/z* = 393 $(M+H)^+$; HPLC purity: 98.7%.
57		^{1}H NMR (300MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.21 (d, *J* = 2.1 Hz, 1H), 7.8 (d, *J* = 2.1 Hz, 1H), 7.39 (d, *J* = 3.3 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 5.65 (bs, 1H), 4.84-4.7 (m, 3H), 4.06 (t, *J* = 4.5 Hz, 2H), 2.18-2.04 (m, 2H), 1.95-1.88 (m, 2H), 1.8-1.6 (m, 4H), 1.4-1.2 (m, 2H).	ESI-MS *m/z* = 379 $(M+H)^+$; HPLC purity: 92.8%.
58		^{1}H NMR (300MHz, DMSO d_6): δ 8.23 (d, *J* = 2.1 Hz, 1H), 8.18 (s, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.73 (d, *J* = 3.6 Hz, 1H), 7.65 (bs, 2H), 6.52 (d, *J* = 3.3 Hz, 1H), 5.07 (m, 1H), 4.67 (t, *J* = 4.2 Hz, 2H), 4.02 (t, *J* = 4.5 Hz, 2H), 1.48 (d, *J* = 6.3 Hz, 6H).	ESI-MS *m/z* = 339 $(M+H)^+$; HPLC purity: 97%.
59		^{1}H NMR (300MHz, DMSO-d_6): δ 8.22 (d, *J* = 2.4 Hz, 1H), 8.18 (s, 1H), 7.97 (d, *J* = 2.1 Hz, 1H), 7.64 (bs, 2H), 7.61 (d, *J* = 3.3 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 4.92 (t, *J* = 5.4 Hz, 1H), 4.67 (t, *J* = 5.1 Hz, 2H), 4.32 (t, *J* = 5.7 Hz, 2H), 4.02 (t, *J* = 4.5 Hz, 2H), 3.75 (q, *J* = 5.7 Hz, 2H).	ESI-MS *m/z* = 341 $(M+H)^+$. HPLC purity: 95%.

60		^{1}H NMR (300MHz, DMSO-d_6-D_2O): δ 8.19 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.7 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 3.6 Hz, 1H), 7.38 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 6.87 (d, J = 3.6 Hz, 1H), 4.66 (t, J = 4.2 Hz, 2H), 4.02 (t, J = 4.5 Hz, 2H), 3.46 (s, 3H).	ESI-MS m/z = 374 $(M+H)^+$; HPLC purity: 98%.
61		^{1}H NMR (300MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.38 (d, J = 3.3 Hz, 1H), 7.13 (dd, J_1 = 1.8 Hz, J_2 = 10.8 Hz, 1H), 6.42 (d, J = 3.0 Hz, 1H), 4.63 (t, J = 3.9 Hz, 2H), 3.98 (t, J = 4.8 Hz, 2H), 3.45 (m, 1H), 1.08 (m, 2H), 0.95 (m, 2H).	ESI-MS m/z = 336 $(M+H)^+$; HPLC purity: 94%.
62		^{1}H NMR (400MHz, DMSO-d_6): δ 13.1 (bs, 1H), 8.18 (s, 1H), 7.68-7.6 (m, 4H), 7.29 (d, J = 10.4 Hz, 1H), 7.23 (s, 1H), 4.64 (t, J = 4.4 Hz, 2H), 4.56 (t, J = 7.6 Hz, 2H), 4.0 (t, J = 4.4 Hz, 2H), 1.72 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H).	ESI-MS m/z = 382 $(M+H)^+$. HPLC purity: 98%.

Example 63: 4-Amino-6-(1-propyl-3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

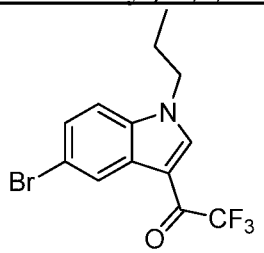


Reagents and conditions: a) TFAA, Et_3N, DCM, RT, 1h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C, 2.5h; c) DCM, Et_3N, RT, 1h; d) 3% HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxane, RT, 2h.

Procedures:

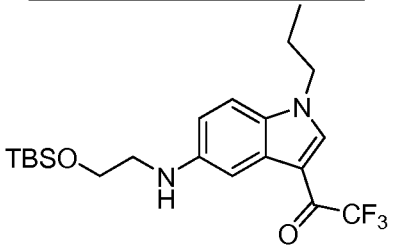
4-Amino-6-(1-propyl-3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

1-(5-Bromo-1-propyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (63A):



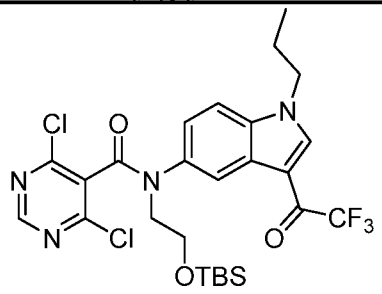
TFAA (5.0 mL, 35.4 mmol) was added to a solution of product of Example 12A (2.5 g, 10.5 mmol) in DCM (10 mL) followed by TEA (2.5 mL, 17.94 mmol) at 0 °C, and the mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with DCM and quenched with water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 5% ethyl acetate in hexane to afford title compound (2.0 g, 57%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (d, J = 1.5 Hz, 1H), 7.90 (d, J = 1.5 Hz, 1H), 7.49-7.45 (dd, J_1 = 1.8 Hz, J_2 = 9.0 Hz, 1H), 7.09 (m, 1H), 4.16 (t, J = 6.9 Hz, 2H), 1.98-1.91 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); ESI-MS m/z = 238 $(M+H)^+$.

1-(5-(2-(tert-Butyldimethylsilyloxy)ethylamino)-1-propyl-1H-indol-3-yl)-2,2,2-trifluoroethanone (63B):



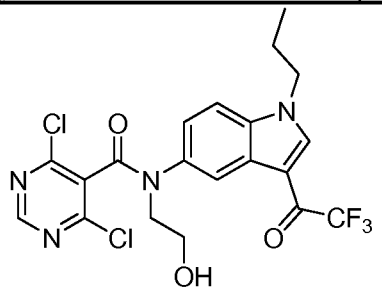
A mixture of product of Example 63A (1.25 g, 3.74 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.656 g,3.74 mmol), cesium carbonate (1.463 g, 4.49 mmol), palladium acetate (0.084 g, 0.374 mmol) and X-PHOS (0.178 g, 0.374 mmol) in toluene (20 mL) under Argon was refluxed at 110 °C for 2 h. The reaction mixture was cooled, diluted with ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and oncentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.7 g, 43.7%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J = 1.5 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.20 (d, J =.9.0 Hz, 1H), 6.75-6.72 (dd, J_1= 2.4 Hz, J_2 = 8.7 Hz, 1H), 4.17 (bs, 1H), 4.09 (t, J = 7.5 Hz, 2H), 3.87 (t, J = 5.1 Hz, 2H), 3.30 (t, J = 7.5 Hz, 1H), 1.96-1.89 (m, 2H), 0.97(t, J = 7.2 Hz, 3H), 0.91(s, 9H), 0.07 (s, 6H); ESI-MS m/z = 429 $(M+H)^+$.

N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(1-propyl-3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)pyrimidine-5-carboxamide (63C):



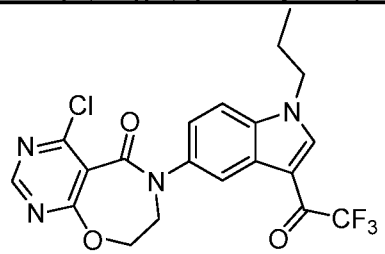
To a stirred, cooled (0 °C) solution of product of Example 63B (0.7 g, 1.633 mmol) and TEA (1.138 g, 8.17 mmol) in DCM (20 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.345 g, 1.633 mmol) in DCM (5 mL). After 1 h, the reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 12% ethyl acetate in hexane as eluent to afford title compound (0.6 g, 60.9%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.46 (d, J = 1.6 Hz , 1H), 7.91 (d, J =1.2 Hz, 1H),7.45-7.43 (dd, J_1= 2.0 Hz J_2 =8.8 Hz ,1H), 7.26(m, 1H), 4.13-4.10 (m, 4H), 3.92 (t, J = 5.6 Hz, 2H),1.93-1.88 (q, J =7.6 Hz , 2H), 0.98 (t, J = 7.2 Hz, 3H), 0.83 (s, 9H), 0.045(s, 6H); ESI-MS m/z = 605 $(M+H)^+$.

4,6-Dichloro-N-(2-hydroxyethyl)-N-(1-propyl-3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)pyrimidine-5-carboxamide (63D):



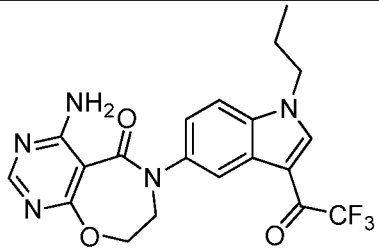
A solution of product of Example 63C (0.6 g, 0.994 mmol), in 10 mL of methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 1 h. Methanol was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.4 g, 82%) as a solid, which was carried on to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.50 (d, J = 1.6 Hz, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.45-7.42 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.29(m, 1H), 4.18 (t, J = 5.2 Hz, 2H), 4.11 (t, J = 7.2 Hz, 2H), 3.95(t, 2H), 1.92 (q, J =7.6 Hz, 2H), 0.98 (t, J = 8.0 Hz, 3H); ESI-MS m/z = 490 $(M+H)^+$.

4-Chloro-6-(1-propyl-3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (63E):



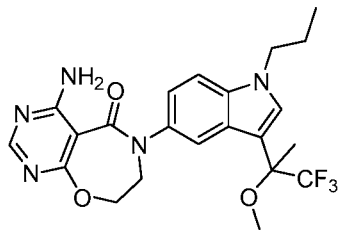
A slurry of product of Example 63D (0.4 g, 0.818 mmol) and TEA (0.57 mL, 4.09 mmol) in acetonitrile (15 mL) was stirred at 80 °C for 16 h. The reaction mixture was cooled and concentrated in vacuo. The residue was diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.25 g, 67.5%) as a white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.35(s , 1H), 7.99 (d, J = 0.9 Hz, 1H), 7.50-7.48 (m , 2H), 4.82(t, J = 7.8 Hz, 2H), 4.21 (t, J = 7.2 Hz , 2H), 4.15 (t, J = 4.8 Hz, 2H), 2.04-1.96 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H),; ESI-MS m/z = 453 $(M+H)^+$.

4-Amino-6-(1-propyl-3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (63):

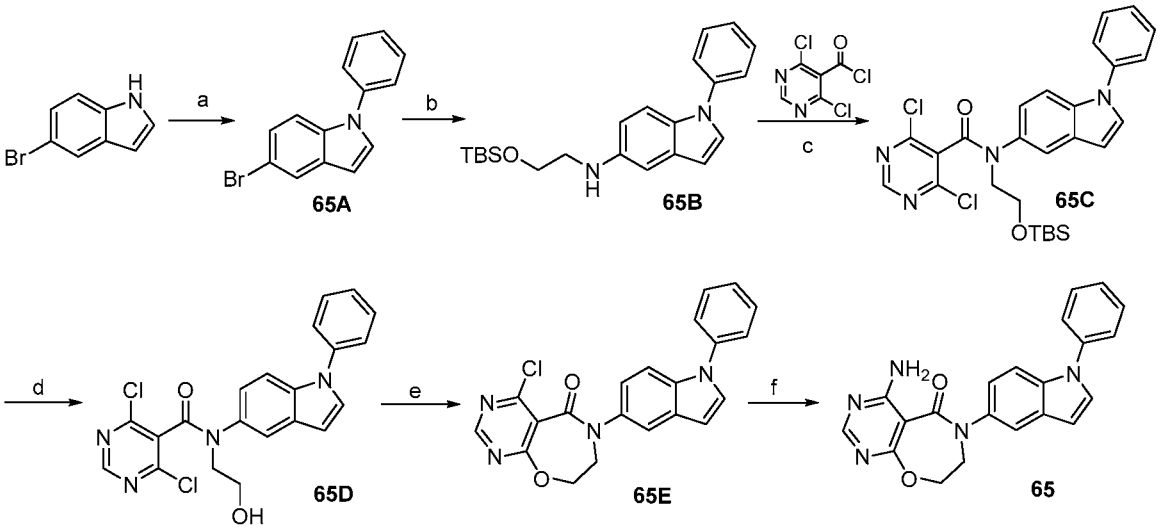


A solution of product of Example 63E (0.25 g, 0.552 mmol) in 0.5M ammonia in p-dioxane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted water ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (70 mg, 27.2%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.65 (d, J = 1.6 Hz, 1H), 8.18 (s, 1H), 8.11 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.65 (bs, 2H), 7.40-7.38 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 4.63 (t, J = 3.6 Hz, 2H), 4.37 (t, J = 6.8 Hz, 2H), 4.04 (t, J = 4.8 Hz, 2H), 1.87-1.82 (m, 2H), 0.870 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 434 $(M+H)^+$; LCMS purity: 92%.

Example 64 was prepared by the procedures analogous to those described in Example 63 using appropriately substituted starting materials.

Ex	Structure	Analytical Data	Mass/Purity
64		^{1}H NMR (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.64-7.54 (m, 3H), 7.15 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 7.03 (bs, 2H), 4.59 (t, J = 4.2 Hz, 2H), 4.17 (t, J = 6.9 Hz, 2H), 4.0 (t, J = 4.5 Hz, 2H), 3.12 (s, 3H), 1.83-1.7 (m, 5H), 0.83 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 464 $(M+H)^+$; HPLC purity: 90%.

Example 65: 4-Amino-6-(1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

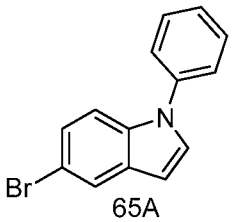


Reagents and conditions: a) Iodo benzene, CuBr, $Cu(OAc)_2$, K_2CO_3, NaOH, 140 °C, 9h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C, 2.5h; c) DCM, Et_3N, RT, 1h; d) 3%HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxane, RT, 2h.

Procedures:

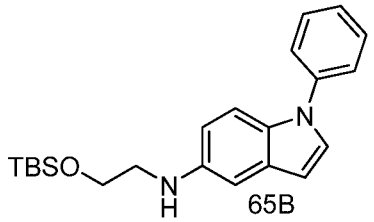
4-Amino-6-(1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

5-bromo-1-phenyl-1H-indole (65A):



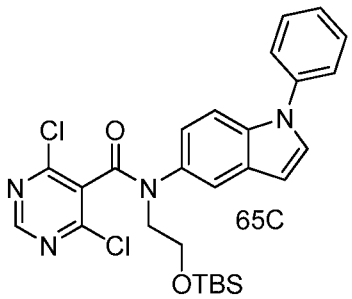
Copper(I) bromide (0.073 g, 0.509 mmol) was added to a solution of 5-bromo indole (1 g, 10.2 mmol) in iodo benzene (13.5 g, 66.2 mmol) followed by potassium carbonate (2.7 g, 19.54 mmol), and the mixture was stirred at 100 °C for 10 min. NaOH (150 mg, 3.75 mmol) and copper(II) acetate (0.01g, 0.055 mmol) was added at 140 °C, and the mixture was stirred for 9 h. Insoluble solids were filtered off, filtrate was concentrated and partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography using 8% ethyl acetate in pet ether to afford title compound (0.5 g, 36%) as an oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.80 (m, 1H), 7.60-7.45 (m, 4H), 7.42-7.38 (m, 2H), 7.35-7.25 (m, 2H), 6.62 (d, J = 3.3 Hz, 1H).

N-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-phenyl-1H-indol-5-amine (65B):



A mixture of product of Example 65A (1.7 g, 6.25 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (1.095 g, 6.25 mmol), cesium carbonate (3.05 g, 9.37 mmol), palladium acetate (0.14 g, 0.625 mmol) and X-PHOS (0.298 g, 0.625 mmol) in toluene (30 mL) under argon was refluxed at 120 °C for 16 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.8 g, 34.9%) as an oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.55-7.48 (m, 4H), 7.45-7.39 (m, 2H), 7.3 (m, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.66 (dd, J_1= 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.52 (d, J = 2.8 Hz, 1H), 3.94 (bs, 1H), 3.86 (t, J = 5.2 Hz, 2H), 3.27 (t, J = 5.2 Hz, 2H), 0.92 (s, 9H), 0.08 (s, 6H).

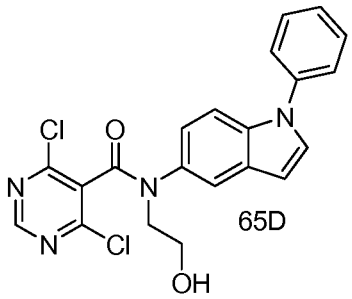
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(1-phenyl-1H-indol-5-yl)pyrimidine-5-carboxamide (65C):



To a stirred, cooled (0 °C) solution of product of Example 65B (0.8 g, 2.182 mmol) and TEA (1.521 mL, 10.91 mmol) in DCM (30 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.461 g, 2.182 mmol) in DCM (5 mL). After 1 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 12% ethyl acetate in hexane as eluent to afford title compound (0.65 g, 5%) as a syrup. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.5 (s, *1*H), 7.74 (d, J = 2.0 Hz,

1H), 7.51 (t, J = 8.0 Hz, 2H), 7.41-7.33 (m, 5H), 7.22 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 4.16 (t, J = 4.8 Hz, 2H), 3.95 (t, J = 5.2 Hz, 2H), 0.92 (s, 9H), 0.08 (s, 6H).

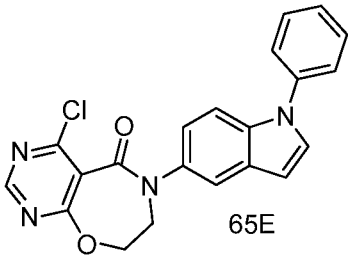
4,6-Dichloro-N-(2-hydroxyethyl)-N-(1-phenyl-1H-indol-5-yl)pyrimidine-5-carboxamide (65D):



65D

A solution of product of Example 65C (0.65 g, 1.2 mmol), in 20.5 mL of methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 1 h. Methanol was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.45 g, 72.8%) as a solid, which was carried on to the next step without further purification. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.40-7.38 (m, 4H), 7.36 (d, J = 3.6 Hz, 1H), 7.23 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 4.16 (t, J = 4.8 Hz, 2H), 3.95 (t, J = 5.2 Hz, 2H).

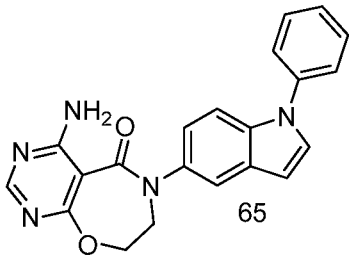
4-Chloro-6-(1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (65E):



65E

A slurry of product of Example 65D (0.45 g, 1.053 mmol) and TEA (0.734 mL, 5.27 mmol) in acetonitrile (20 mL) was stirred at 80 °C for 16 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.3 g, 67.1%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.6 (d, J = 8.8 Hz, 1H), 7.56-7.47 (m, 4H), 7.41-7.38 (m, 2H), 7.20 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.71 (d, J = 3.6 Hz, 1H), 4.18 (t, J = 4.4 Hz, 2H), 4.10 (t, J = 4.8 Hz, 2H).

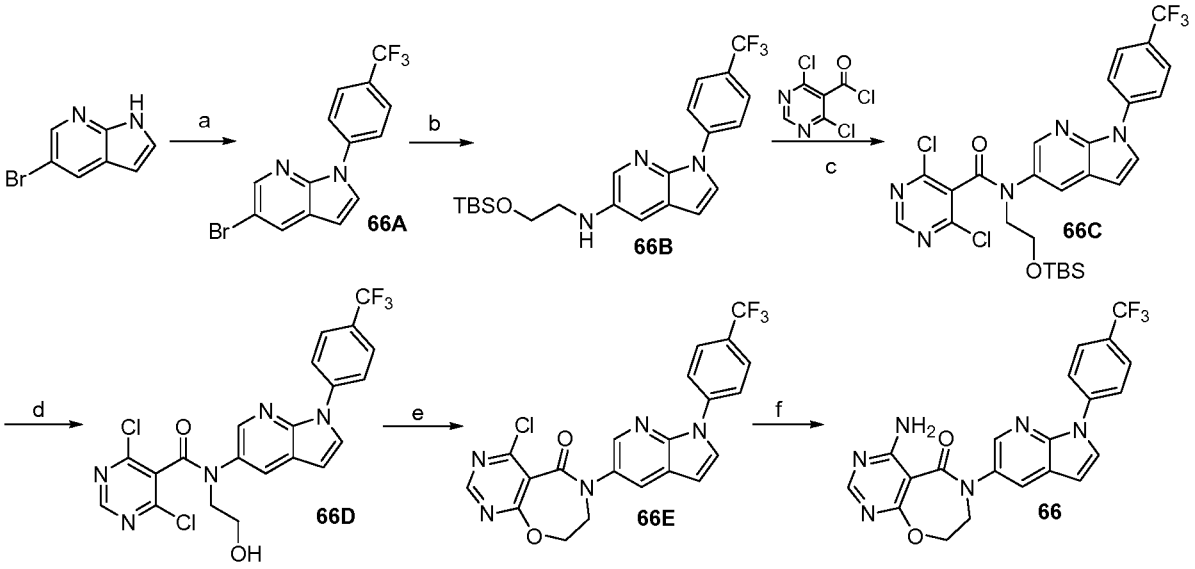
4-Amino-6-(1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (65):



65

A solution of product of Example 65E (0.3 g, 0.768 mmol), in 0.5M ammonia in p-dioxane (15 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.22 g, 73.3%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.73 (d, J = 3.6 Hz, 1H), 7.64-7.56 (m, 5H), 7.45 (m, 1H), 7.18-7.15 (m, 4H), 6.73 (d, J = 3.2 Hz, 1H), 4.65 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H); ESI-MS m/z = 372 $(M+H)^+$; HPLC purity: 95%.

Example 66: 4-Amino-6-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:



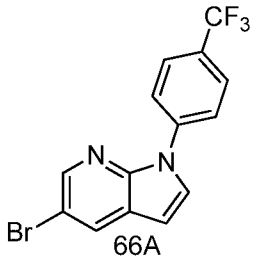
66A 66B 66C 66D 66E 66

Reagents and conditions: a) 1-Iodo-4-(trifluoromethyl)benzene, CuBr, $Cu(OAc)_2$, K_2CO_3, NaOH, DMF, 110 ° C, 16h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 ° C, 12h; c) DCM, Et_3N, RT, 1h; d) TBAF, THF, RT, 1h; e) CH_3CN, Et_3N, 80 ° C, 16h; f) NH_3, Dioxane, RT, 2h.

Procedures:

4-Amino-6-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

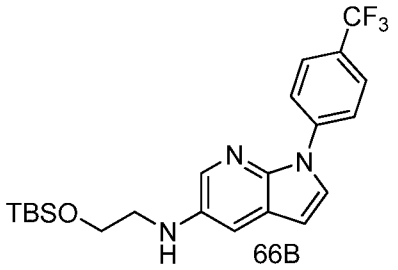
5-Bromo-1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine (66A):



66A

1-Iodo-4-(trifluoromethyl)benzene (1.657 g, 6.09 mmol) was added to a solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine (1 g, 5.08 mmol) and Copper(I) bromide (0.073 g, 0.508 mmol) in DMF (10 mL) followed by potassium carbonate (1.75 g, 12.69 mmol), and the mixture was stirred at 100 °C for 10 min. NaOH (150 mg, 3.75 mmol) and copper(II) acetate (4.61 mg, 0.025 mmol) were added to the reaction mixture at 110 °C, and the mixture was stirred for 16 h. Insoluble solids were filtered off, and the filtrate was concentrated. Residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ethyl acetate in pet ether to afford title compound (0.4 g, 22%) as a off-white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.4 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 4.0 Hz, 1H), 6.63 (d, J = 3.6 Hz, 1H).

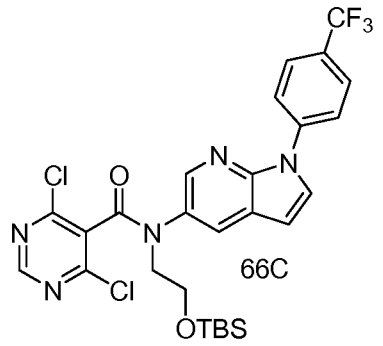
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-amine (66B):



66B

A mixture of product of Example 66A (0.4 g, 1.173 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.247 g, 1.407 mmol), cesium carbonate (0.573 g, 1.759 mmol), palladium acetate (26.3 mg, 0.117 mmol) and X-PHOS (0.0559 g, 0.117 mmol) in Toluene (15 mL) under Argon was refluxed at 120 °C for 2.5 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x5 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.3 g, 50.5%) as an oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 2.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 4.0 Hz, 1H), 7.21 (d, J = 2.8 Hz, 1H), 6.52 (d, J = 4.0 Hz, 1H), 3.88 (t, J = 5.2 Hz, 2H), 3.27 (t, J = 5.6 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 6H).

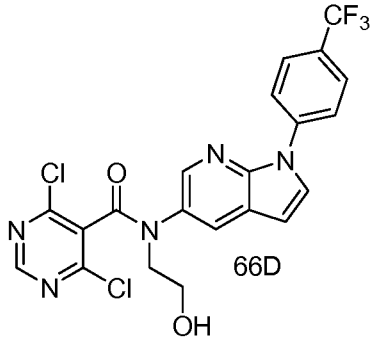
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidine-5-carboxamide (66C):



66C

To a stirred, cooled (0 °C) solution of product of Example 66B (0.3 g, 0.689 mmol) and TEA (0.288 mL, 2.06 mmol) in DCM (10 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.175 g, 0.827 mmol) in DCM (2 mL). After 1 h, the reaction mixturewas concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x5 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford an oil. The residue was purified by flash chromatography using 12% ethyl acetate in pet ether to afford title compound (0.28 g, 62.6%) as a syrup. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 4.0 Hz, 1H), 6.63 (d, J = 4.0 Hz, 1H), 4.09 (t, J = 5.2 Hz, 2H), 3.97 (t, J = 5.2 Hz, 2H), 0.87 (s, 9H), 0.06 (s, 6H).

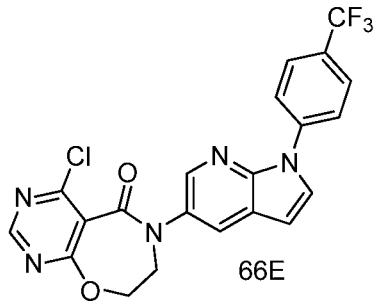
4,6-Dichloro-N-(2-hydroxyethyl)-N-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidine-5-carboxamide (66D):



66D

TBAF (0.3 g, 1.147 mmol) was added to a solution of Example 66C (0.28 g, 0.459 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 1 h. THF was removed in vacuo. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.2 g, 86%) as a solid, which was carried on to the next step without further purification. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.6 (d, J = 4.0 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 4.16 (t, J = 4.8 Hz, 2H), 3.98 (q, J = 4.8 Hz, 2H).

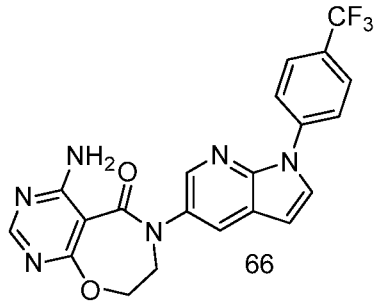
4-Chloro-6-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (66E):



66E

A slurry of product of Example 66D (0.2 g, 0.403 mmol) and TEA (0.169 mL, 1.209 mmol) in acetonitrile (15 mL) was stirred at 80 °C for 6 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.16 g, 83%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.04 (d, J = 2.8 Hz, 1H), 7.96 (d, J = 8.8 Hz, 2H), 7.8 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 3.6 Hz, 1H), 6.74 (d, J = 3.6 Hz, 1H), 4.81 (t, J = 5.2 Hz, 2H), 4.12 (t, J = 4.8 Hz, 2H).

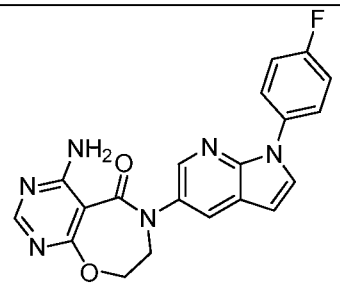
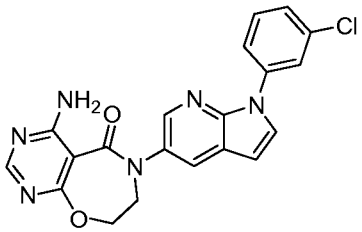
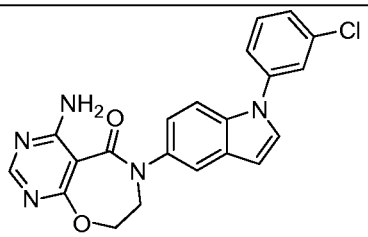
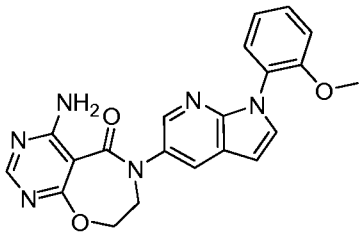
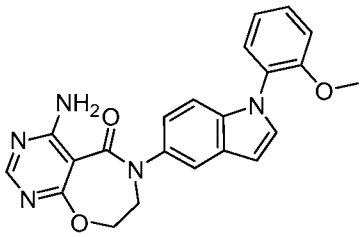
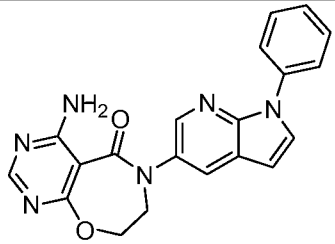
4-Amino-6-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (66):

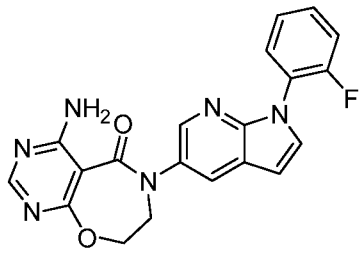
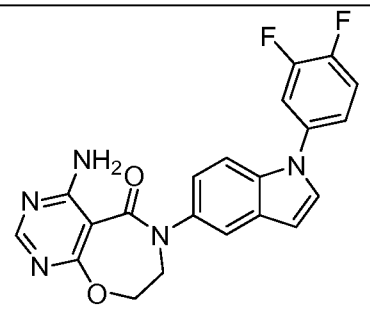
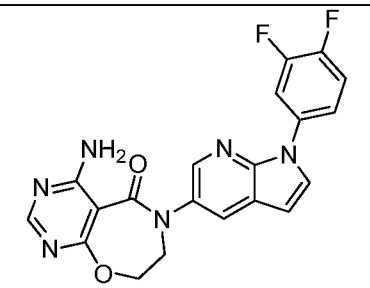
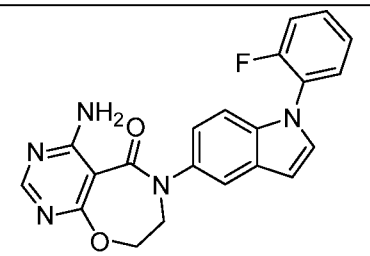
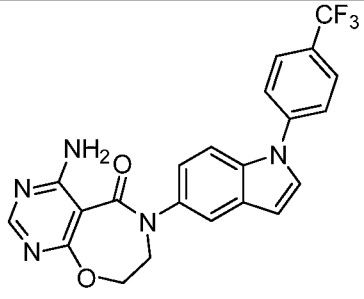


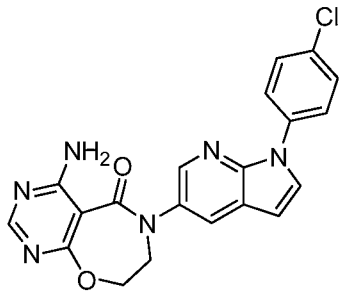
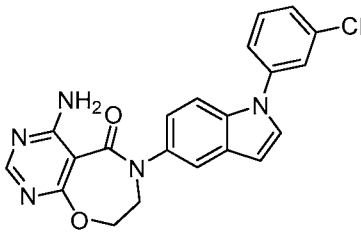
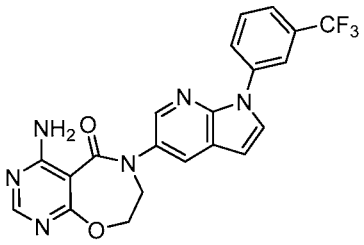
66

A solution of product of Example 66E (0.16 g, 0.348 mmol) in 0.5M ammonia in p-dioxane (12 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.1 g, 64.6%) as a white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.37 (d, J = 2.4 Hz, 1H), 8.23 (d, J = 8.0 Hz, 2H), 8.19 (s, 1H), 8.16 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 4.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.66 (bs, 2H), 6.87 (d, J = 4.0 Hz, 1H), 4.71 (t, J = 4.0 Hz, 2H), 4.07 (t, J = 3.6 Hz, 2H); ESI-MS m/z = 441 $(M+H)^+$; HPLC purity: 99%.

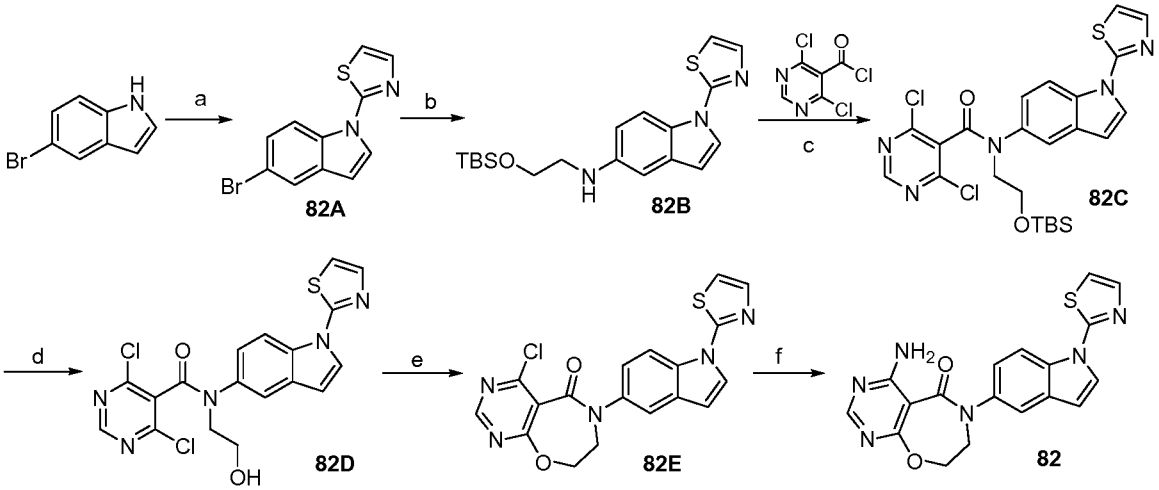
Examples 67 – 81 were prepared by the procedures analogous to those described in Example 65 or Example 66 using appropriately substituted starting materials.

Ex	Structure	Analytical Data	Mass/Purity
67		^{1}H NMR (400MHz, DMSO-d_6): δ 8.32 (d, J = 2.0 Hz, 1H), 8.19 (s, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.0 (d, J = 4.0 Hz, 1H), 7.94-7.91 (m, 2H), 7.66 (bs, 2H), 7.41 (t, J = 8.8 Hz, 2H), 6.76 (d, J = 4.0 Hz, 1H), 4.69 (t, J = 4.4 Hz, 2H), 4.06 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 391 $(M+H)^+$; HPLC purity: 97%.
68		^{1}H NMR (400MHz, DMSO-d_6): δ 8.37 (d, J = 2.4 Hz, 1H), 8.19 (s, 1H), 8.16-8.10 (m, 3H), 7.95 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.67 (bs, 2H), 7.59 (t, J = 8.4 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 6.8 (d, J = 3.6 Hz, 1H), 4.69 (t, J = 4.0 Hz, 2H), 4.06 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 407 $(M+H)^+$; HPLC purity: 97%.
69		^{1}H NMR (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.78 (d, J = 3.3 Hz, 1H), 7.7 (bs, 2H), 7.66-7.58 (m, 5H), 7.48 (m, 1H), 7.22 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 6.76 (d, J = 3.3 Hz, 1H), 4.65 (t, J = 3.6 Hz, 2H), 4.01 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 406 $(M+H)^+$; HPLC purity: 95%.
70		^{1}H NMR (300MHz, DMSO-d_6): δ 8.18 (m, 2H), 8.05 (d, J = 2.1 Hz, 1H), 7.66 (bs, 2H), 7.46 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 6.3 Hz, 2H), 6.66 (d, J = 3.9 Hz, 1H), 4.67 (t, J = 4.5 Hz, 2H), 4.04 (t, J = 4.5 Hz, 2H), 3.74 (s, 3H).	ESI-MS m/z = 403 $(M+H)^+$; HPLC purity: 92%.
71		^{1}H NMR (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.62 (bs, 2H), 7.59 (s, 1H), 7.54-7.46 (m, 2H), 7.39 (d, J = 6.9 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.2-7.05 (m, 3H), 6.66 (d, J = 3.0 Hz, 1H), 4.64 (t, J = 4.5 Hz, 2H), 4.0 (t, J = 4.5 Hz, 2H), 3.77 (s, 3H).	ESI-MS m/z = 402 $(M+H)^+$; HPLC purity: 92%.
72		^{1}H NMR (300MHz, $CDCl_3$): δ 8.3 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.20 (bs, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.74 (m, 2H), 7.6 (d, J = 3.6 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H),	ESI-MS m/z = 373 $(M+H)^+$; HPLC purity: 99%.

		6.66 (d, J = 3.3 Hz, 1H), 5.70 (bs, 1H), 4.76 (t, J = 4.2 Hz, 2H), 4.08 (t, J = 4.5 Hz, 2H).	
73		^{1}H NMR (300MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.25 (d, J = 2.4 Hz, 1H), 8.20 (bs, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.69 (dt, J_1 = 1.5 Hz, J_2 = 7.5 Hz, 1H), 7.49 (m, 1H), 7.46-7.38 (m, 1H), 7.34-7.27 (m, 2H), 6.68 (d, J = 3.3 Hz, 1H), 5.75 (bs, 1H), 4.75 (t, J = 4.5 Hz, 2H), 4.08 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 391 $(M+H)^+$; HPLC purity: 96%.
74		^{1}H NMR (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.80 (m, 1H), 7.73 (d, J = 3.2 Hz, 1H), 7.70-7.58 (m, 5H), 7.50 (m, 1H), 7.20 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 2H), 6.75 (d, J = 3.2 Hz, 1H), 4.65 (t, J = 4.4 Hz, 2H), 4.0 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 408 $M+H)^+$; HPLC purity: 96%.
75		^{1}H NMR (300MHz, DMSO-d_6): δ 8.36 (d, J = 2.1 Hz, 1H), 8.18 (s, 1H), 8.13 (m, 2H), 8.08 (d, J = 3.9 Hz, 1H), 7.85 (m, 1H), 7.70-7.60 (m, 3H), 6.80 (d, J = 3.3 Hz, 1H), 4.69 (t, J = 3.9 Hz, 2H), 4.06 (t, J = 4.2 Hz, 2H).	ESI-MS m/z = 409 $(M+H)^+$; HPLC purity: 90%.
76		^{1}H NMR (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.68-7.60 (m, 5H), 7.55 (m, 2H), 7.43 (m, 1H), 7.24 (d, J = 8.4, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 2.8 Hz, 1H), 4.65 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 390 $(M+H)^+$; LCMS purity: 98%.
78		^{1}H NMR (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 2.8 Hz, 1H), 7.71-7.6 (m, 4H), 7.22 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 3.2 Hz, 1H), 4.65 (t, J = 4.0 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 440 $(M+H)^+$; HPLC purity: 99%.

79		^{1}H NMR (300MHz, DMSO-d_6): δ 8.34 (d, J = 2.1 Hz, 1H), 8.19 (s, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.05 (d, J = 3.6 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.7-7.6 (m, 4H), 6.79 (d, J = 3.3 Hz, 1H), 4.68 (t, J = 4.2 Hz, 2H), 4.06 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 407 (M+H); HPLC purity: 94%.
80		^{1}H NMR (400MHz, DMSO-d_6): δ 8.10 (s, 1H), 7.91-7.84 (m, 2H), 7.8-7.68 (m, 3H), 7.59 (d, J = 2.0 Hz, 1H), 7.55 (bs, 2H), 7.52 (d, J = 8.8 Hz, 1H), 7.14 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.71 (d, J= 3.6 Hz, 1H), 4.58 (t, J = 4.8 Hz, 2H), 3.94 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 440 (M+H)$^+$; HPLC purity: 93%.
81		^{1}H NMR (400MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.19 (m, 2H), 8.15 (d, J = 2.0 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.67 (bs, 2H), 6.83 (d, J = 3.6 Hz, 1H), 4.70 (t, J = 4.0 Hz, 2H), 4.07 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 441 (M+H)$^+$; HPLC purity: 97%.

Example 82: 4-Amino-6-(1-(thiazol-2-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

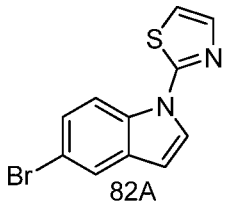


Reagents and conditions: a) 2-Bromo thiazole, Cs_2CO_3, DMF, 100 °C, 2h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C, 2.5h; c) DCM, Et_3N, RT, 1h; d) 3% HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxane, RT, 2h.

Procedures:

4-Amino-6-(1-(thiazol-2-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

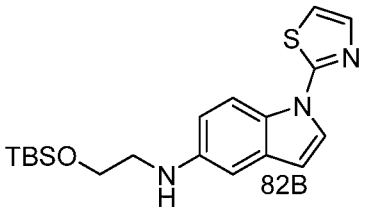
2-(5-Bromo-1H-indol-1-yl)thiazole (82A):



82A

2-Bromo thiazole (0.837 g, 5.10 mmol) was added to a solution of 5-bromo indole (1 g, 5.10 mmol) in DMF (15 mL) followed by cesium carbonate (3.32 g, 10.20 mmol), and the mixture was stirred at 90 °C for 12 h. Insoluble solids were filtered off, the filtrate was concentrated and partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography using 5% ethyl acetate in pet ether to afford title compound (0.75 g, 52.7%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.24 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.62 (dd, J_1 = 3.2 Hz, J_2 = 10.4 Hz, 2H), 7.45 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H), 6.66 (d, J = 4.0 Hz, 1H).

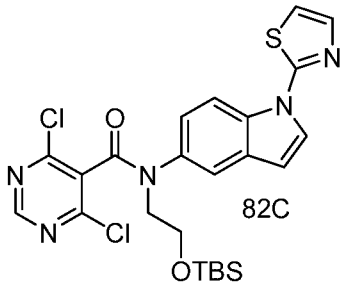
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-(thiazol-2-yl)-1H-indol-5-amine (82B):



82B

A mixture of product of Example 82A (0.75 g, 2.69 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.471 g, 2.69 mmol), cesium carbonate (1.751 g, 5.37 mmol), palladium acetate (0.060 g, 0.269 mmol) and X-PHOS (0.128 g, 0.269 mmol) in Toluene (15 mL) under Argon was refluxed at 120 °C for 4 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.4 g, 40%) as an oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.11 (d, J = 9.0 Hz, 1H), 7.56 (dd, J_1 = 3.6 Hz, J_2 = 9.9 Hz, 2H), 6.99 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.76 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 6.56 (d, J = 3.6 Hz, 1H), 4.03 (bs, 1H), 3.86 (t, J = 4.8 Hz, 2H), 3.27 (t, J = 5.4 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 6H).

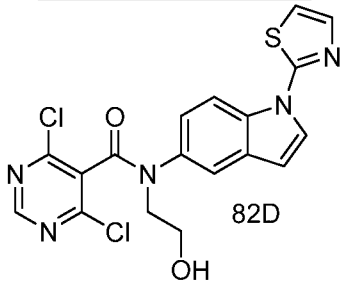
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(1-(thiazol-2-yl)-1H-indol-5-yl)pyrimidine-5-carboxamide (82C):



82C

To a stirred, cooled (0 °C) solution of product of Example 82B (0.4 g, 1.071 mmol) and TEA (0.746 mL, 5.35 mmol) in DCM (15 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.226 g, 1.071 mmol) in DCM (5 mL). After 1 h, the reaction was concentrated in vacuo, diluted into ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 12% ethyl acetate in hexane to afford title compound (0.35 g, 59.6%) as a syrup. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 7.62 (d, J = 3.3 Hz, 1H), 7.59 (d, J = 3.9 Hz, 1H), 7.38 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.63 (d, J = 3.6 Hz, 1H), 4.07 (t, J = 5.4 Hz, 2H), 3.93 (t, J = 5.4 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H).

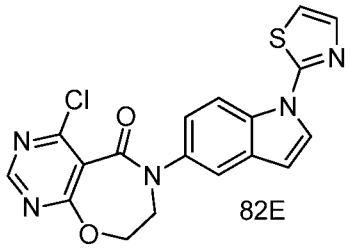
4,6-Dichloro-N-(2-hydroxyethyl)-N-(1-(thiazol-2-yl)-1H-indol-5-yl)pyrimidine-5-carboxamide (82D):



82D

TBAF (1.276 mL, 1.276 mmol) was added to a solution of Example 82C (0.35 g, 0.638 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 1 h. THF was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.25 g, 90%) as a solid, which was carried on to the next step without further purification. ESI-MS m/z = 434 $(M+H)^+$; LCMS purity: 88%.

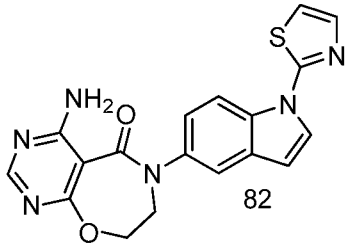
4-Chloro-6-(1-(thiazol-2-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (82E):



82E

A slurry of product of Example 82D (0.25 g, 0.576 mmol) and TEA (0.080 mL, 0.576 mmol) in acetonitrile (12 mL) was stirred at 90 °C for 16 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate and concentrated in vacuo to afford title compound (0.377 g, 65.5%) as a white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.45 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 3.6 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.64 (d, J = 3.9 Hz, 1H), 7.34 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 6.75 (d, J = 3.6 Hz, 1H), 4.81 (t, J = 4.5 Hz, 2H), 4.11 (t, J = 5.1 Hz, 2H).

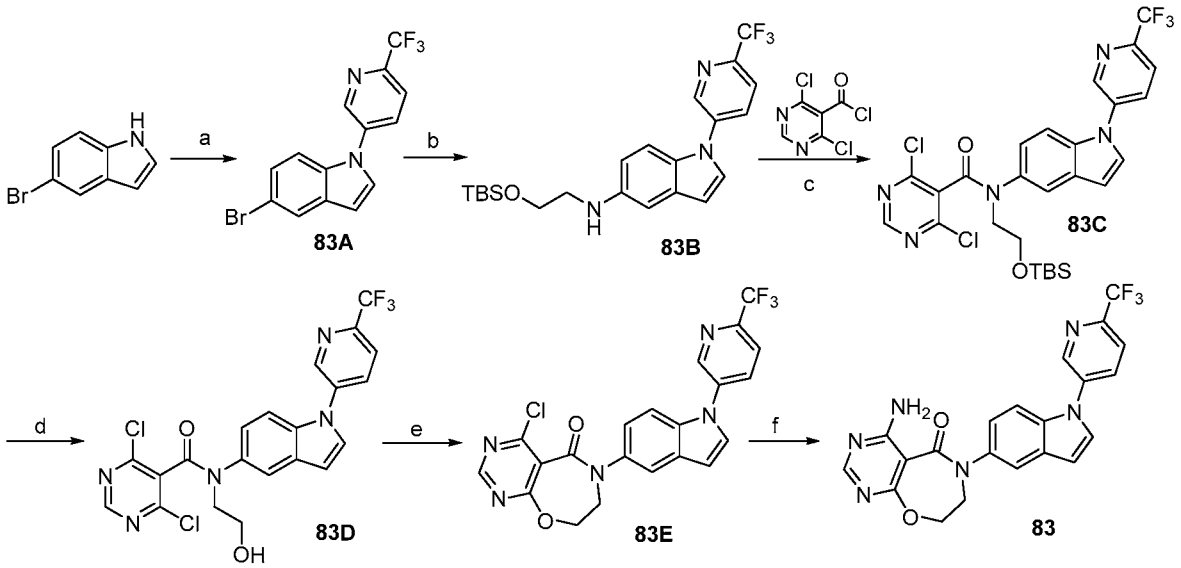
4-Amino-6-(1-(thiazol-2-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (82):



82

A solution of product of Example 82E (0.15 g, 0.377 mmol) in 0.5M ammonia in p-dioxane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.09 g, 58%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.35 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.98 (d, J = 3.2 Hz, 1H), 7.72 (d, J = 3.6 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.63 (bs, 2H), 7.57 (d, J = 3.2 Hz, 1H), 7.35 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.86 (d, J = 3.6 Hz, 1H), 4.82 (t, J = 4.4 Hz, 2H), 4.11 (t, J = 4.8 Hz, 2H); ESI-MS m/z = 379 $(M+H)^+$; HPLC purity: 92%.

Example 83: 4-Amino-6-(1-(6-(trifluoromethyl)pyridin-3-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

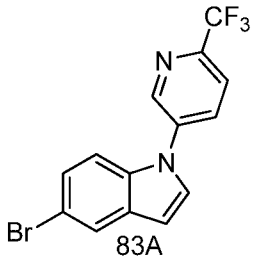


Reagents and conditions: a) 5-Bromo-2-(trifluoromethyl)pyridine, CS_2CO_3, DMF, 90 °C,15h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C, 12h; c) DCM, Et_3N, RT, 1h; d) TBAF, THF, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxane, RT, 2h.

Procedures:

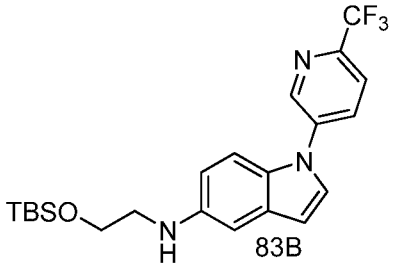
4-Amino-6-(1-(6-(trifluoromethyl)pyridin-3-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

5-Bromo-1-(6-(trifluoromethyl)pyridin-3-yl)-1H-indole (83A):



5-Bromo-2-(trifluoromethyl)pyridine (2.075 g, 9.18 mmol) was added to a solution of 5-bromo-1H-indole (1.5 g, 7.65 mmol) and in DMF (20 mL) followed by cesium carbonate (7.48 g, 22.95 mmol), and the mixture was stirred at 90 °C for 15 min. Insoluble solids were filtered, filtrate was concentrated and partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography using 5% ethyl acetate in pet ether to afford title compound (1.1 g, 42.1%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.09 (d, J = 2.4 Hz, 1H), 8.37 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.91 (m, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.37 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 6.82 (d, J = 3.0 Hz, 1H).

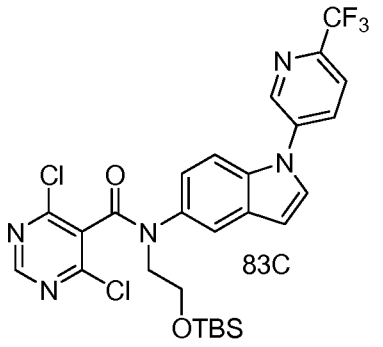
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-1-(6-(trifluoromethyl)pyridin-3-yl)-1H-indol-5-amine (83B):



83B

A mixture of product of Example 83A (0.3 g, 0.879 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.231 g, 1.319 mmol), cesium carbonate (0.86 g, 2.64 mmol), palladium acetate (19 mg, 0.088 mmol) and X-PHOS (0.042 g, 0.088 mmol) in Toluene (25 mL) under Argon was refluxed at 110 °C for 12 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 7% ethyl acetate in hexane to afford title compound (0.15 g, 39.2%) as a pale yellow solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.04 (d, J = 2.4 Hz, 1H), 8.29 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 3.2 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.68 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 5.22 (t, J = 6.0 Hz, 1H) 3.76 (t, J = 6.0 Hz, 2H), 3.18 (q, J = 6.0, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

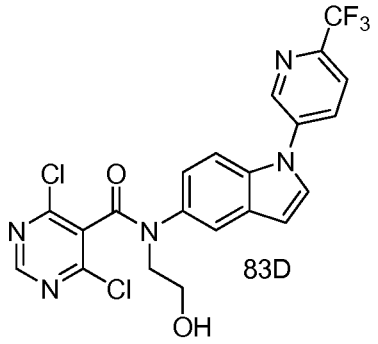
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(1-(6-(trifluoromethyl)pyridin-3-yl)-1H-indol-5-yl)pyrimidine-5-carboxamide (83C):



83C

To a stirred, cooled (0 °C) solution of product of Example 83B (0.5 g, 1.148 mmol) and TEA (0.8 mL, 5.74 mmol) in DCM (10 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.362 g, 1.72 mmol) in DCM (3 mL). After 1 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x5 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane as eluent to afford title compound (0.5 g, 57.5%) as pale yellow solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.02 (d, J = 2.0 Hz, 1H), 8.75 (s, 1H), 8.31 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 3.6 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.28 (dd, J_1 = 1.2 Hz, J_2 = 8.8 Hz, 1H), 6.80 (d, J = 3.2 Hz, 1H), 4.01 (t, J = 4.4 Hz, 2H) 3.79 (t, J = 5.6 Hz, 2H), 0.8 (s, 9H), 0.04 (s, 6H).

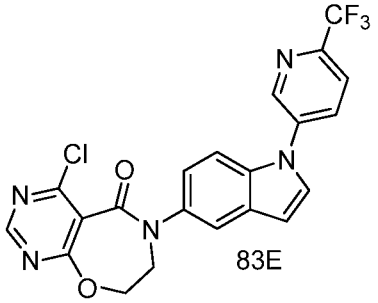
4,6-Dichloro-N-(2-hydroxyethyl)-N-(1-(6-(trifluoromethyl)pyridin-3-yl)-1H-indol-5-yl)pyrimidine-5-carboxamide (83D):



83D

A solution of product of Example 83C (0.5 g, 0.819 mmol), in 15 mL of methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 3 h. Methanol was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.3 g, 67.5%) as a white solid, which was carried on to the next step without further purification. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.03 (d, J = 1.6 Hz, 1H), 8.74 (s, 1H), 8.33 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 4.87 (m, 1H) 3.95 (t, J = 6.4 Hz, 2H), 3.63 (m, 2H).

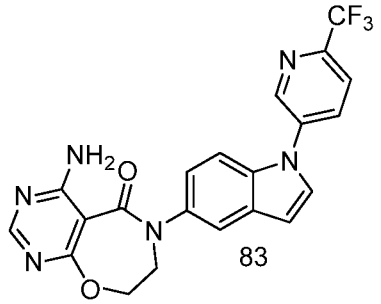
4-Chloro-6-(1-(6-(trifluoromethyl)pyridin-3-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (83E):



83E

A slurry of product of Example 83D (0.3 g, 0.605 mmol) and TEA (0.42 mL, 3.02 mmol) in acetonitrile (25 mL) was stirred at 80 °C for 12 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.2 g, 69.4%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.12 (d, J = 2.4 Hz, 1H), 8.84 (s, 1H), 8.40 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 3.6 Hz, 1H), 7.80 (s, 1H), 7.77 (d, J = 2.4 Hz, 2H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 4.78 (t, J = 5.2 Hz, 2H), 4.19 (t, J = 4.8 Hz, 2H).

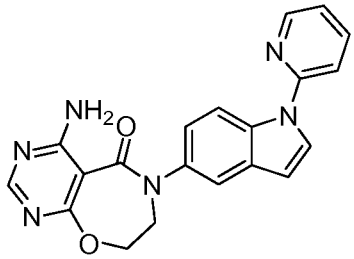
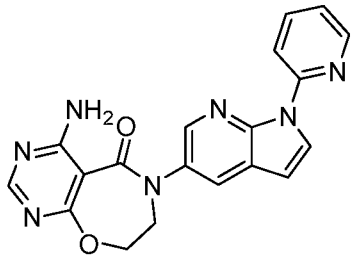
4-Amino-6-(1-(6-(trifluoromethyl)pyridin-3-yl)-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (83):

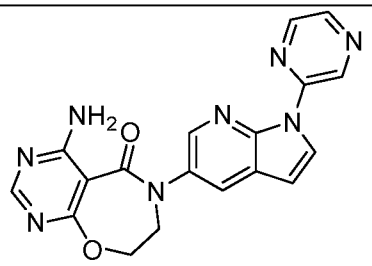
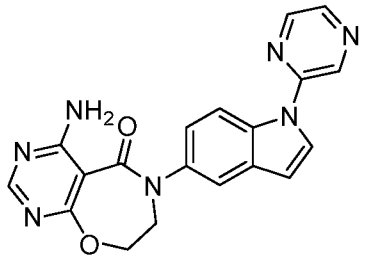
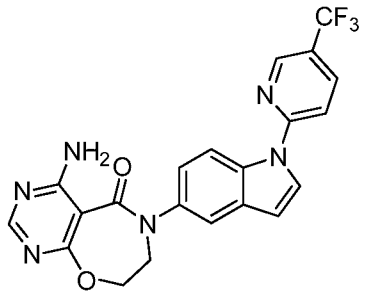
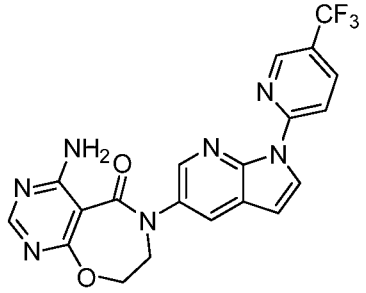
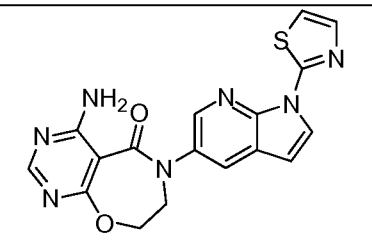


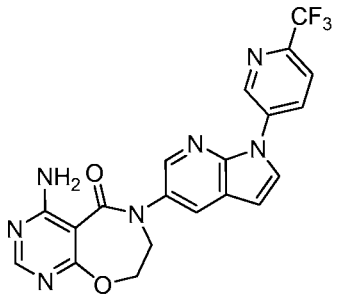
83

A solution of product of Example 83E (0.21 g, 0.457 mmol) in 0.5M ammonia in p-dioxane (10 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.135 g, 65.6%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.12 (d, J = 2.4 Hz, 1H), 8.40 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 8.18 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 3.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.64 (bs, 2H), 7.25 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 4.66 (t, J = 4.0 Hz, 2H), 4.02 (t, J = 5.2 Hz, 2H). ESI-MS m/z: 441 $(M+H)^+$; HPLC purity: 97%.

