SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-074857- -00000-0000

Fecha: 2011-06-15 17:29:08 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 892

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO" INVENTARIO

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 11-074857

54. **TÍTULO** COMPUESTOS DE CARBAZOL CARBOXAMIDA UTILES COMO INHIBIDORES DE CINASA

51. **CLASIFICACIÓN INTERNACIONAL**

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

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS

74. **APODERADO** ALVARO CORREA ORDOÑEZ

19-07-2011

22. **BOGOTÁ, D.C.,** JULIO 15, 2011

(FORMA P-10)

PETIT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-074857- -00000-0000
Fecha: 2011-06-15 17:29:08 Dep. 2020 DIR.NUEVASCR
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Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) **SOLICITUD DE :**

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

(2) SOLICITANTE (71)

Nombre: BRISTOL-MYERS SQUIBB COMPANY

Dirección: Route 206 & Province Line Road Princeton, NJ 08543-4000, US

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 5

Teléfono: 6341500 Fax: 3762211

E-Mail: alvaro.correa@bakermckenzie.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 Usaquén TP 20281

(4) INVENTOR (ES) (72)

Nombre: LIU, Qingjie; BATT, Douglas G.; DELUCCA, George V.; SHI, Qing; TEBBEN, Andrew J.

Dirección: c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US); c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US); c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US); c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US); Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543 (US)

Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)

(5) PCT (85)

Solicitud Internacional No. PCT/US2009/068415 Fecha 17.12.2009

Publicación Internacional No. WO2010/080481 Fecha 15.07.2010

(6) Título (54) COMPUESTOS DE CARBAZOL CARBOXAMIDA UTILES COMO INHIBIDORES DE CINASA

(7) Clasificación Internacional (51) C07D 209; C07D 401/04; C07D 401/06; C07D 401/12; C07D 401/14; C07D 403/04; C07D; 403/06; C07D 403/10; C07D 403/12; C07D 403/14; C07D 405/12; C07D 417/04; C07D 417/10; A61K 31/403; A61P 37/00

(8) Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	19/12/2008	61/139,047

(9) Comprobante de pago No. 11-0051000 – 11-0042527 – 11-0050919 – 11-0046178 **Fecha** 27-05-11 – 05-05-11 – 16-05-11

(10) ANEXOS

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

(11) FIGURA CARATERISTICA

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

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

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

2011/008

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0051000

Bogotá D.C., Mayo 27 de 2011 - 07:32:04

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325074234	26/05/2011	64.920.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr UNDITARIO	Vr CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____
******

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-074857- -00000-0000

Fecha: 2011-06-15 17:29:08 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 892

2011/006 4

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0042527

Bogotá D.C., Mayo 05 de 2011 - 07:17:18

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	444391496	04/05/2011	78.375.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	8.000.00	8.000.00
				$8.000.00

SON: **OCHO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-074857- -00000-0000

Fecha: 2011-06-15 17:29:08 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 892

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0050919

Bogotá D.C., Mayo 27 de 2011 - 07:32:04

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325074234	26/05/2011	64.920.000.00

*** Conceptos Pagados ***

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

SON: **CATORCE MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-074857- -00000-0000
Fecha: 2011-06-15 17:29:08 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 892

2011/007

6

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0046178

Bogotá D.C., Mayo 16 de 2011 - 07:37:16

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	182258694	13/05/2011	56.320.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-074857- -00000-0000

Fecha: 2011-06-15 17:29:08 Dep. 2020 DIR.NUEVASCR
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Industria y Comercio

SUPERINTENDENCIA

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

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

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

(51) Clasificación Internacional: C07D 209; C07D 401/04; C07D 401/06; C07D 401/12; C07D 401/14; C07D 403/04; C07D; 403/06; C07D 403/10; C07D 403/12; C07D 403/14; C07D 405/12; C07D 417/04; C07D 417/10; A61K 31/403; A61P 37/00

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

(72) Inventor(es): LIU, Qingjie; BATT, Douglas G.; DELUCCA, George V.; SHI, Qing; TEBBEN, Andrew J.

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	61/139,047	19/12/2008	US

(85) Fecha inicio fase nacional: 19-07-2011

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 17-12-2009
No. de solicitud: PCT/US2009/068415

(87) Publicación internacional
Fecha: 15.07.2010
N° publicación: WO2010/080481

(54) Titulo: COMPUESTOS DE CARBAZOL CARBOXAMIDA UTILES COMO INHIBIDORES DE CINASA

Industria y Comercio

SUPERINTENDENCIA

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

SUPERINTENDENCIA PATENTE DE INVENCION ____ PCT _X_ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ____

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

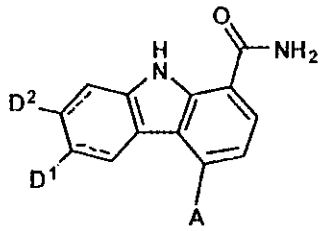
(51) Clasificación Internacional: C07D 209; C07D 401/04; C07D 401/06; C07D 401/12; C07D 401/14; C07D 403/04; C07D; 403/06; C07D 403/10; C07D 403/12; C07D 403/14; C07D 405/12; C07D 417/04; C07D 417/10; A61K 31/403; A61P 37/00

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

(72) Inventor(es): LIU, Qingjie; BATT, Douglas G.; DELUCCA, George V.; SHI, Qing; TEBBEN, Andrew J.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/139,047	19/12/2008	US



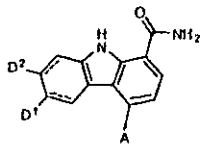
(85) Fecha límite inicio fase nacional: 19-07-2011

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 17-12-2009
No. de solicitud: PCT/US2009/068415

(87) Publicación internacional:
Fecha: 15.07.2010
No. Publicación: WO2010/080481

(54) Titulo: COMPUESTOS DE CARBAZOL CARBOXAMIDA UTILES COMO INHIBIDORES DE CINASA

(57) Resumen: Los compuestos que tienen la fórmula (I), y sus enantiómeros y diastereómeros y sus sales farmacéuticamente aceptables,



son útiles como moduladores de cinasa, incluyendo la modulación de Btk.

CONTINUA AL RESPALDO ...

Industria y Comercio
SUPERINTENDENCIA

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

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) *No.* 61/139,047 32) *Fecha* 19/12/2008 (33) *País* US

(51) Int Cl: C07D 209; C07D 401/04; C07D 401/06; C07D 401/12; C07D 401/14; C07D 403/04; C07D; 403/06; C07D 403/10; C07D 403/12; C07D 403/14; C07D 405/12; C07D 417/04; C07D 417/10; A61K 31/403; A61P 37/00

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

(72) Inventor(es) LIU, Qingjie; BATT, Douglas G.; DELUCCA, George V.; SHI, Qing; TEBBEN, Andrew J.

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

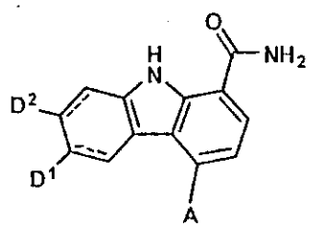
(85) Fecha límite inicio fase nacional: 19-07-2011

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 17-12-2009
No. de PCT/US2009/068415

(87) Publicación internacional
Fecha: 15.07.2010
N° publicación: WO2010/080481

(54) Título: COMPUESTOS DE CARBAZOL CARBOXAMIDA UTILES COMO INHIBIDORES DE CINASA

Reivindicación(es): 1. Un compuesto caracterizado porque tiene la formula (I):



(I)

o una de sus sales, en la que

las líneas discontinuas son ya sea enlaces simples o bien enlaces dobles;

A es halo, carbociclo C_{3-10} sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B;

B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-N(C(=O)O-R^1)_2$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$ o $-NR^{11}-R^1$;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^{1a}, alquinilo C_{2-6} sustituido con 0-3 R^{1a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{1a}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a};

R^{1a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ sustituido con 0-1 R^a;...

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 July 2010 (15.07.2010)

PCT

(10) International Publication Number
WO 2010/080481 A1

(51) International Patent Classification:
C07D 209/88 (2006.01) *C07D 403/12* (2006.01)
C07D 401/04 (2006.01) *C07D 403/14* (2006.01)
C07D 401/06 (2006.01) *C07D 405/12* (2006.01)
C07D 401/12 (2006.01) *C07D 417/04* (2006.01)
C07D 401/14 (2006.01) *C07D 417/10* (2006.01)
C07D 403/04 (2006.01) *A61K 31/403* (2006.01)
C07D 403/06 (2006.01) *A61P 37/00* (2006.01)
C07D 403/10 (2006.01)

(21) International Application Number:
PCT/US2009/068415

(22) International Filing Date:
17 December 2009 (17.12.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/139,047 19 December 2008 (19.12.2008) US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LIU, Qingjie** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **BATT, Douglas G.** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **DELUCCA, George V.** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **SHI, Qing** [CA/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **TEBBEN, Andrew J.** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US).

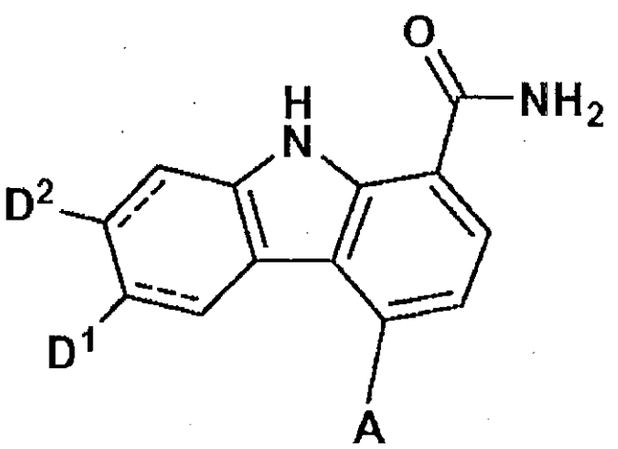
(74) Agents: **VANATTEN, Mary K.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

(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, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

[Continued on next page]

(54) Title: CARBAZOLE CARBOXAMIDE COMPOUNDS USEFUL AS KINASE INHIBITORS

(57) Abstract: Compounds having the formula (I), and enantiomers, and diastereomers, pharmaceutically-acceptable salts, thereof, Formula (I) are useful as kinase modulators, including Btk modulation.



(I)

WO 2010/080481 A1

WO 2010/080481 A1

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

CARBAZOLE CARBOXAMIDE COMPOUNDS USEFUL AS KINASE INHIBITORS

This application claims the benefit of U.S. Provisional Application Serial Number 61/139,047filed December 19, 2008.

FIELD OF THE INVENTION

[0001] This invention relates to fused carbazole carboxamide compounds useful as kinase inhibitors, including the modulation of Bruton's tyrosine kinase (Btk) and other Tec family kinases such as Itk. Provided herein are fused heterocyclic compounds, compositions comprising such compounds, and methods of their use. The invention further pertains to pharmaceutical compositions containing at least one compound according to the invention that are useful for the treatment of conditions related to kinase modulation and methods of inhibiting the activity of kinases, including Btk and other Tec family kinases such as Itk, in a mammal.

BACKGROUND OF THE INVENTION

[0002] Protein kinases, the largest family of human enzymes, encompass well over 500 proteins. Btk is a member of the Tec family of tyrosine kinases, and is a regulator of early B-cell development, as well as mature B-cell activation, signaling and survival.

[0003] B-cell signaling through the B-cell receptor (BCR) leads to a wide range of biological outputs, which in turn depend on the developmental stage of the B-cell. The magnitude and duration of BCR signals must be precisely regulated. Aberrant BCR-mediated signaling can cause disregulated B-cell activation and/or the formation of pathogenic auto-antibodies leading to multiple autoimmune and/or inflammatory diseases. Mutation of Btk in humans results in X-linked agammaglobulinaemia (XLA). This disease is associated with the impaired maturation of B-cells, diminished immunoglobulin production, compromised T-cell-independent immune responses and marked attenuation of the sustained calcium signal upon BCR stimulation.

[0004] Evidence for the role of Btk in allergic disorders and/or autoimmune disease and/or inflammatory disease has been established in Btk-deficient mouse

models. For example, in standard murine preclinical models of systemic lupus erythematosus (SLE), Btk deficiency has been shown to result in a marked amelioration of disease progression. Moreover, Btk deficient mice are also resistant to developing collagen-induced arthritis and are less susceptible to Staphylococcus-induced arthritis.

[0005] A large body of evidence supports the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Protein-based therapeutics (such as Rituxan) developed to deplete B-cells, represent an important approach to the treatment of a number of autoimmune and/or inflammatory diseases. Because of Btk's role in B-cell activation, inhibitors of Btk can be useful as inhibitors of B-cell mediated pathogenic activity (such as autoantibody production).

[0006] Btk is also expressed in mast cells and monocytes and has been shown to be important for the function of these cells. For example, Btk deficiency in mice is associated with impaired IgE-mediated mast cell activation (marked diminution of TNF-alpha and other inflammatory cytokine release), and Btk deficiency in humans is associated with greatly reduced TNF-alpha production by activated monocytes.

[0007] Thus, inhibition of Btk activity can be useful for the treatment of allergic disorders and/or autoimmune and/or inflammatory diseases including, but not limited to: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, multiple sclerosis (MS), transplant rejection, type I diabetes, membranous nephritis, inflammatory bowel disease, autoimmune hemolytic anemia, autoimmune thyroiditis, cold and warm agglutinin diseases, Evan's syndrome, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), sarcoidosis, Sjögren's syndrome, peripheral neuropathies (e.g., Guillain-Barre syndrome), pemphigus vulgaris, and asthma.

[0008] In addition, Btk has been reported to play a role in controlling B-cell survival in certain B-cell cancers. For example, Btk has been shown to be important for the survival of BCR-Abl-positive B-cell acute lymphoblastic leukemia cells. Thus inhibition of Btk activity can be useful for the treatment of B-cell lymphoma and leukemia.

[0009] In view of the numerous conditions that are contemplated to benefit by treatment involving modulation of protein kinases, it is immediately apparent that

new compounds capable of modulating protein kinases such as Btk and methods of using these compounds should provide substantial therapeutic benefits to a wide variety of patients.

[0010] Inhibitors of protein kinases are widely sought and a number of publications report compounds effective in modulating protein kinases. For example, patent publications WO 2005/047290, WO 2005/014599, WO 2005/005429, WO 2006/099075, WO 2006/053121, and US 2006/0183746 disclose certain imidazopyrazine compounds that are said to inhibit protein kinase activity, including Btk activity. Patent publication WO 2008/033858 discloses methods of inhibiting Btk activity with various Btk binding chemical compounds. Patent publication US 2006/0084650 discloses that fused heterocyclic compounds exemplified by imidazopyrimidines and pyrrolotriazines may be used as protein kinase inhibitors. In addition, certain imidazopyridazine and imidazotriazine compounds are disclosed in WO 2007/038314 (published April 5, 2007) and WO 2008/0045536 (published February 21, 2008), both of which are assigned to the present assignee.

[0011] The present invention relates to a new class of substituted fused heterocyclic compounds found to be effective inhibitors of protein kinases including Btk and other Tec family kinases such as Itk.

SUMMARY OF THE INVENTION

[0012] Modulators of kinase activity which may generally be described as substituted carbazoles, tetrahydrocarbazoles, and related compounds are provided herein.

[0013] The invention is directed to compounds of Formula I that which are useful as inhibitors of BTK, and are useful for the treatment of proliferative diseases, allergic diseases, autoimmune diseases and inflammatory diseases, or stereoisomers, tautomers, pharmaceutically acceptable slats, solvates or prodrugs thereof.

[0014] The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

[0015] The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds

of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

[0016] The present invention also provides a method for inhibition of BTK comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

[0017] The present invention also provides a method for treating proliferative diseases, allergic diseases, autoimmune diseases and inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

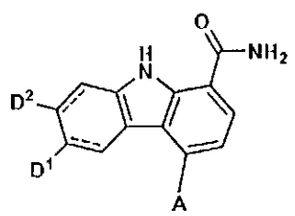
[0018] The present invention also provides the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for use in therapy.

[0019] The present invention also provides the use of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for the manufacture of a medicament for the treatment of cancers.

[0020] These and other features of the invention will be set forth in the expanded form as the disclosure continues.

DETAILED DESCRIPTION OF THE EMBODIMENTS OF THE INVENTION

[0021] Provided herein is at least one chemical entity chosen from compounds of formula (I):



(I)

or an enantiomer, a diastereomer, a prodrug, a salt, or a pharmaceutically-acceptable salt thereof, wherein

the dashed lines are either single or double bonds;

A is halo, C_{3-10} carbocycle substituted with 0-3 B, C_{6-10} mono- or bicyclic aryl substituted with 0-3 B, a 5-14 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 B, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 B;

B is R^1, halogen, cyano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-N(C(=O)O-R^1)_2$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{1a}, C_{2-6} alkynyl substituted with 0-3 R^{1a}, C_{3-10} cycloalkyl substituted with 0-3 R^{1a}, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

one of D^1 and D^2 is D and the other is H or halo;

D is $-R^2$, halogen, $-(C(R^{11})_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-S(=O)-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, $-NR^{11}-R^2$, $-C(=O)NR^{11}-O-R^2$, $-OC(=O)O-R^2$, $-O^1C(=O)-R^2$, or CH=N-OH;

with the proviso that A is not halo when D is $-C(=O)O-R^2$,

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, C_{2-6} alkynyl substituted with 0-3 R^{2a}, C_{3-10} cycloalkyl substituted with 0-3 R^{2a}, C_{6-10} aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing

1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a};

R^{2a} is hydrogen, C=O, F, Cl, Br, OCF_3, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a;

R^{11} is independently hydrogen or C_{1-4} alkyl substituted with 0-1 R^f, CH_2-phenyl, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

alternatively, R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or 4-(C_{1-6} alkyl)piperazinyl;

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, alternatively two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula $-O-(CH_2)_n-O-$, or $-O-CF_2-O-$, wherein n is selected from 1 or 2;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d,.C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-1 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CH2)_rC(O)R^e$, $-NR^eR^e$, $-NR^eC(O)OR^e$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

R^f is hydrogen, halo, NH_2, OH, or OCH_3 ;

r is 0, 1, 2, 3, or 4; and

p is 0, 1, or 2.

[0022] In another embodiment, there is provided a compound of formula I, wherein

the dashed lines are either single or double bonds;

A is halo, C_{3-10} cycloalkyl substituted with 0-3 B, C_{6-10} mono- or bicyclic aryl substituted with 0-3 B, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 B, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 B;

B is R^1, halogen, cyano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{1a}, C_{2-6} alkynyl substituted with 0-3 R^{1a}, C_{3-10} cycloalkyl substituted with 0-3 R^{1a}, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

one of D^1 and D^2 is D and the other is H;

D is $-R^2$, halogen, $-(C(R^{11})_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, or $-NR^{11}-R^2$;

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, C_{2-6} alkynyl substituted with 0-3 R^{2a}, C_{6-10} aryl substituted with 0-3 R^{2a},

a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a};

R^{2a} is hydrogen, C=O, F, Cl, Br, OCF_3, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

R^{11} is independently hydrogen or C_{1-4} alkyl;

alternatively, R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or 4-(C_{1-6} alkyl)piperazinyl;

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, alternatively two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula $-O-(CH_2)_n-O-$, or $-O-CF_2-O-$, wherein n is selected from 1 or 2;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CH2)_rC(O)R^b$, $-NR^eR^e$, $-NR^eC(O)OR^e$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

r is 0, 1, 2, 3, or 4; and

p is 0, 1, or 2.

[0023] In another embodiment, there is provided a compound of formula I, wherein

D is a $-R^2$, $-(CH_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-S(=O)-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, or $-NR^{11}-R^2$;

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, $-C_{6-10}$ aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a};

R^{2a} is hydrogen, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, OR^b, SR^b, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, wherein the carbocycle is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

r is 0, 1, or 2.

[0024] In another embodiment, there is provided a compound of formula I, wherein

A is halo, C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B;

B is R^1, halogen, cyano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}.

[0025] In another embodiment, there is provided a compound of formula I, wherein

R^2 is hydrogen, C_{2-6} alkyl substituted with 0-3 R^{2a}, C_{6-10} aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N,

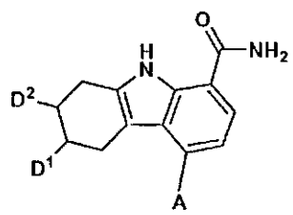
O, and S, substituted with 0-3 R^{2a}, wherein the heterocyclyl is pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heteroaryl is pyridinyl, quinolinyl, isoquinolinyl, or thiazolyl.

[0026] In another embodiment, there is provided a compound of formula I, wherein

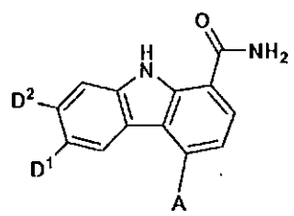
A is C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heterocyclyl is pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heteroaryl is pyridinyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, imidazolyl, pyrazolyl, or thiazolyl;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, wherein the heterocyclyl is pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a} wherein the heteroaryl is pyridinyl or thiazolyl.

[0027] In another embodiment, there is provided a compound of formula I, wherein the compound of formula I is a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt thereof.



(Ia)



(Ib).

[0028] In another embodiment, there is provided a compound of formula I, wherein

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-(CH_2)_r$-3-6 membered carbocycle, or $-(CH_2)_r$-5-7 membered heterocycle

comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein the heterocycle is pyrrolidinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, morpholinyl, thiamorpholinyl, triazolyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, benzopyranyl, benzofuryl, benzisothiazolyl, benzisoxazolyl, benzodiazinyl, or benzofurazanyl;

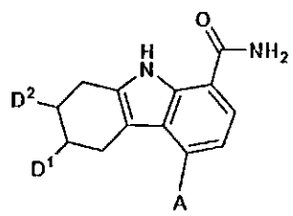
R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

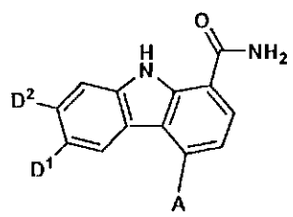
R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO2, $-OR^c$, -C(O)Rb, $-NR^eR^e$, $-NR^cC(O)OR^c$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

[0029] In another embodiment, there is provided a compound of formula I, wherein a compound of formula (I) is (Ia) or (Ib)



(Ia)



(Ib)

A is C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, wherein the aryl group is phenyl or naphthyl; a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heterocyclyl group is pyrrolidinyl or piperidinyl; or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heteroaryl group is pyridinyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, imidazolyl, pyrazolyl or thiazolyl;

B is R^1, halogen, $-C(=O)O-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$;

R^1 is hydrogen, trifluoromethyl, C_{1-4} alkyl substituted with 0-1 R^{1a}, phenyl substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, wherein the heteroaryl is pyridyl or thiazolyl;

One of D^1 and D^2 is D and the other is hydrogen;

D is R^2, $-C(=O)-R^2$, $-C(=O)NR^{11}R^2$, $NR^{11}C(=O)R^2$, $NR^{11}C(=O)NR^{11}-R^2$, $NR^{11}S(=O)_2-R^2$, or $-NR^{11}-R^2$;

R^2 is hydrogen, C_{2-6} alkyl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a} where the heterocyclyl is pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl;

R^{2a} is C_{1-4} alkyl, wherein the alkyl is methyl, ethyl, propyl, i-propyl, butyl, and t-butyl, substituted with 0-1 R^a.

[0030] In another embodiment, there is provided a compound of formula I, wherein

D is a $-R^2$, $-(CH_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, or $-NR^{11}-R^2$;

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, C_{3-10} cycloalkyl substituted with 0-3 R^{2a}, $-C_{6-10}$ aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a};

R^{2a} is hydrogen, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, OR^b, SR^b, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, wherein the carbocycle is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a;

r is 0, 1, or 2.

[0031] In another embodiment, there is provided a compound of formula I, wherein

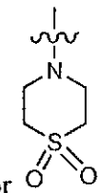
A is halo, C_{3-10} carbocycle substituted with 0-3 B C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, a 5-14 membered heterocyclyl containing 1-4 heteroatoms

selected from N, O, and S, substituted with 0-3 -B, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B;

B is R^1, halogen, cyano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}.

[0032] In another embodiment, there is provided a compound of formula I, wherein

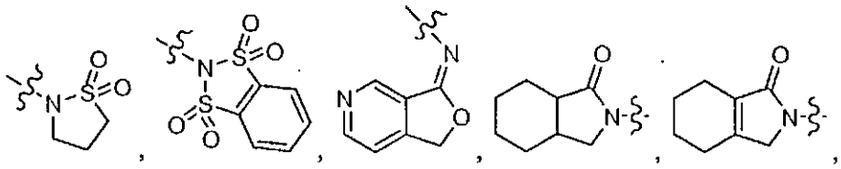
R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, ethenyl, C_{3-10} cycloalkyl substituted with 0-3 R^{2a},, C_{6-10} aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heterocyclyl is pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl, tetrahydropyranyl, oxazolidinyl (oxazolidin-one), imidazolidinyl (imidazolidin-one), dioxalanyl, or 

; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heteroaryl is pyrimidinyl, imidazolyl, pyrazinyl, thiadizaolyl, pyridinyl, quinolinyl, isoquinolinyl, or thiazolyl.

[0033] In another embodiment, there is provided a compound of formula I, wherein

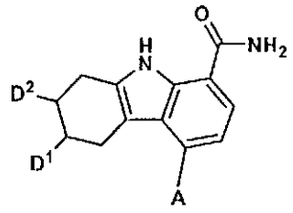
A is C_6 carbocycle substituted with 0-3 B, C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, a 5-14 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heterocyclyl is chromanyl, 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one, pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heteroaryl is pyridinyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl,, imidazolyl, pyrazolyl, or thiazolyl;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, wherein the heterocyclyl is 4,5,6,7-tetrahydrobenzo[d]thiazolyl, isindolinyl, imidazo[1,2-a]pyrazin-8(7H)-one, 1H-pyrrolo[3,4-c]pyridin-3(2H)-one, 1,3-dihydrofuro[3,4-c]pyridine, phthalazine, isoquinolin-1(2H)-one, isoindolinyl, isoindoline-1,3-dione, quinazolin-4(3H)-one,

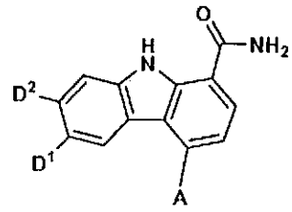


pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a} wherein the heteroaryl is indazolyl, imidazolyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, quinolinyl, quinazolinyl, quinazolin-4(3H)-one pyridinyl or thiazolyl.

[0034] In another embodiment, there is provided a compound of formula I, wherein the compound of formula I is a compound of formula (I) is (Ia) or (Ib)



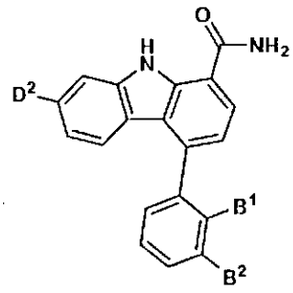
(Ia)



(Ib).

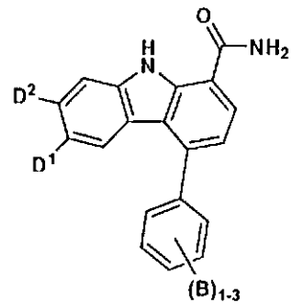
[0035] In another embodiment, there is provided a compound of formula I, wherein the compound of formula I is a compound of formula (I) is (Ic) or (Ib)

[0036] In another embodiment, there is provided a compound of formula I, wherein the compound of formula I is a compound of formula (I) is (Ic)



(Ic).

[0037] In another embodiment, there is provided a compound of formula I, wherein the compound of formula I is a compound of formula (I) is (Id)



(Id).

[0038] In another embodiment, there is provided a compound of formula I, wherein

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $-(CH_2)_r$-3-6 membered carbocycle, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein the heterocycle is pyrrolidinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, morpholinyl, thiamorpholinyl, triazolyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, benzopyranyl, benzofuryl, benzisothiazolyl, benzisoxazolyl, benzodiazinyl, or benzofurazanyl;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-1 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO2, $-OR^e$, $-C(O)R^e$, $-NR^eR^e$, $-NR^eC(O)OR^e$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

R^f is hydrogen, halo, or NH_2;

r is 0 or 1.

[0039] In another embodiment, there is provided a compound of formula I, wherein

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-(CH_2)_r$-3-6 membered carbocycle phenyl, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein the heterocycle is thiazolyl, pyridinyl, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, pyrrolidin-one,

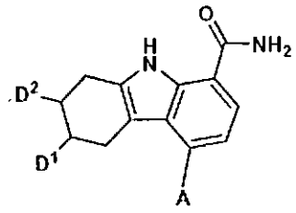
R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

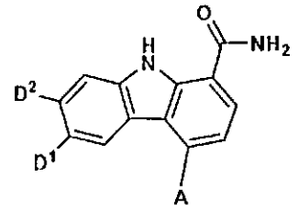
R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO2, $-OR^e$, $-C(O)R^e$, $-NR^eR^e$, $-NR^eC(O)OR^e$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl.

[0040] In another embodiment, there is provided a compound of formula I, wherein the compound of formula (I) is (Ia) or (Ib)



(Ia)



(Ib)

A is C_{3-10} carbocycle substituted with 0-3 B, wherein the carbocycle is cyclohexyl or cyclohexenyl, C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, wherein the aryl group is phenyl or naphthyl; a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heterocyclyl group is chromanyl, 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one, pyrrolidinyl or piperidinyl; or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heteroaryl group is pyridinyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, imidazolyl, pyrazolyl or thiazolyl;

B is R^1, halogen, -C(=O)O-R^1, -$S(=O)_2$-R^1, -$NR^{11}C(=O)$-R^1, -$NR^{11}C(=O)NR^{11}$-R^1, -$NR^{11}S(=O)_2$-R^1, $N(S(=O)_2$-$R^1)_2$, or -NR^{11}-R^1;

R^1 is hydrogen, trifluoromethyl, C_{1-4} alkyl substituted with 0-1 R^{1a}, phenyl substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, wherein the heteroaryl is pyridyl or thiazolyl;

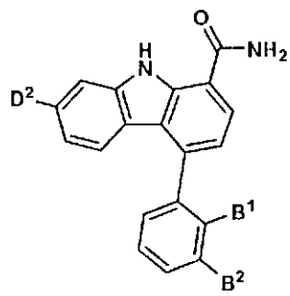
One of D^1 and D^2 is D and the other is hydrogen;

D is R^2, –C(=O)-R^2, -OR^2, -C(=O)$NR^{11}R^2$, $NR^{11}C(=O)R^2$, $NR^{11}C(=O)NR^{11}$-R^2, $NR^{11}S(=O)_2$-R^2, or –NR^{11}-R^2;

R^2 is hydrogen, C_{2-6} alkyl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a} where the heterocyclyl is tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl;

R^{2a} is C_{1-4} alkyl, wherein the alkyl is methyl, ethyl, propyl, i-propyl, butyl, and t-butyl, substituted with 0-1 R^a.

[0041] In another embodiment, there is provided a compound of formula I, wherein the compound of formula (I) is a compound of formula (Ic):

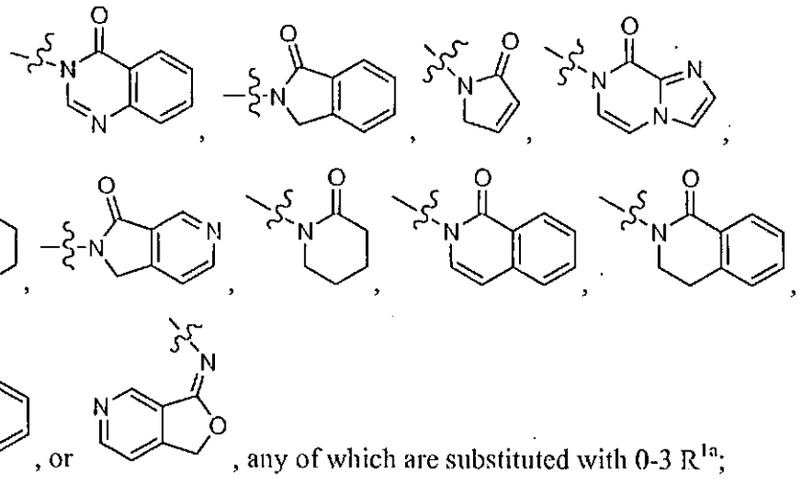


(Ic)

or a salt thereof, wherein

B^1 is methyl or fluorine;

B^2 is R^{1b}, -$NR^{11}C(=O)$- R^{1c}, -$NR^{11}C(=O)NR^{11}$- R^{1d}, or -NR^{11}-R^{1e};

R^{1b} is  , any of which are substituted with 0-3 R^{1a};

R^{1c} is C_{1-6} alkyl, phenyl substituted with 0-2 R^a, cyclopropyl, CH_2-tetrazolyl, or pyridyl, thiazolyl, imidazolyl, benzimidazolyl, pyrimidinyl, any of which are substituted with 0-2 R^a;

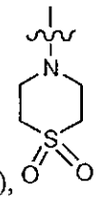
R^{1d} is thiazolyl substituted with 0-1 R^{1a};

R^{1e} is quinazolinyl substituted with 0-1 R^{1a};

R^{1a} is selected from hydrogen, halo, CN, methyl, ethyl, CF_3, OH, O-methyl, CO_2CH_3, $N(CH_3)_2$, $NC(O)CH_3$,

D^2 is $-R^2$, $-(C(R^{11})_2)_r-R^2$, $-OR^2$, $-C(=O)-R^2$, $-C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}-R^2$, - or $-OC(=O)-R^2$;

provided that D^2 is not hydrogen;

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{3-10} cyclopropyl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heterocyclyl is selected from piperazinyl, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, dioxolanyl, piperidinyl, oxazolidinyl (oxazolidin-one), imidazolidinyl (imidazolidin-one),  , a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heteroaryl is selected from pyridinyl, imidazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, thiadiazolyl;

R^{2a} is hydrogen, $-(CH_2)_rOR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-NR^bC(O)NR^{11}R^{11}$, $-NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-2 R^a, or $-(CH_2)_r$-5-7

membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a, wherein the heterocycle is selected from pyridinyl, pyrrolidinyl, pyrrolidinonyl, morpholinyl, imidazolyl, piperidinyl;

R^{11} is hydrogen or C_{1-4} alkyl substituted with 0-1 R^f;

R^a is hydrogen, $-OR^b$, $-NR^{11}R^{11}$, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein the heterocycle is imidazolyl or morpholinyl;

R^b is hydrogen, or C_{1-6} alkyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl;

R^d is hydrogen, $-OR^e$, or $-NR^eR^e$;

R^e is hydrogen, or C_{1-6} alkyl;

R^f is hydrogen, NH_2, OH, or OCH_3.

[0042] In another embodiment, there is provided a compound of formula I, wherein D^1 is hydrogen and D^2 is D.

[0043] In another embodiment, there is provided a compound of formula I, wherein D^2 is hydrogen and D^1 is D.

[0044] In another embodiment, there is provided a compound of formula I, wherein the compound of formula I is a compound of formula (Ia). In another embodiment, the compound of formula (I) is a compound of formula (Ib). In another embodiment, the compound of formula (I) is a compound of formula (Ic).

[0045] In another embodiment, A is halo, C_{3-10} carbocycle substituted with 0-3 B C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, a 5-14 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 –B.

[0046] In another embodiment, there is provided a compound of formula I, wherein A is C_6 carbocycle substituted with 0-3 B, C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, a 5-14 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heterocyclyl is , chromanyl, 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one, pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heteroaryl is

pyridinyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, furanyl, benzofuranyl,, dibenzofuranyl,, imidazolyl, pyrazolyl, or thiazolyl.

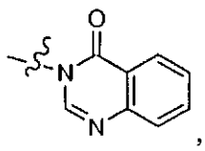
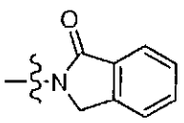
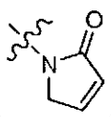
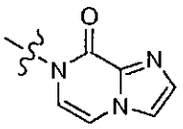
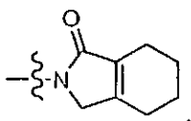
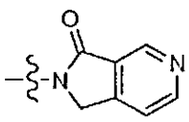
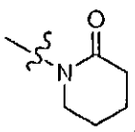
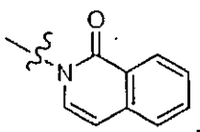
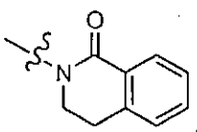
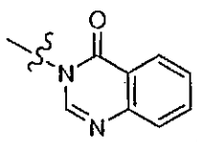
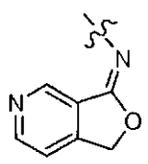
[0047] In another embodiment, there is provided a compound of formula I, wherein A is C_{3-10} carbocycle substituted with 0-3 B, wherein the carbocycle is cyclohexyl or cyclohexenyl, C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, wherein the aryl group is phenyl or naphthyl; a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heterocyclyl group is chromanyl, 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one, pyrrolidinyl or piperidinyl; or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heteroaryl group is pyridinyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, imidazolyl, pyrazolyl or thiazolyl.

[0048] In another embodiment, there is provided a compound of formula I, wherein B is R^1, halogen, cyano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$.

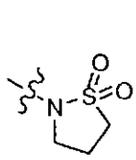
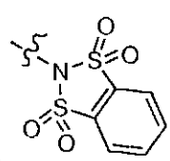
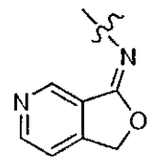
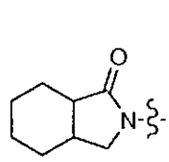
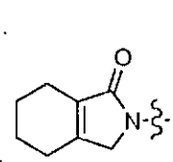
[0049] In another embodiment, there is provided a compound of formula I, wherein B is R^1, halogen, $-C(=O)O-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$;

[0050] In another embodiment, there is provided a compound of formula (Ic), wherein B^1 is methyl or fluorine;

B^2 is R^{1b}, $-NR^{11}C(=O)-R^{1c}$, $-NR^{11}C(=O)NR^{11}-R^{1d}$, or $-NR^{11}-R^{1e}$;

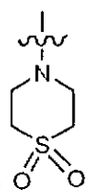
R^{1b} is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  , any of which are substituted with 0-3 R^{1a}.

[0051] In another embodiment, there is provided a compound of formula I, wherein R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, wherein the heterocyclyl is 4,5,6,7-tetrahydrobenzo[d]thiazolyl, isindolinyl, imidazo[1,2-a]pyrazin-8(7H)-one, 1H-pyrrolo[3,4-c]pyridin-3(2H)-one, 1,3-dihydrofuro[3,4-c]pyridine, phthalazine, isoquinolin-1(2H)-one, isoindolinyl, isoindoline-1,3-dione, quinazolin-4(3H)-one,

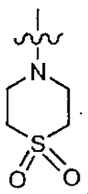






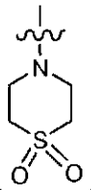
pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a} wherein the heteroaryl is indazolyl, imidazolyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, quinolinyl, quinazolinyl, quinazolin-4(3H)-one pyridinyl or thiazolyl.

[0052] In another embodiment, there is provided a compound of formula I, wherein R^1 is hydrogen, trifluoromethyl, C_{1-4} alkyl substituted with 0-1 R^{1a}, phenyl substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, wherein the heteroaryl is pyridyl or thiazolyl.

[0053] In another embodiment, there is provided a compound of formula I, wherein R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, ethenyl, C_{3-10} cycloalkyl substituted with 0-3 R^{2a},, C_{6-10} aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heterocyclyl is pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl, tetrahydropyranyl, oxazolidinyl (oxazolidin-one), imidazolidinyl (imidazolidin-one), dioxalanyl, or  ; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heteroaryl is pyrimidinyl, imidazolyl, pyrazinyl, thiadizaolyl, pyridinyl, quinolinyl, isoquinolinyl, or thiazolyl.

[0054] In another embodiment, there is provided a compound of formula I, wherein R^2 is hydrogen, C_{2-6} alkyl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a} where the heterocyclyl is tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl.

[0055] In another embodiment, there is provided a compound of formula I, wherein R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, C_{2-6} alkynyl substituted with 0-3 R^{2a}, C_{3-10} cycloalkyl substituted with 0-3 R^{2a}, C_{6-10} aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heterocyclyl is selected from piperazinyl, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, dioxolanyl, piperidinyl, oxazolidinyl (oxazolidin-one), imidazolidinyl (imidazolidin-one),  , a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heteroaryl is selected from pyridinyl, imidazolyl, pyrazinyl, thiadiazolyl.

[0056] In another embodiment, there is provided a compound of formula (I) wherein R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{3-10} cyclopropyl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heterocyclyl is selected from piperazinyl, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, dioxolanyl, piperidinyl, oxazolidinyl (oxazolidin-one), imidazolidinyl (imidazolidin-one),  , a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heteroaryl is selected from pyridinyl, imidazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, thiadiazolyl.

[0057] In another embodiment, R^{2a} is hydrogen, $-(CH_2)_rOR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-NR^bC(O)NR^{11}R^{11}$, $-NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-2

R^a, or -$(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a, wherein the heterocycle is selected from pyridinyl, pyrrolidinyl, pyrrolidinonyl, morpholinyl, imidazolyl, piperidinyl.

[0058] In another embodiment, one of D^1 and D^2 is D and the other is H; provided that D is not hydrogen.

[0059] In another embodiment, D is a -R^2, -$(CH_2)_r$-R^2, –O-R^2, –C(=O)-R^2, -C(=O)O-R^2, -C(=O)NR^{11}-R^2, -$S(=O)_2$-R^2, -NR^{11}C(=O)-R^2, -NR^{11}C(=O)NR^{11}-R^2, -NR^{11}C(=O)O-R^2, -$NR^{11}S(=O)_2$-R^2, or -NR^{11}-R^2.

[0060] In another embodiment, D is a -R^2, -$(CH_2)_r$-R^2, –O-R^2, –C(=O)-R^2, -C(=O)O-R^2, -C(=O)NR^{11}-R^2, -$S(=O)_2$-R^2, -S(=O)-R^2, -NR^{11}C(=O)-R^2, -NR^{11}C(=O)NR^{11}-R^2, -NR^{11}C(=O)O-R^2, -$NR^{11}S(=O)_2$-R^2, or -NR^{11}-R^2.

[0061] In another embodiment, D is R^2, –C(=O)-R^2, -OR^2, -C(=O)$NR^{11}R^2$, NR^{11}C(=O)R^2, NR^{11}C(=O)NR^{11}-R^2, $NR^{11}S(=O)_2$-R^2, or –NR^{11}-R^2.

[0062] In another embodiment, D^2 is -R^2, -$(C(R^{11})_2)_r$-R^2, -OR^2, –C(=O)-R^2, -C(=O)NR^{11}-R^2, -NR^{11}C(=O)-R^2, -NR^{11}C(=O)NR^{11}-R^2, -NR^{11}-R^2, - or -OC(=O)-R^2.

[0063] In another embodiment, D^2 is -R^2, -$(C(R^{11})_2)_r$-R^2, –C(=O)-R^2, -C(=O)NR^{11}-R^2, -NR^{11}C(=O)-R^2, -NR^{11}C(=O)NR^{11}-R^2, -NR^{11}-R^2, - or -OC(=O)-R^2.

[0064] In another embodiment, D^2 is -R^2, -$(C(R^{11})_2)_r$-R^2, –C(=O)-R^2, -C(=O)NR^{11}-R^2, -NR^{11}C(=O)-R^2, -NR^{11}C(=O)NR^{11}-R^2, -NR^{11}-R^2, -S(=O)-R^2, - or -OC(=O)-R^2.

[0065] In another embodiment, there is provided a pharmaceutical composition comprising one or more compounds of formula I and a pharmaceutically acceptable carrier or diluent.

[0066] The present invention is also directed to pharmaceutical compositions useful in treating diseases associated with kinase modulation, including modulation (especially inhibition) of Btk and other Tec family kinases such as Itk, comprising compounds of formula (I), or pharmaceutically-acceptable salts thereof, and pharmaceutically-acceptable carriers or diluents.

[0067] The invention further relates to methods of treating diseases associated with the kinase modulation, including the modulation of Btk and other Tec family kinases such as Itk, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound according to formula (I).

[0068] The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

[0069] The present invention also provides a method for treating proliferative diseases, allergic diseases, autoimmune diseases and inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

[0070] The present invention also provides a method for treating a disease, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I, wherein the disease is systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis (MS), or transplant rejection.

[0071] The present invention also provides a method of treating a condition associated with a proliferative disease, an allergic disease, an autoimmune disease or an inflammatory disease, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I.

[0072] The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I, wherein the condition is selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, solid tumors, ocular neovasculization, and infantile haemangiomas, B cell lymphoma, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, multiple sclerosis (MS), transplant rejection, Type I diabetes, membranous nephritis, inflammatory bowel disease, autoimmune hemolytic anemia, autoimmune thyroiditis, cold and warm agglutinin diseases, Evan's syndrome, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), sarcoidosis, Sjogren's syndrome, peripheral neuropathies, pemphigus vulgaris and asthma.

[0073] The present invention also provides a method for treating a rheumatoid arthritis, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I.

[0074] The present invention also provides a method of treating a B-cell mediated disease, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I

[0075] The present invention also provides a method of treating a B-cell mediated disease, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I, wherein the B-cell mediated disease is a disease modulated by a kinase selected from Btk, Bmx, Itk, Txk and Tec.

[0076] The present invention also provides a method of treating diseases, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I, or pharmaceutically acceptable salt thereof, in combination with other therapeutic agents.

[0077] The present invention also provides the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for use in therapy.

[0078] In another embodiment, compounds of formula I are selected from exemplified examples or combinations of exemplified examples or other embodiments herein.

[0079] In another embodiment are compounds having an IC_{50} <10 μM in the Btk assay described below.

[0080] In another embodiment are compounds having an IC_{50} <=5 nM in the Btk assay described below.

[0081] The present invention also provides the use of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for the manufacture of a medicament for the treatment of cancers, an allergic disease, an autoimmune disease or an inflammatory disease.

[0082] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects and/or embodiments of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in

conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

DETAILED DESCRIPTION OF THE INVENTION

[0083] The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

[0084] Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

[0085] When any variable (e.g., R^3) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^3, then said group may optionally be substituted with up to two R^3 groups and R^3 at each occurrence is selected independently from the definition of R^3. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0086] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to

the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0087] In cases wherein there are nitrogen atoms (e.g., amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

[0088] In accordance with a convention used in the art,



is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

[0089] A dash "-" that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

[0090] The term "optionally substituted" in reference to a particular moiety of the compound of Formula I (*e.g.*, an optionally substituted heteroaryl group) refers to a moiety having 0, 1, 2, or more substituents. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[0091] As used herein, the term "at least one chemical entity" is interchangeable with the term "a compound."

[0092] As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_{1-10} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl groups can be unsubstituted or substituted so that one or more of its hydrogens are replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl

(*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl), and the like.

[0093] Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more double carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

[0094] "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more triple carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

[0095] One skilled in the field will understand that, when the designation "CO_2" is used herein, this is intended to refer to the group $-\overset{O}{\overset{\|}{C}}-O-$.

[0096] When the term "alkyl" is used together with another group, such as in "arylalkyl", this conjunction defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, "arylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is an aryl, such as benzyl. Thus, the term aryl(C_{0-4})alkyl includes a substituted lower alkyl having at least one aryl substituent and also includes an aryl directly bonded to another group, *i.e.*, aryl(C_0)alkyl. The term "heteroarylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is a heteroaryl.

[0097] When reference is made to a substituted alkenyl, alkynyl, alkylene, alkenylene, or alkynylene group, these groups are substituted with one to three substituents as defined above for substituted alkyl groups.

[0098] The term "alkoxy" refers to an oxygen atom substituted by alkyl or substituted alkyl, as defined herein. For example, the term "alkoxy" includes the group -O-C_{1-6}alkyl such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy,

2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. "Lower alkoxy" refers to alkoxy groups having one to four carbons.

[0099] It should be understood that the selections for all groups, including for example, alkoxy, thioalkyl, and aminoalkyl, will be made by one skilled in the field to provide stable compounds.

[00100] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo, or keto, (*i.e.*, =O) then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

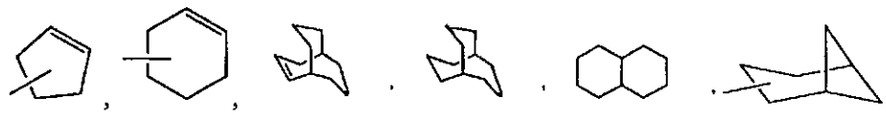
[00101] Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture to a useful degree of purity, and subsequent formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

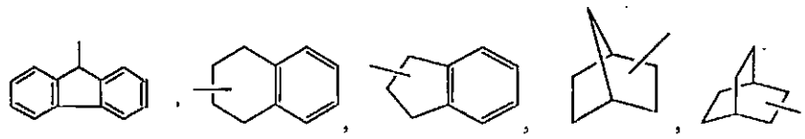
[00102] The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl

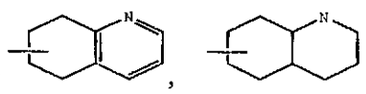
(tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a bicyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00103] The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, and naphthyl groups, each of which may be substituted.

[00104] Accordingly, in compounds of formula (I), the term "cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclooctyl, etc., as well as the following ring systems,







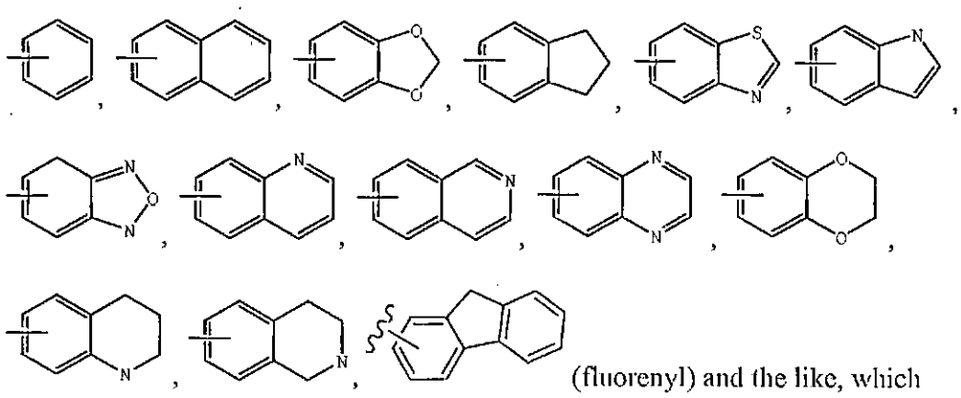
and the like, which optionally may be substituted at any available atoms of the ring(s). Preferred cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, and  .

[00105] The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

[00106] The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

[00107] The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3.

[00108] Thus, examples of aryl groups include:

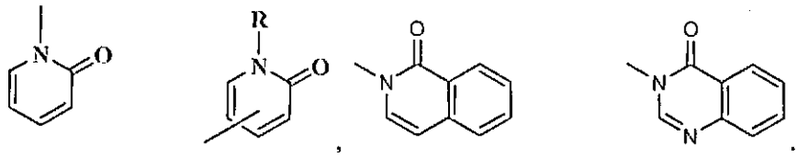


(fluorenyl) and the like, which optionally may be substituted at any available carbon or nitrogen atom. A preferred aryl group is optionally-substituted phenyl.

[00109] The terms "heterocycloalkyl", "heterocyclo", "heterocyclic", or "heterocyclyl" may be used interchangeably and refer to substituted and unsubstituted non-aromatic 3-to 7-membered monocyclic groups, 7-to 11-membered bicyclic groups, and 10-to 15-membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N), said heteroatom containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The heterocyclo group may be attached at any available nitrogen or carbon atom. The term "heterocycle" includes "heteroaryl" groups. As valence allows, if said further ring is cycloalkyl or heterocyclo it is additionally optionally substituted with =O (oxo).

[00110] Exemplary monocyclic heterocyclyl groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 1-pyridonyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like.

Exemplary bicyclic heterocyclo groups include quinuclidinyl. Additional monocyclic heterocyclyl groups include



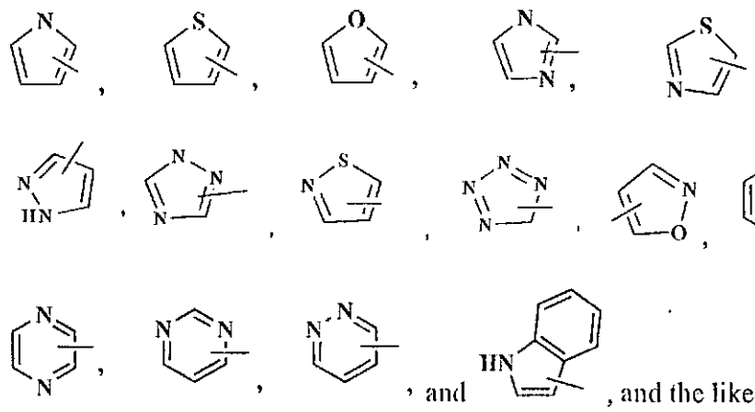
[00111] The term "heteroaryl" refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups, 9- or 10-membered bicyclic groups, and 11- to 14-membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. As valence allows, if said further ring is cycloalkyl or heterocyclo it is additionally optionally substituted with =O (oxo).

[00112] Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

[00113] Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

[00114] Exemplary tricyclic heteroaryl groups include carbazolyl, benzindolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[00115] In compounds of formula (I), preferred heteroaryl groups include



may be substituted at any available carbon or nitrogen atom.

[00116] Unless otherwise indicated, when reference is made to a specifically-named aryl (*e.g.*, phenyl), cycloalkyl (*e.g.*, cyclohexyl), heterocyclo (*e.g.*, pyrrolidinyl, piperidinyl, and morpholinyl) or heteroaryl (*e.g.*, tetrazolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, and furyl) the reference is intended to include rings having 0 to 3, preferably 0-2, substituents selected from those recited above for the aryl, cycloalkyl, heterocyclo and/or heteroaryl groups, as appropriate.

[00117] The term "carbocyclyl" or "carbocyclic" refers to a saturated or unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of mono- and bicyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl and naphthyl. The carbocyclic ring may be substituted in which case the substituents are selected from those recited above for cycloalkyl and aryl groups.

[00118] The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

[00119] When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

[00120] Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and

compounds useful as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds.

[00121] The compounds of formula (I) may exist in a free form (with no ionization) or can form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is understood to include reference to the free form and to salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s) may include zwitterions (inner salts), *e.g.*, when a compound of formula (I), contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a carboxylic acid. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula (I) may be formed, for example, by reacting a compound of the formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[00122] Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

[00123] Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, N,N'-dibenzylethylene-diamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others. Preferred salts include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate salts.

[00124] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00125] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

[00126] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, the disclosure of which is hereby incorporated by reference.

[00127] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. Stereoisomers may include compounds which are optical isomers through possession of one or more chiral atoms, as well as compounds which are optical isomers by virtue of limited rotation about one or more bonds (atropisomers). The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

[00128] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

[00129] Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I), and/or a salt and/or solvate thereof. Any compound that

will be converted *in vivo* to provide the bioactive agent (*i.e.*, the compound for formula (I)) is a prodrug within the scope and spirit of the invention. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula (I) compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula (I) include C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6}alkanoyloxy-C_{1-6}alkyl, *e.g.* acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl, *e.g.* methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

[00130] Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 112, pp. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991); and

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, pp. 1-38 (1992), each of which is incorporated herein by reference.

[00131] Compounds of the formula (I) and salts thereof may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention. Additionally, inventive compounds may have *trans* and *cis* isomers,

[00132] It should further be understood that solvates (*e.g.*, hydrates) of the compounds of Formula (I) are also with the scope of the present invention. Methods of solvation are generally known in the art.

UTILITY

[00133] The compounds of the invention modulate kinase activity, including the modulation of Btk. Other types of kinase activity that may be modulated by the compounds of the instant invention include, but are not limited to, the Tec family of compounds, such as Bmx, Btk, Itk, Txk and Tec, and mutants thereof.

[00134] Accordingly, compounds of formula (I) have utility in treating conditions associated with the modulation of kinase activity, and particularly the selective inhibition of Btk activity or the inhibition of Btk and other Tec family kinases such as Itk. Such conditions include B-cell mediated diseases in which cytokine levels are modulated as a consequence of intracellular signaling. Moreover, the compounds of formula (I) have advantageous selectivity for Btk activity and other Tec family kinases such as Itk over Mk2 activity, preferably from at least 20 fold to over 1,000 fold more selective.

[00135] As used herein, the terms "treating" or "treatment" encompass the treatment of a disease state in a mammal, particularly in a human, and include: (a) preventing or delaying the occurrence of the disease state in a mammal, in particular, when such mammal is predisposed to the disease state but has not yet been diagnosed as having it; (b) inhibiting the disease state, i.e., arresting its development; and/or (c) achieving a full or partial reduction of the symptoms or disease state, and/or alleviating, ameliorating, lessening, or curing the disease or disorder and/or its symptoms.

[00136] In view of their activity as selective inhibitors of Btk or Btk and other Tec family kinase such as Itk, compounds of Formula (I) are useful in treating cytokine-associated conditions including, but not limited to, inflammatory diseases such as Crohn's and ulcerative colitis, asthma, graft versus host disease, chronic obstructive pulmonary disease; autoimmune diseases such as Graves' disease, rheumatoid arthritis, systemic lupus erythematosis, psoriasis; destructive bone disorders such as bone resorption disease, osteoarthritis, osteoporosis, multiple myeloma-related bone disorder; proliferative disorders such as acute myelogenous leukemia, chronic

myelogenous leukemia; angiogenic disorders such as angiogenic disorders including solid tumors, ocular neovasculization, and infantile haemangiomas; infectious diseases such as sepsis, septic shock, and Shigellosis; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury, oncologic and viral diseases such as metastatic melanoma, Kaposi's sarcoma, multiple myeloma, and HIV infection and CMV retinitis, AIDS, respectively.

[00137] More particularly, the specific conditions or diseases that may be treated with the inventive compounds include, without limitation, pancreatitis (acute or chronic), asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosis, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β-cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, meloid formation, scar tissue formation, ulcerative colitis, pyresis, influenza, osteoporosis, osteoarthritis, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, and Shigellosis; Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury; angiogenic disorders including solid tumors, ocular neovasculization, and infantile haemangiomas; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis, AIDS, ARC or malignancy, and herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hyposia, vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin-induced platelet aggregation, endotoxemia and/or

toxic shock syndrome, conditions associated with prostaglandin endoperoxidase syndase-2, and pemphigus vulgaris. Preferred methods of treatment are those wherein the condition is selected from Crohn's and ulcerative colitis, allograft rejection, rheumatoid arthritis, psoriasis, ankylosing spondylitis, psoriatic arthritis, and pemphigus vulgaris. Alternatively preferred methods of treatment are those wherein the condition is selected from ischemia reperfusion injury, including cerebral ischemia reperfusions injury arising from stroke and cardiac ischemia reperfusion injury arising from myocardial infarction. Another preferred method of treatment is one in which the condition is multiple myeloma.

[00138] In addition, the kinse inhibitors of the present invention inhibit the expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxide synthase-2 (PGHS-2), also referred to as cyclooxygenase-2 (COX-2). Accordingly, additional Btk-associated conditions include edema, analgesia, fever and pain, such as neuromuscular pain, headache, pain caused by cancer, dental pain and arthritis pain. The inventive compounds also may be used to treat veterinary viral infections, such as lentivirus infections, including, but not limited to equine infectious anemia virus; or retro virus infections, including feline immunodeficiency virus, bovine immunodeficiency virus, and canine immunodeficiency virus.

[00139] When the terms "Btk-associated condition" or "Btk -associated disease or disorder" are used herein, each is intended to encompass all of the conditions identified above as if repeated at length, as well as any other condition that is affected by Btk kinase activity.

[00140] The present invention thus provides methods for treating such conditions, comprising administering to a subject in need thereof a therapeutically-effective amount of at least one compound of Formula (I) or a salt thereof. "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit Btk and other Tec family kinases and/or treat diseases.

[00141] The methods of treating Btk kinase-associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions. Accordingly, "therapeutically effective amount" is also intended to include an amount

of the combination of compounds claimed that is effective to inhibit Btk and/or treat diseases associated with Btk.

[00142] Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, cytokine-suppressive anti-inflammatory drugs (CSAIDs), Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, Prograf); cytotoxic drugs such as azathiprine and cyclophosphamide; TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

[00143] The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds. The present invention also provides pharmaceutical compositions capable of treating Btk kinase-associated conditions, including IL-1, IL-6, IL-8, IFNγ and TNF-α-mediated conditions, as described above.

[00144] The inventive compositions may contain other therapeutic agents as described above and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (*e.g.*, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

[00145] Accordingly, the present invention further includes compositions comprising one or more compounds of Formula (I) and a pharmaceutically acceptable carrier.

[00146] A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These

include without limitation the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical Sciences*, 17th ed., **1985**, which is incorporated herein by reference in its entirety.

[00147] The compounds of Formula (I) may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques (*e.g.*, as sterile injectable aq. or non-aq. solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or; particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

[00148] Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

[00149] Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, *e.g.*, with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (*e.g.*, GANTREZ®); and agents to control release such as polyacrylic copolymer (*e.g.*, CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

[00150] Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

[00151] Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

[00152] Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

[00153] The therapeutically-effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 1000 mg/kg; 1-1000 mg/kg; 1-50 mg/kg; 5-250 mg/kg; 250-1000 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like. Thus, when the term "patient" is used herein, this term is intended to include all subjects, most preferably mammalian species, that are affected by mediation of Btk enzyme levels.

BIOLOGICAL ASSAYS

Human recombinant Btk enzyme assay

[00154] To V-bottom 384-well plates were added test compounds, human recombinant Btk (1 nM, Invitrogen Corporation), fluoresceinated peptide (1.5 μM), ATP (20 μM), and assay buffer (20 mM HEPES pH 7.4, 10 mM $MgCl_2$, 0.015% Brij35 and 4 mM DTT in 1.6% DMSO), with a final volume of 30 μL. After incubating at room temperature for 60 min, the reaction was terminated by adding 45 μl of 35 mM EDTA to each sample. The reaction mixture was analyzed on the Caliper LabChip 3000 (Caliper, Hopkinton, MA) by electrophoretic separation of the fluorescent substrate and phosphorylated product. Inhibition data were calculated by comparison to no enzyme control reactions for 100% inhibition and no inhibitor controls for 0% inhibition. Dose response curves were generated to determine the concentration required inhibiting 50% of kinase activity (IC_{50}). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations.

[00155] Using this assay, the IC_{50} values of the following compounds were determined. See Table 1.

Table 1.

Example	IC_{50} for Inhibition of Btk, μM
1-3	0.49
2-2	1.3
2-12	0.016
2-13	0.015
2-16	0.016
2-18	0.016
2-24	0.80
2-25	3.1
2-35	0.016
2-43	0.52
3-9	0.017
3-18	2.7
3-19	1.8
3-39	0.016
3-45	0.016
3-48	0.39
3-49	0.69
3-69	0.015
3-75	0.92
3-83	0.94
3-101	0.018
3-114	0.54
3-116	1.6
3-122	0.018
3-124	1.8
3-130	0.002
4-3	0.39

5-2	0.016
5-7	0.018
5-9	0.0019
5-16	0.018
5-19	0.017
5-42	0.015
5-44	0.016
5-58	0.0022
5-62	0.017
5-69	0.002
5-73	0.018
5-86	0.91
8-3	0.016
10-2	4.5
10-3	4.9
10-4	0.017
11-1	0.015
12-1	0.018
17-1	1.1
19-1	0.017
20-1	0.51
24-1	0.017
24-17	0.015
24-33	0.47
24-34	0.41
31-2	0.70
31-3	1.5
33-1	0.0019
34-2	0.0020
38-2	0.0021
38-3	0.0014
39-4	0.0017

41-1	0.016
47-2	4.2
48-2	1.7
50-3	1.3
51-1	0.40
51-4	1.6
52-1	0.52
52-2	0.52
54-7	0.83
57-3	0.0021
57-13	0.015
57-16	0.0021
57-18	0.0022
57-20	0.015
57-37	0.0018
60-1	0.018
61-2	0.0022
66-2	0.016
66-16	0.0020
66-34	0.016
66-37	0.015
67-1	0.0022
70-2	0.0022
70-3	0.0023
70-5	0.0016
70-6	0.00080
70-9	0.0015
70-10	0.0010
70-11	0.0014
70-12	0.0013
70-13	0.00070
70-14	0.00090

73-1	0.54
75-3	0.0011
76-2	0.0013
76-10	0.018
76-15	0.0024
76-18	0.0018
76-25	0.0029
76-32	0.0032
76-41	0.018
76-44	0.018
76-51	0.0014
77-2	0.0019
78-2	0.0016
79-2	0.0169
79-3	0.015
79-4	0.016
80-1	0.0019
81-3	0.0019
81-15	0.0039
81-20	0.0022
82-1	0.0019
83-3	0.0014
83-4	0.0011

Mouse splenic B cell proliferation assay

[00156] Spleens from Balb/c mice (< 12 weeks old) were mashed through screens and red blood cells were removed from splenocytes with RBC lysing buffer (Sigma-Aldrich Chemical Co, St. Louis, MO). T cells were depleted by incubation on nylon wool columns (Wako, Richmond, VA). Resulting splenic B cells prepared this way were routinely > 90% $CD19^+$ as measured by FACS analysis. B cells (1×10^5 cells

per well) were added to serial dilutions of compounds in triplicate in 96-well flat-bottom plates in RPMI 1640 (Invitrogen, Grand Island, NY), supplemented with 10% heat-inactivated fetal calf serum (FCS, Summit Biotechnology, Fort Collins, CO), containing 1% L-glutamine (Invitrogen), 50 μg/ml gentamicin (Invitrogen) and 5 X 10^{-5}M β-mercaptoethanol (Sigma-Aldrich). Cells were stimulated with 10 μg/ml of Affinipure $F(ab')_2$ fragment goat anti-mouse IgG IgM (Jackson Immunoresearch, West Grove, PA). Cultures were incubated for 72 hours, and pulsed for the last 6 hours with one μCi/well of ^{3}[H]- thymidine (PerkinElmer, Boston, MA) prior to harvest on a Packard cell harvester (PerkinElmer), and counted by liquid scintillation on a Packard TopCount NXT (PerkinElmer). The most potent analogs were found to be active below 1 μM.

Human tonsillar B cell proliferation assay

[00157] Tonsils were excised from patients undergoing routine tonsillectomy. Tonsil tissue was minced, mashed through screens and mononuclear cells were isolated on ficoll density gradients (Lymphocyte Separation Media; Mediatech Inc., Herndon, VA). T cells were depleted from mononuclear cells by rosetting with sheep red blood cells (SRBC, Colorado Serum Company; Denver, CO). Tonsillar B cells prepared by this method were routinely > 95% $CD19^+$ as measured by FACS analysis. B cells (1 X 10^5 cells per well) were added to serial dilutions of compounds in triplicate in 96-well flat-bottom plates in RPMI 1640, (Invitrogen, Grand Island, NY), supplemented with 10% heat-inactivated fetal calf serum (FCS, Summit Biotechnology, Fort Collins, CO), and containing antibiotic/antimycotic (Invitrogen, 1:100 dilution) and gentamicin (Invitrogen, 5 μg/ml). Cells were stimulated with 40 μg/ml AffinPure $F(ab')2$ Fragment Goat anti Human IgG + IgM (Jackson Immunoresearch, West Grove, PA) in a total volume of 0.2 ml. Cultures were incubated for 72 hours, and pulsed for the last 6 hours with one μCi/well of ^{3}[H]-thymidine (PerkinElmer, Boston, MA) prior to harvest on a Packard cell harvester (PerkinElmer), and counted by liquid scintillation on a Packard TopCount NXT (PerkinElmer).

Btk phosphorylation assay

[00158] Ramos cells (~6 x 10^6 cells/ml) were incubated in the presence of Btk inhibitors for 1hr at 37°C before being stimulated with anti-human IgM+IgG (F(ab')2 fragment, Jackson ImmunoResearch, catalog #109-006-127) at 50 µg/mL for exactly 2min at 37°C. Cells were immediately fixed by adding an equal volume of pre-warmed BD PhosFlow Fix buffer I (BD Biosciences, catalog number 557870) to the cell suspension. After incubating at 37°C for 10 minutes, the cells were washed once with 3 mL FACS washing buffer (1% FBS/PBS) and permeabilized by adding 0.5 mL of cold BD™ Phosflow Perm Buffer III (BD Biosciences, catalog number 558050) and incubating for 30 minutes on ice. The cells were washed an additional two times with 3 mL BD FACS washing buffer, re-suspended in 100 µL FACS washing buffer, stained with 20 µL Alexa647 anti-Btk (pY551) (BD Biosciences, catalog number 558134), incubated at room temperature for 30 minutes in the dark, and washed once with 3ml of FACS washing buffer. The cells were re-suspended in 400µl FACS wash buffer and analyzed using FACSCalibur (BD Biosciences). Median fluorescent intensity (MFI) on Alexa 647 (FL-4) data were collected and used for calculations of inhibition.

Ramos FLIPR assay

[00159] Ramos RA1 B cells (ATCC CRL-1596) at a density of 2 x 10^6 cells/ml in RPMI minus phenol red (Invitrogen 11835-030) and 50 mM HEPES (Invitrogen 15630-130) containing 0.1% BSA (Sigma A8577) were added to one half volume of calcium loading buffer (BD bulk kit for probenecid sensitive assays, # 640177) and incubated at room temperature in the dark for 1 hour. Dye-loaded cells were pelleted (Beckmann GS-CKR, 1200 rpm, RT, 5 minutes) and resuspended in RT RPMI minus phenol red with 50 mM HEPES and 10% FBS to a density of 1 x 10^6 cells/ml. 150 µl aliquots (150,000/well) were plated into 96 well poly-D-lysine coated assay plates (BD 35 4640) and briefly centrifuged (Beckmann GS-CKR 800 rpm, 5 minutes, without brake). 50 µl compound dilutions in 0.4% DMSO/RPMI minus phenol red + 50 mM HEPES + 10% FBS were added to the wells and the plate was incubated at RT in the dark for 1 hour. Assay plate was briefly centrifuged as above prior to measuring calcium levels.

[00160] Using the FLIPR1 (Molecular devices), cells were stimulated by adding goat anti-human IgM (Invitrogen AHI0601) to 2.5 µg/mL. Changes in intracellular

calcium concentrations were measured for 180 seconds and percent inhibition was determined relative to peak calcium levels seen in the presence of stimulation only. Biological activity of certain compounds as assessed using this assay is shown in Table 2.

Table 2.

Example	IC_{50} for Inhibition of Ramos FLIPR assay, μM
3-61	3.0
3-62	2.9
3-65	1.2
3-66	1.4
3-92	1.4
3-98	1.9
3-120	1.3
3-121	1.5
5-48	1.4
8-1	5.4
11-6	0.28
38-3	0.023
62-1	0.25
66-5	0.26
66-10	0.27
66-14	0.26
66-39	0.26
66-40	0.27
70-13	0.011
70-14	0.014
75-3	0.016
76-7	0.24
76-15	0.048
76-25	0.014

76-26	0.018
76-32	0.038
76-43	0.26
76-49	0.014
76-51	0.017
80-2	0.016
81-1	0.015
81-7	0.26
81-14	0.021
81-15	0.042
82-1	0.017

NFAT-bla RA1 Reporter Assay

[00161] Ramos B cells containing a stable integration of a beta-lactamase reporter gene under the control of an NFAT response element (NFAT-bla RA1, Invitrogen, K1434) at a density of 100 x 103 cells/well were incubated with test compounds at 37°C for 30min prior to stimulation with F(ab')2 anti-human IgM (Jackson ImmunoResearch, 109-006-129) at 2.5µg/ml for 4.5hrs at 37°C. After stimulation, LiveBLAzer™-FRET B/G ubstrate (CCF2/AM, or CCF4/AM, Invitrogen) was added to each well and incubated for 90 min at room temperature in the dark. Assay plates were read on an LJL Analyst, with raw emission values subtracted from a media-only blank containing substrate in assay media (no cells). The ratios of 460nm/530nm emission (405 nm excitation) were used to calculate the amount of stimulation.

KLH antigen challenge and antibody measurement

[00162] Female BALB/c mice (6-8 weeks old) were immunized intraperitoneally (IP) with 250 µg keyhole limit hemocyanin (KLH) (Pierce, Rockford, IL) in phosphate-buffered saline (PBS). Mice in appropriate groups were dosed as indicated. Blood was collected 14 days post-immunization, serum was separated and analyzed for anti-KLH IgG titers by ELISA. Briefly, 96 well plates were coated with KLH in PBS, blocked, and serial dilutions of test serum samples were added. Captured anti-KLH antibodies were detected using horseradish peroxidase-conjugated

antibody specific for mouse IgG (Southern Biotechnology Associates, Birmingham, AL) and the TMB peroxidase substrate system (Kirkegaard and Perry Laboratories, Gaithersburg, MD). Optical densities of developed plates were quantitated in a SpectraMax Plus ELISA plate reader (Molecular Devices, Sunnyvale, CA). When administered twice daily, the compound of Example 76-15 inhibited the anti-KLH IgG response by 29% and 56% at 10 mg/kg and 30 mg/kg, respectively.

METHODS OF PREPARATION

[00163] Compounds of Formula (I) can be prepared by the route outlined in Scheme 1. A 2-hydrazinobenzoic acid **1-1** (where X is either the substituent A of Formula (I) or a suitable precursor to such a substituent, such as bromo) can react with a suitable cyclohexanone **1-2** (where Y represents either the substituent(s) D^1 and/or D^2 of Formula (I) or a precursor to such substituent(s)) in an appropriate solvent with an appropriate catalyst, for example ethanol with hydrochloric acid, or acetic acid (in which case the solvent also can serve as the catalyst), at a suitable temperature (for example, the reflux temperature of the solvent) to provide the corresponding tetrahydrocarbazole derivative **1-3** (where the dotted lines represent single bonds). This reaction is commonly known as the Fischer indole synthesis, and is well known in the chemical literature (for example, see J. Kamata et al., *Chem. Pharm. Bull.* 2004, 52, 1071). Alternatively, the Fischer indole synthesis can be carried out in two consecutive steps: **1-1** can react with **1-2** under suitable conditions (such as in an appropriate solvent such as ethanol or water, optionally with a suitable catalyst such as p-toluenesulfonic acid) to form the hydrazone **1-4**, which can then be reacted further under suitable conditions (for example, ethanol with hydrochloric acid, acetic acid with zinc chloride, or trifluoroacetic acid) to form **1-3** (for example, see J. Lancelot et al, *Chem. Pharm. Bull.* 1983, 31, 2652; X. Li and R. Vince, *Bioorg. Med. Chem.* 2006, 14, 2942; or G. Romeo et al., *Bioorg. Med. Chem.* 2006, 14, 5211).

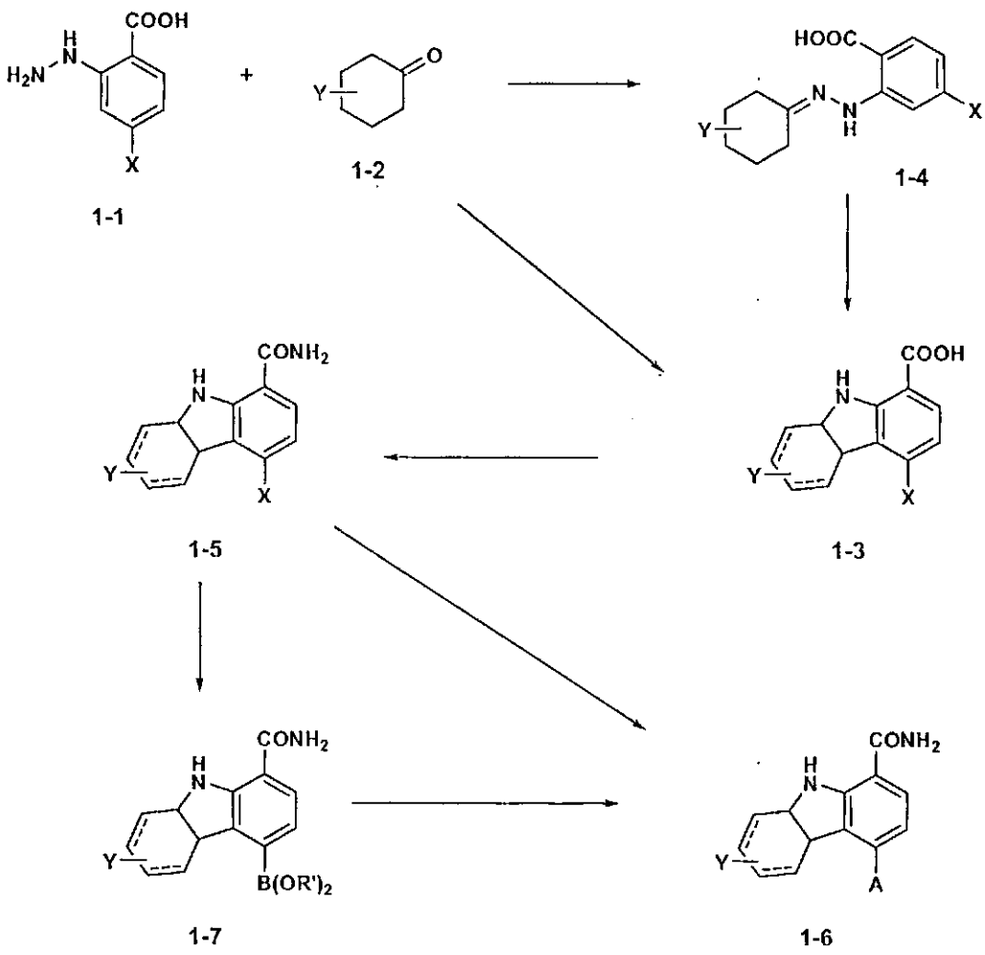


Figure 1.

[00164] The starting materials shown in Figure 1 can be prepared using methods known in the chemical literature. For example, compound **1-1** can be prepared from the corresponding anthranilic acid (see, for example, L. Street et al., *J. Med. Chem.* 1993, 36, 1529). As another example, compound **1-2** where Y is ethoxycarbonyl attached at the 3-position can be prepared from ethyl 3-hydroxybenzoate (see, for example, J. Hirsch et al., *J. Org. Chem.* 1986, 51, 2218.)

[00165] If desired, the tetrahydrocarbazole **1-3** (where the dotted lines represent single bonds) can be converted to the carbazole **1-3** (where the dotted lines represent double bonds) by treatment under suitable oxidizing conditions, for example by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone in a suitable solvent such as toluene, at a suitable temperature (for example, see J. Kamata et al., *Chem. Pharm. Bull.* 2004, 52, 1071). This conversion of a tetrahydrocarbazole to a carbazole may

also be performed in a different sequence with the other synthetic transformations outlined in Figure 1, for example at the stage of structure 1-5 or 1-6.

[00166] The carboxylic acid **1-3** can be converted to the carboxamide **1-5** using methods well known in the chemical literature, for example by conversion of **1-3** to the acid chloride by treatment with oxalyl chloride or sulfonyl chloride, followed by treatment with ammonia; or by treatment with ammonia in the presence of a coupling reagent such as carbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, and 1-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole.

[00167] In the case where X is a suitable precursor to A, such as bromo, **1-5** can be converted to **1-6** using methods known in the literature. For example, **1-5** (X = Br) can be heated with piperidine to provide **1-6** (A = 1-piperidyl). Also, **1-5** (X = Br) can be converted to **1-6** (A = for example, an aromatic group such as optionally substituted phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, or the like) by treatment with a suitable arylboronic acid or arylboronic acid ester in the presence of a suitable catalyst such as (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium or tetrakis(triphenylphosphine)palladium, with a suitable base such as potassium carbonate or tripotassium phosphate, in a suitable solvent or mixture or solvents, such as toluene, 1,4-dioxane, or toluene-ethanol-water. This reaction, commonly known as the Suzuki coupling, is well known in the chemical literature. Alternatively, compound **1-5** (X = Br) can be converted to a boronate ester **1-7** (where $B(OR')_2$ is, for example, 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl), for example by treatment with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) in the presence of a suitable combination of catalyst and ligand, such as tris(dibenzylideneacetone)dipalladium and tricyclohexylphosphine, with a suitable base such as potassium acetate, in a suitable solvent such as 1,4-dioxane (see, for example, L. Wang et al., *J. Med. Chem.* 2007, 50, 4162). The boronate ester **1-7**, or the derived boronic acid **1-7** (R' = H) prepared by hydrolysis of the boronate ester using methods known in the literature, can then be converted to compound **1-6** using the Suzuki coupling reaction or a similar reaction as described above for the direct conversion of **1-5** to **1-6**

[00168] Many boronic acids and boronate esters suitable for use in conversion of **1-5** to **1-6** (where A is an aryl or heteroaryl group) are commercially available, or may be prepared from corresponding aryl or heteroaryl derivatives such as bromides,

chlorides or trifluoromethanesulfonates, using methods known in the literature, for example as described above for the conversion of **1-5** to **1-7**. Such aryl bromides, chlorides or trifluoromethanesulfonates are either available commercially, or are known in the chemical literature, or can be prepared using well-known synthetic transformations.

[00169] In some cases it may be desirable to convert the primary amide of structure **1-5** to a different functional group, for example to prevent unwanted reactions or to enhance solubility for subsequent synthetic transformations. An example is shown in Figure 2. Compound **2-1** (equivalent to compound **1-5** in Figure 1) can be converted to the corresponding nitrile **2-2**, for example by treatment under suitable conditions with phosphorus oxychloride. Compound **2-2** (X = Br) may then be converted to compound **2-4**, either directly or through conversion to an intermediate boronate ester or boronic acid **2-3**, as described above, followed by hydrolysis of the nitrile **2-4** to the carboxamide **2-5** using methods known in the chemical literature.

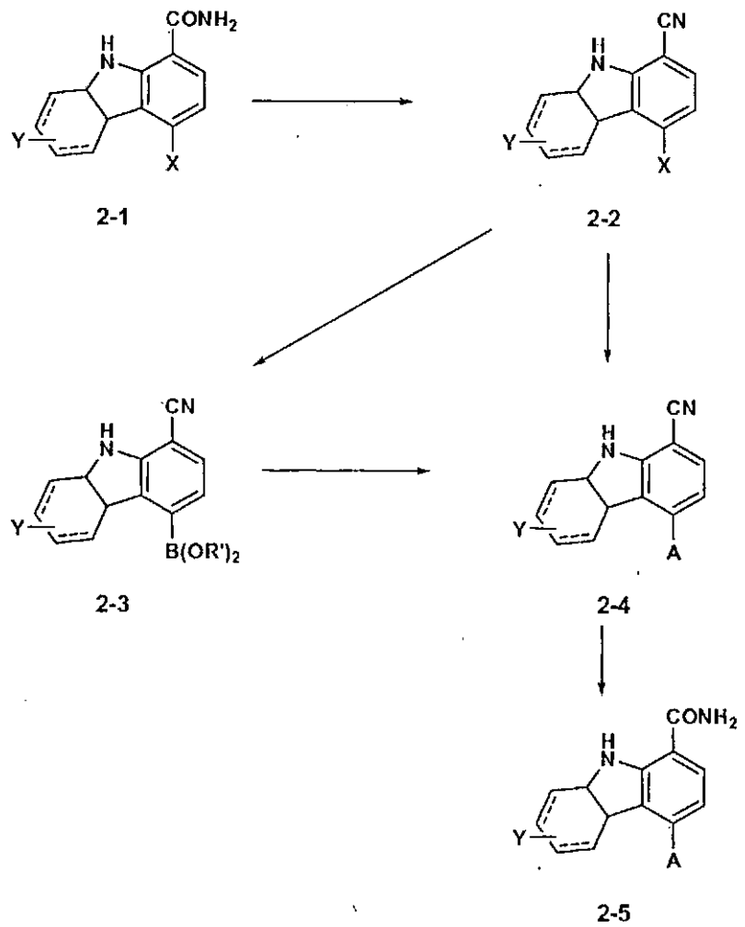


Figure 2.

[00170] Manipulation of substituents in the compounds of Formula (I) can be performed using a variety of methods which are well known in the chemical literature. For example, as shown in Figure 3, if the substituent Y in compound **1-5** (where X is either A of Formula (I) or a precursor to A) is an ester such as an ethyl ester (compound **3-1**), this ester may be converted into another substituent, for example by hydrolysis to the corresponding acid **3-2**, for example using a base such as lithium hydroxide or sodium hydroxide in water, followed by conversion to the amide **3-3** using any of a wide variety of methods well known in the chemical literature.

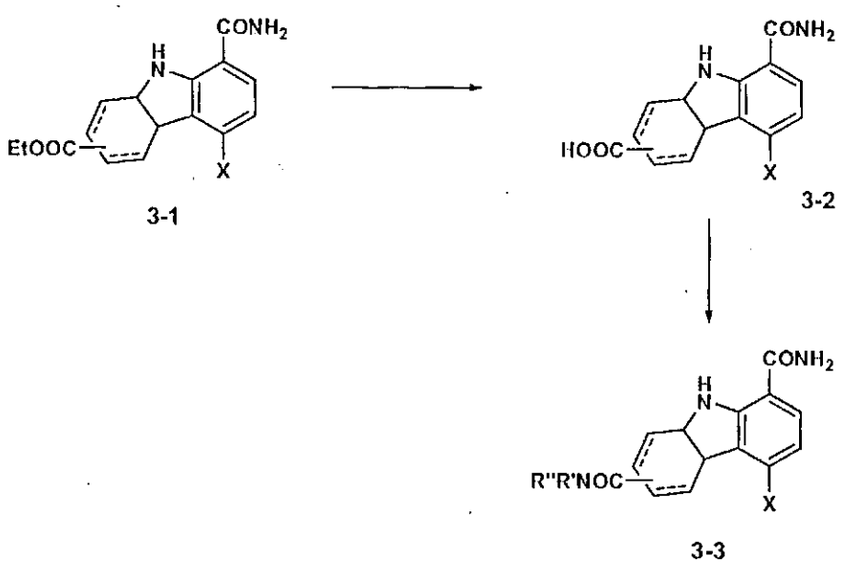


Figure 3.

[00171] Other examples of manipulation of a substituent are shown in Figure 4. An ester such as the ethyl ester (compound **4-1**) may be converted into an alcohol, aldehyde or ketone using standard synthetic methods well known in the literature. For example, treatment of the ester with a reducing agent such as lithium aluminum hydride can provide the primarily carbinol **4-2**. Alternatively, the ester can be converted to a tertiary carbinol **4-3** (where R and R' are the same) by treatment with an appropriate organometallic reagent such as an alkylmagnesium halide or an alkyllithium. Alternatively, the ester can be converted to a ketone **4-4**, for example by hydrolysis to the carboxylic acid, conversion to an N,O-dialkylhydroxamide and treatment of this intermediate with an appropriate organometallic reagent. A ketone **4-4** can be converted to a tertiary alcohol **4-3** (where R and R' are the same or different) by treatment with an appropriate organometallic reagent, or to a secondary alcohol **4-5** by treatment with a reducing agent such as sodium borohydride or lithium aluminum hydride. Alternatively, a primary alcohol **4-2** can be converted to an aldehyde **4-6**, which can be converted to a secondary alcohol **4-5** by treatment with an appropriate organometallic reagent.

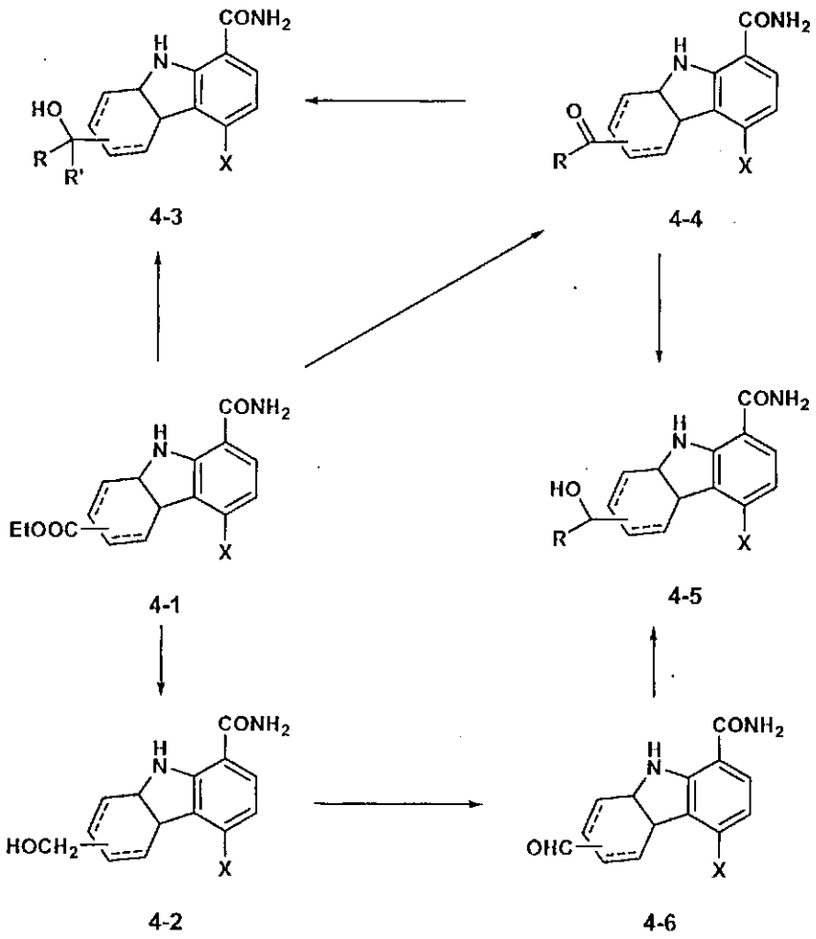


Figure 4.

[00172] Other examples of manipulation of a substituent are shown in Figure 5, which make use of transformations well known in the chemical literature. For example, a carbinol **5-1** (where R and R' can be, for example, hydrogen or alkyl; derived from an ester using transformations exemplified in Figure 4) can be converted to an ether **5-2** (R^1 = for example alkyl) by treatment with an alkylating agent such as an alkyl halide or alkyl trifluoromethanesulfonate in the presence of a base such as sodium hydride, or by treatment with a carbinol R^1OH in the presence of a catalyst such as trifluoroacetic acid. Alternatively, a carbinol **5-1** can be converted into an ester **5-3** (R^2 = for example alkyl or aryl) or carbamate **5-3** (R^2 = for example alkylamino or dialkylamino) by treatment with an acylating agent such as an acid anhydride, acid chloride or carbamyl chloride in the presence of a base such as a trialkylamine or pyridine, or by treatment with an acid in the presence of a coupling agent such as carbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide

hydrochloride, and 1-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole. Alternatively, a carbinol **5-1** can be converted into a derivative **5-4**, where X is a leaving group such as bromide, methanesulfonate, toluenesulfonate or trifluoromethanesulfonate. The compound **5-4** can then be converted into an amine **5-5** (where R^3 and R^4 are for example hydrogen, alkyl or aryl, or R^3 and R^4 form a heterocyclic ring) by treatment with an appropriate amine HNR^3R^4. Alternatively, the compound **5-4** can be converted to a primary amine **5-5** (where R^3 and R^4 are both hydrogen) by treatment with sodium azide to provide **5-4** (where X is N_3) followed by treatment with a reducing agent such as triphenylphosphine in the presence of water (commonly known as the Staudinger reduction). The compound **5-4** can also be converted into a heterocyclic derivative **5-6**, for example by treatment with a heterocycle ZH under appropriate conditions. Examples of Z in structure **5-6** are 2-oxopyrrolidin-1-yl, 2-oxopiperidin-1-yl, pyrazol-1-yl, and imidazol-1-yl.

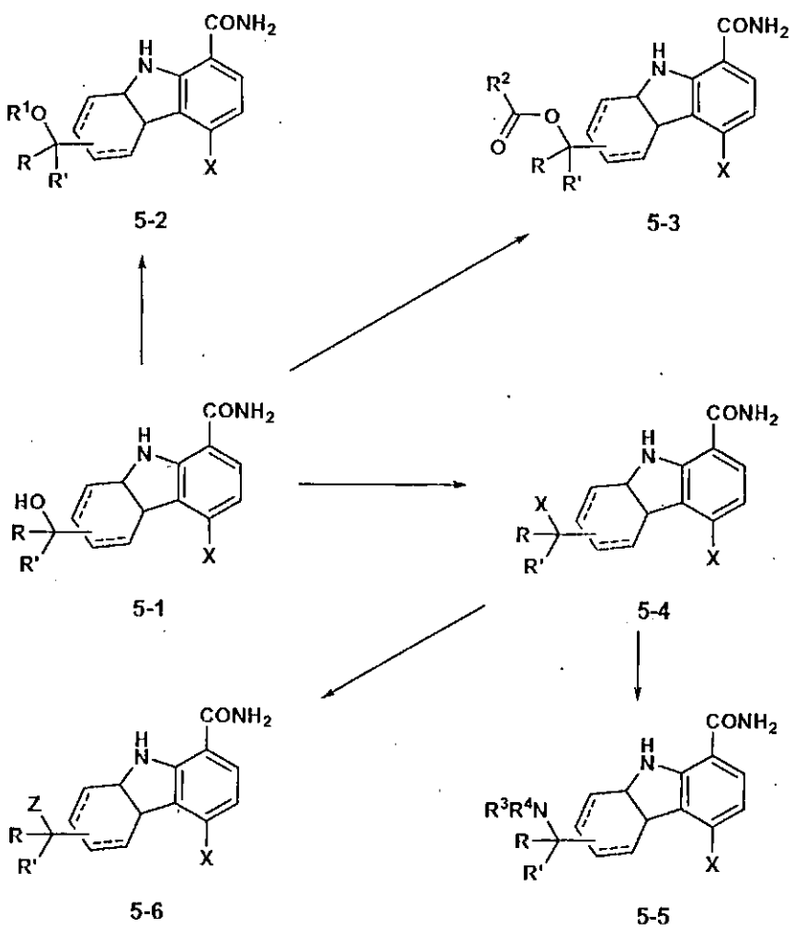


Figure 5.

[00173] Other examples of manipulation of a substituent are shown in Figure 6, which make use of transformations well known in the chemical literature. For example, a carbinol **6-1** having at least one hydrogen beta to the hydroxyl group (where R, R' and R" can be, for example, hydrogen or alkyl; prepared for example using transformations exemplified in Figure 4) can be converted to an alkene **6-2**, for example by dehydration in the presence of an acid catalyst, or by conversion of the hydroxyl to a leaving group such as methanesulfonate, toluenesulfonate or trifluoromethanesulfonate followed by treatment with a suitable base. An alkene **6-2** can be converted to **6-3** by reduction of the double bond, for example by treatment with hydrogen in the presence of a suitable catalyst such as palladium on charcoal. Alternatively, a carbinol **6-1** can be directly reduced to **6-3**, for example by treatment with a trialkylsilane in the presence of an acid such as trifluoroacetic acid. Alternatively, an alkene such as **6-2** can be converted to a diol **6-4**, for example by treatment with 4-methylmorpholine N-oxide in the presence of osmium tetroxide. A diol **6-4** can be converted into a monoester or a diester **6-5** (where one or both of R^1 and R^2 is an acyl group), or to a monoether or a diether **6-5** (where one or both or R^1 and R^2 is, for example, an alkyl group), or to a monocarbamate or a dicarbamate **6-5** (where one or both of R^1 and R^2 is a carbamyl group), or to a compound wherein R^1 and R^2 are independently alkyl, acyl or carbamyl, or to a compound wherein R^1 and R^2 form a heterocyclic ring such as a 1,3-dioxolane, a 1,3-dioxane, or a 1,3-dioxolan-2-one, using standard methods well known in the chemical literature.

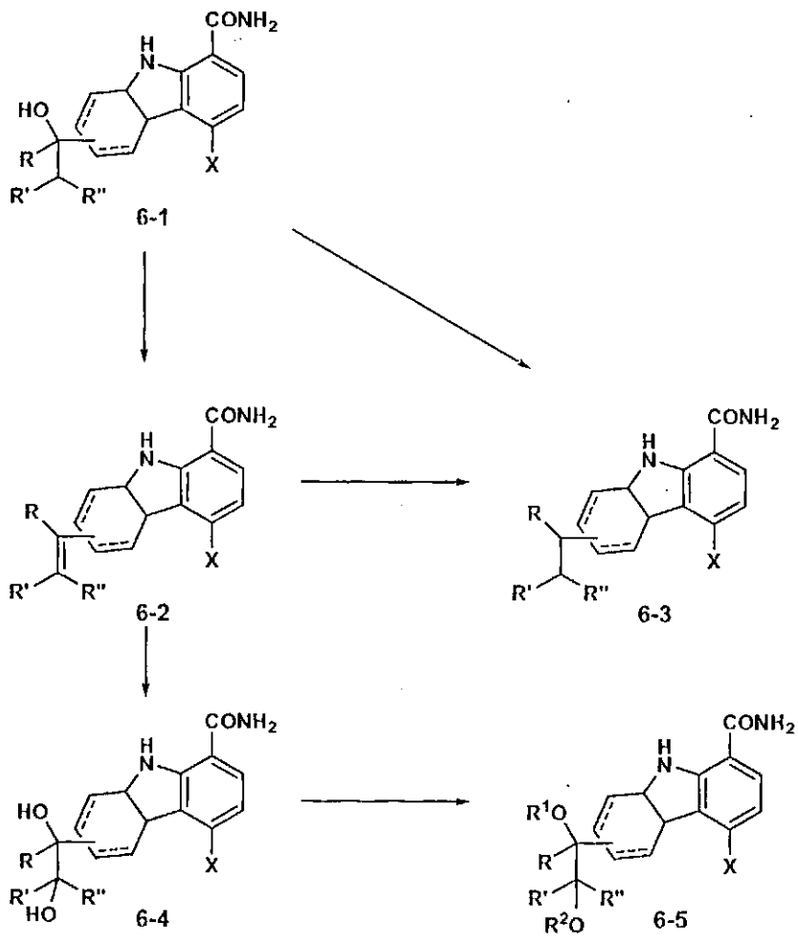


Figure 6.

[00174] Other examples of manipulation of a substituent are shown in Figure 7, which make use of transformations well known in the chemical literature. For example, an aldehyde or ketone **7-1** (R = hydrogen or, for example, alkyl, respectively, prepared for example using the transformations shown in Figure 4) can be converted to an amine **7-2** (where, for example, R^1 and R^2 are independently hydrogen or alkyl, or R^1 and R^2 together for a heterocyclic ring such as piperidine, pyrrolidine or morpholine) by treatment of **7-1** with an amine HNR^1R^2 in the presence of a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride, or by treatment of **7-1** with an amine HNR^1R^2 with removal of water to form an intermediate imine followed by reduction of the imine with a suitable reducing agent. Alternatively, **7-1** can be converted to an olefin **7-3** by treatment with a suitable reagent such as an alkyltriarylphosphonium halide or a dialkyl phosphonate in the presence of a suitable base, a transformation well-known

in the literature as the Wittig reaction. The resulting olefin **7-3** can then be converted to a variety of other compounds, for example by the transformations of **6-2** in Figure 6 as described above. Alternatively, **7-1** can be converted to a phenolic ester or carbinol ester **7-4** (where R = formyl or acyl) by treatment with an oxidizing reagent such as 3-chloroperoxybenzoic acid, peroxyacetic acid, peroxytrifluoroacetic acid or a mixture of hydrogen peroxide and a strong acid such as sulfuric acid, in a reaction well known in the chemical literature as the Baeyer-Villiger rearrangement. A compound **7-4** (R = formyl or acyl) can be converted into a phenol or carbinol **7-4** (R = H) by hydrolysis under well-known methods. The phenol or carbinol **7-4** can then be converted to, for example, an ester **7-4** (R = acyl), ether **7-4** (R = for example alkyl) or carbamate **7-4** (R = carbamyl) using well-known methods.

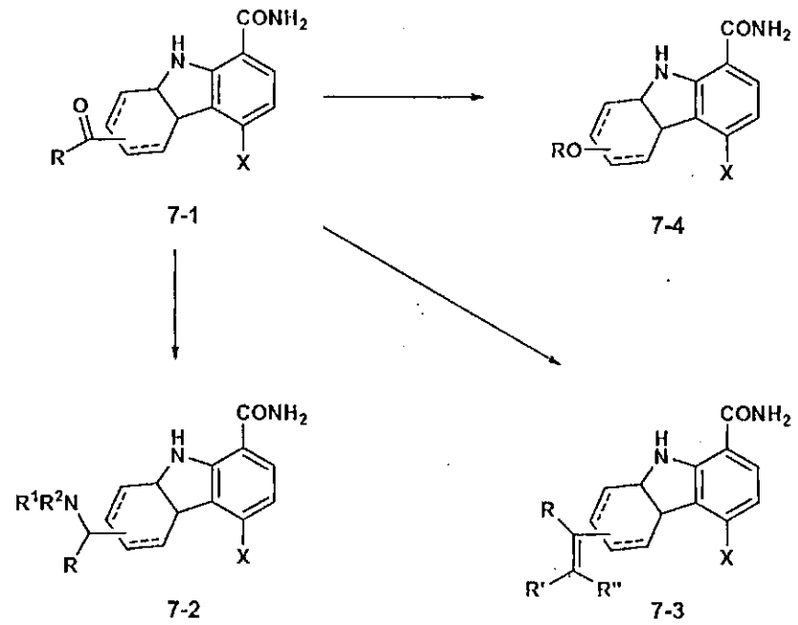


Figure 7.

[00175] Other examples of manipulation of a substituent are shown in Figure 8, which make use of transformations well known in the chemical literature. A carboxylic acid **8-1** (prepared, for example, as shown in Figure 3) can be converted to an acyl azide **8-2**, for example by treatment with diphenyl phosphorazidate (diphenyl phosphoryl azide). The acyl azide can be converted without isolation to an isocyanate **8-3**, for example by heating. The isocyanate can be converted to a urea **8-4** (where R and R' are independently, for example, hydrogen or alkyl, or taken together can form

a ring such as piperidine, pyrrolidine or morpholine). Alternatively, the acyl azide **8-2** can be heated in the presence of an alcohol to provide a carbamate **8-5** (where R is, for example, alkyl or benzyl). The carbamate **8-5** can be converted to a primary amine **8-6** by hydrolysis, or (in the case where R is benzyl) by treatment with, for example, hydrogen or ammonium formate in the presence of a catalyst such as palladium on charcoal, or with hydrogen bromide in acetic acid. In these transformations, an intermediate acyl azide **8-2** and/or isocyanate **8-3** can be isolated, or the entire sequence of steps converting an acid **8-1** to a urea **8-4** or a carbamate **8-5** can be performed without isolating the intermediates.

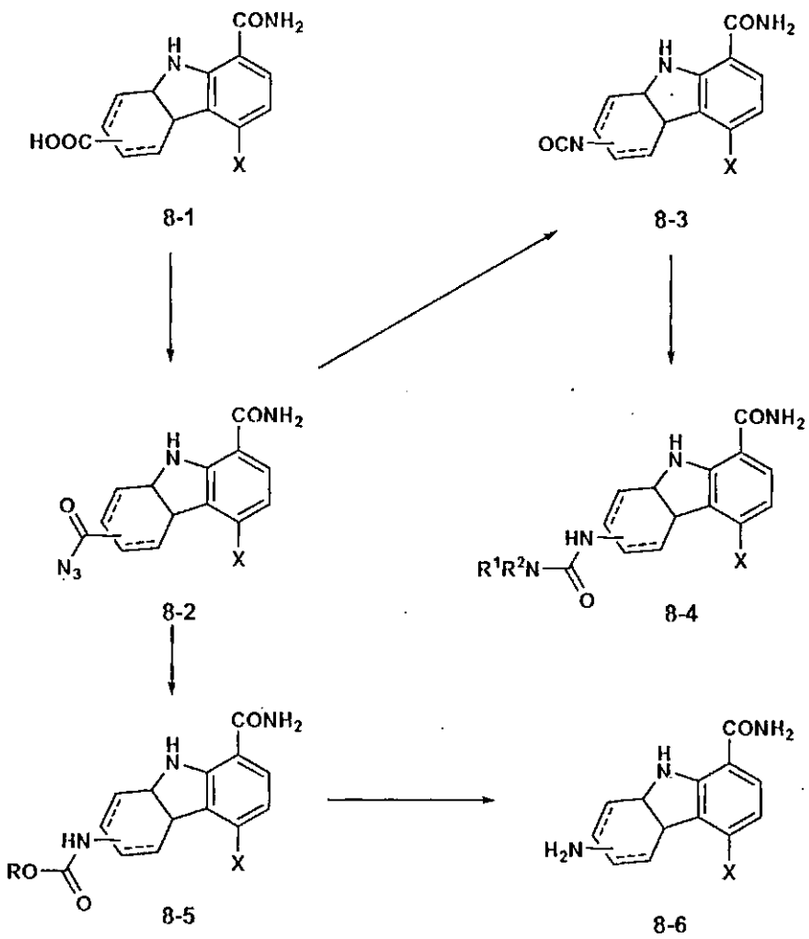


Figure 8.

[00176] Another example of manipulation of a substituent is shown in Figure 9. The nitro substituent of compound **9-1** (where Y can represent D^1 and/or D^2 of Formula (I) or a precursor to D^1 and/or D^2), prepared for example by Suzuki coupling

of compound **1-5** in Figure 1 with a nitro-substituted benzeneboronic acid, can be reduced using well known methods to provide a corresponding aniline **9-2**, for example by treatment with hydrogen in the presence of a catalyst such as palladium on charcoal, or by treatment with a reducing agent such as zinc or tin (II) chloride in an acid such as hydrochloric acid, or iron in acetic acid.

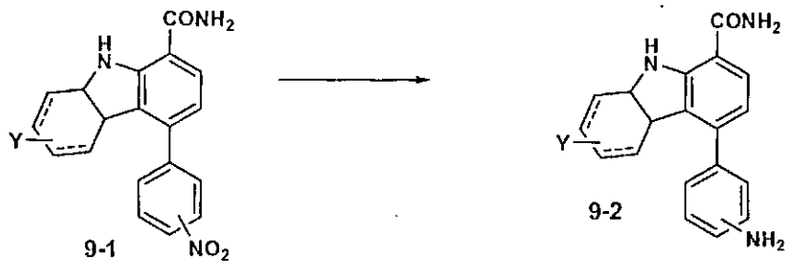


Figure 9.

[00177] Any amine substituent (for example, **5-5** in Figure 5, **7-2** in Figure 7, **8-6** in Figure 8, or **9-2** in Figure 9) wherein the amine is primary or secondary may be converted to other substituents using methods well known in the chemical literature. Examples are reaction with a carboxylic acid, a carboxylic acid halide or a carboxylic acid anhydride to provide an amide; reaction with an isocyanate, aryl carbamate or carbamyl chloride to provide a urea; reaction with a chloroformate ester to provide a carbamate; reaction with a sulfonyl halide or sulfonic anhydride to provide a sulfonamide or sulfonimide; reaction with a sulfamyl halide to provide a sulfamide; and reaction with an aldehyde or ketone in the presence of a suitable reducing agent to provide an alkylated amine.

[00178] Another example of transformations of such an amine substituent is reaction with an aryl or heteroaryl halide (such as for example a 2-chloropyridine, 2-chloroquinoline, 2-chloroisoquinoline or 4-chloroquinazoline), either in the presence or absence of a suitable catalyst such as a palladium catalyst, to provide an arylated amine. (The case where a palladium catalyst is used is commonly known in the chemical literature as the Buchwald amination). Another example is reaction with a bifunctional reagent such as, for example, a hydroxyacid or lactone or haloacyl chloride or haloalkanoic acid (to form a lactam) or a divinylsulfone (to form a thiomorpholine dioxide) under suitable conditions. In the case of reaction with such a bifunctional reagent, both reaction steps may be achieved in one synthetic operation,

or alternatively reaction with one functionality may be followed by isolation of an intermediate followed by reaction with the other functionality.

[00179] Another example of further manipulation of a substituent is the conversion of a suitable substituent on an aryl group (such as bromo, chloro or trifluoromethanesulfonate) to an aryl or heteroaryl group, for example via Suzuki coupling as described previously. Another example of further manipulation of a suitable substituent on an aryl group (such as bromo, chloro or trifluoromethanesulfonate) is the conversion of this substituent to an amine or aniline substituent (by treatment with a primary or secondary amine or aniline under suitable conditions, widely reported in the chemical literature and, when performed in the presence of a suitable catalyst such as a palladium catalyst, commonly know as the Buchwald amination). Another example of further manipulation of a suitable substituent on an aryl group (such as bromo, chloro or trifluoromethanesulfonate) is the conversion of this substituent into an amide by reaction with a primary or secondary amide or a lactam under suitable conditions widely reported in the chemical literature (for example, in the presence of a copper (I) salt and a diamine ligand).

[00180] The sequence of synthetic transformations (for example, the order of manipulations of the X and Y substituents and the carboxylic acid group in compound **1-3**) can be varied depending on the nature of the compound to be prepared, and can be determined by one skilled in the art through consideration of the stabilities of the various substituents to reaction conditions to be performed.

[00181] In some cases, it may be desirable for one or more functional groups in starting materials or intermediates to be present in a protected form. In such cases, removal of the protecting group can be performed at a suitable stage of the synthetic sequence, followed by further manipulation of the functional group if desired. Such protecting groups and their use and removal are well known to those skilled in the art.

[00182] In all the transformations discribed above, and in related transformations, reactions can be performed in suitable solvents, chosen for solubility of or compatibility with the reactants and reagents or for other properties such as boiling point or ability to facilitate the reaction to be performed. Reactions are usually performed at a temperature chosen to provide a convenient rate of reaction, usually from below ambient room temperature to the boiling point of the solvent, or above the

boiling point if the reaction is performed in a sealed vessel. The transformations described are generally well known in the chemical literature, and one skilled in the art of organic synthesis will be familiar with appropriate solvents, catalysts, reagents, and conditions suitable for performing the transformations desired, as well as suitable variations of the sequences of transformations used to provide a desired product.

[00183] In the case where the dashed lines of Formula (I) represent single bonds and substituents D^1 and/or D^2 are present, or if substituents D^1 and/or D^2 bear a chiral center, or if the substituent A bears a chiral center, enantiomers are possible. If the dashed lines represent single bonds and additionally one or more of the substituents A, D^1 and/or D^2 bears a chiral center, or if the dashed lines represent double bonds and two or more of the substituents A, D^1 and/or D^2 bear chiral centers, diastereomers are possible. Additionally, in some cases, restricted rotation about certain bonds, particularly the bond attaching substituent A in Formula (I), can give rise to optical isomers, known as atropisomers, even when no chiral atom is present. An enantiomerically or diastereomerically enriched compound can be prepared by using an enantiomerically or diastereomerically enriched starting material (for example, **1-2** for the synthesis outlined in Figure 1, or coupling of **1-5** or **1-7** with an enantiomerically enriched reactant, or acylation of an amine or hydroxyl substituent with an enantiomerically enriched acylating agent). Alternatively, racemic starting materials or reagents can be used, followed by separation of enantiomers or diastereomers, for example by using chiral HPLC or using chemical methods well known in the chemical literature. Such separation can be performed at any suitable stage in the synthetic sequence, or the final compound of Formula (I) can be separated into enantiomers or diastereomers.

EXAMPLES

[00184] Preparation of compounds of Formula (I), and intermediates used in the preparation of compounds of Formula (I), can be prepared using procedures shown in the following examples and related procedures. The methods and conditions used in these examples, and the actual compounds prepared in these examples, are not meant to be limiting, but are meant to demonstrate how the compounds of Formula (I) can be prepared. Starting materials and reagents used in these examples, when not prepared

by a procedure described herein, are generally either commercially available, or are reported in the chemical literature, or may be prepared by using procedures described in the chemical literature.

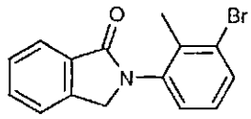
[00185] In the examples given, the phrase "dried and concentrated" generally refers to drying of a solution in an organic solvent over either sodium sulfate or magnesium sulfate, followed by filtration and removal of the solvent from the filtrate (generally under reduced pressure and at a temperature suitable to the stability of the material being prepared). Column chromatography was performed with pre-packed silica gel cartridges using an Isco medium pressure chromatography apparatus (Teledyne Corporation), eluting with the solvent or solvent mixture indicated. Preparative high performance liquid chromatography (HPLC) was performed using a reverse phase column (Waters Sunfire C_{18}, Waters Xbridge C_{18}, Phenomenex Axia C_{18}, YMC S5 ODS or the like) of a size appropriate to the quantity of material being separated, generally eluting with a gradient of increasing concentration of methanol or acetonitrile in water, also containing 0.05% or 0.1% trifluoroacetic acid or 10 mM ammonium acetate, at a rate of elution suitable to the column size and separation to be achieved. Chemical names were determined using ChemDraw Ultra, version 9.0.5 (CambridgeSoft). The following abbreviations are used:

NaHCO3 (aq) – saturated aqueous sodium bicarbonate
brine – saturated aqueous sodium chloride
DCM – dichloromethane
DIEA – N,N-diisopropylethylamine
DMAP – 4-(N,N-dimethylamino)pyridine
DMF – N,N-dimethylformamide
DMSO – dimethyl sulfoxide
EDC – N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EtOAc – ethyl acetate
HOAT – 1-hydroxy-7-azabenzotriazole
HOBT – 1-hydroxybenzotriazole hydrate
rt – ambient room temperature (generally about 20-25 °C)
TEA - triethylamine
TFA – trifluoroacetic acid

THF – tetrahydrofuran

Intermediate 1-1

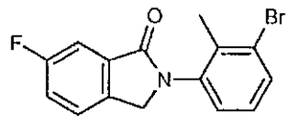
Preparation of 2-(3-bromo-2-methylphenyl)isoindolin-1-one



[00186] A solution of 3-bromo-2-methylaniline (10 g, 53.7 mmol) in DCM (200 mL) at 0 °C was treated with TEA (14.98 mL, 107 mmol), followed by dropwise addition of 2-(chloromethyl)benzoyl chloride (10.16 g, 53.7 mmol) in DCM (50 mL) over 1 h. The mixture was diluted with DCM (ca. 1 L), washed with NaHCO3 (aq) and water, and concentrated to remove most of the solvent. The precipitate was collected by filtration and washed with DCM (2 x 10 mL) to provide N-(3-bromo-2-methylphenyl)-2-(chloromethyl)benzamide as a white solid (8.0 g). The filtrate was concentrated further, resulting in additional precipitate which was collected by filtration and washed with DCM (2 x 10 mL) to provide additional N-(3-bromo-2-methylphenyl)-2-(chloromethyl)benzamide as a white solid (3.06 g), for a combined yield of 61%. Mass spectrum 338, 340, 342 The filtrate was concentrated and purified by column chromatography (hexane-EtOAc) to provide 2-(3-bromo-2-methylphenyl)isoindolin-1-one as a yellow solid (2.0 g, 12%). A solution of the N-(3-bromo-2-methylphenyl)-2-(chloromethyl)benzamide (11.06 g, 32.7 mmol) in DMF (50 mL) was cooled to 0 °C and treated with a mixture of sodium hydride (60% oil dispersion, pre-washed with hexane, 1.70 g, 42.5 mmol) and DMF (10 mL). The mixture was stirred at 0 °C for 1.5 h, then was treated with water. The precipitate was collected by filtration, dried and combined with the material purified by column chromatography (see above) to provide 2-(3-bromo-2-methylphenyl)isoindolin-1-one as a yellow solid (9.41 g, 95%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.96 (1 H, d, *J*=7.5 Hz), 7.58 - 7.67 (2 H, m), 7.49 - 7.57 (2 H, m), 7.20 - 7.25 (1 H, m), 7.15 (1 H, t, *J*=7.9 Hz), 4.72 (2 H, s), 2.31 (3 H, s). Mass spectrum m/z 302, 304 $(M+H)^+$.

Intermediate 1-2

Preparation of 2-(3-bromo-2-methylphenyl)-6-fluoroisoindolin-1-one



[00187] Step 1 A suspension of 5-fluoro-2-methylbenzoic acid (500 mg, 3.24 mmol), N-bromosuccinimide (606 mg, 3.41 mmol) and benzoyl peroxide (47 mg, 0.195 mmol) in tetrachloromethane (10 mL) was heated at 78 °C for 4 h. The hot mixture was filtered and the filtrate was concentrated to provide crude 2-(bromomethyl)-5-fluorobenzoic acid as a white solid (730 mg), used without further purification. ^{1}H NMR (400 MHz, chloroform-d) δ 7.81 (1 H, dd, *J*=9.2, 2.9 Hz), 7.50 (1 H, dd, *J*=8.5, 5.4 Hz), 7.23 - 7.30 (1 H, m), 4.98 (2 H, s).

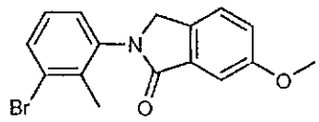
[00188] Step 2 A solution of crude 2-(bromomethyl)-5-fluorobenzoic acid (3.05 g, 13.1 mmol) in DCM (50 mL) was treated with oxalyl chloride (1.66 g, 13.1 mmol) and 6 drops of DMF. The mixture was stirred at rt for 1 h, then was concentrated. The residue was redissolved in DCM (50 mL) and treated with 3-bromo-2-methylaniline (1.705 g, 9.16 mmol). The mixture was stirred at rt for 1 h, then TEA (2.19 mL, 15.7 mmol) was added in portions. The mixture was stirred at rt for 2 h, then was diluted with DCM (100 mL), washed with NaHCO3 (aq) and water, dried and concentrated. The residue was triturated with DCM to provide N-(3-bromo-2-methylphenyl)-2-(bromomethyl)-5-fluorobenzamide as a white solid (0.9 g). The mother liquor was concentrated and the residue was again triturated with DCM to provide additional N-(3-bromo-2-methylphenyl)-2-(bromomethyl)-5-fluorobenzamide as a white solid (0.46 g). The mother liquor was concentrated and the residue was purified by column chromatography (eluting with a gradient from hexane to 70:30 EtOAc-hexane) to provide additional N-(3-bromo-2-methylphenyl)-2-(bromomethyl)-5-fluorobenzamide as a pink solid (1.18 g) for a total of 2.54 g (48%). Mass spectrum m/z 400, 402, 404 $(M+H)^+$.

[00189] Step 3 A mixture of N-(3-bromo-2-methylphenyl)-2-(bromomethyl)-5-fluorobenzamide (2.54 g, 6.33 mmol) and sodium *tert*-butoxide (0.913 g, 9.50 mmol) in THF (80 mL) was stirred at rt for 30 min. The mixture was diluted with water and extracted with twice with DCM. The combined organic phases were washed with water, dried and concentrated. The residue was purified by column chromatography (eluting with hexane-EtOAc) to provide 2-(3-bromo-2-methylphenyl)-6-fluoroisoindolin-1-one as a white solid (1.18 g, 58%). ^{1}H NMR (400 MHz,

chloroform-d) δ 7.59 - 7.65 (2 H, m), 7.45 - 7.50 (1 H, m), 7.33 (1 H, td, *J*=8.6, 2.5 Hz), 7.19 - 7.24 (1 H, m), 7.15 (1 H, t, *J*=7.9 Hz), 4.68 (2 H, s), 2.31 (3 H, s). Mass spectrum m/z 320, 322 $(M+H)^+$.

Intermediate 1-3

Preparation of 2-(3-bromo-2-methylphenyl)-6-methoxyisoindolin-1-one



[00190] Step 1 A suspension of methyl 5-methoxy-2-methylbenzoate (1.00 g, 5.55 mmol), N-bromosuccinimide (1.037 g, 5.83 mmol) and benzoyl peroxide (81 mg, 0.333 mmol) in tetrachloromethane (10 mL) was heated at 77 °C for 3 h. The mixture was diluted with DCM, washed with NaHCO3 (aq), dried and concentrated to provide crude methyl 2-(bromomethyl)-5-methoxybenzoate as a light yellow solid (1.435 g), used without further purification. ^{1}H NMR (400 MHz, chloroform-d) δ 7.48 (1 H, d, J=2.64 Hz), 7.37 (1 H, d, J=8.36 Hz), 7.02 (1 H, dd, J=8.58, 2.86 Hz), 4.93 (2 H, s), 3.95 (3 H, s), 3.85 (3 H, s).

[00191] Step 2 A mixture of methyl 2-(bromomethyl)-5-methoxybenzoate (1.435 g, 5.54 mmol), 3-bromo-2-methylaniline (1.03 g, 5.54 mmol) and TEA (1.158 mL, 8.31 mmol) in methanol (5 mL) was heated at 85 °C for 2 h. The mixture was diluted with DCM, washed with NaHCO3 (aq), and dried and concentrated. The residue was purified by column chromatography (eluting with EtOAc-hexane)to provide methyl 2-((3-bromo-2-methylphenylamino)methyl)-5-methoxybenzoate as a yellow oil (361 mg, 18%). Mass spectrum m/z 364, 366 $(M+H)^+$.

[00192] Step 3 A solution of methyl 2-((3-bromo-2-methylphenylamino)methyl)-5-methoxybenzoate (360 mg, 0.988 mmol) in THF (10 mL) was treated with sodium tert-butoxide (142 mg, 1.483 mmol) and stirred at rt overnight. The mixture was treated with water and extracted twice with DCM. The combined organic phases were washed with water, dried and concentrated. The residue was purified by column chromatography (eluting with EtOAc-hexane) to provide 2-(3-bromo-2-methylphenyl)-6-methoxyisoindolin-1-one as a white solid (246 mg, 75%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.62 (1 H, dd, J=7.9, 1.1 Hz), 7.46 (1 H, d, J=2.4 Hz),

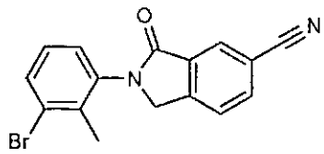
7.42 (1 H, d, J=8.4 Hz), 7.15 - 7.26 (3 H, m), 4.67 (2 H, s), 3.92 (3 H, s), 2.34 (3 H, s). Mass spectrum m/z 332, 334 $(M+H)^+$.

[00193] The following Intermediates were also prepared using procedures used to prepare Intermediates 1-1 through 1-3.

Intermediate	Compound name	Mass spectrum
1-4	2-(3-bromo-2-methylphenyl)-5-methoxyisoindolin-1-one	332, 334 $(M+H)^+$
1-5	2-(3-bromo-2-methylphenyl)-6-(trifluoromethyl)isoindolin-1-one	370, 372 $(M+H)^+$
1-6	2-(3-bromo-2-methylphenyl)-6-methylisoindolin-1-one	316, 318 $(M+H)^+$

Intermediate 2-1

Preparation of 2-(3-bromo-2-methylphenyl)-3-oxoisoindoline-5-carbonitrile



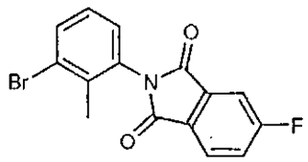
[00194] Step 1 A solution of 3-bromo-2-methylaniline (0.67 g, 3.60 mmol) in DCM (18 mL) was treated dropwise with trimethylaluminum (2 M in toluene, 1.801 mL, 3.60 mmol) and the resulting solution was stirred at rt for 30 min. A solution of 3-oxo-1,3-dihydroisobenzofuran-5-carbonitrile (0.573 g, 3.60 mmol) in DCM (18.00 mL) was added and the resulting mixture was stirred at rt overnight. The mixture was diluted with DCM, washed with an aqueous solution of sodium potassium tartrate (Fehling's Reagent II) and water, then was dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 80:20 hexane-EtOAc to EtOAc) to provide N-(3-bromo-2-methylphenyl)-5-cyano-2-(hydroxymethyl)benzamide as a white solid (170 mg, 14%) which was used without further purification. Mass spectrum m/z 345, 347 $(M+H)^+$.

[00195] Step 2 A solution of N-(3-bromo-2-methylphenyl)-5-cyano-2-(hydroxymethyl)benzamide (170 mg, 0.492 mmol) in THF (20 mL) was treated with di-*tert*-butyl azodicarboxylate (113 mg, 0.492 mmol) and tributylphosphine (0.119

mL, 0.492 mmol) and stirred at rt. After 2 h the mixture was concentrated and the residue was column chromatography (eluting with a gradient from 90:10 to 50:50 hexane-EtOAc) to provide 2-(3-bromo-2-methylphenyl)-3-oxoisoindoline-5-carbonitrile (100 mg, 62%) as a white solid. ^{1}H NMR (400 MHz, chloroform-d) δ 8.07 (1 H, d, *J*=8.1 Hz), 7.82 - 7.89 (2 H, m), 7.64 (1 H, dd, *J*=7.8, 1.4 Hz), 7.13 - 7.25 (2 H, m), 4.78 (2 H, s), 2.30 (3 H, s). Mass spectrum m/z 327, 329 $(M+H)^+$.

Intermediate 3-1

Preparation of 2-(3-bromo-2-methylphenyl)-5-fluoroisoindoline-1,3-dione



[00196] A mixture of 3-bromo-2-methylaniline (200 mg, 1.075 mmol) and 5-fluoroisobenzofuran-1,3-dione (179 mg, 1.075 mmol) in acetic acid (2 mL) was heated at 100 °C for 4.5 h. The mixture was concentrated and the residue was purified by column chromatography (eluting with a gradient from hexane to 60:40 hexane-EtOAc) to give 2-(3-bromo-2-methylphenyl)-5-fluoroisoindoline-1,3-dione as a white solid (235 mg, 59%). Mass spectrum m/z 334, 336 $(M+H)^+$.

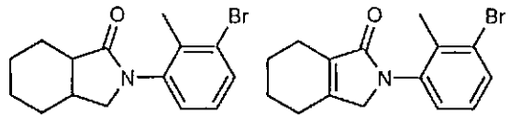
[00197] The following Intermediates were also prepared using procedures used to prepare Intermediate 3-1.

Intermediate	Compound name	Mass spectrum
3-2	2-(3-bromo-2-methylphenyl)-5-*tert*-butylisoindoline-1,3-dione	372, 374 $(M+H)^+$
3-3	2-(3-bromo-2-methylphenyl)-5-chloroisoindoline-1,3-dione	350, 352 $(M+H)^+$
3-4	2-(3-bromo-2-methylphenyl)-5-methylisoindoline-1,3-dione	330, 332 $(M+H)^+$
3-5	2-(3-bromo-2-methylphenyl)-4-fluoroisoindoline-1,3-dione	334, 336 $(M+H)^+$

3-6	2-(3-bromo-2-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione	322, 324 $(M+H)^+$
3-7	2-(3-bromo-2-methylphenyl)-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione	317, 319 $(M+H)^+$

Intermediates 4-1 and 4-2

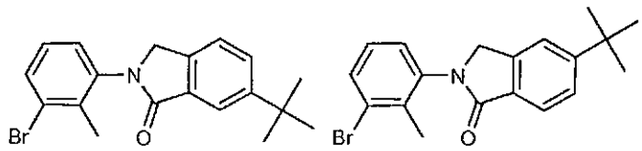
Preparation of 2-(3-bromo-2-methylphenyl)octahydro-1H-isoindol-1-one and 2-(3-bromo-2-methylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one



[00198] A suspension of 2-(3-bromo-2-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione (Intermediate 3-6, 4.5 g, 13.97 mmol) in methanol (150 mL) was treated with sodium borohydride (2.64 g, 69.8 mmol) and stirred at rt for 4 h. The mixture was concentrated, and the residue was dissolved in DCM, washed with NaHCO3 (aq) and water, and dried and concentrated to provide 2-(3-bromo-2-methylphenyl)-3-hydroxyoctahydro-1H-isoindol-1-one as a yellow solid (3.94 g, 87%). Mass spectrum m/z 324, 326 $(M+H)^+$. Without purification, a portion of this material (1.8 g, 5.55 mmol) was dissolved in DCM (50 mL) and treated with triethylsilane (6.46 g, 55.5 mmol). The solution was treated dropwise at rt with TFA (2.14 mL, 27.8 mmol) and stirred at rt for 30 min. The mixture was concentrated and the residue was dissolved in DCM, washed with NaHCO3 (aq) and water. The organic phase was dried and concentrated. The residue was purified by column chromatography (eluting with hexane-EtOAc) to provide 2-(3-bromo-2-methylphenyl)octahydro-1H-isoindol-1-one (Intermediate 4-1, 1.35 g, 79%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.48 - 7.53 (1 H, m), 7.06 - 7.09 (2 H, m), 3.78 (1 H, dd, *J*=9.5, 5.7 Hz), 3.19 (1 H, dd, *J*=9.5, 2.4 Hz), 2.64 - 2.70 (1 H, m), 2.45 - 2.54 (1 H, m), 2.30 (3 H, s), 2.10 - 2.17 (1 H, m), 1.80 - 1.88 (1 H, m), 1.62 - 1.71 (2 H, m), 1.56 - 1.62 (1 H, m), 1.40 - 1.51 (1 H, m), 1.31 (2 H, s). Mass spectrum m/z 308, 310 $(M+H)^+$. Also isolated was 2-(3-bromo-2-methylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (Intermediate 4-2, 224 mg, 13%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.51 - 7.55 (1 H, m), 7.05 - 7.14 (2 H, m), 4.09 (2 H, t, *J*=1.9 Hz), 2.28 - 2.37 (4 H, m), 2.28 (3 H, s), 1.73 - 1.85 (4 H, m). Mass spectrum m/z 306, 308 $(M+H)^+$.

Intermediates 4-3 and 4-4

Preparation of 2-(3-bromo-2-methylphenyl)-6-*tert*-butylisoindolin-1-one and 2-(3-bromo-2-methylphenyl)-5-*tert*-butylisoindolin-1-one



[00199] A suspension of 2-(3-bromo-2-methylphenyl)-5-*tert*-butylisoindoline-1,3-dione (Intermediate 3-2, 1.0 g, 2.69 mmol) in methanol (20 mL) was treated with sodium borohydride (203 mg, 5.37 mmol) and stirred at rt. After a few minutes, additional sodium borohydride (203 mg, 5.37 mmol) was added. After 40 min, the mixture was concentrated, and the residue was dissolved in DCM, washed with water and brine, and dried and concentrated to provide a white solid. This material was dissolved in DCM (10 mL) and treated with TFA (10 mL) and stirred for a few minutes at rt, then was treated with triethylsilane (6.40 mL, 40.1 mmol) and stirred at rt for 2.5 h. The mixture was concentrated and the residue was dissolved in DCM, washed with NaHCO3 (aq) and water. The organic phase was dried and concentrated. The residue was purified by column chromatography (eluting with hexane-EtOAc) to provide 2-(3-bromo-2-methylphenyl)-6-*tert*-butylisoindolin-1-one (Intermediate 4-3, 134 mg, 28%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.99 (1 H, d, J=1.32 Hz), 7.68 (1 H, dd, J=7.91, 1.76 Hz), 7.60 (1 H, dd, J=7.69, 1.10 Hz), 7.45 (1 H, d, J=7.91 Hz), 7.19 - 7.23 (1 H, m), 7.15 (1 H, t, J=7.69 Hz), 4.68 (2 H, s), 2.31 (3 H, s), 1.39 (9 H, s). Mass spectrum m/z 358, 360 $(M+H)^+$. Also isolated was 2-(3-bromo-2-methylphenyl)-5-*tert*-butylisoindolin-1-one (Intermediate 4-4, 250 mg, 52%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.88 (1 H, d, J=7.91 Hz), 7.59 (2 H, dd, J=8.13, 2.86 Hz), 7.53 (1 H, s), 7.20 - 7.23 (1 H, m), 7.12 - 7.17 (1 H, m), 4.69 (2 H, s), 2.31 (3 H, s), 1.40 (9 H, s). Mass spectrum m/z 358, 260 $(M+H)^+$.

[00200] The following Intermediates were also prepared using procedures used to prepare Intermediate 4-1 through 4-4.

Intermediate	Compound name	Mass spectrum

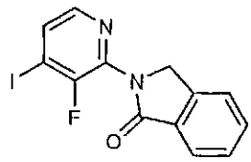
NMR (400 MHz, chloroform-d) δ 8.68 (1 H, s), 8.42 (1 H, s), 7.84 (1 H, d, *J*=7.77 Hz), 7.37 (1 H, d, *J*=7.77 Hz), 7.34 (1 H, s), 4.73 (2 H, s), 2.50 (3 H, s), 2.35 (3 H, s). Mass spectrum m/z 317, 319 $(M+H)^+$.

[00203] The following Intermediate was also prepared using procedures used to prepare Intermediate 5-1.

Intermediate	Compound name	Mass spectrum
5-2	2-(5-bromo-4-methylpyridin-3-yl)isoindolin-1-one	351.2 $(M+H)^+$

Intermediate 6-1

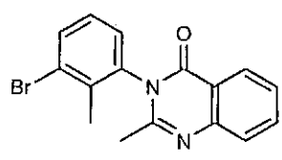
Preparation of 2-(3-fluoro-4-iodopyridin-2-yl)isoindolin-1-one



[00204] A mixture of 3-fluoro-2,4-diiodopyridine (300 mg, 0.860 mmol), isoindolin-1-one (114 mg, 0.860 mmol), copper (I) iodide (8.19 mg, 0.043 mmol), potassium carbonate (238 mg, 1.720 mmol) and N^1,N^2-dimethylethane-1,2-diamine (7.58 mg, 0.086 mmol) in 1,4-dioxane (5 mL) was heated at 110 °C in a sealed tube for 15 h. The mixture was cooled to rt, filtered through Celite and washed with DCM. The filtrate was concentrated and the residue was purified by column chromatography (eluting with a gradient from 80:20 hexane-EtOAc to EtOAc) to give 2-(3-fluoro-4-iodopyridin-2-yl)isoindolin-1-one (125 mg, 41%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.86 - 8.06 (2 H, m), 7.41 - 7.71 (4 H, m), 5.04 (2 H, s). Mass spectrum m/z 354.9 $(M+H)^+$.

Intermediate 7-1

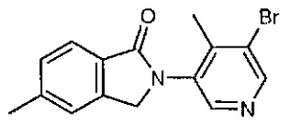
Preparation of 3-(3-bromo-2-methylphenyl)-2-methylquinazolin-4(3H)-one



4-5	2-(3-bromo-2-methylphenyl)-7-fluoroisoindolin-1-one	320, 322 $(M+H)^+$
4-6	2-(3-bromo-2-methylphenyl)-4-fluoroisoindolin-1-one	320, 322 $(M+H)^+$
4-7	2-(3-bromo-2-methylphenyl)-5-methylisoindolin-1-one	316, 318 $(M+H)^+$
4-8	2-(3-bromo-2-methylphenyl)-5-fluoroisoindolin-1-one	320, 322 $(M+H)^+$

Intermediate 5-1

Preparation of 2-(5-bromo-4-methylpyridin-3-yl)-5-methylisoindolin-1-one



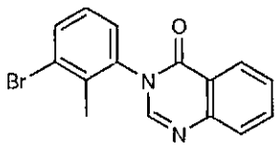
[00201] Step 1 A mixture of 5-methylisoindoline-1,3-dione (5.00 g, 31.0 mmol) and tin shavings (8.84 g, 74.5 mmol) in acetic acid (30 mL) and concentrated hydrochloric acid (15 mL) was heated at reflux for 3 h. The hot solution was filtered and the residual tin shavings were washed with acetic acid. The filtrate was concentrated and the residue was diluted with DCM (200 mL), and washed with water (20 mL) and brine (20 mL), dried and concentrated. The precipitate which formed during the concentration was collected by filtration and washed with DCM (5 mL) and dried under vacuum to give 5-methylisoindolin-1-one (2.3 g, 50%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.70 (1 H, d, *J*=7.77 Hz), 7.43 (1 H, s), 7.35 (1 H, d, *J*=7.77 Hz), 4.46 (2 H, s), 2.48 (3 H, s). Mass spectrum m/z 148.0 $(M+H)^+$.

[00202] Step 2 A mixture of 3,5-dibromo-4-methylpyridine (2.00 g, 7.97 mmol), 6-methylisoindolin-1-one (1.173 g, 7.97 mmol), copper (I) iodide (0.076 g, 0.399 mmol), potassium carbonate (2.203 g, 15.94 mmol) and N^1,N^2-dimethylethane-1,2-diamine (0.070 g, 0.797 mmol) in 1,4-dioxane (20 mL) was heated at 100 °C for 15 h. The mixture was cooled to rt, filtered through Celite and washed with DCM. The filtrate was diluted with DCM (100 mL) and washed with water (10 mL) and brine (10 mL), then was dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 80:20 hexane-EtOAc to EtOAc) to give 2-(5-bromo-4-methylpyridin-3-yl)-5-methylisoindolin-1-one (760 mg, 30%). ^{1}H

[00205] A solution of 2-methyl-4H-benzo[d][1,3]oxazin-4-one (300 mg, 1.862 mmol), 3-bromo-2-methylaniline (346 mg, 1.862 mmol), and triethoxymethane (276 mg, 1.862 mmol) in THF (2 mL) was heated overnight in a sealed tube at 100 °C. The mixture was cooled to rt and diluted with DCM. The solution was washed with water and NaHCO3 (aq), and dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 90:10 to 50:50 hexane-EtOAc) and the crude product was triturated in hexane to give 3-(3-bromo-2-methylphenyl)-2-methylquinazolin-4(3H)-one as an off-white solid (120 mg, 20%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.28 (1 H, dd, J=7.92, 1.10 Hz), 7.77 - 7.82 (1 H, m), 7.68 - 7.73 (2 H, m), 7.47 - 7.52 (1 H, m), 7.22 - 7.25 (1 H, m), 7.13 - 7.17 (1 H, m), 2.20 (6 H, s). Mass spectrum m/z 329, 331 $(M+H)^+$.

Intermediate 8-1

Preparation of 3-(3-bromo-2-methylphenyl)quinazolin-4(3H)-one



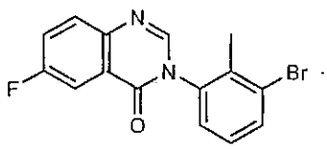
[00206] A mixture of 1H-benzo[d][1,3]oxazine-2,4-dione (200 mg, 1.226 mmol), 3-bromo-2-methylaniline (228 mg, 1.226 mmol), and trimethoxymethane (390 mg, 3.68 mmol) in THF (2 mL) was heated overnight in a sealed tube at 100 °C. The mixture was cooled to rt and concentrated, and the residue was purified by column chromatography (eluting with 90:10 to 50:50 hexane-EtOAc) to give 3-(3-bromo-2-methylphenyl)quinazolin-4(3H)-one (140 mg, 36%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.37 (1 H, dd, *J*=8.3, 1.2 Hz), 7.97 (1 H, s), 7.76 - 7.86 (2 H, m), 7.72 (1 H, t, *J*=4.6 Hz), 7.57 (1 H, ddd, *J*=8.0, 6.7, 1.5 Hz), 7.21 - 7.28 (2 H, m), 2.26 (3 H, s). Mass spectrum m/z 315, 317 $(M+H)^+$.

[00207] The following Intermediates were also prepared using procedures used to prepare Intermediate 8-1.

Intermediate	Compound name	Mass spectrum
8-2	3-(3-bromo-2-methylphenyl)-5-fluoroquinazolin-4(3H)-one	333, 335 $(M+H)^+$
8-3	3-(3-bromo-2-methylphenyl)-6-chloroquinazolin-4(3H)-one	349, 351, 353 $(M+H)^+$

Intermediate 9-1

Preparation of 3-(3-bromo-2-methylphenyl)-6-fluoroquinazolin-4(3H)-one



[00208] A mixture of 2-amino-5-fluorobenzoic acid (1.00 g, 6.45 mmol), 3-bromo-2-methylaniline (1.199 g, 6.45 mmol) and triethoxymethane (0.955 g, 6.45 mmol) in THF (2 mL) was heated at 110 °C overnight in a sealed tube. The mixture was cooled to rt and diluted with EtOAc. The solution was washed with NaHCO3 (aq) and water, then was dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 80:20 to 70:30 hexane-EtOAc) to give 3-(3-bromo-2-methylphenyl)-6-fluoroquinazolin-4(3H)-one as a white solid (1.2g, 56%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.00 (1 H, dd, *J*=8.4, 3.1 Hz), 7.93 (1 H, s), 7.81 (1 H, dd, *J*=9.0, 4.8 Hz), 7.74 (1 H, dd, *J*=6.9, 2.3 Hz), 7.50 - 7.58 (1 H, m), 7.21 - 7.26 (2 H, m), 2.25 (3 H, s). Mass spectrum m/z 333, 335 $(M+H)^+$.

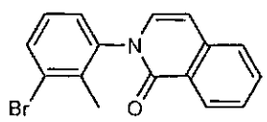
[00209] The following Intermediates were also prepared using procedures used to prepare Intermediate 9-1.