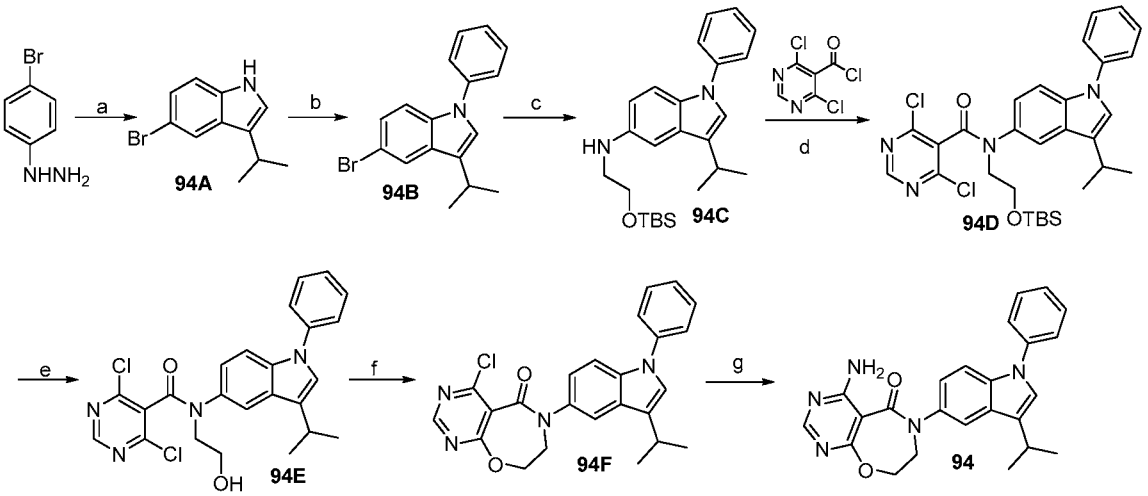
Examples 84 – 93 were prepared by the procedures analogous to those described in Example 82 or Example 83 using appropriately substituted starting materials.

Ex	Structure	Analytical Data	Mass/Purity
84		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (d, J = 3.2 Hz, 1H), 8.44 (d, J = 8.8 Hz, 1H), 8.19 (s, 1H), 8.11 (d, J = 3.2 Hz, 1H), 8.01 (dt, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64 (m, 3H), 7.33 (m, 1H), 7.26 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.79 (d, J = 3.6 Hz, 1H), 4.66 (t, J = 3.6 Hz, 2H), 4.03 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 373 $(M+H)^+$; HPLC purity: 98%.
85		^{1}H NMR (400MHz, $CDCl_3$): δ 8.86 (d, J = 8.4 Hz, 1H), 8.50 (d, J = 3.6 Hz, 1H), 8.45 (d, J = 4.0 Hz, 1H), 8.32 (m, 2H), 8.20 (bs, 1H), 7.88 (dt, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 2H), 7.20 (m, 1H), 6.67 (d, J = 4.0 Hz, 1H), 5.70 (bs, 1H), 4.77 (t, J = 4.4 Hz, 2H), 4.10 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 374 $(M+H)^+$; HPLC purity: 98%.

86		^{1}H NMR (300MHz, DMSO-d_6): δ 10.1 (d, J = 1.2 Hz, 1H), 8.64-8.6 (m, 2H), 8.49 (d, J = 2.4 Hz, 1H), 8.40 (d, J = 3.9 Hz, 1H), 8.20 (m, 2H), 7.68 (bs, 2H), 6.91 (d, J = 4.2 Hz, 1H), 4.71 (t, J = 3.6 Hz, 2H), 4.09 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 375 $(M+H)^+$; HPLC purity: 98%.
87		^{1}H NMR (400MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.63 (s, 1H), 8.55 (d, J = 2.4 Hz, 1H), 8.48 (d, J = 8.8 Hz, 1H), 8.26 (d, J = 3.6 Hz, 1H), 8.19 (s, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.63 (bs, 2H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.87 (d, J = 3.6 Hz, 1H), 4.66 (t, J = 4.4 Hz, 2H), 4.03 (t, J = 5.2 Hz, 2H).	ESI-MS m/z = 374 $(M+H)^+$; HPLC purity: 98%.
88		^{1}H NMR (300MHz, DMSO-d_6): δ 8.9 (s, 1H), 8.59 (d, J = 9.0 Hz, 1H), 8.39 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1H), 8.24 (d, J = 3.3 Hz, 1H), 8.19 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.63 (bs, 2H), 7.32 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 6.88 (d, J = 3.3 Hz, 1H), 4.66 (t, J = 4.2 Hz, 2H), 4.04 (t, J = 4.2 Hz, 2H).	ESI-MS m/z = 441 $(M+H)^+$; HPLC purity: 94%.
89		^{1}H NMR (400MHz, DMSO-d_6): δ 9.18 (d, J = 8.8 Hz, 1H), 8.94 (s, 1H), 8.85 (s, 1H), 8.53 (m, 2H), 8.49 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 4.0 Hz, 1H), 4.82 (t, J = 4.4 Hz, 2H), 4.27 (t, J = 4.8 Hz, 2H).	ESI-MS m/z = 442 $(M+H)^+$; HPLC purity: 98%.
90		^{1}H NMR (300MHz, DMSO-d_6): δ 8.52 (d, J = 2.1 Hz, 1H), 8.37 (d, J = 3.9 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H) 8.19 (s, 1H), 7.69 (m, 3H), 7.58 (d, J = 3.6 Hz, 1H), 6.90 (d, J = 3.6 Hz, 1H), 4.71 (t, J = 4.2 Hz, 2H), 4.09 (t, J = 4.2 Hz, 2H).	ESI-MS m/z = 380 $(M+H)^+$; HPLC purity: 95%.

93		^{1}H NMR (300MHz, DMSO-d_6): δ 9.46 (d, J = 1.8 Hz, 1H), 8.8 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 8.42 (d, J = 2.1 Hz, 1H), 8.28 (d, J = 3.6 Hz, 1H), 8.19 (m, 2H), 8.14 (d, J = 8.4 Hz, 2H), 7.68 (bs, 2H), 6.91 (d, J = 3.9 Hz, 1H), 4.71 (t, J = 4.2 Hz, 2H), 4.07 (t, J = 4.2 Hz, 2H).	ESI-MS m/z: 442 $(M+H)^+$; HPLC purity: 96%.

Example 94: 4-Amino-6-(3-isopropyl-1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

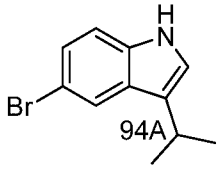


Reagents and conditions: a) Iso-valeraldehyde, AcOH, 120 °C, 3h b) Iodobenzene, CuBr, $Cu(OAc)_2$, K_2CO_3, NaOH, 140 °C, 9h; c) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 120 °C, 2.5h; d) DCM, Et_3N, RT, 1h; e) 3% HCl-MeOH, RT, 1h; f) CH_3CN, Et_3N, 80 °C, 16h; g) NH_3, Dioxane, RT, 2h.

Procedures:

4-Amino-6-(3-isopropyl-1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

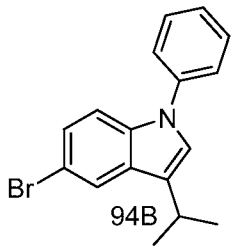
5-Bromo-3-isopropyl-1H-indole (94A):



3-Methylbutanal (0.921 g, 10.69 mmol) was added to a solution of (4-bromophenyl)hydrazine (2 g, 10.69 mmol) in acetic acid (100 mL) at 80 °C, and the mixture was stirred for 3 h at 120 °C. The reaction mixture was concentrated to get the residue, and the residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with saturated bicarbonate solution and brine, dried over sodium sulphate and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography using 2% ethyl acetate in pet ether to afford title compound (1.1 g,

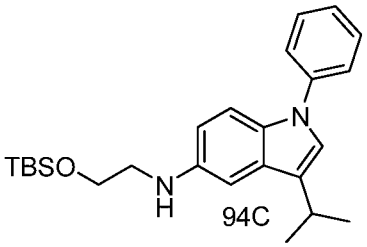
38.4%) as an oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.91 (bs, 1H), 7.76 (m, 1H), 7.25-7.20 (m, 2H), 6.95 (d, J = 2.4 Hz, 1H), 3.18-3.11 (m, 1H), 1.35 (d, J = 6.8 Hz, 6H).

5-Bromo-3-isopropyl-1-phenyl-1H-indole (94B):



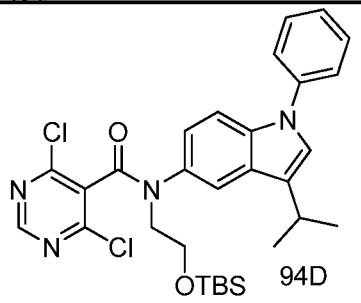
Copper(I) bromide (66 mg, 0.462 mmol) was added to a solution of 94A (1.1 g, 4.62 mmol) in iodo benzene (3.77g, 18.48 mmol) followed by potassium carbonate (2.55 g, 18.48 mmol), and the mixture was stirred at 100 °C for 10 min. NaOH (150 mg, 3.75 mmol) and copper(II) acetate (10 mg, 0.055 mmol) was added at 140 °C, and the mixture was stirred for 9 h. Insoluble solids were filtered, the filtrate was concentrated and partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography using 8% ethyl acetate in hexane to afford title compound (1.0 g, 68.9%) as an oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.80 (d, J = 2.1 Hz, 1H), 7.54-7.42 (m , 5H), 7.4-7.28 (m, 2H), 7.21-7.08 (m, 2H), 3.19 (m, 1H), 1.38 (d, J = 6.9 Hz, 6H).

N-(2-(tert-Butyldimethylsilyloxy)ethyl)-3-isopropyl-1-phenyl-1H-indol-5-amine (94C):



A mixture of product of Example 94B (1 g, 3.18 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.558 g, 3.18 mmol), cesium carbonate (2.074 g, 6.36 mmol), palladium acetate (0.071 g, 0.318 mmol) and X-PHOS (0.152 g, 0.318 mmol) in Toluene (20 mL) under Argon was refluxed at 120 °C for 2.5 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.6 g, 46.1%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.46 (m, 4H), 7.28 (m, 1H), 7.18 (m, 1H), 7.05 (s, 1H), 6.94 (m, 1H), 6.70 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 3.87 (t, J = 5.6 Hz, 2H), 3.31 (t, J = 5. 6 Hz, 2H), 3.18 (m, 1H), 1.38 (d, J = 7.2 Hz, 6H), 0.92 (s, 9H), 0.09 (s, 6H).

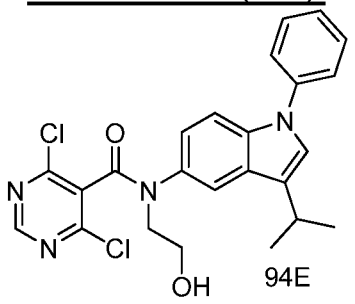
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(3-isopropyl-1-phenyl-1H-indol-5-yl)pyrimidine-5-carboxamide (94D):



94D

To a stirred, cooled (0 °C) solution of product of Example 94C (0.6 g, 1.468 mmol) and TEA (1.023 mL, 7.34 mmol) in DCM (15 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.31 g, 1.468 mmol) in DCM (5 mL). After 1 h, the reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford an oil. The residue was purified by flash chromatography using 12% ethyl acetate in hexane to afford title compound (0.4 g, 46.7%) as a syrup.

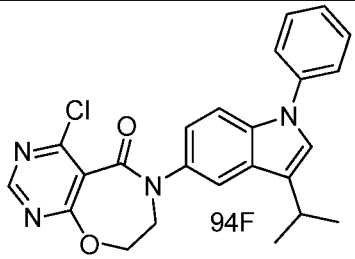
4,6-Dichloro-N-(2-hydroxyethyl)-N-(3-isopropyl-1-phenyl-1H-indol-5-yl)pyrimidine-5-carboxamide (94E):



94E

TBAF (0.358 g, 1.371 mmol) was added to a solution of Example 94D (0.4 g, 0.685 mmol) in THF (15 mL), and the mixture was stirred at room temperature for 1 h. THF was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.2 g, 62.2%) as a solid, which was carried on to the next step without further purification.

4-Chloro-6-(3-isopropyl-1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (94F):

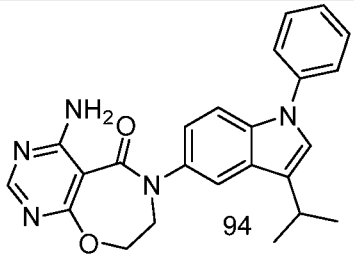


94F

A slurry of product of Example 94E (0.2 g, 0.426 mmol) and TEA (0.297 mL, 2.131 mmol) in acetonitrile (15 mL) was stirred at 80 °C for 16 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated

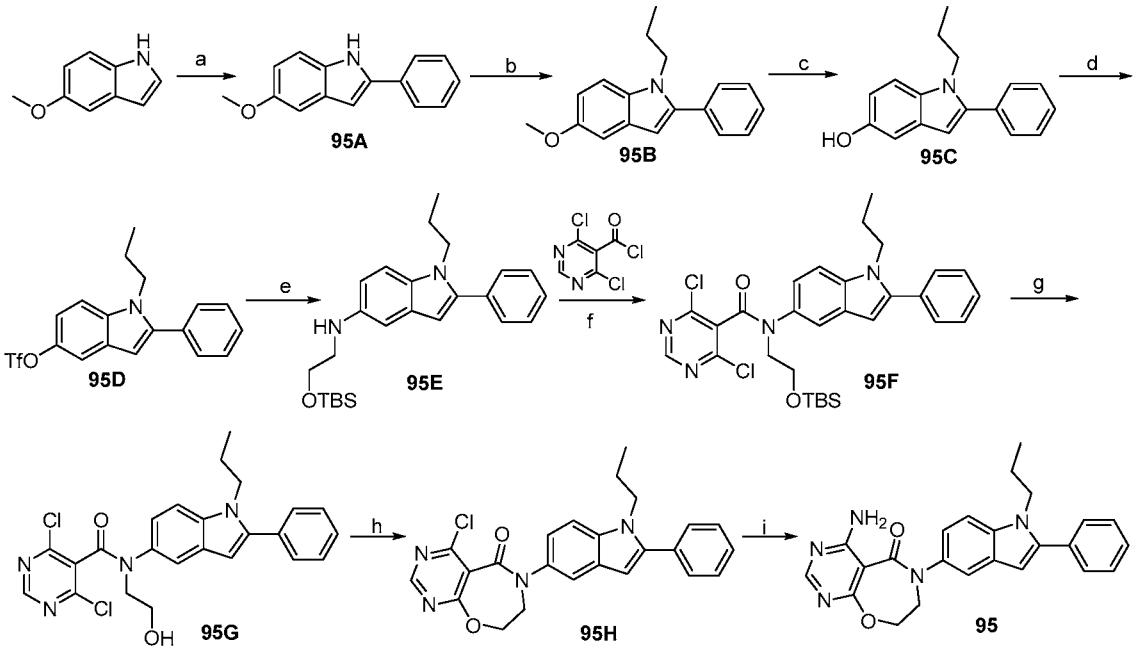
in vacuo to afford title compound (0.1 g, 54.2%) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.60-7.48 (m, 5H), 7.4-7.3 (m, 1H), 7.19-7.12 (m, 2H), 4.95 (t, *J* = 3.9 Hz, 1H), 4.02 (t, *J* = 4.5 Hz, 2H), 3.25-3.21 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 6H).

4-Amino-6-(3-isopropyl-1-phenyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (94):



A solution of product of Example 94F (0.1 g, 0.231 mmol) in 0.5M ammonia in p-dioxane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.06 g, 61.6%) as a white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.64 (d, *J* = 1.5 Hz, 1H), 7.66-7.54 (m, 6H), 7.47 (m, 1H), 7.38 (m, 1H), 7.14 (bs, 2H), 4.65 (t, *J* =3.9 Hz, 2H), 4.02 (t, *J* = 4.5 Hz, 2H), 3.20 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 6H); ESI-LC MS *m/z* = 414 $(M+H)^+$; HPLC purity: 98.30%.

Example 95: 4-Amino-6-(2-phenyl-1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

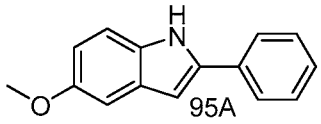


Reagents and conditions: a) Phenyl boronic acid, AcOH, $Pd(OAc)_2$, copper(II) acetate, 25 °C 12h; b) Cs_2CO_3, DMF, 25 °C, 12h; c) BBr_3, DCM, 0 °C, 1h; d) Triflic anhydride, Py, DCM, 0 °C, 1h; e) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 110 °C, 4h; f) Et_3N, DCM, 0 °C, 1h; g) MeOH/HCl, 25 °C, 2h; h) Et_3N, ACN, 70 °C, 24h; i) NH_3 gas, Dioxane, 25 °C, 3h.

Procedures:

4-Amino-6-(2-phenyl-1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

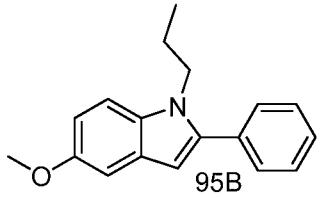
5-methoxy-2-phenyl-1H-indole (95A):



95A

$Pd(OAc)_2$ (0.031 g, 0.136 mmol) was added to a solution of 5-methoxy-1H-indole (0.2g, 1.359 m mol) and phenylboronic acid (0.249 g, 2.038 mmol) in acetic acid (2 mL) followed by copper (II) acetate (0.025 g, 0.138 mmol), and the mixture was stirred at 25 °C for 2 h under oxygen atmosphere. Insoluble solids were filtered off, and filtrate was concentrated. Residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.08 g, 24%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.3 (s, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.32-7.26 (m, 2H), 7.02 (d, J = 2.4 Hz 1H), 6.81 (d, J = 1.2 Hz, 1H), 6.74 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H) 3.78 (s ,3H).

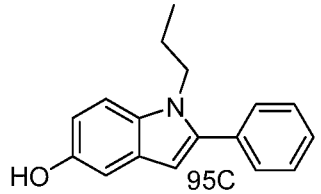
5-Methoxy-2-phenyl-1-propyl-1H-indole (95B):



95B

1-Bromopropane (0.248 g, 2.015 mmol) was added to a solution of 95A (0.15 g, 0.672 mmol) in DMF (5 mL) followed by cesium carbonate (0.657 g, 2.015 mmol), and the mixture was stirred at 25 °C for 12 h. Insoluble solids were filtered off, and filtrate was concentrated. Residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 3% ethyl acetate in hexane as eluent to afford title compound (0.1 g, 56.1%) as a solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.54-7.5 (m, 4H), 7.46-7.39 (m, 2H), 7.06 (d, J = 2.0 Hz, 1H), 6.8 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.42 (s, 1H), 4.12 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 1.54 (m , 2H), 0.63 (t, J = 7.2 Hz).

2-Phenyl-1-propyl-1H-indol-5-ol (95C):

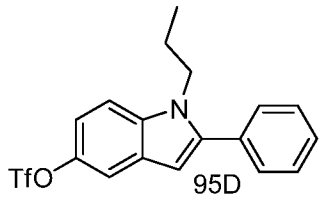


95C

BBr_3 (0.107 mL, 1.131 mmol) was added to a solution of Example 95B (0.1g, 0.398 mmol) in DCM (20 mL) at 0 °C, and the mixture was stirred for 1 h. The reaction mixture

was quenched with saturated bicarbonate solution and extracted with DCM (2x30 mL). Organic layer was separated, washed with water and brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was triturated with diethyl ether to afford title compound (0.05 g, 52.8%) as white solid. ^{1}H NMR (400MHz, DMSO–d_6): δ 8.72 (s, 1H), 7.5 (m, 4H), 7.42 (m, 1H), 7.30 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 6.67 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.32 (s, 1H), 4.07 (t, J = 7.2 Hz, 2H), 1.53 (m, 2H), 0.64 (t, J = 7.2 Hz, 3H).

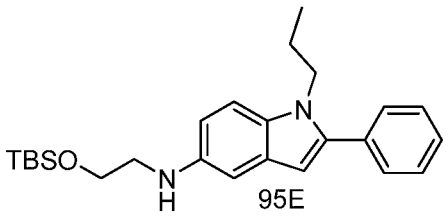
2-Phenyl-1-propyl-1H-indol-5-yl trifluoromethanesulfonate (95D):



95D

Triflic anhydride (0.112 g, 0.398 mmol) was added to an ice cold solution of product of Example 95C (0.1 g, 0.398 mmol) and pyridine (0.048 mL, 0.597 mmol) in dichloromethane (20 mL), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with dichloromethane (10 mL) and extracted with saturated aqueous solution of NaCl (45 mL). The organic layer was dried over sodium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography using 6% ethyl acetate in hexanes to give the title compound (0.08 g, 52.4 %) as a solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 7.73 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 2.7 Hz, 1H), 7.58-7.46 (m, 5H), 7.22 (dd, J_1 = 2.7 Hz, J_2 = 8.7 Hz, 1H), 6.65 (s, 1H), 4.20 (t, J = 6.9 Hz, 2H), 1.56 (m, 2H), 0.65 (t, J = 7.8 Hz, 3H).

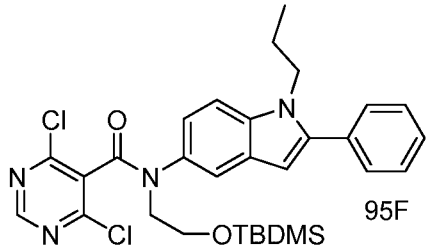
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-2-phenyl-1-propyl-1H-indol-5-amine (95E):



95E

A mixture of product of Example 95D (0.2 g, 0.522 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.183 g, 1.043 mmol), cesium carbonate (0.510 g, 1.565 mmol), palladium acetate (0.012 g, 0.052 mmol) and X-PHOS (0.0025 g, 0.052 mmol) in Toluene (20 mL) under Argon was refluxed at 111 °C for 4 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 15% ethyl acetate in hexane to afford title compound (1.5 g, 53%) as a solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.50 (m, 4H), 7.4 (m, 1H), 7.25 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 1.6 Hz, 1H), 6.61 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.27 (s, 1H), 4.91 (t, J = 6.0 Hz, 1H), 4.05 (t, J = 6.8 Hz, 2H), 3.76 (t, J = 6.4 Hz, 2H), 3.16 (q, J = 6.0 Hz, 2H), 1.52 (m, 2H), 0.87 (s, 9H), 0.63 (t, J = 7.2 Hz, 3H), 0.059 (s, 6H).

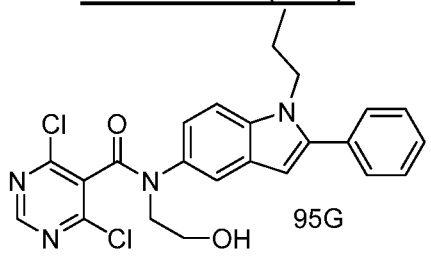
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(2-phenyl-1-propyl-1H-indol-5-yl)pyrimidine-5-carboxamide (95F):



95F

To a stirred, cooled (0 °C) solution of product of Example 95E (0.04 g, 0.98 mmol) and TEA (0.041 mL, 0.294 mmol) in DCM (10 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.030 g, 0.14 mmol) in DCM (3 mL). After 1 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x10 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 20% ethyl acetate in hexane as eluent to afford title compound (0.031 g, 32.1%) as a solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.74 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.54-7.44 (m, 6H), 7.18 (dd, J_1 = 2.0, J_2 = 8.8 Hz, 1H), 6.48 (s, 1H), 4.09 (t, J = 7.2 Hz, 2H), 3.99 (t, J = 6.0 Hz, 2H), 3.8 (t, J = 5.6 Hz, 2H), 1.46 (m, 2H), 0.85 (s, 9H), 0.59 (t, J = 7.2 Hz, 3H), 0.04 (s, 6H).

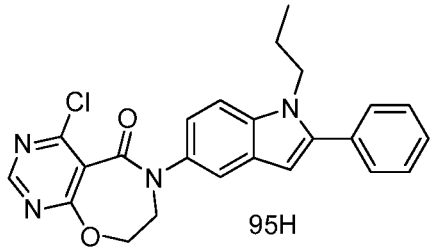
4,6-Dichloro-N-(2-hydroxyethyl)-N-(2-phenyl-1-propyl-1H-indol-5-yl)pyrimidine-5-carboxamide (95G):



95G

A solution of product of Example 95F (0.35 g, 0.6 mmol), in 20 mL of methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 2 h. Methanol was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.225 g, 76%) as a solid, which was carried on to the next step without further purification. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.73 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.53-7.43 (m, 6H), 7.20 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.51 (s, 1H), 4.84 (t, J = 5.2 Hz, 1H), 4.09 (t, J = 7.6 Hz, 2H), 3.93 (t, J = 6.4 Hz, 2H), 3.63 (q, J = 6.0 Hz, 2H), 1.49 (m, 2H), 0.6 (t, J = 7.2 Hz, 3H).

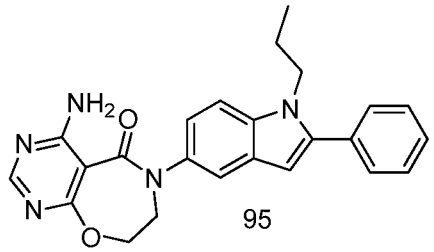
4-Chloro-6-(2-phenyl-1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (95H):



95H

A slurry of product of Example 95G (0.225 g, 0.479 mmol) and TEA (0.334 mL, 2.397 mmol) in acetonitrile (15 mL) was stirred at 80 °C for 16 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.15 g, 72.3%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.83 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.58-7.44 (m, 5H), 7.19 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.58 (s, 1H), 4.77 (t, J = 5.2 Hz, 2H), 4.22-4.15 (m, 4H), 1.58 (m, 2H), 0.66 (t, J = 7.6 Hz, 3H).

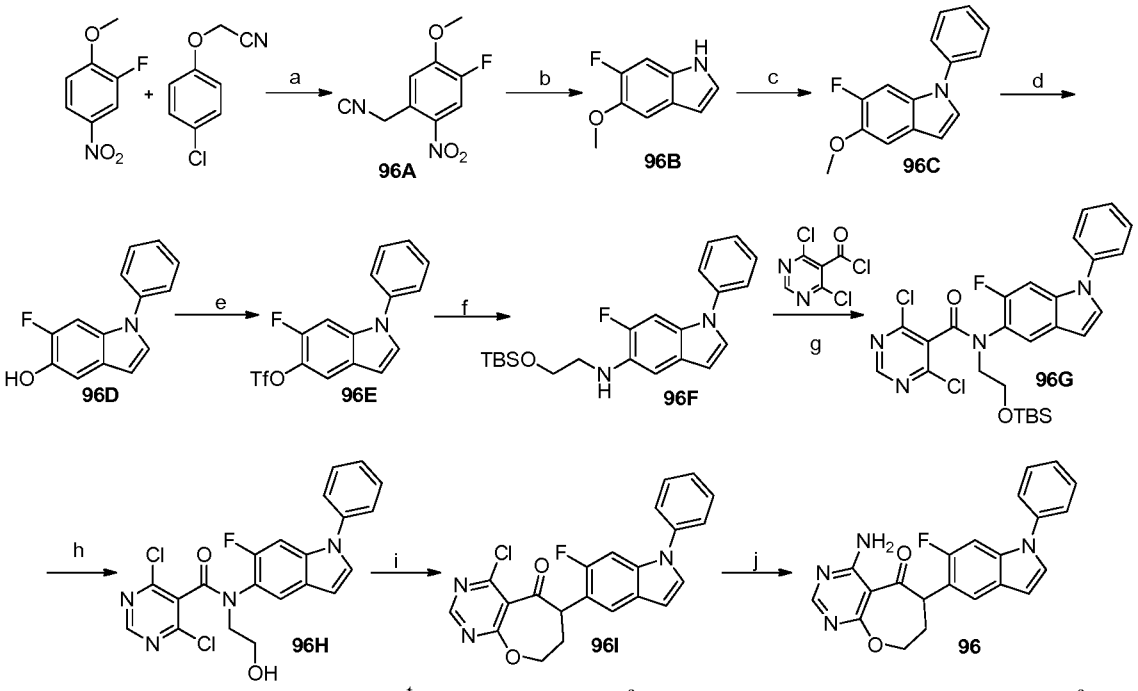
4-Amino-6-(2-phenyl-1-propyl-1H-indol-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (95):



95

A solution of product of Example 95H (0.15 g, 0.346 mmol) in 0.5M ammonia in p-dioxane (20 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.105 g, 71.1%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.68-7.44 (m, 9H), 7.15 (d, J = 8.0 Hz, 1H), 6.55 (s, 1H), 4.65 (m, 2H), 4.19 (t, J = 6.8 Hz, 2H), 4.01 (m, 2H), 1.58 (m, 2H), 0.68 (t, J =7.6 Hz, 3H); ESI-MS m/z = 414.0 $(M+H)^+$; HPLC purity: 97%.

Example 96: 4-Amino-6-(6-fluoro-1-phenyl-1H-indol-5-yl)-7,8-dihydrooxepino[2,3-d]pyrimidin-5(6H)-one:

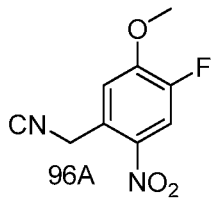


Reagents and conditions: a)K^{t}Obu, DMF, -20 °C, 1h; b) 10% Pd/C, Ethanol, 27 °C, 3h; c) $Cu(OAc)_2$, CuBr, K_2CO_3, NaOH, DMF, 80 °C, 16h; d) Py/HCl, 180 °C, 4h; e) Tf_2O, Pyridine, DCM, 0 °C, 0.5 h; f) $Pd(OAc)_2$, $NH_2(CH_2)_2OTBDMS$, Cs_2CO_3, X-PHOS, Toluene, 100 °C, 4h; g) DCM, Et_3N, RT, 3h; h) 3% HCl-EtOH, RT, 1h; i) CH_3CN, Et_3N, 80 °C, 16h; j) NH_3, Dioxane, RT, 6h.

Procedures:

4-Amino-6-(6-fluoro-1-phenyl-1H-indol-5-yl)-7,8-dihydrooxepino[2,3-d]pyrimidin-5(6H)-one:

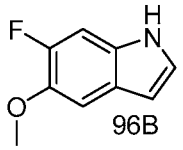
1-Fluoro-4-(isocyanomethyl)-2-methoxy-5-nitrobenzene (96A):



Potassium *t*-butoxide (15.74 g, 140 mmol) in DMF (50 mL) was added to a solution of 2-fluoro-1-methoxy-4-nitrobenzene (12 g, 70.1 mmol) and 2-(4-chlorophenoxy)acetonitrile (11.75 g, 70.1 mmol) in DMF (100 mL) at -20 °C. The reaction mixture was stirred for 1 h and then quenched with water. The aqueous layer was extracted with ethyl acetate. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 3% ethyl acetate in hexane to afford title compound (3.6 g, 23.21%) as a solid. ^{1}H NMR

(400MHz, $CDCl_3$): δ 8.05 (d, *J* = 10.84 Hz, 1H), 7.27-7.23 (m, 1H), 4.28 (s, 2H), 4.05 (s, 3H); ESI-MS *m/z* = 209 $(M-H)^-$; LCMS Purity: 95%

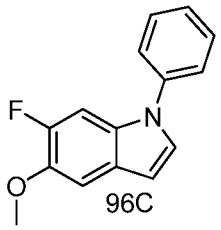
6-Fluoro-5-methoxy-1H-indole (96B):



96B

Palladium on carbon (1 g, 0.940 mmol) was added to a solution of product of Example 96A (3.5 g, 16.65 mmol) in ethanol (40 mL) under hydrogen atmosphere, and the mixture was stirred for 4 h. Insoluble solids were filtered off, and filtrate was concentrated to afford title compound (2.2 g, 78%) as a solid. ^1H NMR (400MHz, $CDCl_3$): δ 8.05 (bs, 1H), 7.20-7.11 (m, 3H), 6.48 (d, *J* = 2.4 Hz, 1H), 3.95 (s, 3H).

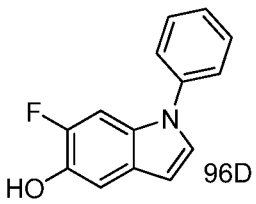
6-Fluoro-5-methoxy-1-phenyl-1H-indole (96C):



96C

Iodo benzene (1.729 g, 8.48 mmol) was added to a solution of product of Example 96B (1.4 g, 8.48 mmol) and Copper(I) bromide (10.46 mg, 0.073 mmol) in DMF (10 mL) followed by potassium carbonate (3.51 g, 25.4 mmol), and the mixture was stirred at 100 °C for 10 min. NaOH (210 mg, 5.25 mmol) and copper(II) acetate (14 mg, 0.077 mmol) was added, and the mixture was stirred at 110 °C for 16 h. Insoluble solids were filtered off, and filtrate was concentrated. Residue was partitioned between diethyl ether and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ethyl acetate in hexane as eluent to afford title compound (1.45 g, 67.4%) as off-white solid. ^1H NMR (300MHz, $CDCl_3$): δ 7.55-7.44 (m, 4H), 7.38-7.26 (m, 3H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 3.95 (s, 3H).

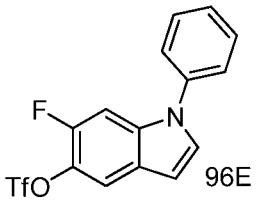
6-Fluoro-1-phenyl-1H-indol-5-ol (96D):



96D

A mixture of product of Example 96C (1.1 g, 4.56 mmol) and pyridine-hydrochloride (0.527 g, 4.56 mmol) was stirred at 160 °C in seal tube for 6 h. The mixture was dissolved in ethyl acetate, washed with water and saturated aqueous brine, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography using 12% ethyl acetate in hexane to afford title compound (0.37 g, 32.5%) as a pale brown solid. ^1H NMR (400MHz, $CDCl_3$): δ 7.6 (d, *J* = 6.8 Hz, 1H), 7.58-7.53 (m, 2H), 7.48-7.34 (m, 5H), 6.7 (d, *J* = 3.6 Hz, 1H).

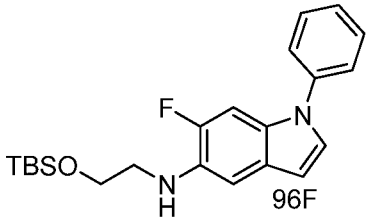
6-Fluoro-1-phenyl-1H-indol-5-yl trifluoromethanesulfonate (96E):



96E

Triflic anhydride (0.372 g, 2.2 mmol) was added to an ice cold solution of product of Example 96D (0.5 g, 2.2 mmol) and pyridine (0.087 mg, 1.1 mmol) in dichloromethane (10 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane (20 mL) and extracted with saturated aqueous solution of NaCl (15 mL). The organic layer dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure to afford title compound (0.7 g, 89%) as an oil. ESI-MS *m/z* = 360 $(M+H)^+$; LCMS Purity: 85%.

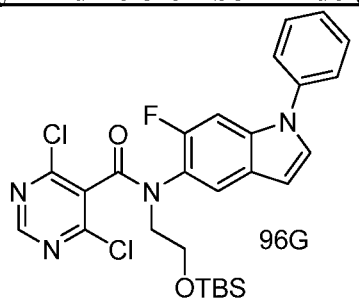
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-6-fluoro-1-phenyl-1H-indol-5-amine (96F):



96F

A mixture of product of Example 96E (0.1 g, 0.278 mmol), 2-(*t*-butyldimethylsilyloxy)ethanamine (0.048 g, 0.278 mmol), cesium carbonate (0.136 g, 0.417 mmol), palladium acetate (6.25 mg, 0.028 mmol) and X-PHOS (13.27 mg, 0.028 mmol) in toluene (10 mL) under Argon was refluxed at 120 °C for 2.5 h. The reaction was cooled, diluted with ethyl acetate, and washed with water (2x5 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (0.03 g, 25%) as an off-white solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.6-7.5 (m, 5H), 7.4-7.25 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 3.0 Hz, 1H), 4.75 (m, 1H), 3.81 (t, *J* = 5.7 Hz, 2H), 3.25 (q, *J* = 5.7 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(6-fluoro-1-phenyl-1H-indol-5-yl)pyrimidine-5-carboxamide (96G):

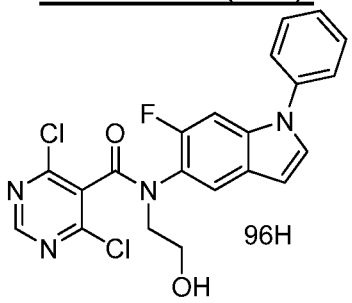


96G

To a stirred, cooled (0 °C) solution of product of Example 96F(0.18 g, 0.468 mmol) and TEA (0.065 mL, 0.468 mmol) in DCM (8 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.098 g, 0.468 mmol) in DCM (2 mL). After 1 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water

(2x5 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford oil. The residue was purified by flash chromatography using 20% ethyl acetate in hexane to afford title compound (100 mg, 38%) as a pale yellow oil.

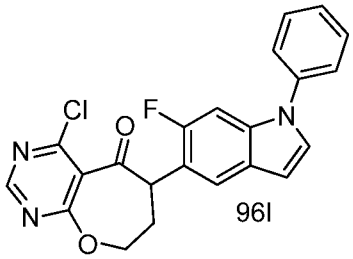
4,6-Dichloro-N-(6-fluoro-1-phenyl-1H-indol-5-yl)-N-(2-hydroxyethyl)pyrimidine-5-carboxamide (96H):



96H

A solution of product of Example 96G (100 mg, 0.179 mmol), in 10 mL of ethanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of ethanol) was stirred at room temperature for 1 h. Ethanol was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.07 g, 77%) as an oil, which was carried on to the next step without further purification.

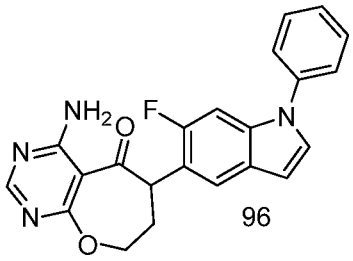
4-Chloro-6-(6-fluoro-1-phenyl-1H-indol-5-yl)-7,8-dihydrooxepino[2,3-d]pyrimidin-5(6H)-one (96I):



96I

A slurry of product of Example 96H (0.07 g, 0.157 mmol) and TEA (0.022 mL, 0.157 mmol) in acetonitrile (8 mL) was stirred at 80 °C for 16 h. The reaction mixture was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.067 g, 87%) as a pale yellow solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.6-7.3 (m, 7H), 6.7 (d, J = 2.8 Hz, 1H), 4.84 (t, J = 4.4 Hz, 2H), 4.04 (t, J = 4.4 Hz, 2H).

4-Amino-6-(6-fluoro-1-phenyl-1H-indol-5-yl)-7,8-dihydrooxepino[2,3-d]pyrimidin-5(6H)-one (96):



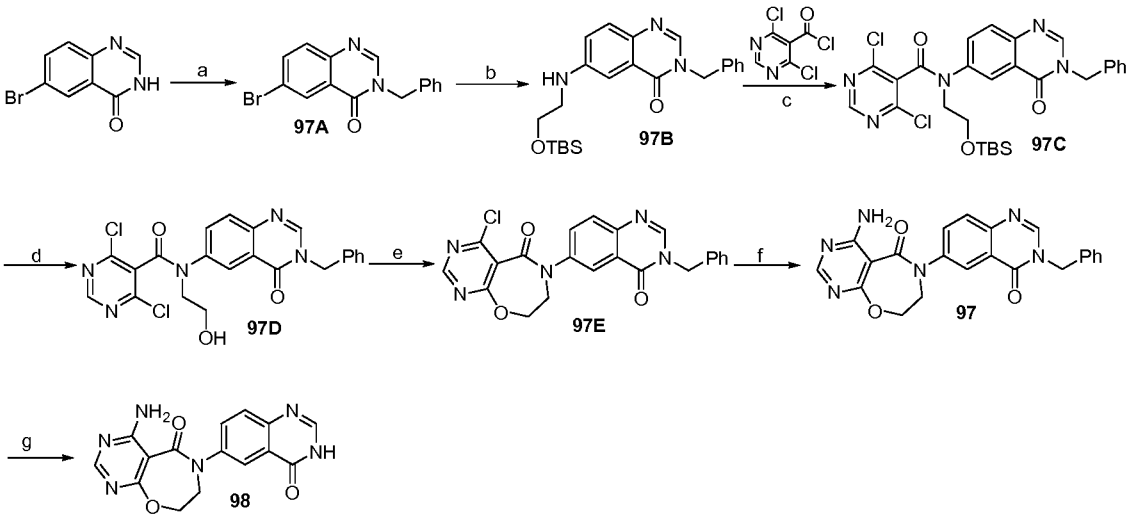
96

A solution of product of Example 96I (0.06 g, 0.147 mmol), in 0.5M ammonia in p-dioxane (8 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.03 g, 48.8%) as a pale yellow solid. ^{1}H NMR (400MHz, DMSO-d_6): δ^1H NMR (400 MHz, DMSO-d_6): δ 8.19 (s, 1H), 7.76-7.56 (m, 7H), 7.5-7.4 (m, 3H), 6.76 (d, J = 2.8 Hz, 1H), 4.64 (t, J = 4.0 Hz, 2H), 4.0 (t, J = 4.0 Hz, 2H); ESI-MS m/z = 390 $(M+H)^+$; HPLC purity: 93%.

Example 97: 4-Amino-6-(3-benzyl-4-oxo-3,4-dihydroquinazolin-6-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

&

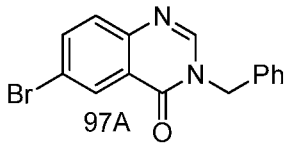
Example 98: 4-Amino-6-(4-oxo-3,4-dihydroquinazolin-6-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:



Reagents and conditions: a) benzyl bromide, NaH, DMF, 80 °C, 4h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Toluene, 110 °C, 16h; c) DCM, Et_3N, RT, 1h; d) 3% HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxane, RT, 2h.

Procedures:

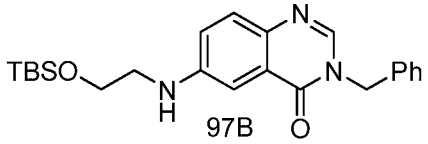
3-Benzyl-6-bromoquinazolin-4(3H)-one (97A):



97A

Benzyl bromide (0.264 mL, 2.22 mmol) was added to a solution of 6-bromoquinazolin-4(3H)-one (0.5 g, 2.22 mmol) and NaH (0.08 g, 3.33 mmol) in DMF (5 mL) at 0 °C. The reaction mixture was heated to 80 °C for 4 h. The reaction mixture was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo to afford title compound (0.4 g, 48.1%) as pale yellow solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.46 (d, J = 1.6 Hz, 1H), 8.09 (s, 1H), 7.83 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.4-7.2 (m, 5H), 5.2 (s, 2H); ESI-MS m/z = 315 $(M+H)^+$; LCMS purity: 84.2%

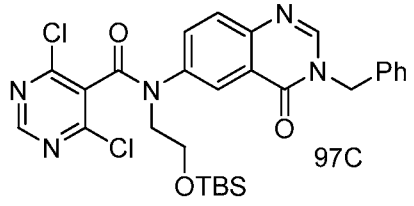
3-Benzyl-6-(2-(tert-butyldimethylsilyloxy)ethylamino)quinazolin-4(3H)-one (97B):



97B

A mixture of product of Example 97A (0.4 g, 1.269 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (0.267 g, 1.523 mmol), cesium carbonate (1.241 g, 3.81 mmol), palladium acetate (0.014 g, 0.063 mmol) and X-PHOS (0.03 g, 0.063 mmol) in Toluene (10 mL) under Argon was refluxed at 110 °C for 16 h. The reaction mixture was cooled, diluted with ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated to obtain dark oil. The residue was purified by flash chromatography using 20% ethyl acetate in hexane to afford title compound (0.2 g, 31.9%) as an off-white solid.

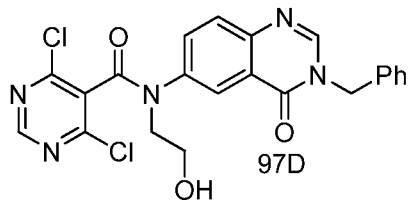
N-(3-Benzyl-4-oxo-3,4-dihydroquinazolin-6-yl)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-4,6-dichloropyrimidine-5-carboxamide (97C):



97C

To a stirred, cooled (0 °C) solution of product of Example 97B (1.2 g, 2.93 mmol) and TEA (1.225 mL, 8.79 mmol) in DCM (20 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (0.61 g, 2.92 mmol) in DCM (5 mL) at -30 °C. After 1 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x15 mL) and saturated aqueous brine, The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford title compound (0.9 g, 25.8%) as a yellow solid.

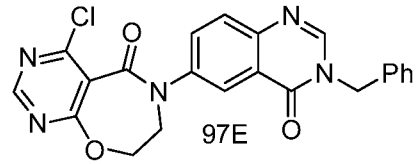
N-(3-Benzyl-4-oxo-3,4-dihydroquinazolin-6-yl)-4,6-dichloro-N-(2-hydroxyethyl)pyrimidine-5-carboxamide (97D):



97D

A solution of product of Example 97C (0.9 g, 1.54 mmol), in 10 mL of methanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of methanol) was stirred at room temperature for 1 h. Methanol was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.5 g, 38%) as a solid, which was used in the next step without further purification.

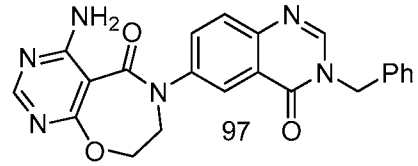
6-(3-Benzyl-4-oxo-3,4-dihydroquinazolin-6-yl)-4-chloro-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (97E):



97E

A slurry of product of Example 97D (0.5 g, 1.063 mmol) and TEA (0.445 g, 3.19 mmol) in acetonitrile (10 mL) was stirred at 80 °C for 16 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.2 g, 38.8%) as a yellow solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.84 (s, 1H), 8.63 (s, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.93 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 7.8 (d, J = 8.4 Hz, 1H), 7.4-7.2 (m, 5H), 5.23 (s, 2H), 4.77 (t, J = 4.5 Hz, 2H), 4.27 (t, J = 4.2 Hz, 2H).

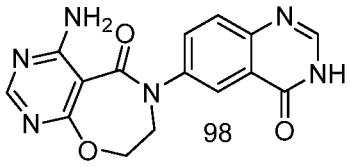
4-Amino-6-(3-benzyl-4-oxo-3,4-dihydroquinazolin-6-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (97):



97

A solution of product of Example 97E (0.18 g, 0.415 mmol) in 0.5M ammonia in p-dioxane (10 mL) was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (0.14 g, 76%) as a white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.61 (s, 1H), 8.18 (s, 1H), 8.11 (d, J = 2.1 Hz, 1H), 7.87 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.67 (bs, 2H), 7.4-7.2 (m, 5H), 5.22 (s, 2H), 4.63 (t, J = 4.5 Hz, 2H), 4.08 (t, J = 4.2 Hz, 2H). ESI-MS m/z = 415 $(M+H)^+$; LCMS purity: 93%.

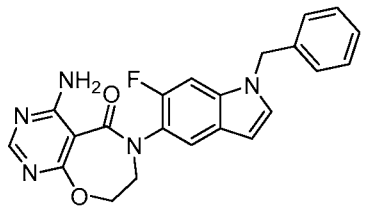
4-Amino-6-(4-oxo-3,4-dihydroquinazolin-6-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (98):



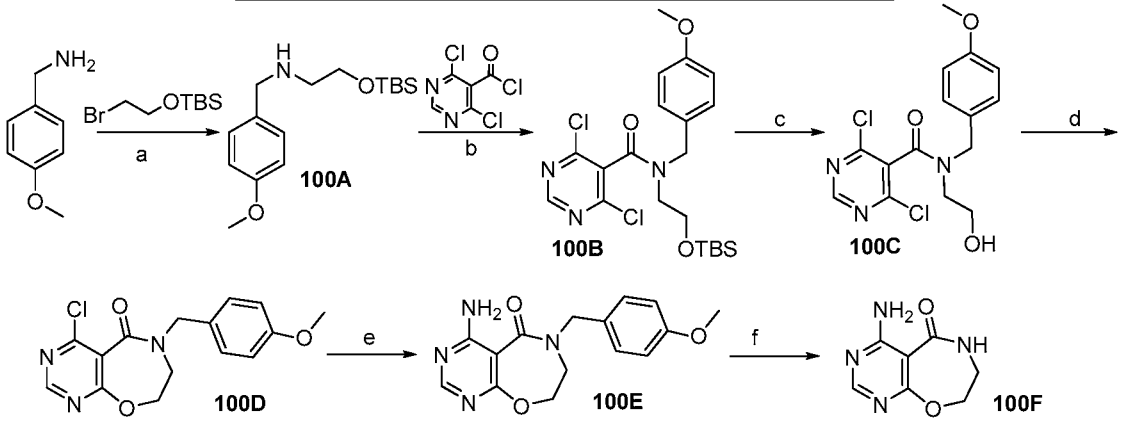
98

Pd/C (0.0514 g, 0.048 mmol) was added to a solution of Example 97 (0.1 g, 0.241 mmol) and ammonium formate (76 mg, 1.207 mmol) in ethanol (5 mL) at 25 °C. The reaction mixture was heated to 80 °C for 16 h. Insoluble solids were filtered off, and filtrate was concentrated. Residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 60% ethyl acetate in hexane to afford title compound (0.02 g, 23.51%) as a solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 12.4 (s, 1H), 8.18 (s, 1H), 8.12 (d, J = 3.0 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.83 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 7.75-7.65 (m, 3H), 4.64 (m, 2H), 4.08 (m, 2H); ESI-MS m/z = 325 $(M+H)^+$; LCMS purity: 93%.

Example 99 was prepared by the methods described above for Example 96 or routine variations thereof starting from the requisite halo-substituted heterocycle ring system.

Ex	Structure	Analytical Data	Mass/Purity
99		^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.51 (d, J = 6.8 Hz, 1H), 7.35-7.28 (m, 5H), 7.18 (d, J = 3.2 Hz, 1H), 7.15-7.07 (m, 3H), 6.55 (d, J = 3.2 Hz, 1H), 5.27 (s, 2H), 4.75 (t, J = 4.0 Hz, 2H), 3.99 (t, J = 4.8 Hz, 2H).	ESI-MS m/z = 404 $(M+H)^+$; HPLC purity: 90.84%.

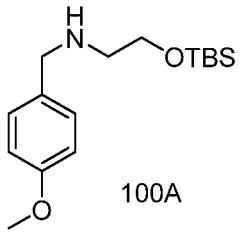
Example 100: 4-Amino-6-(5-propyl-5H-pyrrolo[3,2-d]pyrimidin-2-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:



Reagents and conditions: a) $Br(CH_2)_2OTBDMS$, K_2CO_3, ACN, 80 °C,16h; b) DCM, Et_3N, -78 °C; c) 3% HCl-EtOH, RT, 1h; d) CH_3CN, Et_3N, 80 °C, 16h; e) NH_3, Dioxane, RT, 2h, f) TFA, anisole, 90 °C, 16h.

Procedures:

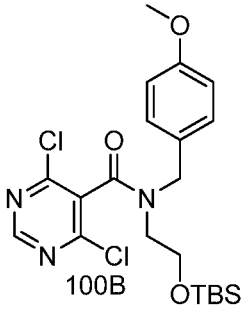
2-(tert-Butyldimethylsilyloxy)-N-(4-methoxybenzyl)ethanamine (100A):



100A

(2-bromoethoxy)(tert-butyl)dimethylsilane (20 g, 84 mmol) was added to a solution of (4-methoxyphenyl) methanamine (11.47 g, 84 mmol) in acetonitrile (200 mL) followed by K_2CO_3 (57.8 g, 418 mmol), and the mixture was stirred at 80 °C for 16 h. Insoluble solids were filtered off, filtrate was concentrated and partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography using 30% ethyl acetate in hexane to afford title compound (19 g, 77%) as an oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.22 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H), 3.62 (m, 4H), 2.56 (t, J = 5.7 Hz, 2H), 2.5 (m, 1H), 0.85 (s, 9H), 0.02 (s, 6H).

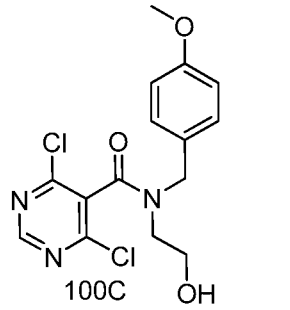
N-(2-(tert-Butyldimethylsilyloxy)ethyl)-4,6-dichloro-N-(4-methoxybenzyl)pyrimidine-5-carboxamide (100B):



100B

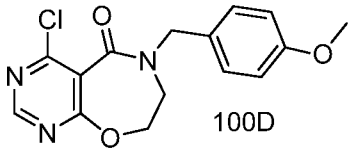
To a stirred, cooled (0 °C) solution of product of Example 100A (7.66 g, 25.9 mmol) and TEA (5.42 mL, 38.9 mmol) in DCM (80 mL) was added drop wise a solution of 4,6-dichloropyrimidine-5-carbonyl chloride (5.46 g, 25.90 mmol) in DCM (10 mL). After 1 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, and washed with water (2x60 mL) and saturated aqueous brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to afford title compound (9.0 g, 48.4%) as a pale yellow solid.

4,6-Dichloro-N-(2-hydroxyethyl)-N-(4-methoxybenzyl)pyrimidine-5-carboxamide (100C):



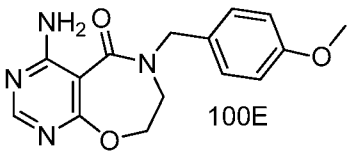
A solution of product of Example 100B (9 g, 9.13 mmol) in 60 mL of ethanolic solution of HCl (3 mL concentrated aqueous HCl in 97 mL of ethanol) was stirred at room temperature for 2 h. Ethanol was removed in vacuo, the residue was dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (4.5 g, 66%) as a pale yellow solid, which was carried on to the next step without further purification.

4-Chloro-6-(4-methoxybenzyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (100D):



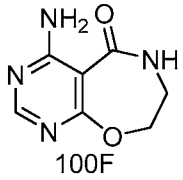
A slurry of product of Example 100C (4.5 g, 12.63 mmol) and TEA (8.8 mL, 63.2 mmol) in acetonitrile (60 mL) was stirred at 80 °C for 16 h. The reaction was cooled, concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (3 g, 74.3%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.77 (s, 1H), 7.3 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 4.68 (s, 2H), 4.41 (t, J = 4.8 Hz, 2H), 3.74 (s, 3H), 3.71 (t, J = 3.6 Hz, 2H).

4-Amino-6-(4-methoxybenzyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (100E):



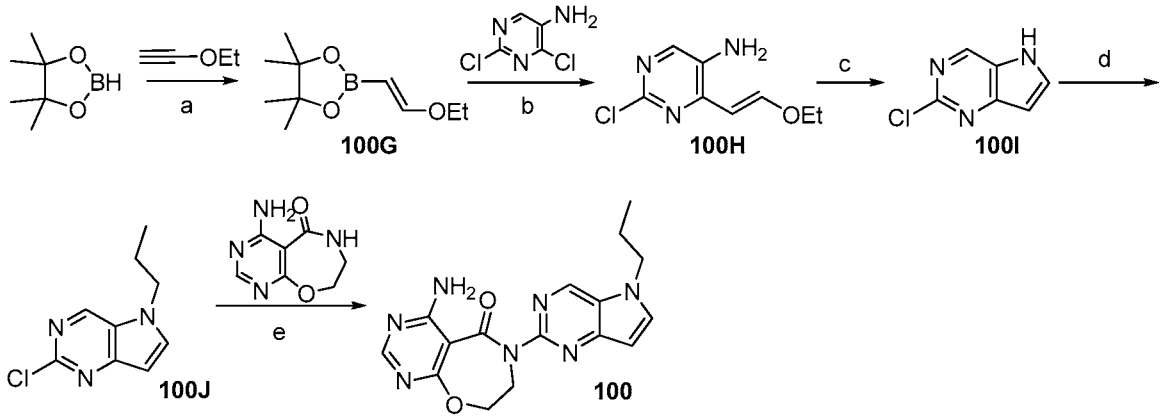
A solution of product of Example 100D (3 g, 9.38 mmol) in 0.5M ammonia in p-dioxane (30 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, and washed with water and saturated aqueous brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to afford title compound (2.5 g, 77%) as a white solid. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.63 (bs, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.65 (s, 2H), 4.31 (t, J = 4.2 Hz, 2H), 3.74 (s, 3H), 3.56 (t, J = 4.8 Hz, 2H).