Intermediate	Compound name	Mass spectrum
9-2	3-(3-bromo-2-methylphenyl)-6-methylquinazolin-4(3H)-one	329, 331 $(M+H)^+$

9-3	3-(3-bromo-2-methylphenyl)-8-fluoroquinazolin-4(3H)-one	333, 335 $(M+H)^+$
9-4	3-(3-bromo-2-methylphenyl)-8-methoxyquinazolin-4(3H)-one	345, 347 $(M+H)^+$
9-5	3-(3-bromo-2-methylphenyl)-5-methoxyquinazolin-4(3H)-one	345, 347 $(M+H)^+$
9-6	3-(3-bromo-2-methylphenyl)-7-methoxyquinazolin-4(3H)-one	345, 347 $(M+H)^+$
9-7	3-(3-bromo-2-methylphenyl)-6-(trifluoromethoxy)quinazolin-4(3H)-one	399, 401 $(M+H)^+$
9-8	3-(3-bromo-2-methylphenyl)-8-methylquinazolin-4(3H)-one	329, 331 $(M+H)^+$
9-9	3-(3-bromo-2-methylphenyl)-6-methoxyquinazolin-4(3H)-one	345, 347 $(M+H)^+$
9-10	3-(3-bromo-2-methylphenyl)-7-fluoroquinazolin-4(3H)-one	333, 335 $(M+H)^+$

Intermediate 10-1

Preparation of 2-(3-bromo-2-methylphenyl)isoquinolin-1(2H)-one



[00210] Step 1 A mixture of 3-bromo-2-methylaniline (1 g, 5.37 mmol) and isochroman-1,3-dione (0.872 g, 5.37 mmol) in acetic acid (15 mL) was heated overnight at 100 °C in a sealed tube. The mixture was cooled to rt and concentrated, and the residue was purified by column chromatography (eluting with a gradient from 80:20 hexane-EtOAc to EtOAc) to give 2-(3-bromo-2-methylphenyl)isoquinoline-1,3(2H,4H)-dione as a tan solid (630 mg, 36%). Mass spectrum m/z 330, 332 $(M+H)^+$.

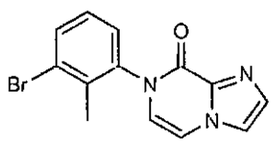
[00211] Step 2 A suspension of 2-(3-bromo-2-methylphenyl)isoquinoline-1,3(2H,4H)-dione (630 mg, 1.908 mmol) in methanol (100 mL) was treated with sodium borohydride (217 mg, 5.72 mmol) at rt. After 1.5 h, additional sodium borohydride (120 mg) was added. After 7 h, the mixture was concentrated and the

residue was partitioned between water and DCM. The organic phase was dried and concentrated to give 2-(3-bromo-2-methylphenyl)-3-hydroxy-3,4-dihydroisoquinolin-1(2H)-one as a light yellow foam (600 mg, 95%), used without further purification. Mass spectrum m/z 332, 334 $(M+H)^+$.

[00212] Step 3 A solution of crude 2-(3-bromo-2-methylphenyl)-3-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (600 mg, 1.806 mmol) in DCM (30 mL) was treated with triethylsilane (15 mL, 94 mmol) and the resulting mixture was treated slowly with TFA (1.392 mL, 18.06 mmol). The mixture was stirred at rt for 2 h, then was concentrated and the residue was dissolved in DCM. The solution was washed with NaHCO3 (aq) and water, then was dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 80:20 to 60:40 hexane-EtOAc) to give 2-(3-bromo-2-methylphenyl)isoquinolin-1(2H)-one as a white solid (380 mg, 67%). Mass spectrum m/z 314, 316 $(M+H)^+$.

Intermediate 11-1

Preparation of (3-bromo-2-methylphenyl)imidazo[1,2-a]pyrazin-8(7H)-one



[00213] Step 1 A solution of 3-bromo-2-methylaniline (0.63g, 3.39 mmol), 1H-imidazole-2-carboxylic acid (0.455 g, 4.06 mmol), HOAT (0.830 g, 6.10 mmol), and EDC (1.298 g, 6.77 mmol) in 2:1 DCM-THF (100 mL) was treated with DIEA (1.774 mL, 10.16 mmol) and stirred at rt overnight. Additional 1H-imidazole-2-carboxylic acid (0.6 eq, 0.228 g), EDC (0.64 g), HOAT (0.41 g), and DIEA (0.8 mL) were added and the mixture was stirred at rt for 6 days. The mixture was partitioned between NaHCO3 (aq) and DCM, and the organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from DCM to 94:6 DCM-methanol) to provide N-(3-bromo-2-methylphenyl)-1H-imidazole-2-carboxamide as a solid (80% purity, 0.76 g, 64%). Mass spectrum m/z 280, 282 $(M+H)^+$.

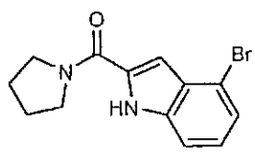
[00214] Step 2 A solution of N-(3-bromo-2-methylphenyl)-1H-imidazole-2-carboxamide (0.70 g, 2.499 mmol) in DMF (12.5 mL) was treated with potassium carbonate (0.794 g, 5.75 mmol) and 2-bromo-1,1-diethoxyethane (0.395 mL, 2.62

mmol). The suspension was heated at 100 °C overnight. The mixture was cooled to rt, diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 85:15 to 20:80 hexane-EtOAc) to provide N-(3-bromo-2-methylphenyl)-1-(2,2-diethoxyethyl)-1H-imidazole-2-carboxamide as a white solid (0.81 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (1 H, s), 7.51 (1 H, d, *J*=2.6 Hz), 7.49 (1 H, d, *J*=2.6 Hz), 7.44 (1 H, d, *J*=1.1 Hz), 7.18 (1 H, t, *J*=8.0 Hz), 7.10 (1 H, d, *J*=1.1 Hz), 4.75 (1 H, t, *J*=5.4 Hz), 4.52 (2 H, d, *J*=5.3 Hz), 3.63 (2 H, dq, *J*=9.7, 7.0 Hz), 3.35 - 3.44 (2 H, m), 2.31 (3 H, s), 1.05 (6 H, t, *J*=7.0 Hz). Mass spectrum m/z 396, 398 $(M+H)^+$.

[00215] Step 3 A suspension of N-(3-bromo-2-methylphenyl)-1-(2,2-diethoxyethyl)-1H-imidazole-2-carboxamide (0.81 g, 2.044 mmol) in water (10.2 mL) was treated with 1 M hydrochloric acid (8.2 mL, 8.2 mmol) and the mixture was heated at reflux overnight. The mixture was cooled to rt, treated with NaHCO3 (aq), and extracted with EtOAc. A precipitate was collected by filtration to provide a white solid (0.33 g), which was a mixture (ca. 1:1) of 7-(3-bromo-2-methylphenyl)imidazo[1,2-a]pyrazin-8(7H)-one and 7-(3-bromo-2-methylphenyl)-6-hydroxy-6,7-dihydroimidazo[1,2-a]pyrazin-8(5H)-one (Mass spectrum m/z 322, 324 $(M+H)^+$). The filtrate was dried and concentrated to afford 7-(3-bromo-2-methylphenyl)imidazo[1,2-a]pyrazin-8(7H)-one as a white solid (0.34 g, 66%) contaminated with a small amount of 7-(3-bromo-2-methylphenyl)-6-hydroxy-6,7-dihydroimidazo[1,2-a]pyrazin-8(5H)-one. Mass spectrum m/z 304, 306 $(M+H)^+$. The mixtures could be converted to 7-(3-bromo-2-methylphenyl)imidazo[1,2-a]pyrazin-8(7H)-one, TFA salt, by heating with TFA at reflux for 2 h.

Intermediate 12-1

Preparation of (4-bromo-1H-indol-2-yl)(pyrrolidin-1-yl)methanone



[00216] A mixture of 4-bromo-1H-indole-2-carboxylic acid (250 mg, 1.04 mmol), pyrrolidine (0.129 mL, 1.56 mmol), and HOAT (213 mg, 1.56 mmol) in acetonitrile (5 mL) was treated with DIEA (0.364 mL, 2.08 mmol) and EDC (399 mg, 2.08 mmol)

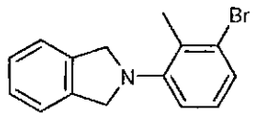
and the mixture was stirred at rt. After 18.25 h, the mixture was diluted with EtOAc, filtered to remove some tan solid, and washed sequentially with 1 M hydrochloric acid and NaHCO3 (aq), and dried and concentrated to provide (4-bromo-1H-indol-2-yl)(pyrrolidin-1-yl)methanone as a tan solid (205 mg, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1 H) 7.46 (d, J=7.9 Hz, 1 H) 7.27 (d, J=7.5 Hz, 1 H) 7.06 - 7.17 (m, 1 H) 6.82 (s, 1 H) 3.85 (t, J=6.8 Hz, 2 H) 3.55 (t, J=6.8 Hz, 2 H) 1.93 - 2.04 (m, 2 H) 1.81 - 1.92 (m, 2 H). Mass spectrum m/z 293, 295 $(M+H)^+$.

[00217] The following Intermediates were also prepared using procedures used to prepare Intermediate 12-1.

Intermediate	Compound name	Mass spectrum
12-2	4-bromo-N-ethyl-1H-indole-2-carboxamide	267, 269 $(M+H)^+$
12-3	4-bromo-N-(4-fluorophenyl)-1H-indole-2-carboxamide	333, 335 $(M+H)^+$

Intermediate 13-1

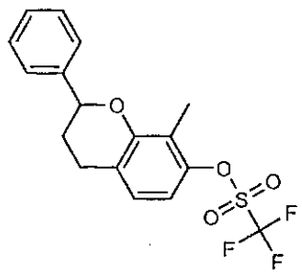
Preparation of 2-(3-bromo-2-methylphenyl)isoindoline



[00218] A mixture of 3-bromo-2-methylaniline (372 mg, 2.00 mmol), 1,2-bis(chloromethyl)benzene (385 mg, 2.20 mmol), and potassium carbonate (304 mg, 2.20 mmol) in water (2 mL) was heated via microwave irradiation in a sealed tube at 120 °C for 25 min. The mixture was extracted with EtOAc and the organic phase was washed with water, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from hexane to 30:70 EtOAc-hexane) to provide 2-(3-bromo-2-methylphenyl)isoindoline as a light yellow oil (360 mg, 63%). Mass spectrum m/z 288, 290 $(M+H)^+$.

Intermediate 14-1

Preparation of 8-methyl-2-phenylchroman-7-yl trifluoromethanesulfonate



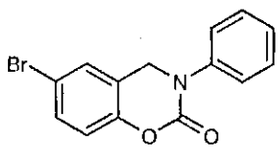
[00219] Step 1 A suspension of (E)-3-phenylprop-2-en-1-ol (2.22 g, 16.51 mmol) and 2-methylbenzene-1,3-diol (2.05 g, 16.51 mmol) in 1,2-dichloroethane (100 mL) was treated with p-toluenesulfonic acid monohydrate (0.157 g, 0.826 mmol) and the mixture was heated at reflux for 1 h. The mixture was cooled to rt and concentrated, and the residue was subjected to column chromatography (eluting with a gradient from 90:10 to 75:25 hexane-EtOAc) provided a mixture of 4-cinnamyl-2-methylbenzene-1,3-diol and 4,6-dicinnamyl-2-methylbenzene-1,3-diol (2:1, 1.97 g). This material (1.89 g) was dissolved in toluene (60 mL) and treated with p-toluenesulfonic acid monohydrate (299 mg, 1.57 mmol) and heated at reflux for 6 h. The mixture was cooled to rt, diluted with EtOAc (100 mL), washed with NaHCO3 (aq) (2x30 mL), water (30 mL) and brine (30 mL), dried and concentrated. Column chromatography (eluting with a gradient from 95:5 to 70:30 hexane-EtOAc) provided 8-methyl-2-phenylchroman-7-ol as a brown liquid (ca. 85% purity, 672 mg, 17%) used without further purification. ^{1}H NMR (400 MHz, chloroform-d) δ 7.35 - 7.50 (4 H, m), 7.27 - 7.35 (1 H, m), 6.79 (1 H, d, J=8.36 Hz), 6.38 (1 H, d, J=8.14 Hz), 5.07 (1 H, dd, J=10.12, 2.42 Hz), 4.64 (1 H, s), 2.83 - 3.02 (1 H, m), 2.71 (1 H, ddd, J=16.01, 4.90, 3.74 Hz), 2.16 - 2.27 (1 H, m), 2.14 (3 H, s), 1.86 - 2.04 (1 H, m). Mass spectrum m/z 241.0 $(M+H)^+$.

[00220] Step 2 Trifluoromethanesulfonic anhydride (0.613 mL, 3.63 mmol) was added dropwise to a solution of 8-methyl-2-phenylchroman-7-ol (671 mg, 2.79 mmol) in DCM (10 mL) and pyridine (10 mL) at 0 °C. After 30 min, the mixture was diluted with EtOAc (70 mL), washed with water (2x30 mL) and brine (30 mL), dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 95:5 to 85:15 hexane-EtOAc) to give 8-methyl-2-phenylchroman-7-yl trifluoromethanesulfonate as colorless liquid (925 mg, 89%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.28 - 7.61 (5 H, m), 6.97 (1 H, d, J=8.58 Hz), 6.79 (1 H, d, J=8.58 Hz), 5.11 (1 H, dd, J=10.23, 2.31 Hz), 2.99 (1 H, ddd, J=16.73, 11.11, 5.83 Hz), 2.68 -

2.88 (1 H, m), 2.17 - 2.32 (4 H, m), 1.88 - 2.12 (1 H, m). Mass spectrum m/z 390.0 $(M+H)^+$.

Intermediate 15-1

Preparation of 6-bromo-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one

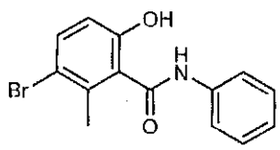


[00221] Step 1 Aniline (1.50 mL, 16.42 mmol) was added to a solution of 5-bromo-2-hydroxybenzaldehyde (3.00 g, 14.92 mmol) in 1,2-dichloroethane (100 mL). After 10 min at rt, sodium triacetoxyborohydride (4.74 g, 22.39 mmol) was added. The mixture was stirred at rt. After four days, additional aniline (1.50 mL, 16.42 mmol) and sodium triacetoxyborohydride (4.74 g, 22.39 mmol) were added. After two more days, saturated aqueous ammonium chloride (200 mL) was added. The mixture was stirred at rt for 3 h. The phases were separated and the aqueous phase was extracted with DCM (2x50 mL). The combined organic phases were dried and concentrated. The residue was treated with toluene (25 mL) and hexanes (25 mL) and the mixture was stirred for 30 min. The precipitate was washed with 1:1 mixture of toluene-hexanes (3 mL) and dried under vacuum to give 4-bromo-2-((phenylamino)methyl)phenol as a white solid (2.64 g, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (1 H, br. s.), 7.18 - 7.46 (4 H, m), 6.95 (1 H, t, J=7.48 Hz), 6.80 - 6.90 (2 H, m), 6.77 (1 H, d, J=8.58 Hz), 4.39 (2 H, s), 3.98 (1 H, br. s.). Mass spectrum m/z 278, 280 $(M+H)^+$.

[00222] Step 2 Carbonyldiimidazole (0.874 g, 5.39 mmol) and DMAP (0.088 g, 0.719 mmol) were added to a solution of 4-bromo-2-((phenylamino)methyl)phenol (1.00 g, 3.60 mmol) in DCM (100 mL) and the resulting mixture was stirred at rt for 60 h. The mixture was diluted with hexanes (100 mL), washed with NaHCO3 (aq) (2x25 mL), 1 M hydrochloric acid (25 mL) and brine (25 mL), dried and filtered through a pad of silica gel. The solids were rinsed with 1:1 EtOAc-hexane and the filtrate was concentrated to give 6-bromo-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one as a white solid (1.09 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 - 7.56 (3 H, m), 7.30 - 7.41 (3 H, m), 7.21 - 7.29 (1 H, m), 7.01 (1 H, d, J=8.80 Hz), 4.80 (2 H, s). Mass spectrum m/z 304, 306 $(M+H)^+$.

Intermediate 16-1

Preparation of 3-bromo-6-hydroxy-2-methyl-N-phenylbenzamide



[00223] Step 1 A solution of ethyl 2-hydroxy-6-methylbenzoate (2.04 g, 11.32 mmol) in methanol (25 mL) was treated at rt with 1 M aqeous sodium hydroxide (45.3 mL, 45.3 mmol) and the mixture was heated at reflux for 6 h. The mixture was cooled to rt and the methanol was removed under vacuum. The aqueous residue was treated with 1 M hydrochloric acid to pH ca. 1. The precipitate was collected by filtration, washed with water and dried under vacuum to give 2-hydroxy-6-methylbenzoic acid as a white solid (1.62 g, 94%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.26 (1 H, t, J=7.92 Hz), 6.75 (2 H, t, J=7.92 Hz), 2.55 (3 H, s). Mass spectrum m/z 153.1 $(M+H)^+$.

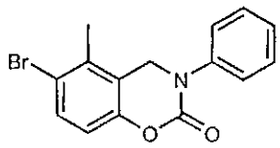
[00224] Step 2 A suspension of 2-hydroxy-6-methylbenzoic acid (1.32 g, 8.68 mmol) in acetonitrile (20 mL) at -20 °C was treated with tetrafluoroboric acid dimethyl ether complex (1.109 mL, 9.11 mmol), followed by portionwise addition of N-bromosuccinimide (1.699 g, 9.54 mmol) over 30 min. The mixture was warmed to 0 °C and stirred for 1 h, then was treated with 40% aqueous sodium bisulfite (10 mL). The acetonitrile was removed under vacuum and the aqueous residue was extracted with EtOAc (3x40 mL). The combined organic layers were washed with water and brine, dried and concentrated to give 3-bromo-6-hydroxy-2-methylbenzoic acid as a white solid (1.60 g, 80%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.47 (1 H, d, *J*=8.80 Hz), 6.67 (1 H, d, *J*=8.80 Hz), 2.50 (3 H, s). Mass spectrum m/z 231, 233 $(M-H)^-$.

[00225] Step 3 Thionyl chloride (0.111 mL, 1.524 mmol) was added to a solution of benzotriazole (594 mg, 4.99 mmol) in DCM (8 mL) at rt and the mixture was stirred for 30 min. A solution of 3-bromo-6-hydroxy-2-methylbenzoic acid (320 mg, 1.385 mmol) in THF (8.00 mL) was added and the mixture was stirred at rt for 2 hrs. The mixture was filtered and the solid was washed with DCM (3 mL). The filtrate was concentrated, and the residue was dissolved in aniline (2 g, 21.48 mmol) and heated in a sealed tube by microwave irradiation at 150 °C for 10 min. The mixture was diluted with EtOAc (100 mL) and washed with 2 M hydrochloric acid (20 mL), water (10 mL) and brine (10 mL), dried and concentrated. The residue was triturated

with DCM (4 mL) to give the 3-bromo-6-hydroxy-2-methyl-N-phenylbenzamide as light-colored solid (290 mg, 68%). Mass spectrum m/z 306, 308 $(M+H)^+$.

Intermediate 17-1

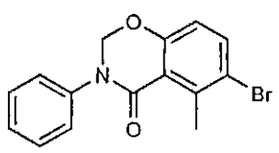
Preparation of 6-bromo-5-methyl-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one



[00226] A solution of 3-bromo-6-hydroxy-2-methyl-N-phenylbenzamide (Intermediate 16-1, 50 mg, 0.163 mmol) in THF (2 mL) was treated at rt with lithium aluminum hydride (50 mg, 1.317 mmol) and the mixture was heated at reflux for 2 h. It was then cooled to rt and carefully treated with saturated aqueous ammonium chloride (2 mL).The mixture was diluted with DCM (60 mL) and washed with water (5 mL) and brine (5 mL), dried and concentrated to give the 4-bromo-3-methyl-2-((phenylamino)methyl)phenol (45 mg). Without purification, this material was dissolved in DCM (3 lM) and treated with carbonyldiimidazole (30.5 mg, 0.188 mmol) and DMAP (2.091 mg, 0.017 mmol) at rt and the mixture was stirred for 1 h. The mixture was diluted with DCM (60 mL) and washed with NaHCO3 (aq) (5 mL) and brine (5 mL), dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 95:5 to 50:50 hexane-EtOAc) to give 6-bromo-5-methyl-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (25 mg). ^{1}H NMR (400 MHz, chloroform-d) δ 7.33 - 7.57 (6 H, m), 6.88 (1 H, d, J=8.88 Hz), 4.82 (2 H, s), 2.30 (3 H, s). Mass spectrum m/z 318, 320 $(M+H)^+$.

Intermediate 18-1

Preparation of 6-bromo-5-methyl-3-phenyl-2H-benzo[e][1,3]oxazin-4(3H)-one

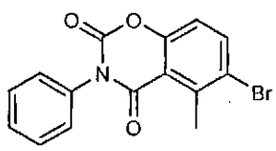


[00227] A mixture of 3-bromo-6-hydroxy-2-methyl-N-phenylbenzamide (Intermediate 16-1, 40 mg, 0.131 mmol) and paraformaldehyde (11.77 mg, 0.392 mmol) in TFA (1 mL) was heated at 100 °C for 4 h. The TFA was removed under

vacuum, and the residue was diluted with EtOAc (80 mL), washed with NaHCO3 (aq) (10 mL), water (10 mL) and brine (10 mL), and dried and concentrated. The residue was purified by column chromatogaphy (eluting with a gradient from 95:5 to 70:30 hexane-EtOAc) to give 6-bromo-5-methyl-3-phenyl-2H-benzo[e][1,3]oxazin-4(3H)-one (25 mg, 45%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.63 (1 H, d, J=8.80 Hz), 7.37 - 7.50 (3 H, m), 7.29 - 7.35 (2 H, m), 6.81 (1 H, d, J=8.80 Hz), 5.48 (2 H, s), 2.80 (3 H, s). Mass spectrum m/z 318, 320 $(M+H)^+$.

Intermediate 19-1

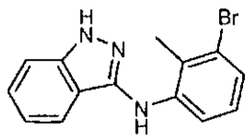
Preparation of 6-bromo-5-methyl-3-phenyl-2H-benzo[e][1,3]oxazine-2,4(3H)-dione



[00228] Step 1 A solution of 3-bromo-6-hydroxy-2-methyl-N-phenylbenzamide (Intermediate 16-1, 40 mg, 0.131 mmol) in pyridine (1 mL) was treated with ethyl chloroformate (0.015 mL, 0.157 mmol) at rt and the mixture was heated to 100 °C for 2 h. Additional ethyl chloroformate (0.015 mL, 0.157 mmol) was added and the mixture was stirred at 100 °C for 15 h. The mixture was cooled and diluted with EtOAc (80 mL), and the solution was washed with NaHCO3 (aq) (10 mL), water (2x10 mL) and brine (10 mL), and dried and concentrated. The residue was purified by column chromatogaphy (eluting with a gradient from 95:5 to 70:30 hexane-EtOAc) to give 6-bromo-5-methyl-3-phenyl-2H-benzo[e][1,3]oxazine-2,4(3H)-dione (19 mg, 44%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.90 (1 H, d, J=9.02 Hz), 7.43 - 7.68 (3 H, m), 7.27 - 7.40 (2 H, m), 7.12 (1 H, d, J=8.80 Hz), 2.90 (3 H, s). Mass spectrum m/z 332, 334 $(M+H)^+$.

Intermediate 20-1

Preparation of N-(3-bromo-2-methylphenyl)-1H-indazol-3-amine



[00229] Step 1 A mixture of 3-bromo-2-methylaniline (1.66 mL, 13.4 mmol), 2-fluorobenzoic acid (1.883 g, 13.4 mmol), and HOAT (2.74 g, 20.2 mmol) in EtOAc

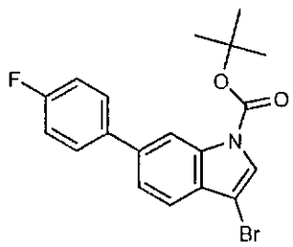
(60 mL) was treated with DIEA (4.7 mL, 26.9 mmol) and EDC (5.15 g, 26.9 mmol) and the mixture was stirred at rt. After 19 h, the mixture was diluted with EtOAc and washed with water, 1 M hydrochloric acid (twice), NaHCO3 (aq) (twice) and brine, dried and concentrated to provide N-(3-bromo-2-methylphenyl)-2-fluorobenzamide as tan fluffy needles (4.11 g, 99%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.34 - 8.50 (1 H, m), 8.20 (1 H, td, J=7.9, 1.8 Hz), 7.96 (1 H, d, J=8.1 Hz), 7.50 - 7.59 (1 H, m), 7.44 (1 H, dd, J=8.0, 0.8 Hz), 7.30 - 7.37 (1 H, m), 7.21 (1 H, dd, J=12.8, 7.9 Hz), 7.12 (1 H, t, J=8.0 Hz), 2.45 (3 H, s). Mass spectrum m/z 308, 310 $(M+H)^+$.

[00230] Step 2 A mixture of N-(3-bromo-2-methylphenyl)-2-fluorobenzamide (2.00 g, 6.49 mmol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson reagent, 1.575 g, 3.89 mmol) in toluene (25 mL) was heated at reflux. After 3.5 h, the solution was cooled to rt and concentrated to provide a dark yellow solid. This was purified by column chromatography (eluting with a gradient from 95:5 to 90:10 hexane-EtOAc) to provide N-(3-bromo-2-methylphenyl)-2-fluorobenzothioamide as a yellow solid (1.892 g, 90%). ^{1}H NMR (400 MHz, chloroform-d) δ 9.18 (1 H, d, J=7.7 Hz), 8.23 (1 H, td, J=8.0, 1.8 Hz), 7.60 (1 H, d, J=7.9 Hz), 7.45 - 7.52 (1 H, m), 7.43 (1 H, d, J=7.7 Hz), 7.23 - 7.30 (1 H, m), 7.11 - 7.21 (2 H, m), 2.41 (3 H, s). Mass spectrum m/z 324, 326 $(M+H)^+$.

[00231] Step 3 A yellow solution of N-(3-bromo-2-methylphenyl)-2-fluorobenzothioamide (500 mg, 1.542 mmol) in DMSO (5 mL) was treated with anhydrous hydrazine (0.484 mL, 15.42 mmol) and heated at 150 °C. After 2 h 20 min the solution was cooled to rt, diluted with NaHCO3 (aq) and extracted twice with EtOAc. The combined organic phases were washed twice with water and once with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 85:15 to 50:50 hexane-EtOAc) to provide N-(3-bromo-2-methylphenyl)-1H-indazol-3-amine as a tan waxy solid (162 mg, 35%). ^{1}H NMR (400 MHz, chloroform-d) δ 9.38 (1 H, br. s.), 7.49 (1 H, d, J=8.1 Hz), 7.45 (1 H, d, J=7.9 Hz), 7.40 (2 H, d, J=3.5 Hz), 7.19 (1 H, dd, J=7.9, 0.9 Hz), 7.10 (1 H, dt, J=8.1, 4.0 Hz), 6.98 (1 H, t, J=8.1 Hz), 6.10 (1 H, s), 2.49 (3 H, s). Mass spectrum m/z 302, 304 $(M+H)^+$.

Intermediate 21-1

Preparation of *tert*-butyl 3-bromo-6-(4-fluorophenyl)-1H-indole-1-carboxylate



[00232] Step 1 A mixture of 6-bromo-1H-indole (0.25 g, 1.275 mmol), 4-fluorophenylboronic acid (0.178 g, 1.275 mmol), and 2 M aqueous sodium carbonate (2.0 mL, 4.00 mmol) in toluene (10 mL) and ethanol (2.500 mL) was purged with argon and treated with tetrakis(triphenylphosphine)palladium (0.074 g, 0.064 mmol). The mixture was heated at 90 °C. After 17 h, the mixture was cooled to rt and partitioned between water and EtOAc. The organic phase was dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 95:5 to 60:40 hexane-EtOAc) to provide 6-(4-fluorophenyl)-1H-indole as a white solid (175.5 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (1 H, br. s.), 7.65 - 7.71 (2 H, m), 7.56 - 7.62 (2 H, m), 7.37 (1 H, t, J=2.9 Hz), 7.22 - 7.31 (3 H, m), 6.44 (1 H, t, J=2.0 Hz). Mass spectrum m/z 212.2 $(M+H)^+$.

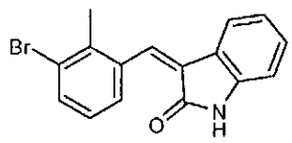
[00233] Step 2 A solution of 6-(4-fluorophenyl)-1H-indole (172 mg, 0.814 mmol) in THF (5 mL) was treated with di-*tert*-butyldicarbonate (213 mg, 0.977 mmol) and DMAP (24.87 mg, 0.204 mmol) and stirred at rt. After 21 h, the mixture was concentrated and the residue was dissolved in EtOAc and washed with 0.2 M hydrochloric acid. The organic phase was dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 95:5 to 50:50 hexane-EtOAc) to provide *tert*-butyl 6-(4-fluorophenyl)-1H-indole-1-carboxylate as a colorless gum (199.7 mg, 79%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.39 (1 H, br. s.), 7.54 - 7.67 (4 H, m), 7.43 (1 H, dd, J=8.1, 1.5 Hz), 7.13 (2 H, t, J=8.6 Hz), 6.58 (1 H, d, J=3.5 Hz), 1.68 (9 H, s). Mass spectrum m/z 312.2 $(M+H)^+$.

[00234] Step 3 A solution of *tert*-butyl 6-(4-fluorophenyl)-1H-indole-1-carboxylate (187.8 mg, 0.603 mmol) in THF (4 mL) was treated with N-bromosuccinimide (118 mg, 0.663 mmol) and stirred at rt. After 18 h, the solution was diluted with ether, washed with 2 x 10 mL aqueous sodium bisulfite (ca. 1.5 M), then with NaHCO3 (aq), dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from hexane to 90:10 hexane-EtOAc) provide *tert*-butyl 3-bromo-6-(4-fluorophenyl)-1H-indole-1-carboxylate as a white glassy foam (134 mg,

57%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.39 (1 H, br. s.), 7.59 - 7.68 (3 H, m), 7.54 - 7.59 (1 H, m), 7.48 - 7.53 (1 H, m), 7.14 (2 H, t, J=8.7 Hz), 1.67 (9 H, s).

Intermediate 22-1

Preparation of 3-(3-bromo-2-methylbenzylidene)indolin-2-one

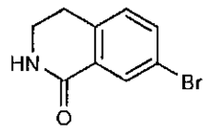


[00235] Step 1 A mixture of (3-bromo-2-methylphenyl)methanol (prepared according to the procedures reported in US Pat. Appl. 2006/0173183, 500 mg, 2.49 mmol) in THF (20 mL) was stirred at rt and treated with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin periodinane, 1.58 g, 3.73 mmol). After 2 h, the mixture was diluted with ether (ca. 100 mL) and washed with 5% aqueous sodium bisulfite, NaHCO3 (aq) and brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from hexane to 55:45 hexane-EtOAc) to provide 3-bromo-2-methylbenzaldehyde as a colorless oil (343 mg, 70%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.26 (1 H, s), 7.78 (2 H, ddd, J=9.7, 8.0, 1.2 Hz), 7.20 - 7.27 (1 H, m), 2.75 (3 H, s).

[00236] Step 2 A solution of 3-bromo-2-methylbenzaldehyde (200 mg, 1.01 mmol) and indolin-2-one (134 mg, 1.01 mmol) in ethanol (10 mL) was treated with piperidine (0.099 mL, 1.01 mmol) and heated at 80-85 °C. After 15.25 h, the solution was cooled to rt and concentrated. The residue was purified by column chromatography (eluting with a gradient from 80:20 to 30:70 hexane-ethyl acetate) to provide 3-(3-bromo-2-methylbenzylidene)indolin-2-one as a bright yellow solid (94.9 mg, 30%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.89 (1 H, br. s.), 7.85 (1 H, s), 7.64 (1 H, d, J=7.9 Hz), 7.47 (1 H, d, J=7.7 Hz), 7.20 (1 H, td, J=7.7, 1.1 Hz), 7.07 - 7.16 (2 H, m), 6.87 (1 H, d, J=7.9 Hz), 6.81 (1 H, td, J=7.6, 1.0 Hz), 2.43 (3 H, s). Mass spectrum m/z 314, 316 $(M+H)^+$.

Intermediate 23-1

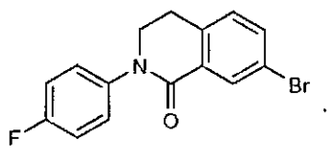
Preparation of 7-bromo-3,4-dihydroisoquinolin-1(2H)-one



[00237] Sodium azide (0.431 g, 6.63 mmol) was added slowly to a mixture of 6-bromo-2,3-dihydro-1H-inden-1-one (1 g, 4.74 mmol) and methanesulfonic acid (15 mL, 231 mmol) in DCM (30 mL) at 0 °C. The mixture was stirred at rt for 15 hrs, then was carefully quenched with 1 M aqueous sodium hydroxide (50 mL). The aqueous layer was extracted with DCM (3x50 mL), and the combined organic layers were washed with water (20 mL) and brine (20 mL), dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 90:10 hexane-EtOAc to EtOAc) to give 7-bromo-3,4-dihydroisoquinolin-1(2H)-one as white solid (650 mg, 61%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.35 (1 H, br. s.), 7.08 - 7.17 (1 H, m), 6.98 - 7.06 (1 H, m), 6.95 (1 H, d, J=1.98 Hz), 2.93 (2 H, t, J=7.59 Hz), 2.49 - 2.68 (2 H, m). Mass spectrum m/z 226, 228 $(M+H)^+$.

Intermediate 24-1

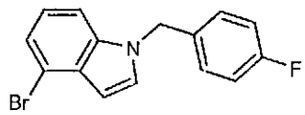
Preparation of 7-bromo-2-(4-fluorophenyl)-3,4-dihydroisoquinolin-1(2H)-one



[00238] A mixture of 7-bromo-3,4-dihydroisoquinolin-1(2H)-one (Intermediate 23-1, 60 mg, 0.265 mmol), 1-fluoro-4-iodobenzene (118 mg, 0.531 mmol), potassium carbonate (36.7 mg, 0.265 mmol) and copper (I) iodide (10.11 mg, 0.053 mmol) in DMF (1.000 mL) was heated at 130 °C for 5 h. The mixture was cooled to rt and filtered through a Celite pad, and the solids were washed with EtOAc. The filtrate was washed with water and brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 90:10 to 60:40 hexane-EtOAc) to give 7-bromo-2-(4-fluorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (40 mg, 47%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.15 - 7.27 (4 H, m), 7.04 - 7.13 (2 H, m), 6.48 (1 H, d, J=1.94 Hz), 2.96 - 3.08 (2 H, m), 2.73 - 2.84 (2 H, m). Mass spectrum m/z 320, 322 $(M+H)^+$.

Intermediate 25-1

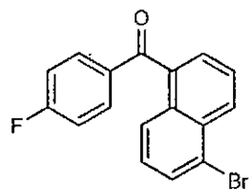
Preparation of 4-bromo-1-(4-fluorobenzyl)-1H-indole



[00239] A suspension of sodium hydride (60% oil dispersion, 112 mg, 2.81 mmol) in THF (12 mL) was stirred at rt and treated with a solution of 4-bromo-1H-indole (500 mg, 2.55 mmol) in THF (3 mL). After 1-2 min, the mixture was treated with 4-fluorobenzyl bromide (0.318 mL, 2.55 mmol) and the slightly cloudy solution was stirred at rt. After 20 h, the mixture was concentrated. The residue was partitioned between EtOAc and 0.1 M hydrochloric acid, and the aqueous phase was again extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 90:10 to 50:50 hexane-EtOAc) to provide 4-bromo-1-(4-fluorobenzyl)-1H-indole as a colorless oil (461.4 mg, 85% purity, 51%) contaminated by ca. 15% by weight of 4-bromo-1,3-bis(4-fluorobenzyl)-1H-indole. ^{1}H NMR (400 MHz, chloroform-d) δ 7.28 (1 H, dd, J=7.6, 0.8 Hz), 7.19 (1 H, d, J=8.4 Hz), 7.16 (1 H, d, J=3.3 Hz), 6.94 - 7.09 (5 H, m), 6.60 (1 H, dd, J=3.1, 0.9 Hz), 5.28 (2 H, s). Mass spectrum m/z 304, 306 $(M+H)^+$.

Intermediate 26-1

Preparation of (5-bromonaphthalen-1-yl)(4-fluorophenyl)methanone

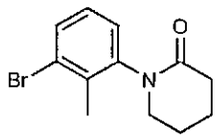


[00240] Step 1 A solution of 5-bromo-1-naphthoic acid (prepared according to the procedure of Hausamann, *Chem. Ber.*, 1876, 9, 1519; 2.00 g, 7.97 mmol) in THF (50 mL) was treated with TEA (2.22 mL, 15.93 mmol), then with isobutyl chloroformate (1.088 g, 7.97 mmol) and the resulting suspension was stirred at rt. After 25 min, the mixture was treated with additional TEA (2.22 mL, 15.93 mmol), then with a solution of N,O-dimethylhydroxylamine hydrochloric acid salt (0.777 g, 7.97 mmol) in water (5 mL), and the mixture was stirred at rt. After 2.5 h, the mixture was concentrated and the residue was taken up in EtOAc and water. The mixture was filtered, the layers

were separated, and the organic phase was washed with NaHCO3 (aq), dried and concentrated to provide 5-bromo-N-methoxy-N-methyl-1-naphthamide as a pasty solid (1.03 g, 30%) contaminated with ca. 30% isobutyl 5-bromo-1-naphthoate. Mass spectrum m/z 294, 296 $(M+H)^+$. Without further purification, a solution of this material (1.01 g, 2.404 mmol) in THF (15 mL) was stirred on ice and treated with (4-fluorophenyl)magnesium bromide, 2M in ether (7.21 mL, 14.42 mmol). The solution was stirred on ice and allowed to slowly warm to rt. After 16 h, the mixture was treated with 1 M hydrochloric acid and extracted twice with EtOAc. The combined organic layers were dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from hexane to 85:15 hexane-EtOAc) to provide (5-bromonaphthalen-1-yl)(4-fluorophenyl)methanone as a pale yellow viscous oil (658 mg, 83%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.49 (1 H, d, J=8.6 Hz), 7.95 (1 H, d, J=8.6 Hz), 7.86 - 7.93 (3 H, m), 7.74 (1 H, dd, J=8.5, 7.2 Hz), 7.64 - 7.68 (1 H, m), 7.40 (1 H, dd, J=8.5, 7.6 Hz), 7.25 (2 H, t, J=8.8 Hz). Mass spectrum m/z 329, 331 $(M+H)^+$.

Intermediate 27-1

Preparation of 1-(3-bromo-2-methylphenyl)piperidin-2-one

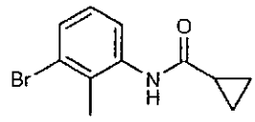


[00241] A solution of 3-bromo-2-methylaniline (1 g, 5.37 mmol) in DCM (15 mL) was treated with TEA (0.749 mL, 5.37 mmol) and then dropwise with a solution of 5-bromopentanoyl chloride (1.072 g, 5.37 mmol) in DCM (4 mL). The mixture was stirred at rt for 30 min, then was diluted with DCM, washed with water and brine, and dried and concentrated. The residue was dissolved in THF (100 mL) and added to a suspension of sodium hydride (60% oil dispersion, pre-washed with hexane, 0.430 g, 10.75 mmol) in THF (50 mL). The resulting mixture was stirred overnight at rt. The mixture was concentrated and the residue was acidified with 1 M hydrochloric acid. The mixture was extracted with DCM and the organic phase was washed with water, dried and concentrated to give 1-(3-bromo-2-methylphenyl)piperidin-2-one as a tan oil (1.4 g, 97%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.49 - 7.54 (1 H, m), 7.07 -

7.13 (2 H, m), 3.38 - 3.60 (2 H, m), 2.54 - 2.59 (2 H, m), 2.26 (3 H, s), 1.91 - 2.02 (4 H, m). Mass spectrum m/z 268, 270 $(M+H)^+$.

Intermediate 28-1

Preparation of N-(3-bromo-2-methylphenyl)cyclopropanecarboxamide



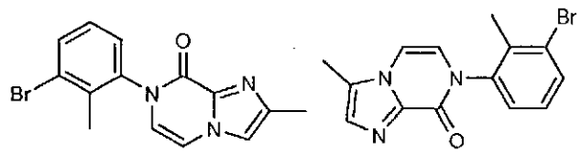
[00242] A solution of 3-bromo-2-methylaniline (2.00 g, 10.75 mmol) in DCM (20 mL) was treated with TEA (3.00 mL, 21.50 mmol) and then with a solution of 4-bromobutanoyl chloride (2.392 g, 12.90 mmol) in DCM (10 mL), and the resulting mixture was stirred at rt. After 2.5 h, the mixture was diluted with DCM, washed with NaHCO3 (aq) and water, and dried and concentrated. The residue was dissolved in THF (20 mL) and treated with hexane-washed sodium hydride (60% oil dispersion, 0.860 g, 21.50 mmol). The mixture was stirred at rt for 1.5 h, then was concentrated. The residue was dissolved in DCM, washed with water, 1 M hydrochloric acid and brine, and dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 80:20 hexane-EtOAc to EtOAc) to provide N-(3-bromo-2-methylphenyl)cyclopropanecarboxamide (900 mg, 33%) as a white solid. Mass spectrum m/z 254, 256 $(M+H)^+$.

Intermediate 29-1 and 29-2

Preparation of

7-(3-bromo-2-methylphenyl)-2-methylimidazo[1,2-a]pyrazin-8(7H)-one

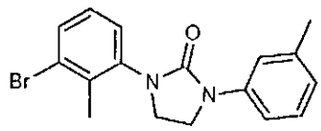
and 7-(3-bromo-2-methylphenyl)-3-methylimidazo[1,2-a]pyrazin-8(7H)-one



[00243] Following the procedures used to prepare Intermediate 11-1 but substituting 4-methyl-1H-imidazole-2-carboxylic acid for 1H-imidazole-2-carboxylic acid, a mixture of 7-(3-bromo-2-methylphenyl)-2-methylimidazo[1,2-a]pyrazin-8(7H)-one and 7-(3-bromo-2-methylphenyl)-3-methylimidazo[1,2-a]pyrazin-8(7H)-one was prepared in 5% overall yield. Mass spectrum m/z 318, 320 $(M+H)^+$.

Intermediate 30-1

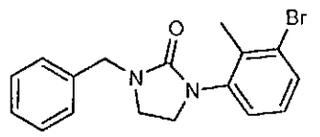
Preparation of 1-(3-bromo-2-methylphenyl)-3-m-tolylimidazolidin-2-one



[00244] A suspension of 1,3-dibromo-2-methylbenzene (185 mg, 0.740 mmol), 1-m-tolylimidazolidin-2-one (50 mg, 0.284 mmol), copper (I) iodide (5.40 mg, 0.028 mmol), tripotassium phophosphate (120 mg, 0.567 mmol) and (+/-)-*trans*-1,2-diaminocyclohexane (3.4 μL, 0.028 mmol) in 1,4-dioxane (1 mL) was purged with nitrogen and heated at 120 °C in a sealed tube. After 21.5 h, the mixture was concentrated and the residue was purified by column chromatography (eluting with a gradient from hexane to 50:50 hexane-EtOAc) to provide 1-(3-bromo-2-methylphenyl)-3-m-tolylimidazolidin-2-one as a white solid (70 mg, 70%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.51 - 7.54 (1 H, m), 7.49 (1 H, s), 7.34 (1 H, dd, J=8.05, 1.94 Hz), 7.24 (2 H, d, J=8.05 Hz), 7.11 (1 H, t, J=7.91 Hz), 6.90 (1 H, d, J=7.49 Hz), 3.98 - 4.04 (2 H, m), 3.81 - 3.87 (2 H, m), 2.38 (3 H, s), 2.36 (3 H, s). Mass spectrum m/z 345, 347 $(M+H)^+$.

Intermediate 30-2

Preparation of 1-benzyl-3-(3-bromo-2-methylphenyl)imidazolidin-2-one



[00245] Step 1 A solution of imidazolidin-2-one (500 mg, 5.81 mmol) in DMF (30 mL) was stirred on ice and treated with sodium hydride, 60% oil dispersion (264 mg, 6.60 mmol). The mixture was stirred at rt for 50 min, then was treated with (bromomethyl)benzene (0.691 mL, 5.81 mmol). After 2 h, the mixture was poured into water and extracted three times with EtOAc. The combined organic layers were dried and concentrated, and the residue was purified by column chromatography (eluting with EtOAc) to provide 1-benzylimidazolidin-2-one as a white solid (160 mg, 16%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.22 - 7.39 (5 H, m), 4.53 (1 H, br. s.), 4.37 (2 H, s), 3.25 - 3.46 (4 H, m).

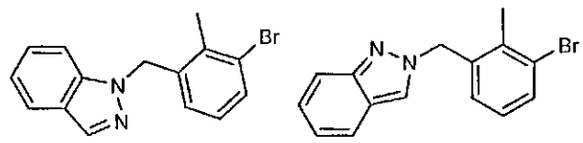
[00246] Step 2 A mixture of 1,3-dibromo-2-methylbenzene (0.147 mL, 1.064 mmol), 1-benzylimidazolidin-2-one (75 mg, 0.426 mmol), copper (I) iodide (8.11 mg, 0.043 mmol), (+/-)-trans-1,2-diaminocyclohexane (5.1 μL, 0.043 mmol) and tripotassium phosphate (181 mg, 0.851 mmol) in dioxane (2 mL) was sonicated while bubbling with argon for 1 min. The mixture was heated in a sealed tube at 120 °C. After 18.25 h, the mixture was cooled to rt, diluted with EtOAc and filtered through Celite. The filtrate was concentrated and the residue was purified by column chromatography (eluting with a gradient from 20:80 EtOAc-hexane to EtOAc) to provide 1-benzyl-3-(3-bromo-2-methylphenyl)imidazolidin-2-one as a waxy white solid (36 mg, 25%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.49 (1 H, dd, J=7.9, 0.9 Hz), 7.28 - 7.40 (5 H, m), 7.19 (1 H, dd, J=7.8, 1.0 Hz), 7.08 (1 H, t, J=7.9 Hz), 4.46 (2 H, s), 3.64 (2 H, dd, J=8.8, 6.8 Hz), 3.37 (2 H, dd, J=8.8, 7.0 Hz), 2.36 (3 H, s). Mass spectrum m/z 346.8 $(M+H)^+$.

[00247] The following Intermediates were also prepared using procedures used to prepare Intermediates 30-1 and 30-2.

Intermediate	Compound name	Mass spectrum
30-3	1-(3-bromo-2-methylphenyl)-3-phenylimidazolidin-2-one	331, 333 $(M+H)^+$
30-4	1-(3-bromo-2-methylphenyl)-3-tert-butylimidazolidin-2-one	311, 313 $(M+H)^+$

Intermediates 31-1 and 31-2

Preparation of 1-(3-bromo-2-methylbenzyl)-1H-indazole and 2-(3-bromo-2-methylbenzyl)-2H-indazole

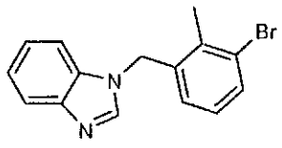


[00248] A mixture of 1-bromo-3-(bromomethyl)-2-methylbenzene (prepared according to the procedures reported in US Pat. Appl. 2006/0173183, 250 mg, 0.947 mmol), 1H-indazole (112 mg, 0.947 mmol) and potassium carbonate (131 mg, 0.947 mmol) in acetonitrile (5 mL) was heated with stirring at 80 °C. After 18.25 h, the mixture was cooled to rt, diluted with water and extracted three times with EtOAc.

The combined organic layers were dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 95:5 to 65:35 hexane-EtOAc) to provide 1-(3-bromo-2-methylbenzyl)-1H-indazole as an oil which crystallized on standing (Intermediate 31-1, 74 mg, 26%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.06 (1 H, d, J=0.9 Hz), 7.76 (1 H, dt, J=8.1, 1.0 Hz), 7.48 (1 H, d, J=7.9 Hz), 7.30 - 7.37 (1 H, m), 7.26 - 7.30 (1 H, m), 7.16 (1 H, ddd, J=8.0, 6.8, 1.0 Hz), 6.93 (1 H, t, J=7.8 Hz), 6.70 (1 H, d, J=7.7 Hz), 5.61 (2 H, s), 2.45 (3 H, s). Mass spectrum m/z 301, 303 $(M+H)^+$. Also obtained was 2-(3-bromo-2-methylbenzyl)-2H-indazole as a pale yellow gum (Intermediate 31-2, 164 mg, 58%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.68 - 7.76 (2 H, m), 7.54 - 7.63 (2 H, m), 7.28 (1 H, ddd, J=8.2, 7.2, 1.1 Hz), 6.97 - 7.10 (3 H, m), 5.63 (2 H, s), 2.37 (3 H, s). Mass spectrum m/z 301, 303 $(M+H)^+$.

Intermediate 31-3

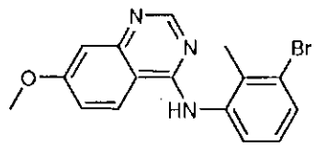
Preparation of 1-(3-bromo-2-methylbenzyl)-1H-benzo[d]imidazole



[00249] A mixture of 1-bromo-3-(bromomethyl)-2-methylbenzene (250 mg, 0.947 mmol), 1H-benzo[d]imidazole (336 mg, 2.84 mmol) and potassium carbonate (131 mg, 0.947 mmol) in acetonitrile (5 mL) was stirred at rt for 5 h, The mixture was diluted with EtOAc and filtered, and the solid was washed with EtOAc. The filtrate was washed with water, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 60:40 hexane-EtOAc to EtOAc). to provide 1-(3-bromo-2-methylbenzyl)-1H-benzo[d]imidazole as a white solid (233 mg, 82%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.14 (1 H, s), 7.68 - 7.78 (1 H, m), 7.56 (1 H, d, J=7.9 Hz), 7.36 - 7.44 (1 H, m), 7.25 - 7.34 (2 H, m), 7.03 (1 H, t, J=7.8 Hz), 6.82 (1 H, d, J=7.7 Hz), 5.58 (2 H, s), 2.45 (3 H, s). Mass spectrum m/z 301, 303 $(M+H)^+$.

Intermediate 32-1

Preparation of N-(3-bromo-2-methylphenyl)-7-methoxyquinazolin-4-amine



[00250] Step 1 A mixture of 2-amino-4-methoxybenzoic acid (0.5 g, 2.99 mmol) and formamidine acetate (0.623 g, 5.98 mmol) in 2-methoxyethanol (4 mL) was heated at 130 °C. After 15.25 h, the mixture was cooled to rt. The resulting precipitate was collected by filtration, washed with methanol and dried to provide 7-methoxyquinazolin-4-ol as a tan solid (473 mg, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (1 H, br. s.), 8.06 (1 H, s), 8.03 (1 H, d, J=9.5 Hz), 7.03 - 7.14 (2 H, m), 3.90 (3 H, s).

[00251] Step 2 A suspension of 7-methoxyquinazolin-4-ol (400 mg, 2.271 mmol) in phosphorus oxychloride (7 mL, 75 mmol) was heated at reflux for 3 h. The solution was concentrated and the residue was suspended in EtOAc and stirred on an ice bath with NaHCO3 (aq) until all the solid was dissolved and gas evolution ceased. The layers were separated and the organic phase was dried and concentrated to provide 4-chloro-7-methoxyquinazoline as a light yellow-tan solid (438 mg, 99%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.94 (1 H, s), 8.15 (1 H, d, J=9.7 Hz), 7.29 - 7.37 (2 H, m), 4.00 (3 H, s).

[00252] Step 3 A mixture of 4-chloro-7-methoxyquinazoline (200 mg, 1.028 mmol) and 3-bromo-2-methylaniline (0.253 mL, 2.055 mmol) in isopropanol (11 mL) was treated with hydrogen chloride (4 M in 1,4-dioxane, 0.385 mL, 1.541 mmol) and heated in a sealed tube by microwave irradiation at 140 °C for 45 min. On cooling a precipitate formed which was collected by filtration and dried under vacuum to provide the hydrochloric acid salt of N-(3-bromo-2-methylphenyl)-7-methoxyquinazolin-4-amine as a tan solid (281 mg, 68%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.65 (1 H, s), 8.48 (1 H, d, J=9.2 Hz), 7.69 (1 H, dd, J=8.0, 1.0 Hz), 7.51 (1 H, dd, J=9.4, 2.5 Hz), 7.37 (1 H, dd, J=7.9, 0.9 Hz), 7.26 - 7.30 (1 H, m), 7.24 (1 H, d, J=2.4 Hz), 4.08 (3 H, s), 2.36 (3 H, s). Mass spectrum m/z 344, 346 $(M+H)^+$. The filtrate was concentrated and the residue was partitioned between NaHCO3 (aq) and EtOAc. The organic phase was dried and concentrated, and the residue was purified by column chromatography (eluting with a gradient from 75:25 to 25:75 hexane-EtOAc) to provide N-(3-bromo-2-methylphenyl)-7-methoxyquinazolin-4-amine as an off-white solid (61 mg, 17%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.64

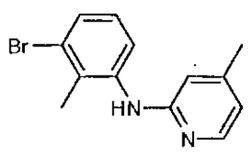
(1 H, s), 7.76 (1 H, d, J=9.0 Hz), 7.62 (1 H, dd, J=8.0, 0.8 Hz), 7.51 (1 H, dd, J=8.1, 0.9 Hz), 7.08 - 7.20 (3 H, m), 5.30 (1 H, s), 3.96 (3 H, s), 2.41 (3 H, s). Mass spectrum m/z 344, 346 $(M+H)^+$.

[00253] The following Intermediates were also prepared using procedures used to prepare Intermediate 32-1.

Intermediate	Compound name	Mass spectrum
32-2	N-(3-bromo-2-methylphenyl)-6-methylquinazolin-4-amine	328, 330 $(M+H)^+$
32-3	N-(3-bromo-2-methylphenyl)-7-fluoroquinazolin-4-amine	332, 334 $(M+H)^+$
32-4	N-(3-bromo-2-methylphenyl)-6-fluoroquinazolin-4-amine	332, 334 $(M+H)^+$
32-5	N-(3-bromo-2-methylphenyl)-7-methylquinazolin-4-amine	328, 330 $(M+H)^+$
32-6	N-(3-bromo-2-methylphenyl)-5-fluoroquinazolin-4-amine	332, 334 $(M+H)^+$
32-7	N-(3-bromo-2-methylphenyl)-8-fluoroquinazolin-4-amine	332, 334 $(M+H)^+$
32-8	N-(3-bromo-2-methylphenyl)-6-methoxyquinazolin-4-amine	344, 346 $(M+H)^+$
32-9	N-(3-bromo-2-methylphenyl)quinazolin-4-amine	314, 316 $(M+H)^+$

Intermediate 33-1

Preparation of N-(3-bromo-2-methylphenyl)-4-methylpyridin-2-amine



[00254] A mixture of 3-bromo-2-methylaniline (200 mg, 1.075 mmol), 2-fluoro-4-methylpyridine (155 mg, 1.397 mmol) and potassium *tert*-butoxide (193 mg, 1.72 mmol) in DMSO (4 mL) was heated in a sealed tube via microwave irradiation at 190

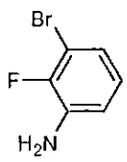
°C for 40 min. The mixture was partitioned between EtOAc and water, and the organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from hexane to 85:15 hexane-EtOAc) to provide N-(3-bromo-2-methylphenyl)-4-methylpyridin-2-amine as a yellow solid (100 mg, 34%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.05 (1 H, d, *J*=5.3 Hz), 7.38 (2 H, d, *J*=8.1 Hz), 7.06 (1 H, t, *J*=8.0 Hz), 6.58 (1 H, d, *J*=5.3 Hz), 6.40 (1 H, s), 6.23 (1 H, br. s.), 2.37 (3 H, s), 2.23 (3 H, s). Mass spectrum m/z 277, 279 $(M+H)^+$.

[00255] The following Intermediates were also prepared using procedures used to prepare Intermediate 33-1.

Intermediate	Compound name	Mass spectrum
33-2	N-(3-bromo-2-methylphenyl)-5-methylpyridin-2-amine	277, 279 $(M+H)^+$
33-3	N-(3-bromo-2-methylphenyl)pyridin-2-amine	263, 265 $(M+H)^+$
33-4	N-(3-bromo-2-methylphenyl)-3-methylpyridin-2-amine	277, 279 $(M+H)^+$

Intermediate 34-1

Preparation of 3-bromo-2-fluoroaniline

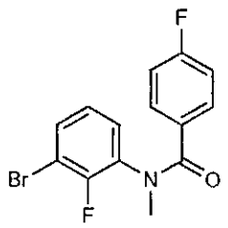


[00256] A solution of 1-bromo-2-fluoro-3-nitrobenzene (1.10 g, 5.00 mmol) in ethanol-acetic acid-water (2:2:1) (25 mL) was treated with iron powder (1.396 g, 25.0 mmol) and the mixture was heated at reflux for 1 h. The mixture was cooled to rt and filtered through a Celite pad. The filtrate was concentrated and the residue was partitioned between EtOAc and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated to provide 3-bromo-2-fluoroaniline as a brown oil (880

mg, 93%). ^{1}H NMR (400 MHz, chloroform-d) δ 6.85 - 6.92 (1 H, m), 6.80 (1 H, td, *J*=8.0, 1.2 Hz), 6.66 - 6.73 (1 H, m), 3.81 (2 H, br. s.).

Intermediate 35-1

Preparation of N-(3-bromo-2-fluorophenyl)-4-fluoro-N-methylbenzamide



[00257] Step 1 A solution of Intermediate 34-1 (205 mg, 1.079 mmol) in formic acid (0.611 mL, 16.18 mmol) was heated at 90 °C for 5.5 h. The mixture was concentrated and partitioned between EtOAc and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated, and the residue was purified column chromatography (eluting with a gradient from 85:15 to 70:30 hexane-EtOAc) to provide N-(3-bromo-2-fluorophenyl)formamide as an off-white solid (216 mg, 92%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.49 (1 H, s), 8.27 - 8.37 (1 H, m), 7.44 (1 H, br. s.), 7.30 (1 H, ddd, *J*=8.1, 6.6, 1.5 Hz), 7.04 (1 H, td, *J*=8.2, 1.5 Hz), 1.58 (3 H, s). Mass spectrum m/z 218, 220 $(M+H)^+$.

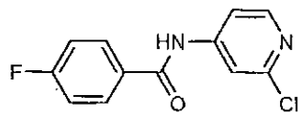
[00258] Step 2 A suspension of N-(3-bromo-2-fluorophenyl)formamide (216 mg, 0.991 mmol) in THF (8 mL) was treated with borane dimethyl sulfide complex (2.0 M in THF, 1.486 mL, 2.97 mmol) and the resulting mixture was heated at reflux for 2 h. 1 M hydrochloric acid was added and the mixture was again heated at reflux for 1 h. The mixture was cooled to rt and concentrated and the residue was partitioned between NaHCO3 (aq) and EtOAc. The organic phase was washed with brine, dried and concentrated to provide 3-bromo-2-fluoro-N-methylaniline as a light yellow oil (60 mg, 30%). Mass spectrum m/z 204, 206 $(M+H)^+$.

[00259] Step 3 A solution of 3-bromo-2-fluoro-N-methylaniline (32 mg, 0.157 mmol) and diisopropylamine (0.055 mL, 0.314 mmol) in DCM (2 mL) was treated with 4-fluorobenzoyl chloride (0.028 mL, 0.235 mmol) and the mixture was stirred at rt for 2 h. The mixture was partitioned between DCM and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 90:10 to 80:20 hexane-EtOAc)

to provide N-(3-bromo-2-fluorophenyl)-4-fluoro-N-methylbenzamide as a white solid (35 mg, 68%). Mass spectrum m/z 326, 328 $(M+H)^+$.

Intermediate 35-2

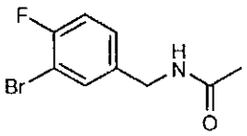
Preparation of N-(2-chloropyridin-4-yl)-4-fluorobenzamide



[00260] A solution of 2-bromopyridin-4-amine (500 mg, 2.89 mmol) in pyridine (8 mL) was stirred on ice and treated with 4-fluorobenzoyl chloride (0.376 mL, 3.18 mmol). The resulting solution was stirred at rt for 20.25 h, then was concentrated and the residue was partitioned between EtOAc and water. The organic phase was washed with NaHCO3 (aq) and water, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 80:20 to 20:80 hexane-EtOAc) to provide N-(2-chloropyridin-4-yl)-4-fluorobenzamide as a white glassy solid (532 mg, 73%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.29 (d, J=5.5 Hz, 1 H) 8.14 (br. s., 1 H) 7.89 (dd, J=8.8, 5.1 Hz, 2 H) 7.77 (d, J=2.0 Hz, 1 H) 7.48 (dd, J=5.7, 2.0 Hz, 1 H) 7.18 (t, J=8.6 Hz, 2 H). Mass spectrum m/z 251, 253 $(M+H)^+$.

Intermediate 35-3

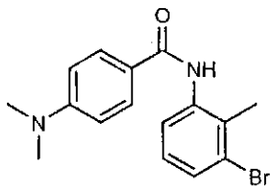
Preparation of N-(3-bromo-4-fluorobenzyl)acetamide



[00261] A solution of (3-bromo-4-fluorophenyl)methanamine hydrochloric acid salt (500 mg, 2.079 mmol) in pyridine (6 mL) was stirred on ice and treated with acetic anhydride (0.235 mL, 2.495 mmol). The resulting solution was stirred at rt for 17 h, then was concentrated. The residue was stirred in 1 M hydrochloric acid, forming a precipitate which was collected by filtration, rinsed with water and dried to provide N-(3-bromo-4-fluorobenzyl)acetamide as a white solid (435 mg, 85%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.47 (dd, J=6.6, 2.2 Hz, 1 H) 7.20 (ddd, J=8.6, 4.6, 2.2 Hz, 1 H) 7.07 (t, J=8.3 Hz, 1 H) 5.84 (br. s., 1 H) 4.38 (d, J=5.9 Hz, 2 H) 2.04 (s, 3 H). Mass spectrum m/z 246, 248 $(M+H)^+$.

Intermediate 35-4

Preparation of N-(3-bromo-2-methylphenyl)-4-(dimethylamino)benzamide



[00262] A suspension of 4-(dimethylamino)benzoic acid (100 mg, 0.605 mmol) in DCM (3 mL) was treated with 1-chloro-N,N,2-trimethylprop-1-en-1-amine (0.120 mL, 0.908 mmol) and the resulting solution was stirred at rt for 1.5 h. 3-Bromo-2-methylaniline (0.053 mL, 0.432 mmol) was added, followed by DIEA (0.264 mL, 1.513 mmol). The mixture was stirred at rt for 1 h, then was diluted with DCM and NaHCO3 (aq). The layers were separated and the organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 85:15 to 65:35 hexane-EtOAc) to provide N-(3-bromo-2-methylphenyl)-4-(dimethylamino)benzamide as a light yellow solid (77 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1 H) 7.85 (d, *J*=9.0 Hz, 2 H) 7.49 (dd, *J*=8.0, 1.0 Hz, 1 H) 7.30 (dd, *J*=7.9, 0.9 Hz, 1 H) 7.15 (t, *J*=7.9 Hz, 1 H) 6.75 (d, *J*=9.0 Hz, 2 H) 2.99 (s, 6 H) 2.25 (s, 3 H). Mass spectrum m/z 331, 333 $(M-H)^-$.

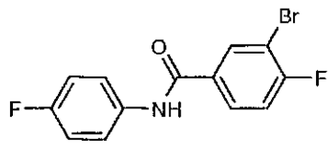
[00263] The following Intermediates were also prepared using procedures used to prepare Intermediates 35-1 through 35-4.

Intermediate	Compound name	Mass spectrum
35-5	N-(3-bromo-4-fluorophenyl)acetamide	232, 234 $(M+H)^+$
35-6	N-(3-bromophenyl)-4-fluorobenzamide	294, 296 $(M+H)^+$
35-7	N-(3-bromo-2-fluorophenyl)-4-fluorobenzamide	312, 314 $(M+H)^+$
35-8	N-(3-bromo-2-fluorophenyl)-4-(dimethylamino)benzamide	337, 339 $(M+H)^+$

35-9	N-(3-bromophenyl)-4-fluoro-N-methylbenzamide	308, 310 $(M+H)^+$
35-10	N-(5-bromo-2-fluorophenyl)-4-fluorobenzamide	312, 314 $(M+H)^+$
35-11	N-(3-bromo-4-fluorophenyl)-4-fluorobenzamide	312, 314 $(M+H)^+$
35-12	N-(3-bromo-4-fluorobenzyl)-4-fluorobenzamide	326, 328 $(M+H)^+$
35-13	N-(3-bromo-2-fluorophenyl)acetamide	232, 234 $(M+H)^+$

Intermediate 36-1

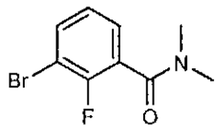
Preparation of 3-bromo-4-fluoro-N-(4-fluorophenyl)benzamide



[00264] A solution of 3-bromo-4-fluorobenzoic acid (976 mg, 4.46 mmol) in DCM (25 mL) was stirred at rt and treated with oxalyl chloride (1.950 mL, 22.28 mmol), followed by a drop of DMF, causing gas evolution to commence. After 2.5 h, the solution was heated to boiling for 1-2 min and allowed to cool to rt. After 3 h total, the solution was concentrated to provide 3-bromo-4-fluorobenzoyl chloride as a white solid (1.00 g, 94%). A portion of this material (200 mg, 0.842 mmol) was added to an ice-cold solution of 4-fluoroaniline (0.081 mL, 0.842 mmol) in pyridine (4 mL), and the solution was stirred at rt for 65 h The solution was concentrated and the residue was stirred in 1 M hydrochloric acid, forming a precipitate which was collected by filtration, washed with water and dried to provide 3-bromo-4-fluoro-N-(4-fluorophenyl)benzamide as an off-white solid (227.5 mg, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1 H) 8.29 (dd, J=6.7, 2.1 Hz, 1 H) 8.01 (ddd, J=8.6, 4.8, 2.2 Hz, 1 H) 7.75 (dd, J=9.0, 5.1 Hz, 2 H) 7.55 (t, J=8.6 Hz, 1 H) 7.20 (t, J=8.9 Hz, 2 H). Mass spectrum m/z 312, 314 $(M+H)^+$.

Intermediate 36-2

Preparation of 3-bromo-2-fluoro-N,N-dimethylbenzamide



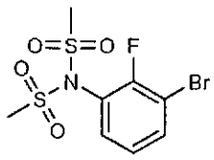
[00265] A suspension of 3-bromo-2-fluorobenzoic acid (1.009 g, 4.61 mmol) in DCM (25 mL) was stirred at rt and treated with oxalyl chloride (2.016 mL, 23.04 mmol), followed by a drop of DMF, causing gas evolution to commence. After 2.5 h, the solution was heated to boiling for 1-2 min and allowed to cool to rt. After 3 h total, the solution was concentrated to provide 3-bromo-2-fluorobenzoyl chloride as a dark yellow liquid (1.078 g, 99%). A portion of this (200 mg, 0.842 mmol) was dissolved in THF (1.5 mL) and added to a solution of dimethylamine (2 M in methanol, 2.0 mL, 4.00 mmol) in THF (2 mL). The mixture was stirred at rt for 18 h, then was concentrated. The residue was dissolved in EtOAc, washed sequentially with 1 M hydrochloric acid, NaHCO3 (aq) and brine, and dried and concentrated to provide 3-bromo-2-fluoro-N,N-dimethylbenzamide as a light yellow oil (192 mg, 93%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.60 (ddd, J=8.1, 6.5, 1.6 Hz, 1 H) 7.32 (ddd, J=7.6, 5.9, 1.6 Hz, 1 H) 7.09 (td, J=7.8, 0.7 Hz, 1 H) 3.14 (s, 3 H) 2.93 (d, J=1.5 Hz, 3 H). Mass spectrum m/z 246, 248 $(M+H)^+$.

[00266] The following Intermediates were also prepared using procedures used to prepare Intermediates 36-1 and 36-2.

Intermediate	Compound name	Mass spectrum
36-3	3-bromo-2-fluoro-N-(4-fluorophenyl)benzamide	312, 314 $(M+H)^+$
36-4	3-bromo-4-fluorobenzamide	218, 220 $(M+H)^+$
36-5	3-bromo-2-fluorobenzamide	218, 220 $(M+H)^+$
36-6	3-bromo-2-fluoro-N-methylbenzamide	232, 234 $(M+H)^+$
36-7	3-bromo-4-fluoro-N,N-dimethylbenzamide	246, 248 $(M+H)^+$

Intermediate 37-1

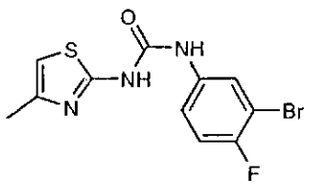
Preparation of N-(3-bromo-2-fluorophenyl)-N-(methylsulfonyl)methanesulfonamide



[00267] A solution of 3-bromo-2-fluoroaniline (Intermediate 34-1, 160 mg, 0.842 mmol) and DIEA (0.368 mL, 2.105 mmol) in DCM (3 mL) was stirred at ca. -5 °C and treated with methanesulfonyl chloride (0.098 mL, 1.263 mmol) and stirred at that temperature for 2 h. The mixture was partitioned between DCM and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated to provide N-(3-bromo-2-fluorophenyl)-N-(methylsulfonyl)methanesulfonamide as a yellow solid (308 mg, quantitative), used without further purification. ^{1}H NMR (400 MHz, chloroform-d) δ 7.70 (1 H, ddd, *J*=8.1, 6.4, 1.5 Hz), 7.33 (1 H, ddd, *J*=8.1, 6.5, 1.6 Hz), 7.15 (1 H, td, *J*=8.1, 1.4 Hz), 3.46 (6 H, s). Mass spectrum m/z 363, 365 $(M+NH_4)^+$.

Intermediate 38-1

Preparation of 1-(3-bromo-4-fluorophenyl)-3-(4-methylthiazol-2-yl)urea



[00268] Step 1 A solution of 2-amino-4-methylthiazole (11.42 g, 0.10 mol) in DCM was cooled to 0 °C and treated with TEA (12.1 g, 0.12 mol), then phenyl chloroformate (15.6 g, 0.10 mol) was added dropwise with stirring. The mixture was stirred for 10 minutes, then was washed with NaHCO3 (aq), water and brine, and dried and concentrated. The residue was purified by column chromatography (eluting with 60:40 hexane-EtOAc) to give phenyl 4-methylthiazol-2-ylcarbamate as a white solid (12 g, 51%). ^{1}H NMR (300 MHz, chloroform-d) δ 12.38 (bs, 1 H) 7.47-7.40 (m, 2 H) 7.30-7.19 (m, 3 H) 6.52 (d, J = 1.1 Hz, 1 H) 2.41 (d, J = 0.8 Hz, 3 H).

[00269] Step 2 A solution of 3-bromo-4-fluoroaniline (250 mg, 1.316 mmol) in THF (6 mL) was stirred on ice and treated with TEA (0.367 mL, 2.63 mmol), then

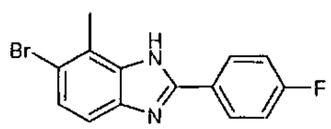
with phenyl 4-methylthiazol-2-ylcarbamate (308 mg, 1.316 mmol) and the resulting solution was stirred at rt for 70 h. The mixture was concentrated and the residue was stirred in 1 M hydrochloric acid, forming a precipitate which was collected by filtration, rinsed with water and dried under vacuum to provide 1-(3-bromo-4-fluorophenyl)-3-(4-methylthiazol-2-yl)urea as an off white solid (400 mg, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1 H) 7.94 (dd, J=6.3, 2.5 Hz, 1 H) 7.37 - 7.45 (m, 1 H) 7.32 (t, J=8.7 Hz, 1 H) 6.67 (d, J=1.1 Hz, 1 H) 2.23 (d, J=1.1 Hz, 3 H). Mass spectrum m/z 330, 332 $(M+H)^+$.

[00270] The following Intermediate was also prepared using procedures used to prepare Intermediate 38-1.

Intermediate	Compound name	Mass spectrum
38-2	1-(3-bromo-4-fluorobenzyl)-3-(4-methylthiazol-2-yl)urea	344, 346 $(M+H)^+$

Intermediate 39-1

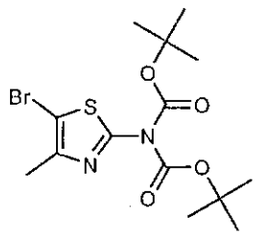
Preparation of 6-bromo-2-(4-fluorophenyl)-7-methyl-1H-benzo[d]imidazole



[00271] A solution of 4-bromo-3-methylbenzene-1,2-diamine (prepared according to the procedure of PCT Pat. Appl. WO 2008/021851, 400 mg, 1.989 mmol) in DCM (10 mL) was treated with TEA (0.693 mL, 4.97 mmol), then was treated dropwise with 4-fluorobenzoyl chloride (0.282 mL, 2.387 mmol). The mixture was stirred at rt for 70 min, then was concentrated. The residue was suspended in ethanol (25 mL), treated with concentrated hydrochloric acid (3 mL, 36.5 mmol) and heated at 90-95 °C. After 42.5 h, the mixture was cooled to rt and the ethanol was removed under vacuum. The residual paste was suspended in water and the pH was adjusted to ca. 8 with NaHCO3 (aq). The precipitate was collected by filtration, washed with water and dried under vacuum to provide 6-bromo-2-(4-fluorophenyl)-7-methyl-1H-benzo[d]imidazole as a pale pink solid (636 mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (2 H, dd, J=8.9, 5.4 Hz), 7.33 - 7.45 (4 H, m), 2.57 (3 H, s). Mass spectrum m/z 305, 307 $(M+H)^+$.

Intermediate 40-1

Preparation of N,N-bis(*tert*-butyloxycarbonyl)-5-bromo-4-methylthiazol-2-ylamine

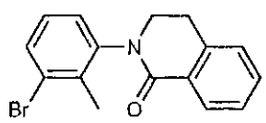


[00272] Step 1 A solution of 5-bromo-4-methylthiazol-2-amine (2.00 g, 10.36 mmol) in pyridine (10 mL) was treated portionwise at rt with di-*tert*-butyl dicarbonate (2.487 g, 11.40 mmol). After stirring at rt overnight significant starting material remained. The mixture was cooled to 0 °C and treated with lithium hexamethyldisilazide (1 M in THF, 25.9 mL, 25.9 mmol) followed by di-*tert*-butyl dicarbonate (2.487 g, 11.40 mmol). The mixture was warmed to rt for 1 h, then was diluted with EtOAc, washed twice with 0.5 M hydrochloric acid, then with 1 M aqueous sodium hydroxide, dried and concentrated. Purification of the residue by column chromatography (elution with hexane-EtOAc) provided *tert*-butyl 5-bromo-4-methylthiazol-2-ylcarbamate (814 mg, 27%). 1H NMR (400 MHz, chloroform-d) δ 2.27 (3 H, s), 1.53 (9 H, s). Mass spectrum m/z 293, 295 $(M+H)^+$.

[00273] Step 2 A mixture of di-*tert*-butyl dicarbonate (667 mg, 3.05 mmol), *tert*-butyl 5-bromo-4-methylthiazol-2-ylcarbamate (814 mg, 2.78 mmol) and DMAP (339 mg, 2.78 mmol) in DCM (10 mL) was stirred at rt overnight. The mixture was concentrated and the residue was purified by column chromatography (eluting with hexane-EtOAc) to provide N,N-bis(*tert*-butyloxycarbonyl)-5-bromo-4-methylthiazol-2-ylamine. Mass spectrum m/z 393, 395 $(M+H)^+$.

Intermediate 41-1

Preparation of 2-(3-bromo-2-methylphenyl)-3,4-dihydroisoquinolin-1(2H)-one



[00274] Step 1 A solution of 2,3-dihydro-1H-inden-1-one (1 g, 7.57 mmol) in DCM (10 mL) was treated with methanesulfonic acid (10 mL) and cooled to 0 °C.

Sodium azide (0.984 g, 15.13 mmol) was added and the mixture was stirred at 0 °C for 2 h, then at rt overnight. The mixture was made basic with 20% aqueous sodium hydroxide and extracted with DCM. The organic phase was washed with water, dried and concentrated. The residue was purified by column chromatography (eluting with hexane-EtOAc) to provide 3,4-dihydroquinolin-2(1H)-one as a white solid (655 mg, 60%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.08 - 7.19 (2 H, m), 6.92 - 6.99 (1 H, m), 6.85 (1 H, d, J=7.9 Hz), 5.47 (1 H, s), 2.92 (2 H, t, J=7.6 Hz), 2.49 - 2.58 (2 H, m). Mass spectrum m/z 148.1 $(M+H)^+$. Also obtained was 3,4-dihydroisoquinolin-1(2H)-one as a colorless oil (162 mg, 15%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.93 (1 H, dd, J=7.8, 1.0 Hz), 7.44 - 7.52 (1 H, m), 7.35 (1 H, td, J=7.6, 1.2 Hz), 7.29 (1 H, d, J=7.7 Hz), 3.50 (2 H, t, J=6.6 Hz), 2.98 (2 H, t, J=6.7 Hz). Mass spectrum m/z 148.1 $(M+H)^+$.

[00275] Step 2 A mixture of 1,3-dibromo-2-methylbenzene (340 mg, 1.359 mmol), 3,4-dihydroisoquinolin-1(2H)-one (100 mg, 0.679 mmol) and potassium carbonate (94 mg, 0.679 mmol) in DMSO (2 mL) was purged with nitrogen, treated with copper (I) iodide (25.9 mg, 0.136 mmol) and heated at 150 °C for 3.5 h. The mixture was combined with that from a second reaction using 1,3-dibromo-2-methylbenzene (2.59 g, 10.36 mmol) and 3,4-dihydroisoquinolin-1(2H)-one (508 mg, 3.45 mmol), diluted with DCM and filtered through Celite. The filtrate was washed with 5% aqueous ammonium hydroxide, dried and concentrated. The residue was purified by column chromatography (eluting with hexane-EtOAc) to provide 2-(3-bromo-2-methylphenyl)-3,4-dihydroisoquinolin-1(2H)-one as a yellow solid (142 mg, 11%).^{1}H NMR (400 MHz, chloroform-d) δ 8.15 (1 H, dd, J=7.70, 1.10 Hz), 7.55 (1 H, dd, J=7.92, 1.10 Hz), 7.46 - 7.51 (1 H, m), 7.37 - 7.42 (1 H, m), 7.24 - 7.28 (1 H, m), 7.17 - 7.21 (1 H, m), 7.09 - 7.16 (1 H, m), 3.95 (1 H, ddd, J=12.21, 10.12, 4.73 Hz), 3.73 (1 H, ddd, J=11.94, 6.33, 5.28 Hz), 3.26 (1 H, ddd, J=15.74, 10.23, 5.28 Hz), 3.06 - 3.14 (1 H, m), 2.36 (3 H, s). Mass spectrum m/z 316, 318 $(M+H)^+$.

[00276] The following Intermediates were also prepared using procedures used to prepare Intermediate 41-1.

Intermediate	Compound name	Mass spectrum

41-2	2-(3-bromo-2-methylphenyl)-6-methoxy-3,4-dihydroisoquinolin-1(2H)-one	346, 348 $(M+H)^+$
41-3	2-(3-bromo-2-methylphenyl)-5-hydroxy-3,4-dihydroisoquinolin-1(2H)-one	332, 334 $(M+H)^+$
41-4[a]	5-(3-bromo-2-methylphenoxy)-3,4-dihydroisoquinolin-1(2H)-one	332, 334 $(M+H)^+$
41-5	2-(3-bromo-2-methylphenyl)-7-chloro-3,4-dihydroisoquinolin-1(2H)-one	350, 352 $(M+H)^+$
41-6	2-(3-bromo-2-methylphenyl)-6-fluoro-3,4-dihydroisoquinolin-1(2H)-one	334, 336 $(M+H)^+$

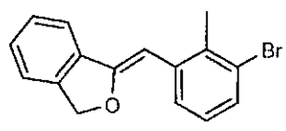
[a] Obtained from the same reaction used to prepare Intermediate 41-3

[00277] The following Intermediates were also prepared using procedures of Step 2 used to prepare Intermediate 41-1.

Intermediate	Compound name	Mass spectrum
41-7	1-(3-bromo-2-methylphenyl)-3,4-dimethyl-1H-pyrrol-2(5H)-one	280, 282 $(M+H)^+$
41-8	1-(3-bromo-2-methylphenyl)-3-methylpyridin-2(1H)-one	278, 280 $(M+H)^+$
41-9	1-(3-bromo-2-methylphenyl)-4,4-dimethylpyrrolidin-2-one	282, 284 $(M+H)^+$
41-10	1-(3-bromo-2-methylphenyl)-5-oxopyrrolidine-3-carboxylic acid	298, 300 $(M+H)^+$

Intermediate 42-1

Preparation of 1-(3-bromo-2-methylbenzylidene)-1,3-dihydroisobenzofuran



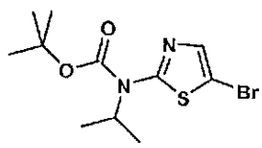
[00278] Step 1 A mixture of (2-ethynylphenyl)methanol (100 mg, 0.757 mmol), 1,3-dibromo-2-methylbenzene (189 mg, 0.757 mmol) and TEA (0.211 mL, 1.513 mmol) in THF (2 mL) was purged with nitrogen and treated with copper (I) iodide

(2.88 mg, 0.015 mmol) and bis(triphenylphosphine)palladium(II) chloride (26.6 mg, 0.038 mmol). The mixture was heated in a sealed tube at 60 °C for 1.5 h. The mixture was filtered, the filtrate was washed with NaHCO3 (aq) and water, and dried and concentrated. The residue was purified by column chromatography (eluting with hexane-EtOAc) to provide (2-((3-bromo-2-methylphenyl)ethynyl)phenyl)methanol as a white solid (130 mg,.57%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.44 - 7.58 (4 H, m), 7.39 (1 H, td, J=7.54, 1.43 Hz), 7.27 - 7.34 (1 H, m), 7.00 - 7.09 (1 H, m), 4.93 (2 H, d, J=6.38 Hz), 2.64 (3 H, s). Mass spectrum m/z 323, 325 $(M+Na)^+$.

[00279] Step 2 A solution of (2-((3-bromo-2-methylphenyl)ethynyl)phenyl)-methanol (50 mg, 0.166 mmol) and tetrabutylammonium fluoride, 1.0 M in THF (0.332 mL, 0.332 mmol) in THF (0.5 mL) was heated at 67 °C for 2 h. The mixture was diluted with EtOAc, washed twice with water and once with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from hexane to 80:20 EtOAc-hexane) to provide 1-(3-bromo-2-methylbenzylidene)-1,3-dihydroisobenzofuran as a light yellow solid (36 mg, 72%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.00 - 8.06 (1 H, m), 7.58 - 7.64 (1 H, m), 7.32 - 7.41 (4 H, m), 7.04 (1 H, t, J=7.92 Hz), 6.07 (1 H, s), 5.49 (2 H, s), 2.51 (3 H, s). Mass spectrum m/z 301, 303 $(M+H)^+$.

Intermediate 43-1

Preparation of *tert*-butyl 5-bromothiazol-2-yl(isopropyl)carbamate

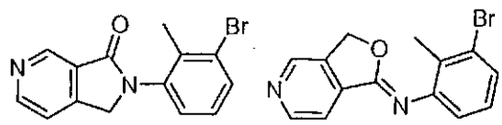


[00280] Step 1 Di-*tert*-butyl dicarbonate (28.90 g, 132.4 mmol) was added portionwise to a suspension of 2-amino-5-bromothiazole hydrobromide (28.64 g, 110.3 mmol) in pyridine (100 mL) over 20 min at rt. The mixture was stirred at rt overnight, then was concentrated. The residue was partitioned between 0.5 M hydrochloric acid (200 mL) and EtOAc (200 mL). The organic layer was dried and concentrated, and the residue was filtered through a pad of silica gel using 90:10 hexane-EtOAc. The filtrate was concentrated to give *tert*-butyl-5-bromothiazol-2-ylcarbamate as a white solid (19.5 g, 63%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.27 (s, 1 H) 1.60 (s, 9 H). Mass spectrum m/z 223, 225 $(M+H)^+$.

[00281] Step 2 A solution of *tert*-butyl 5-bromothiazol-2-ylcarbamate (3 g, 10.7 mmol), isopropanol (6.40 g, 107.4 mmol) and triphenylphosphine (5.63 g, 21.5 mmol) in THF (30 mL) was treated with diethyl azodicarboxylate (3.74 g, 21.5 mmol) dropwise at 0 °C and was stirred overnight while warming slowly to rt. The mixture was concentrated and the residue was dissolved in DCM (20 mL), filtered to remove undissolved solid and concentrated. The residue was purified by column chromatography (eluting with hexane) to give *tert*-butyl 5-bromothiazol-2-yl(isopropyl)carbamate as a light yellow oil (3.10 g, 90%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.34 (s, 1 H) 5.29 (m, 1 H) 1.59 (s, 9 H) 1.45 (d, 6.8 Hz, 6 H). Mass spectrum m/z 265, 267 $(M+H-C_4H_9)^+$.

Intermediates 44-1 and 44-2

Preparation of 2-(3-bromo-2-methylphenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one and (Z)-3-bromo-N-(furo[3,4-c]pyridin-1(3H)-ylidene)-2-methylaniline

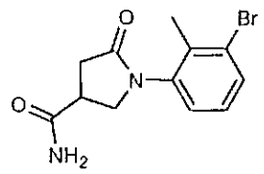


[00282] A suspension of 2-(3-bromo-2-methylphenyl)-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (4.7 g, 14.82 mmol) in methanol (200 mL) was treated with sodium borohydride (2 g, 52.9 mmol) and stirred at rt for 1 h. The mixture was concentrated and the residue was treated with NaHCO3 (aq). The mixture was extracted several times with a mixture of DCM and methanol. The combined organic phases were washed with water, dried and concentrated to give a mixture of N-(3-bromo-2-methylphenyl)-4-(hydroxymethyl)-nicotinamide and N-(3-bromo-2-methylphenyl)-3-(hydroxymethyl)isonicotinamide as an off-white solid. Mass spectrum m/z 321, 323 $(M+H)^+$. Without purification, this material was suspended in THF (250 mL) and treated with triphenylphosphine (polymer supported, 3 mmol P/g resin, 18.44 g, 54.8 mmol) and diethyl azodicarboxylate (6.45 g, 37.1 mmol) and the mixture was stirred at rt for 4 h. The mixture was filtered and concentrated, and the residue was dissolved in DCM, washed with water, NaHCO3 (aq) and brine, and dried and concentrated. The residue was subjected to column chromatography (eluting with EtOAc) to provide 2-(3-bromo-2-methylphenyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one as a white solid (Intermediate 44-1, 2.7 g, 60%). ^{1}H NMR (400 MHz, chloroform-d) δ

9.21 (1 H, d, J=0.88 Hz), 8.84 (1 H, d, J=5.06 Hz), 7.63 (1 H, dd, J=7.70, 1.32 Hz), 7.51 (1 H, dd, J=5.06, 0.88 Hz), 7.22 (1 H, dt, J=7.70, 1.32 Hz), 7.17 (1 H, d, J=7.92 Hz), 4.76 (2 H, s), 2.31 (3 H, s). Mass spectrum m/z 303, 305 $(M+H)^+$. Also obtained was (Z)-3-bromo-N-(furo[3,4-c]pyridin-1(3H)-ylidene)-2-methylaniline as a white solid (Intermediate 44-2, 760 mg, 17%), which also contained the isomeric (Z)-3-bromo-N-(furo[3,4-c]pyridin-3(1H)-ylidene)-2-methylaniline. ^{1}H NMR (400 MHz, chloroform-d) δ 9.26 (1 H, s), 8.80 (1 H, d, J=5.06 Hz), 7.42 (1 H, dd, J=5.06, 0.88 Hz), 7.31 - 7.35 (1 H, m), 7.02 - 7.08 (2 H, m), 5.39 (2 H, s), 2.35 (3 H, s). Mass spectrum m/z 303, 305 $(M+H)^+$.

Intermediate 45-1

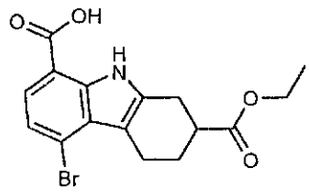
Preparation of 1-(3-bromo-2-methylphenyl)-5-oxopyrrolidine-3-carboxamide



[00283] A mixture of 1-(3-bromo-2-methylphenyl)-5-oxopyrrolidine-3-carboxylic acid (Intermediate 41-10, 100 mg, 0.335 mmol), EDC (129 mg, 0.671 mmol), HOBT (103 mg, 0.671 mmol) and 28% aqueous ammonia in THF (2 mL) was stirred at rt for 5 h. The mixture was diluted with ethyl acetate, washed with NaHCO3 (aq) and water, and dried and concentrated. The residue was purified by column chromatography (eluting with 90:10 DCM-methanol) to provide 1-(3-bromo-2-methylphenyl)-5-oxopyrrolidine-3-carboxamide as a white solid (26 mg, 26%). Mass spectrum m/z 297, 299 $(M+H)^+$.

Intermediate 46-1

Preparation of 5-bromo-2-(ethoxycarbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid



[00284] Step 1 A solution of sodium nitrite (2.448 g, 35.5 mmol) in water (12 mL) was added dropwise to a suspension of 2-amino-4-bromobenzoic acid (7.30 g, 33.8 mmol) in concentrated hydrochloric acid (34 mL) at -5 °C, at such rate that the temperature did not exceed 0 °C. The resulting suspension was stirred at -5 °C for 10 min and was then added dropwise to a rapidly stirred solution of tin (II) chloride (13.46 g, 71.0 mmol) in concentrated hydrochloric acid (10 mL) at -5 °C, at such a rate that the temperature did not exceed 0 °C. The resulting suspension was warmed to rt and stirred for 1 h. The precipitate was collected by filtration, washed with water, and dried to provide 4-bromo-2-hydrazinylbenzoic acid hydrochloric acid salt as a pale tan solid (7.79 g, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (br. s., 1 H) 7.79 (d, J=8.35 Hz, 1 H) 7.34 (d, J=1.76 Hz, 1 H) 7.13 (dd, J=8.35, 1.76 Hz, 1 H). Mass spectrum m/z 231, 233 $(M+H)^+$.

[00285] Step 2 A stirred suspension of 4-bromo-2-hydrazinylbenzoic acid hydrochloric acid salt (16.35 g, 58.1 mmol) in acetic acid (171 mL) was treated with ethyl 3-oxocyclohexanecarboxylate (9.88 g, 58.1 mmol) at rt. The mixture was stirred at reflux for 2.5 h, then was cooled to rt and concentrated to afford a brown solid. This was suspended in EtOAc (20 mL) and the precipitate was collected by filtration, washed with EtOAc and air dried to provide 5-bromo-2-(ethoxycarbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (11.46 g). The filtrate was concentrated and the residue was resuspended in EtOAc, the precipitate collected by filtration and dried to provide additional product (0.82 g) for a total of 12.28 g (58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (br. s., 1 H) 11.06 (s, 1 H) 7.50 (d, J=8.13 Hz, 1 H) 7.19 (d, J=8.13 Hz, 1 H) 4.07 - 4.15 (m, 2 H) 3.08 - 3.19 (m, 1 H) 2.99 - 3.08 (m, 1 H) 2.89 - 2.99 (m, 2 H) 2.79 - 2.89 (m, 1 H) 2.09 - 2.22 (m, 1 H) 1.75 - 1.89 (m, 1 H) 1.20 (t, J=7.14 Hz, 3 H). Mass spectrum m/z 366.0, 368.0 $(M+H)^+$.

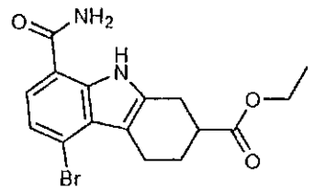
[00286] The following Intermediates were also prepared using the procedures used to prepare Intermediate 46-1 but using the appropriate ketone in place of ethyl 3-oxocyclohexanecarboxylate.

Intermediate	Compound name	Mass spectrum
46-2	5-bromo-3-(ethoxycarbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid	366, 368 $(M+H)^+$

46-3	5-bromo-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid	294, 296 $(M+H)^+$

Intermediate 47-1

Preparation of ethyl 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate



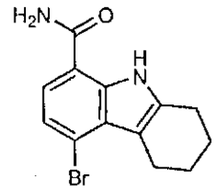
[00287] A suspension of 5-bromo-2-(ethoxycarbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (Intermediate 46-1, 12.28 g, 33.5 mmol), EDC (7.71 g, 40.2 mmol), and HOBT (6.16 g, 40.2 mmol) in THF-DCM (4:1, 335 mL) was treated with 28% aqueous ammonium hydroxide (7.83 mL, 201 mmol), and the resulting suspension was stirred at rt overnight. The mixture was concentrated and the residue was suspended in water. The precipitate was collected by filtration, washed with water and EtOAc and dried to give ethyl 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate (8.92 g). The filtrate was concentrated and the residue was suspended in methanol. A solid was collected by filtration, washed with methanol and air dried to afford additional product (0.39 g) for a total of 9.31 g (76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1 H) 8.02 (br. s., 1 H) 7.43 (d, J=8.13 Hz, 1 H) 7.39 (br. s., 1 H) 7.14 (d, J=8.13 Hz, 1 H) 4.02 - 4.17 (m, 2 H) 3.07 - 3.18 (m, 1 H) 2.97 - 3.06 (m, 1 H) 2.86 - 2.98 (m, 2 H) 2.77 - 2.86 (m, 1 H) 2.09 - 2.19 (m, 1 H) 1.72 - 1.86 (m, 1 H) 1.20 (t, J=7.14 Hz, 3 H). Mass spectrum m/z 365, 367 $(M+H)^+$.

[00288] The following Intermediate was also prepared using the procedure used to prepare Intermediate 47-1 but using Intermediate 46-2 in place of Intermediate 46-1.

Intermediate	Compound name	Mass spectrum
47-2	ethyl 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylate	365, 367 $(M+H)^+$

Intermediate 47-3

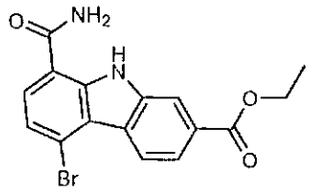
Preparation of 5-bromo-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00289] A mixture of 5-bromo-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (Intermediate 46-3, 70% purity, mixed with Intermediate 47-3 from an incomplete reaction done according to the procedure used to prepare Intermediate 47-1; 3 g, 7.14 mmol) in THF (80 mL) and DCM (20 mL) was treated with HOAT (1.166 g, 8.57 mmol) and EDC (1.642 g, 8.57 mmol). The mixture was stirred at rt for 2.5 h, then was treated with anhydrous ammonia gas for ca. 2 min, forming a very thick slurry. The mixture was stirred for 30 min, then was treated again with ammonia gas for ca. 1 min. After stirring for another hour, the mixture was diluted with water and EtOAc (dissolving the solid). The layers were separated and the aqueous phase was extracted again with EtOAc. The combined organic layers were washed twice with 0.1 M aqueous sodium hydroxide, then with 1 M hydrochloric acid and brine, dried and concentrated to provide 5-bromo-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a pale orange-tan solid (2.47 g, 84%, including the product from the incomplete reaction yielding the starting material). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (1 H, s), 8.02 (1 H, br. s.), 7.44 (1 H, d, J=7.9 Hz), 7.38 (1 H, br. s.), 7.14 (1 H, d, J=8.1 Hz), 2.99 (2 H, br. s.), 2.75 (2 H, br. s.), 1.78 (4 H, br. s.). Mass spectrum m/z 293, 295 $(M+H)^+$.

Intermediate 48-1

Preparation of ethyl 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylate



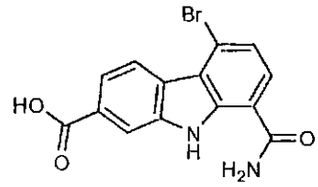
[00290] A stirred suspension of ethyl 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate (Intermediate 47-1, 9.31 g, 25.5 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (12.73 g, 56.1 mmol) in toluene (127 mL) was heated at reflux for 3 h. The mixture was cooled to rt and the precipitate was collected by filtration, washed with toluene and water, and air dried. The solid was suspended in methanol and the precipitate was collected by filtration, washed with methanol and air dried to provide ethyl 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylate (7.68 g). The filtrate was concentrated and the residue was suspended in methanol. The precipitate was collected by filtration, washed with methanol and air dried to provide additional product (0.60 g) for a total of 8.28 g (90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1 H) 8.69 (d, J=8.57 Hz, 1 H) 8.51 (d, J=1.10 Hz, 1 H) 8.26 (br. s., 1 H) 7.93 (d, J=8.13 Hz, 1 H) 7.87 (dd, J=8.57, 1.54 Hz, 1 H) 7.63 (br. s., 1 H) 7.50 (d, J=8.13 Hz, 1 H) 4.37 (q, J=7.03 Hz, 2 H) 1.37 (t, J=7.14 Hz, 3 H). Mass spectrum m/z 361, 363 $(M+H)^+$.

[00291] The following Intermediates were also prepared using the procedure used to prepare Intermediate 48-1 but using the appropriate material in place of Intermediate 47-1.

Intermediate	Compound name	Mass spectrum
48-2	ethyl 5-bromo-8-carbamoyl-9H-carbazole-3-carboxylate	361, 363 $(M+H)^+$
48-3	4-bromo-9H-carbazole-1-carboxamide	289, 291 $(M+H)^+$

Intermediate 49-1

Preparation of 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylic acid



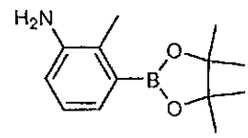
[00292] A suspension of ethyl 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylate (Intermediate 48-1, 1.81 g, 5.01 mmol) and lithium hydroxide monohydrate (0.601 g, 15.03 mmol) in THF-ethanol-water (3:1:1, 50 mL) was heated at reflux for 2 h. The mixture was cooled to rt and concentrated. The residue was stirred in water and treated with 1 M hydrochloric acid to pH 1-2. The precipitate was collected by filtration, washed with water, and dried to afford 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylic acid as a light brown solid (1.84 g, ca. 90% purity, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (br. s., 1 H) 12.02 (s, 1 H) 8.69 (d, J=8.53 Hz, 1 H) 8.47 (s, 1 H) 8.28 (br. s., 1 H) 7.94 (d, J=8.28 Hz, 2 H) 7.87 (d, J=8.28 Hz, 1 H) 7.65 (br. s., 1 H) 7.51 (d, J=8.03 Hz, 1 H). Mass spectrum m/z 331, 333 $(M-H)^-$.

[00293] The following Intermediates were also prepared using the procedure used to prepare Intermediate 49-1 but using the appropriate material in place of Intermediate 48-1.

Intermediate	Compound name	Mass spectrum
49-2	5-bromo-8-carbamoyl-9H-carbazole-3-carboxylic acid	331, 333 $(M-H)^-$
49-3	5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylic acid	335, 337 $(M-H)^-$

Intermediate 50-1

Preparation of 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[00294] A mixture of 3-bromo-2-methylaniline (4.00 g, 21.5 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.55 g, 25.8 mmol) and

potassium acetate (4.22 g, 43.0 mmol) in 1,4-dioxane (44.8 mL) and DMSO (9.0 mL) was purged with nitrogen for 10 min. [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium DCM adduct (0.527 g, 0.645 mmol) was added, the mixture was purged for another 5 min then was heated at reflux for 2 h. The mixture was cooled and filtered through Celite. The solids were washed with EtOAc, and the combined filtrates were washed with water and brine, and dried and concentrated. The residue was purified by column chromatography (eluting with hexane-EtOAc using a gradient from 95:5 to 85:15) to provide 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as a light yellow waxy solid (4.4 g, 88%), used without further purification. ^{1}H NMR (400 MHz, chloroform-d) δ 7.21 (1 H, dd, *J*=7.3, 1.0 Hz), 7.02 (1 H, t, *J*=7.7 Hz), 6.75 (1 H, dd, *J*=7.8, 1.0 Hz), 3.54 (2 H, br. s.), 2.37 (3 H, s), 1.34 (12 H, s). Mass spectrum m/z 233.3, 234.3, 235.3 $(M+H)^+$.

[00295] The following Intermediates were also prepared using the procedure used to prepare Intermediate 50-1 or closely related procedures.

Intermediate	Starting Material[a]	Compound name	Mass spectrum
50-2		2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile	[b]
50-3		3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	256.3 $(M+H)^+$
50-4	Intermediate 1-1	2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	350.3 $(M+H)^+$
50-5	Intermediate 1-2	6-fluoro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	368.1 $(M+H)^+$
50-6	Intermediate 1-4	5-methoxy-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	380.1 $(M+H)^+$
50-7	Intermediate 1-5	2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(trifluoromethyl)isoindolin-1-one	418.1 $(M+H)^+$

50-8	Intermediate 1-6	6-methyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	364.0 $(M+H)^+$
50-9	Intermediate 2-1	2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxoisoindoline-5-carbonitrile	375.3 $(M+H)^+$
50-10	Intermediate 3-1	5-fluoro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindoline-1,3-dione	382.1 $(M+H)^+$
50-11	Intermediate 3-2	5-*tert*-butyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindoline-1,3-dione	420.2 $(M+H)^+$
50-12	Intermediate 4-1	2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)octahydro-1H-isoindol-1-one	356.1 $(M+H)^+$
50-13	Intermediate 4-2	2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one	354.2 $(M+H)^+$
50-14	Intermediate 4-3	6-*tert*-butyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	406.2 $(M+H)^+$
50-15	Intermediate 4-4	5-*tert*-butyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	406.2 $(M+H)^+$
50-16	Intermediate 4-5	7-fluoro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	368.3 $(M+H)^+$
50-17	Intermediate 4-6	4-fluoro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	368.3 $(M+H)^+$

50-18	Intermediate 4-7	5-methyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	364.2 $(M+H)^+$
50-19	Intermediate 4-8	5-fluoro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one	368.2 $(M+H)^+$
50-20	Intermediate 5-1	5-methyl-2-(4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)isoindolin-1-one	365.2 $(M+H)^+$
50-21	Intermediate 5-2	2-(4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)isoindolin-1-on	351.2 $(M+H)^+$
50-22	Intermediate 6-1	2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)isoindolin-1-one	355 $(M+H)^+$
50-23	Intermediate 7-1	2-methyl-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	377.3 $(M+H)^+$
50-24	Intermediate 8-1	3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	363.3 $(M+H)^+$
50-25	Intermediate 8-2	5-fluoro-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	381.3 $(M+H)^+$
50-26	Intermediate 8-3	6-chloro-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	397, 399 $(M+H)^+$
50-27	Intermediate 9-1	6-fluoro-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	381.3 $(M+H)^+$

50-28	Intermediate 9-2	6-methyl-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	377.3 $(M+H)^+$
50-29	Intermediate 10-1	2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoquinolin-1(2H)-on	362.3 $(M+H)^+$
50-30	Intermediate 11-1	7-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)imidazo[1,2-a]pyrazin-8(7H)-one	352.1 $(M+H)^+$
50-31	Intermediate 12-1	pyrrolidin-1-yl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-2-yl)methanone	341.1 $(M+H)^+$
50-32	Intermediate 13-1	2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindoline	336.2 $(M+H)^+$
50-33	Intermediate 17-1	5-methyl-3-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one	366.1 $(M+H)^+$
50-34	Intermediate 18-1	5-methyl-3-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-benzo[e][1,3]oxazin-4(3H)-one	366.1 $(M+H)^+$
50-35	Intermediate 19-1	5-methyl-3-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-benzo[e][1,3]oxazine-2,4(3H)-dione	380.1 $(M+H)^+$
50-36	Intermediate 20-1	N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-indazol-3-amine	350.3 $(M+H)^+$
50-37	Intermediate 21-1	*tert*-butyl 6-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate	438.2 $(M+H)^+$
50-38	Intermediate 9-7	3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(trifluoromethoxy)quinazolin-4(3H)-one	447.1 $(M+H)^+$

50-39	Intermediate 23-1	7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1(2H)-one	274.1 $(M+H)^+$
50-40	Intermediate 24-1	2-(4-fluorophenyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1(2H)-one	368.1 $(M+H)^+$
50-41	Intermediate 25-1	1-(4-fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole	352.2 $(M+H)^+$
50-42	Intermediate 26-1	(4-fluorophenyl)(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)methanone	377.24 $(M+H)^+$
50-43	Intermediate 27-1	1-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-2-one	316.3 $(M+H)^+$
50-44	Intermediate 28-1	N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxamide	302.2 $(M+H)^+$
50-45	Intermediate 34-1	2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	238.1 $(M+H)^+$
50-46	Intermediate 39-1	2-(4-fluorophenyl)-7-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole	353.2 $(M+H)^+$
50-47	Intermediate 40-1	N,N-bis(*tert*-butyloxycarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-methylthiazol-2-ylamine	441.2 $(M+H)^+$
50-48	Intermediate 9-3	8-fluoro-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	381.2 $(M+H)^+$
50-49	Intermediate 44-1	2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrrolo[3,4-c]pyridin-3(2H)-one	351.5 $(M+H)^+$
50-50	Intermediate 44-2	(Z)-N-(furo[3,4-c]pyridin-1(3H)-ylidene)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	351.3 $(M+H)^+$

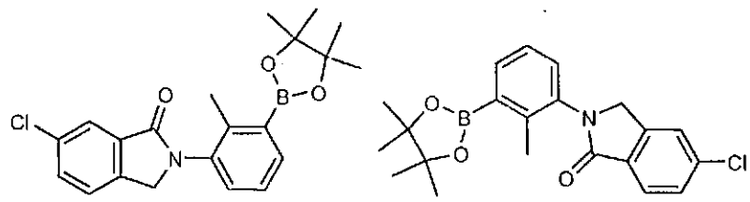
50-51	Intermediate 9-4	8-methoxy-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	393.1 $(M+H)^+$
50-52	Intermediate 9-5	5-methoxy-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	393.1 $(M+H)^+$
50-53	Intermediate 9-6	7-methoxy-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	393.1 $(M+H)^+$
50-54	Intermediate 32-9	N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4-amine	362.0 $(M+H)^+$
50-55	Intermediate 32-6	5-fluoro-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4-amine	379.9 $(M+H)^+$
50-56	Intermediate 32-3	7-fluoro-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4-amine	380.0 $(M+H)^+$
50-57	Intermediate 32-7	8-fluoro-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4-amine	380.0 $(M+H)^+$
50-58	Intermediate 9-8	8-methyl-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	377.1 $(M+H)^+$
50-59	Intermediate 9-9	6-methoxy-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	393.1 $(M+H)^+$
50-60	Intermediate 9-10	7-fluoro-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one	381.1 $(M+H)^+$

[a] Starting materials are not indicated if commercially available.

[b] ^1H NMR (400 MHz, methanol-d_4) δ 7.96 (1 H, dd, J=7.59, 1.21 Hz), 7.72 (1 H, dd, J=7.70, 1.32 Hz), 7.33 (1 H, t, J=7.37 Hz), 2.72 (3 H, s), 1.37 (12 H, s).

Intermediates 51-1 and 51-2

Preparation of 6-chloro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one and 5-chloro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one

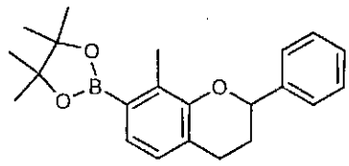


[00296] A suspension of crude 2-(3-bromo-2-methylphenyl)-5-chloroisoindoline-1,3-dione (Intermediate 3-3, 3.77 g, 10.75 mmol) in methanol (100 mL) was treated with sodium borohydride (1.017 g, 26.9 mmol) and stirred at rt for 2 h. The mixture was concentrated to give a solid which was suspended in DCM (20 mL) and treated with triethylsilane (18.12 mL, 113 mmol) and stirred at rt. After a few minutes, the mixture was treated slowly with TFA (4.37 mL, 56.7 mmol) and stirred for 10 min. Additional TFA (4.37 mL, 56.7 mmol) was added and the solution was stirred at rt for 1.5 h. The mixture was concentrated and the residue was dissolved in DCM. The solution was washed with NaHCO3 (aq) and water, and dried and concentrated. The residue was purified column chromatography (eluting with 25:75 EtOAc-hexane) to give a solid, containing both 2-(3-bromo-2-methylphenyl)-6-chloroisoindolin-1-one and 2-(3-bromo-2-methylphenyl)-5-chloroisoindolin-1-one. Using the procedure used to prepare Intermediate 50-1, this material (0.85 g, 2.53 mmol) was converted to a mixture of 6-chloro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one and 5-chloro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one which was separated by column chromatography (eluting with a gradient from 95:5 to 75:25 hexane-EtOAc). 6-chloro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 51-1, 126 mg, 13%): ^{1}H NMR (400 MHz, chloroform-d) δ 7.94 (1 H, d, *J*=1.9 Hz), 7.83 (1 H, dd, *J*=7.1, 1.8 Hz), 7.57 (1 H, dd, *J*=8.0, 1.9 Hz), 7.44 (1 H, d, *J*=8.0 Hz), 7.27 - 7.33 (2 H, m), 4.66 (2 H, s), 2.41 (3 H, s), 1.35 (12 H, s). Mass spectrum m/z 384, 386 $(M+H)^+$. 5-chloro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 51-2, 315 mg, 33%): ^{1}H NMR (400 MHz, chloroform-d) δ 7.88 (1 H, d, *J*=8.6 Hz), 7.82 (1 H, dd, *J*=7.1,

1.8 Hz), 7.48 - 7.54 (2 H, m), 7.27 - 7.32 (2 H, m), 4.66 (2 H, s), 2.41 (3 H, s), 1.35 (12 H, s). Mass spectrum m/z 384, 386 $(M+H)^+$.

Intermediate 52-1

Preparation of 4,4,5,5-tetramethyl-2-(8-methyl-2-phenylchroman-7-yl)-1,3,2-dioxaborolane



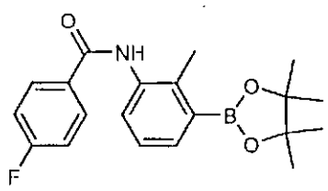
[00297] A mixture of 8-methyl-2-phenylchroman-7-yl trifluoromethanesulfonate (Intermediate 14-1, 0.300 g, 0.806 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.246 g, 0.967 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium DCM adduct (0.066 g, 0.081 mmol), diphenylphosphorylferrocene (0.045 g, 0.081 mmol) and tripotassium phosphate (0.342 g, 1.611 mmol) in DMF was heated in a sealed tube under nitrogen at 80 °C for 15 h. The mixture was cooled and diluted with EtOAc (30 mL), washed with saturated aqueous ammonium chloride (10 mL), water (10 mL) and brine (10 mL), dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 97.5:2.5 to 95:5 hexane-EtOAc) to give 4,4,5,5-tetramethyl-2-(8-methyl-2-phenylchroman-7-yl)-1,3,2-dioxaborolane as colorless liquid (ca. 85% purity). ^{1}H NMR (400 MHz, chloroform-d) δ 7.35 - 7.46 (4 H, m), 7.26 - 7.35 (2 H, m), 6.92 (1 H, d, J=7.48 Hz), 5.11 (1 H, dd, J=9.79, 2.31 Hz), 2.98 (1 H, ddd, J=16.84, 11.11, 6.16 Hz), 2.70 - 2.83 (1 H, m), 2.40 - 2.54 (3 H, m), 2.15 - 2.30 (1 H, m), 1.92 - 2.04 (1 H, m), 1.34 (12 H, s). Mass spectrum m/z 351.1 $(M+H)^+$.

[00298] The following Intermediates were also prepared using the procedure used to prepare Intermediate 52-1.

Intermediate	Starting material	Compound name	Mass spectrum
52-2	Intermediate 15-1	3-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one	352.3 $(M+H)^+$

Intermediate 53-1

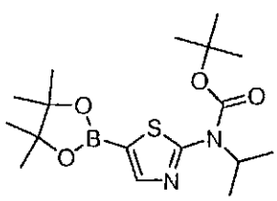
Preparation of 4-fluoro-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzamide



[00299] A solution of 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Intermediate 50-1, 1.10 g, 4.72 mmol) in EtOAc (25 mL) was treated with TEA (0.789 mL, 5.66 mmol), then with 4-fluorobenzoyl chloride (0.577 mL, 4.81 mmol) and the mixture was stirred at rt. After 22 h, the mixture was diluted with EtOAc, washed twice with water, then with brine, and dried and concentrated to provide 4-fluoro-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzamide as a glassy foam (1.705 g, ca. 90% purity, 92%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.96 (d, J=7.5 Hz, 1 H) 7.90 (dd, J=8.6, 5.3 Hz, 2 H) 7.66 (dd, J=7.4, 1.2 Hz, 1 H) 7.63 (br. s., 1 H) 7.22 - 7.29 (m, 1 H) 7.18 (t, J=8.6 Hz, 2 H) 2.53 (s, 3 H) 1.36 (s, 12 H). Mass spectrum m/z 356.1 $(M+H)^+$.

Intermediate 54-1

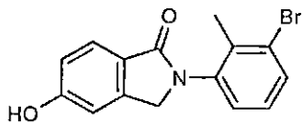
Preparation of *tert*-butyl-isopropyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazol-2-yl)carbamate



[00300] A solution of *tert*-butyl 5-bromothiazol-2-yl(isopropyl)carbamate (Intermediate 43-1, 7.5 g, 23.3 mmol) in THF (50 mL) was treated with n-butyllithium (1.6 M in hexane, 21.8 mL, 34.88 mmol) dropwise at -78 °C. The resulting solution was stirred at -78 °C for 10 min, then was treated dropwise with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.49 g, 34.9 mmol). The mixture was stirred at -78 °C for 2 h, then was warmed to rt and treated with 50% aqueous ammonium chloride (50 mL). The mixture was extracted with EtOAc (100 mL) and the organic layer was washed with water and brine, and dried and concentrated. The residue was slurried in hexane (30 mL) and the precipitate was collected by filtration, washed with hexane (20 mL) and dried to give *tert*-butyl-isopropyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazol-2-yl)carbamate as a yellow solid (4.17 g, 48%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.95 (s, 1 H) 5.37 (m, 1 H) 1.60 (s, 9 H) 1.44 (d, 6.7 Hz, 6 H) 1.34 (s, 12 H).

Intermediate 55-1

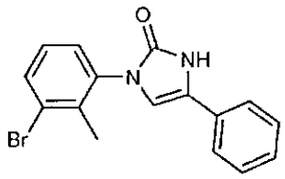
Preparation of 2-(3-bromo-2-methylphenyl)-5-hydroxyisoindolin-1-one



[00301] A mixture of 2-(3-bromo-2-methylphenyl)-5-methoxyisoindolin-1-one (Intermediate 1-4, 100 mg, 0.30 mmol) and 1.0 M boron tribromide in DCM (900 μL, 0.90 mmol) was stirred at rt for 4 h. The reaction mixture was diluted with DCM, washed with NaHCO3 (aq) and dried and concentrated. The residue was purified by column chromatography (eluting with EtOAc-hexane) to provide 2-(3-bromo-2-methylphenyl)-5-hydroxyisoindolin-1-one as an off-white solid (62 mg, 65%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.27 (1 H, br. s.), 7.64 (1 H, dd, J=7.9, 0.9 Hz), 7.59 (1 H, d, J=8.4 Hz), 7.44 (1 H, d, J=7.3 Hz), 7.25 (1 H, t, J=7.9 Hz), 6.98 (1 H, d, J=1.5 Hz), 6.93 (1 H, dd, J=8.3, 2.1 Hz), 4.77 (2 H, s), 2.20 (3 H, s). Mass spectrum m/z 318, 320 $(M+H)^+$.

Intermediate 56-1

Preparation of 1-(3-bromo-2-methylphenyl)-4-phenyl-1H-imidazol-2(3H)-one

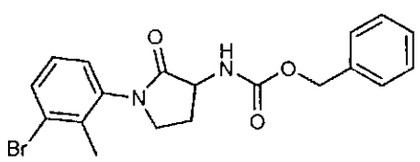


[00302] Step 1 A mixture of 3-bromo-2-methylaniline (0.620 mL, 5.03 mmol) and sodium bicarbonate (565 mg, 6.73 mmol) in acetonitrile (4.5 mL) was treated with 2-bromo-1-phenylethanone (500 mg, 2.51 mmol) and the mixture was stirred at rt. After 24 h, the suspension was filtered and the precipitate was suspended and sonicated in water, collected again by filtration, washed with water and dried to provide 2-(3-bromo-2-methylphenylamino)-1-phenylethanone as an off-white solid (508 mg, 67%). ^{1}H NMR (400 MHz, chloroform-d) δ8.00 - 8.06 (2 H, m), 7.61 - 7.68 (1 H, m), 7.53 (2 H, t, J=7.6 Hz), 6.94 - 7.01 (2 H, m), 6.51 - 6.58 (1 H, m), 5.06 (1 H, t, J=4.1 Hz), 4.62 (2 H, d, J=4.4 Hz), 2.40 (3 H, s). Mass spectrum m/z 304, 306 $(M+H)^+$.

[00303] Step 2 Following the procedure of Congiu et al. (Bioorg. Med. Chem. Lett., 2008, 989), 2-(3-bromo-2-methylphenylamino)-1-phenylethanone (250 mg, 0.822 mmol) was converted, following purification by column chromatography (eluting with a gradient from 25:75 EtOAc-hexane to EtOAc) to 1-(3-bromo-2-methylphenyl)-4-phenyl-1H-imidazol-2(3H)-one as a white solid (59 mg, 22%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (1 H, s), 7.70 (1 H, dd, J=8.0, 1.0 Hz), 7.59 (2 H, d, J=7.3 Hz), 7.34 - 7.43 (3 H, m), 7.21 - 7.32 (3 H, m), 2.27 (3 H, s). Mass spectrum m/z 329, 331 $(M+H)^+$.

Intermediate 57-1

Preparation of racemic benzyl 1-(3-bromo-2-methylphenyl)-2-oxopyrrolidin-3-ylcarbamate



[00304] Step 1 A solution of 3-bromo-2-methylaniline (0.662 mL, 5.37 mmol) and racemic 2-(benzyloxycarbonylamino)-4-(methylthio)butanoic acid (1.523 g, 5.37 mmol) in acetonitrile (25 mL) was treated with 1-hydroxy-7-azabenzotriazole (0.878 g, 6.45 mmol), diisopropylethylamine (1.877 mL, 10.75 mmol) and EDC (1.236 g, 6.45 mmol) and stirred at rt. After 20.5 h, the mixture was diluted with water and

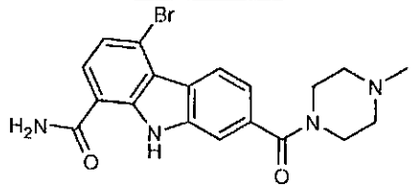
ethyl acetate. The organic phase was separated, washed with 1 M aqueous HCl and NaHCO3 (aq) and filtered to remove a flocculent white solid. The filtrate was dried and concentrated, and the residue was recrystallized from ethanol to give racemic benzyl 1-(3-bromo-2-methylphenylamino)-4-(methylthio)-1-oxobutan-2-ylcarbamate as a tan solid (1.33 g, 69%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.08 (1 H, br. s.), 7.68 (1 H, d, J=7.9 Hz), 7.39 (1 H, d, J=7.9 Hz), 7.34 (5 H, s), 7.04 (1 H, t, J=8.0 Hz), 5.58 (1 H, d, J=7.9 Hz), 5.14 (2 H, s), 4.53 (1 H, q, J=7.0 Hz), 2.55 - 2.72 (2 H, m), 2.28 (3 H, br. s.), 2.17 - 2.27 (1 H, m), 2.12 (3 H, s), 2.01 - 2.10 (1 H, m). Mass spectrum m/z 451, 453 $(M+H)^+$.

[00305] Step 2 A mixture of racemic benzyl 1-(3-bromo-2-methylphenylamino)-4-(methylthio)-1-oxobutan-2-ylcarbamate (1.31 g, 2.90 mmol) and DCM (4 mL) was diluted with iodomethane (7.5 mL, 120 mmol) and the mixture was stirred at rt. After 24.5 h, the mixture (a solution with an insoluble reddish oil) was concentrated under vacuum. The residue was treated three times with DCM and concentrated under vacuum to provide racemic (3-(benzyloxycarbonylamino)-4-(3-bromo-2-methylphenylamino)-4-oxobutyl)dimethylsulfonium iodide as an orange-yellow glassy foam (1.75 g, 97%). ^{1}H NMR (400 MHz, chloroform-d) δ9.16 (1 H, br. s.), 7.28 - 7.46 (7 H, m), 6.99 (1 H, t, J=8.0 Hz), 6.71 (1 H, d, J=6.8 Hz), 5.11 (2 H, s), 4.84 (1 H, br. s.), 3.75 (1 H, br. s.), 3.54 (1 H, br. s.), 3.14 (3 H, br. s.), 2.96 (3 H, s), 2.75 (1 H, br. s.), 2.33 - 2.41 (1 H, m), 2.30 (3 H, br. s.). Mass spectrum m/z 465, 467 $(M)^+$.

[00306] Step 3 A solution of racemic (3-(benzyloxycarbonylamino)-4-(3-bromo-2-methylphenylamino)-4-oxobutyl)dimethylsulfonium iodide (1.96 g, 3.30 mmol) in anhydrous DMSO (33 mL) was stirred at rt and treated with cesium carbonate (2.69 g, 8.26 mmol) in 3 portions over 25 min. After 4.5 h, the mixture was diluted with EtOAc, washed three times with water and twice with brine, dried and concentrated to provide racemic benzyl 1-(3-bromo-2-methylphenyl)-2-oxopyrrolidin-3-ylcarbamate as a tan solid (1.248 g, 94%).. ^{1}H NMR (400 MHz, chloroform-d) δ 7.52 - 7.58 (1 H, m), 7.30 - 7.40 (5 H, m), 7.10 (2 H, d, J=5.1 Hz), 5.47 (1 H, br. s.), 5.15 (2 H, s), 4.39 (1 H, ddd, J=10.6, 8.3, 5.2 Hz), 3.72 (1 H, td, J=9.9, 6.4 Hz), 3.60 (1 H, t, J=9.4 Hz), 2.27 (3 H, s), 2.11 - 2.26 (2 H, m). Mass spectrum m/z 425, 427 $(M+Na)^+$.

Example 1-1

Preparation of 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00307] A suspension of 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylic acid (Intermediate 49-1, 1.84 g, 4.97 mmol), EDC (1.334 g, 6.96 mmol), and HOBT (1.066 g, 6.96 mmol) in THF-DCM-DMF (4:1:1) (124 mL) was treated with 1-methylpiperazine (1.656 mL, 14.91 mmol) and the mixture was stirred at rt for 3 days. The mixture was concentrated and the residue was partitioned between DCM and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated to afford an oil. This was purified by column chromatography (DCM-2 M methanolic ammonia,100:0 to 95:5 to 92.5:7.5). The resulting solid was suspended in EtOAc, collected by filtration and dried to provide 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (1.57 g, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1 H) 8.57 (d, J=8.13 Hz, 1 H) 8.20 (br. s., 1 H) 7.84 (d, J=8.35 Hz, 1 H) 7.79 (s, 1 H) 7.56 (br. s., 1 H) 7.42 (d, J=8.13 Hz, 1 H) 7.22 (d, J=8.13 Hz, 1 H) 3.30 - 3.70 (m, 4 H) 2.19 - 2.39 (m, 4 H) 2.16 (s, 3 H). Mass spectrum m/z 415, 417 $(M+H)^+$.

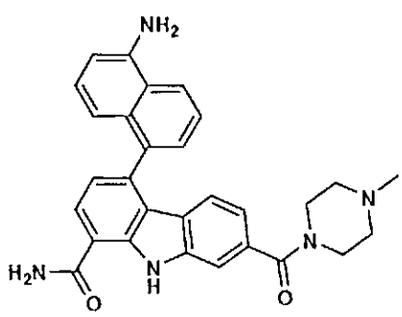
[00308] The following Examples and Intermediates were also prepared using the procedures used to prepare Example 1-1, or closely related procedures.

Example /Intermediate	Starting material	Compound name	Mass spectrum
1-2	Intermediate 49-2	4-bromo-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	415, 417 $(M+H)^+$
1-3	Intermediate 49-3	5-bromo-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	419, 421 $(M+H)^+$

Intermediate 1-4(a)	Intermediate 49-1	4-bromo-7-(morpholine-4-carbonyl)-9H-carbazole-1-carboxamide	402, 404 $(M+H)^+$
Intermediate 1-5(a)	Intermediate 49-3	5-bromo-N^2-(3-(dimethylamino)propyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	421, 423 $(M+H)^+$
Intermediate 1-6(a)	Intermediate 49-3	5-bromo-N^2-(4-(dimethylamino)butyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	435, 437 $(M+H)^+$
Intermediate 1-7(a)	Intermediate 49-3	5-bromo-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	420, 422 $(M+H)^+$
Intermediate 1-8(a)	Intermediate 49-3	5-bromo-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	433, 435 $(M+H)^+$
Intermediate 1-9(a)	Intermediate 49-3	5-bromo-N^2-methyl-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	447, 449 $(M+H)^+$
Intermediate 1-10(a)	Intermediate 49-1	4-bromo-N^7,N^7-dimethyl-9H-carbazole-1,7-dicarboxamide	360, 362 $(M+H)^+$

Example 2-1

Preparation of 4-(5-aminonaphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



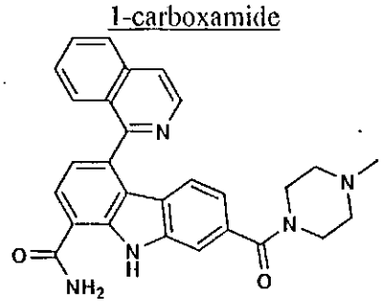
[00309] Step 1 A solution of tris(dibenzylideneacetone)dipalladium (27.6 mg, 0.031 mmol) and tricyclohexylphosphine (1.0 M in toluene, 0.144 mL, 0.144 mmol) in 1,4-dioxane (8 mL) was purged with argon for 10 min. 4-Bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-1, 500 mg, 1.204 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (336 mg, 1.324 mmol) and potassium acetate (177 mg, 1.806 mmol) were added, bubbling was continued for another 5 min, and the mixture was heated in a sealed tube with stirring at 85-90 °C for 18 h. The mixture was cooled to rt and diluted with water and EtOAc and the layers were separated. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried and concentrated. The residue was taken up in acetonitrile, filtered, and the filtrate was concentrated to give 7-(4-methylpiperazine-1-carbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-carbazole-1-carboxamide as a yellow-tan glassy foam (602 mg) which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1 H) 8.86 (d, J=8.3 Hz, 1 H) 8.25 (br. s., 1 H) 7.95 (d, J=7.7 Hz, 1 H) 7.90 - 7.94 (m, 2 H) 7.58 (d, J=7.5 Hz, 1 H) 7.16 (d, J=6.8 Hz, 1 H) 3.36 - 3.72 (m, 4 H) 2.34 (br. s., 4 H) 2.21 (s, 3 H) 1.43 (s, 12 H); aliphatic impurities were observed. Mass spectrum m/z 463.34 $(M+H)^+$.

[00310] Step 2 A mixture of 7-(4-methylpiperazine-1-carbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-carbazole-1-carboxamide (the crude product prepared according to Step 1, 40 mg, 0.065 mmol), 5-bromonaphthalen-1-amine (21.61 mg, 0.097 mmol), and potassium carbonate (13.45 mg, 0.097 mmol) in toluene (1.5 mL) and ethanol (0.75 mL) was treated with [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) DCM complex (5.3 mg, 0.007 mmol) and purged with argon for ca. 5 min. The mixture was heated at 90 °C for 19 h, then was cooled to rt and concentrated. The residue was purified by preparative HPLC, then was partitioned between EtOAc and NaHCO3 (aq), the aqueous phase was extracted again with EtOAc, and the combined organic phases were dried and concentrated to provide 4-(5-aminonaphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a light yellow solid (13.1 mg, 42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1 H) 8.22 - 8.27 (m, 2 H) 8.07 (d, J=7.7 Hz, 1 H) 7.73 (s, 1 H) 7.55 (br. s., 1 H) 7.52 (dd, J=8.6, 6.8 Hz, 1 H) 7.42 (dd, J=6.9, 1.0 Hz, 1 H) 7.09 (d, J=7.7 Hz, 1 H) 6.96 (dd, J=8.2, 7.6 Hz, 1 H) 6.64 - 6.70 (m, 2 H) 6.49 (d, J=8.3 Hz, 1 H) 6.38 (d,

J=8.1 Hz, 1 H) 5.85 (s, 2 H) 3.48 - 3.59 (m, 4 H) 2.17 - 2.37 (m, 4 H) 2.14 (s, 3 H). Mass spec m/z 478.10 $(M+H)^+$.

Example 2-2

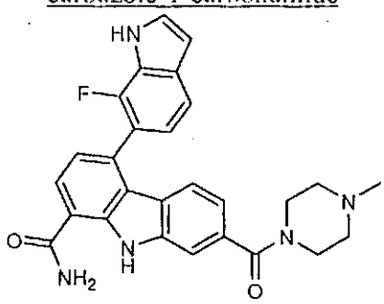
Preparation of 4-(isoquinolin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00311] Using the procedure of Step 2 of Example 2-1, 7-(4-methylpiperazine-1-carbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-carbazole-1-carboxamide (the crude product prepared according to Step 1 of Example 2-1, 40 mg, 0.065 mmol) and 1-chloroisoquinoline (15.92 mg, 0.097 mmol) were converted to 4-(isoquinolin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (6 mg, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1 H) 8.71 (d, J=5.5 Hz, 1 H) 8.32 (br. s., 1 H) 8.15 (d, J=7.7 Hz, 2 H) 8.06 (d, J=5.3 Hz, 1 H) 7.80 (ddd, J=8.2, 6.5, 1.5 Hz, 1 H) 7.77 (s, 1 H) 7.63 (br. s., 1 H) 7.46 - 7.55 (m, 2 H) 7.25 (d, J=7.9 Hz, 1 H) 6.71 (dd, J=8.2, 1.4 Hz, 1 H) 6.24 (d, J=8.1 Hz, 1 H) 3.46 - 3.62 (m, 4 H) 2.18 - 2.34 (m, 4 H) 2.16 (s, 3 H). Mass spectrum m/z 464.3 $(M+H)^+$.

Example 2-3

Preparation of 4-(7-fluoro-1H-indol-6-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide

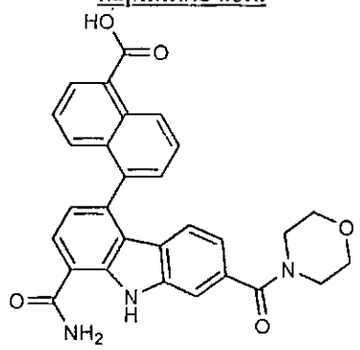


[00312] A mixture of 7-(4-methylpiperazine-1-carbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-carbazole-1-carboxamide (prepared according to the procedure of Step 1 of Example 2-1, 75 mg, 0.065 mmol), 6-bromo-7-fluoro-1H-

indole (prepared according to U.S. pat. appl. 2007/112005, 18.7 mg, 0.087 mmol), and 2 M aqueous sodium carbonate (0.081 mL, 0.162 mmol) in toluene (0.8 mL) and ethanol (0.2 mL) was purged with argon, treated with tetrakis(triphenylphosphine)palladium (7.5 mg, 0.007 mmol) and heated at 90 °C. After 16 h, the mixture was cooled to rt. The residue was purified by preparative HPLC. The resulting TFA salt was partitioned between NaHCO3 (aq) and EtOAc, and the organic extracts were dried and concentrated to provide 4-(7-fluoro-1H-indol-6-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as an off-white solid (9 mg, 30%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.99 (d, J=7.5 Hz, 1 H) 7.68 (d, J=0.9 Hz, 1 H) 7.52 (d, J=7.9 Hz, 1 H) 7.39 (d, J=3.5 Hz, 1 H) 7.25 (dd, J=8.1, 1.1 Hz, 1 H) 7.21 (d, J=7.5 Hz, 1 H) 7.08 (dd, J=8.1, 6.4 Hz, 1 H) 6.92 (dd, J=8.1, 1.5 Hz, 1 H) 6.63 (t, J=3.3 Hz, 1 H) 3.77 (br. s., 2 H) 3.49 (br. s., 2 H) 2.51 (br. s., 2 H) 2.39 (br. s., 2 H) 2.30 (s, 3 H). Mass spectrum m/z 470.1 $(M+H)^+$.

Example 2-4

Preparation of 5-(1-carbamoyl-7-(morpholine-4-carbonyl)-9H-carbazol-4-yl)-1-naphthoic acid



[00313] Using the procedures of Example 2-1, 4-bromo-7-(morpholine-4-carbonyl)-9H-carbazole-1-carboxamide (Intermediate 1-4(a)) and 4-bromo-1-naphthoic acid (prepared according to the procedure of Hausamann, *Chem. Ber.*, 1876, 9, 1519) were converted to 5-(1-carbamoyl-7-(morpholine-4-carbonyl)-9H-carbazol-4-yl)-1-naphthoic acid in 42% overall yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 13.32 (br. s., 1 H) 11.80 (s, 1 H) 9.03 (d, J=9.0 Hz, 1 H) 8.29 (br. s., 1 H) 8.08 - 8.17 (m, 2 H) 7.82 (dd, J=8.7, 7.1 Hz, 1 H) 7.78 (s, 1 H) 7.64 (d, J=6.4 Hz, 1 H) 7.61 (br. s., 1 H) 7.55 (d, J=8.3 Hz, 1 H) 7.37 (dd, J=8.3, 7.3 Hz, 1 H) 7.16 (d, J=7.7 Hz, 1 H) 6.72 (dd, J=8.3, 1.3 Hz, 1 H) 6.28 (d, J=8.3 Hz, 1 H) 3.53 (br. s., 8 H). Mass spectrum m/z 494.3 $(M+H)^+$.

[00314] The Examples in the following table were also prepared using the procedures used to prepare Examples 2-1 through 2-4, or closely related procedures.

Example	Starting materials	Compound name	Mass Spectrum
2-5	Example 1-1 [a]	3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-fluorobenzoic acid (prepared as the TFA salt)	475.3 $(M+H)^+$
2-6	Example 1-1 [a]	2-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-4-fluorophenyl)acetic acid (prepared as the TFA salt)	489.3 $(M+H)^+$
2-7	Example 1-1 [a]	4-(5-amino-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	446.3 $(M+H)^+$
2-8	Example 1-1 [a]	4-(2-fluoro-5-(trifluoromethyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	499.3 $(M+H)^+$
2-9	Example 1-1 [a]	4-(2-fluoro-5-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	445.3 $(M+H)^+$
2-10	Example 1-1 [a]	4-(5-cyano-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	456.3 $(M+H)^+$
2-11	Example 1-1 [a]	4-(5-acetyl-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	473.3 $(M+H)^+$
2-12	Example 1-1 [a]	4-(2,5-difluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	449.2 $(M+H)^+$
2-13	Example 1-1 [a]	4-(5-chloro-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	465, 467 $(M+H)^+$

2-14	Example 1-1 [a]	4-(2,6-difluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	449.2 (M+H)+
2-15	Example 1-1 [a]	4-(5-acetamidoisoquinolin-8-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	521.4 $(M+H)^+$
2-16	Intermediate 1-4(a) [a]	3-(1-carbamoyl-7-(morpholine-4-carbonyl)-9H-carbazol-4-yl)-4-fluorobenzoic acid	462.2 $(M+H)^+$
2-17	Intermediate 1-4(a) [a]	2-(3-(1-carbamoyl-7-(morpholine-4-carbonyl)-9H-carbazol-4-yl)-4-fluorophenyl)acetic acid	476.2 $(M+H)^+$
2-18	Example 1-2 [a]	4-(2-fluorophenyl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	431.2 $(M+H)^+$
2-19	Example 1-1 [a]	4-(1H-indazol-6-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	453.1 $(M+H)^+$
2-20	Example 1-1 [a]	4-(4-amino-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	446.1 $(M+H)^+$
2-21	Example 1-1 [a]	4-(4-acetamido-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	488.1 $(M+H)^+$
2-22	Example 1-1 [a]	4-(isoquinolin-8-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	464.3 $(M+H)^+$
2-23	Example 1-1 [a]	3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-4-fluorobenzoic acid (prepared as the TFA salt)	475.3 $(M+H)^+$
2-24	Example 1-1, Intermediate 12-2	4-(2-(ethylcarbamoyl)-1H-indol-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	523.2 $(M+H)^+$
2-25	Example 1-1, Intermediate 12-3	4-(2-(4-fluorophenylcarbamoyl)-1H-indol-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	589.2 $(M+H)^+$

2-26	Example 1-1, Intermediate 30-1	4-(2-methyl-3-(2-oxo-3-m-tolylimidazolidin-1-yl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	601.5 $(M+H)^+$
2-27	Example 1-1, Intermediate 6-1	4-(3-fluoro-2-(1-oxoisoindolin-2-yl)pyridin-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	563.3 $(M+H)^+$
2-28	Example 1-1 [b]	5-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-1-naphthoic acid (prepared as the TFA salt)	507.3 $(M+H)^+$
2-29	Example 1-1 [a]	4-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-3-fluorobenzoic acid (prepared as the TFA salt)	475.3 $(M+H)^+$
2-30	Example 1-1, Intermediate 33-1	4-(2-methyl-3-(4-methylpyridin-2-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	533.3 $(M+H)^+$
2-31	Example 1-1, Intermediate 33-2	4-(2-methyl-3-(5-methylpyridin-2-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	533.3 $(M+H)^+$
2-32	Example 1-1, Intermediate 33-3	4-(2-methyl-3-(pyridin-2-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	519.3 $(M+H)^+$
2-33	Example 1-1, Intermediate 33-4	4-(2-methyl-3-(3-methylpyridin-2-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	519.3 $(M+H)^+$
2-34	Example 1-1, Intermediate 35-4	4-(3-(4-(dimethylamino)benzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	589.4 $(M+H)^+$

2-35	Example 1-1, Intermediate 35-5	4-(5-acetamido-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	488.3 $(M+H)^+$
2-36	Example 1-1, Intermediate 35-6	4-(3-(4-fluorobenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	550.3 $(M+H)^+$
2-37	Example 1-1, Intermediate 35-3	4-(5-(acetamidomethyl)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	502.3 $(M+H)^+$
2-38	Example 1-1, Intermediate 35-7	4-(2-fluoro-3-(4-fluorobenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	568.2 $(M+H)^+$
2-39	Example 1-1, Intermediate 35-8	4-(3-(4-(dimethylamino)benzamido)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	593.3 $(M+H)^+$
2-40	Example 1-1, Intermediate 35-1	4-(2-fluoro-3-(4-fluoro-N-methylbenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	582.3 $(M+H)^+$
2-41	Example 1-1, Intermediate 35-9	4-(3-(4-fluoro-N-methylbenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	564.1 $(M+H)^+$
2-42	Example 1-1, Intermediate 35-10	4-(4-fluoro-3-(4-fluorobenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	568.1 $(M+H)^+$
2-43	Example 1-1, Intermediate 35-2	4-(4-(4-fluorobenzamido)pyridin-2-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	551.3 $(M+H)^+$
2-44	Example 1-1, Intermediate 35-11	4-(2-fluoro-5-(4-fluorobenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	568.1 $(M+H)^+$

2-45	Example 1-1, Intermediate 35-12	4-(2-fluoro-5-((4-fluorobenzamido)methyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	582.1 $(M+H)^+$
2-46	Example 1-1, Intermediate 35-13	4-(3-acetamido-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	488.3 $(M+H)^+$
2-47	Example 1-1, Intermediate 36-1	4-(2-fluoro-5-(4-fluorophenylcarbamoyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	568.2 $(M+H)^+$
2-48	Example 1-1, Intermediate 36-3	4-(2-fluoro-3-(4-fluorophenylcarbamoyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	568.2 $(M+H)^+$
2-49	Example 1-1, Intermediate 36-4	4-(5-carbamoyl-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	474.2 $(M+H)^+$
2-50	Example 1-1, Intermediate 36-5	4-(3-carbamoyl-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, (prepared as the TFA salt)	474.2 $(M+H)^+$
2-51	Example 1-1, Intermediate 36-6	4-(2-fluoro-3-(methylcarbamoyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	488.2 $(M+H)^+$
2-52	Example 1-1, Intermediate 36-7	4-(5-(dimethylcarbamoyl)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	502.2 $(M+H)^+$
2-53	Example 1-1, Intermediate 36-2	4-(3-(dimethylcarbamoyl)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	502.2 $(M+H)^+$

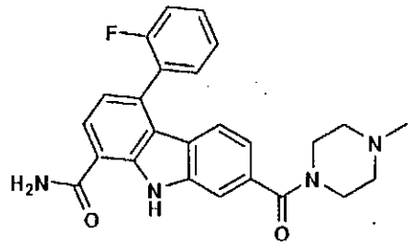
2-54	Example 1-1, Intermediate 37-1	4-(2-fluoro-3-(methylsulfonamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	524.1 $(M+H)^+$
2-55	Example 1-1, Intermediate 38-1	4-(2-fluoro-5-(3-(4-methylthiazol-2-yl)ureido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	586.1 $(M+H)^+$
2-56	Example 1-1, Intermediate 38-2	4-(2-fluoro-5-((3-(4-methylthiazol-2-yl)ureido)methyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	600.1 $(M+H)^+$

[a] Commercially available aryl halide.