4-Amino-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (100F):



100F

TFA (15 mL, 195 mmol) was added to a solution of 100E (2.5 g, 8.32 mmol) in anisole (1 mL, 9.15 mmol) at 0 °C, and the mixture was stirred for 2 h at 90 °C for 16 h in sealed-tube. The reaction mixture was concentrated to get the residue and it was triturated with 25 mL (50%) ethyl acetate in hexane to afford to afford title compound (1.0 g, 66.7%) as an off-white-solid. ^{1}H NMR (400MHz, DMSO-d_6-D_2O): δ 8.26 (s, 1H), 4.57 (t, J = 3.9 Hz, 2H), 3.47 (t, J = 4.2 Hz, 2H).

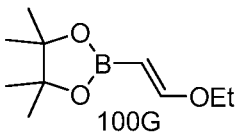


Reagents and conditions: a) di(cyclopenta-2,4-dien-1-yl)zirconium(IV) chloride, CH_2Cl_2, RT, 16h, b) K_3PO_4 dibasic, $Pd(OAc)_2$,,dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine, ACN, water, 80 °C, 16h, c), AcOH, 140 °C, 4h; d) n-propyl bromide, Cs_2CO_3, DMF, 25 °C, 4h, e) K_3PO_4 dibasic, CuI, (1S,2S)-cyclohexane-1,2-diamine, 1,4-dioxane, 110 °C, 24h.

Procedures:

4-Amino-6-(5-propyl-5H-pyrrolo[3,2-d]pyrimidin-2-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

(E)-2-(2-Ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (100G):

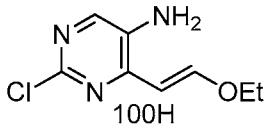


100G

Di(cyclopenta-2,4-dien-1-yl)zirconium(IV) chloride (0.685 g, 2.344 mmol) was added to a solution of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.0 g, 39.1 mmol) in dichloromethane (15 mL) followed by ethoxyethyne (3.01 g, 43.0 mmol) at 0 °C, and the mixture was stirred for 16 h at 25 °C. Insoluble solids were filtered off, and filtrate was concentrated. Residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo to

afford title compound (6.04 g, 78.13%) as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, J = 14.0 Hz, 1H), 4.43 (d, J = 14.8 Hz, 1H), 3.84 (q, J = 7.2 Hz, 2H), 1.32-1.2 (m, 15H).

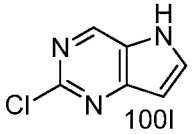
(E)-2-Chloro-4-(2-ethoxyvinyl)pyrimidin-5-amine (100H):



100H

A mixture of 2,4-dichloropyrimidin-5-amine (2.0 g, 12.2 mmol), product of Example 100G (6.04 g, 30.5 mmol), potassium phosphate dibasic (5.31 g, 30.5 mmol), palladium(II) acetate (0.027 g, 0.122 mmol) and dicyclohexyl-(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (0.050 g, 0.122 mmol) in acetonitrile (30 mL) and water (20 mL) under argon was refluxed at 80 °C for 16 h. The reaction mixture was cooled, diluted with ethyl acetate, and washed with water (2x30 mL) and saturated aqueous brine. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography using 30% ethyl acetate in hexane to afford title compound (0.3 g, 12.32%) as an oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.85 (d, J = 11.7 Hz, 1H), 5.69 (d, J = 11.7 Hz, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.49 (bs, 2H), 1.37 (t, J = 7.5 Hz, 3H).

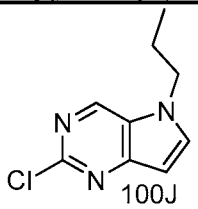
2-Chloro-5H-pyrrolo[3,2-d]pyrimidine (100I):



100I

A solution of product of Example 100H (0.3 g, 1.503 mmol) in acetic acid (20 mL) was stirred at 140 °C for 4 h. Acetic acid was removed in high vacuo, the residue was co-distilled with toluene to afford title compound (0.22 g, 88%) as a yellow solid, which was carried on to the next step without further purification. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.76 (s, 1H), 8.68 (bs, 1H), 7.69 (t, J = 3.2 Hz, 1H), 6.72 (s, 1H).

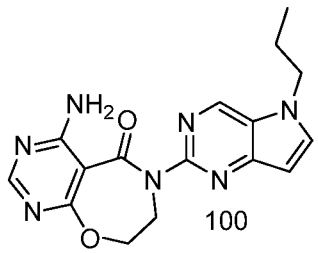
2-Chloro-5-propyl-5H-pyrrolo[3,2-d]pyrimidine (100J):



100J

1-Bromopropane (132 mg, 1.074 mmol) was added to a solution of product of Example 100I (150 mg, 0.977 mmol) in DMF (10 mL) followed by cesium carbonate (0.477 g, 1.074 mmol), and the mixture was stirred at 25 °C for 4 h. Insoluble solids were filtered off, and filtrate was concentrated. Residue was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 5% ethyl acetate in hexane to afford title compound (0.15 g, 74.6%) as a brown color syrup. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.51 (d, J = 3.0 Hz, 1H), 6.62 (d, J = 2.7 Hz, 1H), 4.16 (t, J = 6.9 Hz, 2H), 1.91 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H).

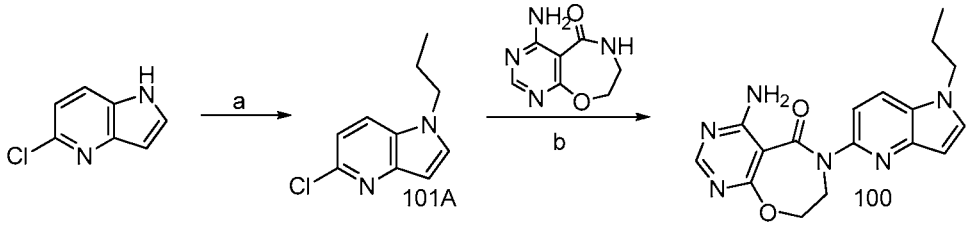
4-Amino-6-(5-propyl-5H-pyrrolo[3,2-d]pyrimidin-2-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (100):



100

A mixture of product of Example 100J (0.195 g, 1.0 mmol), Example 100F (0.15 g, 0.833 mmol), potassium phosphate dibasic (0.29 g, 1.665 mmol), CuI (15.86 mg, 0.083 mmol) and trans (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (0.023 g, 0.167 mmol) in 1,4-dioxane (5 mL) under Argon was refluxed at 110 °C for 24 h in sealed-tube. The reaction mixture was diluted with methanol, insoluble solids were filtered off and filtrate was concentrated to get the residue. The residue was purified by flash chromatography using 3% methanol in ethyl acetate to afford title compound (0.02 g) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.12 (s, 1H), 8.19 (s, 1H), 8.02 (d, J = 3.6 Hz, 1H), 7.69 (bs, 2H), 6.62 (d, J = 2.8 Hz, 1H), 4.61 (t, J = 4.4 Hz, 2H), 4.29 (t, J = 7.2 Hz, 2H), 4.15 (t, J = 4.8 Hz, 2H), 1.83 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 340.1 $(M+H)^{+}$; LCMS Purity: 96.2%.

Example-101: 4-Amino-6-(1-propyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:



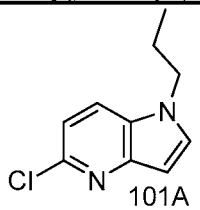
101A 100

Reagents and conditions: a) n-propyl bromide, Cs_2CO_3, DMF, 70 °C, 0.5h; b) CuI, (1*S*,2*S*)-N,N'-Dimethyl cyclohexyl-1,2-diamine, K_3PO_4, Toluene, 120 °C, 2.5h;

Procedures:

4-Amino-6-(1-propyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one:

5-Chloro-1-propyl-1H-pyrrolo[3,2-b]pyridine (101A):

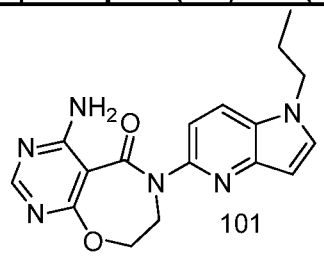


101A

1-Bromopropane (192 mg, 1.57 mmol) was added to a solution of 2-chloro-5H-pyrrolo[3,2-d]pyrimidine (200 mg, 1.31 mmol) in DMF (15 mL) followed by cesium carbonate (0.855 g, 2.63 mmol), and the mixture was stirred at 70 °C for 0.5 h. Insoluble solids were filtered off, filtrate was concentrated and partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried over sodium sulphate and

filtered. The filtrate was concentrated in vacuo to afford title compound (0.22 g, 86%) as an oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.59 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 3.3 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 3.6 Hz, 1H), 4.07 (t , J = 6.9 Hz, 2H), 1.86 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H).

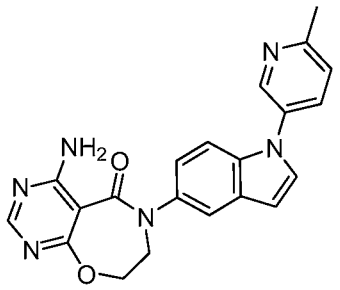
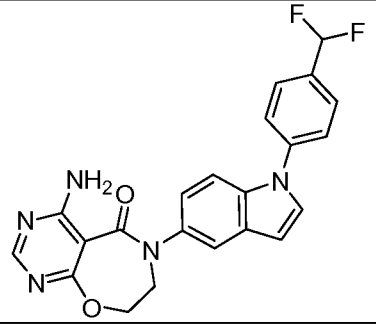
4-Amino-6-(1-propyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (101):

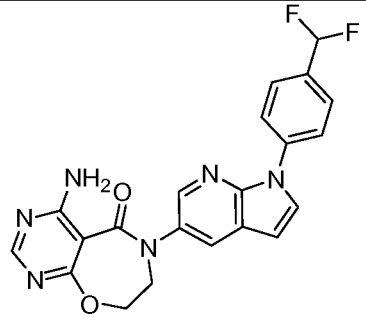
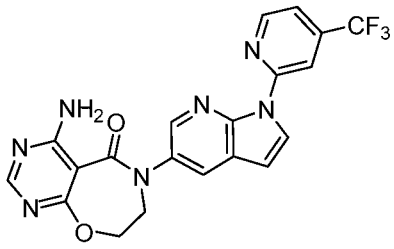


101

A mixture of product of Example 101A (0.064 g, 0.33 mmol), Example 100F (0.05 g, 0.27 mmol), potassium phosphate dibasic (0.117 g, 0.555 mmol), CuI (0.005 g, 0.027 mmol) and trans (1*S*,2*S*)-N1,N2-dimethylcyclohexane-1,2-diamine (0.0076 g, 0.055 mmol) in 1,4-dioxane (5 mL) under argon was refluxed at 110 °C for 24 h in sealed-tube. The reaction mixture was diluted with methanol, insoluble solids were filtered off and filtrate was concentrated to get the residue. The residue was purified by flash chromatography using 3% methanol in ethyl acetate to afford title compound (0.005 g) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.2 (bs, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 3.0 Hz, 1H), 7.60 (bs, 2H), 7.49 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 3.0 Hz, 1H), 4.63 (m, 2H), 4.26 (m, 2H), 4.19 (t, J = 6.9 Hz, 2H), 1.78 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 339.1 $(M+H)^+$;

Examples 102 – 105 were prepared by the procedures analogous to those described in Examples 65, 66, 82 or 83 using appropriately substituted starting materials.

Ex	Structure	Analytical Data	Mass/Purity
102		^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (d, J = 2.4 Hz, 1H), 8.18 (s, 1H), 7.96 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.7-7.6 (m, 3H), 7.54 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.18 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 6.77 (d, J = 2.8 Hz, 1H), 4.65 (t, J = 4.0 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H), 2.57 (s, 3H).	ESI-MS m/z = 387 $(M+H)^+$; HPLC purity: 97%.
103		^{1}H NMR (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.82-7.76 (m, 5H), 7.68-7.60 (m, 4H), 7.21 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.15 (t, J = 56 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 4.65 (t, J = 4.0 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 422 $(M+H)^+$; LCMS purity: 95%.

104		^{1}H NMR (300MHz, DMSO-d_6): δ 8.34 (d, J = 2.4 Hz, 1H), 8.17 (s, 1H), 8.15-8.06 (m, 4H), 7.75 (d, J = 8.7 Hz, 2H), 7.65 (bs, 2H), 7.10 (t, J = 55.8 Hz, 1H), 6.80 (d, J = 3.9 Hz, 1H), 4.68 (t, J = 3.9 Hz, 2H), 4.05 (t, J = 3.9 Hz, 2H).	ESI-MS m/z = 423 $(M+H)^+$; LCMS purity: 97%.
105		^{1}H NMR (400MHz, DMSO-d_6): δ 9.37 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.54-8.50 (m, 2H), 8.21 (d, J = 2.4 Hz, 1H), 8.19 (s, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.68 (bs, 2H), 6.88 (d, J = 4.0 Hz, 1H), 4.71 (t, J = 3.6 Hz, 2H), 4.09 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 442 $(M+H)^+$; LCMS purity: 99%.

Biological Assay

Human DGAT1 was expressed in Sf9 insect cells using a baculovirus expression system. Microsomes were prepared and used as enzyme for in vitro inhibition testing in either of two formats measuring production of coenzyme A or tridecanoylglycerol product, respectively. All steps were performed at 21-23 °C. All data for DGAT1 inhibition by test compounds were collected under conditions where product formation was linear with reaction time.

For inhibition of CoA product formation, test compounds were prepared in 100% DMSO, diluted 100-fold into assay buffer, and 10 uL added to 96-well half-area plates (Greiner 675076). An equal volume (10 uL) of 3X enzyme in buffer was added and the components incubated for 30 minutes pre-reaction incubation to allow enzyme and test compounds to attain binding equilibrium. The 3X enzyme mixture contained 30 uM {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid for fully inhibited control wells. Some assays were performed with inclusion of didecanoylglycerol in the pre-reaction incubation of test compound and enzyme. DGAT reactions (30 uL) were initiated upon addition of 10 uL of 3X substrate solution. Final reaction conditions consisted of 20 mM HEPES pH 7.5, 2 mM $MgCl_2$, 1 mM CHAPS, 50 uM didecanoylglycerol, 3 uM decanoyl-CoA, 1 ug/mL microsomal protein, and 1%

DMSO. Following a 60 minute reaction incubation, reactions were stopped and CoA product derivatized with 30 uL of buffer containing 10 uM {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid and 50 uM 7-diethylamino-3-(4'-maleimidylphenyl)-4-methylcoumarin (CPM). Fluorescence was read using Envision reader at Ex 405 nm/Em 480 nm about 30 minutes after addition of final solution. Inhibition was normalized to controls containing DMSO or 10 uM {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid. IC_{50}s were fitted using GraphPad Prism to a sigmoidal dose response.

For inhibition of triacylglycerol product formation, 11 uL reactions were run in white Polyplate-384 (PerkinElmer6007300) starting with a 30 minute pre-reaction incubation of 5 uL of 2.2X enzyme and 1 uL of 100% DMSO containing test compound or control compound, {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid. Some assays were performed with inclusion of didecanoylglycerol in the pre-reaction incubation of test compounds and enzyme. Reactions were initiated after 30 minute pre-reaction incubation via addition of 5 uL of 2.2X substrate. Final reaction conditions consisted of 50 mM HEPES pH 7.5, 2 mM $MgCl_2$, 1 mM CHAPS, 25 uM didecanoylglycerol, 0.5 uM decanoyl-CoA, 0.3 nCi/uL [^{14}C]-decanoyl-CoA or 0.5 nCi/uL [^{3}H]-decanoyl-CoA, 0.05-4 ug/mL microsomal protein, and 1% DMSO. Following 60 minute reaction incubation, reactions were stopped with 40 uL of 45% isopropanol and 50 mM sodium carbonate in water and mixed. Extraction of tridecanoylglycerol product was accomplished via addition of 30 uL Microscint-E (Perkin Elmer) and 2 hours of incubation (sealed). Plates were read on a Microbeta Microplate reader. Inhibition was normalized to controls containing DMSO or 10 uM {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid. IC_{50}s were fitted using GraphPad Prism to a sigmoidal dose response.

Biological Data

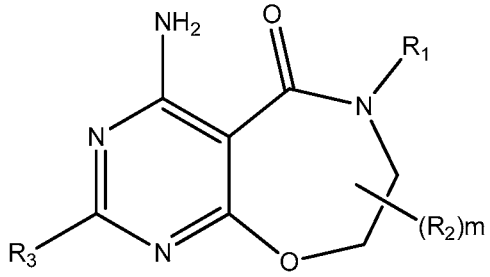
Exemplified compounds of the present invention are inhibitors of DGAT1. All of of the compounds except Example 101 were tested at one or more DGAT assays described above and were found to be inhibitors of DGAT1 with IC_{50} < 10 uM or inhibition >50% at 10 uM. Data for some specific examples tested at the human DGAT1 fluorescene (CPM) or lipid extraction (LE) assays are listed below.

Ex	hDGAT1 CPM Assay IC_{50} (nM)	hDGAT1 LE Assay IC_{50} (nM)
3	371.6	
6	85.8	
10	42.0	
11	6.3	
12	16.3	
33		23.3
34	25.7	
59	49.5	
60		14.8
63		2.3
64		8.8
65		3.9
66	42.5	
68	2.8	
72		9.3
74		4.5
76	2.5	
78	7.3	
80		3.6
81		2.1
82	20.5	
83	40.0	
87	55.1	
94	872.5	
95	10.1	
96		7.3
97		200.8
98		623.0

5

Claims:

1. A compound of Formula (I):



(I)

wherein

R_1 is a bicyclic ring system which contains 9 to 11 ring members including 1 to 4 hetero atoms, in which said bicyclic ring system may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

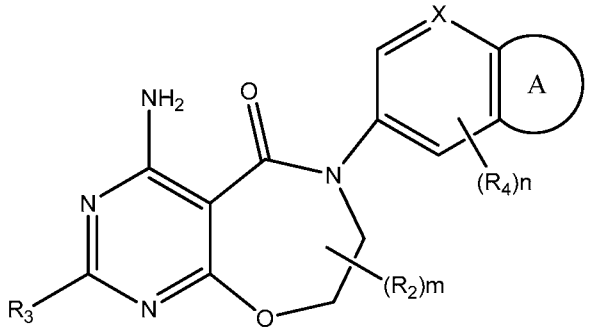
in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or C_1-C_4alkoxy; and

m is 0-2;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, which is represented by Formula (I)(A)



(I)(A)

wherein A is a 5- or 6-membered heterocyclic ring, which may contain 0 to 3 double bonds and may be substituted by 1 to 3 groups selected from the group consisting of

C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or C_1-C_4alkoxy;

R_4 is halo or alkoxy;

X is N or CH; and

m is 0-2;

n is 0-2;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 2, wherein A is a 5-membered heterocyclic ring, which may contain 0-2 double bonds and may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or C_1-C_4alkoxy;

R_4 is halo or alkoxy;

X is N or CH; and

m is 0-2;

n is 0-2;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 2, wherein A is a 6-membered heterocyclic ring, which may contain 0-3 double bonds and may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

each R_2 and R_3 is independently hydrogen, C_1-C_6alkyl, substituted C_1-C_6alkyl, halo, hydroxyl, amide, carboxylic acid or C_1-C_4alkoxy;

R_4 is halo or alkoxy;

X is N or CH; and

m is 0-2;

n is 0-2;

or a pharmaceutically acceptable salt thereof.

5. A compound of any one of claims 2-4,
wherein m is 0;
n is 0;
R_3 is hydrogen; and
X is N;
or a pharmaceutically acceptable salt thereof.

6. A compound of any one of claims 2-4,
wherein m is 0;
n is 0;
R_3 is hydrogen; and
X is CH;
or a pharmaceutically acceptable salt thereof.

7. A compound of claim 1,
wherein m is 0;
R_3 is hydrogen;
R_1 is a bicyclic ring system selected from the group consisting of tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolyl, dihydroindolyl, indazolyl, dihydroindazolyl, benzothiophenyl, benzodiazolyl, dihydrobenzodiazolyl, benzimidazolyl, indolinyl, benzotriazolyl, pyrrolopyridinyl, benzothiazolyl, benzofuranyl, dihydroquinazolinyl, and pyrrolopyrimidinyl;
wherein said bicyclic ring system may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl,

halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

or a pharmaceutically acceptable salt thereof.

8. A compound of claim 7,

wherein m is 0;

R_3 is hydrogen;

R_1 is a bicyclic ring system selected from the group consisting of tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolyl, dihydroindolyl, indazolyl, dihydroindazolyl, and pyrrolopyridinyl;

wherein said bicyclic ring system may be substituted by 1 to 3 groups selected from the group consisting of C_1-C_6alkyl, substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, halo, hydroxyl, oxo, amide, carboxylic acid, -C(O)R_a, -SO_2R_a, arylalkyl, -(C_1-C_3alkyl)aryloxy, aryl, heteroaryl and C_1-C_4alkoxy,

in which each R_a is independently C_1-C_6alkyl, substituted C_1-C_6alkyl or unsubstituted C_3-C_7cycloalkyl;

or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of claims 1-7.

10. A method of treating obesity comprising administering to a human in need thereof an effective amount of a compound according to any one of the above claims.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-7, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038523

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 498/04 (2012.01)
USPC - 540/490
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)
IPC(8) - A61K 31/519, 31/553; C07D 267/02, 498/04 (2012.01)
USPC - 514/211.05, 211.06, 211.07; 540/490, 491

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)
PatBase, Orbit, STN, PubChem Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0036425 A1 (DOW et al) 05 February 2009 (05.02.2009) entire document	1-8
A	US 2010/0204119 A1 (ASPNES et al) 12 August 2010 (12.08.2010) entire document	1-8
A	US 2010/0273768 A1 (DEWDNEY et al) 28 October 2010 (28.10.2010) entire document	1-8
A	US 2010/0210622 A1 (BAELL et al) 19 August 2010 (19.08.2010) entire document	1-8

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2012	10 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038523

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-11
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE DIACILGLICEROL ACILTRANSFERASA

CAMPO DE LA INVENCIÓN

Esta invención se refiere a compuestos novedosos que son inhibidores de la acil coenzimaA: diacilglicerol aciltransferasa 1 (DGAT-1), a composiciones farmacéuticas que los contienen, a procedimientos para su preparación, y a su uso en terapia para la prevención o tratamiento de enfermedades relacionadas a la disfunción de DGAT-1 o donde la modulación de la actividad de DGAT-1 puede tener un beneficio terapéutico incluyendo pero no limitado a obesidad, trastornos relacionados con la obesidad, hipertrigliceridemia, hiperlipoproteinemia, cilomicronemia, dislipidemia, esteatohepatitis no alcohólica, diabetes, resistancia a insulina, síndrome metabólico, virus de la infección de hepatitis C y acné u otros trastornos de la piel.

ANTECEDENTES DE LA INVENCIÓN

La obesidad es una condición médica que está alcanzando proporciones epidémicas entre los humanos en varios países a través del mundo. Es una condición que también está asociada con o que induce otras enfermedades o condiciones que interrumpen las actividades de vida y estilos

de vida. La obesidad es reconocida como un factor grave de riesgo para otras enfermedades y condiciones tales como la diabetes, la hipertensión, y la arteriosclerosis. También se sabe que un peso corporal incrementado debido a la obesidad puede colocar una carga en las articulaciones, tales como las articulaciones de la rodilla, causando artritis, dolor, y rigidez.

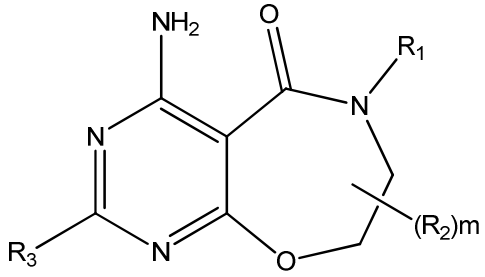
Ya que la comiendo en exceso y la obesidad se han vuelto tal problema en la población general, muchos individuos ahora están interesados en adelgazar, reduciendo peso, y en mantener un peso corporal sano y un estilo de vida deseable. Un acercamiento para tratar la obesidad es reducir la ingesta de alimento y/o la hiperlipidemia. Ha sido sugerido que las moléculas que se desarrollan para prevenir la acumulación de triglicéridos no sólo reducirían la obesidad sino también tendrían el efecto beneficioso adicional de reducir la resistencia a la insulina, un factor primario que contribuye al desarrollo de la diabetes.

La acil coenzimaA: diacilglicerol aciltransferasa 1 (DGAT-1) es una de dos enzimas DGAT conocidas que catalizan el paso final en la síntesis de triglicéridos en mamíferos. La DGAT-1 es una enzima que está implicada en el desarrollo tanto de la diabetes como de la resistencia a la insulina. Estudios de ratones deficientes en DGAT-1 muestran que la deficiencia de DGAT-1 protege contra la resistencia a la insulina y la obesidad, vea Chen, H.C. et al., J Clin Invest., 109(8), 1049-1055 (2002). Por lo tanto, los inhibidores de DGAT-1 deben ser útiles para el tratamiento de trastornos metabólicos, por ejemplo obesidad, diabetes Tipo 2, y síndrome de resistencia

a insulina (o síndrome metabólico) y otras enfermedades y condiciones asociadas o relacionadas.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

La invención se refiere a compuestos de fórmula I:



(I)

en donde

R_1 es un sistema de anillo bicíclico que contiene 9 a 11 miembros del anillo incluyendo 1 a 4 heteroátomos, en donde dicho sistema de anillo bicíclico puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -$C(O)R_a$, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4,

en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido;

cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi de C_1-C_4; y

m es 0-2;

o una sal farmacéuticamente aceptable del mismo.

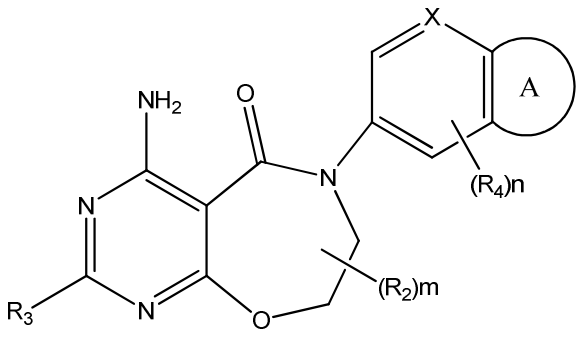
Esta invención también se relaciona a una composición farmacéutica que comprende un compuesto de Fórmula (I) y un portador farmacéuticamente aceptable.

Esta invención también se relaciona a un método para tratar obesidad que comprende administrar a un humano necesitado del mismo una cantidad efectiva de un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en una composición farmacéutica.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Esta invención se relaciona a compuestos de la Fórmula (I) como se definió antes.

Esta invención también se relaciona a compuestos de Fórmula (I)(A):



(I) (A)

en donde A is a anillo heterocíclico de 5 o 6 miembros, que

puede contener 0 a 3 dobles enlaces y puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -C(O)R_a, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4,

en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido;

cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi de C_1-C_4;

R_4 es halo o alcoxi;

X es N o CH; y

m es 0-2;

n es 0-2;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a compuestos de Fórmula (I)(A), en donde A es un anillo heterocíclico de 5 miembros, que puede contener 0-2 dobles enlaces y puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -C(O)R_a, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4,

en donde cada R_a es independientemente alquilo de C_1-C_6,

alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido;

cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi de C_1-C_4;

R_4 es halo o alcoxi;

X es N o CH; y

m es 0-2;

n es 0-2;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a compuestos de Fórmula (I)(A), en donde A es un anillo heterocíclico de 6 miembros, que puede contener 0-3 dobles enlaces y puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -$C(O)R_a$, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4,

en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido;

cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi de C_1-C_4;

R_4 es halo o alcoxi;

X es N o CH; y

m es 0-2;

n es 0-2;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a cualquiera de los compuestos anteriores,

en donde m es 0;

n es 0;

R_3 es hidrógeno; y

X es N o CH;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a compuestos de Fórmula (I),

en donde m es 0;

R_3 es hidrógeno;

R_1 es un sistema de anillo bicíclico seleccionado de grupo que consiste en tetrahidroisoquinolinilo, tetrahidroquinolinilo, indolilo, dihidroindolilo, indazolilo, dihidroindazolilo, benzotiofenilo, benzodiazolilo, dihidrobenzodiazolilo, benzimidazolilo, indolinilo, benzotriazolilo, pirrolopiridinilo, benzotiazolilo, benzofuranilo, dihidroquinazolinilo, y pirrolopirimidinilo;

en donde dicho sistema de anillo bicíclico puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida,

ácido carboxílico, -C(O)R_a, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4,

en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a compuestos de Fórmula (I),

en donde m es 0;

R_3 es hidrógeno;

R_1 es un sistema de anillo bicíclico seleccionado del grupo que consiste en tetrahidroisoquinolinilo, tetrahidroquinolinilo, indolilo, dihidroindolilo, indazolilo, dihidroindazolilo, y pirrolopiridinilo;

en donde dicho sistema de anillo bicíclico puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -C(O)R_a, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4,

en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a compuestos de Fórmula (I),

en donde m es 0;

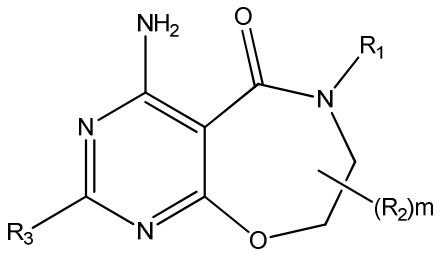
R_3 es hidrógeno;

R_1 es un sistema de anillo bicíclico seleccionado del grupo que consiste en tetrahidroisoquinolinilo, tetrahidroquinolinilo, indolilo, dihidroindolilo, indazolilo, dihidroindazolilo, benzotiofenilo, benzodiazolilo, dihidrobenzodiazolilo, benzimidazolilo, indolinilo, benzotriazolilo, pirrolopiridinilo, benzotiazolilo, benzofuranilo, dihidroquinazolinilo, y pirrolopirimidinilo;

en donde dicho sistema de anillo bicíclico puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en arilo y heteroarilo;

o una sal farmacéuticamente aceptable del mismo.

Esta invención se relaciona a compuestos de Fórmula (I)(B):



(I) (B)

en donde

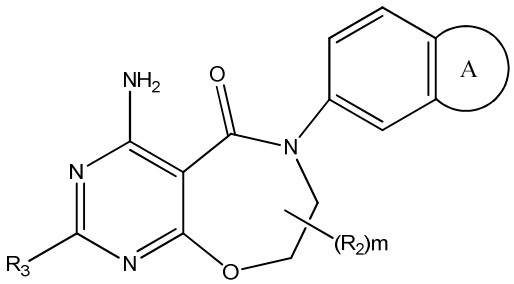
R_1 es un sistema de anillo bicíclico que contiene 9 a 11 miembros del anillo incluyendo 1 a 4 heteroátomos, en donde dicho sistema de anillo bicíclico puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6sustituido, halo, hidroxilo, oxo, amida, ácido carboxílico, y alcoxi;

cada R_2 y R_3 es independientemente hidrógeno, C_1-C_6alquilo, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi; y

m es 0-2;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a compuestos de Fórmula (I)(C):



(I) (C)

en donde A es un anillo heterocíclico de 5 o 6 miembros, que puede contener 0 a 3 dobles enlaces y puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, oxo, amida, ácido carboxílico, y alcoxi;

cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi; y

m es 0-2;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a compuestos de Fórmula (I)(C), en donde A es un anillo heterocíclico de 5 miembros, que puede contener 0 a 3 dobles enlaces y puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6

sustituido, halo, hidroxilo, oxo, amida, ácido carboxílico, y alcoxi;

cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi; y

m es 0-2;

o una sal farmacéuticamente aceptable del mismo.

Esta invención también se relaciona a compuestos de Fórmula (I), (I)(A), (I)(B) o (I)(C), en donde m es 0, y R_3 es hidrógeno, o una sal farmacéuticalmente aceptable de los mismos.

Esta invención también se relaciona a compuestos que se ejemplifican en la sección Experimental.

Compuestos específicos de esta invención incluyen:

Acido 2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-oxo-1,2,3,4-tetrahidroisoquinolin-2-il)acético;

2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-2-oxo-1,2,3,4-tetrahidroquinolin-1-il)acetato de etilo;

Acido 2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-2-oxo-1,2,3,4-tetrahidroquinolin-1-il)acético;

2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-oxo-1,2,3,4-tetrahidroisoquinolin-2-il)acetato de etilo;

6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-metil-1,2,3,4-tetrahidroquinolin-2-ona;

6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-2-metil-1,2,3,4-tetrahidroisoquinolin-1-ona;

6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-2-bencil-1,2,3,4-tetrahidroisoquinolin-1-ona;

6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-2-propil-1,2,3,4-tetrahidroisoquinolin-1-ona;

6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-propil-1,2,3,4-tetrahidroquinolin-2-ona;

5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-2-bencil-1-(prop-2-en-1-il)-2,3-dihidro-1H-indazol-3-ona;

5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-propil-2,3-dihidro-1H-indazol-3-ona;

4-amino-6-(1-propil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-propil-1H-indazol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-benzotiofen-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1,3-dipropil-2,3-dihidro-1H-1,3-benzodiazol-2-ona;

4-amino-6-(2-propil-2H-indazol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1,3-benzotiazol-6-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-

1-propil-2,3-dihidro-1H-indol-2,3-diona;

4-amino-6-(1-benzofuran-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-ciclopropil-1,2,3,4-tetrahidroquinolin-6-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(2-propil-1,2,3,4-tetrahidroisoquinolin-6-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2,2-difluoroetil)-1,2,3,4-tetrahidroquinolin-6-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

5-{4-amino-5-oxo-5H,6H,7H,8H-oxepino[2,3-d]pirimidin-6-il}-1-(propan-2-il)-2,3-dihidro-1H-indazol-3-ona;

5-{4-amino-5-oxo-5H,6H,7H,8H-oxepino[2,3-d]pirimidin-6-il}-1-(2-metoxietil)-2,3-dihidro-1H-indazol-3-ona;

5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-(2,2-difluoroetil)-2,3-dihidro-1H-indazol-3-ona;

5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-ciclopropil-2,3-dihidro-1H-indazol-3-ona;

6-amino-4-(1-propil-1H-1,3-benzodiazol-5-il)-2,3,4,5-tetrahidro-1,4-benzoxazepin-5-ona;

4-amino-6-(1-propil-1H-1,3-benzodiazol-6-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(2-propil-2H-1,2,3-benzotriazol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-propil-1H-1,2,3-benzotriazol-6-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(2-metil-1,3-benzotiazol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(ciclopropilmetil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

Acido 3-(5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1H-indol-1-il)propanóico;

4-amino-6-[1-(ciclohexilmetil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(pentan-3-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[(4-metoxifenil)metil]-1H-indol-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[(4-fluorofenil)metil]-1H-indol-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[2-(benciloxi)etil]-1H-indol-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-bencil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-

f][1,4]oxazepin-5-ona;

4-amino-6-[1-(3-metoxipropil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2,2-difluoroetil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-metil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2-metoxietil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(propan-2-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-propil-2,3-dihidro-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(2,3-dihidro-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2-metoxietil)-2,3-dihidro-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1,2-dimetil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(ciclopropilmetil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-propil-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2-metoxietil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(ciclohexilmetil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-ciclohexil-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(propan-2-il)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2-hidroxietil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-metanosulfonil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-ciclopropil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

Acido 5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-propil-1H-indol-2-carboxílico;

4-amino-6-[1-propil-3-(trifluoroacetil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-propil-3-(1,1,1-trifluoro-2-metoxipropan-2-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-fenil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-

f][1,4]oxazepin-5-ona;

4-amino-6-{1-[4-(trifluorometil)fenil]-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(4-fluorofenil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(3-clorofenil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(3-clorofenil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2-metoxifenil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2-metoxifenil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-fenil-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2-fluorofenil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(3,4-difluorofenil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(3,4-difluorofenil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(2-fluorofenil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[4-(trifluorometil)fenil]-1H-indol-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(4-clorofenil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[3-(trifluorometil)fenil]-1H-indol-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[3-(trifluorometil)fenil]-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(1,3-tiazol-2-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[6-(trifluorometil)piridin-3-il]-1H-indol-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(piridin-2-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(piridin-2-il)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(pirazin-2-il)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(pirazin-2-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[5-(trifluorometil)piridin-2-il]-1H-indol-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[5-(trifluorometil)piridin-2-il]-1H-pirrolo[2,3-b]piridin-

5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-(1,3-tiazol-2-il)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{1-[6-(trifluorometil)piridin-3-il]-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-[1-fenil-3-(propan-2-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(2-fenil-1-propil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(6-fluoro-1-fenil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-3-bencil-3,4-dihidroquinazolin-4-ona;

6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-3,4-dihidroquinazolin-4-ona;

4-amino-6-(1-bencil-6-fluoro-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-{5-propil-5H-pirrolo[3,2-d]pirimidin-2-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona;

4-amino-6-(1-propil-1H-pirrolo[3,2-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona;

4-amino-6-(1-(6-metilpiridin-3-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona;

4-amino-6-(1-(4-(difluorometil)fenil)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona;

4-amino-6-(1-(4-(difluorometil)fenil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona;

4-amino-6-(1-(4-(trifluorometil)piridin-2-il)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona;

o una sal farmacéuticamente aceptable del mismo.

Una persona con experiencia ordinaria en la técnica reconoce que los compuestos de la invención presente pueden tener nombres alternativos cuando se usa diferente software para los nombres.

Los siguientes compuestos ejemplificados tienen nombres químicos alternativos como se ilustra en el cuadro siguiente.

Ej.	**Nombre químico**	**Nombre químico alternativo**
1	Acido 2-(6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-oxo-1,2,3,4-tetrahidroisoquinolin-2-il)acético	Acido 2-(6-(4-amino-5-oxo-5,6,7,8-tetrahidrooxepino(2,3-*d*)pirimidin-6-il)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il) acético
10	5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-2-bencil-1-(prop-2-en-1-il)-2,3-dihidro-1H-indazol-3-ona	6-(1-allil-2-bencil-3-oxo-2,3-dihidro-1H-indazol-5-il)-4-amino-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
11	5-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-1-propil-2,3-dihidro-1H-indazol-3-ona	4-amino-6-(3-oxo-1-propil-2,3-dihidro-1H-indazol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
12	4-amino-6-(1-propil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona

33	4-amino-6-[1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridinpiridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
34	4-amino-6-{1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(1-ciclopropil-1H-pirrolo[2,3-b]piridinpiridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
63	4-amino-6-[1-propil-3-(trifluoroacetil)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(1-propil-3-(2,2,2-trifluoroacetil)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
65	4-amino-6-(1-fenil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
66	4-amino-6-{1-[4-(trifluorometil)fenil]-1H-pirrolo[2,3-b]piridin-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridinpiridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
82	4-amino-6-[1-(1,3-tiazol-2-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(1-(tiazol-2-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
83	4-amino-6-{1-[6-(trifluorometil)piridin-3-il]-1H-indol-5-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(1-(6-(trifluorometil)piridinpiridin-3-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
94	4-amino-6-[1-fenil-3-(propan-2-il)-1H-indol-5-il]-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(3-isopropil-1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
95	4-amino-6-(2-fenil-1-propil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(2-fenil-1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
96	4-amino-6-(6-fluoro-1-fenil-1H-indol-5-il)-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(6-fluoro-1-fenil-1H-indol-5-il)-7,8-dihidrooxepino[2,3-d]pirimidin-5(6H)-ona
97	6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-3-bencil-3,4-dihidroquinazolin-4-ona	4-amino-6-(3-bencil-4-oxo-3,4-dihidroquinazolin-6-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona

98	6-{4-amino-5-oxo-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-6-il}-3,4-dihidroquinazolin-4-ona	4-amino-6-(4-oxo-3,4-dihidroquinazolin-6-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
100	4-amino-6-{5-propil-5H-pirrolo[3,2-d]pirimidin-2-il}-5H,6H,7H,8H-pirimido[5,4-f][1,4]oxazepin-5-ona	4-amino-6-(5-propil-5H-pirrolo[3,2-d]pirimidin-2-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona
101	4-amino-6-(1-propil-1H-pirrolo[3,2-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona	4-amino-6-(1-propil-1H-pirrolo[3,2-b]piridinpiridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona

Esta invención también se relaciona a compuestos de Fórmula (I), (I)(A), (I)(B), (I)(C), o cualquiera de los compuestos ejemplificados, o de sus sales farmacéuticamente aceptables de los mismos, para el uso como un medicamento.

Esta invención también se relaciona a compuestos de Fórmula (I), (I)(A), (I)(B), (I)(C), o cualquiera de los compuestos ejemplificados, o de sus sales farmacéuticamente aceptables de los mismos, para el uso en el tratamiento de la obesidad.

Esta invención también se relaciona a compuestos de Fórmula (I), (I)(A), (I)(B), (I)(C), o cualquiera de los compuestos ejemplificados, o de sus sales farmacéuticamente aceptables de los mismos, en la fabricación de un medicamento para el tratamiento de la obesidad.

Será apreciado por los expertos en la técnica que el compuesto de la invención presente también puede ser utilizado en forma de una sal farmacéuticamente aceptable del mismo.

Normalmente, pero no totalmente, las sales de la presente

invención son sales farmacéuticamente aceptables. Las sales comprendidas dentro del término "sales farmacéuticamente aceptables" se refieren a sales no tóxicas de los compuestos de esta invención. Las sales de los compuestos descritos que contienen una amina básica u otro grupo funcional básico pueden ser preparadas por cualquier método conveniente conocido en la técnica, incluyendo el tratamiento de la base libre con un ácido inorgánico, tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares, o con un ácido orgánico, tal como ácido acético, ácido trifluoroacético, ácido maleico, ácido succínico, ácido mandelico, ácido fumárico, ácido malónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, ácido piranosidílico, tal como ácido glucurónico o ácido galacturónico, ácido alfa-hidroxi, tal como ácido cítrico o ácido tartárico, aminoácidos, tal como ácido aspartico o ácido glutámico, ácidos aromáticos, tal como ácido benzoico o ácido cinnámico, ácido sulfónico, tal como ácido p-toluenosulfónico, ácido metanosulfónico, ácido etanosulfónico o similares. Ejemplos de sales farmacéuticamente aceptables incluyen sulfatos, pirosulfatos, bisulfatos, sulfitos, bisulfitos, fosfatos, cloruros, bromuros, yoduros, acetatos, propionatos, decanoatos, caprilatos, acrilatos, formatos, isobutiratos, caproatos, heptanoatos, propiolatos, oxalatos, malonatos, succinatos, suberatos, sebacatos, fumaratos, maleatos, butin-1,4-dioatos, hexin-1,6-dioatos, benzoatos, clorobenzoatos, metilbenzoatos, dinitrobenzoatos, hidroxibenzoatos, metoxibenzoatos, ftalatos, fenilacetatos, fenilpropionatos, fenilbutratos, citratos, lactatos, γ-hidroxibutiratos, glicolatos,

tartratos, mandelatos, y sulfonatos, tal como xilensulfonatos, metanosulfonatos, propanosulfonatos, naftalen-1-sulfonatos y naftalen-2-sulfonatos.

Las sales de los compuestos descritos que contienen un ácido carboxílico u otro grupo funcional ácido pueden ser preparadas al reaccionar con una base conveniente. Tal sal farmacéuticamente aceptable puede formarse con una base que produce un catión farmacéuticamente aceptable, que incluye sales de metal alcalino (especialmente sodio y potasio), sales de metal alcalino térreo (especialmente calcio y magnesio), sales de aluminio y sales de amonio, así como sales formadas de bases orgánicas fisiológicamente aceptables tal como trimetilamina, trietilamina, morfolina, piridina, piperidina, picolina, diciclohexilamina, N,N'-dibenciletilenediamina, 2-hidroxietilamina, bis-(2-hidroxietil)amina, tri-(2-hidroxietil)amina, procaina, dibencilpiperidina, dehidroabietilamina, N,N'-bisdehidroabietilamina, glucamina, N-metilglucamina, colidina, colina, quinina, quinolina, y aminoácido básico tal como lisina y arginina.

Otras sales, que no son farmacéuticamente aceptables, pueden ser útiles en la preparación de compuestos de esta invención y debe considerarse que estas forman un aspecto adicional de la invención. Estas sales, tales como ácido oxálico o trifluoroacetato, aunque por sí solas no son farmacéuticamente aceptables, pueden ser útiles en la preparación de las sales útiles como intermediarios para obtener los compuestos de la invención y sus sales farmacéuticamente aceptables.

Como se usa en la presente, el término "un compuesto de Fórmula (I)" o "el compuesto de Fórmula (I)" se refiere a uno o más compuestos según la Fórmula (I). El compuesto de Fórmula (I) puede existir en forma sólida o líquida. En el estado sólido, puede existir en la forma cristalina o no cristalina, o como una mezcla de los mismos. El técnico experto apreciará que pueden formarse solvatos farmacéuticamente aceptables para los compuestos cristalinos o no cristalinos. En los solvatos cristalinos, las moléculas de solvente se incorporan en la red cristalina durante la cristalización. Los solvatos pueden involucrar solventes no acuosos tales como, pero no limitados a, etanol, isopropanol, DMSO, ácido acético, etanolamina, o acetato de etilo, o puede involucrar agua como el solvente que se incorpora en la red cristalina. Los solvatos en donde el agua es el solvente incorporado en la red cristalina son normalmente denominados como "hidratos". Los hidratos incluyen hidratos estoiquiométricos, así como las composiciones que contienen cantidades variables de agua. La invención incluye todos esos solvatos.

El experto en la técnica apreciará además que ciertos compuestos de la invención que existen en forma cristalina, incluyendo los diversos solvatos del mismo, pueden presentar polimorfismo (es decir, la capacidad de presentarse en distintas estructuras cristalinas). Estas formas cristalinas diferentes son normalmente conocidas como "polimorfos". La invención incluye todos esos polimorfos. Los polimorfos tienen la misma composición química pero difieren en compactación, disposición geométrica y

otras propiedades descriptivas del estado sólido cristalino. Por ello, los polimorfos pueden tener diferentes propiedades físicas como la forma, densidad, dureza, deformabilidad, estabilidad y propiedades de disolución. Los polimorfos normalmente presentan diferentes puntos de fusión, espectros infrarrojos y los patrones de difracción de polvo de rayos X, que pueden utilizarse para su identificación. El experto en la técnica apreciará que se pueden producir polimorfos diferentes, por ejemplo, al cambiar o ajustar las condiciones de reacción o los reactivos, utilizados para hacer el compuesto. Por ejemplo, los cambios en temperatura, presión o solvente pueden dar lugar a polimorfos. Además, un polimorfo puede convertirse de forma espontánea a otro polimorfo bajo ciertas condiciones.

El compuesto de la Fórmula (I) o una sal del mismo puede existir en formas estereoisométicas (por ejemplo, contiene uno o más carbonos asimétricos). Los estereoisómeros individuales (enantiómeros y diaestereómeros) y mezclas de éstos se incluyen dentro del alcance de la presente invención. De igual manera, se entiende que un compuesto o sal de la Fórmula (I) puede existir en formas tautoméricas diferentes de esa mostrada en la fórmula y éstas también se incluyen dentro del alcance de la presente invención. Se comprenderá que la presente invención incluye todas las combinaciones y subconjuntos de los grupos particulares definidos anteriormente. El alcance de la presente invención incluye las mezclas de estereoisómeros así como enantiómeros purificados o mezclas enantiméricamente/diastereoméricamente enriquecidas. Se comprenderá que

la presente invención incluye todas las combinaciones y subconjuntos de los grupos particulares definidos anteriormente.

Esta invención también incluye compuestos isotópicamente marcados que son idénticos a esos recitados en la fórmula (I) excepto por el hecho de que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número de masa diferente del número atómico o número de masa encontrado más comúnmente en la naturaleza. Ejemplos de isótopos que pueden ser incorporados en los compuestos de la invención y de sales farmacéuticamente aceptables del mismo incluyen isótopos de hidrógeno, del carbono, del nitrógeno, del oxígeno, del fósforo, del azufre, del flúor, del yodo, y del cloro, tal como 2H, 3H, 11C, 13C, 14C, 15N, 17O, 18O, 31P, 32P, 35S, 18F, 36Cl, 123I y 125I.

Los compuestos de la invención presente y sales farmacéuticamente aceptables de dichos compuestos que contienen los isótopos antes mencionados y/o otros isótopos de otros átomos están dentro del alcance de la invención presente. Los compuestos isotópicamente marcados de la invención presente, por ejemplo esos en los que los isótopos radioactivos tales como 3H, 14C son incorporados, son útiles en los ensayos de distribución en tejidos del fármaco y/o sustrato. Los isótopos tritiado, es decir, 3H, y el carbono-14, es decir, 14C, se prefieren especialmente por su facilidad de preparación y detectabilidad. Los isótopos 11C y 18F son particularmente útiles en el PET (tomografía de emisión de positrones), y los isótopos de 125I son particularmente útiles en SPECT (tomografía

computarizada de fotón único), todos útiles en la formación de imagen del cerebro. Además, la sustitución con isótopos más pesados tales como deuterio, es decir 2H, puede proporcionar ciertas ventajas terapéuticas resultantes de su mayor estabilidad metabólica, por ejemplo, un aumento en la vida media en vivo o una reducción en los requerimientos de dosificación y, por tanto, pueden preferirse en algunas circunstancias. Los compuestos isotópicalmente marcados de fórmula I y los siguientes de esta invención pueden prepararse generalmente realizando los procedimientos descritos en los Esquemas y/o en los Ejemplos siguientes, al sustituir un reactivo isotópicamente marcado disponible fácilmente por un reactivo no marcado isotópicamente.

Definiciones

Los términos son utilizados con sus significados aceptados. Las siguientes definiciones tienen la intención de aclarar, pero no limitar, los términos definidos.

Como se usa en la presente, a menos que se defina lo contrario, el término “alquilo” (o “alquileno”) se refiere a un alquilo de cadena recta o ramificada, preferiblemente teniendo uno a doce átomos de carbono, que puede estar saturado o insaturado incluido dentro de la invención presente. Ejemplos de “alquilo” como se usa en la presente incluyen metilo, etilo, propilo, isopropilo, isobutilo, n-butilo, t-butilo, isopentilo, n-pentilo, y similares, así como versiones sustituidas de los mismos.

Como se usa en la presente, a menos que se defina lo contrario, el término “alquilo sustituido” (o “alquileno”) se refiere a un alquilo de cadena recta o ramificada, preferiblemente teniendo de uno a doce átomos de carbono, que pueden estar saturados o insaturados con múltiples grados de sustitución incluidos dentro de la invención presente, preferiblemente uno, dos o tres. Los sustituyentes adecuados son seleccionados del grupo que consiste en cicloalquilo de C_3-C_7 no sustituido, metilo, etilo, propilo, isopropilo, butilo, t-butilo, difluorometilo, trifluorometilo, halo, amino, amino sustituido, urea, ciano, hidroxilo, alcoxi, alquiltio, alquilsulfonilo, sulfonamida, ácido carboxílico (por ejemplo COOH), éster carboxílico (por ejemplo metil éster, etil éster, y carboxamida.

Como se usa en la presente, a menos que se defina lo contrario, el término “amino sustituido” significa –NR’R” en donde cada R’ y R” es independientemente seleccionado de un grupo incluyendo hidrógeno, alquilo de C_1-C_6 no sustituido, acilo, cicloalquilo de C_3-C_7 no sustituido, en donde por lo menos uno de R’ y R” no es hidrógeno. Ejemplos de amino sustituido amino incluyen, pero no se limitan a alquilamino, dialquilaminio, acilamino, y cicloalquiloamino.

Como se usa en la presente, a menos que se defina lo contrario, el término “ariloxi” se refiere al grupo –O-alquilarilo de C_1-C_6. Ejemplos de –O-alquilarilo de C_1-C_6 incluyen, pero no se limitan a fenilmetoxi, naftilmetoxi.

Como se usa en la presente, a menos que se defina lo contrario, el término “arilalquilo” se refiere al grupo -alquilarilo de C_1-C_6. Ejemplos de

alquilarilo de $–C_1$-C_6 incluyen, pero no se limitan a fenilmetilo, naftilmetilo.

Como se usa en la presente, a menos que se indique lo contrario, el término “cicloalquilo” se refiere a un anillo saturado no aromático mono o policíclico no sustituido o sustituido, que opcionalmente incluye un enlazador alquileno a través del cual puede estar unido el cicloalquilo. Los sustituyentes convenientes se definen en la definición de ‘sustituido”. Grupos “cicloalquilo” de ejemplo incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, y similares, así como versiones no sustituidas y sustituidas de los mismos.

Como se usa en la presente, a menos que se defina lo contrario, el término “alcoxi” se refiere al grupo -OR^a, donde R^a is alquilo de C_1-C_4 o cicloalquilo como se definió antes.

Como se usa en la presente, a menos que se defina lo contrario, el término “amida” se refiere al grupo $–C(O)NR^cR^d$, en donde R^c y R^d son cada uno independientemente H, o alquilo de C_1-C_6, o R^c es la porción restante de un aminoácido natural o no natural.

Como se usa en la presente, a menos que se defina lo contrario, el término “heterociclo” o “heterociclilo” o “heterocíclico” se refiere a un sistema de anillo no aromático mono o policíclico no sustituido y sustituido que contiene uno o más heteroátomos. Heteroátomos preferidos incluyen N, O, y S, incluyendo N-óxidos, óxidos de azufre, y dióxidos. Preferiblemente los anillos tienen de tres a ocho miembros y están ya sea completamente saturados o tienen uno o más grados de insaturación. Múltiples grados de

sustitución se incluyen dentro de la definición presente. Ejemplos de grupos "heterocíclicos" incluyen, pero no se limitan a tetrahidrofuranilo, piranilo, 1,4-dioxanilo, 1,3-dioxanilo, piperidinilo, pirrolidinilo, morfolinilo, azetidinilo, piperazinilo, pirrolidinonilo, piperazinonilo, pirazolidinilo, y sus diversos tautómeros.

Como se usa en la presente, a menos que se defina lo contrario, el término "arilo", a menos que se defina lo contrario, significa un sistema de anillo de hidrocarburo, aromático. El sistema de anillo puede ser monocíclico o policíclico fusionado (por ejemplo, bicíclico, tricíclico, etc.), sustituido o no sustituido. Un sistema de anillo de C6, es decir un anillo fenilo, es un grupo arilo adecuado. En varias modalidades, el anillo policíclico es un grupo arilo bicíclico, donde los grupos arilo bicíclicos adecuados son C8-C12, o C9-C10. Un anillo naftilo, que tiene 10 átomos de carbono, es un grupo arilo policíclico adecuado. Sustituyentes adecuados para el arilo se describen en lo siguiente en la definición de "opcionalmente sustituido".

Como se usa en la presente, a menos que se defina lo contrario, el término "heteroarilo",a menos que se defina lo contrario, significa un sistema de anillo aromático que contiene carbono(s) y por lo menos un heteroátomo. El heteroarilo puede ser monocíclico o policíclico, sustituido o no sustituido. Un grupo heteroarilo monocíclico puede tener 1 a 4 heteroátomos en el anillo, mientras un heteroarilo policíclico puede contener 1 a 10 heteroátomos. Un anillo heteroarilo policíclico puede contener uniones de anillo fusionadas, espiro o puenteadas, por ejemplo, el heteroarilo bicíclico es

un heteroarilo policíclico. Los anillos heteroarilo bicíclicos pueden contener de 8 a 12 átomos miembros. Los anillos heteroarilo monocíclicos pueden contener de 5 a 8 átomos miembros (carbonos y heteroátomos). Grupos heteroarilo de ejemplo incluyen pero no se limitan a: benzofurano, benzotiofeno, furano, imidazol, indol, isotiazol, oxazol, pirazina, pirazol, piridazina, piridina, pirimidina, pirrolo, quinolina, quinazolina, quinoxalina, tiazol, y tiofeno. Los sustituyentes adecuados para el heteroarilo se describen en lo siguiente en la definición de "opcionalmente sustituido".

Como se usa en la presente, a menos que se defina lo contrario, el término "ciano" se refiere al grupo -CN.

Como se usa en la presente, a menos que se defina lo contrario, el término "acilo" se refiere al grupo $-C(O)R^b$, donde R^b es alquilo, cicloalquilo, o heterociclilo, como cada uno se define en la presente.

Como se usa en la presente, a menos que se defina lo contrario, el término "opcionalmente" significa que el evento(s) subsiguientemente descrito puede o no puede ocurrir, e incluye tanto los eventos que ocurren como los eventos que no ocurren.

Como se usa en la presente, a menos que se defina lo contrario, la frase "sustituido" o variaciones del mismo denotan una sustitución opcional, incluyendo múltiples grados de sustitución, con uno o más grupos sustituyentes, preferiblemente uno, dos o tres. La frase no debe interpretarse como duplicado de las sustituciones descritas y representadas en la presente. Grupos sustituyentes opcionales adecuados incluyen acilo, alquilo de C_1-C_6,

alquilo de C_1-C_6 sustituido, cicloalquilo de C_3-C_7 no sustituido, alquilosulfonilo, alcoxi, alcoxicarbonilo, ciano, halo, urea, amida, hidroxilo, oxo, y nitro.