[b] 4-bromo-1-naphthoic acid (prepared according to the procedure of Hausamann, *Chem. Ber.*, 1876, 9, 1519).

Example 3-1

Preparation of 4-(2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide

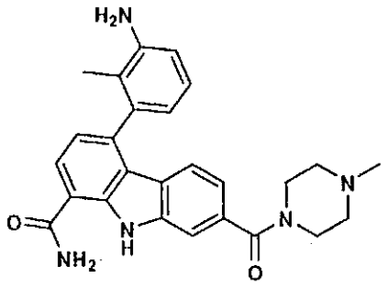


[00315] A suspension of 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-1, 25 mg, 0.06 mmol), 2-fluorophenyl-boronic acid (0.17 mg, 0.12 mmol), potassium carbonate (21 mg, 0.15 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (5 mg, 0.006 mmol) in toluene-ethanol (2:1, 2.4 mL) was purged with nitrogen for 5 min, then was heated at 90 °C overnight. The mixture was concentrated and purified by preparative HPLC to provide 4-(2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (23 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1 H) 8.26 (br. s., 1 H) 8.06 (d, J=7.91 Hz, 1 H) 7.86 (s, 1 H) 7.57 - 7.67 (m, 2 H) 7.55 (td, J=7.58, 1.76 Hz, 1 H) 7.39 - 7.49 (m, 2 H) 7.13 (d, J=7.69 Hz, 1 H)

7.07 - 7.11 (m, 1 H) 7.02 - 7.07 (m, 1 H) 3.81 (br. s., 4 H) 3.10 - 3.30 (m, 4 H) 2.79 (s, 3 H). Mass spectrum m/z 431.2 $(M+H)^+$.

Example 3-2

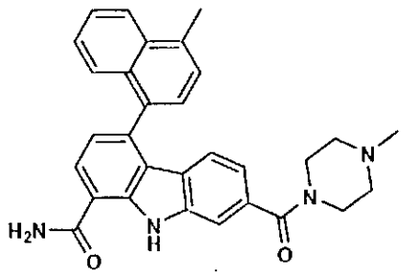
Preparation of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00316] A suspension of 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-1, 300 mg, 0.722 mmol), tetrakis-(triphenylphosphine)palladium (33.4 mg, 0.029 mmol), 2 M aqueous sodium carbonate (0.9 mL, 1.806 mmol), and 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Intermediate 50-1, 253 mg, 1.084 mmol) in toluene-ethanol (4:1, 15 mL) was purged with nitrogen for 5 min and then heated at reflux for 7.5 h. The mixture was concentrated and the residue was partitioned between chloroform and water. The aqueous phase was extracted with chloroform and the combined organic phases were washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with DCM-2 M methanolic ammonia, gradient from 100:0 to 95:5) to provide 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a white solid (207 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1 H) 8.16 (br. s., 1 H) 7.97 (d, J=7.91 Hz, 1 H) 7.78 (s, 1 H) 7.48 (br. s., 1 H) 7.08 (t, J=7.80 Hz, 1 H) 6.81 - 6.97 (m, 4 H) 6.49 - 6.65 (m, 1 H) 3.12 - 3.25 (m, 4 H) 2.92 - 3.10 (m, 4 H) 2.76 (s, 3 H) 1.70 (s, 3 H). Mass spectrum m/z 442.2 $(M+H)^+$.

Example 3-3

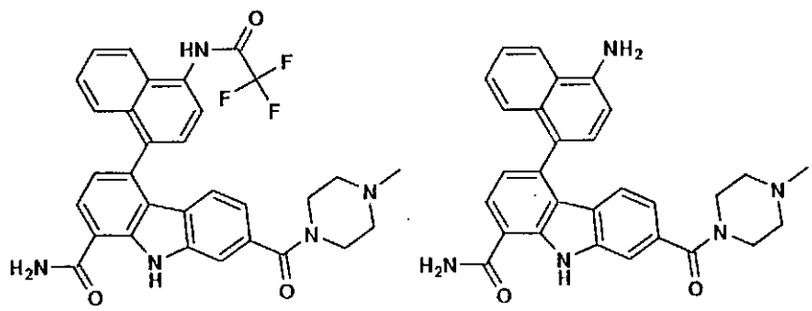
Preparation of 4-(4-methylnaphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00317] Using the procedure of Example 3-1, 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-1, 25 mg, 0.06 mmol) and 4-methylnaphthaleneboronic acid (23 mg, 0.12 mmol) were converted to 4-(4-methylnaphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, isolated as the TFA salt following HPLC purification. This material was partitioned between EtOAc and NaHCO3 (aq), and the aqueous phase was extracted twice with EtOAc. The combined organic phases were dried and concentrated to provide 4-(4-methylnaphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (23 mg, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1 H) 8.26 (br. s., 1 H) 8.16 (d, J=8.3 Hz, 1 H) 8.10 (d, J=7.7 Hz, 1 H) 7.75 (s, 1 H) 7.52 - 7.62 (m, 3 H) 7.45 (d, J=7.0 Hz, 1 H) 7.28 - 7.38 (m, 2 H) 7.11 (d, J=7.7 Hz, 1 H) 6.67 (dd, J=8.2, 1.4 Hz, 1 H) 6.37 (d, J=8.1 Hz, 1 H) 3.32 - 3.67 (m, 4 H) 2.80 (s, 3 H) 2.16 - 2.35 (m, 4 H) 2.14 (s, 3 H). Mass spectrum m/z 477.3$(M+H)^+$.

Examples 3-4 and 3-5

Preparation of 7-(4-methylpiperazine-1-carbonyl)-4-(4-(2,2,2-trifluoroacetamido)naphthalen-1-yl)-9H-carbazole-1-carboxamide and 4-(4-aminonaphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide

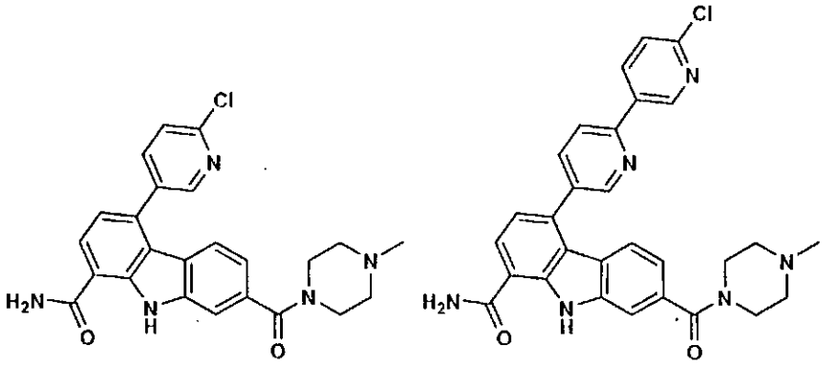


[00318] Using the procedure of Example 3-3, 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-1, 25 mg, 0.06 mmol) and 4-

(2,2,2-trifluoroacetamido)naphthalen-1-ylboronic acid (34 mg, 0.12 mmol) were converted to 7-(4-methylpiperazine-1-carbonyl)-4-(4-(2,2,2-trifluoroacetamido)naphthalen-1-yl)-9H-carbazole-1-carboxamide (9.7 mg, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1 H) 11.63 (br. s., 1 H) 8.25 (br. s., 1 H) 8.09 (d, J=7.7 Hz, 1 H) 8.04 (d, J=8.3 Hz, 1 H) 7.75 (d, J=7.5 Hz, 1 H) 7.73 (d, J=0.7 Hz, 1 H) 7.54 - 7.61 (m, 3 H) 7.31 - 7.38 (m, 2 H) 7.14 (d, J=7.7 Hz, 1 H) 6.63 (dd, J=8.1, 1.5 Hz, 1 H) 6.33 (d, J=8.1 Hz, 1 H) 3.44 - 3.56 (m, 4 H) 2.14 - 2.31 (m, 4 H) 2.11 (s, 3 H). Mass spectrum m/z 574.3 $(M+H)^+$. Also obtained was 4-(4-aminonaphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (14 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1 H) 8.15 (d, J=8.3 Hz, 2 H) 8.01 (d, J=7.5 Hz, 1 H) 7.68 (s, 1 H) 7.48 (br. s., 1 H) 7.32 (t, J=7.3 Hz, 1 H) 7.11 - 7.23 (m, 3 H) 7.03 (d, J=7.7 Hz, 1 H) 6.79 (d, J=7.7 Hz, 1 H) 6.64 (d, J=8.3 Hz, 1 H) 6.49 (d, J=7.9 Hz, 1 H) 5.93 (s, 2 H) 3.34 - 3.60 (m, 4 H) 2.13 - 2.31 (m, 4 H) 2.10 (s, 3 H). Mass spectrum m/z 478.3 $(M+H)^+$.

Examples 3-6 and 3-7

Preparation of 4-(6-chloropyridin-3-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide and 4-(6'-chloro-2,3'-bipyridin-5-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide

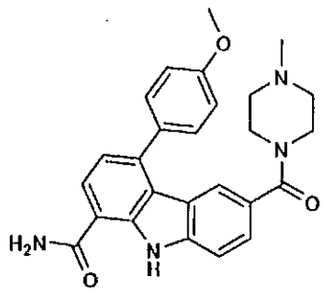


[00319] Using the procedure of Example 3-2, 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-1, 25 mg, 0.060 mmol) and 6-chloropyridin-3-ylboronic acid (19 mg, 0.120 mmol) was converted to 4-(6-chloropyridin-3-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a light yellow solid (11 mg, 26%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1 H) 9.85 (br. s., 1 H) 8.65 (d, *J*=2.0 Hz, 1 H) 8.29 (br. s., 1 H) 8.13 (dd,

J=8.2, 2.5 Hz, 1 H) 8.09 (d, *J*=7.9 Hz, 1 H) 7.90 (s, 1 H) 7.77 (d, *J*=8.3 Hz, 1 H) 7.62 (br. s., 1 H) 7.30 (d, *J*=8.3 Hz, 1 H) 7.16 (d, *J*=7.9 Hz, 1 H) 7.10 (dd, J=8.2, 1.4 Hz, 1 H) 3.03 - 3.27 (m, 8 H) 2.82 (s, 3 H). Mass spectrum m/z 448.1 $(M+H)^+$. Also isolated was 4-(6'-chloro-2,3'-bipyridin-5-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a yellow solid (6 mg, 11%). 1H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1 H) 9.99 (br. s., 1 H) 9.26 (d, J=2.4 Hz, 1 H) 8.96 (d, J=2.2 Hz, 1 H) 8.66 (dd, J=8.3, 2.4 Hz, 1 H) 8.35 (d, J=8.1 Hz, 1 H) 8.30 (br. s., 1 H) 8.22 (dd, J=8.1, 2.2 Hz, 1 H) 8.12 (d, J=7.9 Hz, 1 H) 7.92 (s, 1 H) 7.72 (d, J=8.6 Hz, 1 H) 7.62 (br. s., 1 H) 7.41 (d, J=8.3 Hz, 1 H) 7.22 (d, J=7.7 Hz, 1 H) 7.09 (dd, J=8.2, 1.4 Hz, 1 H) 3.02 - 3.53 (m, 8 H) 2.82 (s, 3 H). Mass spectrum m/z 525.2 $(M+H)^+$.

Example 3-8

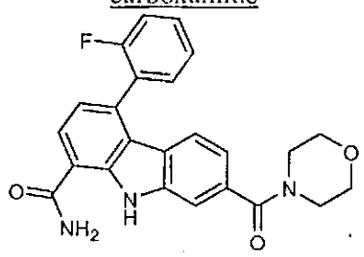
Preparation of 4-(4-methoxyphenyl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00320] Using the procedure of Example 3-1, 4-bromo-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-2, 25 mg, 0.06 mmol) and 4-methoxyphenylboronic acid (14 mg, 0.09 mmol) were converted into 4-(4-methoxyphenyl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, (8 mg, 22%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1 H) 8.22 (br. s., 1 H) 8.03 (d, *J*=7.69 Hz, 1 H) 7.83 (d, *J*=8.35 Hz, 1 H) 7.53 - 7.62 (m, 4 H) 7.51 (dd, *J*=8.57, 1.54 Hz, 1 H) 7.14 (d, *J*=8.79 Hz, 2 H) 7.06 (d, *J*=7.69 Hz, 1 H) 4.11 - 4.38 (m, 2 H) 3.88 (s, 3H) 3.10 - 3.28 (m, 4 H) 2.87 - 3.04 (m, 2 H) 2.81 (s, 3 H). Mass spectrum m/z 443.3 $(M+H)^+$.

Example 3-9

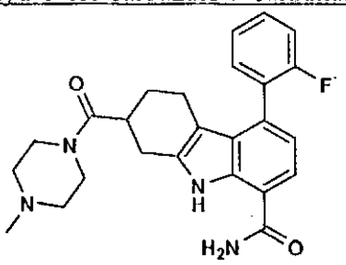
Preparation of 4-(2-fluorophenyl)-7-(morpholine-4-carbonyl)-9H-carbazole-1-carboxamide



[00321] Using the procedure of Example 3-1, 4-bromo-7-(morpholine-4-carbonyl)-9H-carbazole-1-carboxamide (Intermediate 1-4(a), 25 mg, 0.06 mmol) and 2-fluorophenylboronic acid (17.4 mg, 0.124 mmol) were converted into 4-(2-fluorophenyl)-7-(morpholine-4-carbonyl)-9H-carbazole-1-carboxamide (15.9 mg, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1 H) 8.25 (br. s., 1 H) 8.06 (d, J=7.9 Hz, 1 H) 7.82 (s, 1 H) 7.53 - 7.66 (m, 3 H) 7.40 - 7.48 (m, 2 H) 7.12 (d, J=7.7 Hz, 1 H) 7.09 (dd, J=8.2, 0.8 Hz, 1 H) 6.99 (dd, J=8.2, 1.0 Hz, 1 H) 3.59 (br. s., 8 H). Mass spectrum m/z 418.2 $(M+H)^+$.

Example 3-10

Preparation of 5-(2-fluorophenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide

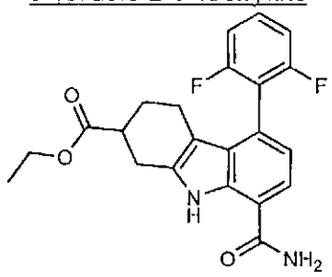


[00322] Following the procedure of Example 3-1, 5-bromo-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Example 1-3, 30 mg, 0.072 mmol) and 2-fluorophenylboronic acid (20 mg, 0.143 mmol) were converted into 5-(2-fluorophenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide, TFA salt, as white solid (25 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (d, 1 H) 8.04 (br. s., 1 H) 7.62 (d, J=7.47 Hz, 1 H) 7.42 - 7.50 (m, 1 H) 7.17 - 7.41 (m, 4 H) 6.76 - 6.89 (m, 1 H) 4.37 - 4.57 (m, 1 H) 4.09 - 4.29 (m, 2 H) 3.46 - 3.62 (m, 2 H) 2.83 - 3.15 (m, 6 H) 2.80 (s, 3 H) 2.10 - 2.42 (m, 1

H) 1.86 - 2.07 (m, 1 H) 1.68 - 1.84 (m, 1 H) 1.27 - 1.60 (m, 1 H). Mass spectrum m/z 435.3 $(M+H)^+$.

Example 3-11

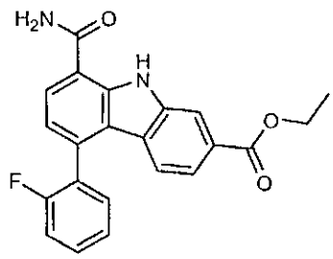
Preparation of ethyl 8-carbamoyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate



[00323] A mixture of ethyl 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate (Intermediate 47-1, 20 mg, 0.055 mmol), 2,6-difluorophenylboronic acid (17.3 mg, 0.110 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (4.5 mg, 11.0 mmol), potassium carbonate (15.1 mg, 0.110 mmol) and tris(dibenzylideneacetone)dipalladium (5.0 mg, 0.005 mmol) in THF (2 mL) was purged with nitrogen for 2 min, then was heated in a sealed tube overnight. The mixture was filtered and concentrated, and the residue was purified by preparative HPLC. The appropriate effluent fractions were made basic with 1 M aqueous sodium hydroxide and extracted twice with DCM. The combined organic phases were washed with water, dried and concentrated to provide ethyl 8-carbamoyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate as a light yellow solid (10 mg, 44%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.10 (1 H, br. s.), 7.31 - 7.44 (2 H, m), 6.95 - 7.06 (3 H, m), 4.10 - 4.22 (2 H, m), 2.96 - 3.12 (2 H, m), 2.80 (1 H, dddd, J=17.52, 5.99, 3.08, 2.86 Hz), 2.27 - 2.41 (1 H, m), 2.15 - 2.27 (1 H, m), 2.04 - 2.14 (1 H, m), 1.69 - 1.85 (1 H, m), 1.26 (3 H, t, J=7.25 Hz). Mass spectrum m/z 399.1 $(M+H)^+$.

Example 3-12

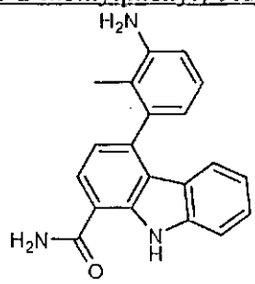
Preparation of ethyl 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazole-2-carboxylate



[00324] Following the procedure of Example 3-1, ethyl 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylate (Intermediate 48-1, 1.00 g, 2.35 mmol) and 2-fluorophenylboronic acid (395 mg, 2.82 mmol) were converted into ethyl 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazole-2-carboxylate as white solid (72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (1 H, s), 8.46 (1 H, s), 8.26 (1 H, br. s.), 8.09 (1 H, d, J=7.7 Hz), 7.52 - 7.68 (4 H, m), 7.39 - 7.49 (2 H, m), 7.15 (2 H, d, J=7.9 Hz), 4.32 (2 H, q, J=7.0 Hz), 1.33 (3 H, t, J=7.1 Hz). Mass spectrum m/z 377.1 $(M+H)^+$.

Example 3-13

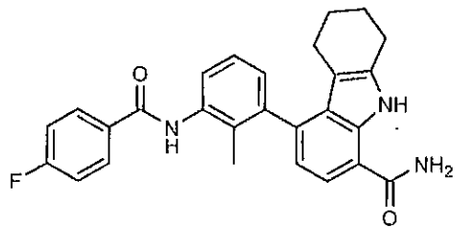
Preparation of 4-(3-amino-2-methylphenyl)-9H-carbazole-1-carboxamide



[00325] Using the procedure of Example 3-2, 4-bromo-9H-carbazole-1-carboxamide (Intermediate 48-3, 100 mg, 0.35 mmol) was converted into 4-(3-amino-2-methylphenyl)-9H-carbazole-1-carboxamide as an off-white solid (109 mg, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (1 H, d, J=7.7 Hz), 7.57 (1 H, d, J=8.1 Hz), 7.33 (1 H, ddd, J=8.2, 7.1, 1.2 Hz), 7.16 (1 H, t, J=7.8 Hz), 6.98 - 7.02 (2 H, m), 6.95 (1 H, dd, J=7.9, 0.9 Hz), 6.87 - 6.93 (1 H, m), 6.72 (1 H, dd, J=7.5, 0.9 Hz), 1.85 (3 H, s). Mass spectrum m/z 316.2 $(M+H)^+$.

Example 3-14

Preparation of 5-(3-(4-fluorobenzamido)-2-methylphenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00326] Using the procedure of Example 3-2, 5-bromo-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Intermediate 47-3, 30 mg, 0.102 mmol) and 4-fluoro-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzamide (Intermediate 53-1, 36.3 mg, 0.102 mmol) were converted into 5-(3-(4-fluorobenzamido)-2-methylphenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as an off-white solid (5.7 mg, 12%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 - 8.15 (2 H, m), 7.62 (1 H, d, J=7.5 Hz), 7.32 - 7.43 (3 H, m), 7.27 (1 H, t, J=7.6 Hz), 7.09 (1 H, d, J=7.3 Hz), 6.73 (1 H, d, J=7.7 Hz), 4.06 (2 H, s), 2.74 (2 H, br. s.), 1.89 (3 H, s), 1.65 - 1.75 (2 H, m), 1.48 - 1.60 (2 H, m). Mass spectrum m/z 442.3 $(M+H)^+$.

[00327] The following compounds were also prepared using procedures demonstrated in Examples 3-1 through 3-14 and similar procedures.

Example /Intermediates	Starting materials	Compound name	Mass spectrum
3-15	Example 1-1 [a]	4-(2,3-difluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	449.2 $(M+H)^+$
3-16	Example 1-1 [a]	4-(2,3-dichlorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	481.1 $(M+H)^+$
3-17	Example 1-1 [a]	4-(2,4-dichlorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	481.1 $(M+H)^+$
3-18	Example 1-1 [a]	4-(2-ethoxynaphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	507.4 $(M+H)^+$

3-19	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(quinolin-8-yl)-9H-carbazole-1-carboxamide	464.3 $(M+H)^+$
3-20	Example 1-1 [a]	4-(isoquinolin-5-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	464.3 $(M+H)^+$
3-21	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(quinolin-5-yl)-9H-carbazole-1-carboxamide	464.3 $(M+H)^+$
3-22	Example 1-1 [a]	4-(isoquinolin-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	464.3 $(M+H)^+$
3-23	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(quinolin-4-yl)-9H-carbazole-1-carboxamide	464.3 $(M+H)^+$
3-24	Example 1-1 [a]	4-(4-aminophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	428.2 $(M+H)^+$
3-25	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(pyridin-3-yl)-9H-carbazole-1-carboxamide, TFA salt	414.2 $(M+H)^+$
3-26	Example 1-1 [a]	4-(4-hydroxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	429.2 $(M+H)^+$
3-27	Example 1-2 [a]	4-(3-methoxyphenyl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	443.3 $(M+H)^+$
3-28	Example 1-2 [a]	4-(4-acetamidophenyl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	470.3 $(M+H)^+$
3-29	Example 1-2 [a]	4-(3-acetamidophenyl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	470.3 $(M+H)^+$
3-30	Example 1-2 [a]	6-(4-methylpiperazine-1-carbonyl)-4-(naphthalen-1-yl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	463.3 $(M+H)^+$

3-31	Example 1-1 [a]	4-(1H-indol-6-yl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	452.2 $(M+H)^+$
3-32	Example 1-1 [a]	4-(1H-indol-4-yl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	452.2 $(M+H)^+$
3-33	Example 1-1 [a]	4-(3-fluoropyridin-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	432.1 $(M+H)^+$
3-34	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(3-methylpyridin-4-yl)-9H-carbazole-1-carboxamide	428.1 $(M+H)^+$
3-35	Example 1-1 [a]	4-(3-chlorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	447.2 $(M+H)^+$
3-36	Example 1-1 [a]	4-(4-chlorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide(prepared as the TFA salt)	447.2 $(M+H)^+$
3-37	Example 1-1, Intermediate 50-45	4-(3-amino-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	446.1 $(M+H)^+$
3-38	Example 1-1 [a]	4-(2-fluoro-5-methoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	461.2 $(M+H)^+$
3-39	Example 1-1 [a]	4-(5-ethoxy-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	475.1 $(M+H)^+$
3-40	Example 1-1 [a]	4-(2-fluoro-5-(hydroxymethyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	461.1 $(M+H)^+$
3-41	Example 1-1 [a]	4-(4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	578.2 $(M+H)^+$

3-42	Example 1-1 [a]	4-(2-ethylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	441.2 $(M+H)^+$
3-43	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(2-(trifluoromethyl)phenyl)-9H-carbazole-1-carboxamide	481.2 $(M+H)^+$
3-44	Example 1-1 [a]	4-(2,6-dimethylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	441.2 $(M+H)^+$
3-45	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-phenyl-9H-carbazole-1-carboxamide (prepared as the TFA salt)	413.1 $(M+H)^+$
3-46	Example 1-1 [a]	4-(5-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	442.2 $(M+H)^+$
3-47	Example 1-1 [a]	4-(1H-indol-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	452.2 $(M+H)^+$
3-48	Example 1-1 [a]	4-(biphenyl-3-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	489.4 $(M+H)^+$
3-49	Example 1-1 [a]	4-(dibenzo[b,d]furan-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	503.4 $(M+H)^+$
3-50	Example 1-1, Intermediate 50-2	4-(3-cyano-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	452.3 $(M+H)^+$
3-51	Example 1-1, Intermediate 50-3	4-(4-amino-2,6-difluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	464.3 $(M+H)^+$
3-52	Example 1-1 [a]	4-(4-methoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	443.3 $(M+H)^+$

3-53	Example 1-1 [a]	4-(3-methoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	443.3 $(M+H)^+$
3-54	Example 1-1 [a]	4-(2,4-difluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide(prepared as the TFA salt)	449.3 $(M+H)^+$
3-55	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(4-phenoxyphenyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	505.3 $(M+H)^+$
3-56	Example 1-1 [a]	4-(3,4-dichlorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	481.2 $(M+H)^+$
3-57	Example 1-1 [a]	4-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)benzoic acid (prepared as the TFA salt)	457.3 $(M+H)^+$
3-58	Example 1-1 [a]	3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)benzoic acid (prepared as the TFA salt)	457.3 $(M+H)^+$
3-59	Example 1-1 [a]	4-(4-acetamidophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	470.3 $(M+H)^+$
3-60	Example 1-1 [a]	4-(3-acetamidophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	470.4 $(M+H)^+$
3-61	Example 1-1 [a]	4-(4-(methylcarbamoyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	470.3 $(M+H)^+$
3-62	Example 1-1 [a]	4-(3-(methylcarbamoyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	470.4 $(M+H)^+$

3-63	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(naphthalen-2-yl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	463.3 $(M+H)^+$
3-64	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(naphthalen-1-yl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	463.3 $(M+H)^+$
3-65	Example 1-1 [a]	4-(4-*tert*-butylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	469.4 $(M+H)^+$
3-66	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-(3-(methylsulfonamido)phenyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	506.3 $(M+H)^+$
3-67	Example 1-1 [a]	7-(4-methylpiperazine-1-carbonyl)-4-o-tolyl-9H-carbazole-1-carboxamide (prepared as the TFA salt)	427.4 $(M+H)^+$
3-68	Example 1-1 [a]	4-(3-chloro-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	461.2 $(M+H)^+$
3-69	Example 1-1 [a]	4-(2-chlorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	447.2 $(M+H)^+$
3-70	Example 1-1 [a]	4-(2-methoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	443.2 $(M+H)^+$
3-71	Example 1-3 [a]	5-(2,4-difluorophenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as the TFA salt)	453.2 $(M+H)^+$
3-72	Example 1-3 [a]	5-(2,3-difluorophenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as the TFA salt)	453.2 $(M+H)^+$

3-73	Example 1-3 [a]	5-(4-acetamidophenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as the TFA salt)	474.3 $(M+H)^+$
3-74	Example 1-3 [a]	2-(4-methylpiperazine-1-carbonyl)-5-(naphthalen-1-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as the TFA salt)	467.3 $(M+H)^+$
3-75	Example 1-1, Intermediate 50-31	7-(4-methylpiperazine-1-carbonyl)-4-(2-(pyrrolidine-1-carbonyl)-1H-indol-4-yl)-9H-carbazole-1-carboxamide	549.2 $(M+H)^+$
3-76	Example 1-1, Intermediate 50-4	4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	558.2 $(M+H)^+$
3-77	Example 1-1, Intermediate 50-32	4-(3-(isoindolin-2-yl)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	544.3 $(M+H)^+$
3-78	Example 1-1, Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	576.3 $(M+H)^+$
3-79	Example 1-1, Intermediate 50-15	4-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	614.4 $(M+H)^+$
3-80	Intermediate 48-3, Intermediate 50-4	4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	432.2 $(M+H)^+$
3-81	Example 1-1, Intermediate 52-1	4-(8-methyl-2-phenylchroman-7-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	559.2 $(M+H)^+$

3-82	Example 1-1, Intermediate 50-33	7-(4-methylpiperazine-1-carbonyl)-4-(2-oxo-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-6-yl)-9H-carbazole-1-carboxamide	560.4 $(M+H)^+$
3-83	Example 1-1, Intermediate 50-37	4-(6-(4-fluorophenyl)-1H-indol-3-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	546.3 $(M+H)^+$
3-84	Intermediate 48-1, Intermediate 50-4	ethyl 8-carbamoyl-5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-2-carboxylate	526.1 $(M+Na)^+$
3-85	Example 1-1, Intermediate 50-46	4-(2-(4-fluorophenyl)-7-methyl-1H-benzo[d]imidazol-6-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	561.2 $(M+H)^+$
3-86	Example 1-1, Intermediate 50-39	7-(4-methylpiperazine-1-carbonyl)-4-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	482.2 $(M+H)^+$
3-87	Example 1-1, Intermediate 50-40	4-(2-(4-fluorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	576.3 $(M+H)^+$
3-88	Example 1-1, Intermediate 50-41	4-(1-(4-fluorobenzyl)-1H-indol-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	560.3 $(M+H)^+$
3-89	Example 1-1, Intermediate 50-33	4-(5-methyl-2-oxo-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-6-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	574.3 $(M+H)^+$

3-90	Example 1-1, Intermediate 50-34	4-(5-methyl-4-oxo-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-6-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	574.3 $(M+H)^+$
3-91	Example 1-1, Intermediate 50-35	4-(4-hydroxy-2-methyl-3-(phenylcarbamoyl)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	562.3 $(M+H)^+$
3-92	Example 1-1, Intermediate 50-21	4-(4-methyl-5-(1-oxoisoindolin-2-yl)pyridin-3-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	559.4 $(M+H)^+$
3-93	Intermediate 1-4(a), Intermediate 50-21	4-(4-methyl-5-(1-oxoisoindolin-2-yl)pyridin-3-yl)-7-(morpholine-4-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	546.4 $(M+H)^+$
3-94	Example 1-1, Intermediate 50-20	4-(4-methyl-5-(5-methyl-1-oxoisoindolin-2-yl)pyridin-3-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	573.4 $(M+H)^+$
3-95	Intermediate 1-4(a), Intermediate 50-20	4-(4-methyl-5-(5-methyl-1-oxoisoindolin-2-yl)pyridin-3-yl)-7-(morpholine-4-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	560.3 $(M+H)^+$
3-96	Example 1-1, Intermediate 50-42	4-(5-(4-fluorobenzoyl)naphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	585.4 $(M+H)^+$
3-97	Intermediate 48-3, Intermediate 53-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	438.2 $(M+H)^+$

3-98	Example 1-1, Intermediate 50-36	4-(3-(1H-indazol-3-ylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	558.5 $(M+H)^+$
3-99	Intermediate 47-3, Intermediate 50-4	5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	436.3 $(M+H)^+$
Intermediate 3-100	Intermediate 48-1, Intermediate 53-1	ethyl 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxylate	510.13 $(M+H)^+$
3-101	Intermediate 1-5(a), Intermediate 50-4	N^2-(3-(dimethylamino)propyl)-5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	564.2 $(M+H)^+$
3-102	Intermediate 1-6(a), Intermediate 50-4	N^2-(4-(dimethylamino)butyl)-5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	578.2 $(M+H)^+$
3-103	Intermediate 1-5(a) [a]	N^2-(3-(dimethylamino)propyl)-5-(2-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	467.2 $(M+H)^+$
3-104	Intermediate 1-5(a) [a]	N^2-(3-(dimethylamino)propyl)-5-(5-ethoxy-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	481.2 $(M+H)^+$
3-105	Intermediate 1-5(a) [a]	N^2-(3-(dimethylamino)propyl)-5-(2-fluoro-5-(hydroxymethyl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	467.2 $(M+H)^+$
3-106	Intermediate 1-7(a), Intermediate 50-4	5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	563.2 $(M+H)^+$

3-107	Intermediate 1-7(a), Intermediate 50-32	5-(3-(isoindolin-2-yl)-2-methylphenyl)-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	549.3 $(M+H)^+$
3-108	Intermediate 1-8(a), Intermediate 53-1	5-(3-(4-fluorobenzamido)-2-methylphenyl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	582.3 $(M+H)^+$
3-109	Intermediate 1-8(a), [a]	5-(2,4-dimethylthiazol-5-yl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	466.2 $(M+H)^+$
3-110	Intermediate 1-8(a), Intermediate 50-4	5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	576.3 $(M+H)^+$
3-111	Intermediate 1-8(a), Intermediate 54-1	*tert*-butyl 5-(8-carbamoyl-2-(1-methylpiperidin-4-ylcarbamoyl)-2,3,4,9-tetrahydro-1H-carbazol-5-yl)thiazol-2-yl(isopropyl)carbamate	595.3 $(M+H)^+$
3-112	Intermediate 1-8(a), [a]	5-(furan-3-yl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	421.1 $(M+H)^+$
3-113	Intermediate 1-8(a), [a]	5-(benzofuran-2-yl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	471.2 $(M+H)^+$
3-114	Intermediate 1-7(a), [a]	5-(3-formylfuran-2-yl)-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	436.1 $(M+H)^+$
3-115	Intermediate 1-7(a), [a]	5-(1-methyl-1H-pyrazol-5-yl)-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	422.2 $(M+H)^+$

3-116	Intermediate 1-7(a), [a]	*tert*-butyl 4-(8-carbamoyl-2-(tetrahydro-2H-pyran-4-ylcarbamoyl)-2,3,4,9-tetrahydro-1H-carbazol-5-yl)-1H-pyrazole-1-carboxylate	408.2 (M+H-Boc)$^+$
3-117	Intermediate 1-7(a), [a]	5-cyclohexenyl-N2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	422.3 (M+H)$^+$
3-118	Example 1-3, Intermediate 50-19	5-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	580.4 (M+H)$^+$
3-119	Example 1-3, Intermediate 50-5	5-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	580.4 (M+H)$^+$
3-120	Example 1-3, Intermediate 50-18	5-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	576.4 (M+H)$^+$
3-121	Example 1-3, Intermediate 50-8	5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	576.4 (M+H)$^+$
3-122	Example 1-3, Intermediate 50-4	5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	562.4 (M+H)$^+$
3-123	Example 1-3, Intermediate 50-43	5-(2-methyl-3-(2-oxopiperidin-1-yl)phenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	528.4 (M+H)$^+$
3-124	Intermediate 1-7(a), Intermediate 50-47	5-(2-(N,N-bis(*tert*-butoxycarbonyl)amino)-4-methylthiazol-5-yl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	654.4 (M+H)$^+$

3-125	Intermediate 1-9(a), Intermediate 50-4	N^2-methyl-5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	590.4 $(M+H)^+$
3-126	Intermediate 1-9(a), Intermediate 50-19	5-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-N^2-methyl-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	608.4 $(M+H)^+$
3-127	Intermediate 1-9(a), Intermediate 50-18	N^2-methyl-5-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	604.5 $(M+H)^+$
3-128	Intermediate 1-9(a), Intermediate 50-29	N^2-methyl-5-(2-methyl-3-(1-oxoisoquinolin-2(1H)-yl)phenyl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	602.5 $(M+H)^+$
3-129	Intermediate 1-9(a), Intermediate 50-9	5-(3-(6-cyano-1-oxoisoindolin-2-yl)-2-methylphenyl)-N^2-methyl-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	615.5 $(M+H)^+$
3-130	Intermediate 1-9(a), Intermediate 50-7	N^2-methyl-5-(2-methyl-3-(1-oxo-6-(trifluoromethyl)isoindolin-2-yl)phenyl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	658.3 $(M+H)^+$
3-131	Example 1-3, Intermediate 50-20	5-(4-methyl-5-(5-methyl-1-oxoisoindolin-2-yl)pyridin-3-yl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as the TFA salt)	577.3 $(M+H)^+$
3-132	Intermediate 48-1, Intermediate 50-24	ethyl 8-carbamoyl-5-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-2-carboxylate	517.0 $(M+H)^+$

3-133	Intermediate 48-1, Intermediate 50-48	ethyl 8-carbamoyl-5-(3-(8-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-2-carboxylate	535.1 $(M+H)^+$
3-134	Intermediate 48-1, Intermediate 50-27	ethyl 8-carbamoyl-5-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-2-carboxylate	535.3 $(M+H)^+$
3-135	Intermediate 48-1, Intermediate 50-29	ethyl 8-carbamoyl-5-(2-methyl-3-(6-methyl-4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-2-carboxylate	531.3 $(M+H)^+$
3-136	Intermediate 1-7(a), Intermediate 50-10	4-(3-(5-fluoro-1,3-dioxoisoindolin-2-yl)-2-methylphenyl)-N^7-(tetrahydro-2H-pyran-4-yl)-9H-carbazole-1,7-dicarboxamide[b]	591.3 $(M+H)^+$
3-137	Example 1-1 [a]	4-(2-fluoro-3-methoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	461.2 $(M+H)^+$
3-138	Intermediate 48-1, Intermediate 50-8	ethyl 8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-2-carboxylate	518.1 $(M+H)^+$
3-139	Intermediate 48-1, Intermediate 50-5	ethyl 8-carbamoyl-5-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-2-carboxylate	544.1 $(M+Na)^+$
3-140	Intermediate 48-1, Intermediate 50-17	ethyl 8-carbamoyl-5-(3-(4-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-2-carboxylate	544.1 $(M+Na)^+$

3-141	Intermediate 48-3, Intermediate 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	463.1 $(M+H)^+$
3-142	Intermediate 48-3, Intermediate 50-24	4-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	445.1 $(M+H)^+$
3-143	Intermediate 1-10(a), Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-N^7,N^7-dimethyl-9H-carbazole-1,7-dicarboxamide	521.0 $(M+H)^+$
3-144	Intermediate 1-10(a), Intermediate 50-24	N^7,N^7-dimethyl-4-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1,7-dicarboxamide	516.0 $(M+H)^+$
3-145	Intermediate 1-10(a), Intermediate 50-8	N^7,N^7-dimethyl-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1,7-dicarboxamide	517.1 $(M+H)^+$
3-146	Intermediate 48-3, Intermediate 50-48	4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	463.1 $(M+H)^+$

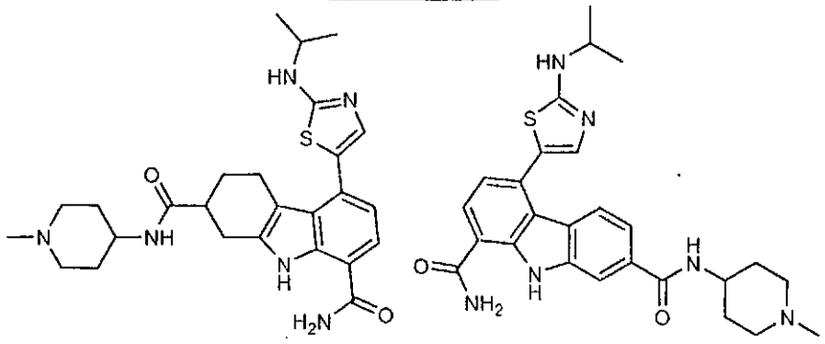
[a] Commercially available boronic acid or boronate ester.

[b] Obtained as a byproduct from reaction of 5-fluoro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindoline-1,3-dione (Intermediate 50-10) with 5-bromo-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide (Intermediate 1-7(a)).

Examples 4-1 and 4-2

Preparation of 5-(2-(isopropylamino)thiazol-5-yl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide and 4-(2-

(isopropylamino)thiazol-5-yl)-N^7-(1-methylpiperidin-4-yl)-9H-carbazole-1,7-dicarboxamide



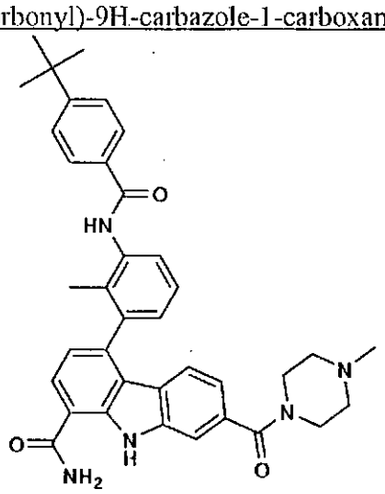
[00328] A solution of *tert*-butyl 5-(8-carbamoyl-2-(1-methylpiperidin-4-ylcarbamoyl)-2,3,4,9-tetrahydro-1H-carbazol-5-yl)thiazol-2-yl(isopropyl)carbamate (Example 3-111, 35 mg, 0.059 mmol) in DCM (1 mL) and TFA (1 mL) was stirred at rt for 2 h. The solution was concentrated and the residue was partitioned between DCM and 1 M aqueous sodium bicarbonate. The organic phase was concentrated and the residue was purified by preparative HPLC. The appropriate effluent fractions were made basic with 1 M aqueous sodium hydroxide, extracted twice with DCM, and the combined organic phases were washed with water, dried and concentrated to provide 5-(2-(isopropylamino)thiazol-5-yl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide (Example 4-1, 18 mg, 61%) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.51 (1 H, d, *J*=7.91 Hz), 6.95 (1 H, d, *J*=7.91 Hz), 6.89 (1 H, s), 3.81 - 3.89 (1 H, m), 3.64 - 3.73 (1 H, m), 2.79 - 3.07 (4 H, m), 2.59 - 2.75 (3 H, m), 2.27 (3 H, s), 2.09 - 2.18 (2 H, m), 1.97 - 2.06 (1 H, m), 1.84 - 1.92 (2 H, m), 1.70 - 1.83 (1 H, m), 1.48 - 1.61 (2 H, m), 1.27 (6 H, d, *J*=6.15 Hz). Mass spectrum m/z 495.2 $(M+H)^+$. Also obtained was 4-(2-(isopropylamino)thiazol-5-yl)-N^7-(1-methylpiperidin-4-yl)-9H-carbazole-1,7-dicarboxamide as a white solid (Example 4-2, 5.2 mg, 18%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.04 - 8.10 (2 H, m), 7.88 - 7.93 (1 H, m), 7.52 - 7.58 (1 H, m), 7.25 (1 H, s), 7.14 - 7.20 (1 H, m), 3.87 - 3.98 (2 H, m), 2.88 - 2.97 (2 H, m), 2.31 (3 H, s), 2.15 - 2.24 (2 H, m), 1.95 - 2.03 (2 H, m), 1.64 - 1.79 (2 H, m), 1.32 (6 H, d, *J*=6.59 Hz). Mass spectrum m/z 491.2 $(M+H)^+$.

[00329] The following compound was also prepared from Example 3-124 using procedures used to prepare Example 4-1:

Example	Compound name	Mass spectrum
4-3	5-(2-amino-4-methylthiazol-5-yl)-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	454.2 $(M+H)^+$

Example 5-1

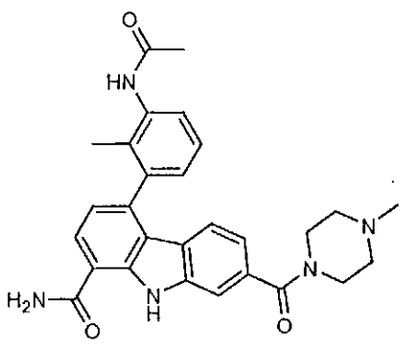
Preparation of 4-(3-(4-*tert*-butylbenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00330] A solution of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 40 mg, 0.045 mmol) and TEA (0.013 mL, 0.091 mmol) in THF (2 mL) was treated with 4-*tert*-butylbenzoyl chloride (0.016 mL, 0.091 mmol). The mixture was stirred at rt for 1 h, then was concentrated and purified by preparative HPLC to provide 4-(3-(4-*tert*-butylbenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (22 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1 H) 10.03 (s, 1 H) 8.25 (br. s., 1 H) 8.08 (d, J=7.69 Hz, 1 H) 7.94 (d, J=8.57 Hz, 2 H) 7.85 (s, 1 H) 7.47 - 7.61 (m, 4 H) 7.41 (t, J=7.69 Hz, 1 H) 7.20 (d, J=7.03 Hz, 1 H) 6.98 - 7.07 (m, 3 H) 2.93 - 3.50 (m, 8 H) 2.81 (s, 3 H) 1.90 (s, 3 H) 1.30 (s, 9 H). Mass spectrum m/z 602.4 $(M+H)^+$.

Example 5-2

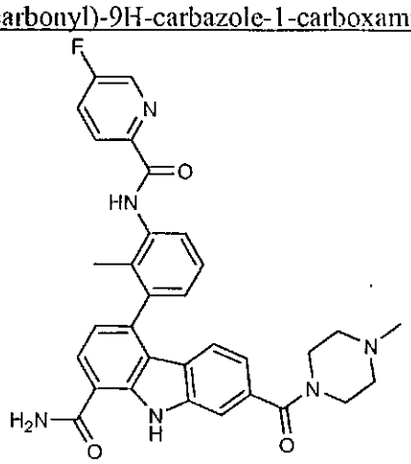
Preparation of 4-(3-acetamido-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00331] A solution of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 20 mg, 0.045 mmol) and DIEA (0.024 mL, 0.136 mmol) in DCM (2 mL) was treated with acetyl chloride (4 µL, 0.054 mmol). The mixture was stirred at rt for 2 h, then was concentrated and purified by preparative HPLC to provide 4-(3-acetamido-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (18 mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (1 H, s), 9.44 (1 H, s), 8.18 (1 H, br. s.), 8.00 (1 H, d, J=7.7 Hz), 7.78 (1 H, s), 7.50 (2 H, d, J=7.3 Hz), 7.28 (1 H, t, J=7.7 Hz), 7.05 (1 H, d, J=7.3 Hz), 6.88 - 6.98 (2 H, m), 6.83 (1 H, d, J=8.1 Hz), 2.86 - 3.11 (4 H, m), 2.75 (3 H, s), 2.02 (3 H, s), 1.80 (3 H, s). Mass spectrum m/z 484.3 $(M+H)^+$.

Example 5-3

Preparation of 4-(3-(5-fluoropicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00332] A mixture of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 100 mg, 0.204 mmol), 5-

fluoropicolinic acid (43.1 mg, 0.306 mmol), and HOAT (41.6 mg, 0.306 mmol) in acetonitrile (2 mL) was treated with DIEA (0.053 mL, 0.306 mmol) and EDC (78 mg, 0.408 mmol) and the mixture was stirred at rt. After 18 h, the mixture was diluted with methanol and purified by preparative HPLC. The aqueous residue from concentration of the appropriate effluent fractions was made basic with NaHCO3 (aq) and extracted three times with EtOAc. The combined organic phases were dried and concentrated to provide 4-(3-(5-fluoropicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a light gray powder (111.5 mg, 92%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.58 (d, J=3.1 Hz, 1 H) 8.31 (dd, J=8.8, 4.8 Hz, 1 H) 7.96 - 8.03 (m, 2 H) 7.82 (td, J=8.6, 2.6 Hz, 1 H) 7.68 (d, J=0.9 Hz, 1 H) 7.45 (t, J=7.9 Hz, 1 H) 7.23 (dd, J=7.5, 0.9 Hz, 1 H) 7.09 (d, J=7.9 Hz, 1 H) 7.03 - 7.08 (m, 1 H) 6.95 - 7.00 (m, 1 H) 3.78 (br. s., 2 H) 3.49 (br. s., 2 H) 2.52 (br. s., 2 H) 2.40 (br. s., 2 H) 2.31 (s, 3 H) 2.04 (s, 3 H). Mass spectrum m/z 565.2 $(M+H)^+$.

[00333] The following compounds were also prepared using procedures demonstrated in Examples 5-1 through 5-3 and similar procedures. In this table, "starting material" refers to the amine reacted with the appropriate commercially available carboxylic acid or acid chloride.

Example	Starting material	Compound name	Mass spectrum
5-4	Example 3-2	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	564.3 $(M+H)^+$
5-5	Example 3-2	4-(2-methyl-3-(picolinamido)phenyl)-6-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	547.2 $(M+H)^+$
5-6	Example 3-2	N-(3-(1-carbamoyl-6-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenyl)thiazole-2-carboxamide	553.2 $(M+H)^+$
5-7	Example 3-2	4-(2-methyl-3-(nicotinamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	547.2 $(M+H)^+$

5-8	Example 3-2	4-(3-(isonicotinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	547.2 $(M+H)^+$
5-9	Example 3-2	4-(3-(1H-imidazole-2-carboxamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	536.3 $(M+H)^+$
5-10	Example 3-2	4-(2-methyl-3-(pyrimidine-4-carboxamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	548.2 $(M+H)^+$
5-11	Example 3-2	4-(3-(1H-benzo[d]imidazole-2-carboxamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	586.2 $(M+H)^+$
5-12	Example 3-2	4-(2-fluoro-4-(4-fluorobenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	568.1 $(M+H)^+$
5-13	Example 3-2	4-(3-(5-ethylpicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	575.2 $(M+H)^+$
5-14	Example 3-2	4-(3-(5-butylpicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	603.3 $(M+H)^+$
5-15	Example 3-2	4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	550.2 $(M+H)^+$
5-16	Example 3-2	N-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenyl)-4-isopropylthiazole-2-carboxamide	595.2 $(M+H)^+$
5-17	Example 3-2	N-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[d]thiazole-2-carboxamide	607.2 $(M+H)^+$

5-18	Example 3-2	N-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenyl)-5-methylthiazole-2-carboxamide	567.2 $(M+H)^+$
5-19	Example 3-2	4-(3-(3-hydroxypicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	563.2 $(M+H)^+$
5-20	Example 3-2	4-(2-methyl-3-(pyrimidine-2-carboxamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	548.2 $(M+H)^+$
5-21	Example 3-2	N-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenyl)benzo[d]thiazole-2-carboxamide	603.2 $(M+H)^+$
5-22	Example 3-2	4-(2-methyl-3-(1-methyl-1H-benzo[d]imidazole-2-carboxamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	600.2 $(M+H)^+$
5-23	Example 3-2	4-(3-(5-chloropicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	581.2 $(M+H)^+$
5-24	Example 3-2	4-(3-(5-bromopicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	625, 627 $(M+H)^+$
5-25	Example 3-2	4-(2-methyl-3-(5-(trifluoromethyl)picolinamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	615.2 $(M+H)^+$
5-26	Example 3-2	4-(3-(6-hydroxypicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	563.2 $(M+H)^+$

5-27	Example 3-2	4-(3-(5-hydroxypicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	563.2 $(M+H)^+$
5-28	Example 3-2	4-(2-methyl-3-(5-methylpicolinamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	561.3 $(M+H)^+$
5-29	Example 3-2	4-(3-(5-bromopyrimidine-2-carboxamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	626, 628 $(M+H)^+$
5-30	Example 3-2	N-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenyl)-2-chlorothiazole-5-carboxamide	587.1 $(M+H)^+$
5-31	Example 3-2	4-(3-(5-cyanopicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	572.2 $(M+H)^+$
5-32	Example 3-2	4-(2-methyl-3-(5-(pyrrolidin-1-yl)picolinamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	616.3 $(M+H)^+$
5-33	Example 3-37	4-(2-fluoro-3-(picolinamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	551.2 $(M+H)^+$
5-34	Example 3-37	4-(2-fluoro-3-(5-fluoropicolinamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	569.2 $(M+H)^+$
5-35	Example 3-37	4-(3-(5-cyanopicolinamido)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	576.2 $(M+H)^+$

5-36	Example 3-37	4-(2-fluoro-3-(5-(pyrrolidin-1-yl)picolinamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	620.3 $(M+H)^+$
5-37	Example 3-37	4-(2-fluoro-3-(pyrimidine-4-carboxamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	552.2 $(M+H)^+$
5-38	Example 3-37	N-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-fluorophenyl)thiazole-2-carboxamide	557.1 $(M+H)^+$
5-39	Example 3-37	4-(2-fluoro-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	554.2 $(M+H)^+$
5-40	Example 3-2	4-(2-methyl-3-(2-(pyridin-2-yl)acetamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	561.2 $(M+H)^+$
5-41	Example 3-2	4-(2-methyl-3-(1-(pyridin-2-yl)cyclopropanecarboxamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	587.3 $(M+H)^+$
5-42	Example 3-2	4-(3-(1-(4-fluorophenyl)cyclopropanecarboxamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	604.2 $(M+H)^+$
5-43	Example 3-2	4-(3-(1-(4-fluorophenyl)cyclobutanecarboxamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	618.2 $(M+H)^+$
5-44	Example 3-2	4-(3-(2-(4-chlorophenyl)-2-methylpropanamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	622.2 $(M+H)^+$

5-45	Example 3-2	4-(3-benzamido-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	546.3 $(M+H)^+$
5-46	Example 3-13	4-(2-methyl-3-(1-methyl-1H-benzo[d]imidazole-2-carboxamido)phenyl)-9H-carbazole-1-carboxamide	474.4 $(M+H)^+$
5-47	Example 3-13	4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-9H-carbazole-1-carboxamide	424.3 $(M+H)^+$
5-48	Example 3-51	4-(2,6-difluoro-4-(4-fluorobenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	586.4 $(M+H)^+$
5-49	Example 3-2	4-(3-(cyclopropanecarboxamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	509.9 $(M+H)^+$
5-50	Example 3-2	4-(3-(cyclohexanecarboxamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	551.9 $(M+H)^+$
5-51	Example 3-2	4-(3-(2-chlorobenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	579.8 $(M+H)^+$
5-52	Example 3-2	4-(3-(3-chlorobenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	579.8 $(M+H)^+$
5-53	Example 3-2	4-(3-(3-(dimethylamino)benzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	588.9 $(M+H)^+$

5-54	Example 3-2	4-(3-(4-cyanobenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	570.8 $(M+H)^+$
5-55	Example 3-2	4-(3-(4-chlorobenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	579.8 $(M+H)^+$
5-56	Example 3-2	4-(3-(4-acetamidobenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	602.8 $(M+H)^+$
5-57	Example 3-2	4-(3-(4-methoxybenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	575.8 $(M+H)^+$
5-58	Example 3-2	4-(2-methyl-3-(4-methylbenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	559.8 $(M+H)^+$
5-59	Example 3-2	4-(3-isobutyramido-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	511.9 $(M+H)^+$
5-60	Example 3-2	4-(3-(2-cyanoacetamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	508.8 $(M+H)^+$
5-61	Example 3-2	4-(3-(3,3-dimethylbutanamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	539.9 $(M+H)^+$

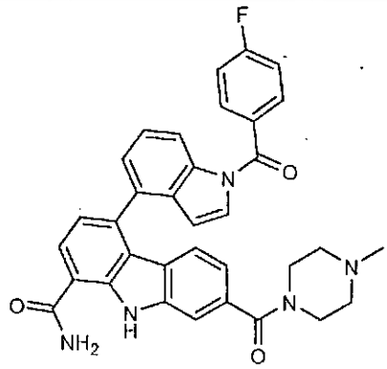
5-62	Example 3-2	4-(2-methyl-3-(3-methylbutanamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	525.8 $(M+H)^+$
5-63	Example 3-2	4-(2-methyl-3-(4-methylpentanamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	539.9 $(M+H)^+$
5-64	Example 3-2	4-(2-methyl-3-pivalamidophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	525.9 $(M+H)^+$
5-65	Example 3-2	4-(3-(2-(dimethylamino)acetamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	526.9 $(M+H)^+$
5-66	Example 3-2	4-(2-methyl-3-(2-phenylacetamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	559.8 $(M+H)^+$
5-67	Example 3-2	4-(2-methyl-3-pent-4-ynamidophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	521.9 $(M+H)^+$
5-68	Example 3-2	4-(2-methyl-3-pentanamidophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	525.9 $(M+H)^+$
5-69	Example 3-2	4-(2-methyl-3-(4-sulfamoylbenzamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	624.8 $(M+H)^+$

5-70	Example 3-2	4-(2-methyl-3-(2-methyl-2-phenylpropanamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	587.9 $(M+H)^+$
5-71	Example 3-2	4-(3-(2-(dimethylamino)benzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	588.8 $(M+H)^+$
5-72	Example 3-2	N-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenyl)-2-phenylthiazole-4-carboxamide (prepared as the TFA salt)	628.8 $(M+H)^+$
5-73	Example 3-2	4-(3-(1-cyanocyclopropanecarboxamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	534.8 $(M+H)^+$
5-74	Example 3-2	N-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenyl)thiazole-4-carboxamide (prepared as the TFA salt)	552.8 $(M+H)^+$
5-75	Example 3-2	4-(2-methyl-3-(3-morpholinopropanamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	582.9 $(M+H)^+$
5-76	Example 3-2	4-(3-(3-(1H-imidazol-1-yl)propanamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	563.8 $(M+H)^+$
5-77	Example 3-2	4-(3-(2-(1H-tetrazol-5-yl)acetamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	551.8 $(M+H)^+$

5-78	Example 3-2	4-(2-methyl-3-(3-(2-oxopyrrolidin-1-yl)propanamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	580.8 $(M+H)^+$
5-79	Example 3-2	4-(2-methyl-3-(2-(pyrazin-2-yl)acetamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	561.8 $(M+H)^+$
5-80	Example 3-2	4-(3-biphenyl-4-ylcarboxamido-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	622.0 $(M+H)^+$
5-81	Example 3-2	methyl 4-(3-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)-2-methylphenylcarbamoyl)benzoate (prepared as the TFA salt)	603.9 $(M+H)^+$
5-82	Example 3-2	4-(2-methyl-3-(3-phenylpropanamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	573.9 $(M+H)^+$
5-83	Example 3-46	4-(2-methyl-5-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	550.2 $(M+H)^+$
5-84	Example 3-46	4-(5-(4-fluorobenzamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	564.2 $(M+H)^+$
5-85	Example 4-1	5-(2-(N-isopropylacetamido)thiazol-5-yl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	495.2 $(M+H)^+$
5-86	Example 4-3	5-(2-benzamido-4-methylthiazol-5-yl)-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	558.1 $(M+H)^+$

Example 6-1

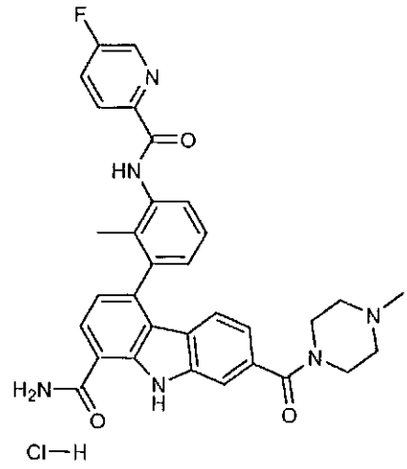
Preparation of 4-(1-(4-fluorobenzoyl)-1H-indol-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00334] A solution of 4-(1H-indol-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-47, 50 mg, 0.100 mmol) in DCM (1 mL) was treated sequentially with DMAP (3.7 mg, 0.030 mmol), TEA (0.028 mL, 0.199 mmol) and 4-fluorobenzoyl chloride (0.013 mL, 0.110 mmol). The mixture was stirred at rt for 17 h, then was treated with additional 4-fluorobenzoyl chloride (0.013 mL, 0.110 mmol) and TEA (0.028 mL, 0.199 mmol) and stirring was continued for 111 h. The mixture was concentrated and the residue was dissolved in methanol and purified by preparative HPLC. The appropriate effluent fractions were partitioned between NaHCO3 (aq) and EtOAc, and the aqueous phase was extracted twice more with EtOAc. The combined organic phases were dried and concentrated to provide 4-(1-(4-fluorobenzoyl)-1H-indol-4-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a yellow solid (19.5 mg, 31%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.51 (1 H, d, J=8.3 Hz), 8.03 (1 H, d, J=7.9 Hz), 7.84 (2 H, dd, J=8.8, 5.3 Hz), 7.68 (1 H, s), 7.57 (1 H, t, J=7.7 Hz), 7.46 (1 H, d, J=7.5 Hz), 7.26 - 7.36 (3 H, m), 7.20 (1 H, d, J=7.9 Hz), 6.96 (1 H, d, J=7.9 Hz), 6.86 (1 H, dd, J=8.3, 1.3 Hz), 6.19 (1 H, d, J=4.0 Hz), 3.77 (2 H, br. s.), 3.46 (2 H, br. s.), 2.51 (2 H, br. s.), 2.38 (2 H, br. s.), 2.30 (3 H, s). Mass spectrum m/z 574.3 $(M+H)^+$.

Example 7-1

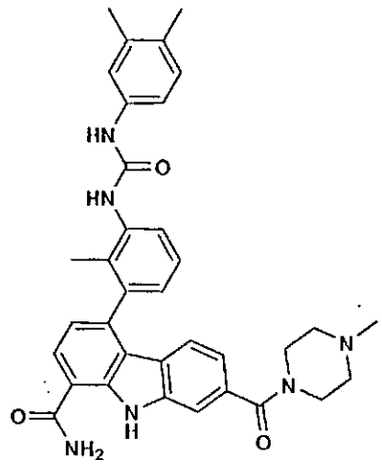
Preparation of 4-(3-(5-fluoropicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as the hydrochloric acid salt



[00335] A solution of 4-(3-(5-fluoropicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 5-3, 32.7 mg, 0.058 mmol) in EtOAc (1 mL) was treated with hydrogen chloride, 4 M in 1,4-dioxane (0.1 mL, 0.400 mmol). The resulting solid was suspended in additional EtOAc with sonication, and the precipitate was collected by filtration, rinsed with EtOAc and dried to provide the hydrochloric acid salt of 4-(3-(5-fluoropicolinamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as an off-white powder (30.5 mg, 88%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.58 (d, J=2.6 Hz, 1 H) 8.31 (dd, J=8.8, 4.4 Hz, 1 H) 8.03 (d, J=7.5 Hz, 1 H) 7.99 (d, J=8.3 Hz, 1 H) 7.82 (td, J=8.6, 2.6 Hz, 1 H) 7.76 (s, 1 H) 7.46 (t, J=7.7 Hz, 1 H) 7.23 (d, J=7.5 Hz, 1 H) 7.10 (s, 3 H) 3.32 - 3.61 (m, 4 H) 3.09 - 3.24 (m, 2 H) 2.94 (s, 3 H) 2.03 (s, 3 H). Mass spectrum m/z 565.2 $(M+H)^+$.

Example 8-1

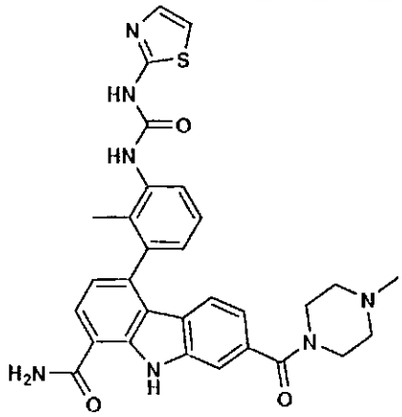
Preparation of 4-(3-(3-(3,4-dimethylphenyl)ureido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00336] A solution of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 25 mg, 0.028 mmol) and TEA (8 μL, 0.057 mmol) in DCM (2 mL) was treated with 4-isocyanato-1,2-dimethylbenzene (8.33 mg, 0.057 mmol) and the mixture was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC to provide 4-(3-(3-(3,4-dimethylphenyl)ureido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (11 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d6) δ 11.70 (s, 1 H) 8.87 (s, 1 H) 8.19 (br. s., 1 H) 8.00 (t, J=7.40 Hz, 3 H) 7.78 (s, 1 H) 7.51 (br. s., 1 H) 7.27 (t, J=7.78 Hz, 1 H) 7.19 (s, 1 H) 7.13 (d, J=6.78 Hz, 1 H) 6.87 - 7.00 (m, 4 H) 6.81 (d, J=8.03 Hz, 1 H) 3.34 - 3.57 (m, 4 H) 2.97 - 3.17 (m, 4 H) 2.69 (br. s., 3 H) 2.13 (s, 3 H) 2.09 (s, 3 H) 1.85 (s, 3 H). Mass spectrum m/z 589.4$(M+H)^+$.

Example 8-2

Preparation of 4-(2-methyl-3-(3-thiazol-2-ylureido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



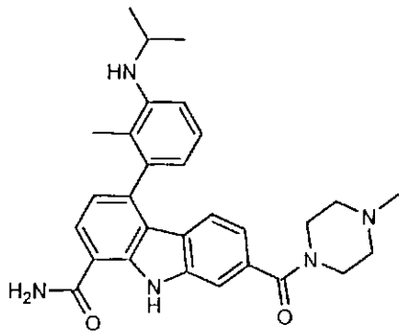
[00337] A solution of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 25 mg, 0.028 mmol) and TEA (8 μL, 0.057 mmol) in DCM (2 mL) was treated with phenyl thiazol-2-ylcarbamate (12.47 mg, 0.057 mmol) and stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC to provide 4-(2-methyl-3-(3-thiazol-2-ylureido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (10 mg, 45%) contaminated with about 15% of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H) 8.58 (br. s., 1 H) 8.28 (br. s., 1 H) 8.08 (t, *J*=7.40 Hz, 2 H) 7.87 (s, 1 H) 7.60 (br. s., 1 H) 7.36 - 7.44 (m, 2 H) 7.15 (d, *J*=3.51 Hz, 1 H) 7.00 - 7.10 (m, 4 H) 6.88 (d, *J*=8.28 Hz, 1 H) 2.98 - 3.56 (m, 8 H) 2.83 (br. s., 3 H) 1.94 (s, 3 H). Mass spectrum m/z 568.3 $(M+H)^+$.

[00338] The following compounds were also prepared using procedures demonstrated in Examples 8-1 through 8-2 and similar procedures. In this table, "starting material" refers to the amine reacted with the appropriate urea-forming reagent.

Example	Starting material	Compound name	Mass spectrum
8-3	Example 3-2	4-(2-methyl-3-(3-phenylureido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	560.8 $(M+H)^+$
8-4	Example 3-2	4-(3-(3-(4-chlorophenyl)ureido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	594.8 $(M+H)^+$
8-5	Example 3-2	4-(3-(3-(4-methoxyphenyl)ureido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	590.8 $(M+H)^+$

Example 9-1

Preparation of 4-(3-(isopropylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



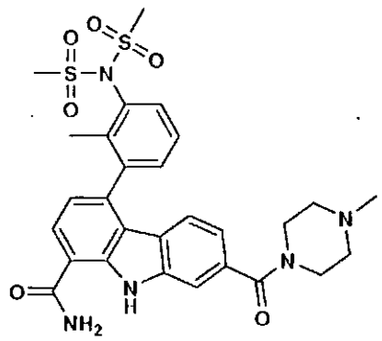
[00339] Sodium triacetoxyborohydride (41 mg, 0.193 mmol) was added to a solution of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 30 mg, 0.068 mmol), acetic acid (0.03 mL, 0.524 mmol) and acetone (0.170 mL, 2.315 mmol) in DCM (0.3 mL) and the mixture was stirred at rt for 4 h. The solvent was evaporated and the residue was dissolved in water and purified by preparative HPLC and lyophilization to provide 4-(3-(isopropylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a white powder (31.7 mg, 56%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.07 (1 H, d, J=7.70 Hz), 7.79 (1 H, s), 7.58 - 7.66 (2 H, m), 7.50 - 7.54 (1 H, m), 7.11 (1 H, d, J=7.70 Hz), 7.03 (1 H, dd, J=8.14, 1.54 Hz), 6.82 (1 H, d, J=7.92 Hz), 3.84 (1 H, dt, J=13.04, 6.57 Hz), 3.37 - 3.69 (4 H, m), 3.05 - 3.27 (4 H, m), 2.94 (3 H, s), 2.11 (3 H, s), 1.50 (3 H, d, J=6.38 Hz), 1.45 (3 H, d, J=6.60 Hz). Mass spectrum m/z 484.2 $(M+H)^+$.

[00340] The following compounds were also prepared using procedures demonstrated in Example 9-1 and similar procedures, substituting the appropriate aldehyde or ketone for acetone.

Example	Compound name	Mass spectrum
9-2	4-(3-(4-fluorobenzylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	550.2 $(M+H)^+$
9-3	4-(3-(1-(4-fluorophenyl)ethylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	564.3 $(M+H)^+$

Example 10-1

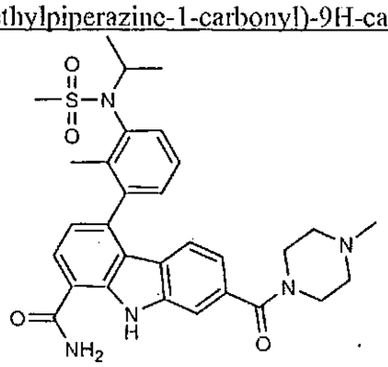
Preparation of 4-(2-methyl-3-(N-(methylsulfonyl)methylsulfonamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00341] A solution of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 20 mg, 0.045 mmol) and DIEA (0.024 mL, 0.136 mmol) in DCM (2 mL) was treated with methanesulfonyl chloride (4 μL, 0.054 mmol) and stirred at rt for 2 h. Additional methanesulfonyl chloride was added and the mixture was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC to provide 4-(2-methyl-3-(N-(methylsulfonyl)methylsulfonamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (16 mg, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1 H) 8.21 (br. s., 1 H) 8.04 (d, *J*=7.9 Hz, 1 H) 7.77 (s, 1 H) 7.63 (dd, *J*=7.9, 1.1 Hz, 1 H) 7.53 (br. s., 1 H) 7.45 (t, *J*=7.8 Hz, 1 H) 7.37 (d, *J*=8.6 Hz, 1 H) 7.03 (d, *J*=7.7 Hz, 1 H) 6.83 - 6.88 (m, 1 H) 6.76 - 6.83 (m, 1 H) 3.53 (s, 6 H) 2.93 - 3.20 (m, 8 H) 2.75 (s, 3 H) 1.97 (s, 3 H). Mass spectrum m/z 598.2 $(M+H)^+$.

Examples 10-2 and 10-3

Preparation of two rotational isomers of 4-(3-(N-isopropylmethylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide

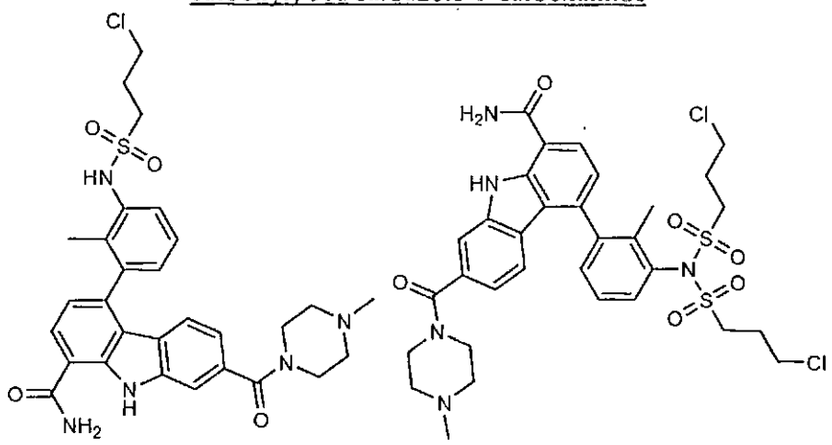


[00342] Methanesulfonyl chloride (1.3 μL, 0.016 mmol) was added to a stirred solution of 4-(3-(isopropylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt (Example 9-1, 13 mg, 0.016 mmol)

in pyridine (0.2 mL) at rt. After 30 min, additional methanesulfonyl chloride (2.4 μL) was added and the mixture was stirred overnight. The mixture was treated with 1 M hydrochloric acid (0.56 mL), dissolved in methanol and purified by preparative HPLC to provide two rotational isomers of 4-(3-(N-isopropylmethylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, isolated separately as TFA salts after lyophilization. Isomer A (3.3 mg, 31%) ^{1}H NMR (400 MHz, chloroform-d) δ 9.58 (1 H, s), 7.81 (1 H, d, J=7.70 Hz), 7.68 (1 H, s), 7.41 - 7.47 (1 H, m), 7.32 - 7.37 (2 H, m), 7.11 (1 H, d, J=7.70 Hz), 7.05 (1 H, d, J=8.14 Hz), 6.86 (1 H, d, J=8.14 Hz), 4.60 - 4.72 (1 H, m), 3.66 (3 H, br. s.), 3.05 (8 H, br. s.), 2.90 (3 H, s), 1.91 (3 H, s), 1.40 (3 H, d, J=6.60 Hz), 1.12 (3 H, d, J=6.82 Hz). Mass spectrum m/z 562.1 $(M+H)^+$. Isomer B (2.9 mg, 27%) ^{1}H NMR (400 MHz, chloroform-d) δ 9.41 (1 H, br. s.), 7.84 (1 H, d, J=7.70 Hz), 7.69 (1 H, s), 7.46 (1 H, t, J=7.81 Hz), 7.36 (2 H, t, J=8.25 Hz), 7.13 (1 H, d, J=7.70 Hz), 7.05 (1 H, dd, J=8.25, 1.21 Hz), 6.92 (1 H, d, J=8.36 Hz), 4.71 - 4.82 (1 H, m), 3.67 (3 H, br. s.), 2.59 - 3.07 (11 H, m), 1.90 (3 H, s), 1.43 (3 H, d, J=6.60 Hz), 1.10 (3 H, d, J=6.60 Hz). Mass spectrum m/z 562.2 $(M+H)^+$.

Examples 10-4 and 10-5

Preparation of 4-(3-(3-chloropropylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide and 4-(3-(3-chloro-N-(3-chloropropylsulfonyl)propylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00343] Using the procedure of Examples 10-2 and 10-3, 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 33.5 mg, 0.076 mmol) was converted into 4-(3-(3-

chloropropylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 10-4, 12.6 mg, 24%), isolated as the TFA salt after HPLC purification and lyophilization. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (1 H, s), 9.79 (1 H, br. s.), 9.41 (1 H, s), 8.26 (1 H, br. s.), 8.07 (1 H, d, J=7.92 Hz), 7.85 (1 H, s), 7.53 - 7.62 (1 H, m), 7.47 - 7.51 (1 H, m), 7.41 (1 H, t, J=7.70 Hz), 7.21 (1 H, dd, J=7.48, 1.10 Hz), 7.03 (1 H, d, J=7.70 Hz), 6.97 (1 H, dd, J=8.14, 1.32 Hz), 6.83 (1 H, d, J=8.14 Hz), 3.80 (2 H, t, J=6.49 Hz), 3.36 - 3.64 (8 H, m), 3.30 - 3.36 (2 H, m), 2.82 (3 H, br. s.), 2.18 - 2.29 (2 H, m), 2.00 (3 H, s). Mass spectrum m/z 582.1 $(M+H)^+$. Also isolated as the TFA salt was 4-(3-(3-chloro-N-(3-chloropropylsulfonyl)propylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a white powder (Example 10-5, 3.7 mg, 6%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (1 H, s), 9.85 (1 H, br. s.), 8.28 (1 H, br. s.), 8.11 (1 H, d, J=7.92 Hz), 7.84 (1 H, s), 7.70 (1 H, dd, J=7.92, 1.10 Hz), 7.58 - 7.63 (1 H, m), 7.55 (1 H, t, J=7.81 Hz), 7.45 (1 H, dd, J=7.59, 0.99 Hz), 7.09 (1 H, d, J=7.70 Hz), 6.92 (1 H, dd, J=8.14, 1.54 Hz), 6.83 (1 H, d, J=8.14 Hz), 3.76 - 4.04 (10 H, m), 2.96 - 3.66 (5 H, m), 2.81 (3 H, br. s.), 2.23 - 2.35 (4 H, m), 2.06 (3 H, s). Mass spectrum m/z 722.0 $(M+H)^+$.

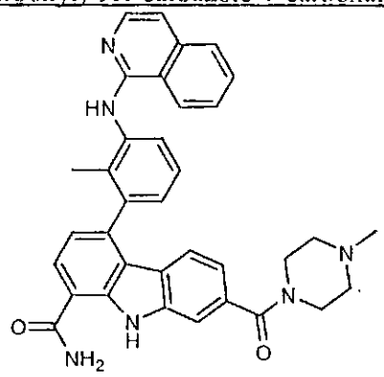
[00344] The following compounds were also prepared using procedures demonstrated in Example 10-1 through 10-5, using the appropriate sulfonyl chloride.

Example	Compound name	Mass spectrum
10-6	4-(2-methyl-3-(phenylsulfonamido)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	581.8 $(M+H)^+$
10-7	4-(3-(4-chlorophenylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	615.7 $(M+H)^+$
10-8	4-(3-(4-methoxyphenylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	611.8 $(M+H)^+$

10-9	4-(3-(1,1,3,3,-tetraoxobenzo[d][1,3,2]dithiazol-2-yl)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	644.0 $(M+H)^+$

Example 11-1

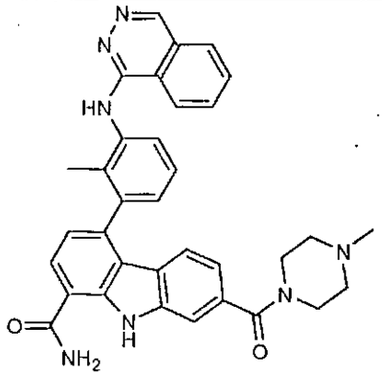
Preparation of 4-(3-(isoquinolin-1-ylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00345] A suspension of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 35 mg, 0.079 mmol) and 1-chloroisoquinoline (19.45 mg, 0.119 mmol) in isopropanol (0.5 mL) was treated with 4M hydrogen chloride in 1,4-dioxane (3 drops) and the mixture was heated in a sealed tube by microwave irradiation at 140 °C for 45 min. Additional 4 M hydrogen chloride in 1,4-dioxane (1 drop) was added and the mixture was again heated in a sealed tube by microwave irradiation at 140 °C for 60 min. The mixture was concentrated and the residue was purified by preparative HPLC. The appropriate effluent fractions were concentrated and the residue was partitioned between NaHCO3 (aq) and EtOAc, and the aqueous phase was extracted twice more with EtOAc. The combined organic phases were dried and concentrated to provide 4-(3-(isoquinolin-1-ylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a white solid (16 mg, 32%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.28 (1 H, d, J=8.3 Hz), 7.91 (1 H, d, J=7.8 Hz), 7.72 (1 H, d, J=6.1 Hz), 7.66 (1 H, d, J=8.3 Hz), 7.56 - 7.61 (2 H, m), 7.48 (1 H, ddd, J=8.0, 7.2, 0.8 Hz), 7.44 (1 H, d, J=7.5 Hz), 7.34 (1 H, t, J=7.8 Hz), 7.22 (1 H, d, J=8.0 Hz), 7.14 (1 H, d, J=6.7 Hz), 7.06 (1 H, d, J=7.8 Hz), 6.97 (1 H, d, J=6.1 Hz), 6.94 (1 H, dd, J=8.2, 1.5 Hz), 3.71 (2 H, br. s.), 3.42 (2 H, br. s.), 2.45 (2 H, br. s.), 2.32 (2 H, br. s.), 2.23 (3 H, s), 1.81 (3 H, s). Mass spectrum m/z 569.4 $(M+H)^+$.

Example 11-2

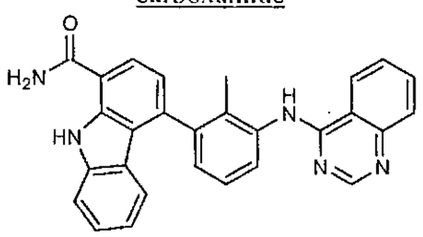
Preparation of 4-(2-methyl-3-(phthalazin-1-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00346] Using the procedure of Example 11-1 but only heating at 140 °C for 45 min, 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-2, 35 mg, 0.079 mmol) and 1-chlorophthalazine (19.57 mg, 0.119 mmol) were converted to 4-(2-methyl-3-(phthalazin-1-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a light yellow solid (7.3 mg, 15%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.88 (1 H, br. s.), 8.47 (1 H, d, J=7.0 Hz), 8.03 (1 H, d, J=7.7 Hz), 7.91 - 8.01 (3 H, m), 7.70 (1 H, s), 7.51 - 7.59 (1 H, m), 7.47 (1 H, t, J=7.7 Hz), 7.24 - 7.34 (2 H, m), 7.18 (1 H, d, J=7.9 Hz), 7.09 (1 H, dd, J=8.1, 1.3 Hz), 3.83 (2 H, br. s.), 3.54 (2 H, br. s.), 2.57 (2 H, br. s.), 2.44 (2 H, br. s.), 2.35 (3 H, s), 1.96 (3 H, s). Mass spectrum m/z 570.4 $(M+H)^+$.

Example 11-3

Preparation of 4-(2-methyl-3-(quinazolin-4-ylamino)phenyl)-9H-carbazole-1-carboxamide



[00347] Using the procedure of Example 11-1 but heating at 140 °C twice for 30 min and once for 45 min, 4-(3-amino-2-methylphenyl)-9H-carbazole-1-carboxamide (Example 3-13, 26.4 mg, 0.084 mmol) and 4-chloroquinazoline (20.67 mg, 0.126 mmol) were converted to 4-(2-methyl-3-(quinazolin-4-ylamino)phenyl)-9H-

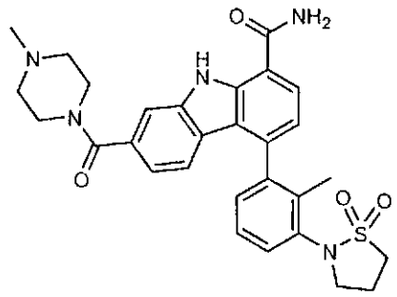
carbazole-1-carboxamide as a white solid (8.0 mg, 20%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.37 (1 H, s), 8.31 (1 H, dd, J=8.4, 0.9 Hz), 7.86 (1 H, d, J=7.9 Hz), 7.75 - 7.83 (1 H, m), 7.66 - 7.73 (1 H, m), 7.56 (1 H, ddd, J=8.3, 7.0, 1.2 Hz), 7.49 (1 H, d, J=8.4 Hz), 7.35 - 7.46 (2 H, m), 7.22 - 7.31 (2 H, m), 7.12 (1 H, d, J=7.7 Hz), 7.00 (1 H, d, J=7.9 Hz), 6.84 - 6.92 (1 H, m), 1.84 (3 H, s). Mass spectrum m/z 444.2 $(M+H)^+$.

[00348] The following compounds were also prepared using procedures demonstrated in Examples 11-1 through 11-3, starting with Example 3-2 and the appropriate substituted chloroquinazoline (prepared according to the procedures of Steps 1 and 2 of Intermediate 32-1).

Example	Compound name	Mass spectrum
11-4	4-(2-methyl-3-(quinazolin-4-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	570.4 $(M+H)^+$
11-5	4-(3-(6-chloroquinazolin-4-ylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	604.4 $(M+H)^+$
11-6	4-(3-(7-chloroquinazolin-4-ylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	604.5 $(M+H)^+$
11-7	4-(3-(7-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	588.5 $(M+H)^+$
11-8	4-(3-(6-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	588.5 $(M+H)^+$
11-9	4-(2-methyl-3-(7-methylquinazolin-4-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	584.5 $(M+H)^+$
11-10	4-(2-methyl-3-(6-methylquinazolin-4-ylamino)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	584.5 $(M+H)^+$

Example 12-1

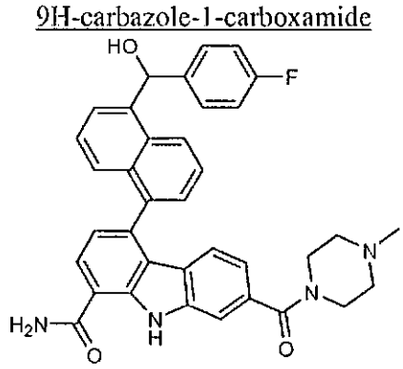
Preparation of 4-(3-(1,1-dioxoisothiazolidin-2-yl)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00349] A solution of 4-(3-(3-chloropropylsulfonamido)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt (Example 10-4, 10.7 mg, 0.015 mmol) in THF (0.5 mL) was treated with a solution of lithium hexamethyldisilazide (1 M in THF, 0.092 mL, 0.092 mmol) at rt. After warming to 60 °C and adding DMF (0.2 mL) and stirring for 5 h, the mixture was concentrated and the residue was purified by preparative HPLC to provide 4-(3-(1,1-dioxoisothiazolidin-2-yl)-2-methylphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, isolated as the TFA salt (3.5 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (1 H, s), 9.85 (1 H, br. s.), 8.26 (1 H, br. s.), 8.08 (1 H, d, J=7.70 Hz), 7.85 (1 H, s), 7.61 (1 H, dd, J=8.03, 0.99 Hz), 7.48 (1 H, t, J=7.70 Hz), 7.30 - 7.34 (1 H, m), 7.06 (1 H, d, J=7.70 Hz), 6.97 (1 H, dd, J=8.25, 1.43 Hz), 6.86 (1 H, d, J=8.14 Hz), 3.69 - 3.76 (2 H, m), 3.29 - 3.64 (10 H, m), 2.82 (3 H, s), 2.42 - 2.48 (2 H, m), 2.00 (3 H, s). Mass spectrum m/z 546.1 $(M+H)^+$.

Examples 13-1 and 13-2

Preparation of two diastereomers of 4-(5-((4-fluorophenyl)(hydroxy)methyl)naphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide

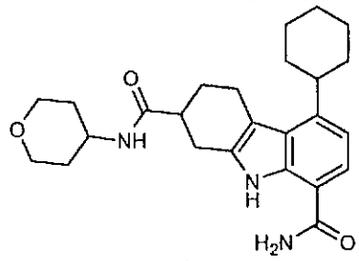


[00350] A solution of 4-(5-(4-fluorobenzoyl)naphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-96, 30 mg, 0.051 mmol) in ethanol (0.5 mL) was treated with a couple granules of sodium

borohydride and stirred at rt. After 90 min, the mixture was treated with 2 drops of 1 M hydrochloric acid and purified by preparative HPLC to provide two diastereomers of 4-(5-((4-fluorophenyl)(hydroxy)methyl)naphthalen-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide. Diastereomer 1 (Example 13-1) was isolated as a white powder (10.4 mg, 31%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.23 (1 H, d, J=8.6 Hz), 7.99 (1 H, d, J=7.7 Hz), 7.48 - 7.61 (3 H, m), 7.36 - 7.46 (3 H, m), 7.31 (1 H, d, J=8.4 Hz), 7.19 (1 H, dd, J=8.4, 7.0 Hz), 7.12 (1 H, d, J=7.7 Hz), 7.02 (2 H, t, J=8.8 Hz), 6.59 (1 H, dd, J=8.1, 1.5 Hz), 6.51 (1 H, s), 6.31 (1 H, d, J=8.1 Hz), 3.68 (2 H, br. s.), 3.35 (2 H, br. s.), 2.43 (2 H, br. s.), 2.28 (2 H, br. s.), 2.23 (3 H, s). Mass spectrum m/z 587.4 $(M+H)^+$. Diastereomer 2 (Example 13-2) was isolated as a white powder (8 mg, 23%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 (1 H, d, J=8.6 Hz), 7.99 (1 H, d, J=7.9 Hz), 7.61 (1 H, d, J=6.8 Hz), 7.59 (1 H, s), 7.49 - 7.56 (1 H, m), 7.43 (1 H, dd, J=6.8, 0.7 Hz), 7.38 (2 H, dd, J=8.5, 5.4 Hz), 7.26 - 7.32 (1 H, m), 7.16 - 7.24 (1 H, m), 7.11 (1 H, d, J=7.7 Hz), 7.00 (2 H, t, J=8.8 Hz), 6.61 (1 H, dd, J=8.1, 1.3 Hz), 6.58 (1 H, s), 6.36 (1 H, d, J=8.1 Hz), 3.68 (2 H, br. s.), 3.35 (2 H, br. s.), 2.43 (2 H, br. s.), 2.28 (2 H, br. s.), 2.22 (3 H, s). Mass spectrum m/z 587.4 $(M+H)^+$.

Example 14-1

Preparation of 5-cyclohexyl-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide

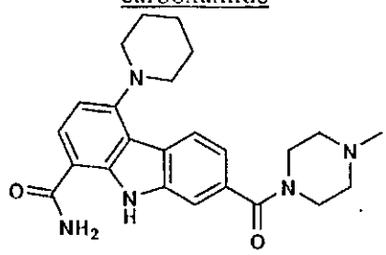


[00351] A solution of 5-cyclohexenyl-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide (Example 3-117, 28 mg, 0.066 mmol) in methanol (10 mL) was combined with 10% palladium on charcoal (80 mg) and shaken under an atmosphere of hydrogen (45 psi) for 1 h. The mixture was filtered, the solid was rinsed with methanol and the filtrates were concentrated to provide 5-cyclohexyl-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide as an off-white solid (28 mg, quantitative). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.46 - 7.50 (1 H, m), 6.91 (1 H, d, *J*=8.05 Hz), 3.89 - 3.98 (3 H, m),

3.46 - 3.54 (2 H, m), 3.13 (1 H, dd, *J*=14.43, 4.16 Hz), 2.95 - 3.06 (2 H, m), 2.87 - 2.94 (1 H, m), 2.65 - 2.73 (1 H, m), 2.15 (1 H, dd, *J*=11.10, 3.05 Hz), 1.77 - 1.99 (8 H, m), 1.47 - 1.61 (6 H, m), 1.26 - 1.40 (2 H, m). Mass spectrum m/z 424.3 $(M+H)^+$.

Example 15-1

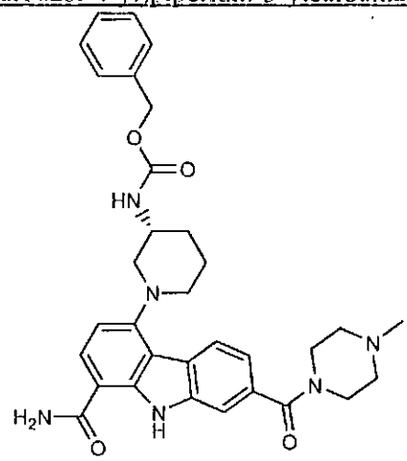
Preparation of 7-(4-methylpiperazine-1-carbonyl)-4-(piperidin-1-yl)-9H-carbazole-1-carboxamide



[00352] A mixture of 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-1, 30 mg, 0.072 mmol) and piperidine (1 mL) was heated overnight via microwave irradiation at 170 °C in a sealed tube. The mixture was cooled to rt and purified by preparative HPLC to provide 7-(4-methylpiperazine-1-carbonyl)-4-(piperidin-1-yl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (22 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1 H) 8.05 (d, J=8.35 Hz, 2 H) 7.95 (d, J=8.13 Hz, 1 H) 7.85 (d, J=1.32 Hz, 1 H) 7.32 (dd, J=8.13, 1.54 Hz, 2 H) 6.82 (d, J=8.35 Hz, 1 H) 3.92 - 4.13 (m, 4 H) 3.21 - 3.57 (m, 6 H) 3.14 (d, J=13.40 Hz, 6 H) 2.84 (s, 3 H) 1.66 (br. s., 2 H). Mass spectrum m/z 420.3 $(M+H)^+$.

Example 16-1

Preparation of (R)-benzyl 1-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)piperidin-3-ylcarbamate



[00353] Step 1 A suspension of ethyl 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylate (Intermediate 48-1, 2.2g, 6.09 mmol) in phosphorus oxychloride (45.4 mL, 487 mmol) was heated at 105 °C for 1 h. The suspension was cooled to rt and concentrated to give a brown solid, which was suspended in water. The precipitate was collected by filtration, washed with water and dried to provide ethyl 5-bromo-8-cyano-9H-carbazole-2-carboxylate (2.05 g, 98%) as light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1 H) 8.71 (d, *J*=8.57 Hz, 1 H) 8.24 (s, 1 H) 7.95 (d, *J*=8.57 Hz, 1 H) 7.89 (d, *J*=8.13 Hz, 1 H) 7.61 (d, *J*=8.13 Hz, 1 H) 4.39 (q, *J*=7.10 Hz, 2 H) 1.37 (t, 2 H). Mass spectrum m/z 360, 362 $(M+NH_4)^+$.

[00354] Step 2 A mixture of cesium carbonate (0.960 g, 2.95 mmol), (RS)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (0.059 g, 0.095 mmol), tris(dibenzylideneacetone)dipalladium (0.058 g, 0.063 mmol), ethyl 5-bromo-8-cyano-9H-carbazole-2-carboxylate (0.85 g, 2.105 mmol) and (R)-benzyl piperidin-3-ylcarbamate (0.493 g, 2.105 mmol) was suspended in 1,4-dioxane (70 mL). The mixture was purged with nitrogen and heated at 100 °C for 18 h. The mixture was cooled to rt and concentrated. The residue was partitioned between EtOAc and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 80:20 to 60:40 hexane-EtOAc) to provide (R)-ethyl 5-(3-(benzyloxycarbonylamino)piperidin-1-yl)-8-cyano-9H-carbazole-2-carboxylate as a brown solid (0.68 g, 70% purity, 37% yield), used without further purification. Mass spectrum m/z 497.2 $(M+H)^+$.

[00355] Step 3 A solution of (R)-ethyl 5-(3-(benzyloxycarbonylamino)piperidin-1-yl)-8-cyano-9H-carbazole-2-carboxylate (0.67 g, 1.349 mmol) and potassium hydroxide (0.379 g, 6.75 mmol) in 10:1 ethanol-water (33 mL) was heated at 85 °C for 2 h. The mixture was cooled to rt and the precipitate was collected by filtration, washed with ethanol and dried to afford (R)-5-(3-(benzyloxycarbonylamino)piperidin-1-yl)-8-cyano-9H-carbazole-2-carboxylic acid as a yellow solid (130 mg, 21%). Mass spectrum m/z 469.1 $(M+H)^+$. (R)-5-(3-aminopiperidin-1-yl)-8-cyano-9H-carbazole-2-carboxylic acid was also isolated from filtrates (150 mg, 33%). Mass spectrum m/z 335.2 $(M+H)^+$.

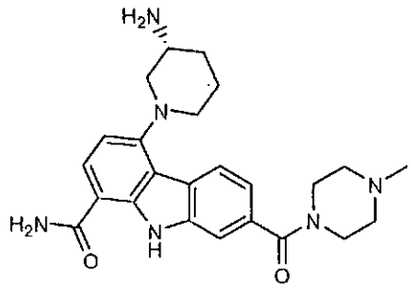
[00356] Step 4 A solution of (R)-5-(3-(benzyloxycarbonylamino)piperidin-1-yl)-8-cyano-9H-carbazole-2-carboxylic acid (130 mg, 0.277 mmol), EDC (74.5 mg, 0.388

mmol), HOBT (59.5 mg, 0.388 mmol), and 1-methylpiperazine (0.092 mL, 0.832 mmol) in THF-DCM-DMF (4:1:1, 6 mL) was stirred at rt over a weekend. The mixture was concentrated and partitioned between EtOAc and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 100:0 to 92.5:7.5 DCM-2 M methanolic ammonia) to provide (R)-benzyl 1-(1-cyano-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)piperidin-3-ylcarbamate as a yellow solid (60 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1 H) 8.09 (d, *J*=8.13 Hz, 1 H) 7.82 (d, *J*=8.35 Hz, 1 H) 7.64 (s, 1 H) 7.49 (d, *J*=7.69 Hz, 1 H) 7.24 - 7.40 (m, 6 H) 6.93 (d, *J*=8.35 Hz, 1 H) 4.87 - 5.11 (m, 2 H) 3.00 - 3.96 (m, 12 H) 2.83 (s, 3 H) 2.55 - 2.70 (m, 1 H) 1.73 - 2.08 (m, 3 H) 1.34 - 1.57 (m, 1 H).). Mass spectrum m/z 551.2 $(M+H)^+$.

[00357] Step 5 A solution of (R)-benzyl 1-(1-cyano-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)piperidin-3-ylcarbamate (108 mg, 0.196 mmol) in DMSO (2 mL) was treated with 22% aqueous potassium hydroxide (0.208 mL, 0.981 mmol), and then dropwise with a solution of 30% aqueous hydrogen peroxide (0.200 mL, 1.961 mmol). The mixture was stirred at rt for 2.5 h. Water was added, the resulting suspension was stirred at rt for 15 min, and the solid was collected by filtration, washed with water and dried to afford (R)-benzyl 1-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)piperidin-3-ylcarbamate as an off-white solid (89 mg, 80%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.17 (d, *J*=8.13 Hz, 1 H) 7.81 (d, *J*=8.35 Hz, 1 H) 7.66 (s, 1 H) 7.30 (d, *J*=7.91 Hz, 1 H) 7.09 - 7.26 (m, 5 H) 6.82 (d, *J*=8.35 Hz, 1 H) 4.90 - 5.03 (m, 2 H) 3.87 - 3.99 (m, 1 H) 3.57 - 3.68 (m, 1 H) 3.27 - 3.54 (m, 5 H) 3.06 - 3.19 (m, 4 H) 2.69 - 2.82 (m, 1 H) 2.47 - 2.65 (m, 1 H) 1.98 - 2.11 (m, 1 H) 1.83 - 1.97 (m, 2 H) 1.32 - 1.53 (m, 1 H). Mass spectrum m/z 569.3 $(M+H)^+$.

Example 17-1

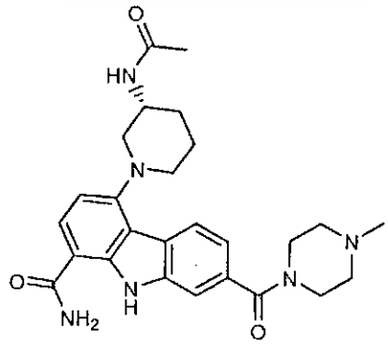
Preparation of (R)-4-(3-aminopiperidin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00358] A mixture of (R)-benzyl 1-(1-carbamoyl-7-(4-methylpiperazine-1-carbonyl)-9H-carbazol-4-yl)piperidin-3-ylcarbamate (Example 16-1, 80 mg, 0.141 mmol), 10% palladium on carbon (14.97 mg, 0.014 mmol) and ammonium formate (53.2 mg, 0.844 mmol) in methanol (8 mL) was flushed with nitrogen and heated at 75 °C for 1 h. The mixture was cooled to rt, diluted with methanol and filtered through a Celite pad. The filtrate was concentrated to provide (R)-4-(3-aminopiperidin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a white solid (75 mg, 98%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.13 (d, *J*=8.13 Hz, 1 H) 7.86 (d, *J*=8.35 Hz, 1 H) 7.68 (s, 1 H) 7.29 (d, *J*=9.67 Hz, 1 H) 6.86 (d, *J*=8.35 Hz, 1 H) 3.54 - 3.72 (m, 2 H) 3.24 - 3.53 (m, 5 H) 2.88 (s, 3 H) 2.11 - 2.29 (m, 1 H) 1.92 - 2.11 (m, 2 H) 1.44 - 1.73 (m, 1 H). Mass spectrum m/z 435.2 $(M+H)^+$.

Example 18-1

Preparation of (R)-4-(3-acetamidopiperidin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00359] A solution of (R)-4-(3-aminopiperidin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 17-1, 25 mg, 0.058 mmol) and TEA (0.016 mL, 0.115 mmol) in DCM-THF (2:1, 3 mL) was treated with acetyl chloride (4.9 µL, 0.069 mmol). The mixture was stirred at rt for 1.5 h, then was then

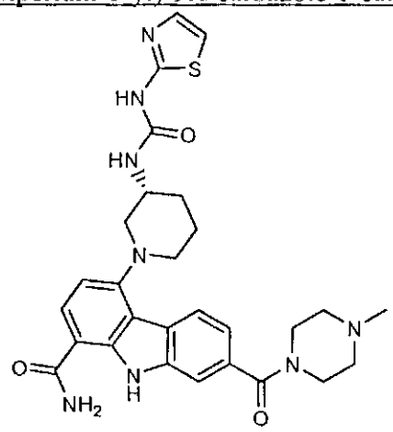
concentrated and the residue was purified by preparative HPLC. The product, isolated as the TFA salt, was partitioned between DCM and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated to provide (R)-4-(3-acetamidopiperidin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a white solid (12 mg, 39%). ^{1}H NMR (500 MHz, ethanol-d_6) δ 8.24 (d, *J*=7.97 Hz, 1 H) 7.89 (d, *J*=8.52 Hz, 1 H) 7.69 (s, 1 H) 7.32 (d, *J*=9.35 Hz, 1 H) 6.90 (d, *J*=8.52 Hz, 1 H) 4.21 - 4.32 (m, 1 H) 3.73 - 3.93 (m, 2 H) 3.42 - 3.72 (m, 5 H) 2.96 - 3.11 (m, 1 H) 2.39 - 2.63 (m, 4 H) 2.35 (s, 3 H) 2.06 - 2.15 (m, 1 H) 1.97 - 2.06 (m, 2 H) 1.95 (s, 3 H) 1.48 – 1.59 (m, 1H). Mass spectrum m/z 477.3 $(M+H)^+$.

[00360] The following compound was also prepared using the procedure demonstrated in Example 18-1, substituting benzoyl chloride for acetyl chloride.

Example	Compound name	Mass spectrum
18-2	(R)-4-(3-benzamidopiperidin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	539.3 $(M+H)^+$

Example 19-1

Preparation of (R)-7-(4-methylpiperazine-1-carbonyl)-4-(3-(3-thiazol-2-ylureido)piperidin-1-yl)-9H-carbazole-1-carboxamide

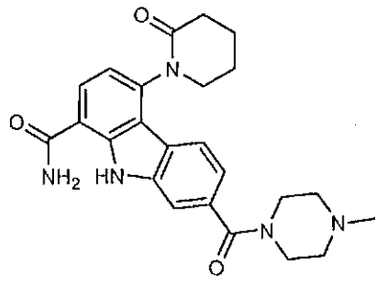


[00361] A solution of (R)-4-(3-aminopiperidin-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 17-1, 23 mg, 0.053 mmol) and TEA (0.015 mL, 0.106 mmol) in THF (3 mL) was treated with phenyl thiazol-2-ylcarbamate (17.49 mg, 0.079 mmol). The mixture was stirred at 60 °C for 1.5 h, then at 70 °C for 2 h, then was concentrated and purified by preparative HPLC. The

isolated TFA salt was partitioned between DCM and NaHCO3 (aq), and the organic phase was dried and concentrated to provide (R)-7-(4-methylpiperazine-1-carbonyl)-4-(3-(3-thiazol-2-ylureido)piperidin-1-yl)-9H-carbazole-1-carboxamide as a white solid (14 mg, 43%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.27 (1 H, d, J=7.9 Hz), 7.87 (1 H, d, J=8.3 Hz), 7.68 (1 H, d, J=1.1 Hz), 7.28 (1 H, d, J=7.9 Hz), 7.18 (1 H, br. s.), 6.93 (1 H, d, J=3.7 Hz), 6.87 (1 H, d, J=8.3 Hz), 4.25 (1 H, br.), 3.82 (2 H, br.), 3.41 - 3.68 (3 H, m), 3.19 (3 H, br.), 2.36 - 2.63 (4 H, m), 2.33 (3H, s), 1.84 - 2.20 (3 H, m), 1.71 (1 H, br. s.). Mass spectrum m/z 561.3 $(M+H)^+$.

Example 20-1

Preparation of 7-(4-methylpiperazine-1-carbonyl)-4-(2-oxopiperidin-1-yl)-9H-carbazole-1-carboxamide



[00362] Step 1 A mixture of 4-bromo-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 1-1, 118.1 mg, 0.284 mmol), sodium azide (37.0 mg, 0.569 mmol), copper (I) iodide (36.4 mg, 0.191 mmol), (RS)-proline (24.6 mg, 0.214 mmol), 1 M aqueous sodium hydroxide (0.191 mL, 0.191 mmol), ethanol (1.5 mL) and water (0.191 mL) was purged with argon and heated at 95 °C in a sealed tube. After 17.5 h, the mixture was cooled to rt, filtered through a pad of silica gel, and the solids were rinsed with methanol. The filtrate was concentrated and treated with 1 M hydrochloric acid, and the resulting precipitate was collected by filtration and dried to provide impure 4-azido-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, hydrochloric acid salt, as a light brown solid (31.8 mg, 27%). The filtrate was purified by preparative HPLC to provide 4-azido-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a brown solid (20.7 mg, 15%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.37 (1 H, d, J=8.14 Hz), 7.97 (1 H, d, J=8.14 Hz), 7.73 (1 H, s), 7.33 (1 H, dd, J=8.14, 1.32 Hz), 7.06 (1 H, d,

J=8.36 Hz), 3.34 - 3.72 (6 H, m), 3.26 (2 H, br. s.), 2.96 (3 H, s). Mass spectrum m/z 378.2 $(M+H)^+$.

[00363] Step 2 A suspension of impure 4-azido-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, hydrochloric acid salt (31.8 mg, 0.060 mmol), ammonium chloride (25 mg, 0.467 mmol) and powdered zinc (60 mg, 0.918 mmol) in methanol (1 mL) and THF (1 mL) was stirred at rt. After 1 h, the mixture was purified by column chromatography (eluting with a gradient from DCM to 80:20 DCM-methanol) to provide 4-amino-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a light yellow solid (11.8 mg, 56%). Mass spectrum m/z 352.3 $(M+H)^+$.

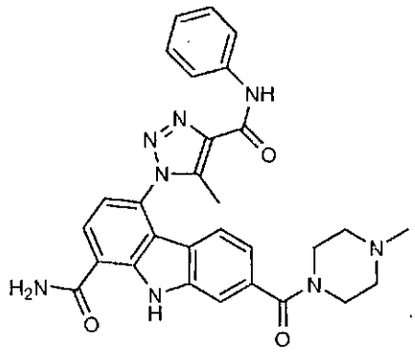
[00364] Step 3 A solution of 4-amino-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (11.8 mg, 0.034 mmol) and TEA (0.047 mL, 0.336 mmol) in DCM (0.5 mL) and DMF (0.25 mL) was treated with 5-chloropentanoyl chloride (0.017 mL, 0.134 mmol) and stirred at rt. Additional 5-chloropentanoyl chloride (0.017 mL, 0.134 mmol) was added after 3 h and the mixture was stirred at rt overnight. The mixture was concentrated and partitioned between EtOAc and saturated aqueous ammonium chloride. The aqueous phase was purified by preparative HPLC to provide 4-(5-chloropentanamido)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a light yellow solid (6.6 mg, 34%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.15 (1 H, d, J=8.14 Hz), 7.96 (1 H, d, J=8.14 Hz), 7.77 (1 H, d, J=0.88 Hz), 7.27 - 7.38 (2 H, m), 3.68 (2 H, br. s.), 3.33 - 3.63 (4 H, m), 3.12 - 3.29 (2 H, m), 2.97 (3 H, s), 2.68 (2 H, br. s.), 1.98 (4 H, br. s.). Mass spectrum m/z 470.4 $(M+H)^+$.

[00365] Step 4 A solution of 4-(5-chloropentanamido)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt (6.6 mg, 0.011 mmol) in DMF (0.5 mL) was treated with sodium hydride (60% oil dispersion, 12.7 mg, 0.318 mmol) and the mixture was stirred at rt for 35 min. The mixture was concentrated, taken up in saturated aqueous ammonium chloride and purified by preparative HPLC to provide 7-(4-methylpiperazine-1-carbonyl)-4-(2-oxopiperidin-1-yl)-9H-carbazole-1-carboxamide, isolated as the TFA salt, as a white powder after lyophilization (4.3 mg, 69%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.03 (1 H, d, J=7.92 Hz), 7.96 (1 H, d, J=8.14 Hz), 7.79 (1 H, d, J=0.88 Hz), 7.36 (1 H, dd, J=8.03, 1.43 Hz), 7.17 (1 H, d, J=7.92 Hz), 3.84 - 3.93 (1 H, m), 3.73 - 3.82 (1 H, m), 3.34 - 3.64 (4 H, m), 3.13 -

3.27 (2 H, m), 2.97 (3 H, s), 2.60 - 2.82 (2 H, m), 2.08 - 2.25 (4 H, m). Mass spectrum m/z 434.4 $(M+H)^+$.

Example 21-1

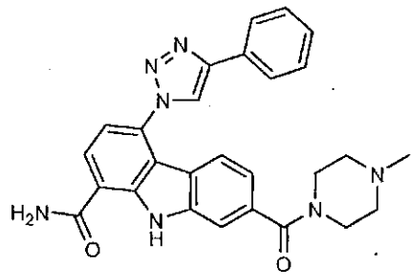
Preparation of 4-(5-methyl-4-(phenylcarbamoyl)-1H-1,2,3-triazol-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00366] A solution of 4-azido-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (free base, prepared from the material prepared according to Step 1 of Example 20-1, 24.1 mg, 0.036 mmol) and 3-oxo-N-phenylbutanamide (17.5 mg, 0.099 mmol) in ethanol (0.5 mL) and THF (0.5 mL) was added at 0 °C to a solution of sodium ethoxide prepared from sodium (6.7 mg, 0.291 mmol) and ethanol (0.5 mL). After 2 h, the mixture was warmed to rt and stirred overnight. The mixture was concentrated and the residue was purified by preparative HPLC to provide 4-(5-methyl-4-(phenylcarbamoyl)-1H-1,2,3-triazol-1-yl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide, TFA salt, as a light yellow powder after lyophilization (2.6 mg, 10%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 (1 H, d, J=7.92 Hz), 7.85 (1 H, s), 7.77 - 7.82 (2 H, m), 7.41 (3 H, t, J=7.70 Hz), 7.17 - 7.23 (2 H, m), 6.75 (1 H, d, J=8.14 Hz), 3.34 - 3.64 (4 H, m), 3.09 - 3.27 (2 H, m), 2.95 (3 H, s), 2.48 (3 H, s). Mass spectrum m/z 537.3 $(M+H)^+$.

Example 22-1

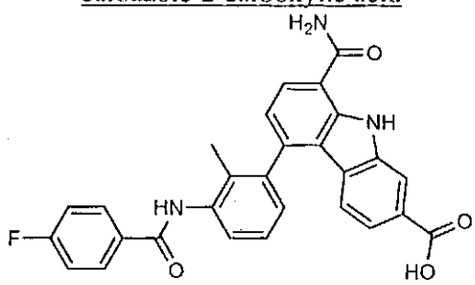
Preparation of 7-(4-methylpiperazine-1-carbonyl)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-carbazole-1-carboxamide



[00367] A solution of 4-azido-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (free base, prepared from the material prepared according to Step 1 of Example 20-1, 10 mg, 0.026 mmol), ethynylbenzene (3.2 μL, 0.029 mmol), copper (II) sulfate (0.42 mg, 0.003 mmol) and sodium L-ascorbate (1.1 mg, 0.005 mmol) in THF (0.5 mL) and water (0.1 mL) was stirred at 45 °C overnight. The reaction was not complete, so the mixture was stirred at 45 °C for 4.5 h, then at 95 °C overnight. The mixture was concentrated, and the residue was dissolved in a mixture of methanol and 1 M hydrochloric acid (2:1), filtered and purified by preparative HPLC and lyophilization to provide 7-(4-methylpiperazine-1-carbonyl)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-carbazole-1-carboxamide, TFA salt, as a white powder (5.2 mg, 33%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.90 (1 H, s), 8.16 (1 H, d, J=7.92 Hz), 8.00 - 8.04 (2 H, m), 7.84 (1 H, s), 7.50 - 7.55 (2 H, m), 7.48 (1 H, d, J=7.92 Hz), 7.40 - 7.46 (1 H, m), 7.36 (1 H, d, J=8.80 Hz), 7.20 (1 H, dd, J=8.25, 1.43 Hz), 3.33 - 3.68 (4 H, m), 3.10 - 3.28 (2 H, m), 2.95 (3 H, s). Mass spectrum m/z 480.3 $(M+H)^+$.

Example 23-1

Preparation of 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxylic acid

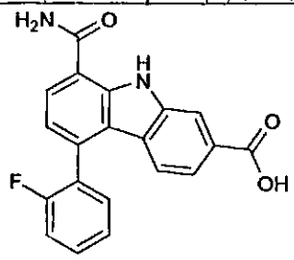


[00368] A suspension of ethyl 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxylate (Intermediate3-100, 1.63 g, 3.20 mmol) in ethanol (12 mL) was treated with 1 M aqueous sodium hydroxide (1.5 mL, 1.500 mmol), forming a yellow suspension which was heated at 90-95 °C for 30 min. The mixture was cooled to rt and acidified with 1 M hydrochloric acid. The precipitate

was collected by filtration, washed with water and dried to provide 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxylic acid as an off-white solid (1.496 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (br. s., 1 H) 11.84 (s, 1 H) 10.15 (s, 1 H) 8.38 (s, 1 H) 8.24 (br. s., 1 H) 8.03 - 8.13 (m, 3 H) 7.56 (br. s., 1 H) 7.46 - 7.54 (m, 2 H) 7.42 (t, J=7.7 Hz, 1 H) 7.35 (t, J=9.0 Hz, 2 H) 7.23 (dd, J=7.5, 1.3 Hz, 1 H) 7.04 (d, J=7.5 Hz, 1 H) 7.01 (d, J=8.3 Hz, 1 H) 1.88 (s, 3 H). Mass spectrum m/z 482.1 $(M+H)^+$.

Example 23-2

Preparation of 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazole-2-carboxylic acid



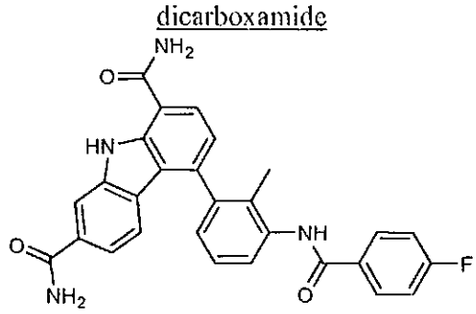
[00369] A suspension of ethyl 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazole-2-carboxylate (Example 3-12, 0.8 g, 2.126 mmol) and lithium hydroxide monohydrate (0.255 g, 6.38 mmol) in THF-ethanol-water (3:1:1) (25.0 mL) was heated at reflux for 4 h. The mixture was concentrated and the residue was suspended in water. The pH was adjusted to 1-2 by addition of 1 M hydrochloric acid. The precipitate was collected by filtration, washed with water and dried to provide 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazole-2-carboxylic acid as a yellow solid (520 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br. s., 1 H) 11.87 (s, 1 H) 8.41 (m, 1 H) 8.26 (br. s., 1 H) 8.08 (d, *J*=7.69 Hz, 1 H) 7.50 - 7.67 (m, 4 H) 7.40 - 7.49 (m, 2 H) 7.09 - 7.17 (m, 2 H). Mass spectrum m/z 349.1 $(M+H)^+$.

[00370] The following compound was also prepared using procedures demonstrated in Example 23-1, using

Intermediate	Starting material	Compound name	Mass spectrum
Intermediate 23-3	Example 3-11	8-carbamoyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylic acid	371.1 $(M+H)^+$

Example 24-1

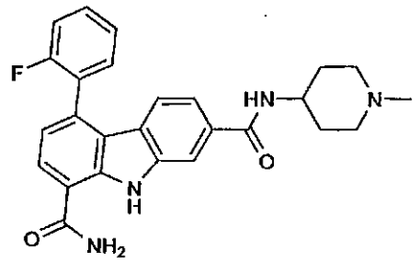
Preparation of 4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1,7-dicarboxamide



[00371] A mixture of 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxylic acid (Example 23-1, 30 mg, 0.062 mmol) and HOAT (12.72 mg, 0.093 mmol) in THF (0.4 mL) was treated with 28% aqueous ammonium hydroxide (0.052 mL, 0.374 mmol) and EDC (23.89 mg, 0.125 mmol) and the mixture was stirred at rt. After 22.5 h, the mixture was concentrated and purified by preparative HPLC. The appropriate effluent fractions were concentrated and the residue was treated with NaHCO3 (aq) and extracted three times with EtOAc. The combined organic phases were dried and concentrated to provide 4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1,7-dicarboxamide as an off-white solid (9.6 mg, 29%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.11 (d, J=1.3 Hz, 1 H) 8.03 - 8.08 (m, 2 H) 8.01 (d, J=7.9 Hz, 1 H) 7.51 - 7.55 (m, 1 H) 7.41 - 7.48 (m, 2 H) 7.29 (dd, J=7.5, 1.3 Hz, 1 H) 7.24 (t, J=8.8 Hz, 2 H) 7.08 - 7.12 (m, 2 H) 1.98 (s, 3 H). Mass spectrum m/z 481.1 $(M+H)^+$.

Example 24-2

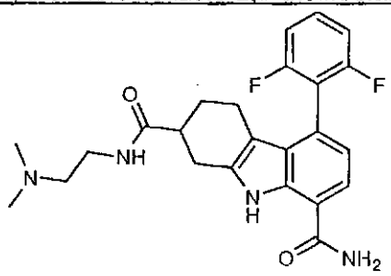
Preparation of 4-(2-fluorophenyl)-N^7-(1-methylpiperidin-4-yl)-9H-carbazole-1,7-dicarboxamide



[00372] A mixture of 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazole-2-carboxylic acid (Example 23-2, 30 mg, 0.086 mmol), EDC (23.11 mg, 0.121 mmol), HOBT (18.46 mg, 0.121 mmol), DIEA (30 μL, 0.172 mmol), and 1-methylpiperidin-4-amine (9.83 mg, 0.086 mmol) in THF and DMF (4:1, 2 mL) was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC. The isolated product was partitioned between DCM and NaHCO3 (aq). The organic phase was dried and concentrated to provide 4-(2-fluorophenyl)-N^7-(1-methylpiperidin-4-yl)-9H-carbazole-1,7-dicarboxamide as a white solid (25 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1 H) 8.24 (br. s., 1 H) 8.20 (s, 1 H) 8.13 (d, *J*=7.69 Hz, 1 H) 8.05 (d, *J*=7.91 Hz, 1 H) 7.52 - 7.68 (m, 3 H) 7.33 - 7.48 (m, 3 H) 7.13 (d, *J*=7.69 Hz, 1 H) 7.05 (d, *J*=8.35 Hz, 1 H) 3.64 - 3.80 (m, 1 H) 2.69 - 2.79 (m, 2 H) 1.87 - 2.00 (m, 2 H) 1.70 - 1.80 (m, 2 H) 1.48 - 1.65 (m, 2 H). Mass spectrum m/z 445.2 $(M+H)^+$.

Example 24-3

Preparation of 5-(2,6-difluorophenyl)-N^2-(2-(dimethylamino)ethyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide



[00373] Using the procedure of Example 24-2, 8-carbamoyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylic acid (Intermediate 23-3, 20 mg, 0.054 mmol) and N^1,N^1-dimethylethane-1,2-diamine (7.1 mg, 0.081 mmol) were converted to 5-(2,6-difluorophenyl)-N^2-(2-(dimethylamino)ethyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide (25 mg, 62%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.08 (1 H, br. s.), 7.35 - 7.39 (2 H, m), 6.99 (3 H, d, J=8.35 Hz), 6.20 (2 H, br. s.), 3.28 - 3.43 (3 H, m), 2.84 - 3.13 (2 H, m), 2.54 - 2.62 (1 H, m), 2.27

- 2.45 (3 H, m), 2.18 (6 H, s), 1.91 - 2.03 (1 H, m), 1.74 - 1.86 (1 H, m). Mass spectrum m/z 441.1 $(M+H)^+$.

[00374] The following compounds were also prepared using procedures demonstrated in Examples 24-1 through 24-3, starting with the appropriate carboxylic acid (prepared according to Examples 23-1 through 23-3) and the appropriate amine.

Example	Starting material	Compound name	Mass spectrum
24-4	Example 23-2	N^7-(2-(dimethylamino)ethyl)-4-(2-fluorophenyl)-N^7-methyl-9H-carbazole-1,7-dicarboxamide	432.9 $(M+H)^+$
24-5	Example 23-2	4-(2-fluorophenyl)-7-(4-(2-methoxyethyl)piperazine-1-carbonyl)-9H-carbazole-1-carboxamide	475.2 $(M+H)^+$
24-6	Example 23-2	4-(2-fluorophenyl)-7-(4-(3-methoxypropyl)piperazine-1-carbonyl)-9H-carbazole-1-carboxamide	489.3 $(M+H)^+$
24-7	Example 23-2	7-(4-(dimethylamino)piperidine-1-carbonyl)-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide	459.2 $(M+H)^+$
24-8	Example 23-2	4-(2-fluorophenyl)-N^7-methyl-N^7-(2-(methylsulfonyl)ethyl)-9H-carbazole-1,7-dicarboxamide	468.1 $(M+H)^+$
24-9	Example 23-2	7-((S)-3-(dimethylamino)pyrrolidine-1-carbonyl)-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide	445.5 $(M+H)^+$
24-10	Example 23-2	7-((R)-3-(dimethylamino)pyrrolidine-1-carbonyl)-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide	445.5 $(M+H)^+$
24-11	Intermediate 23-3	5-(2,6-difluorophenyl)-N^2-(4-(dimethylamino)butyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	469.2 $(M+H)^+$

24-12	Intermediate 23-3	5-(2,6-difluorophenyl)-2-(4-methylpiperazine-1-carbonyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	453.2 $(M+H)^+$
24-13	Intermediate 23-3	5-(2,6-difluorophenyl)-N^2-(3-(dimethylamino)propyl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	455.1 $(M+H)^+$
24-14	Intermediate 23-3	5-(2,6-difluorophenyl)-N^2-(1-methylpiperidin-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	467.2 $(M+H)^+$
24-15	Intermediate 23-3	5-(2,6-difluorophenyl)-N^2-(tetrahydro-2H-pyran-4-yl)-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide	454.2 $(M+H)^+$
24-16	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(2-(1-(RS)-methylpyrrolidin-2-yl)ethyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	592.0 $(M+H)^+$
24-17	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(4-(2-hydroxyethyl)piperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	594.0 $(M+H)^+$
24-18	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(2-morpholinoethyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	594.0 $(M+H)^+$
24-19	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(pyridin-3-ylmethyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	572.0 $(M+H)^+$
24-20	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(pyridin-4-ylmethyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	572.0 $(M+H)^+$

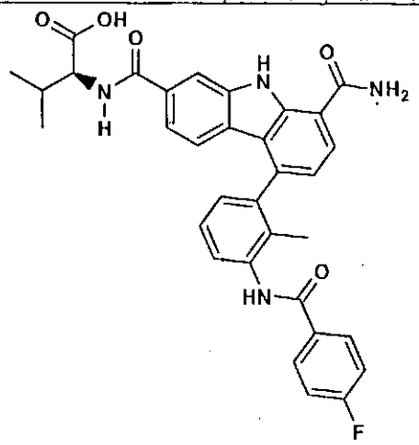
24-21	Example 23-1	N^7-(3-(1H-imidazol-1-yl)propyl)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	589.0 $(M+H)^+$
24-22	Example 23-1	7-(4-(dimethylamino)piperidine-1-carbonyl)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	592.0 $(M+H)^+$
24-23	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-methyl-N^7-(pyridin-3-ylmethyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	586.1 $(M+H)^+$
24-24	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-methyl-N^7-(1-(RS)-methylpyrrolidin-3-yl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	578.0 $(M+H)^+$
24-25	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(2-phenylpropan-2-yl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	599.0 $(M+H)^+$
24-26	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(pyridin-3-yl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	557.9 $(M+H)^+$
24-27	Example 23-1	N^7-(3-(dimethylamino)phenyl)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	600.0 $(M+H)^+$
24-28	Example 23-1	N^7-(2-amino-2-oxoethyl)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	537.9 $(M+H)^+$

24-29	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(4-(hydroxymethyl)piperidine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	580.0 $(M+H)^+$
24-30	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(3-hydroxybenzyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	586.9 $(M+H)^+$
24-31	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-oxopiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	563.9 $(M+H)^+$
24-32	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(thiazol-2-yl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	563.9 $(M+H)^+$
24-33	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(3-methoxyphenyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	586.9 $(M+H)^+$
24-34	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(4-fluorophenyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	575.0 $(M+H)^+$
24-35	Example 23-1	N^7-*tert*-butyl-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	537.0 $(M+H)^+$
24-36	Example 23-1	N^7-benzyl-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	571.0 $(M+H)^+$
24-37	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-methyl-N^7-phenyl-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	571.0 $(M+H)^+$
24-38	Example 23-1	N^7-cyclopropyl-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	520.9 $(M+H)^+$

24-39	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(pyridin-2-yl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	558.0 $(M+H)^+$
24-40	Example 23-1	4-(3-(4-fluorobenzamido)-2-methylphenyl)-N^7-(pyridin-2-ylmethyl)-9H-carbazole-1,7-dicarboxamide (prepared as the TFA salt)	572.1 $(M+H)^+$

Example 25-1

Preparation of (2S)-2-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxamido)-3-methylbutanoic acid



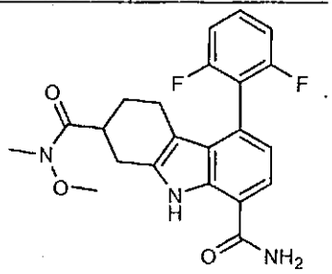
[00375] A mixture of 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxylic acid (Example 23-1, 19.3 mg, 0.04 mmol), EDC (9.6 mg, 0.05 mmol), HOBT (7.7 mg, 0.0.05 mmol),.DIEA (25.8 mg, 0.20 mmol), and (S)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloric acid salt (10.5 mg, 0.05 mmol) in DMF (0.36 mL) was agitated at rt for 21 h. The mixture was concentrated and the residue was agitated in DCM (0.5 mL) and TFA (0.5 mL) for 2 h. The mixture was concentrated and the residue was purified by preparative HPLC to provide (2S)-2-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxamido)-3-methylbutanoic acid, TFA salt (15.3 mg, 55%). Mass spectrum m/z 581.0 $(M+H)^+$.

[00376] The following compounds were also prepared using procedures demonstrated in Example 25-1.

Example	Compound name	Mass spectrum
25-2	(2S,3S)-2-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxamido)-3-methylpentanoic acid (prepared as the TFA salt)	595.0 $(M+H)^+$
25-3	2-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carboxamido)acetic acid (prepared as the TFA salt)	538.9 $(M+H)^+$
25-4	(2R)-1-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carbonyl)pyrrolidine-2-carboxylic acid (prepared as the TFA salt)	579.0 $(M+H)^+$
25-5	(2S)-1-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-2-carbonyl)pyrrolidine-2-carboxylic acid (prepared as the TFA salt)	578.9 $(M+H)^+$

Example 26-1

Preparation of 5-(2,6-difluorophenyl)-N^2-methoxy-N^2-methyl-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide

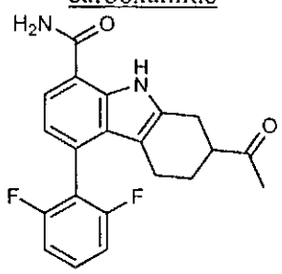


[00377] A solution of 8-carbamoyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylic acid (Intermediate 23-3, 720 mg, 1.944 mmol) and TEA (1.084 mL, 7.78 mmol) in THF (5 mL) was treated with isobutyl chloroformate (266 mg, 1.944 mmol) at 0 °C.After stirring for 10 min, a solution of N,O-dimethylhydroxylamine hydrochloric acid salt (190 mg, 1.944 mmol) in THF (2 mL) and water (0.5 mL) was added. The mixture was stirred for 30 min, then diluted with DCM, washed with NaHCO3 (aq) and water, and dried and concentrated. The residue was purified by column chromatography (eluting with EtOAc) to provide 5-(2,6-difluorophenyl)-N^2-methoxy-N^2-methyl-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide as a white solid (802 mg, 93%). ^{1}H NMR (400 MHz, chloroform-d) δ

1.70 - 1.82 (m, 1 H) 1.90 - 1.99 (m, 1 H) 2.19 - 2.25 (m, 2 H) 2.32 - 2.42 (m, 1 H) 2.84 - 2.92 (m, 1 H) 3.05 - 3.19 (m, 1 H) 3.23 (s, 3 H) 3.70 (s, 3 H) 6.98 - 7.06 (m, 3 H) 7.35 - 7.42 (m, 2 H) 10.10 (s, 1 H). Mass spectrum m/z 414.2 $(M+H)^+$.

Example 27-1

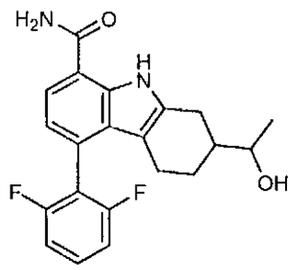
Preparation of 2-acetyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00378] A solution of 5-(2,6-difluorophenyl)-N^2-methoxy-N^2-methyl-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide (Example 26-1, 719 mg, 1.739 mmol) in THF (1 mL) was treated with methylmagnesium bromide (3 M in diethyl ether, 2.90 mL, 8.70 mmol) at 0 °C. After 20 min, additional methylmagnesium bromide (2.90 mL, 8.70 mmol) was added and stirring was continued for 30 min more. The mixture was treated with 1 M hydrochloric acid and extracted four times with DCM. The combined organic phases were washed with water, dried and concentrated. The residue was purified by column chromatography (eluting with hexane-EtOAc) and the resulting material was triturated with DCM to provide 2-acetyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as an off-white solid (210 mg, 33%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.59 (1 H, d, J=7.91 Hz), 7.39 - 7.49 (2 H, m), 7.01 - 7.09 (3 H, m), 6.90 (1 H, d, J=7.91 Hz), 2.86 - 2.97 (3 H, m), 2.24 - 2.33 (1 H, m), 2.22 (3 H, s), 2.01 - 2.18 (2 H, m), 1.54 - 1.66 (1 H, m). Mass spectrum m/z 369.1 $(M+H)^+$.

Examples 28-1 and 28-2

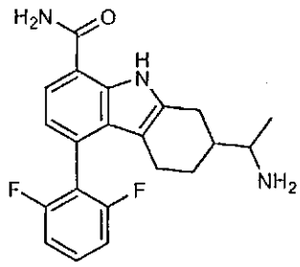
Preparation of two diastereomers of 5-(2,6-difluorophenyl)-2-(1-hydroxyethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00379] A suspension of 2-acetyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Example 27-1, 30 mg, 0.081 mmol) and sodium borohydride (6.2 mg, 0.163 mmol) in methanol (1 mL) was stirred at rt for 1 h. The mixture was diluted with DCM, washed with NaHCO3 (aq) and water, and dried and concentrated. The residue was purified by preparative HPLC to provide two diastereomers of 5-(2,6-difluorophenyl)-2-(1-hydroxyethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide. Each one was partitioned between 1 M aqueous sodium hydroxide and DCM, followed by drying and concentration, to provide the separated racemic diastereomers of 5-(2,6-difluorophenyl)-2-(1-hydroxyethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide. The more polar diastereomer (Example 28-1) was a white solid (10 mg, 33%). ^{1}H NMR (400 MHz, chloroform-d) δ 1.26 (d, J=6.59 Hz, 3 H) 1.30 - 1.43 (m, 1 H) 1.78 - 1.89 (m, 1 H) 1.97 - 2.05 (m, J=12.74 Hz, 1 H) 2.14 - 2.22 (m, 1 H) 2.24 - 2.35 (m, 1 H) 2.57 (dd, J=16.04, 10.77 Hz, 1 H) 2.81 (dd, J=16.48, 5.05 Hz, 1 H) 3.70 - 3.79 (m, 1 H) 6.96 - 7.04 (m, 3 H) 7.32 - 7.41 (m, 2 H) 10.05 (s, 1 H). Mass spectrum m/z 371.1 $(M+H)^+$. The less polar diastereomer (Example 28-2) was a white solid (8 mg, 27%). ^{1}H NMR (400 MHz, chloroform-d) δ 1.26 (d, J=6.15 Hz, 3 H) 1.34 - 1.40 (m, 1 H) 1.42 - 1.53 (m, 1 H) 1.75 - 1.90 (m, 2 H) 2.24 - 2.35 (m, 1 H) 2.68 (dd, J=16.26, 10.11 Hz, 1 H) 2.94 (dd, J=16.26, 5.27 Hz, 1 H) 3.80 (s, 1 H) 6.96 - 7.05 (m, 3 H) 7.34 - 7.40 (m, 2 H) 10.05 (s, 1 H). Mass spectrum m/z 371.1 $(M+H)^+$.

Example 29-1

Preparation of 2-(1-aminoethyl)-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



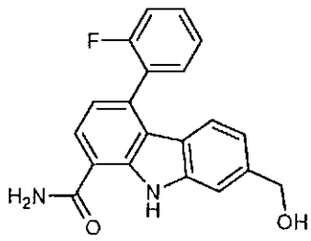
[00380] A suspension of 2-acetyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Example 27-1, 30 mg, 0.081 mmol), ammonium acetate (25.1 mg, 0.326 mmol) and sodium triacetoxyborohydride (25.9 mg, 0.122 mmol) in DCM (1 mL) was heated at 50 °C for 1 h. The mixture was cooled, diluted with DCM, washed with NaHCO3 (aq) and water, and dried and concentrated. The residue was purified by preparative HPLC, and the appropriate effluent fractions were made basic with 1 M aqueous sodium hydroxide and extracted twice with DCM. The combined organic phases were washed with water, dried and concentrated to provide a mixture of diastereomers of 2-(1-aminoethyl)-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a white solid (20 mg, 67%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.59 (1 H, d, J=7.47 Hz), 7.39 - 7.49 (1 H, m), 7.01 - 7.09 (2 H, m), 6.89 (1 H, d), 2.78 - 2.94 (2 H, m), 2.46 - 2.61 (1 H, m), 2.06 - 2.28 (2 H, m), 1.77 - 1.94 (1 H, m), 1.62 - 1.74 (1 H, m), 1.26 - 1.40 (1 H, m), 1.13 (3 H, d, J=6.59 Hz). Mass spectrum m/z 370.1 $(M+H)^+$.

[00381] The following compounds were also prepared using procedures demonstrated in Example 29-1, using the appropriate amine in place of ammonium acetate.

Example	Compound name	Mass spectrum
29-2	5-(2,6-difluorophenyl)-2-(1-(1-methylpiperidin-4-ylamino)ethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as a mixture of diastereomers)	467.2 $(M+H)^+$
29-3	5-(2,6-difluorophenyl)-2-(1-morpholinoethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as a mixture of diastereomers)	440.2 $(M+H)^+$

Example 30-1

Preparation of 4-(2-fluorophenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide



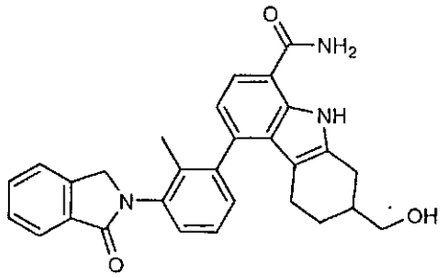
[00382] A solution of ethyl 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazole-2-carboxylate (Example 3-12, 0.81g, 2.152 mmol) in THF (26.9 mL) at 0 °C was treated with lithium aluminum hydride (1.0 M in THF, 3.01 mL, 3.01 mmol), and the mixture was stirred at rt for 5 h. Additional lithium aluminum hydride (1.3 mL, 1.3 mmol) was added and the mixture was stirred at rt overnight. The mixture was treated with methanol and TFA and diluted with EtOAc, washed with brine, dried and concentrated to provide impure 4-(2-fluorophenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (0.78 g) contaminated with starting material. A small amount was purified by preparative HPLC to provide 4-(2-fluorophenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide, isolated as the TFA salt. ^{1}H NMR (500 MHz, methanol-d_4) δ 7.82 (1 H, d, J=7.8 Hz), 7.51 (1 H, s), 7.44 - 7.50 (1 H, m), 7.42 (1 H, td, J=7.5, 1.9 Hz), 7.25 - 7.30 (1 H, m), 7.22 (1 H, t, J=9.2 Hz), 7.05 (1 H, d, J=8.3 Hz), 6.99 (1 H, d, J=7.8 Hz), 6.85 (1 H, dd, J=8.0, 1.4 Hz), 4.62 (2 H, s). Mass spectrum m/z 334.9 $(M+H)^+$.

[00383] The following Examples/Intermediates were also prepared using procedures demonstrated in Example 30-1.

Example/ Intermediates	Starting material	Compound name	Mass spectrum
30-2	Intermediate 48-1	4-bromo-7-(hydroxymethyl)-9H-carbazole-1-carboxamide	319, 321 $(M+H)^+$
Intermediate 30-3(a)	Intermediate 47-1	5-bromo-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	323, 325 $(M+H)^+$

Example 31-1

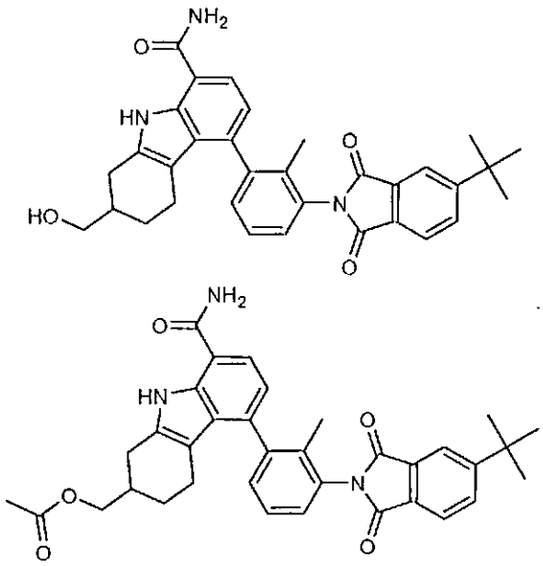
Preparation of 2-(hydroxymethyl)-5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00384] A mixture of 5-bromo-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Intermediate 30-3(a), 80 mg, 0.248 mmol), 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-4, 130 mg, 0.371 mmol), 2 M aqueous tripotassium phosphate (0.371 mL, 0.743 mmol), and tetrakis(triphenylphosphine)palladium (14.30 mg, 0.012 mmol) in toluene (3 mL) and ethanol (1 mL) was sealed in a vial and heated at 100 °C for 6 hrs. The mixture was cooled and diluted with EtOAc, and the solution was washed with water, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from DCM to 96:3.6:0.4 DCM-methanol-28% aqueous ammonium hydroxide) to provide 2-(hydroxymethyl)-5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a light yellow solid (68 mg, 53%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.79 (1 H, d, J=7.91 Hz), 7.46 - 7.53 (1 H, m), 7.38 - 7.44 (2 H, m), 7.30 (1 H, dd, J=7.91, 3.08 Hz), 7.14 - 7.26 (3 H, m), 6.77 (1 H, dd, J=7.69, 2.86 Hz), 4.59 - 4.74 (2 H, m), 3.39 - 3.54 (3 H, m), 2.72 - 2.80 (2 H, m), 2.30 - 2.44 (2 H, m), 1.80 - 2.10 (3 H, m), 1.75 (3 H, d, J=8.35 Hz). Mass spectrum m/z 466.1 $(M+H)^+$.