Composiciones farmaceuticas

La invención además proporciona una composición farmacéutica (también llamada una formulación farmacéutica) que comprende un compuesto de la Fórmula (I) o una sal farmacéuticamente aceptable, del mismo y uno o más excipientes (también llamados portadores y/o diluyentes en las técnicas farmacéuticas). Los excipientes son aceptables en el sentido de ser compatibles con los otros ingredientes de la formulación y no dañinos al recipiente de los mismos (es decir, el paciente).

De acuerdo con otro aspecto de la invención se proporciona un procedimiento para la preparación de una composición farmacéutica que comprende mezclar (o combinar) un compuesto de la Fórmula (I) o sal del mismo con por lo menos un excipiente.

Las composiciones farmacéuticas pueden estar en forma de dosis unitaria que contiene una cantidad predeterminada de ingrediente activo por dosis unitaria. Tal unidad puede contener una dosis terapéuticamente efectiva del compuesto de la Fórmula (I) o sal del mismo o una fracción de una dosis terapéuticamente efectiva de manera que múltiples formas de unidad de dosis pueden administrarse en un momento dado para lograr la dosis terapéuticamente efectiva deseada. Las formulaciones preferidas de la unidad de dosis son esas que contienen una dosis o sub-dosis diaria, como se

recita en la presente antes, o una fracción apropiada del mismo, de un ingrediente activo. Además, tales composiciones farmacéuticas pueden ser preparadas por cualquiera de los métodos bien conocidos en la técnica de la farmacia.

Las composiciones farmacéuticas pueden ser adaptadas para la administración por alguna ruta apropiada, por ejemplo, por rutas orales (incluyendo bucal o sublingual), rectal, nasal, tópica (incluyendo bucal, sublingual, o transdermal), vaginal, o parenteral (incluyendo subcutánea, intramuscular, intravenoso, o intradermal). Tales composiciones pueden ser preparadas por cualquier método conocido en la técnica de la farmacia, por ejemplo, asociando el ingrediente activo con el excipiente(s).

Cuando se adaptan para la administración oral, las composiciones farmacéutica.os pueden estar en unidades discretas tales como tabletas o cápsulas; polvos o gránulos; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o batidos comestibles; emulsiones líquidas de aceite en agua o emulsiones líquidas de agua en aceite. El compuesto o la sal del mismo de la invención o la composición farmacéutica de la invención también pueden incorporarse en un dulce, una oblea, y/o una formulación de disolución en la lengua para la administración como una medicina de rápida disolución.

Por ejemplo para la administración oral en forma de una tableta o cápsula, el componente activo de fármaco puede ser combinado con un portador inerte, farmacéuticamente aceptable, no tóxico y oral tal como el

etanol, el glicerol, el agua y similares. Los polvos o gránulos se preparan triturando el compuesto a un tamaño fino conveniente y mezclando con un portador farmacéutico asimismo triturado tal como un carbohidrato comestible, como, por ejemplo almidón o manitol. También pueden estar presentes agentes saborizantes, conservantes, dispersantes, y colorantes.

Las cápsulas se forman preparando una mezcla de polvo, como se describió antes, y llenando fundas formadas gelatinosas o no gelatinosas. Deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio, puede agregarse polietilenglicol sólido a la mezcla de polvo antes de la operación de llenado. También puede agregarse un agente desintegrante o solubilizante tal como agar-agar, carbonato de calcio, o carbonato de sodio para mejorar la disponibilidad de la medicina cuando la cápsula sea ingerida.

Además, cuando se deseada o es necesario, también pueden incorporarse a la mezcla agentes aglutinantes, lubricantes, y desintegrantes adecuados. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales, tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas tales como acacia, tragacanto, alginato de sodio, carboximetilcelulosa, polietilenglicol, ceras, y similares. Los lubricantes usados en estas formas de dosis incluyen oleato, estearato de sodio, estearato de magnesio, benzoato de sodio, acetato de sodio, cloruro de sodio, y similares. Los desintegradores incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma de xantano, y similares.

Las tabletas se formulan, por ejemplo, preparando una mezcla de polvo, granulando o adhiriendo, agregando un lubricante y desintegrante, y presionando en tabletas. Una mezcla del polvo se prepara mezclando el compuesto, convenientemente triturado, con un diluyente o base como se describió antes, y opcionalmente, con un aglutinante tal como carboximetilcelulosa, y aliginato, gelatina, o polivinil pirrolidona, una solución retardante tal como parafina, un acelerador de resorción tal como una sal cuaternaria, y/o un agente de absorción tal como bentonita, caolín, o fosfato dicálcico. La mezcla en polvo puede granularse humectando un aglutinante tal como un jarabe, pasta de almidón, mucílago de acacia, o soluciones de materiales celulósicos o poliméricos y forzando a través de una criba. Como una alternativa a la granulación, la mezcla de polvo se puede procesar a través de la máquina de comprimidos y el resultado son fragmentos formados de manera imperfecta fraccionados en gránulos. Los gránulos pueden ser lubricados para prevenir la adhesión a los dados formadores de la tableta por medio de la adición de ácido esteárico, de una sal de estearato, talco, o de aceite mineral. La mezcla lubricada se comprime después en tabletas. El compuesto o la sal de la presente invención también pueden ser combinados con un portador inerte de flujo libre y comprimido en tabletas directamente sin pasar po los pasos de granulación o adhesión. Puede proporcionarse un revestimiento protector opaco transparente de un revestimiento sellador de goma laca, un revestimiento de azúcar, o de material polimérico, y un revestimiento de pulidor de cera. Pueden agregarse tintes a estos

revestimientos para distinguir entre diferentes dosis.

Los fluidos orales tales como soluciones, jarabes, y elixires pueden prepararse en la forma de unidad de dosis para que una cantidad dada contenga una cantidad predeterminada de ingrediente activo. Los jarabes pueden prepararse disolviendo el compuesto o la sal del mismo de la invención en una solución acuosa adecuadamente saborizada, mientras que los elixires se preparan por el uso de un vehículo alcohólico no tóxico. Las suspensiones pueden formularse dispersando el compuesto o la sal de la invención en un vehículo no tóxico. También pueden agregarse solubilizantes y emulsionantes, tales como alcoholes isoestearílicos etoxilados y polioxietilen sorbitol éteres, los conservantes, los aditivos saborizantes tales como aceite de menta, edulcorantes naturales, sacarina, u otros edulcorantes artificiales, y similares.

Cuando sea adecuado, las formulaciones de unidad de dosis para la administración oral pueden ser microencapsuladas. La formulación también puede ser preparadas para prolongar o sostener la liberación, por ejemplo, revistiendo o incorporando material particulado en polímeros, cera, o similares.

En la presente invención, las tabletas y las cápsulas se prefieren para el suministro de la composición farmacéutica.

Como se usa en la presente, el término "tratamiento" incluye la profilaxis y se refiere a aliviar la condición especificada, eliminando o reduciendo uno o más síntomas de la condición, alentando o eliminando la

progresión de la condición, y previniendo o demorando la reaparición de la condición en un paciente o sujeto anteriormente afligido o diagnosticado. La profilaxis (o la prevención o la demora del comienzo de la enfermedad) típicamente se efectúa administrando un fármaco en la manera misma o una similar como se haría a un paciente con la enfermedad o la condición desarrolladas.

La invención presente proporciona un método de tratamiento en un mamífero, especialmente un humano, que sufre de obesidad, diabetes, hipertensión, depresión, ansiedad, adicción a fármacos, adicción a sustancias, o una combinación de los mismos. Tal tratamiento comprende el paso de administrar una cantidad terapéuticamente efectiva de un compuesto de la Fórmula (I) o sal del mismo a dicho mamífero, especialmente un humano. El tratamiento también puede comprender el paso de administrar una cantidad terapéuticamente efectiva de una composición farmacéutica que contiene un compuesto de la Fórmula (I) o sal del mismo a dicho mamífero, especialmente un humano.

Como se utiliza en la presente, el término "cantidad efectiva" significa esa cantidad de un fármaco o agente farmacéutico que producirá la respuesta biológica o médica de un tejido, sistema, animal o humano que es buscada, por ejemplo por un investigador o médico.

Además, el término "cantidad terapéuticamente efectiva" significa cualquier cantidad que, en comparación con un correspondiente sujeto que no ha recibido tal cantidad, tiene como resultado tratamiento mejorado, la

curación, la prevención, o la mejora de una enfermedad, trastorno, o del efecto secundario, o una disminución en la tasa de avance de una enfermedad o trastorno. El término también incluye dentro de su alcance cantidades efectivas para mejorar la función fisiológica normal. Para el uso en terapia, las cantidades terapéuticamente efectivas de un compuesto de la Fórmula (I), así como sales del mismo, pueden ser administradas como una sustancia química en bruto. Adicionalmente, el ingrediente activo puede ser presentado como una composición farmacéutica.

Aunque es posible que, para el uso en terapia, una cantidad terapéuticamente efectiva de un compuesto de la Fórmula (I) o sal del mismo pueda administrarse como la sustancia química en bruto, típicamente se presenta como el ingrediente activo de una composición farmacéutica o formulación.

La cantidad terapéuticamente efectiva precisa de un compuesto o sal del mismo de la invención dependerá de varios factores, includos, pero no limitados a, la edad y el peso del sujeto (paciente) que es tratado, el trastorno preciso que requiere tratamiento y su gravedad, la naturaleza de la formulación/composición farmacéutica, y la ruta de la administración, y finalmente será a voluntad del médico o veterinario a cargo. Típicamente, un compuesto de la Fórmula (I) o sal del mismo será dado para el tratamiento en un intercalo de aproximadamente 0.01 a 100 mg/kg de peso corporal del recipiente (paciente, mamífero) por día y más generalmente en el intervalo de 0.1 a 10 mg/kg de peso corporal por día. Las dosis diarias aceptables pueden

ser de aproximadamente 1 a aproximadamente 1000 mg/día, y preferiblemente de aproximadamente 1 a aproximadamente 100 mg/día. Esta cantidad puede ser dada en una dosis única por día o en un número (como dos, tres, cuatro, cinco, o más) de sub-dosis por día de manera que el total de la dosis diaria sea el mismo. Una cantidad efectiva de una sal del mismo puede ser determinada como una proporción de la cantidad efectiva del compuesto de la Fórmula (I) *per se*. Las dosis similares deben ser apropiadas para el tratamiento (incluyendo la profilaxis) de las otras condiciones referidas en presente para tratamiento. En general, la determinación de la dosificación apropiada puede ser alcanzada fácilmente por un experto en la medicina o la técnica de la farmacia.

Adicionalmente, la invención presente comprende un compuesto de Fórmula I o sal del mismo o una composición farmacéutica del mismo con por lo menos un otro fármaco anti-obesidad y/o por lo menos un fármaco anti-diabetes. Tales fármacos anti-obesidad pueden incluir, por ejemplo, Metformina (o glucófago), antagonistas del receptor de CB1, agonistas de GLP-1, antagonistas de opioide, e inhibidores de la recaptación de neurotransmisor. Cuando un compuesto de la invención es empleado en combinación con otro fármaco anti-obesidad o fármaco anti-diabetes, será apreciado por los expertos en la técnica que la dosis de cada compuesto o fármaco de la combinación puede variar de ese cuando el fármaco o compuesto se utiliza solo. Las dosis apropiadas serán fácilmente apreciadas y determinadas por los expertos en la técnica. La dosis apropiada del

compuesto de Fórmula I o la sal del mismo y los otros agentes terapéuticamente activos y los programas relativos de administración serán seleccionados para lograr el efecto terapéutico combinado deseado, y está dentro de la experiencia y la discreción del médico o clínico que asiste.

Preparación de compuestos

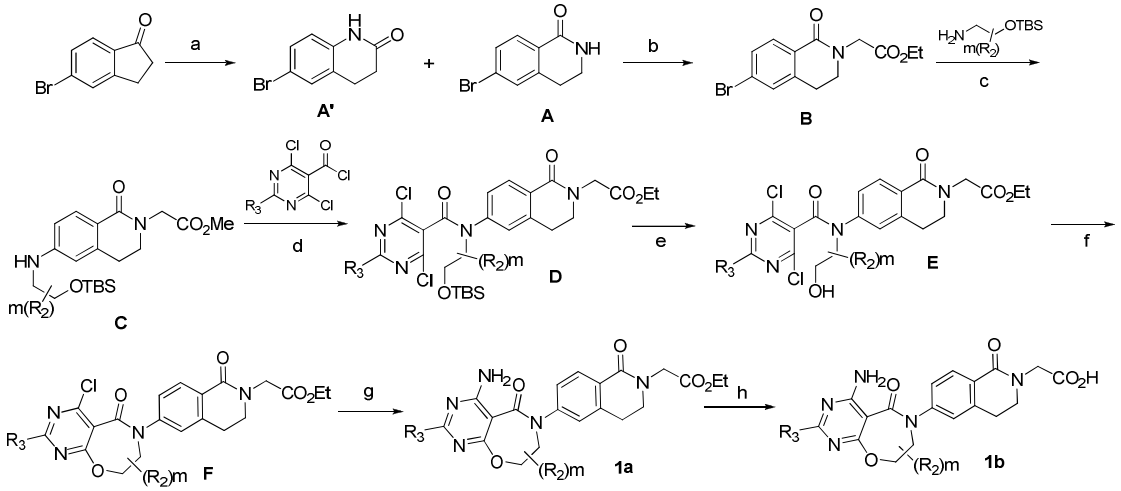
Esquemas de la Síntesis Genérica

Los compuestos de esta invención pueden formarse por una variedad de métodos, incluyendo métodos de síntesis estándar bien conocidos. Métodos de síntesis general ilustrativos se establecen a continuación y luego los compuestos específicos de la invención son preparados en los ejemplos de trabajo. El experto en la técnica apreciará que si un sustituyente descrito en la presente no es compatible con los métodos de síntesis descritos en la presente, el sustituyente puede ser protegido con un grupo protector conveniente que es estable en las condiciones de reacción. El grupo protector puede ser eliminado en un punto conveniente en la secuencia de la reacción para proporcionar un intermediario deseado o el compuesto objetivo. En todos los esquemas descritos a continuación, los grupos protectores para grupos sensibles o reactivos se emplean en donde sea necesario, de conformidad con los principios generales de la química de síntesis. Los grupos protectores son manipulados según métodos estándar de la síntesis orgánica (T.W. Green and P.G.M. Wuts, (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons, incorporado como

referencia con relación a los grupos protectores). Estos grupos se remueven en una etapa conveniente de la síntesis del compuesto utilizando métodos que son fácilmente evidentes para los expertos en la técnica. La selección de los procedimientos, así como las condiciones de la reacción y el orden de su ejecución deberán ser congruentes con la preparación de los compuestos de la presente invención.

La síntesis de los compuestos de la Fórmula general (I) y derivados y sales farmacéuticamente aceptables del mismo pueden ser logrados tal como se plantea abajo los Esquemas 1 – 10 por los expertos en la técnica. En la descripción siguiente, los grupos son como se definión antes para los compuestos de Fórmula (I) a menos que de otro modo indicado. Los materiales de partida están disponibles comercialmente o son formados de materiales de partida disponibles comercialmente utilizando métodos conocidos por los expertos en la técnica.

ESQUEMA 1

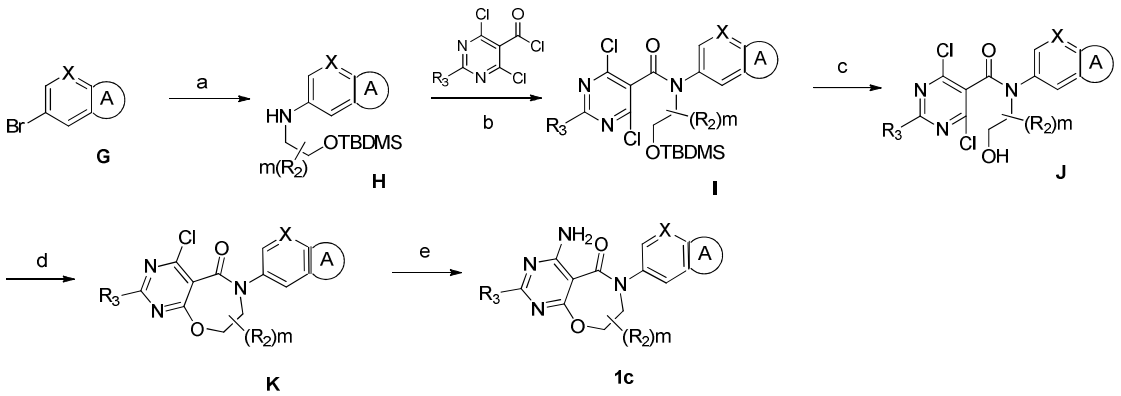


Reactivos y condiciones: a) NaN_3, $MeSO_3H$, CH_2Cl_2, RT; b) NaH, $BrCH_2CO_2Et$, THF, RT; c) $Pd(OAc)_2$, Cs_2CO_3, X-Phos, Tolueno, 120 °C; d) THF, Et_3N, RT; e) 3%HCl-MeOH, RT; f) CH_3CN, Et_3N, 80 °C; g) NH_3, Dioxano, RT; h) LiOH, Dioxano-H_2O, RT

Los compuestos de Fórmula (I) pueden prepararse como se ilustra en el Esquema 1. El Intermediario A puede obtenerse por una reacción de rearreglo de 5-bromo-1-indanona con NaN_3 en $MeSO_3H$ en solventes tal como CH_2Cl_2. La alquilación del Intermediario A con un haluro de alquilo adecuado tal como bromoacetato de etilo en la presencia de una base adecuada tal como NaH da el Intermediario B. El Intermediario A' también puede ser alquilado de manera similar y procesado similar a ese del Intermediario A. El Intermediario B puede luego ser sometido a aminación bajo condiciones de Buchwald usando una amina apropiada en la presencia de reactivos tal como acetato de paladio, ligando tal como X-Phos y una base tal como carbonato de cesio en tolueno a 120 °C. El Intermediario C así obtenido puede luego ser acoplado al cloruo ácido apropiadamente sustituido para producir D. La destilación del Intermediario D bajo condiciones ácidas estándar lleva a E que luego se somete a un cierre de anillo al calentar la mezcla de reacción en acetonitrilo a 80 °C en la presencia de una base tal como trietilamina para dar F. La sustitución del residuo de cloro en el Intermediario F con un grupo amino por tratamiento con amoniaco a temperatura ambiente resulta en compuestos de Fórmula (I) (1a). La hidrólisis del grupo éster en el compuesto 1a con una base tal como LiOH proporciona

otro compuesto de Fórmula (I) (1b).

ESQUEMA 2

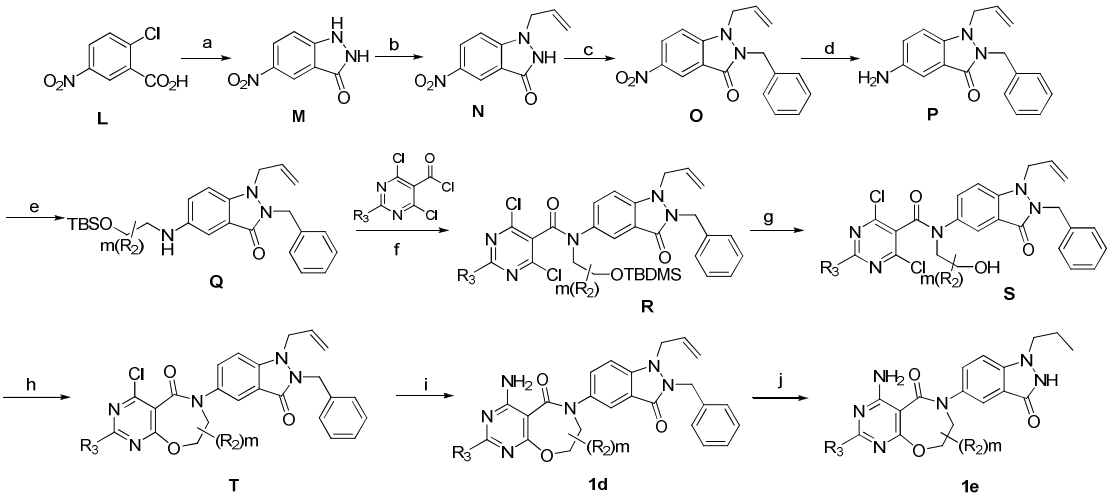


Reactivos y condiciones: a) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 °C; b) THF, Et_3N, RT; c) 3% HCl-MeOH, RT; d) CH_3CN, Et_3N, 80 °C; e) NH_3, Dioxano, RT.

Los compuestos de Fórmula (I) también pueden prepararse como se ilustra en el Esquema 2. El Intermediario H puede ser obtenido por la aminación de un compuesto G heterocíclico sustituido con bromo apropiadamente con una amina convenientemente protegida bajo las condiciones estándar de Buchwald. El bromuro G está disponible ya sea comercialmente o es sintetizado según métodos estándar de síntesis orgánica conocida por los expertos en la técnica con o sin grupos protectores apropiados. El intermediario H de amina entonces puede ser convertido a la amida terciaria I con un cloruro ácido apropiadamente sustituido utilizando trietilamina como una base. La destilación del intermediario I seguido por el

cierre del anillo del alcohol J resultante bajo condiciones de calentamiento en acetonitrilo produce el intermediario K. La sustitución del residuo de cloro en el intermediario K con un grupo amino por tratamiento con amoniaco a temperatura ambiente tiene como resultado los compuestos de Fórmula (I) (1c). Si es necesario, el compuesto 1c puede ser sometido a una reacción de desprotección del grupo funcional bajo condiciones estándar para remover el grupo que fue introducido durante la preparación del bromuro G.

ESQUEMA 3

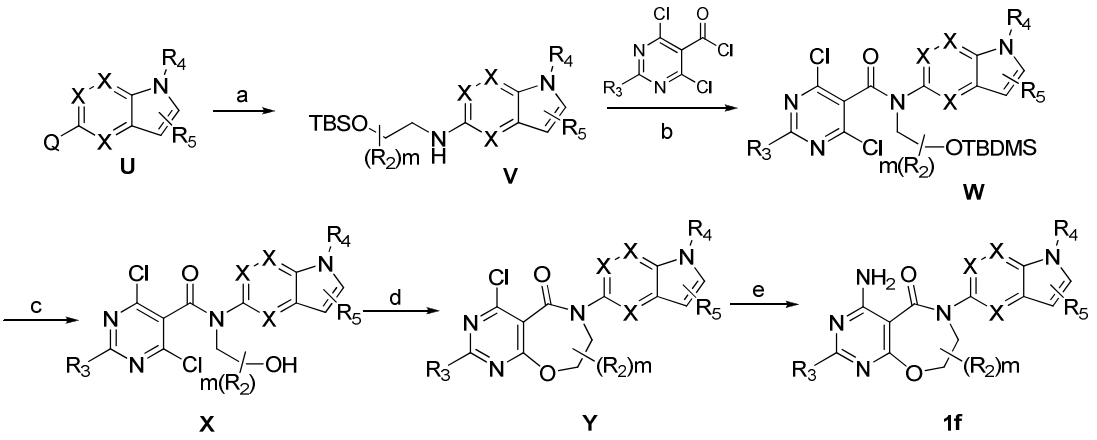


Reactivos y condiciones: a) $NH_2NH_2.H_2O$, EtOH, 80 ºC; b) Bromuro de alilo, KOH, NaOH, 100 ºC; c) Bromuro de bencilo, NaH, DMF, RT; d) Fe/NH_4Cl, $EtOH-H_2O$, 85 ºC; e) $Br(CH_2)_2OTBDMS$, CH_3CN, K_2CO_3, 80 ºC; f)DCM, Et_3N, rt; g) 3% HCl-MeOH, RT; h) CH_3CN, Et_3N, 80 ºC; i) NH_3, Dioxano, RT; j) 10% Pd/C, H_2, MeOH, RT.

Los compuestos de Fórmula (I) también pueden prepararse como se ilustra en el Esquema 3. Acido 2-cloro-5-nitro benzoico L disponible

comercialmente fue tratado con hidrato de hidrazina en etanol a reflujo para dar la indazolona M. El Intermediario M entonces se protegió doblemente primero con un grupo alilo en el nitrógeno de anilina para dar N y entonces con un grupo bencilo en el nitrógeno de lactama para proporcionar O. El Intermediario O entonces fue reducido a la correspondiente amina P bajo condiciones estándar. La anilina P fue entonces alquilada con un bromuro de alquilo conveniente para proporcionar Q que entonces fue convertido a una amida terciaria R que utiliza un cloruro ácido apropiadamente sustituido. La destilación del intermediario R seguido por el cierre del anillo del alcohol resultante S bajo condiciones de calentamiento en acetonitrilo proporciona el intermediario T. La sustitución del residuo de cloro en el intermediario T con un grupo amino por tratamiento con amoniaco a temperatura ambiente tiene como resultado los compuestos de Fórmula (I) (1d). La desprotección del grupo bencilo en el nitrógeno de lactama del compuesto 1d con la reducción concomitante de la olefina en la porción del alilo proporciona otro compuesto de Fórmula (I) (1e).

ESQUEMA 4

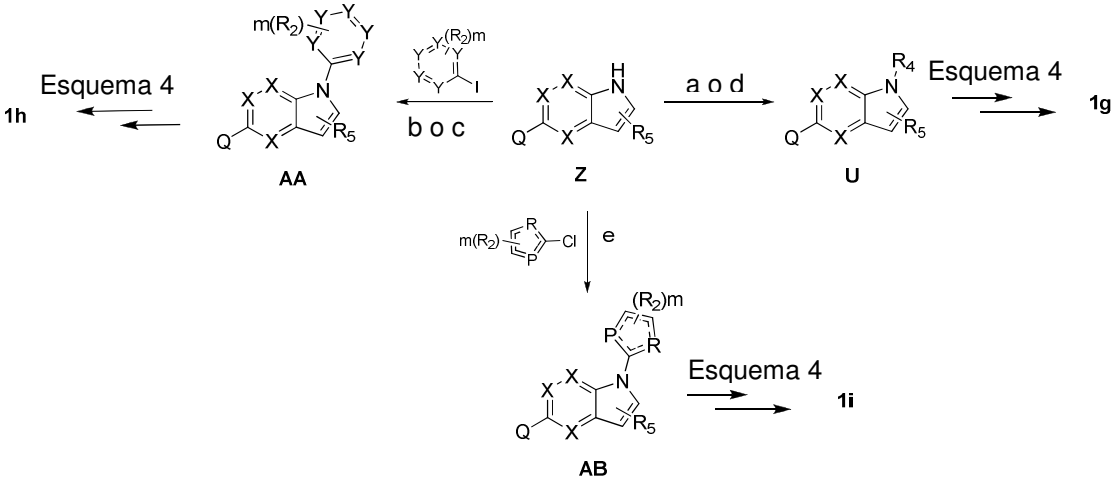


Reactivos y condiciones: a) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-Phos, Tolueno, 120 °C; b) DCM, Et_3N, RT; c) 3% HCl-MeOH, RT; d) CH_3CN, Et_3N, 80 °C; e) NH_3, Dioxano, RT.

Los compuestos de Fórmula (I) también pueden prepararse como se ilustra en el Esquema 4. Un indol apropiadamente sustituido o un derivado del mismo U, puede ser sometido a aminación bajo condiciones de Buchwald utilizando una amina apropiada en la presencia de reactivos tales como acetato de paladio, ligando tal como X-Phos y una base tal como carbonato de cesio en tolueno a 120° C. El Intermediario V así obtenido entonces puede ser acoplado a un cloruro ácido apropiadamente sustituido para proporcionar W. La destilación del intermediario W bajo condiciones ácidas estándar lleva a X que es entonces sometido al cierre del anillo por calentamiento de la mezcla de reacción en el acetonitrilo a 80°C en la presencia de una base tal como trietilamina para dar Y. La sustitución del residuo de cloro en el intermediario Y con un grupo amino por tratamiento con

amoniaco a temperatura ambiente tiene como resultado los compuestos de Fórmula (I) (1f).

ESQUEMA 5

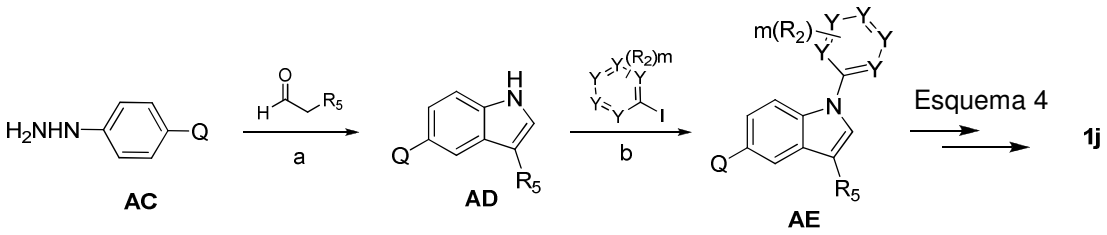


Reactivos y condiciones: a) R_4-Br/ R_4-I, Cs_2CO_3, DMF, 100 ºC; b) Cu(I)Br, $Cu(OAc)_2$, K_2CO_3, NaOH, 140 ºC; c) Cu(I)Br, $Cu(OAc)_2$, K_2CO_3, NaOH, DMF, 110 ºC; d) R_4-$B(OH)_2$, 2,2'-bipiridina, Na_2CO_3, $Cu(OAc)_2$, DCE, 110 ºC; e) Cs_2CO_3, DMF, 100 ºC.

Los compuestos de Fórmula (I) también pueden ser preparados a través de los intermediarios U, AA y AB como se ilustra en el Esquema 5. Un indol adecuadamente sustituido o un derivado del mismo Z es alquilado o arilado usando el bromuro de alquilo R_4-Br apropiado (o yoduro R_4-I) o ácido borónico de arilo/heteroarilo R_4-$B(OH)_2$ respectivamente bajo condiciones estándar para producir el Intermediario U tapado en el nitrógeno. Esto puede ser convertido a compuestos de fórmula (I) 1g utilizando este intermediario U a través del Esquema 4. Asimismo Z también puede ser arilado bajo

condiciones catalizadas con cobre (I) bromuro y acetato cúprico utilizando un yoduro de arilo apropiadamente sustituido para proporcionar el intermdiario AA. Este intermediario otra vez puede ser transformado en compuestos de fórmula (I) 1h a través del Esquema 4. El Intermediario Z puede ser tratado con heterociclos sustituidos con 2-cloro bajo condiciones de claentamiento en la presencia de una base suave tal como carbonato de cesio. El intermediario AB así obtenido puede ser transformado en compuestos de Fórmula (I) 1i a través del Esquema 4.

ESQUEMA 6

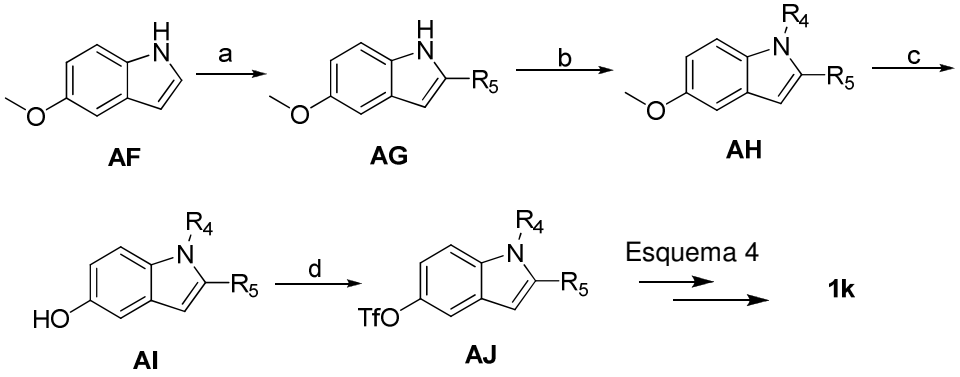


Reactivos y condiciones: a) AcOH, 120 °C; b) Cu(I)Br, $Cu(OAc)_2$, K_2CO_3, NaOH, 140 °C.

Los compuestos de Fórmula (I) también pueden ser sintetizados a través del intermediario AE cuya síntesis es mostrada en el Esquema 6. Una fenil hidrazina AC apropiadamente sustituida es calentada con un aldehído α-sustituido conveniente en ácido acético a 120 °C para producir el indol 3-sustituido AD. El Intermediario AD luego es acoplado a un yoduro de arilo o heteroarilo apropiadamente sustituido bajo condiciones catalizadas con cobre (similar a ese descrito para la síntesis del Intermediario AA) para producir el

Intermediario AE. Esto entonces puede ser tomado a través de una secuencia de síntesis similar a esa en el Esquema 4 para proporcionar los compuestos de Fórmula (I) 1j.

ESQUEMA 7

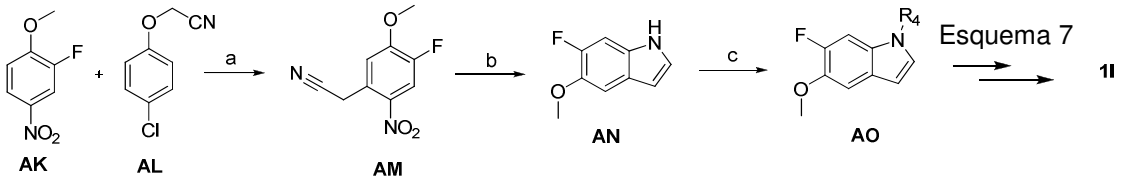


Reactivos y condiciones: a) R_5-$B(OH)_2$, AcOH, $Pd(OAc)_2$, acetato de cobre(II), 25 °C; b) R_4-Br/ R_4-I, Cs_2CO_3, DMF, 25 °C; c) BBr_3, DCM, 0 °C; d) anhídrido tríflico, Py, DCM, 0 °C.

Los compuestos de Fórmula (I) también pueden ser sintetizados a través del intermediario AJ cuya síntesis es descrita en el Esquema 7. El 5-metoxi indol AF comercialmente disponible sustituido convenientemente con la porción R_5 usando el ácido borónico sustituido en R_5 bajo condiciones catalizadas con paladio para producir el derivado de indol 2-sustituido AG. El Intermediario AG a su vez es alquilado (o arilado) bajo condiciones estándar usando un agente de alquilación conveniente tal como bromuro de R_4 (o el correspondiente yoduro) para producir AH. La desmetilación del grupo metozi con tribromuro de boro y la triflación del intermediario AI resultante da el

derivado de indol AJ apropiadamente sustituido. Este intermediario entonces puede ser tomado por los varios pasos de síntesis del Esquema 4 para producir los compuestos de Fórmula (I) 1k.

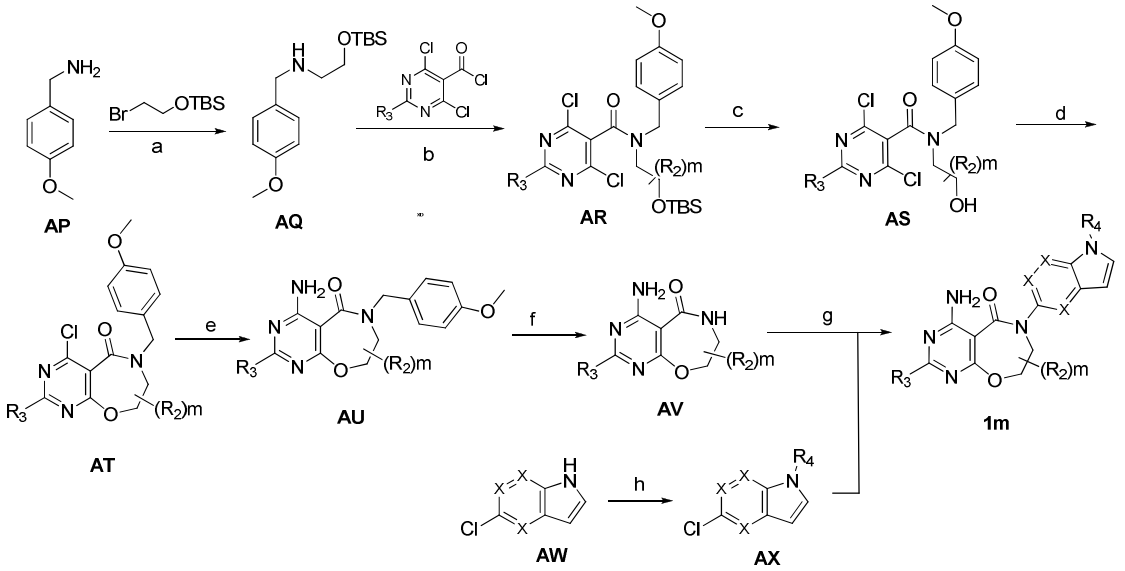
ESQUEMA 8



Reactivos y condiciones: a) K^{t}OBu, DMF, -20 ^{o}C; b) 10% Pd/C, Etanol, 27 ^{o}C; c) R_4-Br/ R_4-I, $Cu(OAc)_2$, CuBr, K_2CO_3, NaOH, DMF, 80 ^{o}C

Los compuestos de Fórmula (I) también pueden ser sintetizados a través del intermediario AO cuya síntesis es descrita en el Esquema 8. El Intermediario AM puede ser preparado por una reacción de transferencia de cianometilo usando un agente tal como AL cuando se trata con el sustrato AK en la presencia de una base fuerte tal como *ter*-butóxido de potasio. El nitro areno AM puede entonces someterse a una reducción usando paladio en carbono y la anilina transitoria resultante se condensa internamente para ciclizarse para formar el indol AN perdiendo así un equivalente de amoniaco. El indol AN entonces puede ser convenientemente alquilado (o arilado) bajo condiciones estándar para proporcionar AO. El fluoro indol AO puede ser tomado por pasos similares a esos descritos en el Esquema 7 para el intermediario AH, seguido por ésos en el Esquema 4 llevando finalmente a la síntesis de compuestos de Fórmula (I) 1l.

ESQUEMA 9

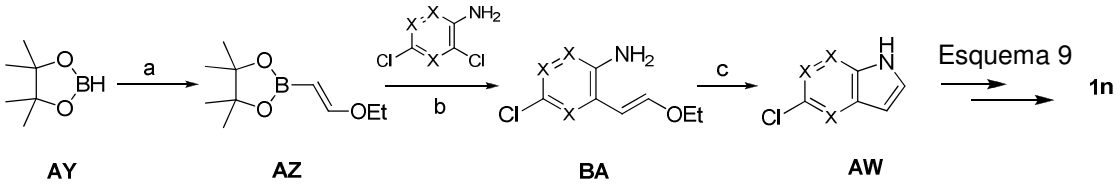


Reactivos y condiciones: a) $Br(CH_2)_2OTBDMS$, K_2CO_3, ACN, 80 °C; b) DCM, Et_3N, RT; c) 3% HCl-MeOH, RT; d) CH_3CN, Et_3N, 80 °C; e) NH_3, Dioxano, RT; f) TFA, anisol, 90 °C; g) K_3PO_4 dibásico, CuI, (1*S*,2*S*)-ciclohexano-1,2-diamina, 1,4-dioxano, 110 °C; h) R_4-Br, Cs_2CO_3, DMF, 25 °C.

Una metodología alternativa es descrita en el Esquema 9 hacia la síntesis de los compuestos de Fórmula (I). *p*-metoxi bencilamina se alquila con bromoetanol protegido con TBS en acetonitrilo usando una base suave tal como carbonato de potasio bajo condiciones de calentamiento para producir la amina secundaria AQ. El Intermediario AQ fue convertido a la amida terciaria AR con tratamiento con un cloruro ácido apropiadamente sustituidp bajo condiciones estándar. La destilación de AR bajo condiciones ácidas seguido por el cierre del anillo del alcohol AS resultante por calentamiento en acetonitrilo produjo laoxazepinona sustituida con PMB AT. La conversión del grupo cloro en AT a una amina fue realizado por tratamiento con amoniaco en

dioxano para proporcionar AU. La eliminación del grupo PMB bajo condiciones de TFA en la presencia de un anisol captor a 90 ^{O}C proporcionó el intermediario clave AV. La oxazepinona AV luego fue acoplada al 5-cloro indol sustituido apropiadamente AX bajo condiciones catalizadas con cobre para producir los compuestos de Fórmula (I) 1m. El Intermediario AX puede ser preparado por sí mismo por alquilación del 5-cloro indol AW con un bromuro adecuado (o yoduro) bajo condiciones estándar.

ESQUEMA 10



Reactivos y condiciones: a) cloruro de di(ciclopenta-2,4-dien-1-il)circonio(IV), etoxietino, DCM, RT, b) K_3PO_4 dibásico, $Pd(OAc)_2$,,diciclohexil(2',6'-dimetoxi-[1,1'-bifenil]-2-il)fosfina, ACN, agua, 80 ^{o}C ; c), AcOH, 140 ^{o}C.

Los compuestos de Fórmula (I) también pueden ser sintetizados a través de intermediarios tales como AW como es descrito en el Esquema 10. Varios indoles sustituidos representados por AW pueden ser sintetizados comenzando de etoxi vinil boronato AZ que por sí mismo es preparado por tratamiento de pinacolato borano AY con etoxietino en la presencia de un catalizador de circonio a temperatura ambiente. El Intermediario AZ es luego tratado con anilina sustituida con 2, 4-dicloro bajo condiciones catalizadas con

paladio usando un ligando adecuado y una base tal como fosfato dibásico de potasio para proporcionar la anilina BA. El Intermediario BA es luego calentado en ácido acético a 140 °C para dar el indol AW. El Intermediario AW puede luego ser llevado a través de los pasos de síntesis adecuados descritos en el Esquema 9 para finalmente producir los compuestos de Fórmula (I) 1n.

Experimental

Los ejemplos siguientes ilustran la invención. Estos ejemplos no pretenden limitar el alcance de la presente invención, sino proporcionar guía al técnico experto para preparar y utilizar los compuestos, las composiciones, y los métodos de la presente invención. Aunque modalidades particulares de la invención presente son descritas, el técnico experto apreciará que varios cambios y modificaciones pueden ser realizados sin separarse del espíritu y el alcance de la invención. A menos que se indique de otro modo, los reactivos estén disponibles comercialmente o son preparados según procedimientos en la literatura. Los símbolos y convenciones usadas en las descripciones de los procedimientos, esquemas y ejemplos son consistentes con esos usados en la literatura científica contemporánea, por ejemplo, el Journal of the American Chemical Society o el Journal of Biological Chemistry.

En los Ejemplos:

Los desplazamientos químicos se expresan en unidades de partes por millón (ppm). Las constantes de acoplamiento (J) se encuentran en unidades de Hertz (Hz). Los patrones de división describen multiplicidades

aparentes y se designan como s (singlete), d (doblete), t (triplete), q (cuarteto), dd (doble doblete), dt (doble triplete), m (multiplete), br (amplia).

La cromatografía de columna instantánea fue realizada en gel de sílice.

Los programas de asignación de nombres usados son ACDLABs 11.0 Namebatch, ACD IUPAC o Chem Draw.

Abreviaturas:

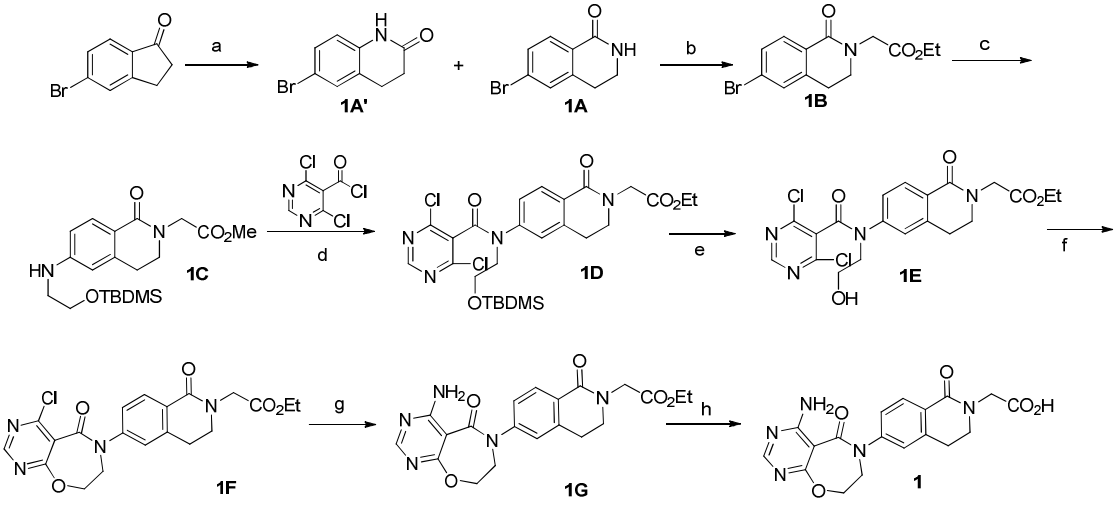
Ac	acetilo
ACN	acetonitrilo
AcOH	ácido acético
BBr_3	tribromide de boro
CH_2Cl_2	diclorometano
CH_3CN	acetonitrilo
C_2CO_3	carbonato de cesio
Cu(I)Br	bromuro de cobre (I)
$Cu(OAc)_2$	acetato de cobre (II)
DCE	dicloroetano
DCM	diclorometano
DMF	dimetilformamida
DMSO	dimetilsulfóxido
Et_3N	trietilamina
g	gramos

hr	horas
LiOH	hidróxido de litio
K_2CO_3	carbonato de potasio
K^tOBu	ter-butóxido de potasio
KOH	hidróxido de potasio
m/z	proporción de masa a carga
MeOH	metanol
$MeSO_3$	Hácido metil sulfónico
mmol	milimoles
Na_2CO_3	carbonato de sodio
NaH	hidruro de sodio
NaN_3	azida de sodio
NaOH	hidróxido de sodio
RMN	resonancia magnética nuclear
Pd	paladio
Pd/C	paladio en carbono
$Pd(OAc)_2$	acetato de paladio (II)
Py	piridina
Ta	temperatura ambiente
TBAF	fluoruro de tetrabutil amonio
TBDMS (TBS)	*ter*-butil dimetilsililo
Tf_2O	anhídrido tríflico
TFA	ácido trifluoroacético

TFAA	anhídrido trifluoroacético
THF	tetrahidrofurano
X-Phos	2-diciclohexilfosfino-2′,4′,6′-triisopropilbifenilo

EJEMPLO 1

Acido 2-(6-(4-Amino-5-oxo-5,6,7,8-tetrahidrooxepino(2,3-*d*)pirimidin-6-il)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético:

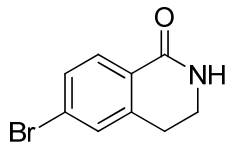


Reactivos y condiciones: a) NaN_3, $MeSO_3H$, CH_2Cl_2, RT, 8h; b) NaH, $BrCH_2CO_2Et$, THF, RT, 5h; c) $NH_2(CH_2)_2OTBDMS$, $Pd(OAC)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 ºC, 24h; d) THF, Et_3N, RT, 16h; e) 3%HCl-MeOH, RT, 4h; f) CH_3CN, Et_3N, 80 ºC, 16h; g) NH_3, Dioxano, RT, 16h; h) LiOH, Dioxano-H_2O, RT, 16h.

Procedimientos:

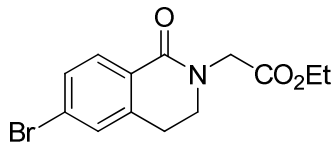
Acido 2-(6-(4-Amino-5-oxo-5,6,7,8-tetrahidrooxepino(2,3-*d*)pirimidin-6-il)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético:

6-Bromo-3,4-dihidroisoquinolin-1(2H)-ona (1A):



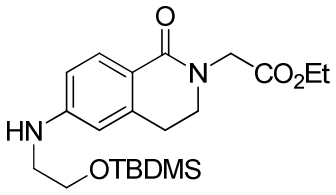
NaN_3 (6.2 g, 94.78 mmoles) se agregó a una solución de 5-bromo-1-indanona (10 g, 47.39 mmoles) en 40 mL de mezcla de ácido metano sulfónico y diclorometano (1:1) en porciones a 0 ºC-5 ºC. La mezcla de reacción se agitó por 8 hr a temperatura ambiente. La mezcla de reacción se enfrió a 0 ºC en baño de hielo, se neutralizó con solución ac. al 5 % de NaOH, y la capa acuosa se extrajo con acetato de etilo (2x100 mL). La capa orgánica combinada se lavó con agua y solución de salmuera, se secó sobre sulfato de sodio, se filtró y concentró bajo vacío. El residuo se purificó por cromatografía de columna instantánea de gel de sílice al eluir con 30 % de acetato de etilo en hexano para producir el compuesto del título (6.4 g, 60%) como un sólido. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.5 (d, *J* = 8.4 Hz, 1H), 7.4 (s, 1H), 6.1 (bs, 1H), 3.6 (t, *J* = 6.8 Hz, 2H), 3.0 (t, *J* = 6.4 Hz, 2H).

2-(6-bromo-2-oxo-3,4-dihidroquinolin-1(2H)-il) acetato de etilo (1B):



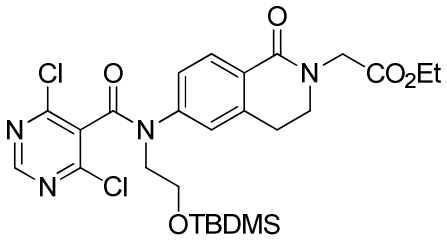
Hidruro de sodio (0.63 g, 26.25 mmoles) se agregó por porciones a una solución enfriada en hielo de producto del Ejemplo 1A (3 g, 13.3 mmoles) en THF (40 mL), y la mezcla se agitó por 30 min. Acetato de etil bromo (3.3 g, 19.9 mmoles) ahora se agregó lentamente, y la mezcla se agitó a temperatura ambiente por 5 h. La reacción luego se enfrió a 0 °C, el exceso de NaH se templó con agua helada, y la capa acuosa se extrajo dos veces con acetato de etilo (2x50 mL). Las capas orgánicas combinadas se lavaron con agua seguido de solución de salmuera, se secaron sobre sulfato de sodio, se filtraron y concentraron bajo vacío. El residuo se purificó usando cromatografía en columna instantánea al eluir con 15% de acetato de etilo en hexano para producir el compuesto del título (2 g, 48%) como un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 7.4 (m, 2H), 6.6 (m, 1H), 4.6 (s, 2H), 4.2 (q, *J* = 6.9 Hz, 2H), 2.9 (m, 2H), 2.7 (m, 2H), 1.2 (t, *J* = 6.9 Hz, 3H).

2-(6-(2-(ter-butildimetilsililoxi)etilamino)-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1C):



Una mezcla de producto del Ejemplo 1B (1.5 g, 4.8 mmoles), 2-(ter-butildimetilsililoxi)etanamina (1.0 g, 5.71 mmoles), carbonato de cesio (1.87 g, 5.73 mmoles), acetato de paladio (0.11 g, 0.47 mmoles) y X-PHOS (0.23 g, 0.47 mmoles) en tolueno (15 mL) bajo argón se calentó a reflujo a 120 °C por 24 h. La reacción se enfrió, la mezcla se diluyó en acetato de etilo y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% de acetato de etilo en hexano para producir el compuesto del título (0.95 g, 48%) como un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 1H), 6.51 (m, 1H), 6.32 (s, 1H), 4.4 (m, 1H), 4.29 (s, 2H), 4.2 (q, *J* = 6.9 Hz, 2H), 3.81 (t, *J* = 5.1 Hz, 2H), 3.59 (t, *J* = 6.3 Hz, 2H), 3.25 (q, *J* = 5.7 Hz, 2H), 2.94 (t, *J* = 6.9 Hz, 2H), 1.27 (t, *J* = 6.9 Hz, 3H), 0.9 (s, 9H), 0.06 (s, 6H); ESI-MS *m/z* = 407 $(M+H)^+$.

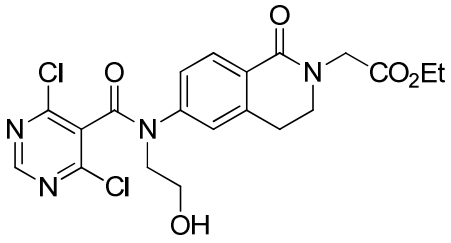
2-(6-(N-(2-(ter-butildimetilsililoxi)etil)-4,6-dicloropirimidina-5-carboxamido)-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1D):



A una solución agitada, enfriada (0 °C) de producto del Ejemplo 1C (0.95 g, 2.33 mmoles) y TEA (1.18 g, 11.67 mmoles) en THF (15 mL) se

agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.74 g, 3.5 mmoles) en THF (5 mL). Después de 16 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.75 g, 55%) como un sólido. ^{1}H RMN (300 MHz, $CDCl_3$): δ 8.6 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.34 (dd, J_1 = 1.2 Hz, J_2 = 7.5 Hz, 1H), 7.29 (s, 1H), 4.34 (s, 2H), 4.21 (q, J = 6.9 Hz, 2H), 4.03 (t, J = 5.7 Hz, 2H), 3.93 (t, J = 4.8 Hz, 2H), 3.6 (t, J = 6.3 Hz, 2H), 2.94 (t, J = 7.2 Hz, 2H), 1.27 (t, J = 7.8 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ESI-MS m/z = 581 $(M+H)^+$.

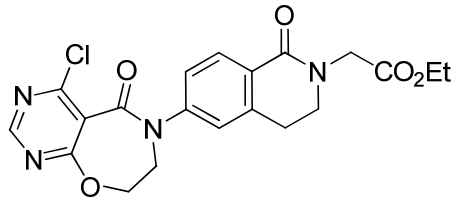
2-(6-(4,6-dicloro-N-(2-hidroxietil)pirimidina-5-carboxamido)-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1E):



A solución de producto del Ejemplo 1D (0.75 g, 1.29 mmoles), en una solución metanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 4 h. El metanol se removió al vacío. El residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de

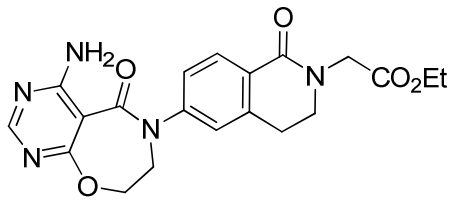
sodio acuoso saturado y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.45 g, 75%) como un sólido, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.36 (m, 1H), 7.31 (s, 1H), 4.28 (s, 2H), 4.2 (q, *J* = 7.2 Hz, 2H), 4.1 (m, 2H), 3.96 (m, 2H), 3.62 (t, *J* = 6.4 Hz, 2H), 3.0 (t, *J* = 6.4 Hz, 2H), 2.1 (t, *J* = 5.6 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H); ESI-MS *m/z* = 467 $(M+H)^+$.

2-(6-(4-cloro-5-oxo-7,8-dihidropirimido[5,4-f][1,4]oxazepin-6(5H)-il)-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1F):



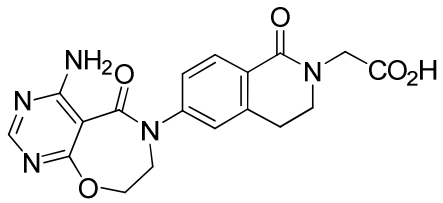
Un lodo del producto del Ejemplo 1E (0.4 g, 0.85 mmoles) y TEA (0.43 g, 4.28 mmoles) en acetonitrilo (10 mL) se agitó a 80 °C por 16 h. La reacción se enfrió, concentró al vacío, y diluyó con acetato de etilo. La mezcla se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.35 g, 95%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.35 (s, 1H), 7.29 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 4.78 (t, *J* = 4.8 Hz, 2H), 4.34 (s, 2H), 4.23 (q, *J* =7.6 Hz, 2H), 4.1 (t, *J* = 4.8 Hz, 2H), 3.7 (t, *J* = 6.8 Hz, 2H), 3.1 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ESI-MS *m/z* = 431 $(M+H)^+$.

2-(6-(4-amino-5-oxo-7,8-dihidropirimido[5,4-f][1,4]oxazepin-6(5H)-il)-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1G):



Una solución del producto del Ejemplo 1F (0.3 g, 0.697 mmoles) en amoniaco 0.5M en p-dioxano (10 mL) se agitó a temperatura ambiente por 16 h. La mezcla de reacción se concentró al vacío y se diluyó con acetato de etilo. La capa orgánica se lavó con agua, salmuera acuosa saturada, se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.22 g, 70%) como un sólido blanco. ^{1}H RMN (300 MHz, $CDCl_3$): δ 8.3 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.2 (m, 2H), 4.71 (t, *J* = 4.2 Hz, 2H), 4.34 (s, 2H), 4.23 (q, *J* = 6.9 Hz, 2H), 4.04 (t, *J* = 4.8 Hz, 2H), 3.69 (m, 2H), 3.1 (t, *J* = 6.3 Hz, 2H), 1.29 (t, *J* = 6.9 Hz, 3H); LC-MS: 91% puro, *m/z* = 412 $(M+H)^+$.

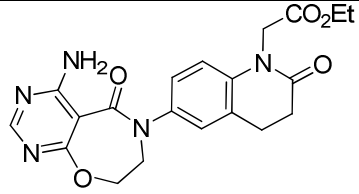
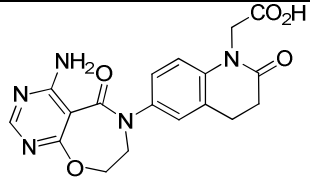
Acido 2-(6-(4-Amino-5-oxo-5,6,7,8-tetrahidrooxepino(2,3-*d*)pirimidin-6-il)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il) acético (1):

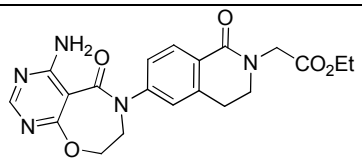
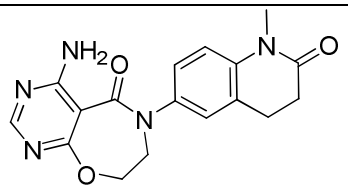
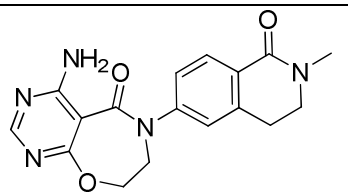
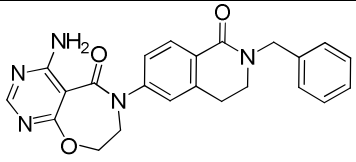
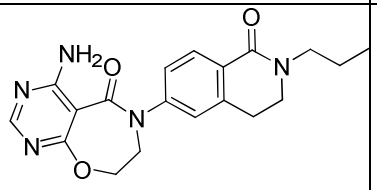


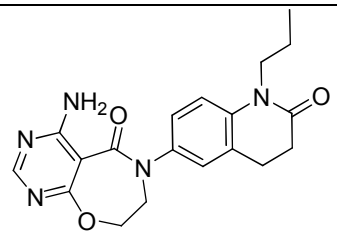
Una solución del producto del Ejemplo 1G (0.18 g, 0.43 mmoles) e hidróxido de litio (0.055 g, 1.309 mmoles) en 5 mL de una mezcla de p-

dioxano-agua (4:1) se agitó a temperatura ambiente por 16 h. Después de que el solvente se removió al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó usando solución acuosa 2N de HCl hasta que se alcanzó pH 2. La solución resultante se enfrió a 0 ºC, y los sólidos resultantes se filtraron y secaron al vacío para producir el compuesto del título (0.12 g, 72%) como un sólido blanco. ^{1}H RMN (300 MHz, DMSO-d_6): δ 12.8 (bs, 1H), 8.45 (bs, 2H), 8.36 (s, 1H), 7.9 (d, J = 9.0 Hz, 1H), 7.4 (m, 2H), 4.7 (m, 2H), 4.21 (m, 2H), 4.13 (m, 2H), 3.64 (t, J = 6.3 Hz, 2H), 3.03 (t, J = 5.7 Hz, 2H); HPLC pureza: 99%, *m/z* = 384 $(M+H)^+$.

Los Ejemplos 2 - 9 se prepararon por el método descrito antes por el Ejemplo 1 o variaciones rutinarias del mismo comenzando de la halo-quinolinona requerida.

Ej.	Estructura	Datos analíticos:	Masa/pureza
2		^{1}H RMN (300 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.29 (m, 1H), 7.23 (dd, J_1 = 2.1 Hz, J_2 = 8.1 Hz, 1H), 7.0 (d, J = 9.0 Hz, 1H), 4.67 (s, 2H), 4.6 (t, J = 4.2 Hz, 2H), 4.15 (q, J = 7.8 Hz, 2H), 3.96 (t, J = 4.2 Hz, 2H), 2.91 (t, J = 6.9 Hz, 2H), 2.6 (t, J = 7.8 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H).	ESI-MS *m/z* = 412 $(M+H)^+$; LC-MS pureza: 97%.
3		^{1}H RMN (400 MHz, DMSO-d_6): δ 13.0 (bs, 1H), 8.17 (s, 1H), 7.61 (bs, 2H), 7.28 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.6 (m, 4H), 3.96 (m, 2H), 2.9 (t, J = 6.8 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H).	ESI-MS *m/z* = 384 $(M+H)^+$; LC-MS pureza: 99%.

4		^{1}H RMN (300 MHz, $CDCl_3$): δ 8.3 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.2 (m, 2H), 4.71 (t, *J* = 4.2 Hz, 2H), 4.34 (s, 2H), 4.23 (q, *J* = 6.9 Hz, 2H), 4.04 (t, *J* = 4.8 Hz, 2H), 3.69 (m, 2H), 3.1 (t, *J* = 6.3 Hz, 2H), 1.29 (t, *J* = 6.9 Hz, 3H).	ESI-MS *m/z* = 412 $(M+H)^+$; LC-MS pureza: 91%.
5		^{1}H RMN (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.62 (bs, 2H), 7.25 (m, 1H), 7.12 (m, 1H), 4.6 (t, *J* = 4.0 Hz, 2H), 3.95 (t, *J* = 4.4 Hz, 2H), 3.27 (s, 3H), 2.88 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 8.4 Hz, 2H).	ESI-MS *m/z* = 340 $(M+H)^+$; HPLC pureza: 96%.
6		^{1}H RMN (300 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.9 (d, *J* = 9.0 Hz, 1H), 7.62 (bs, 2H), 7.35 (m, 2H), 4.6 (t, *J* = 4.2 Hz, 2H), 4.02 (t, *J* = 4.8 Hz, 2H), 3.56 (t, *J* = 6.3 Hz, 2H), 2.99 (m, 5H).	ESI-MS *m/z* = 340 $(M+H)^+$; LC-MS pureza: 96.6 %.
7		^{1}H RMN (400 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.62 (bs, 2H), 7.41-7.27 (m, 6H), 7.15 (s, 1H), 4.72 (s, 2H), 4.61 (t, *J* = 4.4 Hz, 2H), 4.02 (t, *J* = 4.4 Hz, 2H), 3.5 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H).	ESI-MS *m/z* = 416 $(M+H)^+$; HPLC pureza: 97%.
8		1H RMN (400 MHz, DMSO-d6): δ 8.18 (s, 1H), 7.9 (d, J = 9.2 Hz, 1H), 7.62 (bs, 2H), 7.35 (m, 2H), 4.6 (t, J = 4.0 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H), 3.55 (m, 2H), 3.44 (t, J = 6.8 Hz, 2H), 2.97 (t, J = 6.4 Hz, 2H), 1.58 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H).	ESI-MS m/z = 368 (M+H)+; HPLC pureza: 97%.

9		^{1}H RMN (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.21 (m, 3H), 4.6 (t, *J* = 4.4 Hz, 2H), 3.96 (t, *J* = 4.4 Hz, 2H), 3.8 (t, *J* = 7.6 Hz, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.55 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H).	ESI-MS *m/z* = 368 $(M+H)^+$; HPLC pureza: 99%.

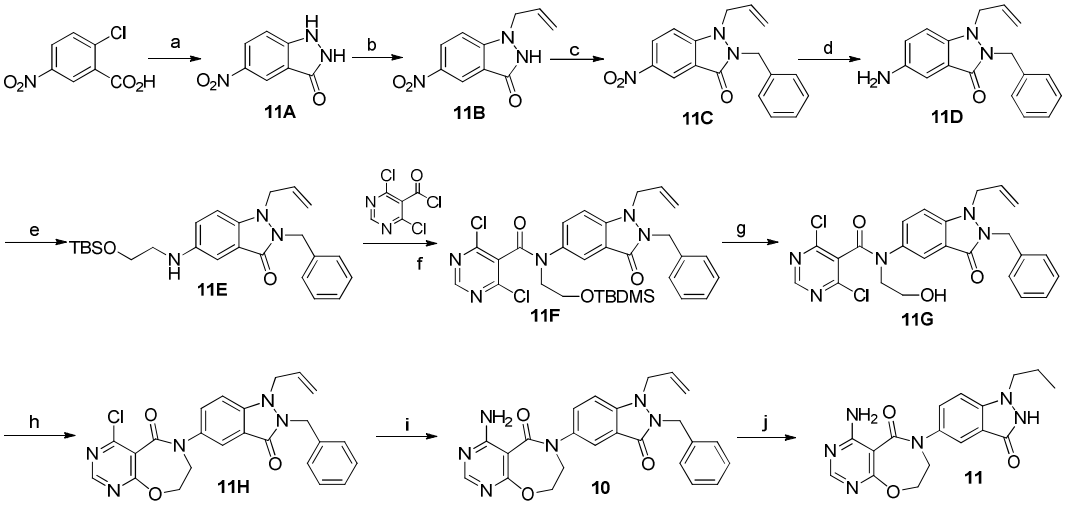
EJEMPLO 10

6-(1-Alil-2-bencil-3-oxo-2,3-dihidro-1H-indazol-5-il)-4-amino-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona

y

EJEMPLO 11

4-Amino-6-(3-oxo-1-propil-2,3-dihidro-1H-indazol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

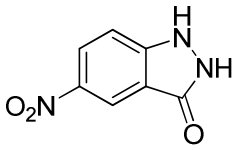


Reactivos y condiciones: a) $NH_2NH_2.H_2O$, EtOH, 80 ºC, 16h; b) Bromuro de alilo, KOH, NaOH, 100 ºC, 3h; c) Bromuro de bencilo, NaH, DMF,

RT, 16h; d) Fe/NH_4Cl, EtOH-H_2O, 85 ^oC, 3h; e) $Br(CH_2)_2OTBDMS$, CH_3CN, K_2CO_3, 80 ^oC, 24h; f) DCM, Et_3N, rt, 6h; g) 3%HCl-MeOH, RT, 1h; h) CH_3CN, Et_3N, 80 ^oC, 16h; i) NH_3, Dioxano, RT, 2h; j) 10% Pd/C, H_2, MeOH, RT, 2h.

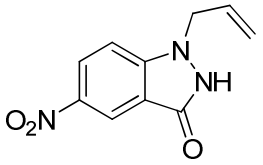
Procedimientos:

5-nitro-1H-indazol-3(2H)-ona (11A):



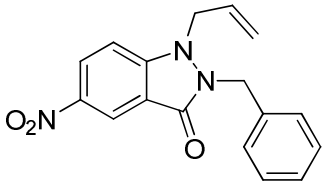
Hidrato de hidrazina (4 mL, 124 mmoles) se agregó a una solución de ácido 2-cloro-5-nitro benzoico (5 g, 24.8 mmoles) en etanol absoluto (30 mL), y la mezcla resultante se calentó a reflujo por 16 h. La mezcla de reacción se concentró bajo presión reducida. El residuo se trituró con metanol para dar 6.5 g de intermediario crudo. HCl 2N ac. (40 mL) se agregó al producto crudo, y la mezcla se calentó a reflujo por 8 h. La mezcla de reacción se enfrió a 0 ^oC, los sólidos se recolectaron vía filtración, se lavaron con agua fría y se secaron bajo vacío. El residuo se purificó por cromatografía instantánea usando 1% metanol en cloroformo como eluyente para producir el compuesto del título (2 g, 27%) como un sólido. ^1H RMN (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 11.3 (bs, 1H), 8.67 (s, 1H), 8.12 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 7.5 (d, J = 9.0 Hz, 1H); ESI-MS *m/z*: 179 (M+H)$^+$.

1-Alil-5-nitro-1H-indazol-3(2H)-ona (11B):



Bromuro de alilo (2.7 g, 22.34 mmoles) se agregó a una mezcla de producto del Ejemplo 11A (4 g, 22.34 mmoles) y solución acuosa 1N de KOH (25 mL), y la mezcla se calentó a reflujo por 2h. 15% NaOH (2 mL) y bromuro de alilo (0.54 mg, 0.04 mmoles) se agregaron, y de nuevo la mezcla se calentó a reflujo por 1 h. La mezcla de reacción se enfrió a temperatura ambiente y se neutralizó usando solución acuosa 3N de HCl. Los sólidos resultantes se recolectaron vía filtración, se lavaron con agua y se secaron bajo vacío para producir el producto del título (4.5 g, 92%) como un sólido. ^{1}H RMN (300 MHz, DMSO-d_6): δ 11.5 (bs, 1H), 8.67 (s, 1H), 8.15 (dd, J_1 = 2.1 Hz, J_2 = 9.9 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 5.96 (m, 1H), 5.13 (m, 2H), 4.93 (d, J = 5.7 Hz, 2H).

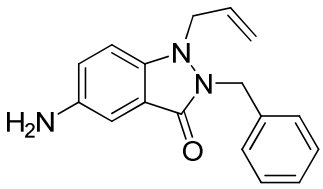
1-Alil-2-bencil-5-nitro-1H-indazol-3(2H)-ona (11C):



Hidruro de sodio (0.55 g, 13.68 mmoles) se agregó por porciones a una solución enfriada en hielo de producto del Ejemplo 11B (2.5 g, 11.4 mmoles) en DMF (20 mL), y la mezcla se agitó por 30 min. Bromuro de

bencilo (3.9 g, 22.8 mmoles) ahora se agregó lentamente, y la mezcla se agitó a temperatura ambiente por 16 h. La reacción luego se enfrió a 0 °C y se templó con agua helada. La capa acuosa se extrajo dos veces con acetato de etilo (2x50 mL). Las capas orgánicas combinadas se lavaron con agua seguido de solución de salmuera, se secaron sobre sulfato de sodio, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en columna instantánea usando 5% acetato de etilo en hexano como eluyente para producir el compuesto del título (2.2 g, 62%) como un sólido. ^{1}H RMN (400 MHz, DMSO-d_6): δ 8.57 (d, J = 2.0 Hz, 1H), 8.23 (dd, J_1 = 2.0 Hz, J_2 = 9.2 Hz, 1H), 7.7 (d, J = 9.2 Hz, 1H), 7.5 (d, J = 5.7 Hz, 2H), 7.4 (m, 3H), 5.98 (m, 1H), 5.44 (s, 2H), 5.2 – 5.07 (m, 2H), 4.98 (d, J = 5.2 Hz, 2H).

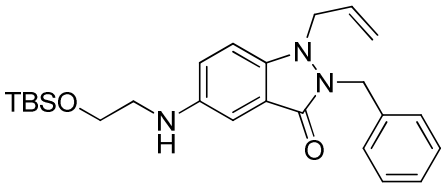
1-Alil-5-amino-2-bencil-1H-indazol-3(2H)-ona (11D):



Polvo de hierro (0.77 g, 14.22 mmoles) se agregó a una solución de producto del Ejemplo 11C (2.2 g, 7.11 mmoles) en 80 mL de mezcla de etanol-agua (4:1) seguido de NH_4Cl (0.19 g, 3.55 mmoles), y la mezcla se calentó a reflujo por 4 h. El solvente se removió bajo presión reducida, y el residuo se dividió entre acetato de etilo y agua. La capa orgánica se secó sobre sulfato de sodio, se filtró y removió al vacío. El residuo se purificó por cromatografía instantánea usando 20% acetato de etilo en hexano como

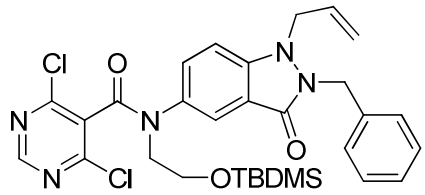
eluyente para producir el compuesto del título como un sólido (1.6 g, 66%). ^{1}H RMN (300 MHz, DMSO-d_6): δ 7.5 (m, 2H), 7.39 (m, 3H), 7.19 (d, J = 8.4 Hz, 1H), 6.81 (dd, J_1 = 2.1 Hz, J_2 = 9.3 Hz, 1H), 6.64 (m, 1H), 5.9 (m, 1H), 5.3 (s, 2H), 5.06 (m ,2H), 4.73 (m, 2H); ESI-MS m/z = 280 $(M+H)^+$.

1-Alil-2-bencil-5-(2-(ter-butildimetilsililoxi)etilamino)-1H-indazol-3(2H)-ona (11E):



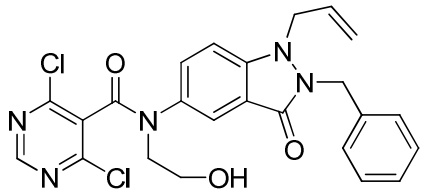
Carbonato de potasio (2.6 g, 19.32 mmoles) se agregó a una mezcla de (2-bromoetoxi)(ter-butil)dimetilsilano (0.92 g, 3.87 mmoles) y producto del Ejemplo 11D (0.9 g, 3.22 mmoles) en acetonitrilo (70 mL), y la mezcla se calentó a reflujo por 24 h. La mezcla de reacción se enfrió a temperatura ambiente y se dividió entre acetato de etilo y agua. La capa orgánica separada se lavó con solución de salmuera, se secó sobre sulfato de sodio, se filtró y concentró bajo vacío. El residuo se purificó por cromatografía instantánea usando 15% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.35 g, 25%) como un sólido. ^{1}H RMN (400 MHz, DMSO-d_6): δ 7.48 (m, 2H), 7.34 (m, 3H), 7.21 (d, J = 8.8 Hz, 1H), 6.84 (dd, J_1 = 2.0 Hz, J_2 = 9.6 Hz, 1H), 6.49 (d, J = 1.6 Hz, 1H), 5.86 (m, 1H), 5.28 (s, 2H), 5.21 (t, J = 6.0 Hz, 1H), 5.05 (m, 2H), 4.72 (d, J = 5.2 Hz, 2H), 3.69 (t, J = 6.4 Hz, 2H), 3.11 (q, J = 5.6 Hz, 2H), 0.82 (s, 9H), 0.03 (s ,6H).

N-(1-Alil-2-bencil-3-oxo-2,3-dihidro-1H-indazol-5-il)-N-(2-(ter-butildimetilsililoxi)etil)-4,6-dicloropirimidina-5-carboxamida (11F):



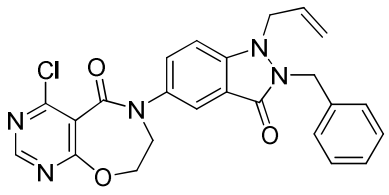
A una solución agitada, enfriada (0 °C) de producto del 11E (0.55 g, 1.23 mmoles) y TEA (0.5 g, 5.0 mmoles) en DCM (12 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.26 g, 1.23 mmoles) en DCM (5 mL). Después de 6 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.35 g, 46%) como un aceite. ^{1}H RMN (400 MHz, DMSO-d_6): δ 8.75 (s, 1H), 7.75 (s, 1H), 7.46 (m, 3H), 7.36 (m, 4H), 5.94 (m, 1H), 5.34 (s, 2H), 5.08 (m, 1H), 4.96 (m ,1H), 4.82 (m, 2H), 4.0 (m, 2H), 3.77 (t, J = 4.8 Hz, 2H), 0.8 (s, 9H), 0.01 (s, 6H); ESI-MS m/z = 611 $(M+H)^+$.

N-(1-Alil-2-bencil-3-oxo-2,3-dihidro-1H-indazol-5-il)-4,6-dicloro-N-(2-hidroxietil)pirimidina-5-carboxamida (11G):



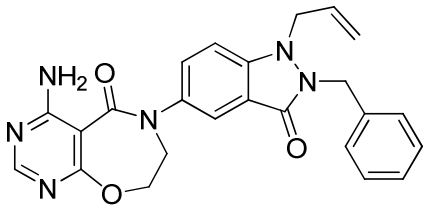
Una solución del producto del Ejemplo 11F (0.35 g, 0.57 mmoles) en una solución metanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 1 h. El metanol se removió al vacío. El residuo se disolvió en acetato de etilo, se lavó con bicarbonato de sodio acuoso saturado y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.25 g, 88%) como un aceite, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400 MHz, DMSO-d_6): δ 8.75 (s, 1H), 7.75 (s, 1H), 7.46 (m, 3H), 7.36 (m, 4H), 5.94 (m, 1H), 5.34 (s, 2H), 5.12 (m, 1H), 5.03 (m ,1H), 4.86 (m, 2H), 3.9 (t, J = 6.0 Hz, 2H), 3.77 (t, J = 4.8 Hz, 2H); ESI-MS m/z = 498 $(M+H)^+$.

6-(1-Alil-2-bencil-3-oxo-2,3-dihidro-1H-indazol-5-il)-4-cloro-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (11H):



Un lodo del producto del Ejemplo 11G (0.25 g, 0.5 mmoles) y TEA (0.22 g, 2.2 mmoles) en acetonitrilo (20 mL) se agitó a 80 ºC por 16 h. La reacción se enfrió, concentró al vacío, y se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.22 g, 94%) como un sólido blanco. ^{1}H RMN (300 MHz, DMSO-d_6): δ 8.8 (s, 1H), 7.68 (s, 1H), 7.55 (m, 3H), 7.38 (m, 4H), 5.94 (m, 1H), 5.4 (s, 2H), 5.17 (m, 1H), 5.05 (m, 1H), 4.93 (d, *J* = 4.8 Hz, 2H), 4.76 (t, J = 4.0 Hz, 2H), 4.15 (t, *J* = 4.8 Hz, 2H); ESI-MS *m/z* = 462 $(M+H)^+$.

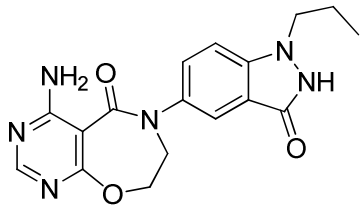
6-(1-Alil-2-bencil-3-oxo-2,3-dihidro-1H-indazol-5-il)-4-amino-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (10):



Una solución del producto del Ejemplo 11H (0.22 g, 0.46 mmoles) en amoniaco 0.5M en p-dioxano (40 mL) se agitó a temperatura ambiente por 4 h. La mezcla de reacción se concentró al vacío y se diluyó con acetato de etilo. La capa orgánica se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.17 g, 82%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.62 (s, 1H), 7.55 (m, 3H), 7.38 (m, 4H), 7.19 (bs, 2H), 5.97 (m, 1H), 5.39 (s, 2H), 5.16 (m,

1H), 5.09 (m, 1H), 4.91 (d, *J* = 5.6 Hz, 2H), 4.65 (t, J = 4.4 Hz, 2H), 3.98 (t, *J* = 4.4 Hz, 2H); LC-MS pureza: 94%, *m/z* = 443 $(M+H)^+$.

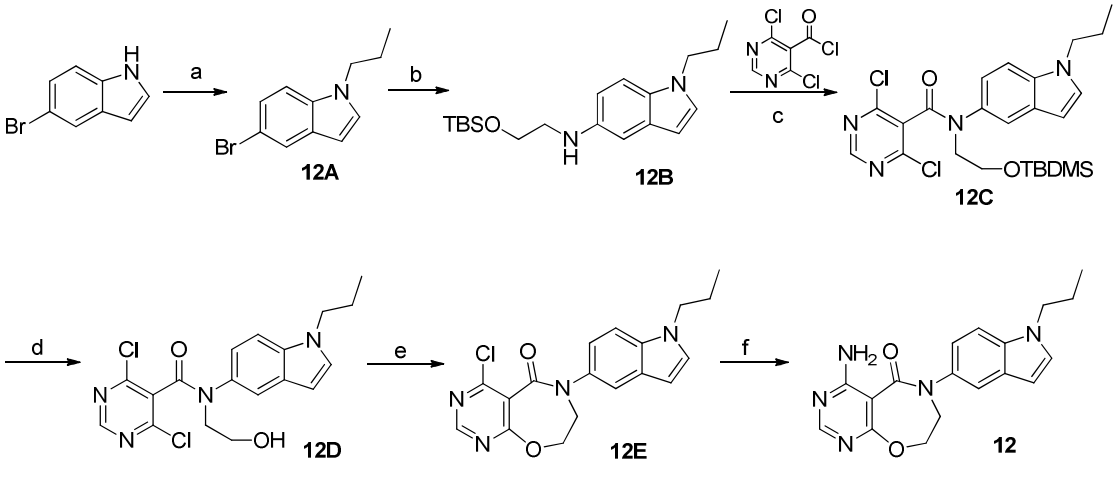
4-Amino-6-(3-oxo-1-propil-2,3-dihidro-1H-indazol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (11):



Exceso de 10% de Pd/C (0.15 g) se agregó a una solución de producto del Ejemplo 10 (0.15 g, 0.226 mmoles) en 120 mL de metanol, y la mezcla se agitó a temperatura ambiente por 2 h. La mezcla de reacción se filtró sobre lecho de celite, el filtrado se concentró bajo presión reducida, y el residuo se dividió entre acetato de etilo y agua. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se trituró con acetato de etilo para producir el compuesto del título (0.09 g, 75%) como un sólido marrón. ^{1}H RMN (300 MHz, DMSO-d_6): δ□10.5 (bs, 1H), 8.17 (s, 1H), 7.63 (bs, 2H), 7.56 (m, 1H), 7.51 (d, *J* = 9.3 Hz, 1H), 7.3 (dd, J_1 = 1.2 Hz, J_2= 9.0 Hz, 1H), 4.63 (t, *J* = 4.2 Hz, 2H), 4.1 (t, *J* = 7.2 Hz, 2H), 3.98 (t, *J* = 4.2 Hz, 2H), 1.76 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); HPLC pureza: 95%, ESI-MS *m/z* = 355 $(M+H)^+$.

EJEMPLO 12

4-Amino-6-(1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

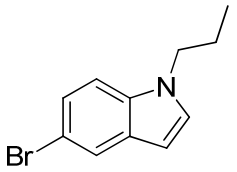


Reactivos y condiciones: a) bromuro de n-propilo, Cs_2CO_3, DMF, 100 ºC, 2h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 ºC, 2.5h; c) DCM, Et_3N, RT, 1h; d) 3%HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 ºC, 16h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

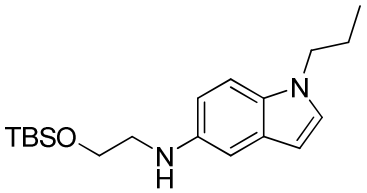
4-Amino-6-(1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

5-bromo-1-propil-1H-indol (12A):



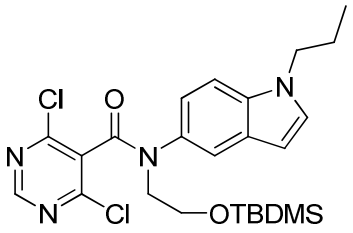
1-Bromopropano (1.25 g, 10.2 mmoles) se agregó a una solución de 5-bromo indol (2 g, 10.2 mmoles) en DMF (30 mL) seguido de carbonato de cesio (6.63 g, 20.4 mmoles), y la mezcla se agitó a 100 °C por 2 h. Los sólidos insolubles se filtraron, y el filtrado se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 5% acetato de etilo en hexano como eluyente para producir el compuesto del título (1.8 g, 74%) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.74 (d, J = 1.6 Hz, 1H), 7.28 (m, 1H), 7.20 (m, 1H), 7.09 (d, J = 3.2 Hz, 1H), 6.41 (d, J = 2.4 Hz, 1H), 4.05 (t, J = 7.2 Hz, 2H), 1.87 (m, 2H), 0.9 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 238 $(M+H)^+$.

N-(2-(ter-Butildimetilsililoxi)etil)-1-propil-1H-indol-5-amina (12B):



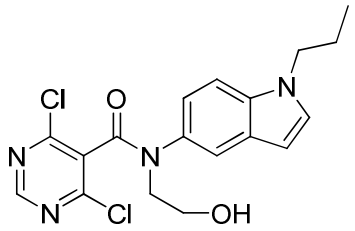
Una mezcla de producto del Ejemplo 12A (2 g, 8.4 mmoles), 2-(ter-butildimetilsililoxi)etanamina (1.5 g, 8.4 mmoles), carbonato de cesio (4.09 g, 12.6 mmoles), acetato de paladio (0.18 g, 0.84 mmoles) y X-PHOS (0.4 g, 0.84 mmoles) en Tolueno (25 mL) bajo Argón se calentó a reflujo a 120 °C por 2.5 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% de acetato de etilo en hexano para producir el compuesto del título (1.5 g, 53%) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.16 (d, J = 8.8 Hz, 1H), 7.0 (d, J = 2.8 Hz, 1H), 6.86 (d, J = 2.08 Hz, 1H), 6.68-6.65 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.30 (d, J = 3.2 Hz, 1H), 4.01 (t, J = 7.2 Hz, 2H), 3.85 (t, J = 5.6 Hz, 2H), 3.25 (t, J = 5.2 Hz, 2H), 1.86-1.81 (m, 2H), 0.93 (t, J = 5.6 Hz, 3H), 0.91 (s, 9H), 0.07(s, 6H); ESI-MS m/z = 333 $(M+H)^+$.

N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(1-propil-1H-indol-5-il)pirimidina-5-carboxamida (12C):



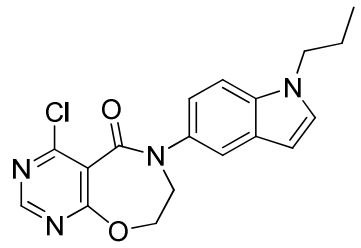
A una solución agitada enfriada (0 ºC) de producto del Ejemplo 12B (1.5 g, 4.51 mmoles) y TEA (1.82 g, 18 mmoles) en DCM (30 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.95 g, 4.5 mmoles) en DCM (5 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó en acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano como eluyente para producir el compuesto del título (1 g, 43%) como un jarabe. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.66 (m, 1H), 7.21-7.13 (m, 2H), 7.09 (d, *J* = 3.6 Hz, 1H), 6.39 (d, *J* = 3.2 Hz, 1H), 4.06 (t, *J* = 6.4 Hz, 2H), 4.01 (t, *J* = 7.2 Hz, 2H), 3.91 (t, *J* = 5.6 Hz, 2H), 1.84-1.78 (m, 2H), 0.94 (t, *J* = 8.0 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ESI-MS *m/z* = 507 $(M+H)^+$.

4,6-Dicloro-N-(2-hidroxietil)-N-(1-propil-1H-indol-5-il)pirimidina-5-carboxamida (12D):



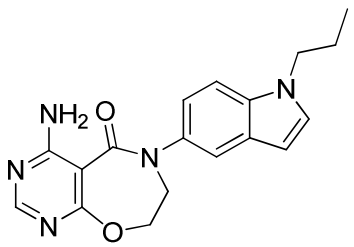
Una solución del producto del Ejemplo 12C (1 g, 1.97 mmoles), en 15 mL de solución metanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 1 h. El metanol se removió al vacío, el residuo se disolvió en acetato de etilo, se lavó con bicarbonato de sodio acuoso saturado solución y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.6 g, 77%) como un sólido, que se llevó al el paso siguiente sin purificación adicional. ^{1}H RMN (400 MHz, DMSO-d_6): δ 8.49 (s, 1H), 7.65 (s, 1H), 7.17 (m, 2H), 7.11 (d, J = 2.8 Hz, 1H), 6.42 (d, J = 2.8 Hz, 1H), 4.15 (t, J = 5.2 Hz, 2H), 4.02 (t, J = 6.8 Hz, 2H), 3.93 (q, J = 4.8 Hz, 2H), 1.84-1.77 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H); ESI-MS m/z = 393 $(M+H)^+$.

4-Cloro-6-(1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (12E):



Un lodo del producto del Ejemplo 12D (0.6 g, 1.68 mmoles) y TEA (1.36 g, 13.44 mmoles) en acetonitrilo (25 mL) se agitó a 80 °C por 16 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.3 g, 55%) como un sólido blanco. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.82 (s, 1H), 7.57 (m, 2H), 7.46 (d, J = 3.0 Hz, 1H), 7.13 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 6.48 (d, J = 3.0 Hz, 1H), 4.75 (t, J = 4.5 Hz, 2H), 4.16 (m, 4H), 1.82 (m, 2H), 0.84 (t, J = 7.5 Hz, 3H); ESI-MS m/z = 357 $(M+H)^+$.

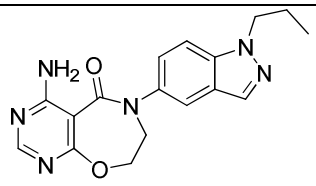
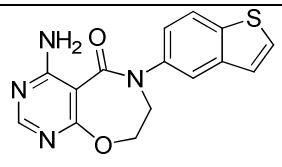
4-Amino-6-(1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (12):

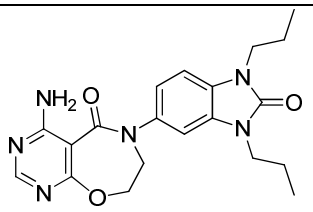
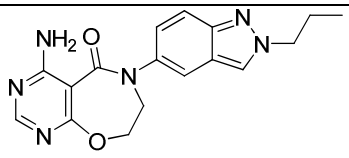
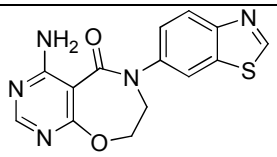
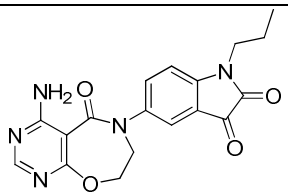
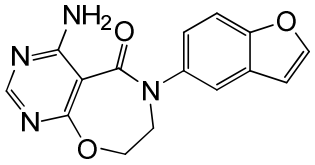


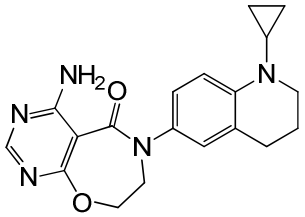
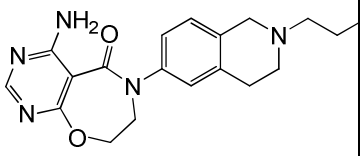
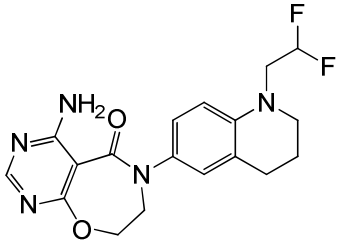
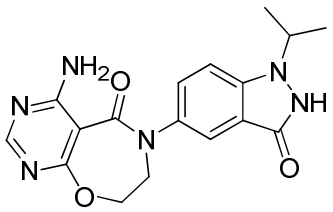
Una solución del producto del Ejemplo 12E (0.3 g, .84 mmoles)

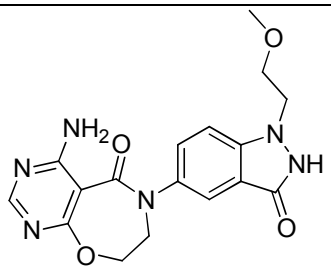
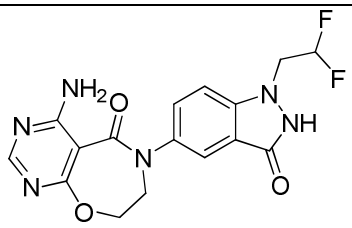
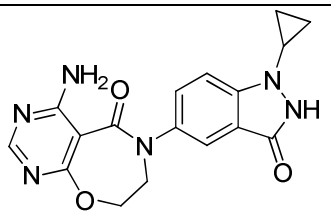
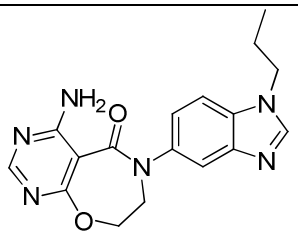
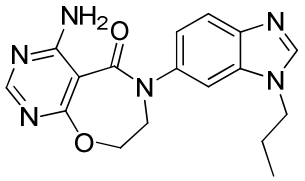
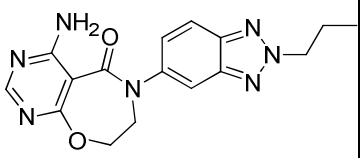
en amoniaco 0.5M en p-dioxano (15 mL) se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.2 g, 71%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.52 (s, 1H), 7.5 (m, 1H), 7.42 (d, J = 3.2 Hz, 1H), 7.09 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 4.63 (t, J = 3.6 Hz, 2H), 4.15 (t, J = 6.8 Hz, 2H), 3.98 (t, J = 4.4 Hz, 2H), 1.76 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 338 $(M+H)^+$; HPLC pureza: 92.5%.

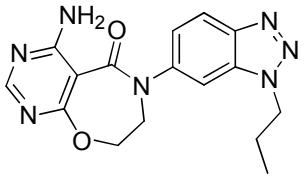
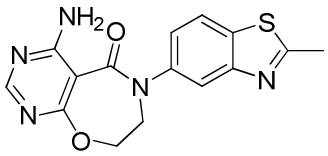
Los Ejemplos 13 – 31 se prepararon por el método descrito antes por Ejemplo 12 o variaciones rutinarias del mismo usando los materiales de partida apropiadamente sustituidos.

Ej.	Estructura	Datos analíticos:	Masa/pureza
13		^{1}H RMN (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.08 (s, 1H), 7.74 (m, 2H), 7.6 (bs, 2H), 7.38 (d, J = 1.8 Hz, 1H), 4.65 (t, J = 4.2 Hz, 2H), 4.39 (t, J = 6.9 Hz, 2H), 4.01 (t, J = 4.5 Hz, 2H), 1.9-1.83 (m, 2H), 0.82 (t, J = 7.5 Hz, 3H).	ESI-MS m/z = 339 $(M+H)^+$; HPLC pureza: 99%.
14		^{1}H RMN (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.9 (m, 1H), 7.84 (d, J = 5.7 Hz, 1H), 7.64 (bs, 2H), 7.47 (d, J = 5.4 Hz, 1H), 7.38 (dd, J_1 = 2.1 Hz, J_2= 8.7 Hz, 1H), 4.65 (t, J = 4.2 Hz, 2H), 4.04 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 313 $(M+H)^+$. Pureza por HPLC: 94%,

15		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.62 (bs, 2H), 7.24 (m, 2H), 7.02 (d, J = 7.6 Hz, 1H), 4.63 (m, 2H), 3.97 (m, 2H), 3.83-3.56 (q, J = 7.2 Hz, 4H), 1.68-1.65 (m, 4H), 0.86 (t, J = 6.8 Hz, 6H).	ESI-MS m/z = 397 $(M+H)^+$; LCMS pureza: 98%.
16		^{1}H RMN (300MHz, DMSO-d_6): δ 8.4 (s, 1H), 8.17 (s, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.19 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 7.15 (bs, 2H), 4.64 (t, J = 4.2 Hz, 2H), 4.39 (t, J = 7.2 Hz, 2H), 4.0 (t, J = 4.2 Hz, 2H), 2.0 (m, 2H), 0.83 (t, J = 7.5 Hz, 3H).	ESI-MS m/z = 339 $(M+H)^+$; HPLC pureza: 96%.
17		^{1}H RMN (300MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.23 (d, J = 1.5 Hz, 1H), 8.19 (s, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.9 (bs, 2H), 7.57 (dd, J_1 = 1.8 Hz, J_2= 8.7 Hz, 1H), 4.66 (t, J = 4.5 Hz, 2H), 4.07 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 314 $(M+H)^+$; HPLC pureza: 96%.
18		^{1}H RMN (300MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.66 (bs, 2H), 7.63 (m, 2H), 7.26 (d, J = 8.1 Hz, 1H), 4.64 (t, J = 4.5 Hz, 2H), 3.97 (t, J = 4.5 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 1.64 (m, 2H), 0.92 (t, J = 7.2 Hz, 2H).	ESI-MS m/z = 368 $(M+H)^+$; HPLC pureza: 93%.
19		^{1}H RMN (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.66-7.63 (m, 3H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.4Hz, 1H), 7.1 (bs, 2H), 4.65 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 4.8 Hz, 2H).	ESI-MS m/z: 297 $(M+H)^+$; Pureza por HPLC: 97%.

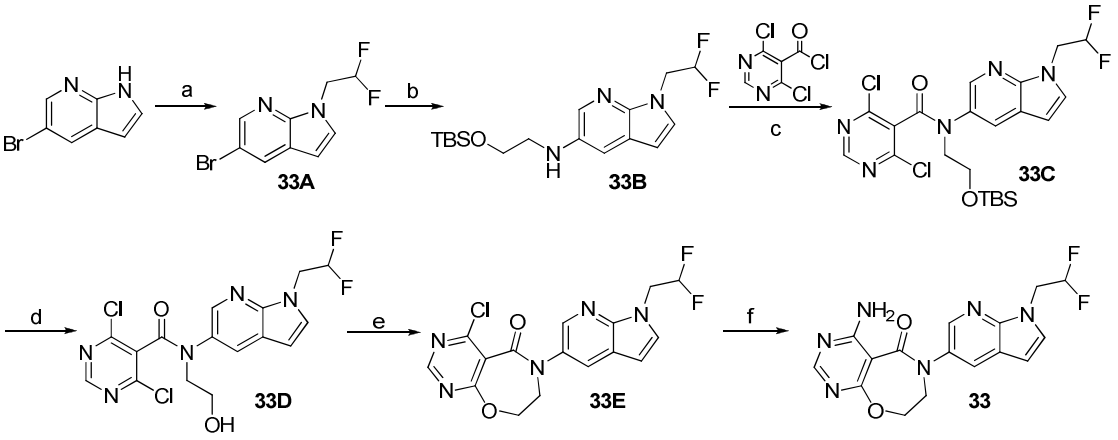
20		^{1}H RMN (300MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.57 (bs, 2H), 7.04 (d, J = 8.7 Hz, 1H), 7.0 (dd, J_1 = 2.4 Hz, J_2 = 8.7 Hz, 1H), 6.89 (d, J = 2.7 Hz, 1H), 4.57 (t, J = 4.8 Hz, 2H), 3.88 (t, J = 4.5 Hz, 2H), 3.20 (t, J = 5.4 Hz, 2H), 2.67 (t, J = 6.3 Hz, 2H), 2.28 (m, 1H), 1.84 (m, 2H), 0.80 (m, 2H), 0.53 (m, 2H).	ESI-MS m/z = 352 $(M+H)^+$; HPLC pureza: 99.2%.
21		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.24 (m, 3H), 4.60 (m, 2H), 4.12 (s, 2H), 3.97 (m, 2H), 3.31-3.25 (m, 2H), 3.0 (m, 2H), 2.82 (m, 2H), 1.73 (m, 2H), 0.84 (t, J = 6.8 Hz, 3H).	ESI-MS m/z = 354 $(M+H)^+$; HPLC pureza: 95%.
22		^{1}H RMN (400MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.58 (bs, 2H), 6.94 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.21 (tt, J_1 = 4.0 Hz, J_2 = 55.2 Hz, 1H), 4.56 (t, J = 4.8 Hz, 2H), 3.87 (t, J = 4.4 Hz, 2H), 3.70 (dt, J_1 = 3.6 Hz, J_2 = 15.6 Hz, 2H), 3.37 (m, 2H), 2.70 (t, J = 6.0 Hz, 2H), 1.85 (m, 2H).	ESI-MS m/z = 376 $(M+H)^+$; HPLC pureza: 98.24%.
23		^{1}H RMN (400MHz, DMSO-D_2O): δ 8.18 (s, 1H), 7.56 (d, J = 1.2 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.28 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 4.76 (m, 1H), 4.64 (t, J = 4.8 Hz, 2H), 3.99 (t, J = 4.4 Hz, 2H), 1.38 (d, J = 6.8 Hz, 6H).	ESI-MS m/z = 354 $(M+H)^+$; HPLC pureza: 96.4%.

24		^{1}H RMN (300MHz, DMSO-d_6): δ 10.65 (bs, 1H), 8.17 (s, 1H), 7.64 (bs, 2H), 7.55 (s, 1H), 7.49 (d, *J* = 9.3 Hz, 1H), 7.29 (m, 1H), 4.63 (m, 2H), 4.30 (m, 2H), 3.99 (m, 2H), 3.66 (m, 2H), 3.19 (s, 3H).	ESI-MS *m/z* = 370 $(M+H)^+$; HPLC pureza: 95.2%.
25		1H RMN (300MHz, DMSO-d6): □□ 10.85 (bs, 1H), 8.17 (s, 1H), 7.64 (bs, 2H), 7.6-7.56 (m, 2H), 7.37 (dd, J1 = 1.8 Hz, J2 = 8.7 Hz, 1H), 6.50 (tt, J1 = 3.3 Hz, J2 = 54.9 Hz, 1H), 4.74-4.58 (m, 4H), 4.0 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 377 (M+H)+; HPLC pureza: 97%.
26		1H RMN (300MHz, DMSO-d6): □□□10.85 (bs, 1H), 8.17 (s, 1H), 7.63 (bs, 2H), 7.58 (d, J = 1.5 Hz, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.32 (dd, J1 = 2.1 Hz, J2 = 9.0 Hz, 1H), 4.61 (t, J = 3.9 Hz, 2H), 3.96 (t, J = 4.2 Hz, 2H), 3.38 (m, 1H), 0.99 (d, J = 5.4 Hz, 4H).	ESI-MS m/z = 353 (M+H)+, HPLC pureza: 93%.
27		1H RMN (400MHz, DMSO-d6): δ 8.29 (s, 1H), 8.18 (s, 1H), 7.7-7.6 (m, 4H), 7.23 (dd, J1 = 1.6 Hz, J2 = 8.4 Hz, 1H), 4.66 (t, J = 4.4 Hz, 2H), 4.20 (t, J = 6.8 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H), 1.81 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 337 (M+H)+; LCMS pureza: 95%.
28		1H RMN (400MHz, DMSO-d6): δ 8.28 (s, 1H), 8.18 (s, 1H), 7.7-7.6 (m, 4H), 7.18 (dd, J1 = 1.6 Hz, J2 = 8.4 Hz, 1H), 4.66 (t, J = 4.4 Hz, 2H), 4.2 (t, J = 6.8 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H), 1.81 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 339 (M+H)+; LCMS pureza: 99%.
29		1H RMN (300MHz, DMSO-d6): δ 8.18 (s, 1H), 7.97-7.93 (m, 2H), 7.67 (bs, 2H), 7.44 (dd, J1 = 1.8 Hz, J2 = 9.3 Hz, 1H), 4.72 (t, J = 6.9 Hz, 2H), 4.66 (t, J = 4.2 Hz, 2H), 4.06 (t, J = 4.5 Hz, 2H), 2.04 (m, 2H), 0.86 (t, J = 7.5 Hz, 3H).	ESI-MS m/z = 340 (M+H)+-; HPLC Pureza: 98%.

30		^{1}H RMN (400MHz, DMSO-d_6): δ 8.19 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.66 (bs, 2H), 7.43 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 4.67 (m, 4H), 4.09 (t, J = 4.4 Hz, 2H), 1.95 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H).	ESI-MS m/z = 340 $(M+H)^{+-}$; HPLC Pureza: 97%.
31		^{1}H RMN (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.65 (bs, 2H), 7.42 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 4.66 (t, J = 4.4 Hz, 2H), 4.05 (t, J = 4.4 Hz, 2H), 2.82 (s, 3H).	ESI-MS m/z = 328 $(M+H)^{+}$; HPLC pureza: 92%.

EJEMPLO 33

4-Amino-6-(1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:



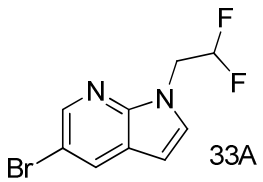
Reactivos y condiciones: a) 1,1-Difluoro-2-yodoetano, Cs_2CO_3, DMF, 70 ºC, 1h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 110 ºC, 3h; c) DCM, Et_3N, RT, 1h; d) 3% HCl-MeOH, RT, 1h; e)

CH_3CN, Et_3N, 70 °C, 4h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

4-Amino-6-(1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

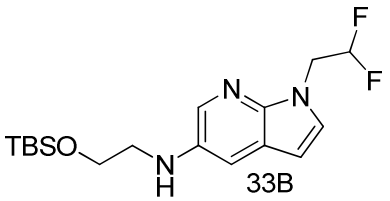
5-Bromo-1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridina (33A):



33A

1,1-Difluoro-2-yodoetano (2.19 g, 11.42 mmoles) se agregó a una solución de 5-bromo,7-azaindol (1.5 g, 7.61 mmoles) en DMF (30 mL) seguido de carbonato de cesio (4.96 g, 15.2 mmoles), y la mezcla se agitó a 70 °C por 1 h. Los sólidos insolubles se filtraron, y el filtrado se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró en presión reducida y se purificó por cromatografía instantánea usando 5% acetato de etilo en hexano para producir el compuesto del título (1.3 g, 65%) como un aceite. ^{1}H RMN (300 MHz, $CDCl_3$): δ 8.33 (d, J = 2.1 Hz, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 2.1 Hz, 1H), 6.46 (d, J = 3.6 Hz, 1H), 6.28-5.88 (tt, J_1 = 3.9 Hz, J_2 = 55.8 Hz, 1H), 4.60 (dt, J_1 = 4.2 Hz, J_2 = 14.1 Hz, 2H).

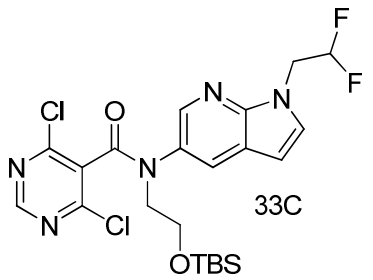
N-(2-(ter-Butildimetilsililoxi)etil)-1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-amina (33B):



33B

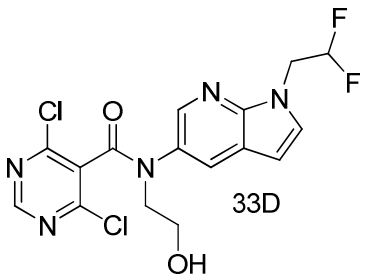
Una mezcla de producto del Ejemplo 33A (1.3 g, 8.4 mmoles), 2-(ter-butildimetilsililoxi)etanamina (1.0 g, 5.98 mmoles), carbonato de cesio (3.24 g, 9.96 mmoles), acetato de paladio (0.11 g, 0.49 mmoles) y X-PHOS (0.23 g, 0.49 mmoles) en tolueno (25 mL) bajo Argón se calentó a reflujo a 110 °C por 3 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% de acetato de etilo en hexano para producir el compuesto del título (0.61 g, 34.5%) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.87 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 3.2 Hz, 1H), 6.34 (d, J = 3.6 Hz, 1H), 6.23-5.92 (tt, J_1 = 4.4 Hz, J_2 = 55.6 Hz, 1H), 4.54 (dt, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 2H), 3.94 (bs, 1H), 3.85 (t, J = 5.6 Hz, 2H), 3.25 (t, J = 4.8 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 6H).

N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-il)pirimidina-5-carboxamida (33C):



A una solución agitada, enfriada (0 °C) de producto del Ejemplo 33B (0.61 g, 1.71 mmoles) y TEA (0.52 g, 5.15 mmoles) en DCM (25 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.43 g, 2.05 mmoles) en DCM (5 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.67 g, 73%) como un jarabe. ^{1}H RMN (300MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 6.45 (d, J = 3.9 Hz, 1H), 6.24-5.84 (tt, J_1 = 4.2 Hz, J_2 = 55.5 Hz, 1H), 4.55 (dt, J_1 = 4.2 Hz, J_2 = 14.1 Hz, 2H), 4.06 (t, J = 5.1 Hz, 2H), 3.94 (t, J = 4.8 Hz, 2H), 0.86 (s, 9H), 0.058 (s, 6H).

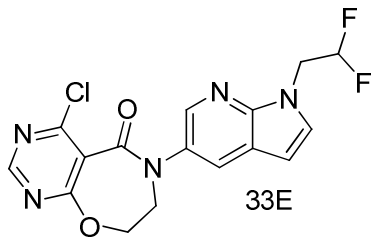
4,6-Dicloro-N-(1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-il)-N-(2-hidroxietil)pirimidina-5-carboxamida (33D):



33D

Una solución del producto del Ejemplo 33C (0.67 g, 1.26 mmoles), en 20 mL de solución metanólica de HCl (3 mL de HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 1 h. El metanol se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado solución y salmuera acuosa saturada. La capa orgánica se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró en presión reducida para producir el compuesto del título (0.4 g, 76%) como un sólido, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (300MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 6.49 (d, J = 3.6 Hz, 1H), 6.25-5.85 (tt, J_1 = 4.2 Hz, J_2 = 55.5 Hz, 1H), 4.56 (dt, J_1 = 4.2 Hz, J_2 = 14.1 Hz, 2H), 4.14 (t, J = 4.8 Hz, 2H), 3.96 (t, J = 4.8 Hz, 2H).

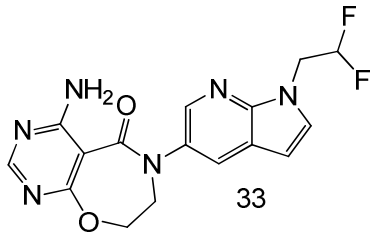
4-Cloro-6-(1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (33E):



33E

Un lodo del producto del Ejemplo 33D (0.4 g, 0.96 mmoles) y TEA (0.19 g, 1.92 mmoles) en acetonitrilo (20 mL) se agitó a 70 °C por 4 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró en presión reducida para producir el compuesto del título (0.3 g, 82%) como un sólido blanco. ^{1}H RMN (300MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.33 (d, J = 2.4 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 3.9 Hz, 1H), 6.57 (d, J = 3.6 Hz, 1H), 6.31-5.91 (tt, J_1 = 3.9 Hz, J_2 = 56.1 Hz, 1H), 4.81 (t, J = 4.5 Hz, 2H), 4.66 (dt, J_1 = 3.9 Hz, J_2 = 13.8 Hz, 2H), 4.10 (t, J = 4.8 Hz, 2H).

4-Amino-6-(1-(2,2-difluoroetil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (33):

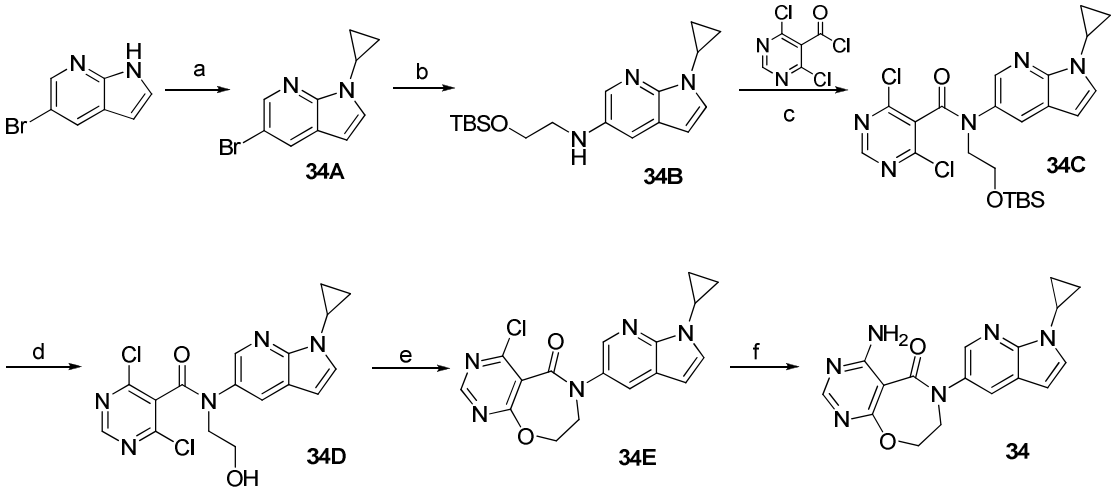


33

Una solución del producto del Ejemplo 33E (0.3 g, 0.79 mmoles) en amoniaco 0.5M en p-dioxano (15 mL) se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró en presión reducida para producir el compuesto del título (0.25 g, 86%) como un sólido blanco mate. ^{1}H RMN (300MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.20 (bs, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 3.3 Hz, 1H), 6.55 (d, J = 3.6 Hz, 1H), 6.31-5.91 (tt, J_1 = 4.5 Hz , J_2 = 55.8 Hz, 1H), 5.67 (bs, 1H), 4.75 (t, J = 4.5 Hz, 2H), 4.65 (dt, J_1 = 3.9 Hz, J_2 = 13.8 Hz, 2H), 4.07 (t, J = 4.5 Hz, 2H) ; ESI-MS m/z = 361 $(M+H)^+$. Pureza por HPLC: 98.14%.

EJEMPLO 34

4-Amino-6-(1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:



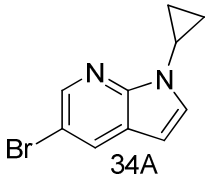
Reactivos y condiciones: a) ácido ciclopropil boronico, 2,2'-

bipiridina, Na_2CO_3, $Cu(OAc)_2$, DCE, 110 °C, 8h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 °C, 2.5h; c) DCM, Et_3N, RT, 1h; d) TBAF, THF, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

4-Amino-6-(1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

5-Bromo-1-ciclopropil-1H-pirrolo[2,3-b]piridina (34A):

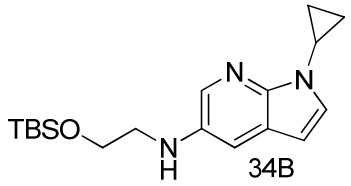


34A

Acido ciclopropilboronico (0.872 g, 10.15 mmoles) se agregó a una solución de 5-bromo-1H-pirrolo[2,3-b]piridina (1 g, 5.08 mmoles), Na_2CO_3 (1.076 g, 10.15 mmoles), acetato de cobre(II) (0.922 g, 5.08 mmoles) y 2,2'-bipiridina (0.793 g, 5.08 mmoles) en dicloroetano (20 mL), y la mezcla se agitó a 110 °C por 8h. La mezcla de reacción se concentró, y luego se diluyó con acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró en presión reducida y se purificó por cromatografía instantánea usando 10% acetato de etilo en pet éter para producir el compuesto del título (0.38 g, 31.3%) como un aceite. ^1H RMN (300 MHz, $CDCl_3$): δ 8.38 (d, J = 2.1 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.20 (d,

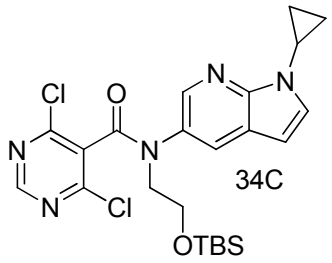
J = 3.3 Hz, 1H), 6.34 (d, *J* = 3.6 Hz, 1H), 3.5 (m, 1H), 1.15 (m, 2H), 1.03 (m, 2H).