Examples 31-2 and 31-3

Preparation of 5-(3-(5-*tert*-butyl-1,3-dioxoisoindolin-2-yl)-2-methylphenyl)-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide and (5-(3-(5-*tert*-butyl-1,3-dioxoisoindolin-2-yl)-2-methylphenyl)-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)mEtOAc

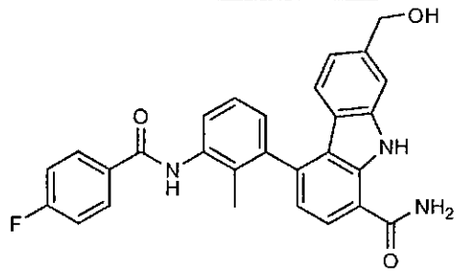


[00385] A mixture of 5-bromo-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Intermediate 30-3(a), 50 mg, 0.155 mmol), 5-*tert*-butyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindoline-1,3-dione (Intermediate 50-11, 97 mg, 0.232 mmol), 2 M aqueous tripotassium phosphate (0.232 mL, 0.464 mmol), and tetrakis(triphenylphosphine)palladium (8.9 mg, 7.7 μmol) in toluene (3 mL) and ethanol (1 mL) was heated at 100 °C in a sealed tube overnight. The mixture was cooled to rt, treated with 1 M hydrochloric acid, extracted with EtOAc, and the organic phase was dried and concentrated to provide 5-*tert*-butyl-2-(3-(8-carbamoyl-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazol-5-yl)-2-methylphenylcarbamoyl)benzoic acid (Mass spectrum m/z 554.4 $(M+H)^+$). Without purification, this material was dissolved in acetic acid (4 mL) and heated at 100 °C for 2 h, then was concentrated. The residue was purified by column chromatography (eluting with a gradient from DCM to 90:9:1 DCM-methanol-28% aqueous ammonium hydroxide), followed by purification by preparative HPLC. The appropriate effluent fractions were made basic with NaHCO3 (aq) and extracted with DCM, dried and concentrated to provide 5-(3-(5-*tert*-butyl-1,3-dioxoisoindolin-2-yl)-2-methylphenyl)-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Example 31-2) as a light yellow solid (18 mg, 18%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.05 (1 H, s), 7.98 - 8.02 (1 H, m), 7.86 - 7.91 (1 H, m), 7.79 - 7.84 (1 H, m), 7.33 - 7.45 (4 H, m), 7.24 - 7.28 (2 H, m), 6.89 - 6.94 (1 H, m), 3.56 - 3.71 (2 H, m), 2.91 (1 H, dd, J=16.70, 4.83 Hz), 2.48 - 2.61 (1 H, m), 1.99 - 2.10 (2 H, m), 1.88 - 1.99 (2 H, m), 1.86 (3 H, s), 1.43 - 1.55 (2 H, m), 1.41 (9 H, s). Mass spectrum

m/z 536.3 $(M+H)^+$. Also obtained was (5-(3-(5-*tert*-butyl-1,3-dioxoisoindolin-2-yl)-2-methylphenyl)-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)mEtOAc (Example 31-3) as a light yellow solid (15 mg, 14%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.05 (1 H, s), 7.97 - 8.05 (1 H, m), 7.86 - 7.91 (1 H, m), 7.79 - 7.84 (1 H, m), 7.33 - 7.41 (3 H, m), 7.26 - 7.28 (1 H, m), 4.00 - 4.13 (2 H, m), 2.90 (2 H, td, J=10.88, 5.05 Hz), 2.46 - 2.71 (2 H, m), 2.12 - 2.34 (2 H, m), 2.08 (4 H, s), 1.87 (3 H, d, J=7.03 Hz), 1.45 - 1.54 (1 H, m), 1.41 (9 H, s). Mass spectrum m/z 578.3 $(M+H)^+$.

Example 31-4

Preparation of 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide



[00386] Using the procedure of Example 3-2, 4-bromo-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (Example 30-2, 800 mg, 2.51 mmol) and 4-fluoro-N-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzamide (Intermediate 53-1, 979 mg, 2.76 mmol) were converted to 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (550 mg, 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (1 H, s), 10.15 (1 H, s), 8.21 (1 H, br. s.), 8.05 - 8.15 (2 H, m), 7.99 (1 H, d, J=7.9 Hz), 7.70 (1 H, s), 7.46 - 7.57 (2 H, m), 7.32 - 7.46 (3 H, m), 7.22 (1 H, dd, J=7.6, 1.0 Hz), 6.97 (1 H, d, J=7.7 Hz), 6.80 - 6.93 (2 H, m), 5.18 (1 H, t, J=5.7 Hz), 4.58 (2 H, d, J=5.5 Hz), 1.90 (3 H, s). Mass spectrum m/z 466.3 $(M-H)^-$.

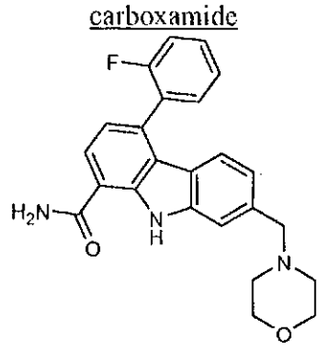
[00387] The following compounds were also prepared using procedures demonstrated in Examples 31-1 through 31-4, from the starting materials indicated.

Example	Starting materials	Compound name	Mass spectrum
31-5	Intermediate 30-3(a), Intermediate 50-15	5-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	522.3 $(M+H)^+$
31-6	Intermediate 30-3(a), Intermediate 50-14	5-(3-(6-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	522.3 $(M+H)^+$
31-7	Intermediate 30-3(a), Intermediate 50-19	5-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(hydroxymethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	484.2 $(M+H)^+$
31-8	Intermediate 30-3(a), Intermediate 50-18	2-(hydroxymethyl)-5-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	480.2 $(M+H)^+$
31-9	Example 30-2, Intermediate 50-24	7-(hydroxymethyl)-4-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	475.0 $(M+H)^+$
31-10	Example 30-2, Intermediate 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide	493.0 $(M+H)^+$
31-11	Example 30-2, Intermediate 50-8	7-(hydroxymethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	458.0 $(M+H-H_2O)^+$
31-12	Example 30-2, Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide	462.1 $(M+H-H_2O)^+$

31-13	Example 30-2, Intermediate 50-38	7-(hydroxymethyl)-4-(2-methyl-3-(4-oxo-6-(trifluoromethoxy)quinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	541.0 $(M+H-H_2O)^+$
31-14	Example 30-2, Intermediate 50-48	4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide	475.1 $(M+H-H_2O)^+$
31-15	Example 30-2, Intermediate 50-54	7-(hydroxymethyl)-4-(2-methyl-3-(quinazolin-4-ylamino)phenyl)-9H-carbazole-1-carboxamide	474.0 $(M+H)^+$
31-16	Example 30-2, Intermediate 50-55	4-(3-(5-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide	492.1 $(M+H)^+$
31-17	Example 30-2, Intermediate 50-56	4-(3-(7-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide	492.1 $(M+H)^+$
31-18	Example 30-2, Intermediate 50-57	4-(3-(8-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide	492.1 $(M+H)^+$

Example 32-1

Preparation of 4-(2-fluorophenyl)-7-(morpholinomethyl)-9H-carbazole-1-carboxamide



[00388] A solution of 4-(2-fluorophenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (Example 30-1, 223 mg, 0.667 mmol) and TEA (0.279 mL, 2.001 mmol) in THF (8 mL) was treated with methanesulfonyl chloride (0.104 mL, 1.334 mmol). The resulting suspension was stirred at rt for 15 min. The mixture was diluted with EtOAc, washed with water and brine, and dried and concentrated to provide crude (8-

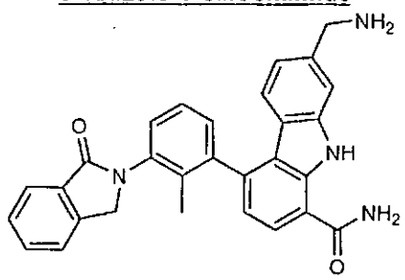
carbamoyl-5-(2-fluorophenyl)-9H-carbazol-2-yl)methyl methanesulfonate as a yellow glassy foam (300 mg, ca. 50% purity). A portion of this material (80 mg, 0.097 mmol) was dissolved in DMF (1 mL), treated with morpholine (84 mg, 0.970 mmol) and heated at 45 °C for 3 days. The mixture was purified by preparative HPLC to provide 4-(2-fluorophenyl)-7-(morpholinomethyl)-9H-carbazole-1-carboxamide (9.6 mg, 23%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.94 (1 H, d, J=7.8 Hz), 7.59 (1 H, s), 7.52 - 7.58 (1 H, m), 7.48 - 7.52 (1 H, m), 7.33 - 7.39 (1 H, m), 7.30 (1 H, t, J=9.0 Hz), 7.21 (1 H, d, J=8.3 Hz), 7.14 (1 H, d, J=7.8 Hz), 6.99 (1 H, dd, J=8.3, 1.5 Hz), 3.81 (2 H, s), 3.71 - 3.77 (4 H, m), 2.66 (4 H, br. s.). Mass spectrum m/z 404.2 $(M+H)^+$.

[00389] The following compounds were also prepared using procedures demonstrated in Example 32-1, using the appropriate amine in place of morpholine.

Example	Compound name	Mass spectrum
32-2	4-(2-fluorophenyl)-7-((4-methylpiperazin-1-yl)methyl)-9H-carbazole-1-carboxamide	417.2 $(M+H)^+$
32-3	4-(2-fluorophenyl)-7-(piperidin-1-ylmethyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	402.2 $(M+H)^+$

Example 33-1

Preparation of 7-(aminomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00390] Step 1 A suspension of 4-bromo-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (Example 30-2, 300 mg, 0.940 mmol) and TEA (0.262 mL, 1.880 mmol) in THF (9.4 mL) was treated dropwise with methanesulfonyl chloride (0.077 mL, 0.987 mmol) and the mixture was stirred at rt for 1 hr. It was treated with NaHCO3 (aq) and extracted with EtOAc. The organic phase was washed with brine, dried and concentrated to provide crude (5-bromo-8-carbamoyl-9H-carbazol-2-yl)methyl methanesulfonate as a light yellow solid (390 mg, 89%). This material was suspended

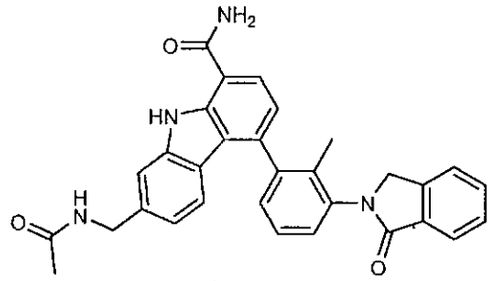
in DMF (8.3 mL) and treated with sodium azide (271 mg, 4.17 mmol). After being stirred overnight at rt, the mixture was diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried and concentrated to provide crude 7-(azidomethyl)-4-bromo-9H-carbazole-1-carboxamide as a light yellow solid (350 mg, 97%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (1 H, s), 8.62 (1 H, d, J=8.4 Hz), 8.22 (1 H, br. s.), 7.88 (1 H, d, J=8.1 Hz), 7.83 (1 H, s), 7.58 (1 H, br. s.), 7.46 (1 H, d, J=8.4 Hz), 7.28 (1 H, dd, J=8.1, 1.5 Hz), 4.63 (2 H, s).

[00391] Step 2 A mixture of 7-(azidomethyl)-4-bromo-9H-carbazole-1-carboxamide (350 mg, 0.814 mmol), triphenylphosphine (427 mg, 1.627 mmol), and water (18 µL, 0.976 mmol) in THF (10 mL) was heated at 70 °C for 3.5 h. The mixture was cooled to rt and partitioned between EtOAc and 1 M hydrochloric acid. The pH of the aqueous phase was raised to 8-9 with sodium hydroxide pellets, and then was extracted with EtOAc. The organic phase was dried and concentrated to provide crude 7-(aminomethyl)-4-bromo-9H-carbazole-1-carboxamide as a yellow glassy foam (320 mg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (1 H, br.), 8.47 - 8.55 (1 H, m), 8.19 (1 H, br. s.), 7.81 - 7.84 (1 H, m), 7.76 (1 H, s), 7.63 - 7.66 (1 H, m), 7.53 - 7.59 (2 H, m), 7.41 (1 H, d, J=8.1 Hz), 7.27 (1 H, dd, J=8.4, 1.3 Hz), 3.90 (2 H, s).

[00392] Step 3 Using the procedure of Example 3-2, crude 7-(aminomethyl)-4-bromo-9H-carbazole-1-carboxamide (320 mg, 0.;805 mmol) and Intermediate 50-4 (309 mg, 0.885 mmol) were converted into crude 7-(aminomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a light yellow solid (ca. 50% pure, 570 mg, 77%). A small amount was purified by preparative HPLC to provide the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (1 H, s), 8.11 (3 H, br.), 7.98 (1 H, d, J=7.9 Hz), 7.68 - 7.74 (2 H, m), 7.62 (2 H, d, J=4.0 Hz), 7.57 (1 H, dd, J=7.9, 1.1 Hz), 7.51 (1 H, dd, J=7.8, 3.6 Hz), 7.44 (2 H, t, J=7.6 Hz), 7.27 (1 H, dd, J=7.6, 1.0 Hz), 6.96 - 7.08 (3 H, m), 4.78 - 5.00 (2 H, m), 4.06 (2 H, d, J=5.3 Hz), 1.76 (3 H, s). Mass spectrum m/z 483.2 $(M+Na)^+$.

Example 34-1

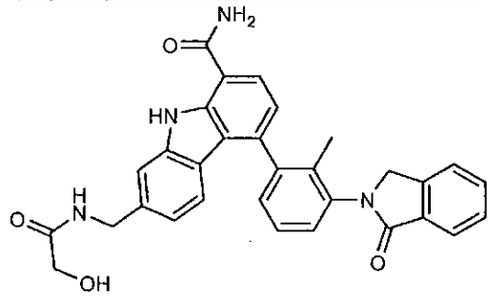
Preparation of 7-(acetamidomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00393] A solution of crude 7-(aminomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 33-1, 60 mg, 0.065 mmol) and TEA (23 µL, 0.163 mmol) in THF (1.3 mL) was treated with acetic anhydride (7.4 µL, 0.078 mmol) and the mixture was stirred at rt overnight. The mixture was concentrated and the residue was purified by preparative HPLC. The appropriate effluent fractions were concentrated and the residue was partitioned between NaHCO3 (aq) and EtOAc. The organic phase was washed with brine, dried and concentrated to provide 7-(acetamidomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as an off-white solid (12 mg, 36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (1 H, s), 8.29 - 8.45 (1 H, m), 8.18 (1 H, br. s.), 8.01 (1 H, d, J=7.9 Hz), 7.81 (1 H, d, J=7.5 Hz), 7.69 (2 H, d, J=4.0 Hz), 7.60 - 7.65 (2 H, m), 7.57 (1 H, ddd, J=7.9, 4.2, 4.0 Hz), 7.50 (2 H, t, J=7.8 Hz), 7.34 (1 H, dd, J=7.7, 1.1 Hz), 6.94 - 7.06 (2 H, m), 6.87 (1 H, dd, J=8.3, 1.4 Hz), 4.90 - 5.04 (2 H, m), 4.35 (2 H, t, J=5.2 Hz), 1.89 (3 H, s), 1.84 (3 H, s). Mass spectrum m/z 503.2 $(M+H)^+$.

Example 34-2

Preparation of 7-((2-hydroxyacetamido)methyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00394] A solution of crude 7-(aminomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 33-1, 25 mg, 0.054 mmol), glycolic acid (8.26 mg, 0.109 mmol), HOAT (13.30 mg, 0.098 mmol), and EDC (20.81 mg, 0.109 mmol) in acetonitrile-THF (2:1) (5 mL) was treated with DIEA

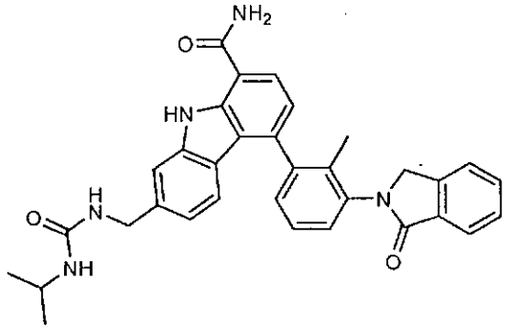
(0.028 mL, 0.163 mmol) and stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC. The appropriate effluent fractions were concentrated to afford an aqueous suspension, which was treated with NaHCO3 (aq). The precipitate was collected by filtration, washed with water and dried to provide 7-((2-hydroxyacetamido)methyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (17 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (1 H, s), 8.22 - 8.28 (1 H, m), 8.17 (1 H, br. s.), 7.97 - 8.05 (1 H, m), 7.81 (1 H, d, J=7.5 Hz), 7.69 (2 H, d, J=3.7 Hz), 7.54 - 7.66 (3 H, m), 7.42 - 7.54 (2 H, m), 7.28 - 7.38 (1 H, m), 7.03 (1 H, d, J=7.9 Hz), 6.94 - 7.00 (1 H, m), 6.86 - 6.94 (1 H, m), 5.45 (1H, br.), 4.88 - 5.05 (2 H, m), 4.33 - 4.48 (2 H, m), 3.88 (2 H, s), 1.83 (3 H, s). Mass spectrum m/z 519.2 $(M+H)^+$.

[00395] The following compounds were also prepared using procedures demonstrated in Example 34-1, using appropriate acid anhydrides or acid chlorides.

Example	Compound name	Mass spectrum
34-3	4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-(pivalamidomethyl)-9H-carbazole-1-carboxamide	545.3 $(M+H)^+$
34-4	7-(isobutyramidomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	531.3 $(M+H)^+$

Example 35-1

Preparation of 7-((3-isopropylureido)methyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide

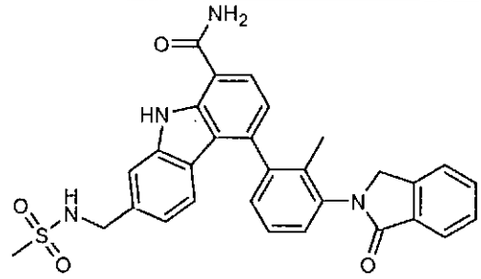


[00396] A solution of 7-(aminomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 33-1, 30 mg, 0.065 mmol) and 2-isocyanatopropane (0.019 mL, 0.195 mmol) in THF (3 mL) was stirred at 40 °C overnight. The mixture was concentrated and purified by preparative HPLC. The

appropriate effluent fractions were concentrated and partitioned between EtOAc and NaHCO3 (aq). The organic phase was dried and concentrated to provide 7-((3-isopropylureido)methyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a white solid (5.8 mg, 14%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.84 (1 H, d, J=7.7 Hz), 7.77 (1 H, d, J=7.5 Hz), 7.53 - 7.63 (2 H, m), 7.38 - 7.51 (4 H, m), 7.30 (1 H, dd, J=7.2, 1.7 Hz), 6.93 - 6.99 (2 H, m), 6.85 (1 H, dd, J=8.3, 1.4 Hz), 4.79 - 4.91 (2 H, m), 4.33 (2 H, s), 3.69 - 3.78 (1 H, m), 1.79 (3 H, s), 1.03 (6 H, d, J=6.4 Hz). Mass spectrum m/z 546.3 $(M+H)^+$.

Example 36-1

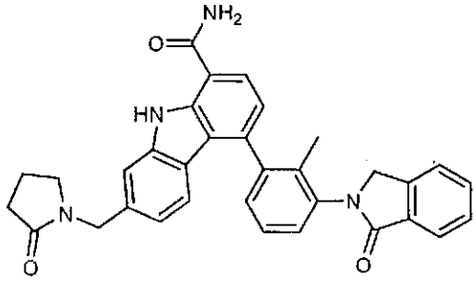
Preparation of 4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-(methylsulfonamidomethyl)-9H-carbazole-1-carboxamide



[00397] A solution of 7-(aminomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 33-1, 60 mg, 0.065 mmol) and TEA (23 μL, 0.163 mmol) in THF (1.3 mL) was treated with methanesulfonyl chloride (5.6 μL, 0.072 mmol) and the mixture was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC. The appropriate effluent fractions were concentrated and partitioned between EtOAc and NaHCO3 (aq). The organic phase was dried and concentrated, and the residue was purified further by column chromatography (eluting with a gradient from 40:60 hexane-EtOAc to EtOAc) to provide 4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-(methylsulfonamidomethyl)-9H-carbazole-1-carboxamide as an off-white solid (7 mg, 18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (1 H, s), 8.19 (1 H, br. s.), 8.02 (1 H, d, J=7.7 Hz), 7.81 (1 H, d, J=7.7 Hz), 7.73 (1 H, s), 7.69 (2 H, d, J=3.7 Hz), 7.61 - 7.65 (1 H, m), 7.54 - 7.61 (2 H, m), 7.51 (2 H, t, J=7.7 Hz), 7.35 (1 H, dd, J=7.5, 1.1 Hz), 7.00 - 7.08 (2 H, m), 6.93 - 6.99 (1 H, m), 4.88 - 5.05 (2 H, m), 4.26 (2 H, d, J=5.9 Hz), 2.87 (3 H, s), 1.84 (3 H, s). Mass spectrum m/z 539.2 $(M+H)^+$.

Example 37-1

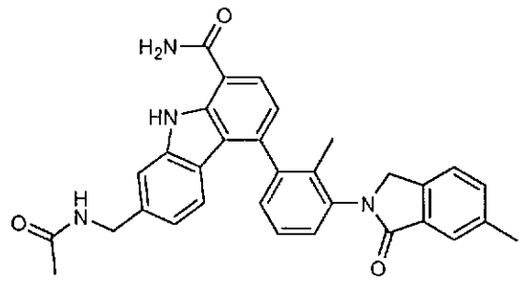
Preparation of 4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-((2-oxopyrrolidin-1-yl)methyl)-9H-carbazole-1-carboxamide



[00398] A solution of 7-(aminomethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 33-1, 80 mg, 0.087 mmol) in THF (3 mL) was treated with DIEA (0.030 mL, 0.174 mmol) and a solution of 4-bromobutanoyl chloride (10 μL, 0.087 mmol) in DCM (1 mL) and the mixture was stirred at rt for 35 min. The reaction mixture was diluted with EtOAc, washed with NaHCO3 (aq) and brine, and dried and concentrated. The residue was dissolved in THF (6 mL) and treated with sodium hydride (60% oil dispersion, 24.32 mg, 0.608 mmol). The resulting mixture was stirred at 50 °C for 2 h, then was diluted with water and extracted with EtOAc. The organic phase was dried and concentrated, and the residue was purified by preparative HPLC to provide 4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-((2-oxopyrrolidin-1-yl)methyl)-9H-carbazole-1-carboxamide as a white solid (2 mg, 3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (1 H, s), 8.11 (1 H, br. s.), 7.95 (1 H, d, J=7.9 Hz), 7.73 (1 H, d, J=7.5 Hz), 7.62 (2 H, d, J=3.7 Hz), 7.46 - 7.57 (3 H, m), 7.42 (2 H, t, J=7.7 Hz), 7.23 - 7.29 (1 H, m), 6.90 - 6.99 (2 H, m), 6.74 (1 H, dd, J=8.1, 1.5 Hz), 4.79 - 5.00 (2 H, m), 4.25 - 4.51 (2 H, m), 3.11 - 3.22 (2 H, m), 2.19 - 2.29 (2 H, m), 1.80 - 1.93 (2 H, m), 1.77 (3 H, s). Mass spectrum m/z 529.2 $(M+H)^+$.

Example 38-1

Preparation of 7-(acetamidomethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00399] Step 1 A suspension of 7-(aminomethyl)-4-bromo-9H-carbazole-1-carboxamide (prepared according to Step 2 of Example 33-1, 168 mg, 0.528 mmol) and TEA (0.184 mL, 1.320 mmol) in THF (18 mL) was treated with acetic anhydride (0.080 mL, 0.845 mmol). The mixture was stirred at rt for 2 h, then was partitioned between EtOAc and 1 M hydrochloric acid. The organic phase was washed with NaHCO3 (aq) and brine, dried and concentrated to provide 7-(acetamidomethyl)-4-bromo-9H-carbazole-1-carboxamide as an off-white solid. Mass spectrum m/z 359.9 $(M+H)^+$.

[00400] Step 2 Using the procedure of Example 3-2, 7-(acetamidomethyl)-4-bromo-9H-carbazole-1-carboxamide (25 mg, 0.069 mmol) and Intermediate 50-8 (30.3 mg, 0.083 mmol) were converted to 7-(acetamidomethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide, obtained as a white solid (19 mg, 52%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (1 H, s), 8.36 (1 H, t, J=5.8 Hz), 8.18 (1 H, br. s.), 8.01 (1 H, d, J=7.7 Hz), 7.54 - 7.66 (4 H, m), 7.49 (3 H, t, J=7.6 Hz), 7.33 (1 H, dd, J=7.7, 1.1 Hz), 6.93 - 7.07 (2 H, m), 6.87 (1 H, dd, J=8.1, 1.3 Hz), 4.83 - 4.99 (2 H, m), 4.27 - 4.43 (2 H, m), 2.44 (3 H, s), 1.89 (3 H, s), 1.83 (3 H, s). Mass spectrum m/z 517.2 $(M+H)^+$.

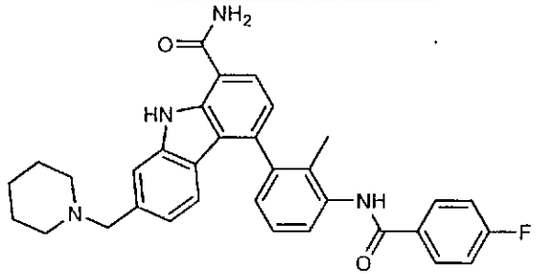
[00401] The following compounds were also prepared using procedures demonstrated in Example 38-1 and similar procedures, using the starting material shown in place of Intermediate 50-8.

Example	Starting material	Compound name	Mass spectrum
38-2	Intermediate 50-5	7-(acetamidomethyl)-4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	521.2 $(M+H)^+$

38-3	Intermediate 50-27	7-(acetamidomethyl)-4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	534.1 $(M+H)^+$
38-4	Intermediate 50-24	7-(acetamidomethyl)-4-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	516.1 $(M+H)^+$
38-5	Intermediate 50-48	7-(acetamidomethyl)-4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	534.1 $(M+H)^+$
38-6	Intermediate 50-51	7-(acetamidomethyl)-4-(3-(8-methoxy-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	546.1 $(M+H)^+$

Example 39-1

Preparation of 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(piperidin-1-ylmethyl)-9H-carbazole-1-carboxamide



[00402] Step 1 A solution of 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (Example 31-4, 0.54 g, 1.155 mmol) in THF (38.5 mL) was treated with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin periodinane, 0.784 g, 1.848 mmol) at rt and the mixture was stirred for 2 h. The mixture was partitioned between NaHCO3 (aq) and EtOAc. The organic phase was washed with brine, dried and concentrated. The residue was triturated with methanol and the solid was collected by filtration and dried to provide 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-formyl-9H-carbazole-1-carboxamide as an orange solid (458 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (1 H, s), 10.16 (1 H, s), 10.03 (1 H, s), 8.23 - 8.32 (2 H, m), 8.05 - 8.14 (3 H, m), 7.60 (1 H, br. s.), 7.49 - 7.55 (1 H, m), 7.39 - 7.49 (2 H, m), 7.32 - 7.39 (2 H, m),

7.21 - 7.27 (1 H, m), 7.09 (2 H, t, J=8.1 Hz), 1.88 (3 H, s). Mass spectrum m/z 466.3 $(M+H)^+$.

[00403] Step 2 A suspension of 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-formyl-9H-carbazole-1-carboxamide (30 mg, 0.064 mmol) in THF (3 mL) was treated with piperidine (16.46 mg, 0.193 mmol) and sodium triacetoxyborohydride (34.1 mg, 0.161 mmol). The mixture was stirred at rt for 3.5 h, the was treated again with additional piperidine (16.5 mg, 0.193 mmol) and sodium triacetoxyborohydride (20 mg). After stirring overnight, the mixture was diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried and concentrated. The residue was purified by preparative HPLC to provide 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(piperidin-1-ylmethyl)-9H-carbazole-1-carboxamide (14 mg, 39%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.06 (2 H, dd, J=8.7, 5.4 Hz), 7.98 (1 H, d, J=7.8 Hz), 7.63 (1 H, s), 7.52 (1 H, d, J=7.3 Hz), 7.44 (1 H, t, J=7.8 Hz), 7.18 - 7.31 (3 H, m), 7.07 (2 H, d, J=7.5 Hz), 6.96 - 7.02 (1 H, m), 3.96 (2 H, s), 2.72 - 2.88 (4 H, m), 1.99 (3 H, s), 1.63 - 1.75 (4 H, m), 1.48 - 1.60 (2 H, m). Mass spectrum m/z 535.2 $(M+H)^+$.

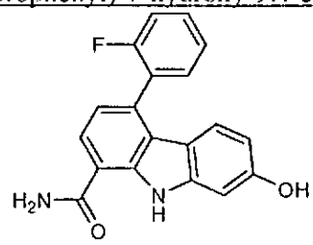
[00404] The following compounds were also prepared using procedures demonstrated in Example 39-1, using the appropriate amine in place of piperidine.

Example	Compound name	Mass spectrum
39-2	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(morpholinomethyl)-9H-carbazole-1-carboxamide	537.1 $(M+H)^+$
39-3	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-((4-methylpiperazin-1-yl)methyl)-9H-carbazole-1-carboxamide	550.1 $(M+H)^+$
39-4	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(pyrrolidin-1-ylmethyl)-9H-carbazole-1-carboxamide	521.1 $(M+H)^+$
39-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-((2-hydroxyethylamino)methyl)-9H-carbazole-1-carboxamide	511.0 $(M+H)^+$
39-6	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-((2-methoxyethylamino)methyl)-9H-carbazole-1-carboxamide	525.1 $(M+H)^+$
39-7	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(((RS)-3-hydroxypyrrolidin-1-yl)methyl)-9H-carbazole-1-carboxamide	537.1 $(M+H)^+$

39-8	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(((2-hydroxyethyl)(methyl)amino)methyl)-9H-carbazole-1-carboxamide	524.9 $(M+H)^+$
39-9	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(((RS)-2-(hydroxymethyl)morpholino)methyl)-9H-carbazole-1-carboxamide	567.2 $(M+H)^+$
39-10	7-(cyclobutylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	507.3 $(M+H)^+$
39-11	7-(cyclopentylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	520.9 $(M+H)^+$
39-12	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(neopentylamino)-9H-carbazole-1-carboxamide	522.9 $(M+H)^+$
39-13	7-(cyclopropylmethylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	506.8 $(M+H)^+$
39-14	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(tetrahydro-2H-pyran-4-ylamino)-9H-carbazole-1-carboxamide	536.8 $(M+H)^+$
39-15	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-((1-methyl-1H-imidazol-2-yl)methylamino)-9H-carbazole-1-carboxamide	546.8 $(M+H)^+$
39-16	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-((1-methylpiperidin-4-yl)methylamino)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	563.9 $(M+H)^+$
39-17	7-(cyclopentylmethylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	534.9 $(M+H)^+$
39-18	7-(cyclohexylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	534.9 $(M+H)^+$

Example 40-1

Preparation of 4-(2-fluorophenyl)-7-hydroxy-9H-carbazole-1-carboxamide



[00405] Step 1 A solution of 4-(2-fluorophenyl)-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (Example 30-1, 147 mg, 0.440 mmol) in DCM (3 mL), acetonitrile (5 mL) and THF (3 mL) was treated with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin periodinane, 373 mg, 0.879 mmol). After 30 min at rt, the mixture was diluted with EtOAc (30 mL), washed twice with 1 M aqueous sodium sulfite and brine, dried and concentrated to give 4-(2-fluorophenyl)-7-formyl-9H-carbazole-1-carboxamide as a tan solid (ca. 80% purity, 163 mg, 87%), used without purification. Mass spectrum m/z 333.1 $(M+H)^+$.

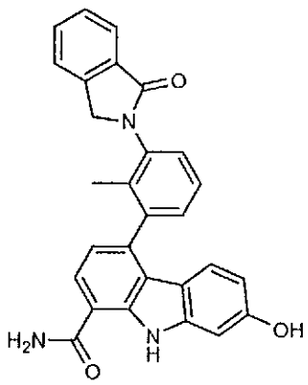
[00406] Step 2 A solution of crude 4-(2-fluorophenyl)-7-formyl-9H-carbazole-1-carboxamide (25.2 mg, 0.076 mmol) in methanol (2 mL) at 0 °C was treated with 30% aqueous hydrogen peroxide (0.039 mL, 0.379 mmol) and sulfuric acid (0.020 mL, 0.379 mmol). After 1.5 h, additional hydrogen peroxide (0.100 mL) and sulfuric acid (0.050 mL) were added and the mixture was stirred at rt overnight. After 16 h, 1 M aqueous sodium hydroxide (2 mL) was added and the mixture was stirred for 1 h. The pH was adjusted to ca. 4 and the organic solvent was removed under vacuum. The aqueous residue was diluted with water and the precipitate was collected by filtration, washed with water and dried. The residue was purified by preparative HPLC to provide 4-(2-fluorophenyl)-7-hydroxy-9H-carbazole-1-carboxamide as tan solid after lyopholization (5.1 mg, 21%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.81 (1 H, d, *J*=7.70 Hz), 7.45 - 7.64 (2 H, m), 7.21 - 7.42 (2 H, m), 7.03 (1 H, d, *J*=7.92 Hz), 6.90 - 6.99 (2 H, m), 6.45 (1 H, dd, *J*=8.58, 2.20 Hz). Mass spectrum m/z 321.0 $(M+H)^+$.

[00407] The following compound was also prepared using the procedures demonstrated in Example 40-1, substituting Example 31-11 in place of Example 30-1 as starting material:

Example	Compound name	Mass spectrum
40-2	7-hydroxy-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	462.0 $(M+H)^+$

Example 41-1

Preparation of 7-hydroxy-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00408] Step 1 A partial solution of 4-bromo-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (Example 30-2, 1.00 g, 3.13 mmol) in THF (75 mL) was stirred at rt and treated with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin periodinane, 1.993 g, 4.70 mmol). After 45 min, the solution was diluted with EtOAc and washed with 5% aqueous sodium sulfite, NaHCO3 (aq), and brine, then was dried and concentrated. The residue was triturated with methanol, and the precipitate was collected by filtration, washed with methanol and dried to provide 4-bromo-7-formyl-9H-carbazole-1-carboxamide as a tan powder (ca. 85% purity, 948 mg, 81%) used without purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (1 H, s), 10.14 (1 H, s), 8.80 (1 H, d, J=8.1 Hz), 8.38 (1 H, d, J=0.9 Hz), 8.28 (1 H, br. s.), 7.97 (1 H, d, J=8.1 Hz), 7.83 (1 H, dd, J=8.3, 1.4 Hz), 7.64 (1 H, br. s.), 7.54 (1 H, d, J=8.1 Hz). Mass spectrum m/z 317, 319 $(M+H)^+$.

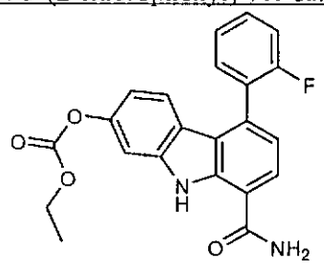
[00409] Step 2 Using the procedure of Example 3-2, 4-bromo-7-formyl-9H-carbazole-1-carboxamide (75 mg, 0.236 mmol) and 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-4, 83 mg, 0.236 mmol) were converted to 7-formyl-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a gray-green powder (ca. 90% purity, 97 mg, 89%), used without further purification. Mass spectrum m/z 460.2 $(M+H)^+$.

[00410] Step 3 A suspension of 7-formyl-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (30 mg, 0.052 mmol) in methanol (1 mL) was treated with sulfuric acid (4.2 µL, 0.078 mmol) followed by 30% aqueous hydrogen peroxide (0.032 mL, 0.313 mmol), and stirred at rt for 23 h, The mixture was treated with 1 M aqueous sodium hydroxide (200 µL) and stirred for 1 h. The mixture was diluted with water and the precipitate was collected by filtration, washed with water and dried. The residue was purified by preparative HPLC to provide 7-

hydroxy-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a tan powder (3.6 mg, 15%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.90 (1 H, d, J=7.5 Hz), 7.86 (1 H, d, J=7.9 Hz), 7.65 - 7.76 (2 H, m), 7.48 - 7.63 (3 H, m), 7.42 (1 H, d, J=6.6 Hz), 7.03 (1 H, d, J=7.9 Hz), 6.98 (1 H, s), 6.92 (1 H, d, J=8.8 Hz), 6.54 (1 H, d, J=9.0 Hz), 4.97 (2 H, s), 1.94 (3 H, s). Mass spectrum m/z 448.1 $(M+H)^+$.

Example 42-1

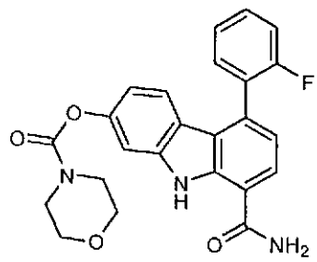
Preparation of 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazol-2-yl ethyl carbonate



[00411] Ethyl chloroformate (8.19 mg, 0.075 mmol) was added to a solution of 4-(2-fluorophenyl)-7-hydroxy-9H-carbazole-1-carboxamide (Example 40-1, 18.6 mg, 0.058 mmol) in pyridine (1 mL). After 17 h, additional ethyl chloroformate (8.19 mg, 0.075 mmol) was added. After 5 h more, additional ethyl chloroformate (0.05 mL) was added. After 15 h more, the mixture was diluted with EtOAc (30 mL), washed with water (10 mL) and brine (5 mL), dried and concentrated. The residue was purified by preparative HPLC to provide 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazol-2-yl ethyl carbonate as a white solid (7.0 mg, 28%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.44 (1 H, br. s.), 7.62 (1 H, dd, J=7.92, 1.98 Hz), 7.41 - 7.57 (2 H, m), 7.20 - 7.40 (4 H, m), 7.16 (1 H, dd, J=7.81, 1.65 Hz), 6.79 - 6.92 (1 H, m), 6.60 (2 H, br. s.), 4.34 (2 H, q, J=7.26 Hz), 1.41 (3 H, t, J=7.15 Hz). Mass spectrum m/z 393.0 $(M+H)^+$.

Example 43-1

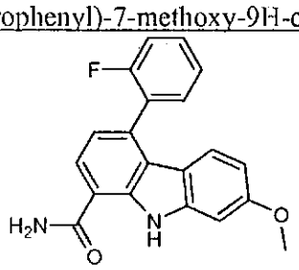
Preparation of 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazol-2-yl morpholine-4-carboxylate



[00412] Morpholine-4-carbonyl chloride (11.29 mg, 0.075 mmol) was added to a solution of 4-(2-fluorophenyl)-7-hydroxy-9H-carbazole-1-carboxamide (Example 40-1, 18.6 mg, 0.058 mmol) in pyridine (1 mL). After 22 h at rt, additional morpholine-4-carbonyl chloride (11.29 mg, 0.075 mmol) was added. After 15 h, the mixture was diluted with EtOAc (30 mL), washed with water (10 mL) and brine (5 mL), and dried and concentrated. The residue was purified by preparative HPLC to provide 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazol-2-yl morpholine-4-carboxylate as a white solid (7.9 mg, 27%). ^{1}H NMR (400 MHz, chloroform-d) δ 9.94 (1 H, br. s.), 7.41 - 7.65 (3 H, m), 7.33 (2 H, t, J=8.14 Hz), 7.20 (1 H, d, J=8.58 Hz), 6.92 - 7.15 (4 H, m), 6.73 (1 H, dd, J=8.58, 1.98 Hz), 3.80 (4 H, t, J=4.62 Hz), 3.67 - 3.76 (2 H, m), 3.62 (2 H, br. s.). Mass spectrum m/z 434.0 $(M+H)^+$.

Example 44-1

Preparation of 4-(2-fluorophenyl)-7-methoxy-9H-carbazole-1-carboxamide

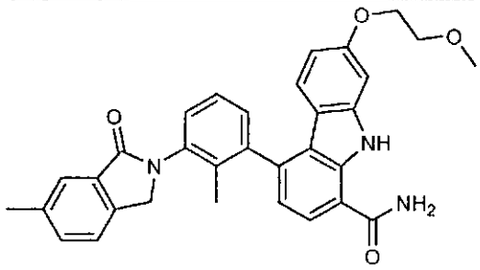


[00413] Potassium carbonate (25.1 mg, 0.182 mmol) and iodomethane (4.9 µL, 0.079 mmol) were added to a solution of 4-(2-fluorophenyl)-7-hydroxy-9H-carbazole-1-carboxamide (Example 40-1, 19.4 mg, 0.061 mmol) in DMSO (1 mL) and the mixture was stirred at rt. After 17 h, the mixture was diluted with EtOAc (30 mL), washed with saturated aqueous ammonium chloride (5 mL), water (2x5 mL), and brine (5 mL), dried and concentrated. The residue was purified by preparative HPLC to provide 4-(2-fluorophenyl)-7-methoxy-9H-carbazole-1-carboxamide (1.9 mg, 9%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.39 (1 H, br. s.), 7.58 (1 H, d, J=7.70 Hz), 7.44 - 7.55 (2 H, m), 7.28 - 7.39 (2 H, m), 7.07 - 7.22 (2 H, m), 7.00 (1 H, d, J=2.20

Hz), 6.65 (1 H, dd, J=8.80, 2.42 Hz), 6.57 (2 H, br. s.), 3.88 (3 H, s). Mass spectrum m/z 335.0 $(M+H)^+$.

Example 44-2

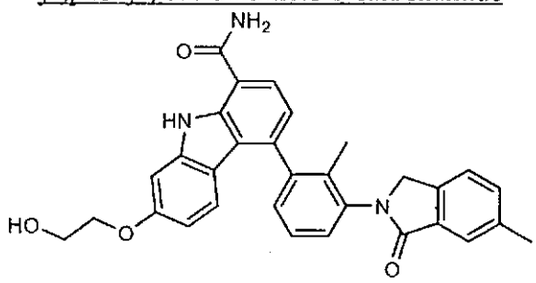
Preparation of 7-(2-methoxyethoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00414] A mixture of 7-hydroxy-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 40-2, 30 mg, 0.065 mmol) and potassium carbonate (18 mg, 0.130 mmol) in DMF (1.0 mL) was stirred at rt for 30 min, then was treated with 1-bromo-2-methoxyethane (14 mg, 0.098 mmol). The mixture was heated at 90 °C for 4 h, cooled to rt and concentrated under vacuum. The residue was purified by preparative HPLC to provide 7-(2-methoxyethoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a white solid (12.5 mg, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (1 H, s), 8.17 (1 H, br. s.), 7.95 (1 H, d, J=7.9 Hz), 7.54 - 7.64 (3 H, m), 7.49 (3 H, t, J=8.0 Hz), 7.27 - 7.38 (2 H, m), 7.00 (1 H, d, J=7.9 Hz), 6.91 (1 H, d, J=8.8 Hz), 6.59 (1 H, dd, J=8.8, 2.4 Hz), 4.91 (2 H, d, J=3.3 Hz), 4.12 (2 H, dd, J=5.5, 3.1 Hz), 3.63 - 3.75 (2 H, m), 3.33 (3 H, s), 2.44 (3 H, s), 1.83 (3 H, s). Mass spectrum m/z 520.1 $(M+H)^+$.

Example 44-3

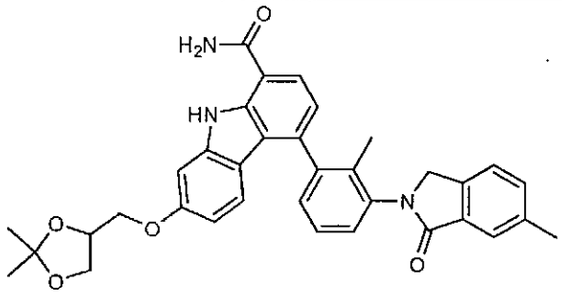
Preparation of 7-(2-hydroxyethoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00415] A mixture of 7-hydroxy-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 40-2, 30 mg, 0.065 mmol) and potassium carbonate (36 mg, 0.260 mmol) in DMF (1.0 mL) was stirred at rt for 30 min, then was treated with (2-bromoethoxy)(*tert*-butyl)dimethylsilane (62.2 mg, 0.260 mmol) and heated at 90 °C for 4 h. The mixture was filtered, the filtrate was treated with hydrogen chloride (4 M in dioxane, 1 mL) and the solution was stirred at rt overnight. The solution was concentrated under vacuum and the residue was purified by preparative HPLC to provide 7-(2-hydroxyethoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as an off-white solid (16.5 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (1 H, s), 8.17 (1 H, br. s.), 7.94 (1 H, d, J=7.9 Hz), 7.53 - 7.65 (3 H, m), 7.49 (3 H, t, J=7.8 Hz), 7.27 - 7.39 (2 H, m), 6.99 (1 H, d, J=7.7 Hz), 6.92 (1 H, d, J=8.8 Hz), 6.59 (1 H, dd, J=8.8, 2.4 Hz), 4.75 - 4.98 (3 H, m), 3.95 - 4.07 (2 H, m), 3.69 - 3.80 (2 H, m), 2.44 (3 H, s). Mass spectrum m/z 506.0 $(M+H)^+$.

Example 44-4

Preparation of racemic 7-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide

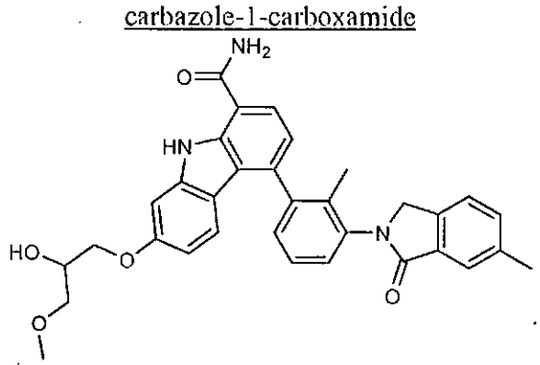


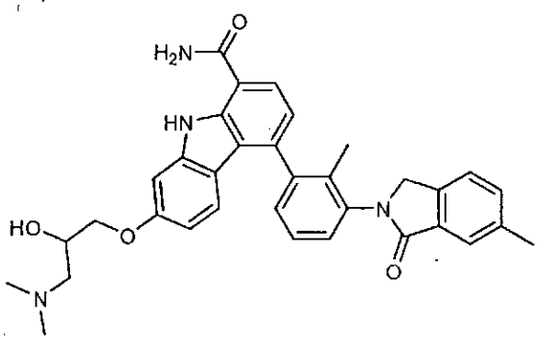
[00416] A mixture of 7-hydroxy-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 40-2, 50 mg, 0.108 mmol) and potassium carbonate (30 mg, 0.217 mmol) in DMF (1.7 mL) was stirred at rt for 30 min, then was treated with racemic (4,4-dimethyl-1,3-dioxolan-2-yl)methyl 4-methylbenzenesulfonate (46.5 mg, 0.163 mmol). The resulting mixture was heated at 80 °C overnight. The mixture was cooled to rt, diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 50:50 to 80:20 EtOAc-hexane) to provide racemic 7-((2,2-dimethyl-1,3-dioxolan-4-

yl)methoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a light yellow solid (30 mg, 48%). Mass spectrum m/z 576.1 $(M+H)^+$.

Examples 44-5 and 44-6

Preparation of 7-(2-hydroxy-3-methoxypropoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide and 7-(3-(dimethylamino)-2-hydroxypropoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide





[00417] A mixture of 7-hydroxy-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 40-2, 30 mg, 0.065 mmol) and potassium carbonate (36 mg, 0.260 mmol) in DMF (1.0 mL) was stirred at rt for 30 min, then was treated with 2-(bromomethyl)oxirane (27 mg, 0.195 mmol). The resulting mixture was heated at 90 °C for 3.5 h, cooled to rt and filtered. The filtrate was treated with methanol, stirred at rt for 2 h, then was then heated at 90 °C for 1 h. The mixture was concentrated under vacuum and purified by preparative HPLC to provide 7-(2-hydroxy-3-methoxypropoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 44-5, 4.7 mg, 13%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.83 (1 H, d, J=7.9 Hz), 7.72 (1 H, d, J=0.7 Hz), 7.46 - 7.52 (4 H, m), 7.38 - 7.45 (1 H, m), 7.04 - 7.12 (2 H, m), 6.99 (1 H, d, J=8.8 Hz), 6.70 (1 H, dd, J=8.7, 2.3 Hz), 4.86 (2 H, d, J=1.8 Hz), 4.03 - 4.22 (3 H, m), 3.53 - 3.65 (2 H, m), 3.42 (3 H, s), 2.50 (3 H, s), 1.93 (3 H, s). Mass spectrum m/z 550.1 $(M+H)^+$.

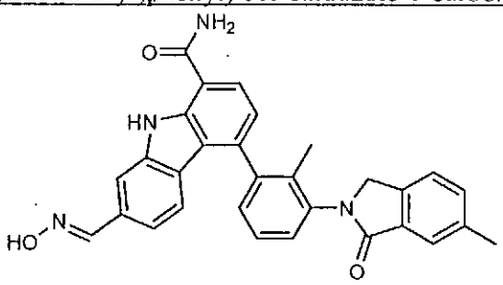
Also isolated was 7-(3-(dimethylamino)-2-hydroxypropoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 44-6, 2.0 mg, 5%). Mass spectrum m/z 563.1 $(M+H)^+$.

[00418] The following compounds were also prepared using the procedures demonstrated in Example 44-2:

Example	Compound name	Mass spectrum
44-7	7-(2-fluoroethoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	508.1 $(M+H)^+$
44-8	7-(2-hydroxypropoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	520.1 $(M+H)^+$

Example 45-1

Preparation of (E)-7-((hydroxyimino)methyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



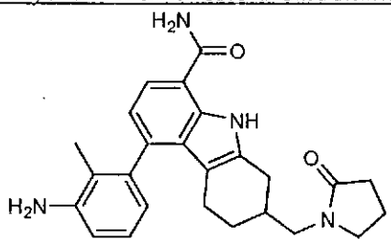
[00419] Step 1 A mixture of 4-bromo-7-formyl-9H-carbazole-1-carboxamide (prepared according to Step 1 of Example 41-1, 200 mg, 0.631 mmol) and hydroxylamine hydrochloric acid salt (65.7 mg, 0.946 mmol) in ethanol (3 mL) was treated with 2 M aqueous sodium carbonate (0.236 mL, 0.473 mmol) and heated at 80-90 °C. After 17.5 h, the mixture was cooled to rt and partitioned between EtOAc and water. The organic phase was dried and concentrated, and the residue was triturated with methanol, and the precipitate was collected by filtration, rinsed with methanol and dried to provide (E)-4-bromo-7-((hydroxyimino)methyl)-9H-carbazole-1-carboxamide as a gray-tan solid (110 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (1 H, s), 11.33 (1 H, s), 8.65 (1 H, d, J=8.4 Hz), 8.32 (1 H, s), 8.28 (1 H, br. s.), 8.09 (1 H, s), 7.92 (1 H, d, J=8.1 Hz), 7.64 (1 H, br. s.), 7.58 (1 H, d, J=8.6 Hz), 7.51 (1 H, d, J=8.1 Hz). Mass spectrum m/z 332, 334 $(M+H)^+$.

[00420] Step 2 Using the procedure of Example 3-2, (E)-4-bromo-7-((hydroxyimino)methyl)-9H-carbazole-1-carboxamide (82 mg, 0.247 mmol) and 6-

methyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-8, 90 mg, 0.247 mmol) were converted to (E)-7-((hydroxyimino)methyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a pale pink solid (52 mg, 40%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 (1 H, s), 8.00 (1 H, d, J=7.7 Hz), 7.82 (1 H, s), 7.70 (1 H, s), 7.49 - 7.59 (4 H, m), 7.43 (1 H, dd, J=6.7, 2.1 Hz), 7.31 (1 H, dd, J=8.3, 1.2 Hz), 7.11 (2 H, d, J=7.7 Hz), 4.92 (2 H, s), 2.50 (3 H, s), 1.92 (3 H, s). Mass spectrum m/z 489.3 $(M+H)^+$.

Example 46-1

Preparation of 5-(3-amino-2-methylphenyl)-2-((2-oxopyrrolidin-1-yl)methyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00421] Step 1 A solution of 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylic acid (Intermediate 49-3, 2 g, 5.93 mmol) and TEA (2.067 mL, 14.83 mmol) in THF (20 mL) was treated with isobutyl chloroformate (0.810 g, 5.93 mmol) at 0 °C. The mixture was stirred for 10 min, then was treated with a solution of N,O-dimethylhydroxylamine hydrochloric acid salt (0.579 g, 5.93 mmol) in THF (2 mL) and water (1 mL). The mixture was stirred at 0 °C for 1 h, then was diluted with DCM, washed with NaHCO3 (aq) and water, dried and concentrated. The residue was triturated with DCM to provide 5-bromo-N^2-methoxy-N^2-methyl-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide as a light yellow solid (1.73 g, 77%). Mass spectrum m/z 380, 382 $(M+H)^+$.

[00422] Step 2 A suspension of 5-bromo-N^2-methoxy-N^2-methyl-2,3,4,9-tetrahydro-1H-carbazole-2,8-dicarboxamide (1.73 g, 4.55 mmol) in THF (40 mL) was treated with lithium aluminum hydride (0.259 g, 6.82 mmol) portionwise over 30 min at 0 °C. After 20 min, more lithium aluminum hydride (120 mg) was added portionwise, and the mixture was stirred at rt for 20 min. The reaction mixture was cooled to 0 °C and treated dropwise with 0.5 M hydrochloric acid, and the resulting mixture was extracted three times with DCM. The combined organic phases were

washed with NaHCO3 (aq) and water, dried and concentrated to provide 5-bromo-2-formyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a yellow solid (1.31 g, 90%), used without further purification. Mass spectrum m/z 321, 323 $(M+H)^+$.

[00423] Step 3 A solution of crude 5-bromo-2-formyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (1 g, 3.11 mmol) in DCM (20 mL) was treated with ammonium acetate (3.60 g, 46.7 mmol) and sodium triacetoxyborohydride (0.990 g, 4.67 mmol) at rt and stirred for 10 min. THF (2 mL) was added to try to dissolve the starting material, but no reaction was observed after 1 h. The mixture was concentrated and the residue was dissolved in DMSO (10 mL). Additional sodium triacetoxyborohydride (500 mg) was added and the mixture was stirred at rt overnight. The mixture was diluted with water and the precipitate was removed by filtration. The filtrate was treated with 1 M aqueous sodium hydroxide and extracted three times with EtOAc. The combined organic phases were washed with water, dried and concentrated to provide 2-(aminomethyl)-5-bromo-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a white solid (130 mg, 13%), used without further purification. Mass spectrum m/z 322, 324 $(M+H)^+$.

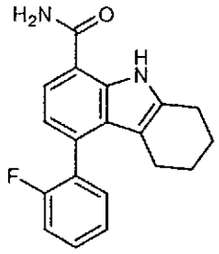
[00424] Step 4 A suspension of 2-(aminomethyl)-5-bromo-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (130 mg, 0.403 mmol) and TEA (0.067 mL, 0.484 mmol) in THF (2 mL) was treated with 4-bromobutanoyl chloride (74.8 mg, 0.403 mmol). The mixture was stirred at rt for 20 min, diluted with DCM, washed with NaHCO3 (aq), dried and concentrated. The residue was purified by column chromatography (eluting with EtOAc) to provide 5-bromo-2-((4-bromobutanamido)methyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a white solid (80 mg, 42%). Mass spectrum m/z 470, 472, 474 $(M+H)^+$.

[00425] Step 5 A solution of 5-bromo-2-((4-bromobutanamido)methyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (80 mg, 0.170 mmol) in DMF (1 mL) was treated with NaH (60% in mineral oil, pre-washed with hexane, 34 mg, 0.849 mmol). The mixture was stirred at rt for 30 min, the was diluted with water and extracted three times with DCM. The combined organic phases were dried and concentrated, and the residue was purified by column chromatography (eluting with 5% aqueous ammonium hydroxide-methanol-DCM) to provide 5-bromo-2-((2-oxopyrrolidin-1-yl)methyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a light yellow solid, used without further purification (40 mg, 60%). Mass spectrum m/z 390, 392 $(M+H)^+$.

[00426] Step 6 Using the procedure of Example 3-2, 5-bromo-2-((2-oxopyrrolidin-1-yl)methyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (40 mg, 0.102 mmol) and Intermediate 50-1 (22.5 mg, 0.102 mmol) were converted into 5-(3-amino-2-methylphenyl)-2-((2-oxopyrrolidin-1-yl)methyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a white solid (2 mg, 5%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.51 - 7.56 (1 H, m), 6.94 - 7.01 (1 H, m), 6.72 - 6.81 (2 H, m), 6.57 (1 H, t, *J*=6.59 Hz), 3.44 - 3.53 (2 H, m), 3.28 - 3.32 (7 H, m), 2.84 (1 H, dd, *J*=16.70, 4.83 Hz), 2.36 - 2.50 (3 H, m), 2.11 - 2.22 (1 H, m), 1.96 - 2.10 (4 H, m), 1.77 - 1.85 (3 H, m), 1.65 (1 H, sxt), 1.20 - 1.37 (2 H, m). Mass spectrum m/z 417.3 $(M+H)^+$.

Example 47-1

Preparation of 5-(2-fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00427] Step 1 A mixture of methyl 2-amino-4-bromobenzoate (3.06 g, 13.3 mmol), 2-fluorophenylboronic acid (2.23 g, 16.0 mmol), tetrakis(triphenylphosphine)palladium (1.54 g, 1.33 mmol) and 1 M aqueous sodium carbonate (16.6 mL, 16.6 mmol) in 1,2-dimethoxyethane (66.5 mL) was stirred at 90 °C overnight. The mixture was cooled to rt, filtered through a pad of Celite and the solids were rinsed with EtOAc. The filtrate was washed with water and brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from hexane to 90:10 hexane-EtOAc) to provide methyl 3-amino-2'-fluorobiphenyl-4-carboxylate (2.63 g, 81 %) as a white solid. ^{1}H NMR (400 MHz, chloroform-d) δ 7.90 (d, J = 8.25 Hz, 1H), 7.38-7.46 (m, 1H), 7.27-7.35 (m, 1H), 7.08-7.22 (m, 2H), 6.85 (s, 1H), 6.82 (d, J = 8.25 Hz, 1H), 5.83 (br s, 1H), 3.88 (s, 3H). Mass spectrum m/z 246.1 $(M+H)^+$.

[00428] Step 2 A solution of methyl 3-amino-2'-fluorobiphenyl-4-carboxylate (0.425 g, 1.73 mmol) in 1 M aqueous sodium hydroxide (6.9 mL, 6.9 mmol) and THF (3.5 mL) was heated at reflux overnight. The mixture was cooled to rt and concentrated almost to dryness. 6 M hydrochloric acid (0.1 mL) was added to the

solution at 0 °C and the precipitate was collected by filtration, washed with water and dried to give 3-amino-2'-fluorobiphenyl-4-carboxylic acid (0.338 g, 84 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87, d, 8.25, 1H), 7.50 (t, J = 7.97, 1H), 7.47-7.55 (m, 1H), 7.25-7.36 (m, 2H), 6.92 (br s, 1H), 6.76 (s, 1H), 6.59 (d, J = 7.70, 1H). Mass spectrum m/z 232.1 $(M+H)^+$.

[00429] Step 3 A solution of 3-amino-2'-fluorobiphenyl-4-carboxylic acid (0.104 g, 0.452 mmol) in concentrated hydrochloric acid (1.13 mL) at -10 °C was treated with a solution of sodium nitrite (0.037 g, 0.542 mmol) in water (1.13 mL). The mixture was maintained at ca. 0 °C for 30 min, then was treated with a cold solution of tin(II) chloride dihydrate (0.306 g, 1.355 mmol) in water (1.13 mL) while maintaining the temperature between 0-3 °C. The mixture was stirred while warming to room temperature overnight. The precipitate was collected by filtration, washed with water and ether and dried to give 2'-fluoro-3-hydrazinylbiphenyl-4-carboxylic acid as the hydrochloric acid salt (0.068 g, 48 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (br s, 1H), 7.91 (d, J = 8.25 Hz, 1H), 7.58 (t, J = 7.15 Hz, 1H), 7.38-7.49 (m, 1H), 7.19-7.33 (m, 3H), 7.12 (d, J = 8.25 Hz, 1H). Mass spectrum m/z 247.1 $(M+H)^+$.

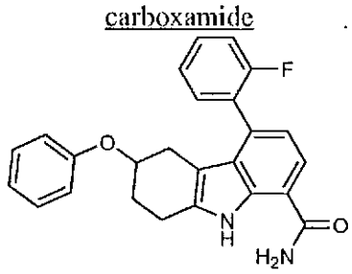
[00430] Step 4 A solution of 2'-fluoro-3-hydrazinylbiphenyl-4-carboxylic acid (0.306 g, 1.24 mmol) and cyclohexanone (0.183 g, 1.86 mmol) in acetic acid (6.2 mL) was heated at reflux under nitrogen for 2 h. The mixture was cooled to rt and concentrated. The residue was partitioned between EtOAc and 1 M hydrochloric acid. The organic layer was washed with brine, dried and concentrated. The residue was triturated with EtOAc and DCM to give 5-(2-fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (0.132 g) as a white solid. The filtrate was purified by column chromatography (eluting with a gradient from hexane to 50:50 EtOAc-hexane) to give additional product (0.029 g, 41% total). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 10.79 (s, 1H), 7.68 (d, J = 7.15, 1H), 7.42-7.51 (m, 1H), 7.24-7.34 (m, 3H), 6.87 (d, J = 7.15, 1H), 2.67-2.82 (m, 2H), 1.89-2.10 (m, 2H), 1.65-1.81 (m, 2H), 1.44-1.63 (m, 2H). Mass spectrum m/z 310.1 $(M+H)^+$.

[00431] Step 5 A solution of 5-(2-fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (0.097 g, 0.314 mmol), EDC (0.072 g, 0.376 mmol) and HOBT (0.058 g, 0.376 mmol) in THF (2.5 mL) and DCM (0.6 mL) was treated with 28% aqueous ammonium hydroxide (0.073 mL, 1.88 mmol). The mixture was stirred

overnight. More EDC (0.072 g, 0.376 mmol), HOBT (0.058 g, 0.376 mmol) and 28% aqueous ammonium hydroxide (0.073 mL, 1.88 mmol) were added, and the mixture was heated at 50 °C in a sealed tube for 2 days. The mixture was cooled to rt, dissolved in EtOAc, washed with NaHCO3 (aq) and brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from DCM to 98:2 DCM-methanol) to give 5-(2-fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (0.030 g, 30 %) as an off-white solid. Mass spectrum m/z 309.0 $(M+H)^+$.

Example 47-2

Preparation of 5-(2-fluorophenyl)-3-phenoxy-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00432] Step 1 A solution of 1,4-dioxaspiro[4.5]decan-8-ol (1.00 g, 6.32 mmol), phenol (0.714 g, 7.59 mmol) and triphenylphosphine (1.824 g, 6.95 mmol) in DCM (21.07 mL) was treated with diisopropyl azodicarboxylate (1.48 mL, 7.59 mmol) and the mixture was stirred at rt for 5 days. The mixture was concentrated and the residue was purified by column chromatography, eluting with a gradient from hexane to 80:20 hexane-EtOAc). The crude product was dissolved in EtOAc and the solution was washed twice with 1 M aqueous sodium hydroxide and brine, dried and concentrated to provide 8-phenoxy-1,4-dioxaspiro[4.5]decane as a colorless liquid (0.468 g, 32%). ^{1}H NMR (500 MHz, chloroform-d) δ 7.16 - 7.24 (2 H, m), 6.81 - 6.89 (3 H, m), 4.30 - 4.38 (1 H, m), 3.85 - 3.93 (4 H, m), 1.80 - 1.90 (6 H, m), 1.50 - 1.59 (2 H, m).

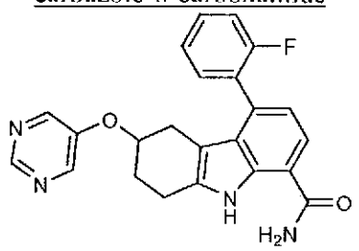
[00433] Step 2 A solution of 8-phenoxy-1,4-dioxaspiro[4.5]decane (0.460 g, 1.963 mmol) in THF (5.0 mL) and 3 M hydrochloric acid (5 mL) was stirred at rt for 2 days. The mixture was extracted with EtOAc, and the organic phase was washed with brine, dried and concentrated to provide 4-phenoxycyclohexanone as a colorless oil (0.344 g, 92%). ^{1}H NMR (500 MHz, chloroform-d) δ 7.22 - 7.27 (2 H, m), 6.87 - 6.94 (3 H,

m), 4.62 - 4.66 (1 H, m), 2.59 - 2.68 (2 H, m), 2.19 - 2.30 (4 H, m), 1.96 - 2.04 (2 H, m). Mass spectrum m/z 191.1 $(M+H)^+$.

[00434] Step 3 Using the procedures of Example 47-1 Steps 4 and 5, 4-phenoxycyclohexanone was converted to 5-(2-fluorophenyl)-3-phenoxy-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide in 2.1% overall yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.06 (1 H, s), 8.13 (1 H, br. s.), 7.71 (1 H, d, *J*=7.1 Hz), 7.26 - 7.53 (7 H, m), 6.89 - 6.97 (4 H, m), 4.65 - 4.78 (1 H, m), 2.95 (2 H, t, *J*=6.3 Hz), 2.48 (1 H, dd, *J*=15.4, 3.8 Hz), 2.24 - 2.41 (1 H, m), 2.13 (1 H, br. s.), 1.91 - 2.04 (1 H, m). Mass spectrum m/z 401.2 $(M+H)^+$.

Intermediate 47-3(a)

Preparation of 5-(2-fluorophenyl)-3-(pyrimidin-5-yloxy)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00435] Step 1 Using the procedure of Example 47-1 Step 4, 2'-fluoro-3-hydrazinylbiphenyl-4-carboxylic acid (0.190 g, 0.770 mmol) and 4-hydroxycyclohexanone (0.132 g, 1.154 mmol) were converted into 5-(2-fluorophenyl)-3-hydroxy-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid as a light yellow solid (0.089 g, 36%). Mass spectrum m/z 326.1 $(M+H)^+$.

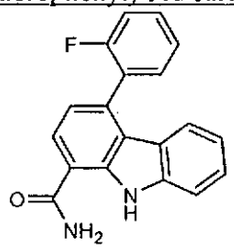
[00436] Step 2 A solution of 5-(2-fluorophenyl)-3-hydroxy-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (0.069 g, 0.213 mmol) in DMF (1.07 mL) was treated with ammonium chloride (0.023 g, 0.427 mmol), HOAT (0.058 g, 0.427 mmol), EDC (0.082 g, 0.427 mmol) and DIEA (0.149 mL, 0.853 mmol) and stirred over a weekend. The mixture was diluted with DCM, washed with 5% hydrochloric acid, NaHCO3 (aq), brine and 10% aqueous lithium chloride, dried and concentrated to give 5-(2-fluorophenyl)-3-hydroxy-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a light yellow foam (0.045 g, 65%). Mass spectrum m/z 325.1 $(M+H)^+$.

[00437] Step 3 Using the procedure of Example 47-2 Step 1, 5-(2-fluorophenyl)-3-hydroxy-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (0.099 g, 0.306 mmol) and pyrimidin-5-ol (0.035 g, 0.368 mmol) were converted to 5-(2-fluorophenyl)-3-

(pyrimidin-5-yloxy)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a light yellow foam (0.054 g, 34%). Mass spectrum m/z 403.1 $(M+H)^+$.

Example 48-1

Preparation of 4-(2-fluorophenyl)-9H-carbazole-1-carboxamide



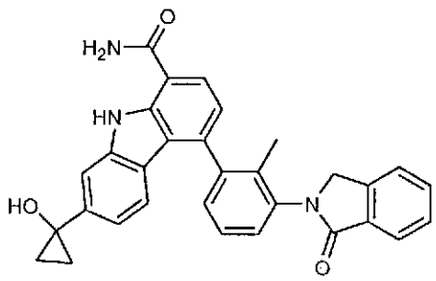
[00438] A solution of 5-(2-fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Example 47-1, 0.024 g, 0.078 mmol) in toluene (0.39 mL) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.039 g, 0.171 mmol), and the mixture was heated to reflux. After 4 h, the mixture was cooled to rt. The solid was removed by filtration and rinsed with EtOAc. The filtrate was concentrated, diluted with methanol and subjected to preparative HPLC. The product-containing effluent was treated with NaHCO3 (aq) and concentrated. The residue was extracted three times with DCM, and the combined organic layers were dried and concentrated to give 4-(2-fluorophenyl)-9H-carbazole-1-carboxamide (0.0045 g, 19%) as a light tan solid. Mass spectrum m/z 305.0 $(M+H)^+$.

[00439] The following compounds were also prepared using procedures demonstrated in Example 48-1.

Example	Starting material	Compound name	Mass spectrum
48-2	Example 47-2	4-(2-fluorophenyl)-6-phenoxy-9H-carbazole-1-carboxamide	397.0 $(M+H)^+$
48-3	Intermediate 47-3(a)	4-(2-fluorophenyl)-6-(pyrimidin-5-yloxy)-9H-carbazole-1-carboxamide	399.0 $(M+H)^+$
48-4	Example 24-15	4-(2,6-difluorophenyl)-N^7-(tetrahydro-2H-pyran-4-yl)-9H-carbazole-1,7-dicarboxamide	450.2 $(M+H)^+$

Example 49-1

Preparation of 7-(1-hydroxycyclopropyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00440] Step 1 A solution of ethyl 5-bromo-8-carbamoyl-9H-carbazole-2-carboxylate (Intermediate 48-1, 0.275 g, 0.761 mmol) was treated with titanium (IV) isopropoxide (0.31 mL, 1.07 mmol), followed by ethylmagnesium chloride (2 M in THF, 3.81 mL, 7.61 mmol). The mixture was stirred at rt for 1 h, then was cooled on ice and treated with water (10 mL). After 30 min, the solid was removed by filtration and rinsed with ether (150 mL). The organic layer was dried and concentrated to give 4-bromo-7-(1-hydroxycyclopropyl)-9H-carbazole-1-carboxamide as a yellow solid (0.220 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (1 H, s), 8.52 (1 H, d, *J*=8.4 Hz), 8.25 (1 H, br. s.), 7.84 - 7.89 (2 H, m), 7.61 (1 H, br. s.), 7.45 (1 H, d, *J*=8.1 Hz), 7.13 (1 H, dd, *J*=8.5, 1.7 Hz), 6.11 (1 H, s), 1.21 - 1.27 (2 H, m), 1.06 - 1.11 (2 H, m).

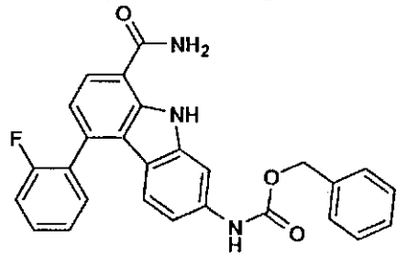
[00441] Step 2 A solution of 4-bromo-7-(1-hydroxycyclopropyl)-9H-carbazole-1-carboxamide (0.151 g, 0.436 mmol), *tert*-butylchlorodimethylsilane (0.079 g, 0.524 mmol) and imidazole (0.074 g, 1.091 mmol) in DMF (2.2 mL) was stirred at rt for 18 h. Additional *tert*-butylchlorodimethylsilane (0.079 g, 0.524 mmol) and imidazole (0.074 g, 1.091 mmol) were added and stirring was continued for 1 h. The mixture was diluted with EtOAc (75 mL) and washed seven times with brine. The organic layer was dried and concentrated and the residue was purified by column chromatography (eluting with a gradient from 90:10 to 50:50 hexane-EtOAc) to give 4-bromo-7-(1-(*tert*-butyldimethylsilyloxy)cyclopropyl)-9H-carbazole-1-carboxamide (0.144 g, 67%).