N-(2-(ter-Butildimetilsililoxi)etil)-1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-amina (34B):



A mezcla de producto del Ejemplo 34A (0.38 mg, 1.603 mmoles), 2-(ter-butildimetilsililoxi)etanamina (0.337 g, 1.923 mmoles), carbonato de cesio (0.783 g, 2404 mmoles), acetato de paladio (0.036 g, 0.160 mmoles) y X-PHOS (0.076 g, 0.160 mmoles) en Tolueno (15 mL) bajo Argón se calentó a reflujo a 120 °C por 12 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x5 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró en presión reducida y se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano para producir el compuesto del título (0.25 g, 40.5%) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 2.4 Hz, 1H), 7.16 (d, *J* = 2.8 Hz, 1H), 7.10 (d, *J* = 3.6 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 3.84 (t, *J* = 5.2 Hz, 2H), 3.46 (m, 1H), 3.24 (t, *J* = 5.2 Hz, 2H), 1.1 (m, 2H), 1.01 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H).

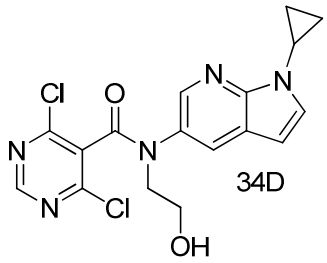
N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-il)pirimidina-5-carboxamida (34C):



34C

A una solución agitada, enfriada (0 °C) de producto del Ejemplo 34B (0.25 g, 0.754 mmoles) y TEA (0.315 mL, 2.262 mmoles) en DCM (10 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.191 g, 0.905 mmoles) en DCM (5 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x5 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en pet éter para producir el compuesto del título (0.25 g, 60.2%) como un jarabe. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.37 (s, 1H), 8.0 (s, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.33 (d, *J* = 3.2 Hz, 1H), 4.05 (t, *J* = 5.6 Hz, 2H), 3.92 (t, *J* = 5.2 Hz, 2H), 3.45 (m, 1H), 1.13 (m, 2H), 1.0 (m, 2H), 0.86 (s, 9H), 0.05 (s, 6H).

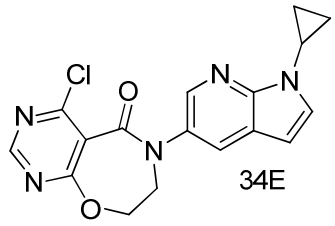
4,6-Dicloro-N-(1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-il)-N-(2-hidroxietil)pirimidina-5-carboxamida (34D):



34D

TBAF (0.387 g, 1.481 mmoles) se agregó a una solución de Ejemplo 34C (0.25 g, 0.494 mmoles) en THF (10 mL), y la mezcla se agitó a temperatura ambiente por 1 h. THF se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado solución y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.19 g, 91%) como un sólido, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.42 (s, 1H), 7.97 (s, 1H), 7.24 (d, *J* = 3.2 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.15 (m, *2*H), 3.97 (q, *J* = 4.8 Hz, 2H), 3.45 (m, 1H), 2.11 (t, *J* = 5.2 Hz, 1H), 1.12 (m, 2H), 1.01 (m, 2H).

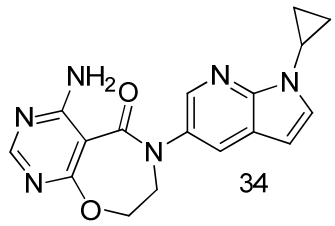
4-Cloro-6-(1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (34E):



34E

Un lodo del producto del Ejemplo 34D (0.19 g, 0.484 mmoles) y TEA (0.203 mL, 1.453 mmoles) en acetonitrilo (15 mL) se agitó a 80 ºC por 6 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.17 g, 98%) como un sólido blanco. ^{1}H RMN (300MHz, $CDCl_3$): δ □8.78 (s, 1H), 8.36 (d, *J* = 2.4 Hz, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 3.9 Hz, 1H), 6.45 (d, *J* = 3.3 Hz, 1H), 4.8 (t, *J* = 4.8 Hz, 2H), 4.09 (t, *J* = 4.5 Hz, 2H), 3.56 (m, 1H), 1.16 (m, 2H), 1.08 (m, 2H).

4-Amino-6-(1-ciclopropil-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (34):

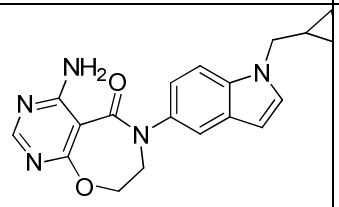
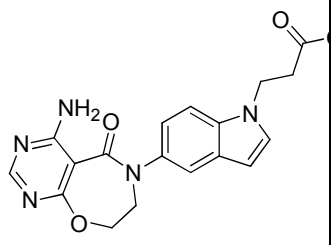


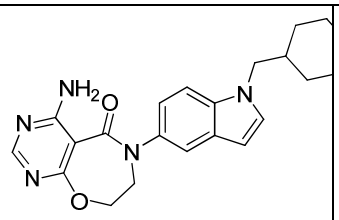
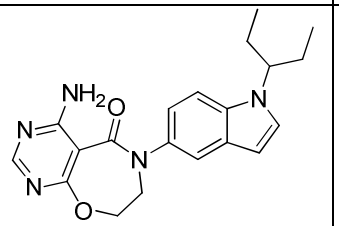
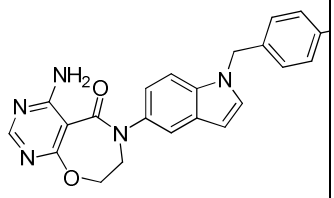
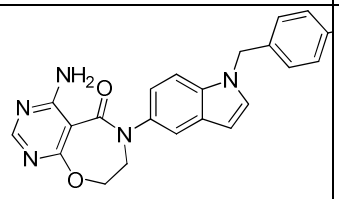
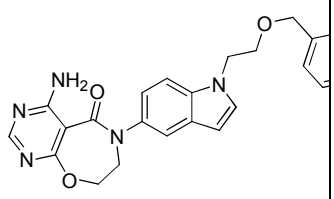
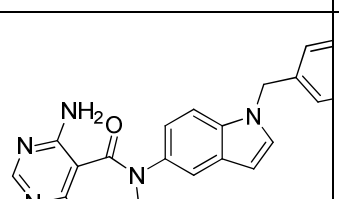
34

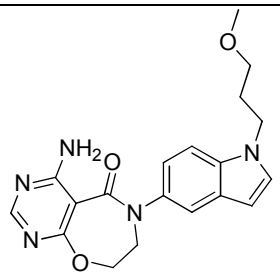
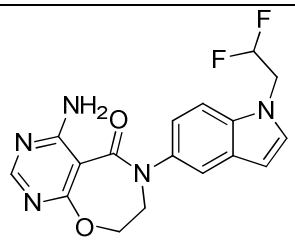
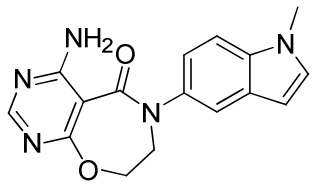
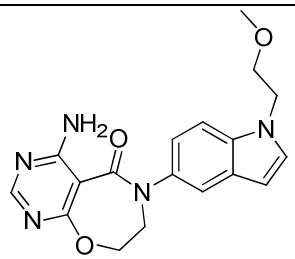
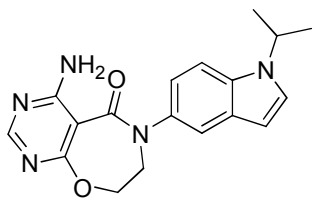
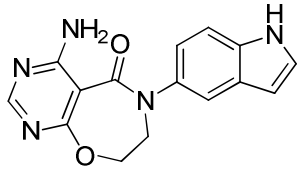
Una solución del producto del Ejemplo 34E (0.17 g, 0.478 mmoles) en amoniaco 0.5M en p-dioxano (15 mL) se agitó a temperatura

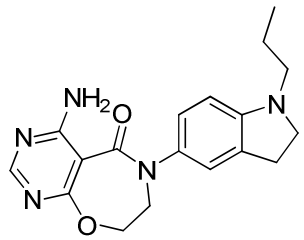
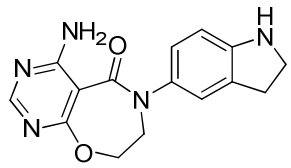
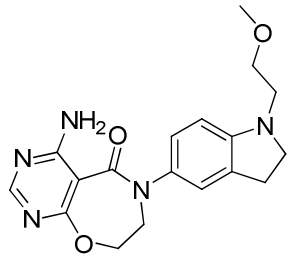
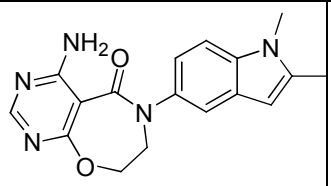
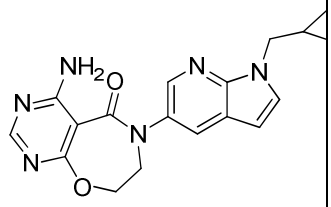
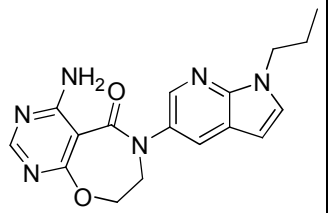
ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.1 g, 60.4%) como un sólido blanco. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.26 (d, J = 2.1 Hz, 1H), 8.18 (s, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.65 (bs, 2H), 7.54 (d, J = 3.6 Hz, 1H), 6.46 (d, J = 3.3 Hz, 1H), 4.67 (t, J = 3.6 Hz, 2H), 4.02 (t, J = 4.2 Hz, 2H), 3.62 (m, 1H), 1.1-1.0 (m, 4H); ESI-MS m/z = 337 $(M+H)^+$; HPLC pureza: 97%.

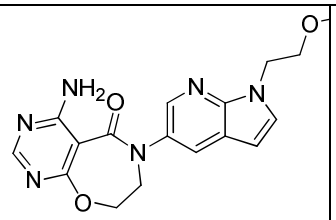
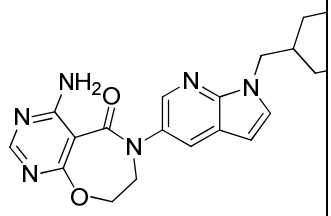
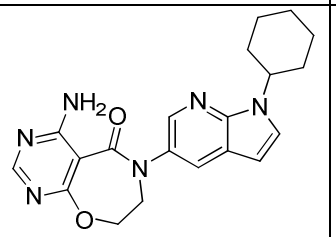
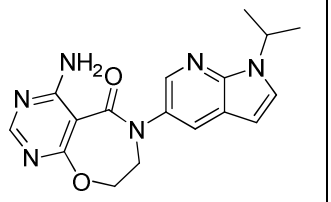
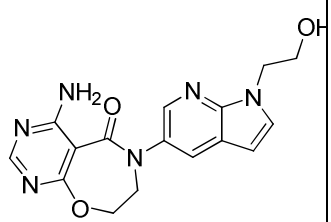
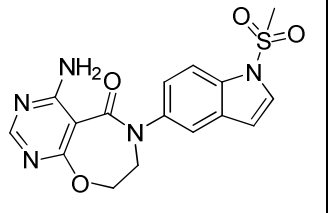
Los Ejemplos 35 – 62 se prepararon por procedimientos análogos a esos descritos en el Ejemplo 33 o Ejemplo 34 usando materiales de partida apropiadamente sustituidos.

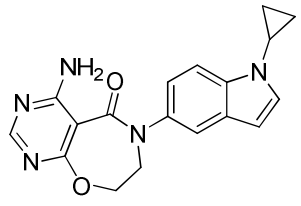
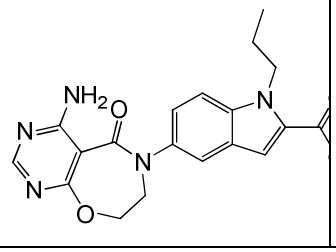
Ej.	Estructura	Datos analíticos:	Masa/pureza
35		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.49 (m, 2H), 7.08 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 2H), 6.52 (d, J = 3.2 Hz, 1H), 4.64 (t, J = 4.4 Hz, 2H), 4.06 (d, J = 6.8 Hz, 2H), 3.98 (t, J = 4.8 Hz, 2H), 1.25 (m, 1H), 0.52 (m, 2H), 0.38 (m, 2H).	ESI-MS m/z = 350 $(M+H)^+$; HPLC pureza: 98.7%.
36		^{1}H RMN (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 8.17 (s, 1H), 7.61 (bs, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 3.6 Hz, 1H), 7.09 (dd, J_1 = 1.6 Hz, J_2 = 10.8 Hz, 1H), 6.44 (d, J = 3.6 Hz, 1H), 4.63 (t, J = 4.4 Hz, 2H), 4.41 (t, J = 6.8 Hz, 2H), 3.98 (t, J = 4.4 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H)	ESI-MS m/z = 366 $(M-H)^-$; HPLC pureza: 97.7%.

37		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.52 (m, 2H), 7.38 (d, J = 3.3 Hz, 1H), 7.06 (dd, J_1 = 2.1 Hz, J_2 = 10.8 Hz, 1H), 6.44 (d, J = 2.7 Hz, 1H), 4.63 (t, J = 3.9 Hz, 2H), 4.04 (m, 4H), 1.79 (m, 1H), 1.7-1.45 (m, 5H), 1.2-0.9 (m, 5H).	ESI-MS m/z = 392 $(M+H)^+$; HPLC pureza: 97%.
38		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.60 (bs, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.49 (m, 2H), 7.05 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 4.63 (t, J = 4.0 Hz, 2H), 4.27 (m, 1H), 4.0 (t, J = 3.6 Hz, 2H), 1.86 (m, 4H), 0.66 (t, J = 7.2 Hz, 6H).	ESI-MS m/z = 366 $(M+H)^+$; HPLC pureza: 96%.
39		^{1}H RMN (300MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.60 (bs, 2H), 7.55 (d, J = 3.3 Hz, 1H), 7.49 (m, 2H), 7.2 (d, J = 8.4 Hz, 2H), 7.04 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 3.0 Hz, 1H), 5.35 (s, 2H), 4.61 (t, J = 3.9 Hz, 2H), 3.96 (t, J = 4.5 Hz, 2H), 3.69 (s, 3H).	ESI-MS m/z = 416 $(M+H)^+$; HPLC pureza: 96%.
40		^{1}H RMN (300MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.58 (m, 3H), 7.52 (m, 2H), 7.28-7.25 (m, 2H), 7.22-7.0 (m, 3H), 6.51 (d, J = 3.3 Hz, 1H), 5.43 (s, 2H), 4.62 (t, J = 4.5 Hz, 2H), 3.97 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 404 $(M+H)^+$; HPLC pureza: 97%.
41		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.56-7.5 (m, 2H), 7.44 (d, J = 2.8 Hz, 1H), 7.32-7.16 (m, 4H), 7.09 (d, J = 8.8 Hz, 1H), 6.46 (d, J =2.8 Hz, 1H), 4.64 (t, J = 4.0 Hz, 2H), 4.45 (s, 2H), 4.41 (t, J = 4.8 Hz, 2H), 3.98 (t, J = 4.4 Hz, 2H), 3.75 (t, J = 4.8 Hz, 2H).	ESI-MS m/z = 430 $(M+H)^+$; HPLC pureza: 99 %.
42		^{1}H RMN (400MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.60 (bs, 2H), 7.58 (d, J = 2.8 Hz, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.33-7.29 (m, 1H), 7.26-7.20 (m, 4H), 7.06 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.51 (d, J = 3.2 Hz, 1H), 5.44 (s, 2H), 4.61 (t, J = 4.4 Hz, 2H), 3.97 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 386 $(M+H)^+$; HPLC pureza: 98%.

43		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.50 (m, 2H), 7.40 (d, *J* = 2.8 Hz, 1H), 7.1 (d, *J* = 8.8 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 4.63 (m, 2H), 4.24 (t, *J* = 6.8 Hz, 2H), 3.98 (m, 2H), 3.24 (m, 5H), 1.97 (m, 2H).	ESI-MS *m/z* = 368 $(M+H)^+$; HPLC pureza: 99%.
44		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.60 (bs, 2H), 7.58-7.53 (m, 2H), 7.43 (d, *J* = 2.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 3.2 Hz, 1H), 6.5-6.2 (m, 1H), 4.76-4.6 (m, 4H), 4.0 (t, *J* = 4.4 Hz, 2H).	ESI-MS *m/z* = 360 $(M+H)^+$; HPLC pureza: 95%.
45		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 3.0 Hz, 1H), 7.12 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 6.44 (d, *J* = 3.0 Hz, 1H), 4.64 (t, *J* = 4.2 Hz, 2H), 3.98 (t, *J* = 4.5 Hz, 2H), 3.8 (s, 3H).	ESI-MS *m/z* = 310 $(M+H)^+$; HPLC pureza: 92%.
46		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.50 (m, 2H), 7.41 (d, *J* = 2.8 Hz, 1H), 7.08 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.44 (d, *J* = 2.8 Hz, 1H), 4.64 (t, *J* = 4.4 Hz, 2H), 4.35 (t, *J* = 5.2 Hz, 2H), 3.98 (t, *J* = 4.4 Hz, 2H), 3.65 (t, *J* = 5.2 Hz, 2H), 3.22 (s, 3H)	ESI-MS *m/z* = 354 $(M+H)^+$; HPLC pureza: 99%.
47		^{1}H RMN (300MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.56-7.49 (m, 2H), 7.5 (d, *J* = 1.8 Hz, 1H), 7.08 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 6.48 (d, *J* = 3.0 Hz, 1H), 4.77 (m, 1H), 4.63 (t, *J* = 4.2 Hz, 2H), 3.98 (t, *J* = 4.5 Hz, 2H), 1.46 (d, *J* = 6.9 Hz, 6H).	ESI-MS *m/z* = 338 $(M+H)^+$; HPLC pureza: 96%.
48		^{1}H RMN (400MHz, DMSO-d_6): δ 11.2 (bs, 1H), 8.17 (s, 1H), 7.60 (bs, 2H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.40 (m, 2H), 7.04 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.44 (m, 1H), 4.63 (t, *J* = 4.4 Hz, 2H), 3.97 (t, *J* = 4.8 Hz, 2H).	ESI-MS *m/z* = 296 $(M+H)^+$; HPLC pureza: 93%.

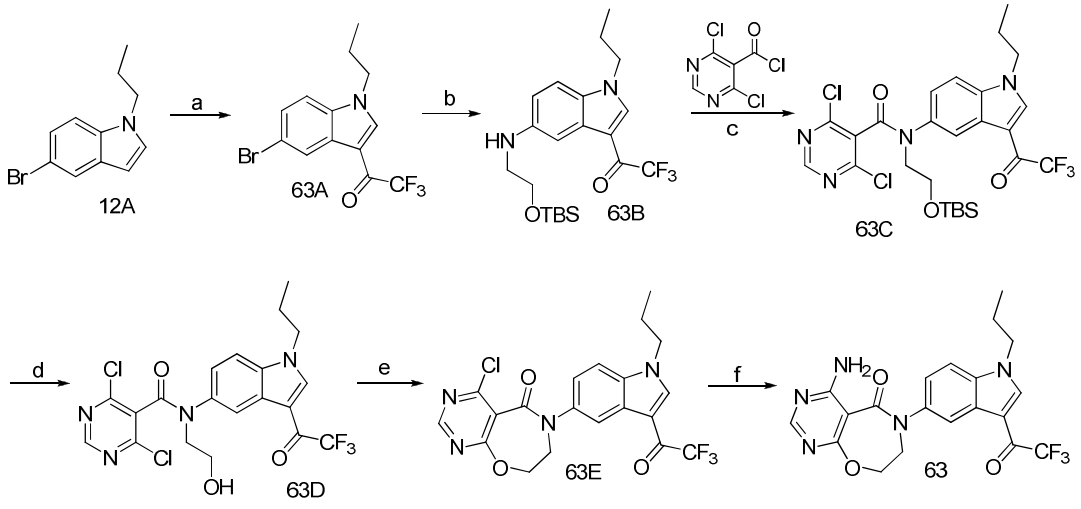
49		^{1}H RMN (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.57 (bs, 2H), 6.98 (s, 1H), 6.92 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 4.57 (t, J = 4.4 Hz, 2H), 3.86 (t, J = 4.8 Hz, 2H), 3.33 (t, J = 8.0 Hz, 2H), 3.0 (t, J = 7.6 Hz, 2H), 2.89 (t, J = 8.4 Hz, 2H), 1.55 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).	ESI-MS m/z = 340 $(M+H)^{+-}$; LCMS Pureza: 99%.
50		^{1}H RMN (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.57 (bs, 2H), 6.98 (s, 1H), 6.84 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 5.58 (bs, 1H), 4.57 (t, J = 4.4 Hz, 2H), 3.86 (t, J = 4.4 Hz, 2H), 3.44 (t, J = 8.4 Hz, 2H), 2.91 (t, J = 8.0 Hz, 2H).	ESI-MS m/z = 298 $(M+H)^{+-}$; HPLC Pureza: 94%.
51		^{1}H RMN (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.58 (bs, 2H), 6.98 (s, 1H), 6.92 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 4.57 (t, J = 4.4 Hz, 2H), 3.87 (t, J = 4.4 Hz, 2H), 3.53 (t, J = 6.0 Hz, 2H), 3.41 (t, J = 8.0 Hz, 2H), 3.28 (s, 3H), 3.23 (t, J = 5.6 Hz, 2H), 2.89 (t, J = 8.4 Hz, 2H).	ESI-MS m/z = 356 $(M+H)^{+-}$; HPLC Pureza: 97%.
52		^{1}H RMN (400MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.02-6.98 (m, 2H), 7.01 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.23 (s, 1H), 4.63 (t, J = 4.0 Hz, 2H), 3.96 (t, J = 4.4 Hz, 2H), 3.67 (s, 3H), 2.87 (s, 3H).	ESI-MS m/z = 324 $(M+H)^{+}$; HPLC pureza: 96%.
53		^{1}H RMN (400MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 3.2 Hz, 1H), 6.50 (d, J = 3.6 Hz, 1H), 5.64 (bs, 1H), 4.75 (t, J = 4.0 Hz, 2H), 4.17 (d, J = 6.8 Hz, 2H), 4.07 (t, J = 4.4 Hz, 2H), 1.29 (m, 1H), 0.61 (q, J = 6.0 Hz, 2H), 0.42 (q, J = 4.8 Hz, 2H).	ESI-MS m/z = 351 $(M+H)^{+}$; HPLC pureza: 96%.
54		^{1}H RMN (400MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 6.48 (d, J = 3.6 Hz, 1H), 5.64 (bs, 1H), 4.75 (t, J = 4.4 Hz, 2H), 4.26 (t, J = 6.8 Hz, 2H), 4.07 (t, J = 4.4 Hz, 2H), 1.91 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H);	ESI-MS m/z = 339 $(M+H)^{+}$; HPLC pureza: 93.5%.

55		^{1}H RMN (400MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 3.6 Hz, 1H), 6.48 (d, *J* = 3.6 Hz, 1H), 5.71 (bs, 1H), 4.75 (t, *J* = 4.4 Hz, 2H), 4.48 (t, *J* = 5.2 Hz, 2H), 4.06 (t, *J* = 4.4 Hz, 2H), 3.74 (t, *J* = 4.8 Hz, 2H), 3.33 (s, 3H);	ESI-MS *m/z* = 355 $(M+H)^+$; HPLC pureza: 91.63%.
56		^{1}H RMN (400MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 5.65 (bs, 1H), 4.75 (t, *J* = 4.4 Hz, 2H), 4.12 (d, *J* = 7.2 Hz, 2H) 4.07 (t, *J* = 4.4 Hz, 2H), 1.93 (m, 1H), 1.7-1.6 (m, 4H), 1.25-1.14 (m, 3H), 1.03 (m, 2H).	ESI-MS *m/z* = 393 $(M+H)^+$; HPLC pureza: 98.7%.
57		^{1}H RMN (300MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.21 (d, *J* = 2.1 Hz, 1H), 7.8 (d, *J* = 2.1 Hz, 1H), 7.39 (d, *J* = 3.3 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 5.65 (bs, 1H), 4.84-4.7 (m, 3H), 4.06 (t, *J* = 4.5 Hz, 2H), 2.18-2.04 (m, 2H), 1.95-1.88 (m, 2H), 1.8-1.6 (m, 4H), 1.4-1.2 (m, 2H).	ESI-MS *m/z* = 379 $(M+H)^+$; HPLC pureza: 92.8%.
58		^{1}H RMN (300MHz, DMSO d_6): δ 8.23 (d, *J* = 2.1 Hz, 1H), 8.18 (s, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.73 (d, *J* = 3.6 Hz, 1H), 7.65 (bs, 2H), 6.52 (d, *J* = 3.3 Hz, 1H), 5.07 (m, 1H), 4.67 (t, *J* = 4.2 Hz, 2H), 4.02 (t, *J* = 4.5 Hz, 2H), 1.48 (d, *J* = 6.3 Hz, 6H).	ESI-MS *m/z* = 339 $(M+H)^+$; HPLC pureza: 97%.
59		^{1}H RMN (300MHz, DMSO-d_6): δ 8.22 (d, *J* = 2.4 Hz, 1H), 8.18 (s, 1H), 7.97 (d, *J* = 2.1 Hz, 1H), 7.64 (bs, 2H), 7.61 (d, *J* = 3.3 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 4.92 (t, *J* = 5.4 Hz, 1H), 4.67 (t, *J* = 5.1 Hz, 2H), 4.32 (t, *J* = 5.7 Hz, 2H), 4.02 (t, *J* = 4.5 Hz, 2H), 3.75 (q, *J* = 5.7 Hz, 2H).	ESI-MS *m/z* = 341 $(M+H)^+$. Pureza por HPLC: 95%.
60		^{1}H RMN (300MHz, DMSO-d_6-D_2O): δ 8.19 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.7 (d, *J* = 2.1 Hz, 1H), 7.65 (d, *J* = 3.6 Hz, 1H), 7.38 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 6.87 (d, *J* = 3.6 Hz, 1H), 4.66 (t, *J* = 4.2 Hz, 2H), 4.02 (t, *J* = 4.5 Hz, 2H), 3.46 (s, 3H).	ESI-MS *m/z* = 374 $(M+H)^+$; HPLC pureza: 98%.

61		^{1}H RMN (300MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.61 (bs, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 3.3 Hz, 1H), 7.13 (dd, J_1 = 1.8 Hz, J_2 = 10.8 Hz, 1H), 6.42 (d, *J* = 3.0 Hz, 1H), 4.63 (t, *J* = 3.9 Hz, 2H), 3.98 (t, *J* = 4.8 Hz, 2H), 3.45 (m, 1H), 1.08 (m, 2H), 0.95 (m, 2H).	ESI-MS *m/z* = 336 $(M+H)^+$; HPLC pureza: 94%.
62		^{1}H RMN (400MHz, DMSO-d_6): δ 13.1 (bs, 1H), 8.18 (s, 1H), 7.68-7.6 (m, 4H), 7.29 (d, *J* = 10.4 Hz, 1H), 7.23 (s, 1H), 4.64 (t, *J* = 4.4 Hz, 2H), 4.56 (t, *J* = 7.6 Hz, 2H), 4.0 (t, *J* = 4.4 Hz, 2H), 1.72 (m, 2H), 0.83 (t, *J* = 7.6 Hz, 3H).	ESI-MS *m/z* = 382 $(M+H)^+$. Pureza por HPLC: 98%.

EJEMPLO 63

4-Amino-6-(1-propil-3-(2,2,2-trifluoroacetil)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona



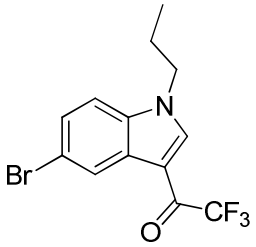
Reactivos y condiciones: a) TFAA, Et_3N, DCM, RT, 1h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 ºC, 2.5h; c)

DCM, Et_3N, RT, 1h; d) 3% HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 °C, 16h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

4-Amino-6-(1-propil-3-(2,2,2-trifluoroacetil)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

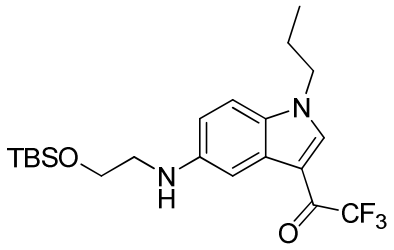
1-(5-Bromo-1-propil-1H-indol-3-il)-2,2,2-trifluoroetanona (63A):



TFAA (5.0 mL, 35.4 mmoles) se agregó a una solución de producto del Ejemplo 12A (2.5 g, 10.5 mmoles) en DCM (10 mL) seguido de TEA (2.5 mL, 17.94 mmoles) a 0 °C, y la mezcla se agitó a 25 °C por 1 h. La mezcla de reacción se diluyó con DCM y se templó con agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 5% acetato de etilo en hexano para producir el compuesto del título (2.0 g, 57%) como un sólido amarillo. ^{1}H RMN (300 MHz, $CDCl_3$): δ 8.57 (d, J = 1.5 Hz, 1H), 7.90 (d, J = 1.5 Hz, 1H), 7.49-7.45 (dd, J_1 = 1.8 Hz, J_2 = 9.0 Hz, 1H), 7.09 (m, 1H), 4.16 (t, J = 6.9 Hz, 2H), 1.98-1.91 (m, 2H), 0.98 (t,

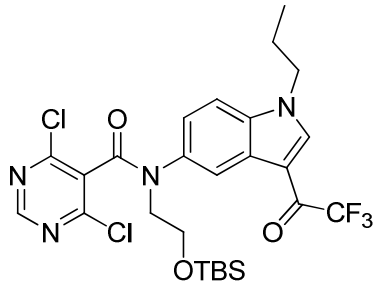
J = 7.5 Hz, 3H); ESI-MS *m/z* = 238 $(M+H)^+$.

1-(5-(2-(ter-Butildimetilsililoxi)etilamino)-1-propil-1H-indol-3-il)-2,2,2-trifluoroetanona (63B):



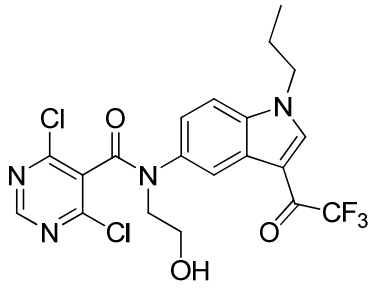
Una mezcla de producto del Ejemplo 63A (1.25 g, 3.74 mmoles), 2-(ter-butildimetilsililoxi)etanamina (0.656 g,3.74 mmoles), carbonato de cesio (1.463 g, 4.49 mmoles), acetato de paladio (0.084 g, 0.374 mmoles) y X-PHOS (0.178 g, 0.374 mmoles) en tolueno (20 mL) bajo Argón se calentó a reflujo a 110 ºC por 2 h. La mezcla de reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano para producir el compuesto del título (0.7 g, 43.7%) como un aceite. ^{1}H RMN (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 1.5 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* =.9.0 Hz, 1H), 6.75-6.72 (dd, J_1= 2.4 Hz, J_2 = 8.7 Hz, 1H), 4.17 (bs, 1H), 4.09 (t, *J* = 7.5 Hz, 2H), 3.87 (t, *J* = 5.1 Hz, 2H), 3.30 (t, *J* = 7.5 Hz, 1H), 1.96-1.89 (m, 2H), 0.97(t, *J* = 7.2 Hz, 3H), 0.91(s, 9H), 0.07 (s, 6H); ESI-MS *m/z* = 429 $(M+H)^+$.

N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(1-propil-3-(2,2,2-trifluoroacetil)-1H-indol-5-il)pirimidina-5-carboxamida (63C):



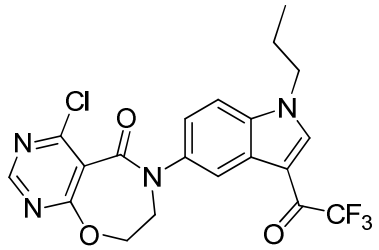
A una solución agitada, enfriada (0 °C) de producto del Ejemplo 63B (0.7 g, 1.633 mmoles) y TEA (1.138 g, 8.17 mmoles) en DCM (20 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.345 g, 1.633 mmoles) en DCM (5 mL). Después de 1 h, la mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.6 g, 60.9%) como un jarabe. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.46 (d, *J* = 1.6 Hz , 1H), 7.91 (d, *J* =1.2 Hz, 1H),7.45-7.43 (dd, J_1= 2.0 Hz J_2 =8.8 Hz ,1H), 7.26(m, 1H), 4.13-4.10 (m, 4H), 3.92 (t, *J* = 5.6 Hz, 2H),1.93-1.88 (q, *J* =7.6 Hz , 2H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.83 (s, 9H), 0.045(s, 6H); ESI-MS *m/z* = 605 $(M+H)^+$.

4,6-Dicloro-N-(2-hidroxietil)-N-(1-propil-3-(2,2,2-trifluoroacetil)-1H-indol-5-il)pirimidina-5-carboxamida (63D):



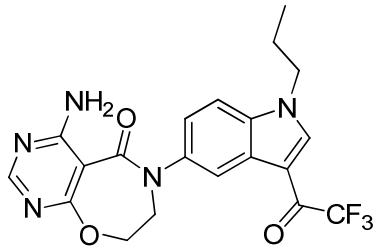
Una solución del producto del Ejemplo 63C (0.6 g, 0.994 mmoles), en 10 mL de solución metanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 1 h. El metanol se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.4 g, 82%) como un sólido, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.50 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.45-7.42 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.29(m, 1H), 4.18 (t, *J* = 5.2 Hz, 2H), 4.11 (t, *J* = 7.2 Hz, 2H), 3.95(t, 2H), 1.92 (q, *J* =7.6 Hz, 2H), 0.98 (t, *J* = 8.0 Hz, 3H); ESI-MS *m/z* = 490 $(M+H)^+$.

4-Cloro-6-(1-propil-3-(2,2,2-trifluoroacetil)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (63E):



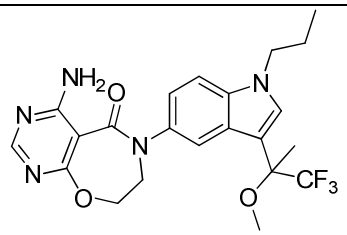
Un lodo del producto del Ejemplo 63D (0.4 g, 0.818 mmoles) y TEA (0.57 mL, 4.09 mmoles) en acetonitrilo (15 mL) se agitó a 80 °C por 16 h. La mezcla de reacción se enfrió y concentró al vacío. El residuo se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.25 g, 67.5%) como un sólido blanco. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.35(s , 1H), 7.99 (d, J = 0.9 Hz, 1H), 7.50-7.48 (m , 2H), 4.82(t, J = 7.8 Hz, 2H), 4.21 (t, J = 7.2 Hz , 2H), 4.15 (t, J = 4.8 Hz, 2H), 2.04-1.96 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H),; ESI-MS m/z = 453 $(M+H)^+$.

4-Amino-6-(1-propil-3-(2,2,2-trifluoroacetil)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (63):



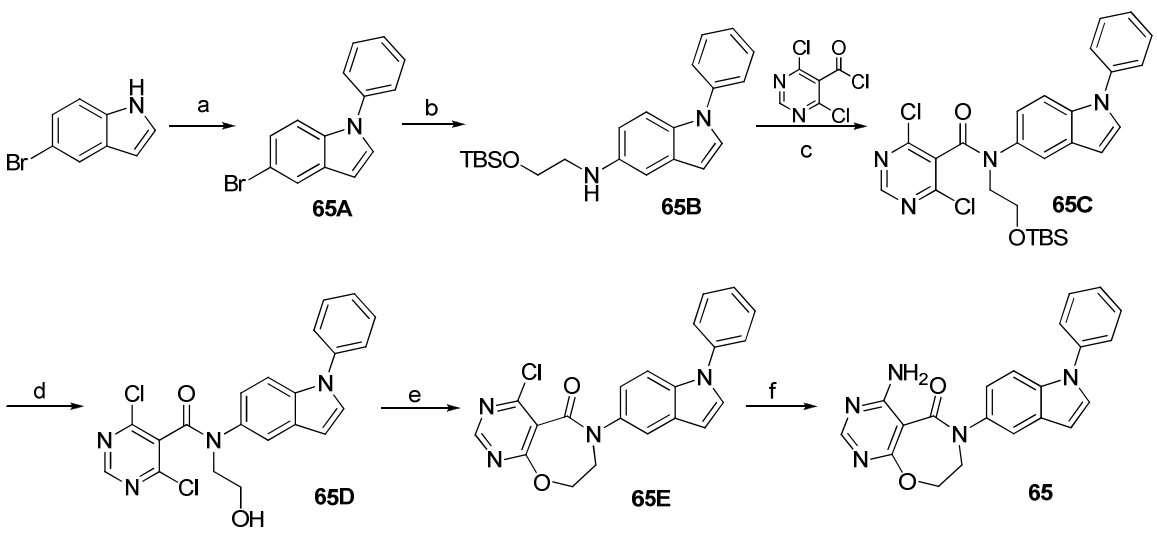
Una solución del producto del Ejemplo 63E (0.25 g, 0.552 mmoles) en amoniaco 0.5M en p-dioxano (10 mL) se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó en agua acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (70 mg, 27.2%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.65 (d, J = 1.6 Hz, 1H), 8.18 (s, 1H), 8.11 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.65 (bs, 2H), 7.40-7.38 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 4.63 (t, J = 3.6 Hz, 2H), 4.37 (t, J = 6.8 Hz, 2H), 4.04 (t, J = 4.8 Hz, 2H), 1.87-1.82 (m, 2H), 0.870 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 434 $(M+H)^+$; LCMS pureza: 92%.

El Ejemplo 64 se preparó por procedimientos análogos a esos descritos en el Ejemplo 63 usando materiales de partida apropiadamente sustituidos.

Ej.	Estructura	Datos analíticos:	Masa/pureza
64		^{1}H RMN (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.64-7.54 (m, 3H), 7.15 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 7.03 (bs, 2H), 4.59 (t, J = 4.2 Hz, 2H), 4.17 (t, J = 6.9 Hz, 2H), 4.0 (t, J = 4.5 Hz, 2H), 3.12 (s, 3H), 1.83-1.7 (m, 5H), 0.83 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 464 $(M+H)^+$; HPLC pureza: 90%.

EJEMPLO 65

4-Amino-6-(1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona

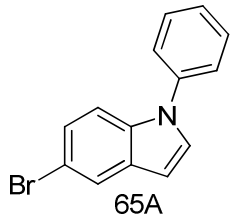


Reactivos y condiciones: a) Yodo benceno, CuBr, $Cu(OAc)_2$, K_2CO_3, NaOH, 140 ºC, 9h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 ºC, 2.5h; c) DCM, Et_3N, RT, 1h; d) 3%HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 ºC, 16h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

4-Amino-6-(1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

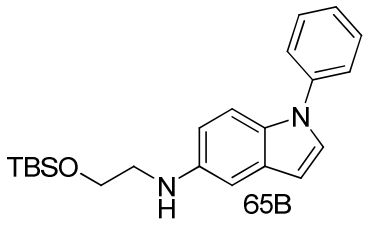
5-bromo-1-fenil-1H-indol (65A):



65A

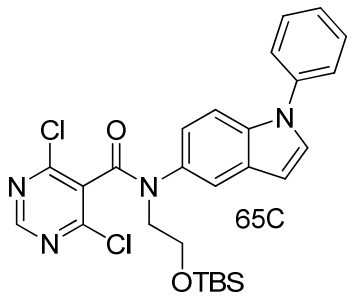
Bromuro de cobre(I) (0.073 g, 0.509 mmoles) se agregó a una solución de 5-bromo indol (1 g, 10.2 mmoles) en yodo benceno (13.5 g, 66.2 mmoles) seguido de carbonato de potasio (2.7 g, 19.54 mmoles), y la mezcla se agitó a 100 ºC por 10 min. NaOH (150 mg, 3.75 mmoles) y acetato de cobre(II) (0.01g, 0.055 mmoles) se agregó a 140 ºC, y la mezcla se agitó por 9 h. Los sólidos insolubles se filtraron, el filtrado se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio y se filtró. El filtrado se concentró bajo presión reducida y se purificó por cromatografía instantánea usando 8% acetato de etilo en pet éter para producir el compuesto del título (0.5 g, 36%) como un aceite. ^{1}H RMN (300MHz, $CDCl_3$): δ 7.80 (m, 1H), 7.60-7.45 (m, 4H), 7.42-7.38 (m, 2H), 7.35-7.25 (m, 2H), 6.62 (d, *J* = 3.3 Hz, 1H).

N-(2-(ter-Butildimetilsililoxi)etil)-1-fenil-1H-indol-5-amina (65B)



Una mezcla de producto del Ejemplo 65A (1.7 g, 6.25 mmoles), 2-(ter-butildimetilsililoxi)etanamina (1.095 g, 6.25 mmoles), carbonato de cesio (3.05 g, 9.37 mmoles), acetato de paladio (0.14 g, 0.625 mmoles) y X-PHOS (0.298 g, 0.625 mmoles) en tolueno (30 mL) bajo argón se calentó a reflujo a 120 °C por 16 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano para producir el compuesto del título (0.8 g, 34.9%) como un aceite. ^{1}H RMN (400MHz, $CDCl_3$): δ 7.55-7.48 (m, 4H), 7.45-7.39 (m, 2H), 7.3 (m, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.66 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.52 (d, J = 2.8 Hz, 1H), 3.94 (bs, 1H), 3.86 (t, J = 5.2 Hz, 2H), 3.27 (t, J = 5.2 Hz, 2H), 0.92 (s, 9H), 0.08 (s, 6H).

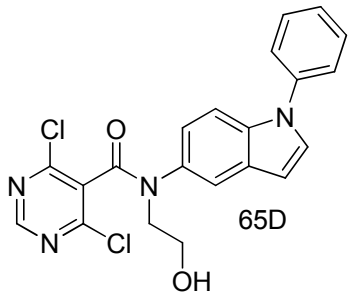
N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(1-fenil-1H-indol-5-il)pirimidina-5-carboxamida (65C):



65C

A una solución agitada, enfriada (0 °C) de producto del Ejemplo 65B (0.8 g, 2.182 mmoles) y TEA (1.521 mL, 10.91 mmoles) en DCM (30 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.461 g, 2.182 mmoles) en DCM (5 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.65 g, 5%) como un jarabe. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.5 (s, *1*H), 7.74 (d, J = 2.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 2H), 7.41-7.33 (m, 5H), 7.22 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 4.16 (t, J = 4.8 Hz, 2H), 3.95 (t, J = 5.2 Hz, 2H), 0.92 (s, 9H), 0.08 (s, 6H).

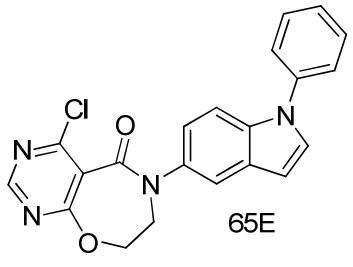
4,6-Dicloro-N-(2-hidroxietil)-N-(1-fenil-1H-indol-5-il)pirimidina-5-carboxamida (65D):



65D

Una solución del producto del Ejemplo 65C (0.65 g, 1.2 mmoles), en 20.5 mL de solución metanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 1 h. El metanol se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.45 g, 72.8%) como un sólido, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.40-7.38 (m, 4H), 7.36 (d, J = 3.6 Hz, 1H), 7.23 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 4.16 (t, J = 4.8 Hz, 2H), 3.95 (t, J = 5.2 Hz, 2H).

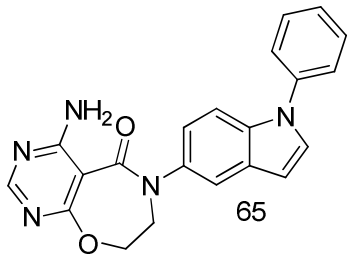
4-Cloro-6-(1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (65E):



65E

Un lodo del producto del Ejemplo 65D (0.45 g, 1.053 mmoles) y TEA (0.734 mL, 5.27 mmoles) en acetonitrilo (20 mL) se agitó a 80 °C por 16 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.3 g, 67.1%) como un sólido blanco. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.6 (d, J = 8.8 Hz, 1H), 7.56-7.47 (m, 4H), 7.41-7.38 (m, 2H), 7.20 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.71 (d, J = 3.6 Hz, 1H), 4.18 (t, J = 4.4 Hz, 2H), 4.10 (t, J = 4.8 Hz, 2H).

4-Amino-6-(1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (65):

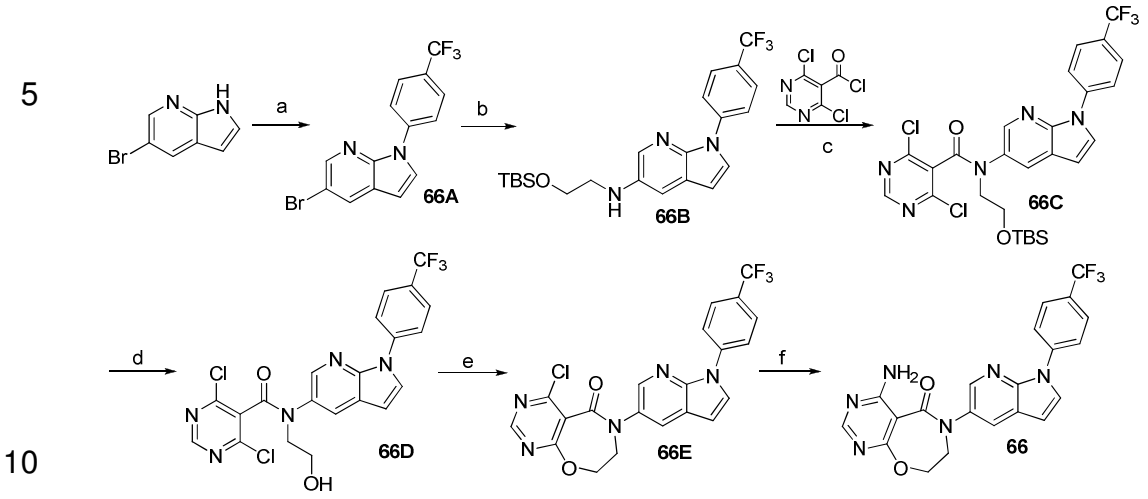


65

Una solución del producto del Ejemplo 65E (0.3 g, 0.768 mmoles), en amoniaco 0.5M en p-dioxano (15 mL) se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.22 g, 73.3%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.73 (d, J = 3.6 Hz, 1H), 7.64-7.56 (m, 5H), 7.45 (m, 1H), 7.18-7.15 (m, 4H), 6.73 (d, J = 3.2 Hz, 1H), 4.65 (t, J = 4.4 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H); ESI-MS m/z = 372 $(M+H)^+$; HPLC pureza: 95%.

EJEMPLO 66

4-Amino-6-(1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

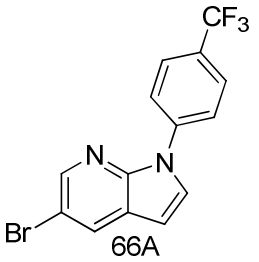


Reactivos y condiciones: a) 1-Yodo-4-(trifluorometil)benceno, CuBr, $Cu(OAc)_2$, K_2CO_3, NaOH, DMF, 110 º C, 16h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 º C, 12h; c) DCM, Et_3N, RT, 1h; d) TBAF, THF, RT, 1h; e) CH_3CN, Et_3N, 80 º C, 16h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

4-Amino-6-(1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

5-Bromo-1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridina (66A):

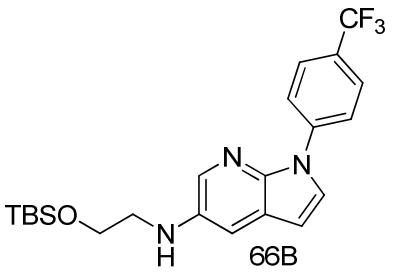


66A

1-yodo-4-(trifluorometil)benceno (1.657 g, 6.09 mmoles) se agregó a una solución de 5-bromo-1H-pirrolo[2,3-b]piridina (1 g, 5.08 mmoles) y bromuro de cobre(I) (0.073 g, 0.508 mmoles) en DMF (10 mL) seguido de carbonato de potasio (1.75 g, 12.69 mmoles), y la mezcla se agitó a 100 °C por 10 min. NaOH (150 mg, 3.75 mmoles) y acetato de cobre(II) (4.61 mg, 0.025 mmoles) se agregaron a la mezcla de reacción a 110 °C, y la mezcla se agitó por 16 h. Los sólidos insolubles se filtraron, y el filtrado se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 10% acetato de etilo en pet éter para producir el compuesto del título (0.4 g, 22%) como un sólido blanco mate. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.4 (d, J =

2.0 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 4.0 Hz, 1H), 6.63 (d, *J* = 3.6 Hz, 1H).

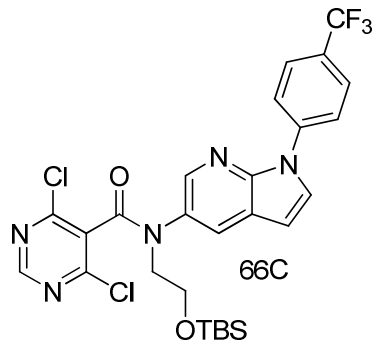
N-(2-(ter-Butildimetilsililoxi)etil)-1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridin-5-amina (66B):



66B

Una mezcla de producto del Ejemplo 66A (0.4 g, 1.173 mmoles), 2-(ter-butildimetilsililoxi)etanamina (0.247 g, 1.407 mmoles), carbonato de cesio (0.573 g, 1.759 mmoles), acetato de paladio (26.3 mg, 0.117 mmoles) y X-PHOS (0.0559 g, 0.117 mmoles) en Tolueno (15 mL) bajo Argón se calentó a reflujo a 120 ºC por 2.5 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x5 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano para producir el compuesto del título (0.3 g, 50.5%) como un aceite. ^{1}H RMN (400MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 2.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 4.0 Hz, 1H), 7.21 (d, *J* = 2.8 Hz, 1H), 6.52 (d, *J* = 4.0 Hz, 1H), 3.88 (t, *J* = 5.2 Hz, 2H), 3.27 (t, *J* = 5.6 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 6H).

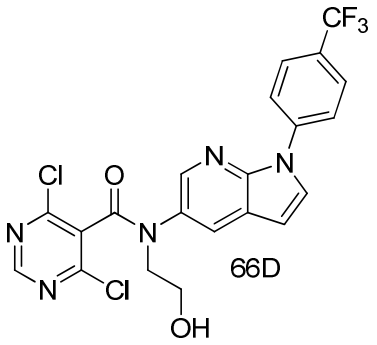
N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridin-5-il)pirimidina-5-carboxamida (66C):



66C

A una solución agitada, enfriada (0 °C) de producto del Ejemplo 66B (0.3 g, 0.689 mmoles) y TEA (0.288 mL, 2.06 mmoles) en DCM (10 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.175 g, 0.827 mmoles) en DCM (2 mL). Después de 1 h, la mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x5 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en pet éter para producir el compuesto del título (0.28 g, 62.6%) como un jarabe. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 4.0 Hz, 1H), 6.63 (d, *J* = 4.0 Hz, 1H), 4.09 (t, *J* = 5.2 Hz, 2H), 3.97 (t, *J* = 5.2 Hz, 2H), 0.87 (s, 9H), 0.06 (s, 6H).

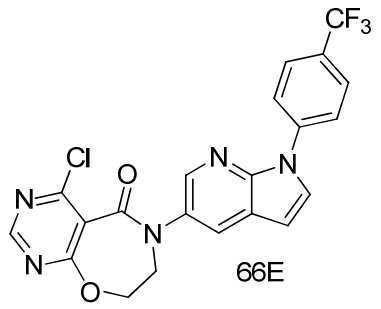
4,6-Dicloro-N-(2-hidroxietil)-N-(1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridin-5-il)pirimidina-5-carboxamida (66D):



66D

TBAF (0.3 g, 1.147 mmoles) se agregó a una solución de Ejemplo 66C (0.28 g, 0.459 mmoles) en THF (10 mL), y la mezcla se agitó a temperatura ambiente por 1 h. THF se removió al vacío. El residuo se disolvió en acetato de etilo, se lavó con bicarbonato de sodio acuoso saturado solución y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.2 g, 86%) como un sólido, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.6 (d, J = 4.0 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 4.16 (t, J = 4.8 Hz, 2H), 3.98 (q, J = 4.8 Hz, 2H).

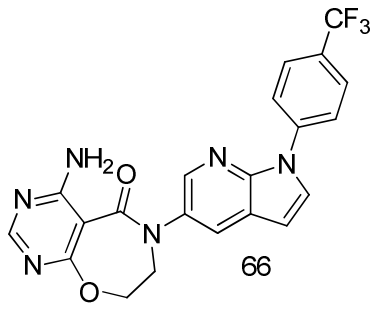
4-Cloro-6-(1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (66E):



66E

Un lodo del producto del Ejemplo 66D (0.2 g, 0.403 mmoles) y TEA (0.169 mL, 1.209 mmoles) en acetonitrilo (15 mL) se agitó a 80 °C por 6 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.16 g, 83%) como un sólido blanco. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.39 (d, *J* = 2.4 Hz, 1H), 8.04 (d, *J* = 2.8 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.8 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 3.6 Hz, 1H), 6.74 (d, *J* = 3.6 Hz, 1H), 4.81 (t, *J* = 5.2 Hz, 2H), 4.12 (t, *J* = 4.8 Hz, 2H).

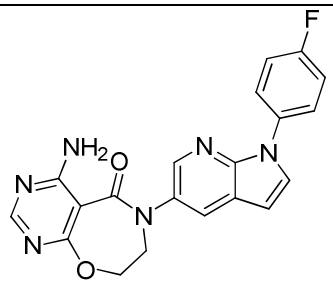
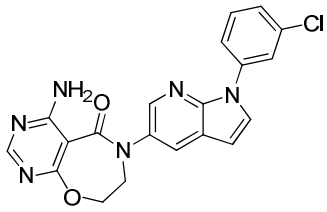
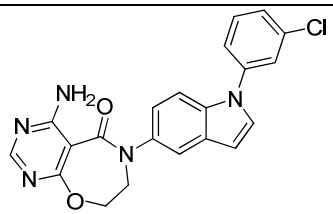
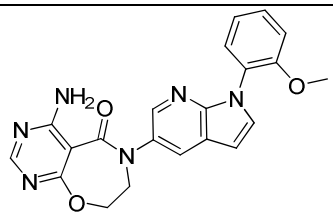
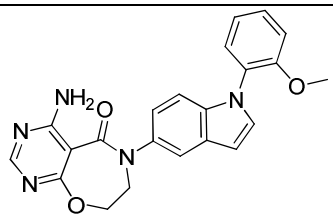
4-Amino-6-(1-(4-(trifluorometil)fenil)-1H-pirrolo[2,3-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (66):

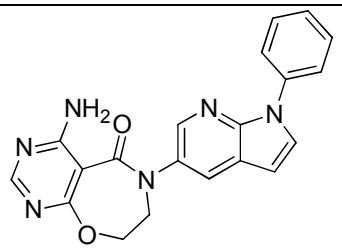
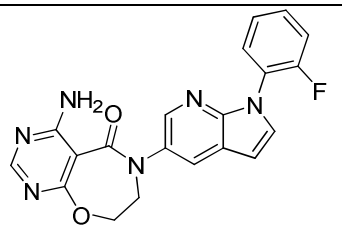
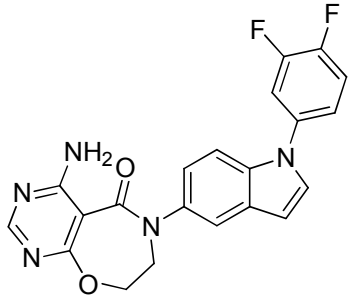
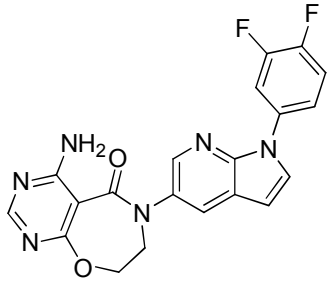
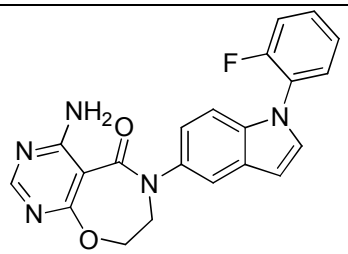


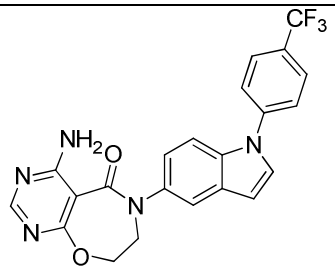
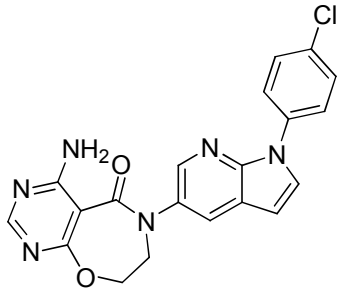
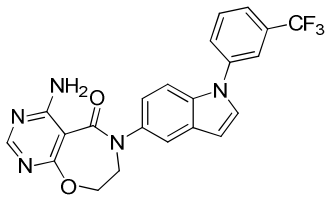
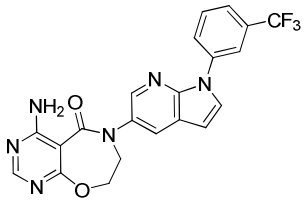
66

Una solución del producto del Ejemplo 66E (0.16 g, 0.348 mmoles) en amoniaco 0.5M en p-dioxano (12 mL) se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.1 g, 64.6%) como un sólido blanco. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.37 (d, J = 2.4 Hz, 1H), 8.23 (d, J = 8.0 Hz, 2H), 8.19 (s, 1H), 8.16 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 4.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.66 (bs, 2H), 6.87 (d, J = 4.0 Hz, 1H), 4.71 (t, J = 4.0 Hz, 2H), 4.07 (t, J = 3.6 Hz, 2H); ESI-MS m/z = 441 $(M+H)^+$; HPLC pureza: 99%.

Los Ejemplos 67 – 81 se prepararon por procedimientos análogos a esos descritos en el Ejemplo 65 o Ejemplo 66 usando materiales de partida apropiadamente sustituidos.

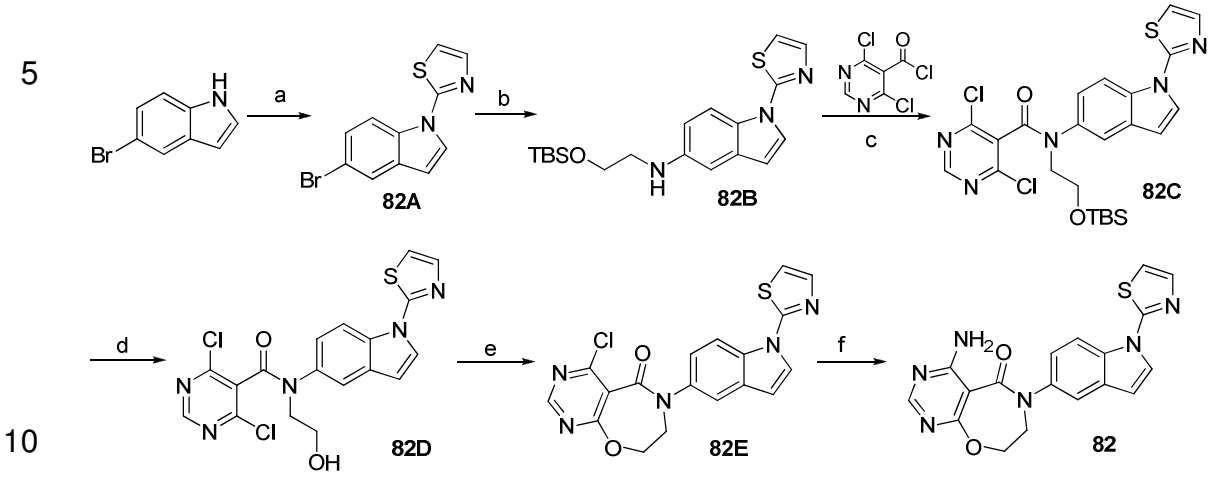
Ej.	Estructura	Datos analíticos:	Masa/pureza
67		^{1}H RMN (400MHz, DMSO-d_6): δ 8.32 (d, J = 2.0 Hz, 1H), 8.19 (s, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.0 (d, J = 4.0 Hz, 1H), 7.94-7.91 (m, 2H), 7.66 (bs, 2H), 7.41 (t, J = 8.8 Hz, 2H), 6.76 (d, J = 4.0 Hz, 1H), 4.69 (t, J = 4.4 Hz, 2H), 4.06 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 391 $(M+H)^+$; HPLC pureza: 97%.
68		^{1}H RMN (400MHz, DMSO-d_6): δ 8.37 (d, J = 2.4 Hz, 1H), 8.19 (s, 1H), 8.16-8.10 (m, 3H), 7.95 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.67 (bs, 2H), 7.59 (t, J = 8.4 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 6.8 (d, J = 3.6 Hz, 1H), 4.69 (t, J = 4.0 Hz, 2H), 4.06 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 407 $(M+H)^+$; HPLC pureza: 97%.
69		^{1}H RMN (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.78 (d, J = 3.3 Hz, 1H), 7.7 (bs, 2H), 7.66-7.58 (m, 5H), 7.48 (m, 1H), 7.22 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 6.76 (d, J = 3.3 Hz, 1H), 4.65 (t, J = 3.6 Hz, 2H), 4.01 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 406 $(M+H)^+$; HPLC pureza: 95%.
70		^{1}H RMN (300MHz, DMSO-d_6): δ 8.18 (m, 2H), 8.05 (d, J = 2.1 Hz, 1H), 7.66 (bs, 2H), 7.46 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 6.3 Hz, 2H), 6.66 (d, J = 3.9 Hz, 1H), 4.67 (t, J = 4.5 Hz, 2H), 4.04 (t, J = 4.5 Hz, 2H), 3.74 (s, 3H).	ESI-MS m/z = 403 $(M+H)^+$; HPLC pureza: 92%.
71		^{1}H RMN (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.62 (bs, 2H), 7.59 (s, 1H), 7.54-7.46 (m, 2H), 7.39 (d, J = 6.9 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.2-7.05 (m, 3H), 6.66 (d, J = 3.0 Hz, 1H), 4.64 (t, J = 4.5 Hz, 2H), 4.0 (t, J = 4.5 Hz, 2H), 3.77 (s, 3H).	ESI-MS m/z = 402 $(M+H)^+$; HPLC pureza: 92%.

72		^{1}H RMN (300MHz, $CDCl_3$): δ 8.3 (s, 1H), 8.28 (d, *J* = 2.4 Hz, 1H), 8.20 (bs, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.74 (m, 2H), 7.6 (d, *J* = 3.6 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 3.3 Hz, 1H), 5.70 (bs, 1H), 4.76 (t, *J* = 4.2 Hz, 2H), 4.08 (t, *J* = 4.5 Hz, 2H).	ESI-MS *m/z* = 373 $(M+H)^+$; HPLC pureza: 99%.
73		^{1}H RMN (300MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.25 (d, *J* = 2.4 Hz, 1H), 8.20 (bs, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.69 (dt, J_1 = 1.5 Hz, J_2 = 7.5 Hz, 1H), 7.49 (m, 1H), 7.46-7.38 (m, 1H), 7.34-7.27 (m, 2H), 6.68 (d, *J* = 3.3 Hz, 1H), 5.75 (bs, 1H), 4.75 (t, *J* = 4.5 Hz, 2H), 4.08 (t, *J* = 4.5 Hz, 2H).	ESI-MS *m/z* = 391 $(M+H)^+$; HPLC pureza: 96%.
74		^{1}H RMN (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.80 (m, 1H), 7.73 (d, *J* = 3.2 Hz, 1H), 7.70-7.58 (m, 5H), 7.50 (m, 1H), 7.20 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 2H), 6.75 (d, *J* = 3.2 Hz, 1H), 4.65 (t, *J* = 4.4 Hz, 2H), 4.0 (t, *J* = 4.4 Hz, 2H).	ESI-MS *m/z* = 408 M+H)$^+$; HPLC pureza: 96%.
75		^{1}H RMN (300MHz, DMSO-d_6): δ 8.36 (d, *J* = 2.1 Hz, 1H), 8.18 (s, 1H), 8.13 (m, 2H), 8.08 (d, *J* = 3.9 Hz, 1H), 7.85 (m, 1H), 7.70-7.60 (m, 3H), 6.80 (d, *J* = 3.3 Hz, 1H), 4.69 (t, *J* = 3.9 Hz, 2H), 4.06 (t, *J* = 4.2 Hz, 2H).	ESI-MS *m/z* = 409 $(M+H)^+$; HPLC pureza: 90%.
76		^{1}H RMN (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.68-7.60 (m, 5H), 7.55 (m, 2H), 7.43 (m, 1H), 7.24 (d, *J* = 8.4, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 2.8 Hz, 1H), 4.65 (t, *J* = 4.4 Hz, 2H), 4.01 (t, *J* = 4.4 Hz, 2H).	ESI-MS *m/z* = 390 $(M+H)^+$; LCMS pureza: 98%.

78		^{1}H RMN (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 2.8 Hz, 1H), 7.71-7.6 (m, 4H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 3.2 Hz, 1H), 4.65 (t, *J* = 4.0 Hz, 2H), 4.02 (t, *J* = 4.4 Hz, 2H).	ESI-MS *m/z* = 440 (M+H) $^+$; HPLC pureza: 99%.
79		^{1}H RMN (300MHz, DMSO-d_6): □ □8.34 (d, *J* = 2.1 Hz, 1H), 8.19 (s, 1H), 8.13 (d, *J* = 1.8 Hz, 1H), 8.05 (d, *J* = 3.6 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.7-7.6 (m, 4H), 6.79 (d, *J* = 3.3 Hz, 1H), 4.68 (t, *J* = 4.2 Hz, 2H), 4.06 (t, *J* = 4.5 Hz, 2H).	ESI-MS *m/z* = 407 (M+H); HPLC pureza: 94%.
80		^{1}H RMN (400MHz, DMSO-d_6): δ 8.10 (s, 1H), 7.91-7.84 (m, 2H), 7.8-7.68 (m, 3H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.55 (bs, 2H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.71 (d, *J*= 3.6 Hz, 1H), 4.58 (t, *J* = 4.8 Hz, 2H), 3.94 (t, *J* = 4.4 Hz, 2H).	ESI-MS *m/z* = 440 (M+H) $^+$; HPLC pureza: 93%.
81		^{1}H RMN (400MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.39 (d, *J* = 2.4 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.19 (m, 2H), 8.15 (d, *J* = 2.0 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.67 (bs, 2H), 6.83 (d, *J* = 3.6 Hz, 1H), 4.70 (t, *J* = 4.0 Hz, 2H), 4.07 (t, *J* = 4.4 Hz, 2H).	ESI-MS *m/z* = 441 (M+H) $^+$; HPLC pureza: 97%.

EJEMPLO 82

4-Amino-6-(1-(tiazol-2-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

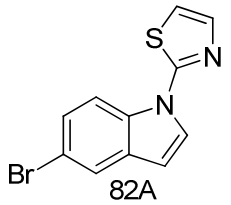


Reactivos y condiciones: a) 2-Bromo tiazol, Cs_2CO_3, DMF, 100 ^oC, 2h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 ^oC, 2.5h; c) DCM, Et_3N, RT, 1h; d) 3% HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 ^oC, 16h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

4-Amino-6-(1-(tiazol-2-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

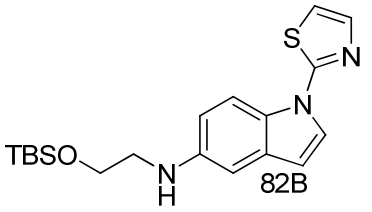
2-(5-Bromo-1H-indol-1-il)tiazol (82A):



82A

2-Bromo tiazol (0.837 g, 5.10 mmoles) se agregó a una solución de 5-bromo indol (1 g, 5.10 mmoles) en DMF (15 mL) seguido de carbonato de cesio (3.32 g, 10.20 mmoles), y la mezcla se agitó a 90 °C por 12 h. Los sólidos insolubles se filtraron, el filtrado se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, y se filtró. El filtrado se concentró bajo presión reducida y se purificó por cromatografía instantánea usando 5% acetato de etilo en pet éter para producir el compuesto del título (0.75 g, 52.7%) como un sólido blanco. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.24 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.62 (dd, J_1 = 3.2 Hz, J_2 = 10.4 Hz, 2H), 7.45 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H), 6.66 (d, J = 4.0 Hz, 1H).

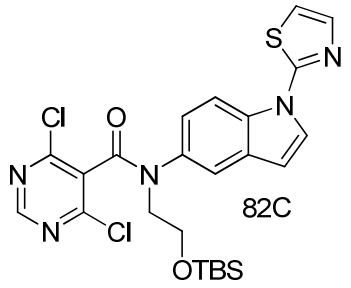
N-(2-(ter-Butildimetilsililoxi)etil)-1-(tiazol-2-il)-1H-indol-5-amina (82B):



82B

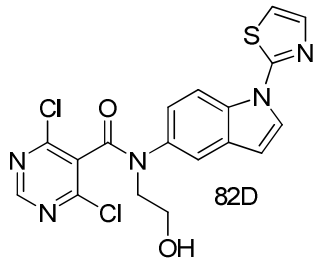
Una mezcla de producto del Ejemplo 82A (0.75 g, 2.69 mmoles), 2-(ter-butildimetilsililoxi)etanamina (0.471 g, 2.69 mmoles), carbonato de cesio (1.751 g, 5.37 mmoles), acetato de paladio (0.060 g, 0.269 mmoles) y X-PHOS (0.128 g, 0.269 mmoles) en Tolueno (15 mL) bajo Argón se calentó a reflujo a 120 °C por 4 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano para producir el compuesto del título (0.4 g, 40%) como un aceite. ^{1}H RMN (300MHz, $CDCl_3$): δ 8.11 (d, J = 9.0 Hz, 1H), 7.56 (dd, J_1 = 3.6 Hz, J_2 = 9.9 Hz, 2H), 6.99 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.76 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 6.56 (d, J = 3.6 Hz, 1H), 4.03 (bs, 1H), 3.86 (t, J = 4.8 Hz, *2*H), 3.27 (t, J = 5.4 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 6H).

N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(1-(tiazol-2-il)-1H-indol-5-il)pirimidina-5-carboxamida (82C):



A una solución agitada, enfriada (0 °C) solución de producto del Ejemplo 82B (0.4 g, 1.071 mmoles) y TEA (0.746 mL, 5.35 mmoles) en DCM (15 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.226 g, 1.071 mmoles) en DCM (5 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó en acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano para producir el compuesto del título (0.35 g, 59.6%) como un jarabe. ^{1}H RMN (300MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 7.62 (d, J = 3.3 Hz, 1H), 7.59 (d, J = 3.9 Hz, 1H), 7.38 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.63 (d, J = 3.6 Hz, 1H), 4.07 (t, J = 5.4 Hz, 2H), 3.93 (t, J = 5.4 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H).

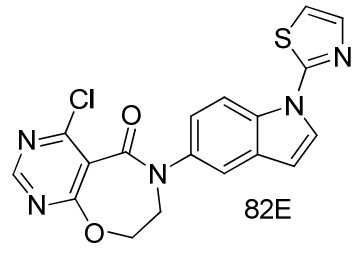
4,6-Dicloro-N-(2-hidroxietil)-N-(1-(tiazol-2-il)-1H-indol-5-il)pirimidina-5-carboxamida (82D):



82D

TBAF (1.276 mL, 1.276 mmoles) se agregó a una solución de Ejemplo 82C (0.35 g, 0.638 mmoles) en THF (10 mL), y la mezcla se agitó a temperatura ambiente por 1 h. THF se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado solución y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.25 g, 90%) como un sólido, que se llevó al paso siguiente sin purificación adicional. ESI-MS *m/z* = 434 $(M+H)^+$; LCMS pureza: 88%.

4-Cloro-6-(1-(tiazol-2-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (82E):

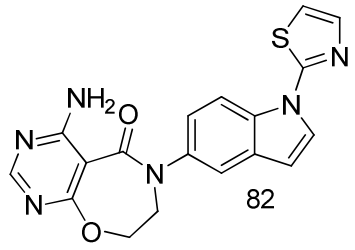


82E

Un lodo del producto del Ejemplo 82D (0.25 g, 0.576 mmoles) y TEA (0.080 mL, 0.576 mmoles) en acetonitrilo (12 mL) se agitó a 90 ºC por 16

h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio y concentró al vacío para producir el compuesto del título (0.377 g, 65.5%) como un sólido blanco. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.45 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 3.6 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.64 (d, J = 3.9 Hz, 1H), 7.34 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 6.75 (d, J = 3.6 Hz, 1H), 4.81 (t, J = 4.5 Hz, 2H), 4.11 (t, J = 5.1 Hz, 2H).

4-Amino-6-(1-(tiazol-2-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (82):



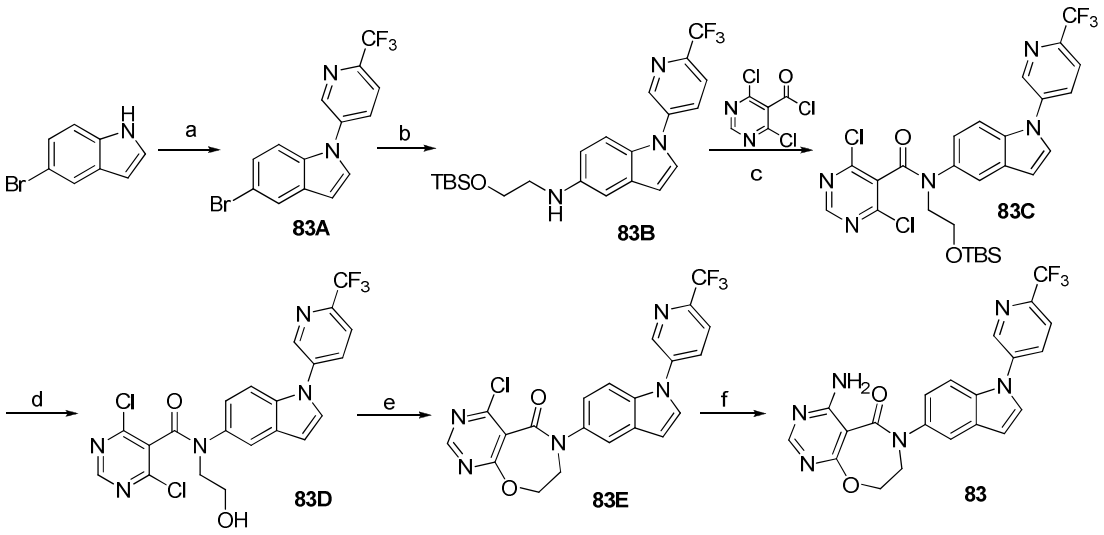
82

Una solución del producto del Ejemplo 82E (0.15 g, 0.377 mmoles) en amoniaco 0.5M en p-dioxano (10 mL) se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.09 g, 58%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.35 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.98 (d, J = 3.2

Hz, 1H), 7.72 (d, *J* = 3.6 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.63 (bs, 2H), 7.57 (d, *J* = 3.2 Hz, 1H), 7.35 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.86 (d, *J* = 3.6 Hz, 1H), 4.82 (t, *J* = 4.4 Hz, 2H), 4.11 (t, *J* = 4.8 Hz, 2H); ESI-MS *m/z* = 379 $(M+H)^+$; HPLC pureza: 92%.

EJEMPLO 83

4-Amino-6-(1-(6-(trifluorometil)piridin-3-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona

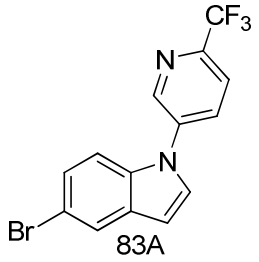


Reactivos y condiciones: a) 5-Bromo-2-(trifluorometil)piridina, CS_2CO_3, DMF, 90 ºC,15h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 ºC, 12h; c) DCM, Et_3N, RT, 1h; d) TBAF, THF, RT, 1h; e) CH_3CN, Et_3N, 80 ºC, 16h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

4-Amino-6-(1-(6-(trifluorometil)piridin-3-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

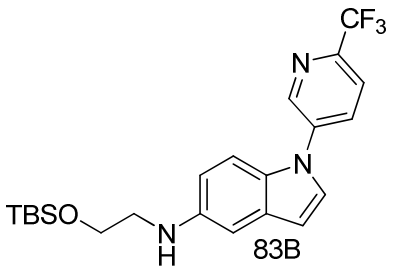
5-Bromo-1-(6-(trifluorometil)piridin-3-il)-1H-indol (83A):



83A

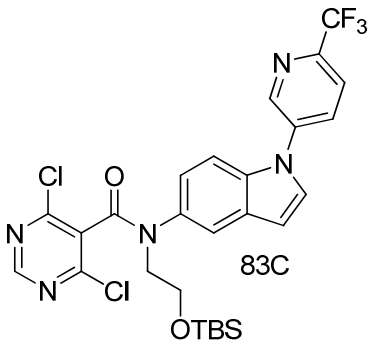
5-Bromo-2-(trifluorometil)piridina (2.075 g, 9.18 mmoles) se agregó a una solución de 5-bromo-1H-indol (1.5 g, 7.65 mmoles) y en DMF (20 mL) seguido de carbonato de cesio (7.48 g, 22.95 mmoles), y la mezcla se agitó a 90 °C por 15 min. Insoluble sólidos were se filtró, filtrado was concentró y se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio y se filtró. El filtrado se concentró al vacío y se purificó por cromatografía instantánea usando 5% acetato de etilo en pet éter para producir el compuesto del título (1.1 g, 42.1%) como un sólido blanco mate. ^{1}H RMN (300 MHz, DMSO-d_6): δ 9.09 (d, J = 2.4 Hz, 1H), 8.37 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.91 (m, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.37 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 6.82 (d, J = 3.0 Hz, 1H).

N-(2-(ter-Butildimetilsililoxi)etil)-1-(6-(trifluorometil)piridin-3-il)-1H-indol-5-amina (83B):



A mezcla de producto del Ejemplo 83A (0.3 g, 0.879 mmoles), 2-(ter-butildimetilsililoxi)etanamina (0.231 g, 1.319 mmoles), carbonato de cesio (0.86 g, 2.64 mmoles), acetato de paladio (19 mg, 0.088 mmoles) y X-PHOS (0.042 g, 0.088 mmoles) en Tolueno (25 mL) bajo Argón se calentó a reflujo a 110 ^{o}C por 12 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 7% acetato de etilo en hexano para producir el compuesto del título (0.15 g, 39.2%) como un sólido amarillo pálido. ^{1}H RMN (400MHz, DMSO-d_6): δ 9.04 (d, J = 2.4 Hz, 1H), 8.29 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 3.2 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.68 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 5.22 (t, J = 6.0 Hz, 1H) 3.76 (t, J = 6.0 Hz, 2H), 3.18 (q, J = 6.0, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

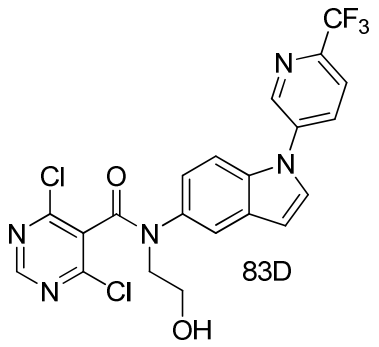
N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(1-(6-(trifluorometil)piridin-3-il)-1H-indol-5-il)pirimidina-5-carboxamida (83C):



83C

A una solución agitada, enfriada (0 °C) de producto del Ejemplo 83B (0.5 g, 1.148 mmoles) y TEA (0.8 mL, 5.74 mmoles) en DCM (10 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.362 g, 1.72 mmoles) en DCM (3 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x5 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.5 g, 57.5%) como un sólido amarillo pálido. ^{1}H RMN (400MHz, DMSO-d_6): δ 9.02 (d, J = 2.0 Hz, 1H), 8.75 (s, 1H), 8.31 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 3.6 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.28 (dd, J_1 = 1.2 Hz, J_2 = 8.8 Hz, 1H), 6.80 (d, J = 3.2 Hz, 1H), 4.01 (t, J = 4.4 Hz, 2H) 3.79 (t, J = 5.6 Hz, 2H), 0.8 (s, 9H), 0.04 (s, 6H).

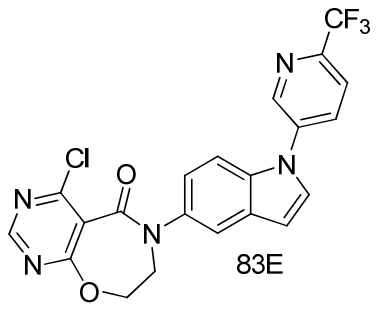
4,6-Dicloro-N-(2-hidroxietil)-N-(1-(6-(trifluorometil)piridin-3-il)-1H-indol-5-il)pirimidina-5-carboxamida (83D):



83D

Una solución del producto del Ejemplo 83C (0.5 g, 0.819 mmoles), en 15 mL de solución metanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 3 h. El metanol se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.3 g, 67.5%) como un sólido blanco, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400MHz, DMSO-d_6): δ 9.03 (d, J = 1.6 Hz, 1H), 8.74 (s, 1H), 8.33 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 4.87 (m, 1H) 3.95 (t, J = 6.4 Hz, 2H), 3.63 (m, 2H).

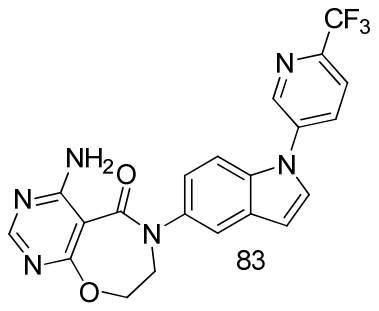
4-Cloro-6-(1-(6-(trifluorometil)piridin-3-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (83E):



83E

Un lodo del producto del Ejemplo 83D (0.3 g, 0.605 mmoles) y TEA (0.42 mL, 3.02 mmoles) en acetonitrilo (25 mL) se agitó a 80 ºC por 12 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.2 g, 69.4%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 9.12 (d, J = 2.4 Hz, 1H), 8.84 (s, 1H), 8.40 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 3.6 Hz, 1H), 7.80 (s, 1H), 7.77 (d, J = 2.4 Hz, 2H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 4.78 (t, J = 5.2 Hz, 2H), 4.19 (t, J = 4.8 Hz, 2H).

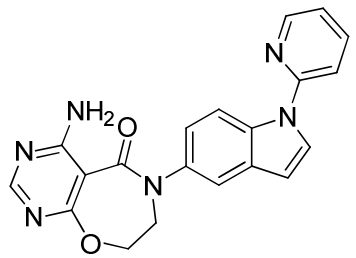
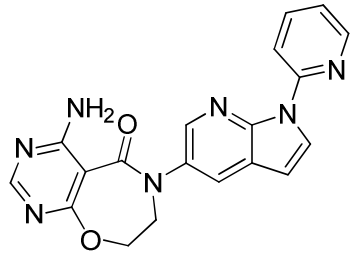
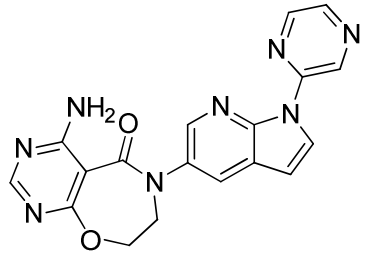
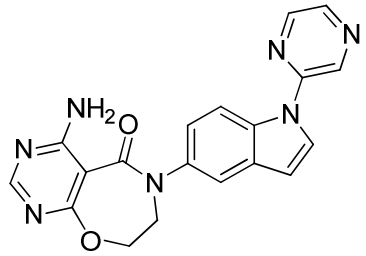
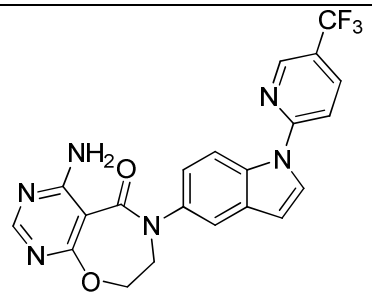
4-Amino-6-(1-(6-(trifluorometil)piridin-3-il)-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (83):

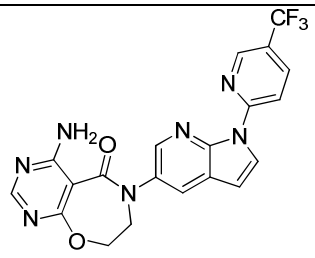
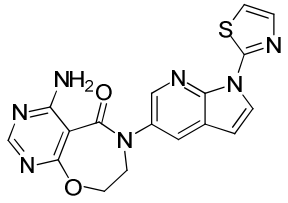
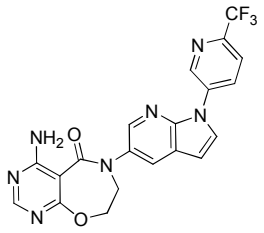


83

Una solución del producto del Ejemplo 83E (0.21 g, 0.457 mmoles) en amoniaco 0.5M en p-dioxano (10 mL) se agitó a temperatura ambiente por 4 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.135 g, 65.6%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 9.12 (d, J = 2.4 Hz, 1H), 8.40 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 8.18 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 3.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.64 (bs, 2H), 7.25 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 4.66 (t, J = 4.0 Hz, 2H), 4.02 (t, J = 5.2 Hz, 2H). ESI-MS m/z: 441 $(M+H)^+$; HPLC pureza: 97%.

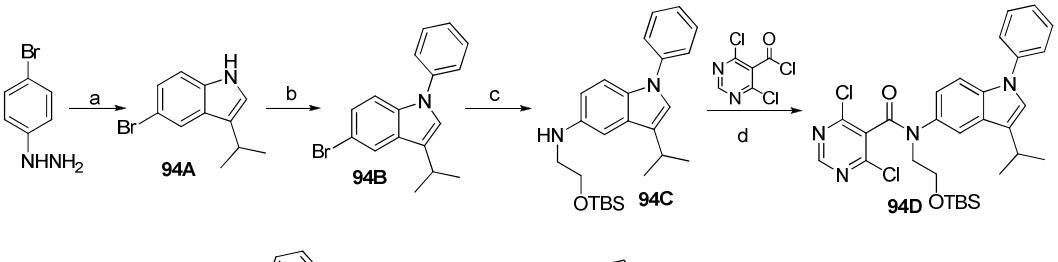
Los Ejemplos 84 – 93 se prepararon por procedimientos análogos a esos descritos en el Ejemplo 82 o Ejemplo 83 usando materiales de partida apropiadamente sustituidos.

Ej.	Estructura	Datos analíticos:	Masa/pureza
84		^{1}H RMN (400 MHz, DMSO-d_6): δ 8.59 (d, J = 3.2 Hz, 1H), 8.44 (d, J = 8.8 Hz, 1H), 8.19 (s, 1H), 8.11 (d, J = 3.2 Hz, 1H), 8.01 (dt, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64 (m, 3H), 7.33 (m, 1H), 7.26 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.79 (d, J = 3.6 Hz, 1H), 4.66 (t, J = 3.6 Hz, 2H), 4.03 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 373 $(M+H)^+$; HPLC pureza: 98%.
85		^{1}H RMN (400MHz, $CDCl_3$): δ 8.86 (d, J = 8.4 Hz, 1H), 8.50 (d, J = 3.6 Hz, 1H), 8.45 (d, J = 4.0 Hz, 1H), 8.32 (m, 2H), 8.20 (bs, 1H), 7.88 (dt, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 2H), 7.20 (m, 1H), 6.67 (d, J = 4.0 Hz, 1H), 5.70 (bs, 1H), 4.77 (t, J = 4.4 Hz, 2H), 4.10 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 374 $(M+H)^+$; HPLC pureza: 98%.
86		^{1}H RMN (300MHz, DMSO-d_6): δ 10.1 (d, J = 1.2 Hz, 1H), 8.64-8.6 (m, 2H), 8.49 (d, J = 2.4 Hz, 1H), 8.40 (d, J = 3.9 Hz, 1H), 8.20 (m, 2H), 7.68 (bs, 2H), 6.91 (d, J = 4.2 Hz, 1H), 4.71 (t, J = 3.6 Hz, 2H), 4.09 (t, J = 4.5 Hz, 2H).	ESI-MS m/z = 375 $(M+H)^+$; HPLC pureza: 98%.
87		^{1}H RMN (400MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.63 (s, 1H), 8.55 (d, J = 2.4 Hz, 1H), 8.48 (d, J = 8.8 Hz, 1H), 8.26 (d, J = 3.6 Hz, 1H), 8.19 (s, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.63 (bs, 2H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.87 (d, J = 3.6 Hz, 1H), 4.66 (t, J = 4.4 Hz, 2H), 4.03 (t, J = 5.2 Hz, 2H).	ESI-MS m/z = 374 $(M+H)^+$; HPLC pureza: 98%.
88		^{1}H RMN (300MHz, DMSO-d_6): δ 8.9 (s, 1H), 8.59 (d, J = 9.0 Hz, 1H), 8.39 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1H), 8.24 (d, J = 3.3 Hz, 1H), 8.19 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.63 (bs, 2H), 7.32 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 6.88 (d, J = 3.3 Hz, 1H), 4.66 (t, J = 4.2 Hz, 2H), 4.04 (t, J = 4.2 Hz, 2H).	ESI-MS m/z = 441 $(M+H)^+$; HPLC pureza: 94%.

89		^{1}H RMN (400MHz, DMSO-d_6): δ 9.18 (d, J = 8.8 Hz, 1H), 8.94 (s, 1H), 8.85 (s, 1H), 8.53 (m, 2H), 8.49 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 4.0 Hz, 1H), 4.82 (t, J = 4.4 Hz, 2H), 4.27 (t, J = 4.8 Hz, 2H).	ESI-MS m/z = 442 $(M+H)^+$; HPLC pureza: 98%.
90		^{1}H RMN (300MHz, DMSO-d_6): δ 8.52 (d, J = 2.1 Hz, 1H), 8.37 (d, J = 3.9 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H) 8.19 (s, 1H), 7.69 (m, 3H), 7.58 (d, J = 3.6 Hz, 1H), 6.90 (d, J = 3.6 Hz, 1H), 4.71 (t, J = 4.2 Hz, 2H), 4.09 (t, J = 4.2 Hz, 2H).	ESI-MS m/z = 380 $(M+H)^+$; HPLC pureza: 95%.
93		^{1}H RMN (300MHz, DMSO-d_6): δ 9.46 (d, J = 1.8 Hz, 1H), 8.8 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 8.42 (d, J = 2.1 Hz, 1H), 8.28 (d, J = 3.6 Hz, 1H), 8.19 (m, 2H), 8.14 (d, J = 8.4 Hz, 2H), 7.68 (bs, 2H), 6.91 (d, J = 3.9 Hz, 1H), 4.71 (t, J = 4.2 Hz, 2H), 4.07 (t, J = 4.2 Hz, 2H).	ESI-MS m/z: 442 $(M+H)^+$; Pureza por HPLC: 96%.

EJEMPLO 94

4-Amino-6-(3-isopropil-1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

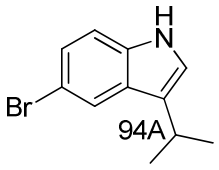


Reactivos y condiciones: a) Iso-valeraldehído, AcOH, 120 ºC, 3h b) Yodobenceno, CuBr, $Cu(OAc)_2$, K_2CO_3, NaOH, 140 ºC, 9h; c) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 120 ºC, 2.5h; d) DCM, Et_3N, RT, 1h; e) 3% HCl-MeOH, RT, 1h; f) CH_3CN, Et_3N, 80 ºC, 16h; g) NH_3, Dioxano, RT, 2h.

Procedimientos:

4-Amino-6-(3-isopropil-1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

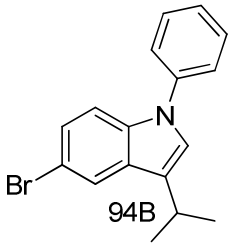
5-Bromo-3-isopropil-1H-indol (94A):



3-Metilbutanal (0.921 g, 10.69 mmoles) se agregó a una solución de (4-bromofenil)hidrazina (2 g, 10.69 mmoles) en ácido acético (100 mL) a 80 ºC, y la mezcla se agitó por 3 h a 120 ºC. La mezcla de reacción se concentró para obtener el residuo, y el residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con solución saturada de bicarbonato y salmuera, se secó sobre sulfato de sodio y se filtró. El filtrado se concentró al vacío y se purificó por cromatografía instantánea usando 2% acetato de etilo

en pet éter para producir el compuesto del título (1.1 g, 38.4%) como un aceite. ^{1}H RMN (400MHz, $CDCl_3$): δ 7.91 (bs, 1H), 7.76 (m, 1H), 7.25-7.20 (m, 2H), 6.95 (d, *J* = 2.4 Hz, 1H), 3.18-3.11 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 6H).

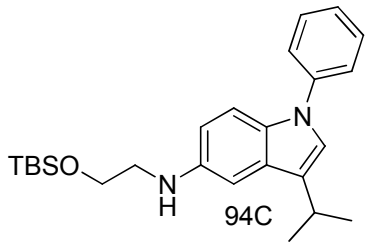
5-Bromo-3-isopropil-1-fenil-1H-indol (94B):



94B

Bromuro de cobre(I) (66 mg, 0.462 mmoles) se agregó a una solución de 94A (1.1 g, 4.62 mmoles) en yodo benceno (3.77g, 18.48 mmoles) seguido de carbonato de potasio (2.55 g, 18.48 mmoles), y la mezcla se agitó a 100 °C por 10 min. NaOH (150 mg, 3.75 mmoles) y acetato de cobre(II) (10 mg, 0.055 mmoles) se agregó a 140 °C, y la mezcla se agitó por 9 h. Los sólidos insolubles se filtraron, el filtrado se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio y se filtró. El filtrado se concentró al vacío y se purificó por cromatografía instantánea usando 8% acetato de etilo en hexano para producir el compuesto del título (1.0 g, 68.9%) como un aceite. ^{1}H RMN (300MHz, $CDCl_3$): δ 7.80 (d, *J* = 2.1 Hz, 1H), 7.54-7.42 (m , 5H), 7.4-7.28 (m, 2H), 7.21-7.08 (m, 2H), 3.19 (m, 1H), 1.38 (d, *J* = 6.9 Hz, 6H).

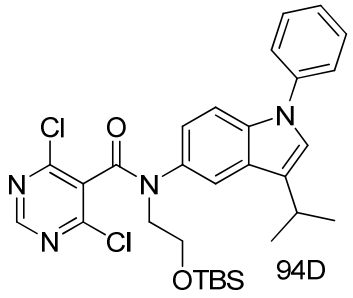
N-(2-(ter-Butildimetilsililoxi)etil)-3-isopropil-1-fenil-1H-indol-5-amina (94C):



94C

Una mezcla de producto del Ejemplo 94B (1 g, 3.18 mmoles), 2-(ter-butildimetilsililoxi)etanamina (0.558 g, 3.18 mmoles), carbonato de cesio (2.074 g, 6.36 mmoles), acetato de paladio (0.071 g, 0.318 mmoles) y X-PHOS (0.152 g, 0.318 mmoles) en Tolueno (20 mL) bajo Argón se calentó a reflujo a 120 °C por 2.5 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano para producir el compuesto del título (0.6 g, 46.1%) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.47-7.46 (m, 4H), 7.28 (m, 1H), 7.18 (m, 1H), 7.05 (s, 1H), 6.94 (m, 1H), 6.70 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 3.87 (t, *J* = 5.6 Hz, *2*H), 3.31 (t, *J = 5.* 6 Hz, 2H), 3.18 (m, 1H), 1.38 (d, *J* = 7.2 Hz, 6H), 0.92 (s, 9H), 0.09 (s, 6H).

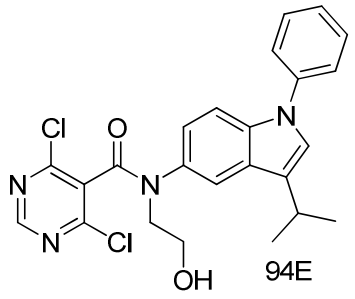
N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(3-isopropil-1-fenil-1H-indol-5-il)pirimidina-5-carboxamida (94D):



94D

A una solución agitada, enfriada (0 °C) de producto del Ejemplo 94C (0.6 g, 1.468 mmoles) y TEA (1.023 mL, 7.34 mmoles) en DCM (15 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.31 g, 1.468 mmoles) en DCM (5 mL). Después de 1 h, la mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano para producir el compuesto del título (0.4 g, 46.7%) como un jarabe.

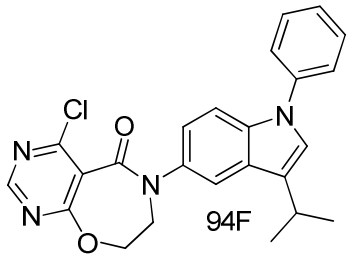
4,6-Dicloro-N-(2-hidroxietil)-N-(3-isopropil-1-fenil-1H-indol-5-il)pirimidina-5-carboxamida (94E):



94E

TBAF (0.358 g, 1.371 mmoles) se agregó a una solución de Ejemplo 94D (0.4 g, 0.685 mmoles) en THF (15 mL), y la mezcla se agitó a temperatura ambiente por 1 h. THF se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.2 g, 62.2%) como un sólido, que se llevó al paso siguiente sin purificación adicional.

4-Cloro-6-(3-isopropil-1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (94F):

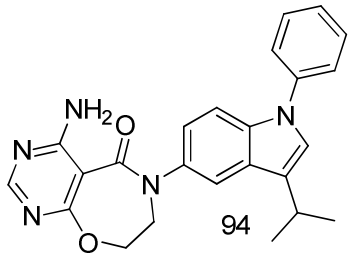


94F

Un lodo del producto del Ejemplo 94E (0.2 g, 0.426 mmoles) y

TEA (0.297 mL, 2.131 mmoles) en acetonitrilo (15 mL) se agitó a 80 °C por 16 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.1 g, 54.2%) como un sólido blanco. ^{1}H RMN (300MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.60-7.48 (m, 5H), 7.4-7.3 (m, 1H), 7.19-7.12 (m, 2H), 4.95 (t, *J* = 3.9 Hz, 1H), 4.02 (t, *J* = 4.5 Hz, *2*H), 3.25-3.21 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 6H).

4-Amino-6-(3-isopropil-1-fenil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (94):

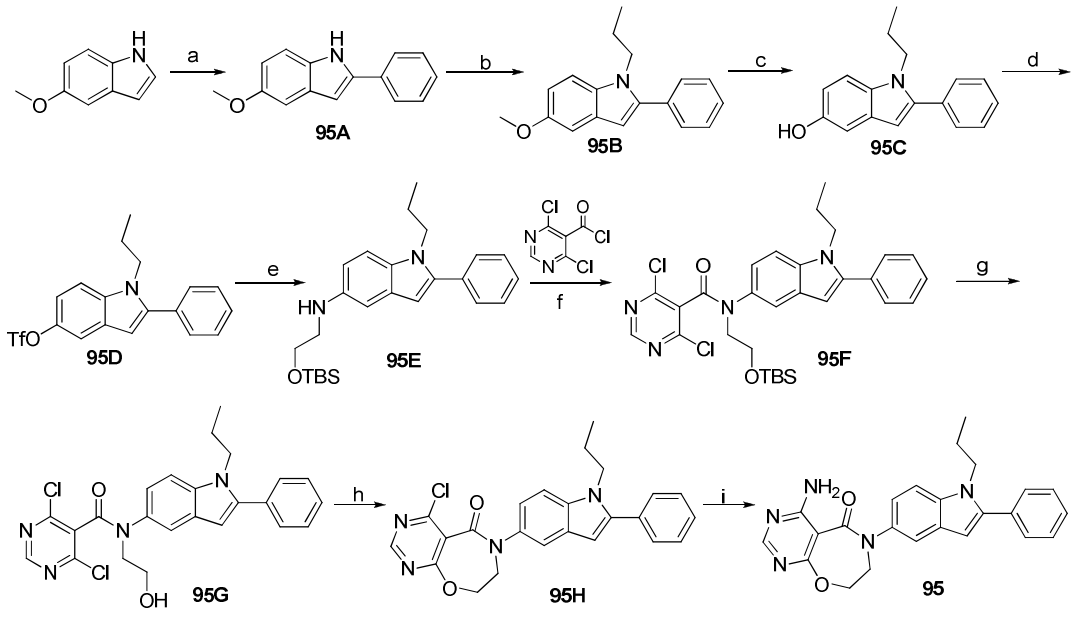


Una solución del producto del Ejemplo 94F (0.1 g, 0.231 mmoles) en amoniaco 0.5M en p-dioxano (10 mL) se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.06 g, 61.6%) como un sólido blanco. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.64 (d, *J* = 1.5 Hz, 1H), 7.66-7.54 (m, 6H), 7.47 (m, 1H), 7.38 (m, 1H), 7.14 (bs, 2H), 4.65 (t, *J* =3.9 Hz, 2H), 4.02

(t, *J* = 4.5 Hz, 2H), 3.20 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 6H); ESI-LC MS *m/z* = 414 $(M+H)^+$; HPLC pureza: 98.30%.

EJEMPLO 95

4-Amino-6-(2-fenil-1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

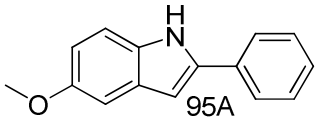


Reactivos y condiciones: a) Acido fenil boronico, AcOH, $Pd(OAc)_2$, acetato de cobre(II), 25 ºC 12h; b) Cs_2CO_3, DMF, 25 ºC, 12h; c) BBr_3, DCM, 0 ºC, 1h; d) anhídrido tríflico, Py, DCM, 0 ºC, 1h; e) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 110 ºC, 4h; f) Et_3N, DCM, 0 ºC, 1h; g) MeOH/HCl, 25 ºC, 2h; h) Et_3N, ACN, 70 ºC, 24h; i) NH_3 gas, Dioxano, 25 ºC, 3h.

Procedimientos:

4-Amino-6-(2-fenil-1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

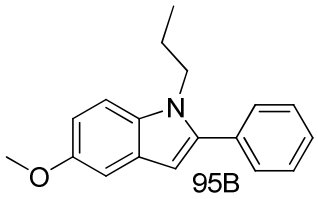
5-metoxi-2-fenil-1H-indol (95A):



95A

$Pd(OAc)_2$ (0.031 g, 0.136 mmoles) se agregó a una solución de 5-metoxi-1H-indol (0.2g, 1.359 mmoles) y ácido fenilboronico (0.249 g, 2.038 mmoles) en ácido acético (2 mL) seguido de acetato de cobre (II) (0.025 g, 0.138 mmoles), y la mezcla se agitó a 25 °C por 2 h bajo atmósfera de oxígeno. Los sólidos insolubles se filtraron, y filtrado se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano para producir el compuesto del título (0.08 g, 24%) como un sólido. ^{1}H RMN (400 MHz, DMSO-d_6): δ 11.3 (s, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.32-7.26 (m, 2H), 7.02 (d, J = 2.4 Hz 1H), 6.81 (d, J = 1.2 Hz, 1H), 6.74 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H) 3.78 (s ,3H).

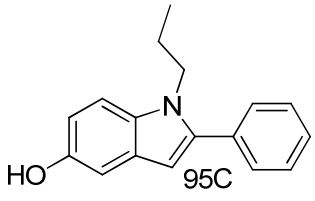
5-Metoxi-2-fenil-1-propil-1H-indol (95B):



95B

1-Bromopropano (0.248 g, 2.015 mmoles) se agregó a una solución de 95A (0.15 g, 0.672 mmoles) en DMF (5 mL) seguido de carbonato de cesio (0.657 g, 2.015 mmoles), y la mezcla se agitó a 25 ºC por 12 h. Los sólidos insolubles se filtraron, y filtrado se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 3% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.1 g, 56.1%) como un sólido. ^{1}H RMN (400MHz, DMSO-d_6): δ 7.54-7.5 (m, 4H), 7.46-7.39 (m, 2H), 7.06 (d, J = 2.0 Hz, 1H), 6.8 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.42 (s, 1H), 4.12 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 1.54 (m , 2H), 0.63 (t, J = 7.2 Hz).

2-fenil-1-propil-1H-indol-5-ol (95C):

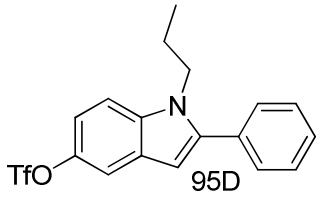


95C

BBr_3 (0.107 mL, 1.131 mmoles) se agregó a una solución de Ejemplo 95B (0.1g, 0.398 mmoles) en DCM (20 mL) a 0 ºC, y la mezcla se

agitó por 1 h. La mezcla de reacción se templó con solución saturada de bicarbonato y se extrajo con DCM (2x30 mL). La capa orgánica se separó, se lavó con agua y salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se trituró con dietil éter para producir el compuesto del título (0.05 g, 52.8%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO–d_6): δ 8.72 (s, 1H), 7.5 (m, 4H), 7.42 (m, 1H), 7.30 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 6.67 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.32 (s, 1H), 4.07 (t, J = 7.2 Hz, 2H), 1.53 (m, 2H), 0.64 (t, J = 7.2 Hz, 3H).

2-fenil-1-propil-1H-indol-5-il trifluorometanosulfonato (95D):

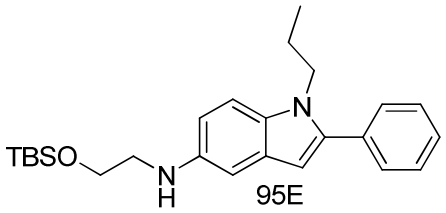


95D

Anhídrido tríflico (0.112 g, 0.398 mmoles) se agregó a una solución enfriada en hielo del producto del Ejemplo 95C (0.1 g, 0.398 mmoles) y piridina (0.048 mL, 0.597 mmoles) en diclorometano (20 mL), y la mezcla se agitó a 0 °C por 1 h. La mezcla de reacción se diluyó con diclorometano (10 mL) y se extrajo con solución acuosa saturada de NaCl (45 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y evaporó bajo presión reducida. El producto crudo se purificó por cromatografía instantánea usando 6% acetato de etilo en hexanos para dar el compuesto del título (0.08 g, 52.4 %) como un sólido. ^{1}H RMN (300MHz, DMSO-d_6): δ 7.73 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 2.7 Hz, 1H), 7.58-7.46 (m, 5H), 7.22 (dd, J_1 = 2.7 Hz, J_2 = 8.7 Hz,

1H), 6.65 (s, 1H), 4.20 (t, *J* = 6.9 Hz, 2H), 1.56 (m, 2H), 0.65 (t, *J* = 7.8 Hz, 3H).

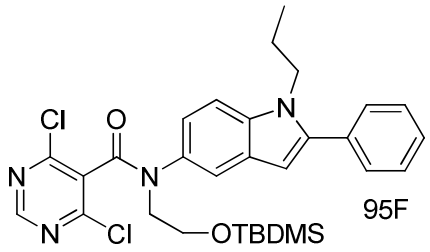
N-(2-(ter-Butildimetilsililoxi)etil)-2-fenil-1-propil-1H-indol-5-amina (95E):



95E

A mezcla de producto del Ejemplo 95D (0.2 g, 0.522 mmoles), 2-(ter-butildimetilsililoxi)etanamina (0.183 g, 1.043 mmoles), carbonato de cesio (0.510 g, 1.565 mmoles), acetato de paladio (0.012 g, 0.052 mmoles) y X-PHOS (0.0025 g, 0.052 mmoles) en Tolueno (20 mL) bajo Argón se calentó a reflujo a 111 ºC por 4 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 15% acetato de etilo en hexano para producir el compuesto del título (1.5 g, 53%) como un sólido. ^{1}H RMN (400MHz, DMSO-d_6): δ 7.50 (m, 4H), 7.4 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 1.6 Hz, 1H), 6.61 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.27 (s, 1H), 4.91 (t, *J* = 6.0 Hz, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.16 (q, *J* = 6.0 Hz, 2H), 1.52 (m, 2H), 0.87 (s, 9H), 0.63 (t, *J* = 7.2 Hz, 3H), 0.059 (s, 6H).

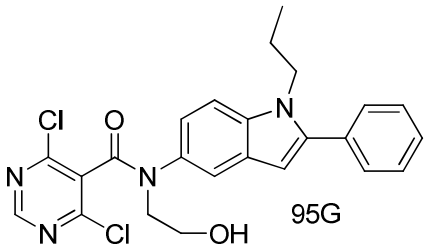
N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(2-fenil-1-propil-1H-indol-5-il)pirimidina-5-carboxamida (95F):



95F

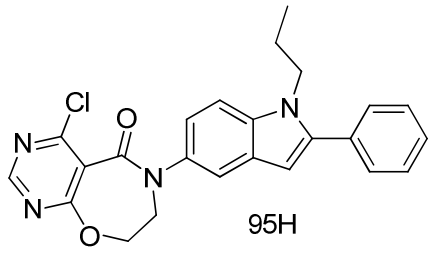
A una solución agitada, enfriada (0 °C) de producto del Ejemplo 95E (0.04 g, 0.98 mmoles) y TEA (0.041 mL, 0.294 mmoles) en DCM (10 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.030 g, 0.14 mmoles) en DCM (3 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x10 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 20% acetato de etilo en hexano como eluyente para producir el compuesto del título (0.031 g, 32.1%) como un sólido. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.74 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.54-7.44 (m, 6H), 7.18 (dd, J_1 = 2.0, J_2 = 8.8 Hz, 1H), 6.48 (s, 1H), 4.09 (t, J = 7.2 Hz, 2H), 3.99 (t, J = 6.0 Hz, 2H), 3.8 (t, J = 5.6 Hz, 2H), 1.46 (m, 2H), 0.85 (s, 9H), 0.59 (t, J = 7.2 Hz, 3H), 0.04 (s, 6H).

4,6-Dicloro-N-(2-hidroxietil)-N-(2-fenil-1-propil-1H-indol-5-il)pirimidina-5-carboxamida (95G):



Una solución del producto del Ejemplo 95F (0.35 g, 0.6 mmoles), en 20 mL de solución metanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 2 h. El metanol se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado solución y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.225 g, 76%) como un sólido, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.73 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.53-7.43 (m, 6H), 7.20 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.51 (s, 1H), 4.84 (t, J = 5.2 Hz, 1H), 4.09 (t, J = 7.6 Hz, 2H), 3.93 (t, J = 6.4 Hz, 2H), 3.63 (q, J = 6.0 Hz, 2H), 1.49 (m, 2H), 0.6 (t, J = 7.2 Hz, 3H).

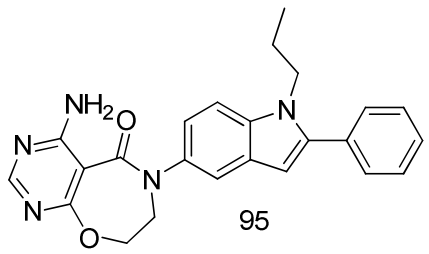
4-Cloro-6-(2-fenil-1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (95H):



95H

Un lodo del producto del Ejemplo 95G (0.225 g, 0.479 mmoles) y TEA (0.334 mL, 2.397 mmoles) en acetonitrilo (15 mL) se agitó a 80 °C por 16 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.15 g, 72.3%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.83 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.58-7.44 (m, 5H), 7.19 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.58 (s, 1H), 4.77 (t, J = 5.2 Hz, 2H), 4.22-4.15 (m, 4H), 1.58 (m, 2H), 0.66 (t, J = 7.6 Hz, 3H).

4-Amino-6-(2-fenil-1-propil-1H-indol-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (95):



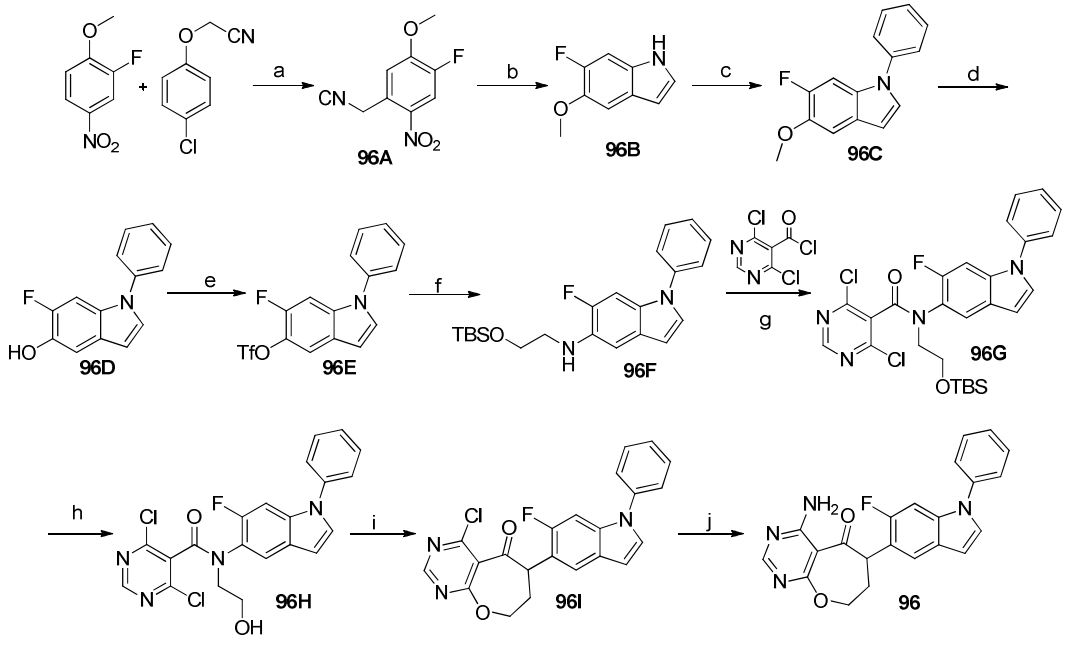
95

Una solución del producto del Ejemplo 95H (0.15 g, 0.346

mmoles) en amoniaco 0.5M en p-dioxano (20 mL) se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.105 g, 71.1%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.68-7.44 (m, 9H), 7.15 (d, J = 8.0 Hz, 1H), 6.55 (s, 1H), 4.65 (m, 2H), 4.19 (t, J = 6.8 Hz, 2H), 4.01 (m, 2H), 1.58 (m, 2H), 0.68 (t, J =7.6 Hz, 3H); ESI-MS m/z = 414.0 $(M+H)^+$; HPLC pureza: 97%.

EJEMPLO 96

4-Amino-6-(6-fluoro-1-fenil-1H-indol-5-il)-7,8-dihidrooxepino[2,3-d]pirimidin-5(6H)-ona

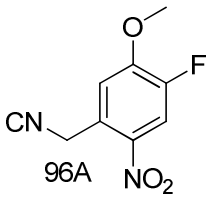


Reactivos y condiciones: a) K^{t}Obu, DMF, -20 ^{o}C, 1h; b) 10% Pd/C, Etanol, 27 ^{o}C, 3h; c) $Cu(OAc)_2$, CuBr, K_2CO_3, NaOH, DMF, 80 ^{o}C, 16h; d) Py/HCl, 180 ^{o}C, 4h; e) Tf_2O, Piridina, DCM, 0 ^{o}C, 0.5 h; f) $Pd(OAc)_2$, $NH_2(CH_2)_2OTBDMS$, Cs_2CO_3, X-PHOS, Tolueno, 100 ^{o}C, 4h; g) DCM, Et_3N, RT, 3h; h) 3% HCl-EtOH, RT, 1h; i) CH_3CN, Et_3N, 80 ^{o}C, 16h; j) NH_3, Dioxano, RT, 6h.

Procedimientos:

4-Amino-6-(6-fluoro-1-fenil-1H-indol-5-il)-7,8-dihidrooxepino[2,3-d]pirimidin-5(6H)-ona:

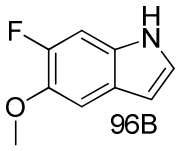
1-Fluoro-4-(isocianometil)-2-metoxi-5-nitrobenceno (96A):



t-butóxido de potasio (15.74 g, 140 mmoles) en DMF (50 mL) se agregó a una solución de 2-fluoro-1-metoxi-4-nitrobenceno (12 g, 70.1 mmoles) y 2-(4-clorofenoxi)acetonitrilo (11.75 g, 70.1 mmoles) en DMF (100 mL) a -20 ^{o}C. La mezcla de reacción se agitó por 1 h y luego se templó con agua. La capa acuosa se extrajo con acetato de etilo. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y

concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 3% acetato de etilo en hexano para producir el compuesto del título (3.6 g, 23.21%) como un sólido. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.05 (d, *J* = 10.84 Hz, 1H), 7.27-7.23 (m, 1H), 4.28 (s, 2H), 4.05 (s, 3H); ESI-MS *m/z* = 209 $(M-H)^-$; LCMS Pureza: 95%

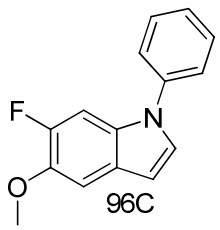
6-Fluoro-5-metoxi-1H-indol (96B):



96B

Paladio en carbono (1 g, 0.940 mmoles) se agregó a una solución de producto del Ejemplo 96A (3.5 g, 16.65 mmoles) en etanol (40 mL) bajo atmósfera de hidrógeno, y la mezcla se agitó por 4 h. Los sólidos insolubles se filtraron, y filtrado se concentró para producir el compuesto del título (2.2 g, 78%) como un sólido. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.05 (bs, 1H), 7.20-7.11 (m, 3H), 6.48 (d, *J* = 2.4 Hz, 1H), 3.95 (s, 3H).

6-Fluoro-5-metoxi-1-fenil-1H-indol (96C):

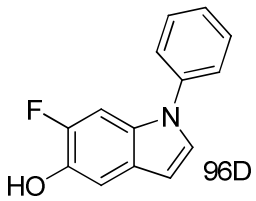


96C

Yodo benceno (1.729 g, 8.48 mmoles) se agregó a una solución

de producto del Ejemplo 96B (1.4 g, 8.48 mmoles) y bromuro de Cobre(I) (10.46 mg, 0.073 mmoles) en DMF (10 mL) seguido de carbonato de potasio (3.51 g, 25.4 mmoles), y la mezcla se agitó a 100 °C por 10 min. NaOH (210 mg, 5.25 mmoles) y acetato de cobre(II) (14 mg, 0.077 mmoles) se agregó, y la mezcla se agitó a 110 °C por 16 h. Los sólidos insolubles se filtraron, y filtrado se concentró. El residuo se dividió entre dietil éter y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano como eluyente para producir el compuesto del título (1.45 g, 67.4%) como un sólido blanco mate. ^{1}H RMN (300MHz, $CDCl_3$): δ 7.55-7.44 (m, 4H), 7.38-7.26 (m, 3H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 3.95 (s, 3H).

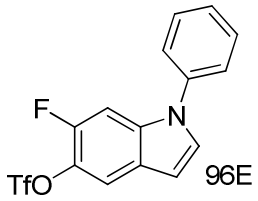
6-Fluoro-1-fenil-1H-indol-5-ol (96D):



Una mezcla de producto del Ejemplo 96C (1.1 g, 4.56 mmoles) y clorhidrato de piridina (0.527 g, 4.56 mmoles) se agitó a 160 °C en un tubo sellado por 6 h. La mezcla se disolvió en acetato de etilo, se lavó con agua y salmuera acuosa saturada, se secó sobre sulfato de sodio y se filtró. El filtrado se concentró al vacío y se purificó por cromatografía instantánea usando 12% acetato de etilo en hexano para producir el compuesto del título (0.37 g,

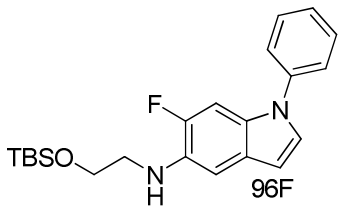
32.5%) como un sólido marrón pálido. ^{1}H RMN (400MHz, $CDCl_3$): δ 7.6 (d, *J* = 6.8 Hz, 1H), 7.58-7.53 (m, 2H), 7.48-7.34 (m, 5H), 6.7 (d, *J* = 3.6 Hz, 1H).

6-Fluoro-1-fenil-1H-indol-5-il trifluorometanosulfonato (96E):



Anhídrido tríflico (0.372 g, 2.2 mmoles) se agregó a una solución enfriada en hielo de producto del Ejemplo 96D (0.5 g, 2.2 mmoles) y piridina (0.087 mg, 1.1 mmoles) en diclorometano (10 mL), y la mezcla se agitó a temperatura ambiente por 1 h. La mezcla de reacción se diluyó con diclorometano (20 mL) y se extrajo con solución acuosa saturada de NaCl (15 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo presión reducida para producir el compuesto del título (0.7 g, 89%) como un aceite. ESI-MS *m/z* = 360 $(M+H)^+$; LCMS Pureza: 85%.

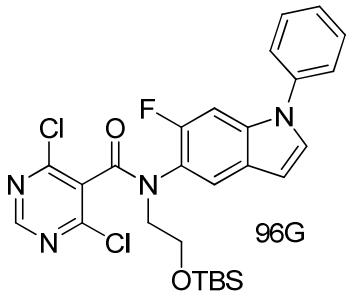
N-(2-(ter-Butildimetilsililoxi)etil)-6-fluoro-1-fenil-1H-indol-5-amina (96F):



Una mezcla de producto del Ejemplo 96E (0.1 g, 0.278 mmoles),

2-(*t*-butildimetilsililoxi)etanamina (0.048 g, 0.278 mmoles), carbonato de cesio (0.136 g, 0.417 mmoles), acetato de paladio (6.25 mg, 0.028 mmoles) y X-PHOS (13.27 mg, 0.028 mmoles) en tolueno (10 mL) bajo Argón se calentó a reflujo a 120 ºC por 2.5 h. La reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x5 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 10% acetato de etilo en hexano para producir el compuesto del título (0.03 g, 25%) como un sólido blanco mate. ^{1}H RMN (300MHz, $CDCl_3$): δ 7.6-7.5 (m, 5H), 7.4-7.25 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 3.0 Hz, 1H), 4.75 (m, 1H), 3.81 (t, *J* = 5.7 Hz, 2H), 3.25 (q, *J* = 5.7 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(6-fluoro-1-fenil-1H-indol-5-il)pirimidina-5-carboxamida (96G):

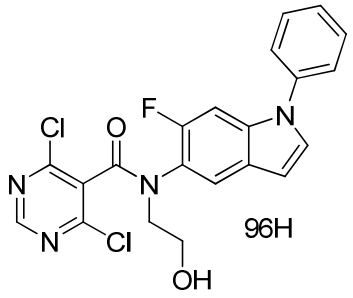


96G

A una solución agitada, enfriada (0 ºC) de producto del Ejemplo 96F(0.18 g, 0.468 mmoles) y TEA (0.065 mL, 0.468 mmoles) en DCM (8 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-

carbonilo (0.098 g, 0.468 mmoles) en DCM (2 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x5 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir un aceite. El residuo se purificó por cromatografía instantánea usando 20% acetato de etilo en hexano para producir el compuesto del título (100 mg, 38%) como un aceite amarillo pálido.

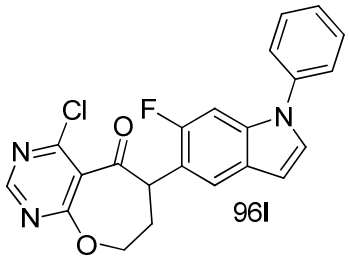
4,6-Dicloro-N-(6-fluoro-1-fenil-1H-indol-5-il)-N-(2-hidroxietil)pirimidina-5-carboxamida (96H):



96H

Una solución del producto del Ejemplo 96G (100 mg, 0.179 mmoles), en 10 mL de solución etanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de etanol) se agitó a temperatura ambiente por 1 h. El etanol se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.07 g, 77%) como un aceite, que se llevó al paso siguiente sin purificación adicional.

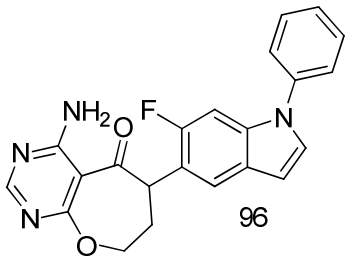
4-Cloro-6-(6-fluoro-1-fenil-1H-indol-5-il)-7,8-dihidrooxepino[2,3-d]pirimidin-5(6H)-ona (96I):



96I

Un lodo del producto del Ejemplo 96H (0.07 g, 0.157 mmoles) y TEA (0.022 mL, 0.157 mmoles) en acetonitrilo (8 mL) se agitó a 80 °C por 16 h. La mezcla de reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.067 g, 87%) como un sólido amarillo pálido. ^{1}H RMN (400MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.6-7.3 (m, 7H), 6.7 (d, J = 2.8 Hz, 1H), 4.84 (t, J = 4.4 Hz, 2H), 4.04 (t, J = 4.4 Hz, 2H).

4-Amino-6-(6-fluoro-1-fenil-1H-indol-5-il)-7,8-dihidrooxepino[2,3-d]pirimidin-5(6H)-ona (96):



96

Una solución del producto del Ejemplo 96I (0.06 g, 0.147 mmoles), en amoniaco 0.5M en p-dioxano (8 mL) se agitó a temperatura

ambiente por 1 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.03 g, 48.8%) como un sólido amarillo pálido. ^{1}H RMN (400MHz, DMSO-d_6): □□^{1}H RMN (400 MHz, DMSO-d_6): δ 8.19 (s, 1H), 7.76-7.56 (m, 7H), 7.5-7.4 (m, 3H), 6.76 (d, J = 2.8 Hz, 1H), 4.64 (t, J = 4.0 Hz, 2H), 4.0 (t, J = 4.0 Hz, 2H); ESI-MS m/z = 390 $(M+H)^+$; HPLC pureza: 93%.

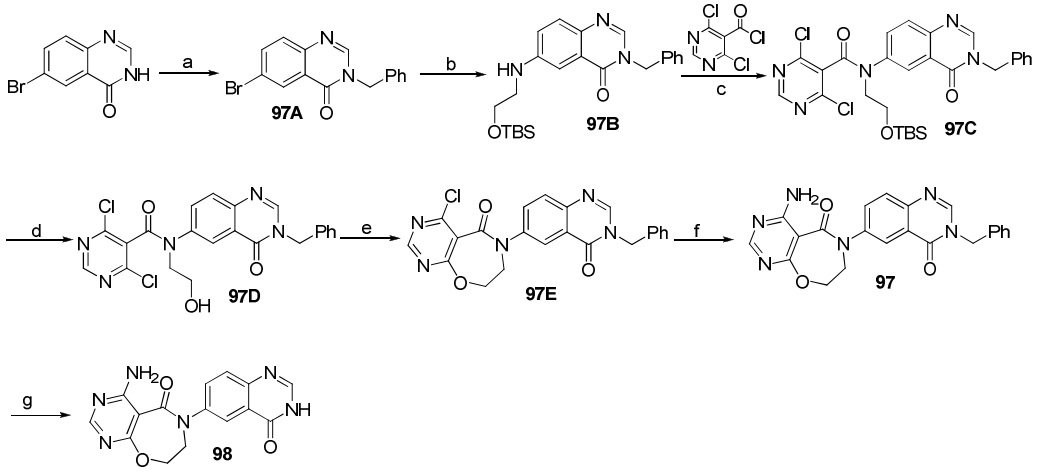
EJEMPLO 97

4-Amino-6-(3-bencil-4-oxo-3,4-dihidroquinazolin-6-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona

Y

EJEMPLO 98

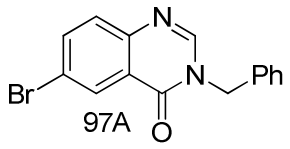
4-Amino-6-(4-oxo-3,4-dihidroquinazolin-6-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona



Reactivos y condiciones: a) bromuro de bencilo, NaH, DMF, 80 ^oC, 4h; b) $NH_2(CH_2)_2OTBDMS$, $Pd(OAc)_2$, Cs_2CO_3, X-PHOS, Tolueno, 110 ^oC, 16h; c) DCM, Et_3N, RT, 1h; d) 3% HCl-MeOH, RT, 1h; e) CH_3CN, Et_3N, 80 ^oC, 16h; f) NH_3, Dioxano, RT, 2h.

Procedimientos:

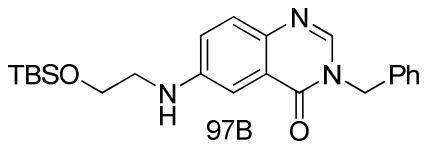
3-Bencil-6-bromoquinazolin-4(3H)-ona (97A):



97A

Bromuro de bencilo (0.264 mL, 2.22 mmoles) se agregó a una solución de 6-bromoquinazolin-4(3H)-ona (0.5 g, 2.22 mmoles) y NaH (0.08 g, 3.33 mmoles) en DMF (5 mL) a 0 ^oC. La mezcla de reacción se calentó a 80 ^oC por 4 h. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.4 g, 48.1%) como un sólido amarillo pálido. ^1H RMN (400MHz, $CDCl_3$): δ 8.46 (d, J = 1.6 Hz, 1H), 8.09 (s, 1H), 7.83 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.4-7.2 (m, 5H), 5.2 (s, 2H); ESI-MS m/z = 315 $(M+H)^+$; LCMS pureza: 84.2%

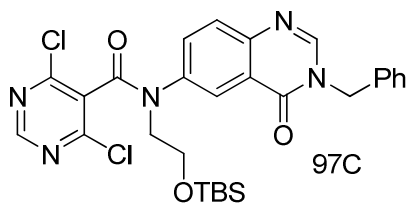
3-Bencil-6-(2-(ter-butildimetilsililoxi)etilamino)quinazolin-4(3H)-ona (97B):



97B

Una mezcla de producto del Ejemplo 97A (0.4 g, 1.269 mmoles), 2-(ter-butildimetilsililoxi)etanamina (0.267 g, 1.523 mmoles), carbonato de cesio (1.241 g, 3.81 mmoles), acetato de paladio (0.014 g, 0.063 mmoles) y X-PHOS (0.03 g, 0.063 mmoles) en Tolueno (10 mL) bajo Argón se calentó a reflujo a 110 °C por 16 h. La mezcla de reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró para obtener un aceite oscuro. El residuo se purificó por cromatografía instantánea usando 20% acetato de etilo en hexano para producir el compuesto del título (0.2 g, 31.9%) como un sólido blanco mate.

N-(3-Bencil-4-oxo-3,4-dihidroquinazolin-6-il)-N-(2-(ter-butildimetilsililoxi)etil)-4,6-dicloropirimidina-5-carboxamida (97C):

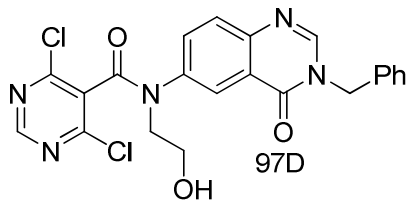


97C

A una solución agitada, enfriada (0 °C) de producto del Ejemplo 97B (1.2 g, 2.93 mmoles) y TEA (1.225 mL, 8.79 mmoles) en DCM (20 mL) se

agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (0.61 g, 2.92 mmoles) en DCM (5 mL) a -30 ºC. Después de 1 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x15 mL) y salmuera acuosa saturada, La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.9 g, 25.8%) como un sólido amarillo.

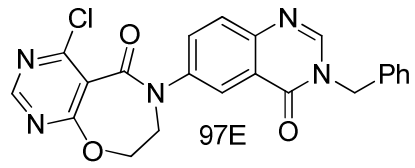
N-(3-Bencil-4-oxo-3,4-dihidroquinazolin-6-il)-4,6-dicloro-N-(2-hidroxietil)pirimidina-5-carboxamida (97D):



97D

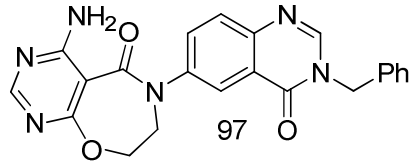
Una solución del producto del Ejemplo 97C (0.9 g, 1.54 mmoles), en 10 mL de solución metanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de metanol) se agitó a temperatura ambiente por 1 h. El metanol se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado solución y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.5 g, 38%) como un sólido, que se usó en el paso siguiente sin purificación adicional.

6-(3-Bencil-4-oxo-3,4-dihidroquinazolin-6-il)-4-cloro-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (97E):



Un lodo del producto del Ejemplo 97D (0.5 g, 1.063 mmoles) y TEA (0.445 g, 3.19 mmoles) en acetonitrilo (10 mL) se agitó a 80 ºC por 16 h. La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.2 g, 38.8%) como un sólido amarillo. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.84 (s, 1H), 8.63 (s, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.93 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 7.8 (d, J = 8.4 Hz, 1H), 7.4-7.2 (m, 5H), 5.23 (s, 2H), 4.77 (t, J = 4.5 Hz, 2H), 4.27 (t, J = 4.2 Hz, 2H).

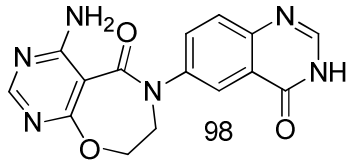
4-Amino-6-(3-bencil-4-oxo-3,4-dihidroquinazolin-6-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (97):



Una solución del producto del Ejemplo 97E (0.18 g, 0.415 mmoles) en amoniaco 0.5M en p-dioxano (10 mL) se agitó a temperatura ambiente por 5 h. La mezcla de reacción se concentró al vacío, se diluyó con

acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (0.14 g, 76%) como un sólido blanco. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.61 (s, 1H), 8.18 (s, 1H), 8.11 (d, J = 2.1 Hz, 1H), 7.87 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.67 (bs, 2H), 7.4-7.2 (m, 5H), 5.22 (s, 2H), 4.63 (t, J = 4.5 Hz, 2H), 4.08 (t, J = 4.2 Hz, 2H). ESI-MS m/z = 415 $(M+H)^+$; LCMS pureza: 93%.

4-Amino-6-(4-oxo-3,4-dihidroquinazolin-6-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (98):

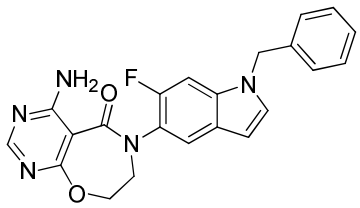


98

Pd/C (0.0514 g, 0.048 mmoles) se agregó a una solución de Ejemplo 97 (0.1 g, 0.241 mmoles) y formato de amonio (76 mg, 1.207 mmoles) en etanol (5 mL) a 25 °C. La mezcla de reacción se calentó a 80 °C por 16 h. Los sólidos insolubles se filtraron, y el filtrado se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 60% acetato de etilo en hexano para producir el compuesto del título (0.02 g, 23.51%) como un sólido. ^{1}H RMN (300MHz, DMSO-d_6): δ 12.4 (s, 1H), 8.18 (s, 1H), 8.12 (d, J = 3.0 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.83 (dd, J_1 = 1.8 Hz,

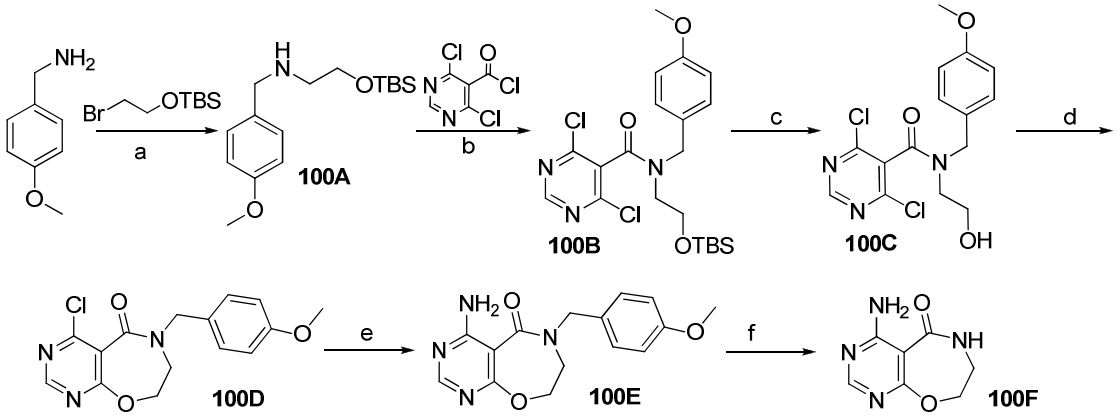
J_2 = 8.4 Hz, 1H), 7.75-7.65 (m, 3H), 4.64 (m, 2H), 4.08 (m, 2H); ESI-MS *m/z* = 325 $(M+H)^+$; LCMS pureza: 93%.

El Ejemplo 99 se preparó por los métodos descritos antes para el Ejemplo 96 o variaciones rutinarias de los mismos comenzando del sistema de anillo heterociclo sustituido con halo requerido.

Ej.	Estructura	Datos analíticos:	Masa/pureza
99		^{1}H RMN (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.51 (d, *J* = 6.8 Hz, 1H), 7.35-7.28 (m, 5H), 7.18 (d, *J* = 3.2 Hz, 1H), 7.15-7.07 (m, 3H), 6.55 (d, *J* = 3.2 Hz, 1H), 5.27 (s, 2H), 4.75 (t, *J* = 4.0 Hz, 2H), 3.99 (t, *J* = 4.8 Hz, 2H).	ESI-MS *m/z* = 404 $(M+H)^+$; HPLC pureza: 90.84%.

EJEMPLO 100

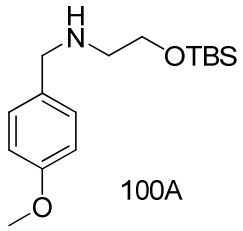
4-Amino-6-(5-propil-5H-pirrolo[3,2-d]pirimidin-2-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona



Reactivos y condiciones: a) $Br(CH_2)_2OTBDMS$, K_2CO_3, ACN, 80 ºC,16h; b) DCM, Et_3N, -78 ºC; c) 3% HCl-EtOH, RT, 1h; d) CH_3CN, Et_3N, 80 ºC, 16h; e) NH_3, Dioxano, RT, 2h, f) TFA, anisol, 90 ºC, 16h.

Procedimientos:

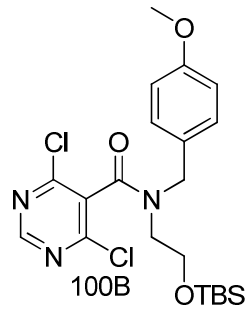
2-(ter-Butildimetilsililoxi)-N-(4-metoxibencil)etanamina (100A):



100A

(2-bromoetoxi)(ter-butil)dimetilsilan (20 g, 84 mmoles) se agregó a una solución de (4-metoxifenil) metanamina (11.47 g, 84 mmoles) en acetonitrilo (200 mL) seguido de K_2CO_3 (57.8 g, 418 mmoles), y la mezcla se agitó a 80 °C por 16 h. Los sólidos insolubles se filtraron, filtrado se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio y se filtró. El filtrado se concentró al vacío y se purificó por cromatografía instantánea usando 30% acetato de etilo en hexano para producir el compuesto del título (19 g, 77%) como un aceite. ^{1}H RMN (300 MHz, DMSO-d_6): δ 7.22 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 3.62 (m, 4H), 2.56 (t, *J* = 5.7 Hz, 2H), 2.5 (m, 1H), 0.85 (s, 9H), 0.02 (s, 6H).

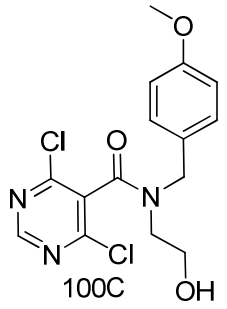
N-(2-(ter-Butildimetilsililoxi)etil)-4,6-dicloro-N-(4-metoxibencil)pirimidina-5-carboxamida (100B):



100B

A una solución agitada, enfriada (0 °C) de producto del Ejemplo 100A (7.66 g, 25.9 mmoles) y TEA (5.42 mL, 38.9 mmoles) en DCM (80 mL) se agregó por goteo una solución de cloruro de 4,6-dicloropirimidina-5-carbonilo (5.46 g, 25.90 mmoles) en DCM (10 mL). Después de 1 h, la reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua (2x60 mL) y salmuera acuosa saturada. La capa orgánica se se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (9.0 g, 48.4%) como un sólido amarillo pálido.

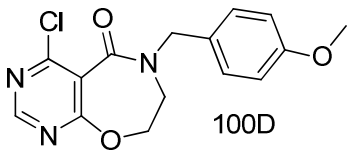
4,6-Dicloro-N-(2-hidroxietil)-N-(4-metoxibencil)pirimidina-5-carboxamida (100C):



100C

Una solución del producto del Ejemplo 100B (9 g, 9.13 mmoles) en 60 mL de solución etanólica de HCl (3 mL HCl acuoso concentrado en 97 mL de etanol) se agitó a temperatura ambiente por 2 h. El etanol se removió al vacío, el residuo se disolvió en acetato de etilo, y se lavó con bicarbonato de sodio acuoso saturado solución y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (4.5 g, 66%) como un sólido amarillo pálido, que se llevó al el paso siguiente sin purificación adicional.

4-Cloro-6-(4-metoxibencil)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (100D):

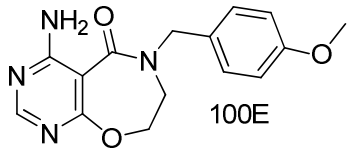


100D

Un lodo del producto del Ejemplo 100C (4.5 g, 12.63 mmoles) y TEA (8.8 mL, 63.2 mmoles) en acetonitrilo (60 mL) se agitó a 80 °C por 16 h.

La reacción se enfrió, concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (3 g, 74.3%) como un sólido blanco. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.77 (s, 1H), 7.3 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 4.68 (s, 2H), 4.41 (t, J = 4.8 Hz, 2H), 3.74 (s, 3H), 3.71 (t, J = 3.6 Hz, 2H).

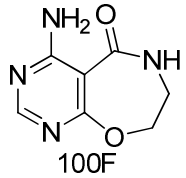
4-Amino-6-(4-metoxibencil)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (100E):



100E

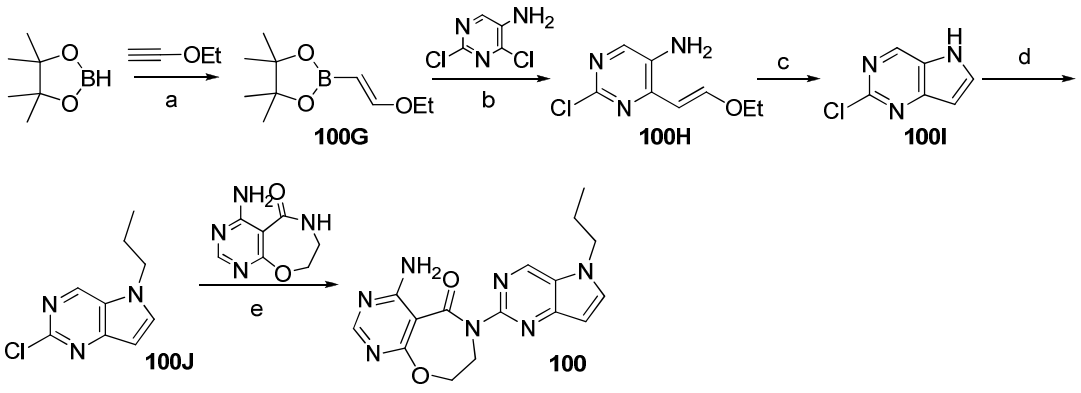
Una solución del producto del Ejemplo 100D (3 g, 9.38 mmoles) en amoniaco 0.5M en p-dioxano (30 mL) se agitó a temperatura ambiente por 3 h. La mezcla de reacción se concentró al vacío, se diluyó con acetato de etilo, y se lavó con agua y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (2.5 g, 77%) como un sólido blanco. ^{1}H RMN (300MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.63 (bs, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.65 (s, 2H), 4.31 (t, J = 4.2 Hz, 2H), 3.74 (s, 3H), 3.56 (t, J = 4.8 Hz, 2H).

4-Amino-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (100F):



100F

TFA (15 mL, 195 mmoles) se agregó a una solución de 100E (2.5 g, 8.32 mmoles) en anisol (1 mL, 9.15 mmoles) a 0 °C, y la mezcla se agitó por 2 h a 90 °C por 16 h en un tubo sellado. La mezcla de reacción se concentró para obtener el residuo y se trituró con 25 mL (50%) acetato de etilo en hexano para producir el compuesto del título (1.0 g, 66.7%) como un sólido blanco mate. ^{1}H RMN (400MHz, DMSO-d_6-D_2O): □ 8.26 (s, 1H), 4.57 (t, J = 3.9 Hz, 2H), 3.47 (t, J = 4.2 Hz, 2H).



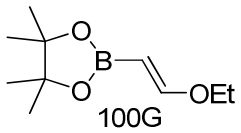
Reactivos y condiciones: a) cloruro de di(ciclopenta-2,4-dien-1-il)circonio(IV), CH_2Cl_2, RT, 16h, b) K_3PO_4 dibásico, $Pd(OAc)_2$,,diciclohexil(2',6'-dimetoxi-[1,1'-bifenil]-2-il)fosfina, ACN, agua, 80 °C, 16h, c), AcOH, 140 °C, 4h; d) bromuro de n-propilo, Cs_2CO_3, DMF, 25 °C, 4h,

e) K_3PO_4 dibásico, CuI, (1S,2S)-ciclohexano-1,2-diamina, 1,4-dioxano, 110 °C, 24h.

Procedimientos:

4-Amino-6-(5-propil-5H-pirrolo[3,2-d]pirimidin-2-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

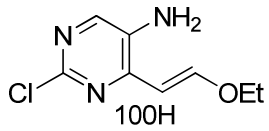
(E)-2-(2-Etoxivinil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (100G):



100G

Cloruro de di(ciclopenta-2,4-dien-1-il)circonio(IV) (0.685 g, 2.344 mmoles) se agregó a una solución de 4,4,5,5-tetrametil-1,3,2-dioxaborolano (5.0 g, 39.1 mmoles) en diclorometano (15 mL) seguido de etoxietino (3.01 g, 43.0 mmoles) a 0 °C, y la mezcla se agitó por 16 h a 25 °C. Los sólidos insolubles se filtraron, y filtrado se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío para producir el compuesto del título (6.04 g, 78.13%) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 14.0 Hz, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 3.84 (q, *J* = 7.2 Hz, 2H), 1.32-1.2 (m, 15H).

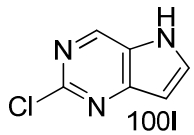
(E)-2-Cloro-4-(2-etoxivinil)pirimidin-5-amina (100H):



100H

Una mezcla de 2,4-dicloropirimidin-5-amina (2.0 g, 12.2 mmoles), producto del Ejemplo 100G (6.04 g, 30.5 mmoles), fosfato de potasio dibásico (5.31 g, 30.5 mmoles), acetato de paladio(II) (0.027 g, 0.122 mmoles) y diciclohexil-(2',6'-dimetoxi-[1,1'-bifenil]-2-il)fosfina (0.050 g, 0.122 mmoles) en acetonitrilo (30 mL) y agua (20 mL) bajo argón se calentó a reflujo a 80 °C por 16 h. La mezcla de reacción se enfrió, se diluyó con acetato de etilo, y se lavó con agua (2x30 mL) y salmuera acuosa saturada. La capa orgánica se secó sobre sulfato de sodio y se filtró. El filtrado se concentró y se purificó por cromatografía instantánea usando 30% acetato de etilo en hexano para producir el compuesto del título (0.3 g, 12.32%) como un aceite. ^{1}H RMN (300MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.85 (d, J = 11.7 Hz, 1H), 5.69 (d, J = 11.7 Hz, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.49 (bs, 2H), 1.37 (t, J = 7.5 Hz, 3H).

2-Cloro-5H-pirrolo[3,2-d]pirimidina (100I):

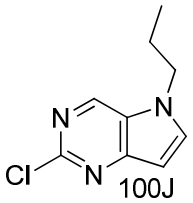


100I

Una solución del producto del Ejemplo 100H (0.3 g, 1.503 mmoles) en ácido acético (20 mL) se agitó a 140 °C por 4 h. El ácido acético

se removió al alto vacío, el residuo se destiló con tolueno para producir el compuesto del título (0.22 g, 88%) como un sólido amarillo, que se llevó al paso siguiente sin purificación adicional. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.76 (s, 1H), 8.68 (bs, 1H), 7.69 (t, J = 3.2 Hz, 1H), 6.72 (s, 1H).

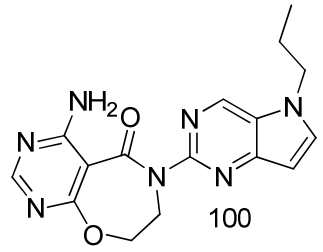
2-Cloro-5-propil-5H-pirrolo[3,2-d]pirimidina (100J):



100J

1-Bromopropano (132 mg, 1.074 mmoles) se agregó a una solución de producto del Ejemplo 100I (150 mg, 0.977 mmoles) en DMF (10 mL) seguido de carbonato de cesio (0.477 g, 1.074 mmoles), y la mezcla se agitó a 25 °C por 4 h. Los sólidos insolubles se filtraron, y el filtrado se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 5% acetato de etilo en hexano para producir el compuesto del título (0.15 g, 74.6%) como un jarabe color marrón. ^{1}H RMN (300MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.51 (d, J = 3.0 Hz, 1H), 6.62 (d, J = 2.7 Hz, 1H), 4.16 (t, J = 6.9 Hz, 2H), 1.91 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H).

4-Amino-6-(5-propil-5H-pirrolo[3,2-d]pirimidin-2-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (100):

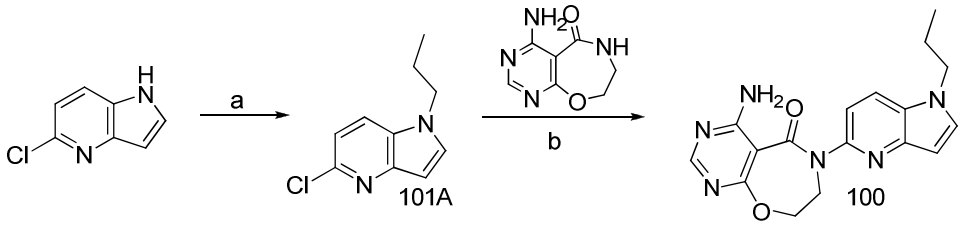


100

Una mezcla de producto del Ejemplo 100J (0.195 g, 1.0 mmoles), Ejemplo 100F (0.15 g, 0.833 mmoles), fosfato de potasio dibásico (0.29 g, 1.665 mmoles), CuI (15.86 mg, 0.083 mmoles) y trans (1S,2S)-N1,N2-dimetilciclohexano-1,2-diamina (0.023 g, 0.167 mmoles) en 1,4-dioxano (5 mL) bajo Argón se calentó a reflujo a 110 ºC por 24 h en un tubo sellado. La mezcla de reacción se diluyó con metanol, los sólidos insolubles se filtraron y el filtrado se concentró para obtener el residuo. El residuo se purificó por cromatografía instantánea usando 3% de metanol en acetato de etilo para producir el compuesto del título (0.02 g) como un sólido amarillo. ^{1}H RMN (400MHz, DMSO-d_6): δ 9.12 (s, 1H), 8.19 (s, 1H), 8.02 (d, J = 3.6 Hz, 1H), 7.69 (bs, 2H), 6.62 (d, J = 2.8 Hz, 1H), 4.61 (t, J = 4.4 Hz, 2H), 4.29 (t, J = 7.2 Hz, 2H), 4.15 (t, J = 4.8 Hz, 2H), 1.83 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ESI-MS *m/z* = 340.1 $(M+H)^{+-}$; LCMS Pureza: 96.2%.

EJEMPLO-101

4-Amino-6-(1-propil-1H-pirrolo[3,2-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona

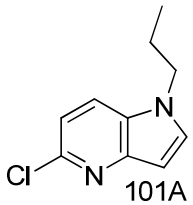


Reactivos y condiciones: a) bromuro de n-propilo, Cs_2CO_3, DMF, 70 °C, 0.5h; b) CuI, (1*S*,2*S*)-N,N'-Dimetil ciclohexil-1,2-diamina, K_3PO_4, Tolueno, 120 °C, 2.5h;

Procedimientos:

4-Amino-6-(1-propil-1H-pirrolo[3,2-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona:

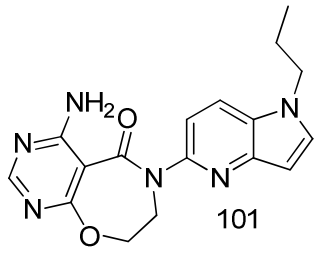
5-Cloro-1-propil-1H-pirrolo[3,2-b]piridina (101A):



1-Bromopropano (192 mg, 1.57 mmoles) se agregó a una solución de 2-cloro-5H-pirrolo[3,2-d]pirimidina (200 mg, 1.31 mmoles) en DMF

(15 mL) seguido de carbonato de cesio (0.855 g, 2.63 mmoles), y la mezcla se agitó a 70 °C por 0.5 h. Los sólidos insolubles se filtraron, el filtrado se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se separó, se lavó con salmuera, se secó sobre sulfato de sodio y se filtró. El filtrado se concentró al vacío para producir el compuesto del título (0.22 g, 86%) como un aceite. ^{1}H RMN (300MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.7 Hz, 1H), 7.34 (d, *J* = 3.3 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 4.07 (t , *J* = 6.9 Hz, 2H), 1.86 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H).

4-Amino-6-(1-propil-1H-pirrolo[3,2-b]piridin-5-il)-7,8-dihidropirimido[5,4-f][1,4]oxazepin-5(6H)-ona (101):

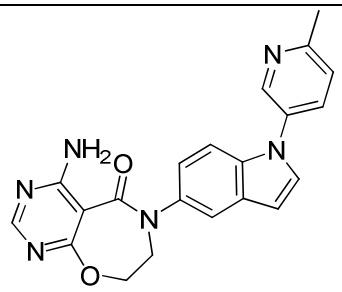
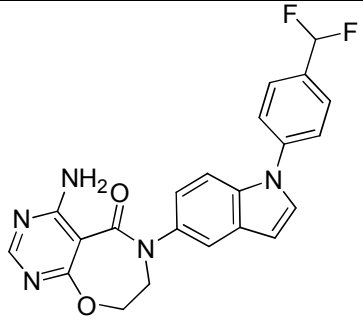
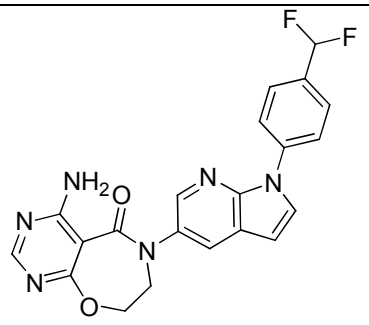


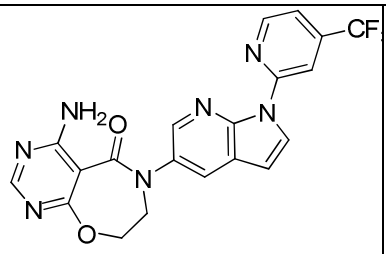
101

Una mezcla de producto del Ejemplo 101A (0.064 g, 0.33 mmoles), Ejemplo 100F (0.05 g, 0.27 mmoles), fosfato de potasio dibásico (0.117 g, 0.555 mmoles), CuI (0.005 g, 0.027 mmoles) y trans (1*S*,2*S*)-N1,N2-dimetilciclohexano-1,2-diamina (0.0076 g, 0.055 mmoles) en 1,4-dioxano (5 mL) bajo argón se calentó a reflujo a 110 °C por 24 h en un tubo sellado. La mezcla de reacción se diluyó con metanol, los sólidos insolubles se filtraron y el filtrado se concentró para obtener el residuo. El residuo se purificó por cromatografía instantánea usando 3% metanol en acetato de etilo para

producir el compuesto del título (0.005 g) como un sólido amarillo. ^{1}H RMN (400MHz, DMSO-d_6): δ 8.2 (bs, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 3.0 Hz, 1H), 7.60 (bs, 2H), 7.49 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 3.0 Hz, 1H), 4.63 (m, 2H), 4.26 (m, 2H), 4.19 (t, J = 6.9 Hz, 2H), 1.78 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 339.1 $(M+H)^+$;

Los Ejemplos 102 – 105 se prepararon por procedimientos análogos a esos descritos en Ejemplos 65, 66, 82 o 83 usando materiales de partida apropiadamente sustituidos.

Ej.	Estructura	Datos analíticos:	Masa/pureza
102		^{1}H RMN (400 MHz, DMSO-d_6): δ 8.71 (d, J = 2.4 Hz, 1H), 8.18 (s, 1H), 7.96 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.7-7.6 (m, 3H), 7.54 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.18 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 6.77 (d, J = 2.8 Hz, 1H), 4.65 (t, J = 4.0 Hz, 2H), 4.01 (t, J = 4.4 Hz, 2H), 2.57 (s, 3H).	ESI-MS m/z = 387 $(M+H)^+$; HPLC pureza: 97%.
103		^{1}H RMN (400MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.82-7.76 (m, 5H), 7.68-7.60 (m, 4H), 7.21 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.15 (t, J = 56 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 4.65 (t, J = 4.0 Hz, 2H), 4.02 (t, J = 4.4 Hz, 2H).	ESI-MS m/z = 422 $(M+H)^+$; LCMS pureza: 95%.
104		^{1}H RMN (300MHz, DMSO-d_6): δ 8.34 (d, J = 2.4 Hz, 1H), 8.17 (s, 1H), 8.15-8.06 (m, 4H), 7.75 (d, J = 8.7 Hz, 2H), 7.65 (bs, 2H), 7.10 (t, J = 55.8 Hz, 1H), 6.80 (d, J = 3.9 Hz, 1H), 4.68 (t, J = 3.9 Hz, 2H), 4.05 (t, J = 3.9 Hz, 2H).	ESI-MS m/z = 423 $(M+H)^+$; LCMS pureza: 97%.

105		^{1}H RMN (400MHz, DMSO-d_6): δ 9.37 (s, 1H), 8.82 (d, *J* = 4.8 Hz, 1H), 8.54-8.50 (m, 2H), 8.21 (d, *J* = 2.4 Hz, 1H), 8.19 (s, 1H), 7.72 (d, *J* = 5.2 Hz, 1H), 7.68 (bs, 2H), 6.88 (d, *J* = 4.0 Hz, 1H), 4.71 (t, *J* = 3.6 Hz, 2H), 4.09 (t, *J* = 4.4 Hz, 2H).	ESI-MS *m/z* = 442 $(M+H)^+$; LCMS pureza: 99%.

Ensayo biológico

El DGAT1 humano fue expresado en células de insecto Sf9 utilizando un sistema de expresión de baculovirus. Los microsomas se prepararon y usaron como enzima para la prueba de inhibición *in vitro* en cualquiera de dos formatos midiendo la producción de coenzima A o producto de tridecanoilglicerol, respectivamente. Todos los pasos se realizaron a 21-23°C. Todos los datos de la inhibición de DGAT1 por los compuestos de prueba se recolectaron bajo condiciones donde la formación de producto fue lineal con el tiempo de reacción.

Para la inhibición de formación de producto de CoA, los compuestos de prueba fueron preparados en 100% de DMSO, diluido 100 veces en búfer de ensayo, y 10 uL añadido a placas de media área de 96 pozos (Greiner 675076). Un volumen igual (10 uL) de enzima 3X en búfer se agregó y los componentes se incubaron por 30 minutos de incubación pre-reacción para permitir a la enzima y compuestos de prueba lograr el equilibrio de unión. La mezcla de enzima 3X contuvo 30 uM de ácido {4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}acético para los pozos de control completamente inhibidos. Algunos ensayos fueron

realizados con inclusión de didecanoilglicerol en la incubación pre-reacción del compuesto de prueba y enzima. Las reacciones de DGAT (30 uL) fueron iniciadas con la adición de 10 uL de solución de sustrato de 3X. Las condiciones finales de reacción consistieron de 20 mM HEPES pH 7.5, 2 mM $MgCl_2$, 1 mM CHAPS, 50 uM didecanoilglicerol, 3 uM decanoil-CoA, 1 ug/mL proteína microsomal, y 1% DMSO. Después de 60 minutos de incubación de reacción, las reacciones se detuvieron y el producto de CoA derivatizado con 30 uL de búfer conteniendo 10 uM de ácido {4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}ácido y 50 uM de 7-dietilamino-3-(4'-maleimidilfenil)-4-metilcoumarina (CPM). La fluorescencia se midió usando un lector Envision a Ex 405 nm/Em 480 nm aproximadamente 30 minutos después de ña adición de la solución final. La inhibición se normalizó a los controless que contenían DMSO o 10 uM de ácido {4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}acético. Las IC_{50} se ajustaron usando GraphPad Prism como una respuesta de dosis sigmoidea.

Para la inhibición de la formación de producto de triacilglicerol, las reacciones de 11 uL se corrieron en un Polyplate-384 (PerkinElmer6007300) blanco comenzando con una incubación de 30 minutos pre-reacción de 5 uL de 2.2X enzima y 1 uL de 100% DMSO que contenia el compuesto de prueba o compuesto de control, ácido {4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}acético. Algunos ensayos fueron realizados con inclusión de didecanoilglicerol en la incubación pre-reacción de los compuestos de prueba y enzima. Las reacciones fueron

iniciadas después de 30 minutos de incubación pre-reacción vía adición de 5 uL de sustrato 2.2X. Las condiciones finales de reacción consistieron de 50 mM HEPES pH 7.5, 2 mM $MgCl_2$, 1 mM CHAPS, 25 uM didecanoilglicerol, 0.5 uM decanoil-CoA, 0.3 nCi/uL [^{14}C]-decanoil-CoA o 0.5 nCi/uL [^{3}H]-decanoil-CoA, 0.05-4 ug/mL proteína microsomal, y 1% DMSO. Después de 60 minutos de incubación de reacción, las reacciones se detuvieron con 40 uL de 45% isopropanol y 50 mM de carbonato de sodio en agua y se mezcló. La extracción del producto de tridecanoilglicerol se efectuó vía adición de 30 uL de Microscint-E (Perkin Elmer) y 2 horas de incubación (sellado). Las placas se leyeron en un lector de Microplaca Microbeta. La inhibición se normalizó a los controles que contenían DMSO o 10 uM de ácido {4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}acético. Las IC_{50} se ajustaron usando GraphPad Prism como una respuesta de dosis sigmoidea.

Datos biológicos

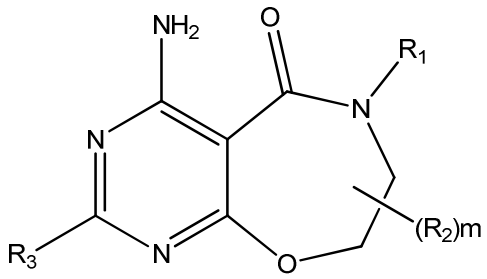
Los compuestos ejemplificados de la invención presente son inhibidores de DGAT1. Todos los compuestos excepto el Ejemplo 101 se probaron en uno o más ensayos de DGAT descritos antes y se encontró que fueron inhibidores de DGAT1 con IC_{50} < 10 uM o inhibición >50% a 10 uM. Los datos para algunos ejemplos específicos probados en la fluorescencia de DGAT1 humana (CPM) o ensayos de extracción de lípidos (LE) se enlistan a continuación.

Ej.	Ensayo de hDGAT1 CPM CI_{50} (nM)	Ensayo de hDGAT1 LE IC_{50} (nM)
3	371.6	
6	85.8	
10	42.0	
11	6.3	
12	16.3	
33		23.3
34	25.7	
59	49.5	
60		14.8
63		2.3
64		8.8
65		3.9
66	42.5	
68	2.8	
72		9.3
74		4.5
76	2.5	
78	7.3	
80		3.6
81		2.1
82	20.5	
83	40.0	
87	55.1	
94	872.5	
95	10.1	
96		7.3
97		200.8
98		623.0

NOVEDAD DE LA INVENCIÓN

REIVINDICACIONES

1. Un compuesto de la Fórmula (I):

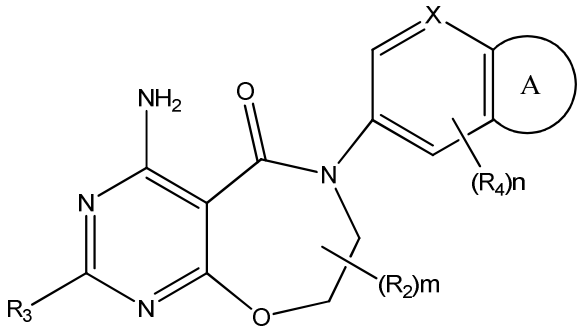


(I)

en donde R_1 es un sistema de anillo bicíclico que contiene 9 a 11 miembros del anillo incluyendo 1 a 4 heteroátomos, en donde dicho sistema de anillo bicíclico puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -$C(O)R_a$, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4, en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido; cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi de C_1-C_4; y m es 0-2; o una sal farmacéuticamente aceptable del mismo.

2. El compuesto de conformidad con la reivindicación 1,

caracterizado además porque está representado por la Fórmula (I)(A)



(I)(A)

en donde A es un anillo heterocíclico de 5 o 6 miembros, que puede contener 0 a 3 dobles enlaces y puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -C(O)R_a, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4, en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido; cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi de C_1-C_4; R_4 es halo o alcoxi; X es N o CH; y m es 0-2; n es 0-2; o una sal farmacéuticamente aceptable del mismo.

3. El compuesto de conformidad con la reivindicación 2, caracterizado además porque A es un anillo heterocíclico de 5 miembros, que puede contener 0-2 dobles enlaces y puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -

$C(O)R_a$, $-SO_2R_a$, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4, en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido; cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi de C_1-C_4; R_4 es halo o alcoxi; X es N o CH; y m es 0-2; n es 0-2; o una sal farmacéuticamente aceptable del mismo.

4. El compuesto de conformidad con la reivindicación 2, caracterizado además porque A es un anillo heterocíclico de 6 miembros, que puede contener 0-3 dobles enlaces y puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -$C(O)R_a$, $-SO_2R_a$, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4, en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido; cada R_2 y R_3 es independientemente hidrógeno, alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido, halo, hidroxilo, amida, ácido carboxílico o alcoxi de C_1-C_4; R_4 es halo o alcoxi; X es N o CH; y m es 0-2; n es 0-2; o una sal farmacéuticamente aceptable del mismo.

5. El compuesto de conformidad con cualquiera de las reivindicaciones 2 a 4, caracterizado además porque m es 0; n es 0; R_3 es hidrógeno; y X es N; o una sal farmacéuticamente aceptable del mismo.

6. El compuesto de conformidad con cualquiera de las

reivindicaciones 2 a 4, caracterizado además porque m es 0; n es 0; R_3 es hidrógeno; y X es CH; o una sal farmacéuticamente aceptable del mismo.

7. El compuesto de conformidad con la reivindicación 1, caracterizado además porque m es 0; R_3 es hidrógeno; R_1 es un sistema de anillo bicíclico seleccionado de grupo que consiste en tetrahidroisoquinolinilo, tetrahidroquinolinilo, indolilo, dihidroindolilo, indazolilo, dihidroindazolilo, benzotiofenilo, benzodiazolilo, dihidrobenzodiazolilo, benzimidazolilo, indolinilo, benzotriazolilo, pirrolopiridinilo, benzotiazolilo, benzofuranilo, dihidroquinazolinilo, y pirrolopirimidinilo; en donde dicho sistema de anillo bicíclico puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo, amida, ácido carboxílico, -C(O)R_a, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4, en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido; o una sal farmacéuticamente aceptable del mismo.

8. El compuesto de conformidad con la reivindicación 7, caracterizado además porque m es 0; R_3 es hidrógeno; R_1 es un sistema de anillo bicíclico seleccionado del grupo que consiste en tetrahidroisoquinolinilo, tetrahidroquinolinilo, indolilo, dihidroindolilo, indazolilo, dihidroindazolilo, y pirrolopiridinilo; en donde dicho sistema de anillo bicíclico puede estar sustituido por 1 a 3 grupos seleccionados del grupo que consiste en alquilo de C_1-C_6, alquilo de C_1-C_6sustituido, cicloalquilo de C_3-C_7, halo, hidroxilo, oxo,

amida, ácido carboxílico, -C(O)R_a, -SO_2R_a, arilalquilo, -(alquilo de C_1-C_3)ariloxi, arilo, heteroarilo y alcoxi de C_1-C_4, en donde cada R_a es independientemente alquilo de C_1-C_6, alquilo de C_1-C_6 sustituido o cicloalquilo de C_3-C_7no sustituido; o una sal farmacéuticamente aceptable del mismo.

9. El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 7.

10. Un método para tratar obesidad que comprende administrar a un humano necesitado del mismo una cantidad efectiva de un compuesto de cualquiera de las reivindicaciones anteriores.

11. Una composición farmacéutica que comprende un compuesto de cualquiera de las reivindicaciones 1 a 7 y un portador farmacéuticamente aceptable.

RESUMEN DE LA INVENCIÓN

Esta invención se refiere a compuestos novedosos que son inhibidores de la acil coenzimaA: diacilglicerol aciltransferasa 1 (DGAT-1), a composiciones farmacéuticas que los contienen, a procedimientos para su preparación, y a su uso en terapia para la prevención o tratamiento de enfermedades relacionadas a la disfunción de DGAT-1 o donde la modulación de la actividad de DGAT-1 puede tener un beneficio terapéutico incluyendo pero no limitado a obesidad, trastornos relacionados con la obesidad, hipertrigliceridemia, hiperlipoproteinemia, cilomicronemia, dislipidemia, esteatohepatitis no alcohólica, diabetes, resistancia a insulina, síndrome metabólico, virus de la infección de hepatitis C y acné u otros trastornos de la piel.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

PENG, Tony, W.
GlaxoSmithKline
Corporate Intellectual Property, UW2220
709 Swedeland Road, P.O. Box 1539
King of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
06 March 2013 (06.03.2013)

Applicant's or agent's file reference
PU64642

IMPORTANT NOTIFICATION

International application No.
PCT/US2012/038523

International filing date *(day/month/year)*
18 May 2012 (18.05.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
GLAXOSMITHKLINE LLC
One Franklin Plaza
200 North 16th Street
Philadelphia, PA 19102
United States of America

State of Nationality: US
State of Residence: US
Telephone No.: 610-270-4918
Facsimile No.: 610-270-5090
E-mail address: us_cipkop@gsk.com

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.: 610-270-5030
Facsimile No.: 610-270-5090
E-mail address: us_cipkop@gsk.com
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 80

Authorized officer
Campin Helene
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PU64642	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2012/038523	International filing date *(day/month/year)* 18 May 2012	(Earliest) Priority Date *(day/month/year)* 20 May 2011
Applicant GLAXOSMITHKLINE LLC		

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.

☐ 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:

   ☒ 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**,

   ☒ 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**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038523

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-11
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038523

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 498/04 (2012.01)
USPC - 540/490
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)
IPC(8) - A61K 31/519, 31/553; C07D 267/02, 498/04 (2012.01)
USPC - 514/211.05, 211.06, 211.07; 540/490, 491

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)
PatBase, Orbit, STN, PubChem Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0036425 A1 (DOW et al) 05 February 2009 (05.02.2009) entire document	1-8
A	US 2010/0204119 A1 (ASPNES et al) 12 August 2010 (12.08.2010) entire document	1-8
A	US 2010/0273768 A1 (DEWDNEY et al) 28 October 2010 (28.10.2010) entire document	1-8
A	US 2010/0210622 A1 (BAELL et al) 19 August 2010 (19.08.2010) entire document	1-8

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2012	10 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774