[00442] Step 3 Using the procedure of Example 31-1, 4-bromo-7-(1-(*tert*-butyldimethylsilyloxy)cyclopropyl)-9H-carbazole-1-carboxamide (0.059 g, 0.129 mmol) and 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-4, 0.054 g, 0.154 mmol) were converted to 7-(1-(*tert*-butyldimethylsilyloxy)cyclopropyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (0.048 g, 60%).

[00443] Step 4 A solution of 7-(1-(*tert*-butyldimethylsilyloxy)cyclopropyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (0.039 g, 0.065 mmol) in THF (0.66 mL) was treated with tetra-n-butylammonium fluoride (1 M in THF, 0.098 mL, 0.098 mmol). After 10 min, the mixture was combined with an identical reaction mixture done on 22% of the scale described, and the mixture was concentrated. The residue was purified by preparative HPLC. The appropriate effluent fractions were treated with NaHCO3 (aq) and partially concentrated. The aqueous residue was extracted three times with DCM and the combined organic phases were dried and concentrated to give 7-(1-hydroxycyclopropyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a white solid (23.3 mg, 60%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.42 (1 H, s), 8.18 (1 H, br. s.), 7.98 (1 H, d, *J*=7.7 Hz), 7.80 (1 H, d, *J*=7.7 Hz), 7.72 (1 H, s), 7.68 (2 H, d, *J*=3.8 Hz), 7.60 (1 H, d, *J*=7.7 Hz), 7.56 (1 H, ddd, *J*=7.8, 4.1, 4.0 Hz), 7.49 (2 H, t, *J*=7.7 Hz), 7.33 (1 H, d, *J*=7.1 Hz), 7.01 (1 H, d, *J*=7.7 Hz), 6.95 (1 H, d, *J*=8.2 Hz), 6.79 (1 H, d, *J*=8.2 Hz), 5.95 (1 H, s), 4.90 - 5.02 (2 H, m), 1.84 (3 H, s), 1.07 - 1.15 (2 H, m), 0.91 - 1.00 (2 H, m). Mass spectrum m/z 488.3 $(M+H)^+$.

Example 50-1

Preparation of benzyl 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazol-2-ylcarbamate



[00444] A suspension of 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazole-2-carboxylic acid (Example 23-2, 320 mg, 0.919 mmol) and 4Å molecular sieves (60 mg) in 1,4-dioxane (15 mL) at 50 °C was treated with TEA (0.316 mL, 2.269 mmol) and diphenylphosphoryl azide (0.491 mL, 2.269 mmol). The mixture was stirred at 50 °C for 1.5 h, followed by addition of phenylmethanol (0.951 mL, 9.19 mmol). The mixture was then stirred at 80 °C for 18 h. The cooled mixture was partitioned between EtOAc and NaHCO3 (aq). The organic phase was washed with brine, dried and concentrated The residue was purified by column chromatography (eluting with 35:65 hexane-EtOAc). The residue after concentration was suspended in hexane and

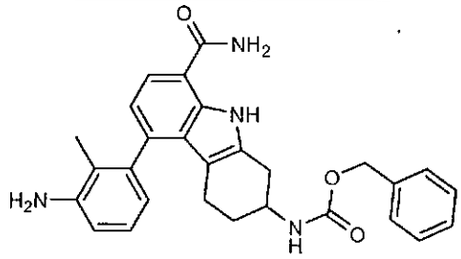
the precipitate was collected by filtration to provide benzyl 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazol-2-ylcarbamate as an off-white solid (400 mg, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1 H) 9.83 (s, 1 H) 8.15 (br. s., 1 H) 8.00 (s, 1 H) 7.91 (d, *J*=7.69 Hz, 1 H) 7.45 - 7.64 (m, 3 H) 7.32 - 7.46 (m, 7 H) 7.03 (d, *J*=7.91 Hz, 1 H) 6.87 - 6.98 (m, 2 H) 5.15 (s, 2 H). Mass spectrum m/z 454.1 $(M+H)^+$.

[00445] The following Examples/Intermediates were also prepared using procedures demonstrated in Example 50-1.

Example/ Intermediate	Starting material	Compound name	Mass spectrum
Intermediate 50-2(a)	Intermediate 23-3	benzyl 8-carbamoyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate	476.1 $(M+H)^+$
50-3	Intermediate 49-1	benzyl 5-bromo-8-carbamoyl-9H-carbazol-2-ylcarbamate	438, 440 $(M+H)^+$
Intermediate 50-4(a)	Intermediate 49-3	benzyl 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate	442, 444 $(M+H)^+$

Example 51-1

Preparation of benzyl 5-(3-amino-2-methylphenyl)-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate

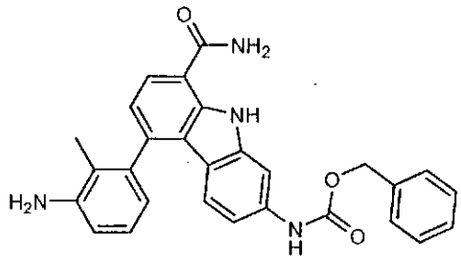


[00446] Using the procedure of Example 3-2, benzyl 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate (Intermediate 50-4(a), 300 mg, 0.678 mmol) and 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Intermediate 50-1, 237 mg, 1.017 mmol) were converted into benzyl 5-(3-amino-2-methylphenyl)-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate, TFA salt,

isolated as a white solid after preparative HPLC purification (60 mg, 15%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.63 (1 H, dd, J=7.7, 2.9 Hz), 7.18 - 7.46 (8 H, m), 6.82 (1 H, dd, J=7.5, 2.8 Hz), 5.10 (2 H, s), 3.90 (1 H, br. s.), 3.14 (1 H, d, J=4.8 Hz), 2.72 (1 H, br. s.), 1.77 - 2.19 (6 H, m), 1.51 - 1.68 (1 H, m). Mass spectrum m/z 469.3 $(M+H)^+$.

Example 51-2

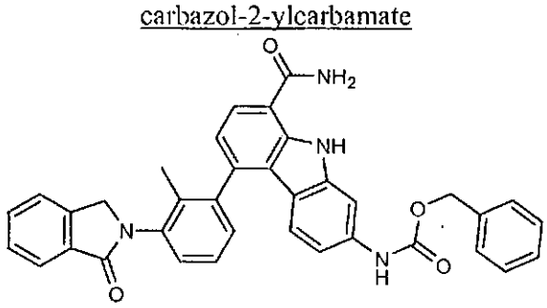
Preparation of benzyl 5-(3-amino-2-methylphenyl)-8-carbamoyl-9H-carbazol-2-ylcarbamate



[00447] Using the procedure of Example 3-2, benzyl 5-bromo-8-carbamoyl-9H-carbazol-2-ylcarbamatee (Example 50-3, 1.00 g, 2.28 mmol) and 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Intermediate 50-1, 638 mg, 2.74 mmol) were converted into benzyl 5-(3-amino-2-methylphenyl)-8-carbamoyl-9H-carbazol-2-ylcarbamate isolated as an off-white solid after trituration in methanol (ca. 80-85% purity, 860 mg, 65%). A portion was purified by preparative HPLC to provide the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (1 H, s), 9.81 (1 H, s), 8.13 (1 H, br. s.), 7.95 (1 H, s), 7.89 (1 H, d, J=7.5 Hz), 7.29 - 7.51 (6 H, m), 7.25 (1 H, d, J=7.9 Hz), 7.16 (1 H, d, J=7.5 Hz), 6.81 - 6.96 (3 H, m), 6.65 (1 H, d, J=8.8 Hz), 5.14 (2 H, s), 1.83 (3 H, s). Mass spectrum m/z 465.1 $(M+H)^+$.

Example 51-3

Preparation of benzyl 8-carbamoyl-5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-ylcarbamate



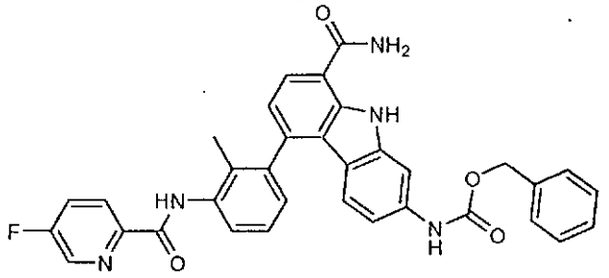
[00448] Using the procedure of Example 31-1, benzyl 5-bromo-8-carbamoyl-9H-carbazol-2-ylcarbamate (Example 50-3, 400 mg, 0.913 mmol) and 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-4, 414 mg, 1.19 mmol) were converted into benzyl 8-carbamoyl-5-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-ylcarbamate as a white solid (90% purity, 530 mg, 90%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.58 (1 H, s), 7.96 (1 H, d, J=7.91 Hz), 7.85 (1 H, br. s.), 7.61 (2 H, d, J=7.47 Hz), 7.54 (2 H, d, J=4.83 Hz), 7.33 - 7.45 (7 H, m), 7.06 (2 H, dd, J=12.52, 8.13 Hz), 6.93 (1 H, s), 6.84 - 6.88 (1 H, m), 5.22 (2 H, s), 4.82 (2 H, s), 1.94 (3 H, s). Mass spectrum m/z 581.3 $(M+H)^+$.

[00449] The following compound was also prepared using procedures demonstrated in Example 51-3, using Intermediate 50-15 in place of Intermediate 50-4.

Example	Compound name	Mass spectrum
51-4	benzyl 5-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-8-carbamoyl-9H-carbazol-2-ylcarbamate	637.2 $(M+H)^+$

Example 52-1

Preparation of benzyl 8-carbamoyl-5-(3-(5-fluoropicolinamido)-2-methylphenyl)-9H-carbazol-2-ylcarbamate

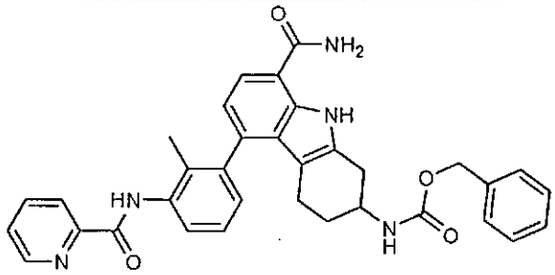


[00450] A mixture of benzyl 5-(3-amino-2-methylphenyl)-8-carbamoyl-9H-carbazol-2-ylcarbamate (Example 51-2, 100 mg, 0.215 mmol), 5-fluoropicolinic acid (45.6 mg, 0.323 mmol), HOAT (44.0 mg, 0.323 mmol), and EDC (83 mg, 0.431 mmol) in DCM-THF (80:20, 12 mL) was treated with DIEA (0.150 mL, 0.861 mmol) and the solution was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC to provide benzyl 8-carbamoyl-5-(3-(5-fluoropicolinamido)-2-methylphenyl)-9H-carbazol-2-ylcarbamate as a white solid (47 mg, 36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (1 H, s), 10.41 (1 H, s), 9.83 (1 H,

s), 8.74 (1 H, d, J=3.0 Hz), 8.27 (1 H, dd, J=8.8, 4.8 Hz), 8.09 - 8.21 (1 H, m), 7.96 - 8.03 (2 H, m), 7.94 (1 H, d, J=7.8 Hz), 7.85 (1 H, d, J=7.5 Hz), 7.29 - 7.51 (7 H, m), 7.15 - 7.21 (1 H, m), 6.91 - 6.98 (2 H, m), 6.79 (1 H, d, J=8.8 Hz), 5.16 (2 H, s), 1.96 (3 H, s). Mass spectrum m/z 588.1 $(M+H)^+$.

Example 52-2

Preparation of benzyl 8-carbamoyl-5-(2-methyl-3-(picolinamido)phenyl)-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate



[00451] A solution of benzyl 5-(3-amino-2-methylphenyl)-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate, TFA salt (Example 51-1, 55 mg, 0.094 mmol), TEA (0.066 mL, 0.472 mmol), and picolinoyl chloride hydrochloric acid salt (50.4 mg, 0.283 mmol) in DCM (8 mL) was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC to provide benzyl 8-carbamoyl-5-(2-methyl-3-(picolinamido)phenyl)-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate, isolated as the TFA salt, as a white solid (26 mg, 39%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.59 (1 H, t, J=4.8 Hz), 8.14 (1 H, d, J=8.3 Hz), 7.89 - 7.99 (1 H, m), 7.85 (1 H, dd, J=9.9, 8.1 Hz), 7.50 (2 H, dd, J=7.7, 2.0 Hz), 7.11 - 7.32 (6 H, m), 7.01 (1 H, d, J=7.9 Hz), 6.74 (1 H, d, J=7.5 Hz), 4.96 (2 H, s), 3.68 - 3.87 (1 H, m), 2.96 - 3.10 (1 H, m), 2.49 - 2.66 (1 H, m), 1.82 - 2.11 (5 H, m), 1.73 (1 H, br. s.), 1.34 - 1.62 (1 H, m). Mass spectrum m/z 575.1 $(M+H)^+$.

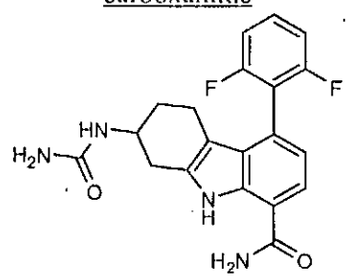
The following compounds were also prepared using procedures demonstrated in Examples 52-1 and 52-2, using the appropriate carboxylic acid or carboxylic acid chloride.

Example/ Intermediate	Compound name	Mass spectrum

52-3	benzyl 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazol-2-ylcarbamate	585.4 $(M-H)^-$
52-4	benzyl 8-carbamoyl-5-(2-methyl-3-(picolinamido)phenyl)-9H-carbazol-2-ylcarbamate (prepared as the TFA salt)	570.0 $(M+H)^+$
Intermediate 52-5	benzyl 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-2,3,4,9-tetrahydro-1H-carbazol-2-ylcarbamate	591.3 $(M+H)^+$
Intermediate 52-6	benzyl 8-carbamoyl-5-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-9H-carbazol-2-ylcarbamate	573.4 $(M+H)^+$

Example 53-1

Preparation of 5-(2,6-difluorophenyl)-2-ureido-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide

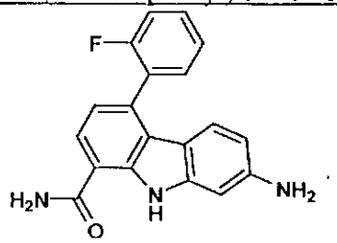


[00452] A solution of 8-carbamoyl-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylic acid (Intermediate 23-3, 30 mg, 0.081 mmol), diphenyl phosphorazidate (55.7 mg, 0.203 mmol) and TEA (0.028 mL, 0.203 mmol) in 1,4-dioxane (2 mL) was heated at 50 °C for 2 h. The mixture was cooled to rt and treated with 28% aqueous ammonium hydroxide (2 mL). After 20 min the mixture was diluted with DCM, washed with water, dried and concentrated, and the residue was purified by preparative HPLC. The appropriate effluent fractions were made basic with 1 M aqueous sodium hydoxide and extracted twice with DCM. The combined organic phases were washed with water, dried and concentrated to provide 5-(2,6-difluorophenyl)-2-ureido-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide as a white solid (9 mg, 28%). ^{1}H NMR (400 MHz, methanol-d_4) δ 1.60 - 1.72 (m, 1 H) 1.79 - 1.89 (m, 1 H) 2.13 - 2.32 (m, 2 H) 2.68 (dd, *J*=16.48, 7.25 Hz, 1 H) 3.13 (dd, *J*=16.70, 5.27 Hz, 1 H) 3.98 - 4.09 (m, *J*=6.15 Hz, 1 H) 4.58 (s, 1 H) 6.91 (d, *J*=7.91 Hz, 1 H)

7.05 (t, *J*=8.13 Hz, 2 H) 7.38 - 7.50 (m, 1 H) 7.60 (d, *J*=7.91 Hz, 1 H). Mass spectrum m/z 385.1 $(M+H)^+$.

Example 54-1

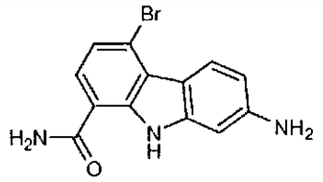
Preparation of 7-amino-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide



[00453] A mixture of benzyl 8-carbamoyl-5-(2-fluorophenyl)-9H-carbazol-2-ylcarbamate (Example 50-1, 400 mg, 0.882 mmol), 10% palladium on charcoal (94 mg, 0.088 mmol) and ammonium formate (334 mg, 5.29 mmol) in methanol (20 mL) was heated at reflux for 1 h. The mixture was cooled to rt, diluted with methanol and filtered through a Celite pad. The filtrate was concentrated to give 7-amino-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1 H) 8.11 (br. s., 1 H) 7.78 (d, *J*=7.78 Hz, 1 H) 7.51 (d, *J*=2.01 Hz, 2 H) 7.35 - 7.47 (m, 3 H) 6.93 (d, *J*=7.78 Hz, 1 H) 6.79 - 6.84 (m, 1 H) 6.72 (d, *J*=8.03 Hz, 1 H) 6.24 (dd, *J*=8.41, 1.88 Hz, 1 H) 5.22 (s, 2 H). Mass spectrum m/z 320.1 $(M+H)^+$.

Example 54-2

Preparation of 7-amino-4-bromo-9H-carbazole-1-carboxamide

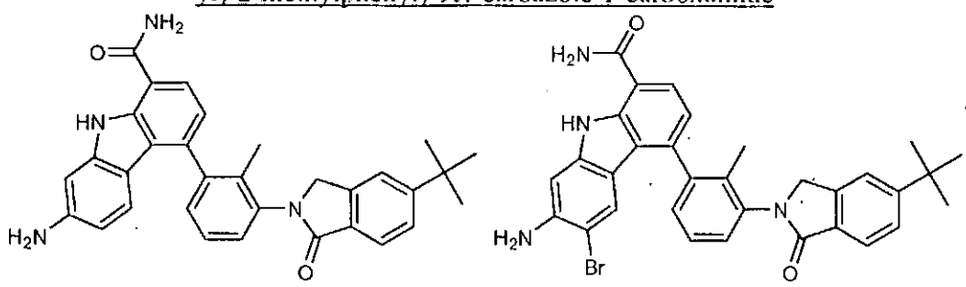


[00454] A suspension of benzyl 5-bromo-8-carbamoyl-9H-carbazol-2-ylcarbamate (Example 50-3, 2.18 g, 4.97 mmol) in hydrogen bromide (30-35% in acetic acid, 11.9 mL, 59.7 mmol) was stirred at rt for 30 min. The mixture was diluted with ether (100 mL) and the precipitate was collected by filtration, washed with ether and dried to provide 7-amino-4-bromo-9H-carbazole-1-carboxamide, hydrobromide salt, as a light yellow solid (2.20 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (1 H, s), 8.69 (1 H, d, J=8.5 Hz), 8.28 (1 H, br. s.), 7.91 (1 H, d, J=8.0 Hz), 7.84 (1 H, d, J=1.8 Hz), 7.65 (1

H, br. s.), 7.51 (1 H, d, J=8.3 Hz), 7.25 (1 H, dd, J=8.4, 1.9 Hz). Mass spectrum m/z 304, 306 $(M+H)^+$. The salt was partitioned between EtOAc and NaHCO3 (aq). Residual solid was collected by filtration, washed with EtOAc and water and dried. The organic phase of the filtrate was separated, washed with brine, and dried and concentrated. The solid residue was combined with the filtered solid, dissolved in acetone, filtered to remove undissolved solid, and the filtrate was concentrated to provide 7-amino-4-bromo-9H-carbazole-1-carboxamide, hydrobromide salt, as a light yellow solid (1.62 g, 96%).

Examples 54-3 and 54-4

Preparation of 7-amino-4-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide and 7-amino-6-bromo-4-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide

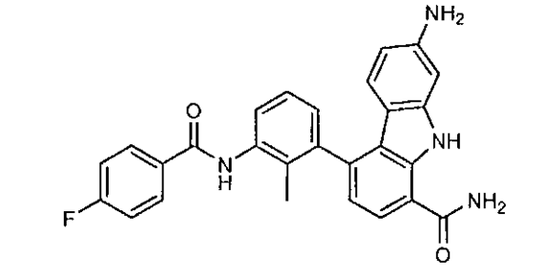


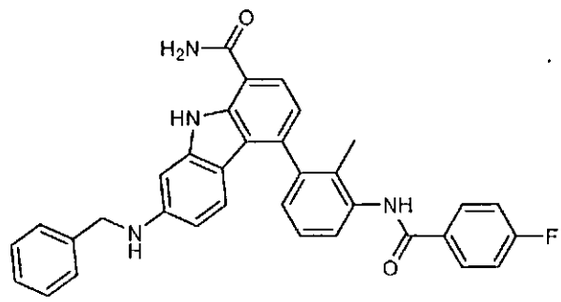
[00455] A solution of benzyl 5-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-8-carbamoyl-9H-carbazol-2-ylcarbamate (Example 51-4, 65 mg, 0.102 mmol) in hydrogen bromide (30-35% in acetic acid, 5 mL, 27.6 mmol) was stirred at rt for 1.5 h. The mixture was diluted with DCM and concentrated. The residue was dissolved in DCM containing a small amount of methanol and the solution was mixed with 1 M aqueous sodium hydroxide. The organic phase was separated, washed with water, dried and concentrated, and the residue was triturated with hexane. The residue was purified by column chromatography (eluting with a gradient from 97:2.7:0.3 to 90:9:1 DCM-methanol-28% aqueous ammonium hydroxide) to provide 7-amino-4-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide as a white solid (Example 54-3, 45 mg, 88%) as a white solid. ^{1}H NMR (400 MHz, chloroform-d) δ 10.32 (1 H, s), 7.89 (1 H, d, J=8.35 Hz), 7.57 (1 H, d, J=7.91 Hz), 7.49 - 7.55 (2 H, m), 7.35 - 7.47 (3 H, m), 7.04 (1 H, d, J=7.47 Hz), 6.93 (1 H, d, J=8.35 Hz), 6.74 (1 H, d, J=1.76 Hz), 6.46 (1 H, dd, J=8.57, 1.98 Hz), 4.79 (2 H, d, J=2.20 Hz), 3.84 (2 H, br. s.), 1.96 (3 H, s), 1.40 (9 H, s). Mass spectrum m/z 503.3

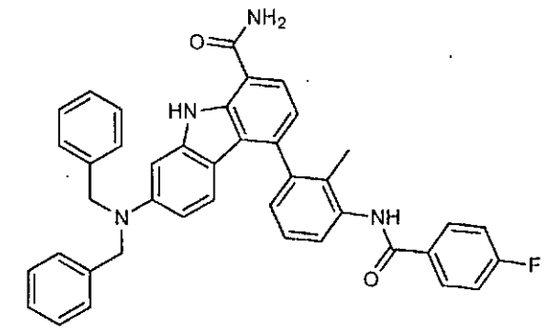
$(M+H)^+$. Also obtained was 7-amino-6-bromo-4-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide as a white solid (Example 54-4, 5 mg, 8%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.34 (1 H, s), 7.89 (1 H, d, J=7.91 Hz), 7.53 - 7.59 (3 H, m), 7.44 - 7.48 (2 H, m), 7.35 (1 H, dd, J=5.71, 3.08 Hz), 7.05 - 7.08 (2 H, m), 6.84 (1 H, s), 4.83 (2 H, s), 4.22 (2 H, br. s.), 1.95 (3 H, s), 1.40 (9 H, s). Mass spectrum m/z 581, 583 $(M+H)^+$.

Example 54-5, 54-6 and 54-7

Preparation of 7-amino-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide, 7-(benzylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide and 7-(dibenzylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide







[00456] Using the procedure of Examples 54-3 and 54-4, benzyl 8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazol-2-ylcarbamate (Example 52-3, 720 mg, 1.227 mmol) was converted into 7-amino-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide, purified by preparative HPLC and

conversion to the free base (Example 54-5, 330 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (1 H, s), 10.10 (1 H, s), 8.00 - 8.17 (3 H, m), 7.77 (1 H, d, J=7.9 Hz), 7.43 - 7.48 (1 H, m), 7.29 - 7.42 (4 H, m), 7.17 (1 H, d, J=6.6 Hz), 6.73 - 6.86 (2 H, m), 6.60 (1 H, d, J=8.8 Hz), 6.21 (1 H, dd, J=8.6, 2.0 Hz), 5.17 (2 H, s), 1.90 (3 H, s). Mass spectrum m/z 453.0 $(M+H)^+$. Also obtained was 7-(benzylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (Example 54-6, 4.1 mg, 0.6%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (1 H, br. s.), 10.09 (1 H, s), 8.02 - 8.12 (3 H, m), 7.79 (1 H, d, J=7.5 Hz), 7.43 - 7.48 (1 H, m), 7.25 - 7.41 (8 H, m), 7.18 - 7.24 (1 H, m), 7.16 (1 H, d, J=6.2 Hz), 6.84 (2 H, d, J=7.9 Hz), 6.61 (1 H, d, J=8.3 Hz), 6.28 - 6.36 (1 H, m), 4.29 (2 H, s), 1.89 (3 H, s). Mass spectrum m/z 543.0 $(M+H)^+$. Also obtained was 7-(dibenzylamino)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (Example 54-7, 4.2 mg, 0.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (1 H, s), 10.04 (1 H, s), 8.05 (3 H, dd, J=8.8, 5.3 Hz), 7.79 (1 H, d, J=7.9 Hz), 7.16 - 7.45 (15 H, m), 7.12 (1 H, d, J=6.2 Hz), 7.04 (1 H, d, J=2.2 Hz), 6.83 (1 H, d, J=7.5 Hz), 6.57 (1 H, d, J=8.8 Hz), 6.33 (1 H, dd, J=8.8, 2.2 Hz), 4.71 (4 H, s), 1.88 (3 H, s). Mass spectrum m/z 633.1 $(M+H)^+$.

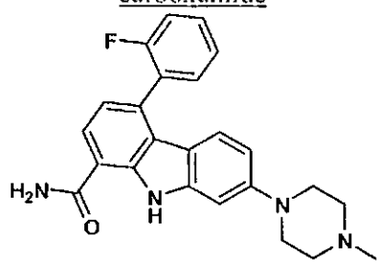
[00457] The following compounds were also prepared using procedures demonstrated in Examples 54-1 through 54-7.

Example	Starting material	Compound name	Mass spectrum
54-8	Example 52-4	7-amino-4-(2-methyl-3-(picolinamido)phenyl)-9H-carbazole-1-carboxamide (prepared as the bis TFA salt)	436.1 $(M+H)^+$
54-9	Intermediate 52-5	2-amino-5-(3-(4-fluorobenzamido)-2-methylphenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as the TFA salt)	457.2 $(M+H)^+$
54-10	Example 51-2	7-amino-4-(3-amino-2-methylphenyl)-9H-carbazole-1-carboxamide	331.2 $(M+H)^+$
54-11	Example 52-1	7-amino-4-(3-(5-fluoropicolinamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	450.0 $(M+H)^+$

54-12	Example 52-1	7-(benzylamino)-4-(3-(5-fluoropicolinamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	544.0 $(M+H)^+$
54-13	Example 52-2	2-amino-5-(2-methyl-3-(picolinamido)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (prepared as the bis TFA salt)	440.1 $(M+H)^+$
54-14	Example 51-3	7-amino-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	447.2 $(M+H)^+$
54-15	Intermediate 52-6	7-amino-4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-9H-carbazole-1-carboxamide	439.2 $(M+H)^+$
54-16	Intermediate 50-2(a)	2-amino-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	342.1 $(M+H)^+$

Example 55-1

Preparation of 4-(2-fluorophenyl)-7-(4-methylpiperazin-1-yl)-9H-carbazole-1-carboxamide



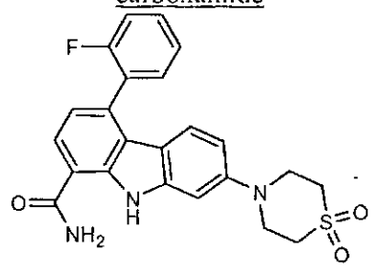
[00458] A mixture of 7-amino-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide (Example 54-1, 30 mg, 0.094 mmol), 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloric acid salt (27.1 mg, 0.141 mmol) and sodium carbonate (49.8 mg, 0.470 mmol) in *tert*-butanol (2 mL) was heated at reflux overnight. The mixture was cooled to rt and concentrated. The residue was purified by preparative HPLC to provide 4-(2-fluorophenyl)-7-(4-methylpiperazin-1-yl)-9H-carbazole-1-carboxamide, TFA salt, as a light yellow solid (11 mg, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1 H) 8.13 (br. s., 1 H) 7.85 (d, *J*=7.91 Hz, 1 H) 7.41 - 7.59 (m, 3 H) 7.30 - 7.41 (m, 2 H) 7.25 (d, *J*=2.20 Hz, 1 H) 6.97 (d, *J*=7.91 Hz, 1 H) 6.89 (d, *J*=0.88 Hz, 1 H) 6.67 (d, *J*=2.20 Hz, 1 H) 3.70 - 3.82 (m, 2 H) 3.43 - 3.52 (m, 2 H) 3.08 - 3.19 (m, 2 H) 2.86 - 2.99 (m, 2 H) 2.80 (s, 3 H). Mass spectrum m/z 403.2 $(M+H)^+$.

[00459] The following Examples/Intermediates were also prepared using procedures demonstrated in Example 55-1, using (in the case of Example 55-2) 1-chloro-2-(2-chloroethoxy)ethane in place of 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloric acid salt.

Example/ Intermediate	Starting material	Compound name	Mass spectrum
55-2	Example 54-1	4-(2-fluorophenyl)-7-morpholino-9H-carbazole-1-carboxamide, (prepared as the trifluroacetic acid salt)	390.1 $(M+H)^+$
Intermediate 55-3	Example 54-2	4-bromo-7-(4-methylpiperazin-1-yl)-9H-carbazole-1-carboxamide	387, 389 $(M+H)^+$

Example 56-1

Preparation of 4-(2-fluorophenyl)-7-(1,1-dioxothiomorpholino)-9H-carbazole-1-carboxamide



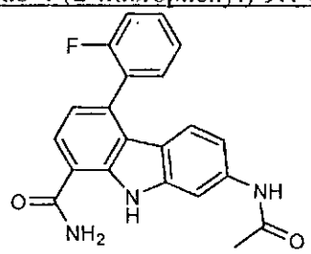
[00460] A suspension of 7-amino-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide (Example 54-1, 36 mg, 0.113 mmol) in 2-propanol (1.0 mL) was treated with vinylsulfonylethene (20μL, 0.199 mmol) at rt. The reaction mixture was heated at 100 °C for 26 h. The mixture was cooled to rt, concentrated and the residue was purified by preparative HPLC to provide 4-(2-fluorophenyl)-7-(1,1-dioxothiomorpholino)-9H-carbazole-1-carboxamide as a yellow solid (14 mg, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 (1 H, s), 8.17 (1 H, br. s.), 7.90 (1 H, d, *J*=7.9 Hz), 7.47 - 7.62 (3 H, m), 7.37 - 7.46 (2 H, m), 7.35 (1 H, d, *J*=1.8 Hz), 7.01 (1 H, d, *J*=7.9 Hz), 6.93 (1 H, d, *J*=8.3 Hz), 6.74 (1 H, dd, *J*=9.0, 2.4 Hz), 3.77 - 3.81 (4 H, m), 3.08 - 3.19 (4 H, m). Mass spectrum m/z 438.1 $(M+H)^+$.

[00461] The following compound was also prepared using procedures demonstrated in Example 56-1, using Example 54-5 in place of Example 54-1 as the starting material.

Example	Compound name	Mass spectrum
56-2	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(1,1-dioxothiomorpholino)-9H-carbazole-1-carboxamide	571.3 $(M-H)^-$

Example 57-1

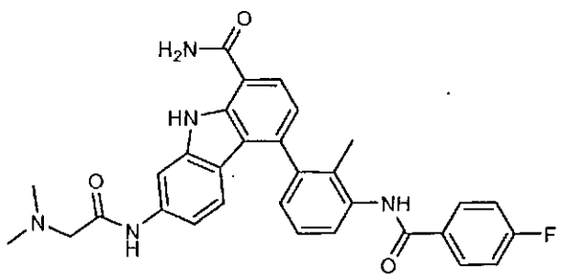
Preparation of 7-acetamido-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide



[00462] A solution of 7-amino-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide (Example 54-1, 25 mg, 0.078 mmol) and TEA (0.022 mL, 0.157 mmol) in DCM-THF (2:1, 3 mL) was treated with acetyl chloride (6.7 μL, 0.094 mmol). The mixture was stirred at rt for 1 h, then was concentrated. The residue was purified by preparative HPLC to provide 7-acetamido-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (13 mg, 45%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.95 (s, 1 H) 7.79 (d, *J*=7.91 Hz, 1 H) 7.36 - 7.53 (m, 2 H) 7.13 - 7.33 (m, 2 H) 6.98 (d, *J*=7.69 Hz, 2 H) 6.85 (d, *J*=10.33 Hz, 1 H) 2.05 (s, 3 H). Mass spectrum m/z 360.3 $(M+H)^+$.

Example 57-2

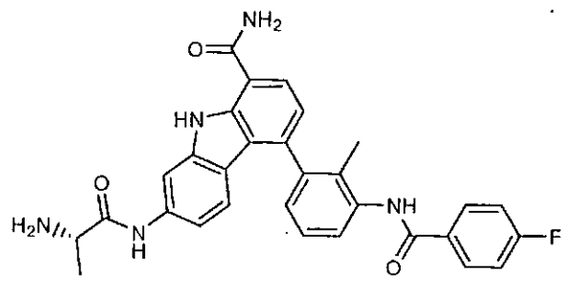
Preparation of 7-(2-(dimethylamino)acetamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide



[00463] A solution of 7-amino-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (Example 54-5, 30 mg, 0.066 mmol), 2-(dimethylamino)acetic acid hydrochloric acid salt (13.9 mg, 0.099 mmol), HOAT (18.1 mg, 0.133 mmol), EDC (31.8 mg, 0.166 mmol), and TEA (0.037 mL, 0.265 mmol) in DCM-THF (2:1, 3 mL) was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC to provide 7-(2-(dimethylamino)acetamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide, TFA salt, as a white solid (22 mg, 50%). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.02 (1 H, d, J=1.1 Hz), 7.96 (2 H, dd, J=8.7, 5.4 Hz), 7.84 (1 H, d, J=7.8 Hz), 7.42 (1 H, d, J=7.2 Hz), 7.34 (1 H, t, J=7.6 Hz), 7.12 - 7.21 (3 H, m), 6.95 (1 H, d, J=7.8 Hz), 6.86 - 6.94 (2 H, m), 4.04 (2 H, s), 2.91 (s, 6H), 1.90 (3 H, s). Mass spectrum m/z 538.1 $(M+H)^+$.

Example 57-3

Preparation of 7-((S)-2-aminopropanamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide



[00464] A solution of 7-amino-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (Example 54-5, 21.8 mg, 0.049 mmol), (S)-2-(*tert*-butoxycarbonylamino)propanoic acid (10.6 mg, 0.056 mmol), HOBT (8.6 mg, 0.056 mmol), EDC (10.8 mg, 0.056 mmol), and DIEA (0.043 mL, 0.250 mmol) in DMF (0.675 mL) was agitated at rt overnight. The mixture was concentrated and treated with TFA (0.5 mL) and DCM (0.5 mL). After 2 h, the solution was concentrated and the residue was purified by preparative HPLC to provide 7-((S)-2-aminopropanamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide, TFA salt (5.7 mg, 15%). Mass spectrum m/z 523.9 $(M+H)^+$.

[00465] The following Examples/Intermediates were also prepared using procedures demonstrated in Examples 57-1 through 57-3, using the appropriate acid or acid chloride.

Example/ Intermediate	Starting material	Compound name	Mass spectrum
57-4	Example 54-16	2-acetamido-5-(2,6-difluorophenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	384.2 $(M+H)^+$
57-5	Example 54-5	7-acetamido-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	495.2 $(M+H)^+$
57-6	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(nicotinamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	558.1 $(M+H)^+$
57-7	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(isonicotinamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	558.1 $(M+H)^+$
57-8	Example 54-5	7-(3-(dimethylamino)propanamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	552.1 $(M+H)^+$
57-9	Example 54-5	7-(cyclopropanecarboxamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	521.0 $(M+H)^+$
57-10	Example 54-1	7-acrylamido-4-(2-fluorophenyl)-9H-carbazole-1-carboxamide	374.0 $(M+H)^+$
57-11	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-(4-hydroxyphenyl)propanamido)-9H-carbazole-1-carboxamide	600.9 $(M+H)^+$
57-12	Example 54-5	2-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazol-2-ylamino)-2-oxoEtOAc	552.9 $(M+H)^+$

57-13	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(2-(pyridin-4-yl)acetamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	571.9 $(M+H)^+$
57-14	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-hydroxypropanamido)-9H-carbazole-1-carboxamide	524.9 $(M+H)^+$
57-15	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(2-(pyridin-3-yl)acetamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	571.9 $(M+H)^+$
57-16	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(4-morpholinobutanamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	608.0 $(M+H)^+$
57-17	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(1-methyl-1H-imidazole-2-carboxamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	560.9 $(M+H)^+$
57-18	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-morpholinopropanamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	594.0 $(M+H)^+$
57-19	Example 54-5	7-(4-chlorobenzamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	590.9 $(M+H)^+$
57-20	Example 54-5	7-(4-cyanobenzamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	581.9 $(M+H)^+$
57-21	Example 54-5	7-(4-(dimethylamino)benzamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	599.9 $(M+H)^+$
57-22	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(4-methoxybenzamido)-9H-carbazole-1-carboxamide	586.9 $(M+H)^+$

57-23	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-isobutyramido-9H-carbazole-1-carboxamide	522.9 $(M+H)^+$
57-24	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-pivalamido-9H-carbazole-1-carboxamide	537.0 $(M+H)^+$
57-25	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(2-phenylacetamido)-9H-carbazole-1-carboxamide	570.9 $(M+H)^+$
57-26	Example 54-5	N-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazol-2-yl)-1,2,3-thiadiazole-4-carboxamide	564.8 $(M+H)^+$
57-27	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(2-hydroxy-2-phenylacetamido)-9H-carbazole-1-carboxamide	586.9 $(M+H)^+$
57-28	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(pyrimidine-5-carboxamido)-9H-carbazole-1-carboxamide	558.9 $(M+H)^+$
57-29	Example 54-5	7-(2-cyanoacetamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	519.9 $(M+H)^+$
57-30	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-methoxypropanamido)-9H-carbazole-1-carboxamide	538.9 $(M+H)^+$
57-31	Example 54-5	7-(2-(1H-tetrazol-5-yl)acetamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	562.8 $(M+H)^+$
57-32	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-(2-oxopyrrolidin-1-yl)propanamido)-9H-carbazole-1-carboxamide	591.9 $(M+H)^+$

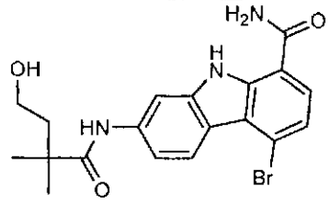
57-33	Example 54-5	7-(3-(1H-imidazol-1-yl)propanamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	574.9 $(M+H)^+$
57-34	Example 54-5	N-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazol-2-yl)morpholine-2-carboxamide (prepared as the TFA salt)	565.9 $(M+H)^+$
57-35	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(piperidine-3-carboxamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	564.0 $(M+H)^+$
57-36	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-((R)-piperidine-2-carboxamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	564.0 $(M+H)^+$
57-37	Example 54-5	7-(2-aminoacetamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	509.9 $(M+H)^+$
57-38	Example 54-5	7-(3-chlorobenzamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	590.8 $(M+H)^+$
57-39	Example 54-5	7-benzamido-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	556.9 $(M+H)^+$
57-40	Example 54-5	7-(2-chlorobenzamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	590.8 $(M+H)^+$
57-41	Example 54-5	7-(4-acetamidobenzamido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	613.9 $(M+H)^+$

57-42	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-methylbutanamido)-9H-carbazole-1-carboxamide	536.9 $(M+H)^+$
57-43	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(pyrazine-2-carboxamido)-9H-carbazole-1-carboxamide	558.9 $(M+H)^+$
57-44	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(picolinamido)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	557.9 $(M+H)^+$
57-45	Example 54-5	N-(8-carbamoyl-5-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazol-2-yl)thiazole-4-carboxamide	563.8 $(M+H)^+$
57-46	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(2-(pyrazin-2-yl)acetamido)-9H-carbazole-1-carboxamide	572.9 $(M+H)^+$
57-47	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(2-(pyridin-2-yl)acetamido)-9H-carbazole-1-carboxamide	571.9 $(M+H)^+$
57-48	Example 54-14	7-isobutyramido-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	517.3 $(M+H)^+$
57-49	Example 54-14	4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-pivalamido-9H-carbazole-1-carboxamide	531.3 $(M+H)^+$
57-50	Example 54-15	4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-7-pivalamido-9H-carbazole-1-carboxamide (prepared as the TFA salt)	523.4 $(M+H)^+$
Intermediate 57-51	Example 54-2	4-bromo-7-pivalamido-9H-carbazole-1-carboxamide	388, 390 $(M+H)^+$

Intermediate 57-52	Example 54-2	4-bromo-7-(cyclopropanecarboxamido)-9H-carbazole-1-carboxamide	372, 374 $(M+H)^+$

Intermediate 58-1

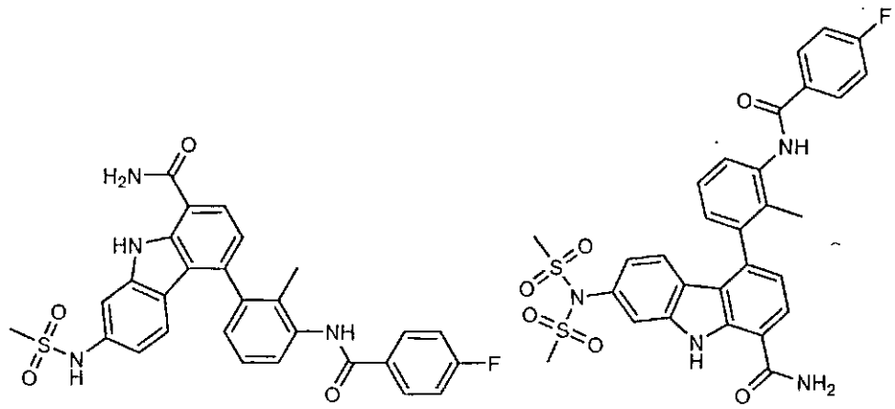
Preparation of 4-bromo-7-(4-hydroxy-2,2-dimethylbutanamido)-9H-carbazole-1-carboxamide



[00466] A mixture of 7-amino-4-bromo-9H-carbazole-1-carboxamide hydrobromide (Example 54-2, 500 mg, 1.299 mmol) and 3,3-dimethyldihydrofuran-2(3H)-one (222 mg, 1.948 mmol) in THF (10 mL) was treated with trimethylaluminum (2 M in toluene, 562 mg, 7.79 mmol) dropwise at rt. The mixture was heated at 50 °C for 1.5 h, cooled to rt and treated with water. The mixture was filtered through Celite and the solids were washed thoroughly with DCM and methanol. The filtrate was washed with water, dried and concentrated, and the residue was purified by column chromatography (eluting with a gradient from DCM to 10% ammonia-methanol-DCM) to provide 4-bromo-7-(4-hydroxy-2,2-dimethylbutanamido)-9H-carbazole-1-carboxamide as a yellow solid (250 mg, 46%). Mass spectrum m/z 418, 420 $(M+H)^+$.

Examples 59-1 and 59-2

Preparation of 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(methylsulfonamido)-9H-carbazole-1-carboxamide and 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(N-(methylsulfonyl)methylsulfonamido)-9H-carbazole-1-carboxamide

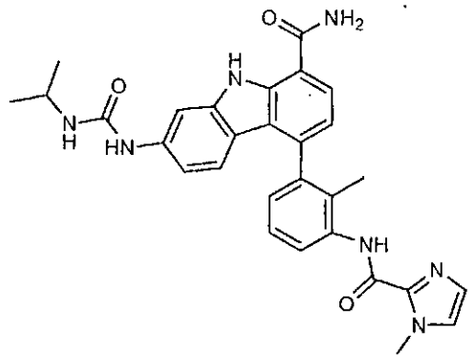


[00467] A solution of 7-amino-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (Example 54-5, 30 mg, 0.066 mmol) and TEA (0.018 mL, 0.133 mmol) in DCM-THF (2:1, 3 mL) was treated with methanesulfonyl chloride (10 µL, 0.133 mmol). The mixture was stirred at rt for 1.5 h, and was concentrated and purified by preparative HPLC to provide 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(methylsulfonamido)-9H-carbazole-1-carboxamide as a white solid (Example 59-1, 3.5 mg, 9%). ^{1}H NMR (500 MHz, methanol-d_4) δ 7.91 - 8.01 (2 H, m), 7.83 (1 H, d, J=7.8 Hz), 7.45 (1 H, d, J=1.7 Hz), 7.42 (1 H, d, J=7.8 Hz), 7.34 (1 H, t, J=7.8 Hz), 7.12 - 7.20 (3 H, m), 6.95 (1 H, d, J=7.8 Hz), 6.88 (1 H, d, J=8.6 Hz), 6.73 (1 H, dd, J=8.5, 2.1 Hz), 2.85 (3 H, s), 1.90 (3 H, s). Mass spectrum m/z 531.0 $(M+H)^+$. Also obtained was 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(N-(methylsulfonyl)methylsulfonamido)-9H-carbazole-1-carboxamide as a white solid (Example 59-2, 14 mg, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (1 H, s), 10.08 (1 H, s), 8.21 (1 H, br. s.), 7.97 - 8.08 (3 H, m), 7.79 (1 H, d, J=1.8 Hz), 7.53 (1 H, br. s.), 7.48 (1 H, d, J=7.3 Hz), 7.26 - 7.39 (3 H, m), 7.15 (1 H, d, J=6.5 Hz), 6.93 - 7.03 (2 H, m), 6.86 (1 H, d, J=8.3 Hz), 3.46 (6 H, d, J=9.0 Hz), 1.86 (3 H, s). Mass spectrum m/z 607.2 $(M-H)^-$.

[00468] The following compound was also prepared using the procedure demonstrated in Examples 59-1 and 59-2, substituting Example 54-1 in place of Example 54-5 as starting material:

Example	Compound name	Mass spectrum
59-3	4-(2-fluorophenyl)-7-(methylsulfonamido)-9H-carbazole-1-carboxamide	398.1 $(M+H)^+$

Example 60-1
Preparation of 7-(3-isopropylureido)-4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-9H-carbazole-1-carboxamide



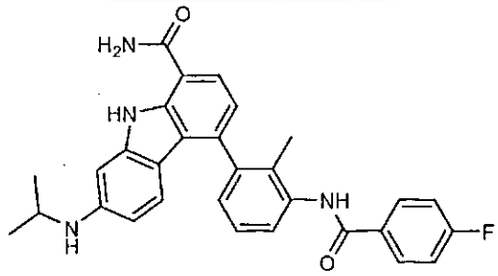
[00469] A solution of 7-amino-4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-9H-carbazole-1-carboxamide (Example 54-15, 29 mg, 0.066 mmol) and 2-isocyanatopropane (0.019 mL, 0.198 mmol) in 1,2-dichloroethane (3 mL) was stirred at rt for 2.5 h, then at 50 °C for 2 h. Additional 2-isocyanatopropane was added and the mixture was stirred at 40 °C for 16 h. The mixture was concentrated and purified by HPLC. The appropriate effluent fractions were partially concentrated, treated with NaHCO3 (aq) and extracted with EtOAc. The organic phase was dried and concentrated to provide 7-(3-isopropylureido)-4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-9H-carbazole-1-carboxamide as a pale pink solid (15 mg, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.32 (1 H, s), 9.97 (1 H, s), 8.37 (1 H, s), 8.13 (1 H, br. s.), 7.88 (1 H, d, J=7.9 Hz), 7.81 (1 H, d, J=1.8 Hz), 7.76 (1 H, d, J=7.9 Hz), 7.40 - 7.48 (2 H, m), 7.38 (1 H, t, J=7.7 Hz), 7.13 (1 H, d, J=7.5 Hz), 7.06 (1 H, s), 6.82 - 6.92 (2 H, m), 6.73 (1 H, d, J=8.3 Hz), 5.98 (1 H, d, J=7.5 Hz), 4.01 (3 H, s), 3.68 - 3.81 (1 H, m), 1.89 - 1.95 (3 H, m), 1.07 (6 H, d). Mass spectrum m/z 524.3 $(M+H)^+$.

[00470] The following compounds were also prepared using the procedure demonstrated in Example 60-1, substituting Example 54-5 in place of Example 54-15 as starting material and using the appropriate isocyanate in place of 2-isocyanatopropane.

Example	Compound name	Mass spectrum
60-2	7-(3-(4-chlorophenyl)ureido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	605.8 $(M+H)^+$
60-3	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-phenylureido)-9H-carbazole-1-carboxamide	571.9 $(M+H)^+$
60-4	7-(3-ethylureido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	523.9 $(M+H)^+$
60-5	7-(3-*tert*-butylureido)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	551.9 $(M+H)^+$
60-6	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(3-isopropylureido)-9H-carbazole-1-carboxamide	537.9 $(M+H)^+$

Example 61-1

Preparation of 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(isopropylamino)-9H-carbazole-1-carboxamide



[00471] A suspension of 7-amino-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide (Example 54-5, 1 g, 2.210 mmol), acetone (3.4 mL, 20 eq.), and acetic acid (0.443 mL, 7.74 mmol) in 1,2-dichloroethane (220 mL) was treated with sodium triacetoxyborohydride (1.639 g, 7.74 mmol) and stirred at 40 °C for 4 h. Additional sodium triacetoxyborohydride (520 mg, 1.1 eq) and acetic acid (0.19 mL, 1.5 eq) were added and the mixture was stirred overnight. The mixture was treated with NaHCO3 (aq) and the organic phase was separated, washed with brine, dried and concentrated. The residue was purified by preparative HPLC. The appropriate effluent fractions were made basic with NaHCO3 (aq) and extracted with EtOAc. The organic phase was washed with brine, dried and concentrated. The residue was triturated with methanol to provide 4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(isopropylamino)-9H-carbazole-1-carboxamide as an off-white solid (520 mg, 48%). ^{1}H NMR (400

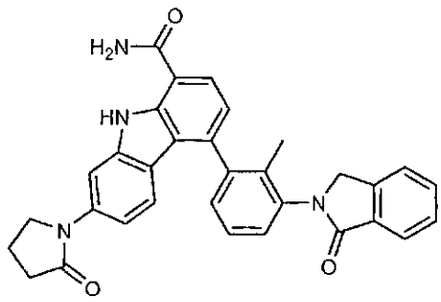
MHz, DMSO-d_6) δ 11.01 (1 H, s), 10.09 (1 H, s), 8.07 (3 H, dd, J=8.8, 5.3 Hz), 7.77 (1 H, d, J=7.9 Hz), 7.27 - 7.51 (5 H, m), 7.17 (1 H, d, J=6.2 Hz), 6.73 - 6.88 (2 H, m), 6.60 (1 H, d, J=8.3 Hz), 6.23 (1 H, dd, J=8.8, 2.2 Hz), 5.49 (1 H, d, J=7.9 Hz), 3.53 (1 H, dd, J=13.8, 6.4 Hz), 1.90 (3 H, s), 1.04 - 1.21 (6 H, m). Mass spectrum m/z 495.1 $(M+H)^+$.

[00472] The following Examples/Intermediates were also prepared using procedures demonstrated in Example 61-1, using the appropriate aldehyde or ketone in place of acetone.

Example/ Intermediate	Starting material	Compound name	Mass spectrum
61-2	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(1-methylpiperidin-4-ylamino)-9H-carbazole-1-carboxamide	550.1 $(M+H)^+$
61-3	Example 54-14	7-(isopropylamino)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	489.3 $(M+H)^+$
61-4	Example 54-15	7-(isopropylamino)-4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-9H-carbazole-1-carboxamide	481.2 $(M+H)^+$
61-5	Example 54-2	4-bromo-7-(isopropylamino)-9H-carbazole-1-carboxamide	346, 348 $(M+H)^+$
Intermediate 61-6	Example 54-2	(S)-4-bromo-7-((2,2-dimethyl-1,3-dioxolan-4-ylmethyl)amino)-9H-carbazole-1-carboxamide	418, 420 $(M+H)^+$

Example 62-1

Preparation of 4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide



[00473] A solution of 7-amino-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 54-14, 60 mg, 0.134 mmol) in THF (3 mL) was treated with TEA (0.019 mL, 0.134 mmol) and a solution of 4-bromobutanoyl chloride (24.92 mg, 0.134 mmol) in DCM (1 mL). The mixture was stirred at rt for 40 min, then was diluted with DCM, washed with water, dried and concentrated. The residue was dissolved in THF (5 mL) and added to a suspension of sodium hydride (60% oil dispersion, 40 mg, 1.000 mmol, pre-washed with hexane) in THF (5 mL). The mixture was stirred at rt overnight, then was heated at 65 °C for 30 min. The mixture was cooled to rt, poured into water and extracted with EtOAc. The organic phase was dried and concentrated, and the residue was purified by column chromatography (eluting with a gradient from 99:0.9:0.1 to 90:9:1 DCM-methanol-28% aqueous ammonium hydroxide) to provide 4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide (50 mg, 66%) as a white solid. ^{1}H NMR (400 MHz, chloroform-d) δ 10.67 (1 H, s), 7.96 (1 H, d, J=7.47 Hz), 7.91 (1 H, s), 7.74 (1 H, d, J=7.91 Hz), 7.62 - 7.67 (1 H, m), 7.52 - 7.58 (2 H, m), 7.45 - 7.48 (2 H, m), 7.38 - 7.42 (1 H, m), 7.22 (1 H, dd, J=8.79, 1.76 Hz), 7.11 (2 H, d, J=7.91 Hz), 4.86 (2 H, s), 3.90 - 4.02 (2 H, m), 2.66 (2 H, t, J=8.13 Hz), 2.16 - 2.25 (2 H, m), 1.94 (3 H, s). Mass spectrum m/z 515.3 $(M+H)^+$.

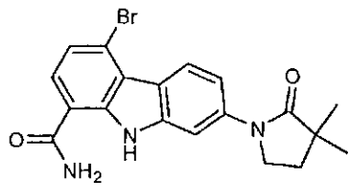
[00474] The following compounds were also prepared using procedures demonstrated in Example 62-1.

Example/ Intermediate	Starting material	Compound name	Mass spectrum
62-2	Example 54-5	4-(3-(4-fluorobenzamido)-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-	521.1 $(M+H)^+$

		carboxamide	
62-3	Example 54-15	4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	507.1 $(M+H)^+$
Intermediate 62-4	Example 54-2	4-bromo-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	372, 374 $(M+H)^+$

Intermediate 63-1

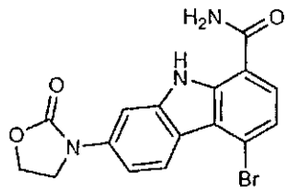
Preparation of 4-bromo-7-(3,3-dimethyl-2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide



[00475] A solution of 4-bromo-7-(4-hydroxy-2,2-dimethylbutanamido)-9H-carbazole-1-carboxamide (Intermediate 58-1, 89 mg, 0.213 mmol), diethyl azodicarboxylate (0.051 mL, 0.319 mmol) and triphenylphosphine (84 mg, 0.319 mmol) in THF (1 mL) was stirred at rt for 1 h. More diethyl azodicarboxylate (0.051 mL, 0.319 mmol) and triphenylphosphine (84 mg, 0.319 mmol) were added, and these additions repeated again after 1 h more. The mixture was diluted with DCM, washed with NaHCO3 (aq) and water, and dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from DCM to 90:9:1 DCM-methanol-28% aqueous ammonium hydroxide), then by preparative HPLC. The appropriate effluent fractions were made basic with 1 M aqueous sodium hydroxide and extracted twice with DCM. The combined organic phases were washed with water, dried and concentrated to provide 4-bromo-7-(3,3-dimethyl-2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide as a yellow solid (44 mg, 52%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.66 (1 H, d, J=8.58 Hz), 7.94 (1 H, d, J=1.54 Hz), 7.73 (1 H, d, J=8.36 Hz), 7.55 (1 H, dd, J=8.80, 1.98 Hz), 7.39 (1 H, d, J=8.14 Hz), 3.97 (2 H, t, J=6.93 Hz), 2.11 (2 H, t, J=6.93 Hz), 1.28 (6 H, s). Mass spectrum m/z 400, 402 $(M+H)^+$.

Intermediate 64-1

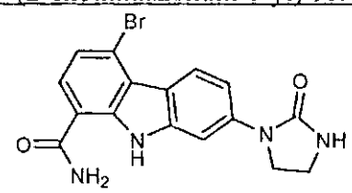
Preparation of 4-bromo-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide



[00476] Using the procedure of Example 62-1, 7-amino-4-bromo-9H-carbazole-1-carboxamide (Example 54-2, 650 mg, 2.14 mmol) and 2-bromoethyl chloroformate (534 mg, 2.56 mmol) were converted to 4-bromo-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide as a light yellow solid (688 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (1 H, s), 8.55 (1 H, d, J=8.88 Hz), 8.20 (1 H, br. s.), 8.02 (1 H, d, J=2.22 Hz), 7.82 (1 H, d, J=8.32 Hz), 7.52 - 7.60 (2 H, m), 7.42 (1 H, d, J=8.05 Hz), 4.47 - 4.52 (2 H, m), 4.14 - 4.20 (2 H, m). Mass spectrum m/z 374, 376 $(M+H)^+$.

Intermediate 65-1

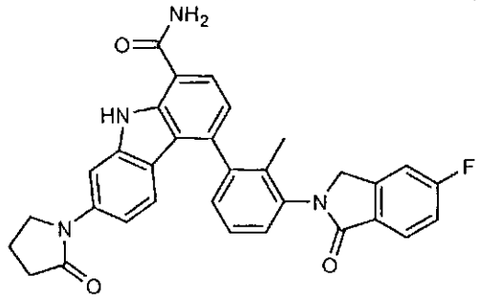
Preparation of 4-bromo-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide



[00477] A solution of 7-amino-4-bromo-9H-carbazole-1-carboxamide hydrobromide (Example 54-2, 700 mg, 1.818 mmol) and DIEA (0.381 mL, 2.182 mmol) in DMF (5 mL) was treated with 1-chloro-2-isocyanatoethane (230 mg, 2.182 mmol). After 2 h, the mixture was treated with NaH (60% in mineral oil, 582 mg, 14.54 mmol). After 10 min, the mixture was diluted with water. The precipitate was collected by filtration, dried, triturated with methanol, collected again by filtration and dried to provide 4-bromo-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide as a light yellow solid (410 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (1 H, s), 8.46 (1 H, d, J=8.80 Hz), 8.16 (1 H, br. s.), 7.92 (1 H, s), 7.77 (1 H, d, J=8.14 Hz), 7.63 - 7.68 (1 H, m), 7.52 (1 H, br. s.), 7.36 - 7.41 (1 H, m), 6.99 (1 H, s), 3.92 - 3.98 (2 H, m), 3.43 - 3.50 (2 H, m). Mass spectrum m/z 373, 375 $(M+H)^+$.

Example 66-1

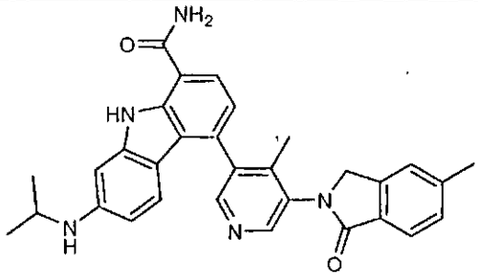
Preparation of 4-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide



[00478] Using the procedure of Example 31-1, 4-bromo-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide (Intermediate 62-4, 40 mg, 0.107 mmol) and 5-fluoro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-19, 51.3 mg, 0.140 mmol) were converted into 4-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide (30 mg, 52%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.86 - 7.96 (3 H, m), 7.46 - 7.53 (2 H, m), 7.40 - 7.45 (1 H, m), 7.35 (1 H, dd, J=8.03, 2.01 Hz), 7.25 - 7.32 (1 H, m), 7.20 (1 H, dd, J=8.53, 2.01 Hz), 7.07 - 7.13 (2 H, m), 4.92 (2 H, s), 3.97 - 4.06 (2 H, m), 2.66 (2 H, t, J=8.03 Hz), 2.18 - 2.29 (2 H, m), 1.94 (3 H, s). Mass spectrum m/z 533.1 $(M+H)^+$.

Example 66-2

Preparation of 7-(isopropylamino)-4-(4-methyl-5-(5-methyl-1-oxoisoindolin-2-yl)pyridin-3-yl)-9H-carbazole-1-carboxamide



[00479] Using the procedure of Example 3-2, 4-bromo-7-(isopropylamino)-9H-carbazole-1-carboxamide (Example 61-5, 19.01 mg, 0.055 mmol) and 5-methyl-2-(4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)isoindolin-1-one (Intermediate 50-20, 20 mg, 0.055 mmol) were converted into 7-(isopropylamino)-4-(4-methyl-5-(5-methyl-1-oxoisoindolin-2-yl)pyridin-3-yl)-9H-carbazole-1-carboxamide (18 mg, 65%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.65 (1 H, s), 8.46 (1

H, s), 7.79 (1 H, d, J=7.92 Hz), 7.73 (1 H, d, J=7.70 Hz), 7.40 (1 H, s), 7.36 (1 H, d, J=7.70 Hz), 6.96 (1 H, d, J=7.92 Hz), 6.80 (1 H, d, J=8.58 Hz), 6.74 (1 H, d, J=1.98 Hz), 6.35 - 6.54 (1 H, m), 4.81 - 4.97 (2 H, m), 3.53 - 3.82 (1 H, m), 2.45 (3 H, s), 1.97 (3 H, s), 1.06 - 1.24 (6 H, m). Mass spectrum m/z 504.3 $(M+H)^+$.

[00480] The following compounds were prepared using the procedures demonstrated in Examples 66-1 and 66-2 and closely related procedures, and using the Examples and Intermediates shown as starting materials.

Example	Starting materials	Compound name	Mass spectrum
66-3	Intermediate 55-3, Intermediate 50-1	4-(3-amino-2-methylphenyl)-7-(4-methylpiperazin-1-yl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	414.2 $(M+H)^+$
66-4	Example 61-5, Intermediate 50-1	4-(3-amino-2-methylphenyl)-7-(isopropylamino)-9H-carbazole-1-carboxamide	373.3 $(M+H)^+$
66-5	Intermediate 62-4, Intermediate 50-18	4-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	529.3 $(M+H)^+$
66-6	Intermediate 62-4, Intermediate 51-2	4-(3-(5-chloro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	549.2 $(M+H)^+$
66-7	Intermediate 62-4, Intermediate 50-1	4-(3-amino-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	399.1 $(M+H)^+$
66-8	Intermediate 64-1, Intermediate 50-18	4-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	531.3 $(M+H)^+$

66-9	Intermediate 64-1, Intermediate 51-2	4-(3-(5-chloro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	551.2 $(M+H)^+$
66-10	Intermediate 64-1, Intermediate 50-4	4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	517.3 $(M+H)^+$
66-11	Intermediate 65-1, Intermediate 50-4	4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	516.3 $(M+H)^+$
66-12	Intermediate 65-1, Intermediate 50-18	4-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	530.3 $(M+H)^+$
66-13	Intermediate 65-1, Intermediate 51-2	4-(3-(5-chloro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	550.3 $(M+H)^+$
66-14	Intermediate 65-1, Intermediate 50-19	4-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	534.3 $(M+H)^+$
66-15	Intermediate 61-6, Intermediate 50-4	7-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylamino)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	561.3 $(M+H)^+$
66-16	Intermediate 62-4, Intermediate 50-8	4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	529.3 $(M+H)^+$

66-17	Intermediate 62-4, Intermediate 50-44	4-(3-(cyclopropanecarboxamido)-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	467.2 $(M+H)^+$
66-18	Intermediate 62-4, Intermediate 50-43	4-(2-methyl-3-(2-oxopiperidin-1-yl)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	481.3 $(M+H)^+$
66-19	Intermediate 62-4, Intermediate 50-29	4-(2-methyl-3-(1-oxoisoquinolin-2(1H)-yl)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	527.4 $(M+H)^+$
66-20	Intermediate 62-4, Intermediate 50-9	4-(3-(6-cyano-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	540.4 $(M+H)^+$
66-21	Intermediate 64-1, Intermediate 50-44	4-(3-(cyclopropanecarboxamido)-2-methylphenyl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	469.2 $(M+H)^+$
66-22	Intermediate 64-1, Intermediate 50-19	4-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	535.1 $(M+H)^+$
66-23	Intermediate 64-1, Intermediate 50-29	4-(2-methyl-3-(1-oxoisoquinolin-2(1H)-yl)phenyl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	529.3 $(M+H)^+$
66-24	Intermediate 65-1, Intermediate 50-29	4-(2-methyl-3-(1-oxoisoquinolin-2(1H)-yl)phenyl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	528.3 $(M+H)^+$

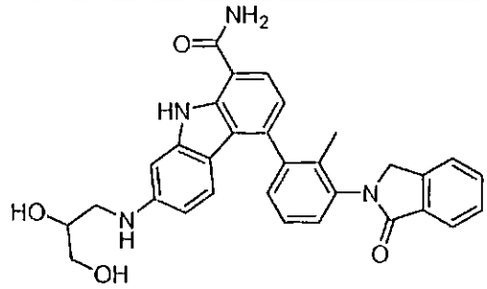
66-25	Intermediate 64-1, Intermediate 51-1	4-(3-(6-chloro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	551.1 $(M+H)^+$
66-26	Intermediate 64-1, Intermediate 50-8	4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	531.2 $(M+H)^+$
66-27	Intermediate 65-1, Intermediate 50-8	4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	530.1 $(M+H)^+$
66-28	Intermediate 65-1, Intermediate 51-1	4-(3-(6-chloro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	550.1 $(M+H)^+$
66-29	Intermediate 65-1, Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	534.2 $(M+H)^+$
66-30	Intermediate 57-51, Intermediate 50-8	4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-7-pivalamido-9H-carbazole-1-carboxamide	545.2 $(M+H)^+$
66-31	Intermediate 57-51, Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-pivalamido-9H-carbazole-1-carboxamide	549.2 $(M+H)^+$
66-32	Intermediate 57-51, Intermediate 50-18	4-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-7-pivalamido-9H-carbazole-1-carboxamide	545.2 $(M+H)^+$

66-33	Intermediate 57-51, Intermediate 51-2	4-(3-(5-chloro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-pivalamido-9H-carbazole-1-carboxamide	565.2 $(M+H)^+$
66-34	Intermediate 57-51, Intermediate 50-19	4-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-pivalamido-9H-carbazole-1-carboxamide	549.3 $(M+H)^+$
66-35	Intermediate 58-1, Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(4-hydroxy-2,2-dimethylbutanamido)-9H-carbazole-1-carboxamide	579.4 $(M+H)^+$
66-36	Intermediate 58-1, Intermediate 50-8	7-(4-hydroxy-2,2-dimethylbutanamido)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	575.2 $(M+H)^+$
66-37	Intermediate 63-1, Intermediate 50-8	7-(3,3-dimethyl-2-oxopyrrolidin-1-yl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	557.4 $(M+H)^+$
66-38	Intermediate 63-1, Intermediate 50-5	7-(3,3-dimethyl-2-oxopyrrolidin-1-yl)-4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	561.4 $(M+H)^+$
66-39	Intermediate 57-52, Intermediate 50-4	7-(cyclopropanecarboxamido)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	515.1 $(M+H)^+$
66-40	Intermediate 64-1, Intermediate 50-20	4-(4-methyl-5-(5-methyl-1-oxoisoindolin-2-yl)pyridin-3-yl)-7-(2-oxooxazolidin-3-yl)-9H-carbazole-1-carboxamide	532.2 $(M+H)^+$

66-41	Intermediate 65-1, Intermediate 50-20	4-(4-methyl-5-(5-methyl-1-oxoisoindolin-2-yl)pyridin-3-yl)-7-(2-oxoimidazolidin-1-yl)-9H-carbazole-1-carboxamide	531.3 $(M+H)^+$

Example 67-1

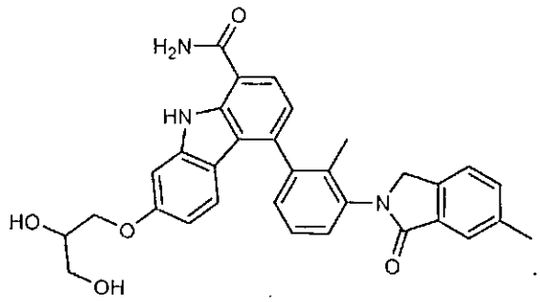
Preparation of 7-(2,3-dihydroxypropylamino)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00481] A solution of 7-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylamino)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 66-15, 50 mg, 0.089 mmol) in THF (1 mL) was treated with 2 M hydrochloric acid (4.46 mL, 8.92 mmol) and the mixture was stirred at rt for 1 h. The mixture was made basic with 1 M aqueous sodium hydroxide and extracted twice with DCM. The combined organic phases, along with some insoluble precipitate, were dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from DCM to 90:9:1 DCM-methanol-28% aqueous ammonium hydroxide) to provide 7-(2,3-dihydroxypropylamino)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as an orange solid (20 mg, 39%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.90 (1 H, d, J=7.49 Hz), 7.79 (1 H, d, J=7.77 Hz), 7.67 - 7.74 (2 H, m), 7.58 - 7.62 (1 H, m), 7.49 - 7.55 (2 H, m), 7.42 (1 H, dd, J=6.94, 1.94 Hz), 6.99 (1 H, d, J=7.77 Hz), 6.86 (1 H, d, J=8.32 Hz), 6.81 (1 H, d, J=1.94 Hz), 6.45 (1 H, dd, J=8.74, 1.80 Hz), 4.97 (2 H, s), 3.88 - 3.93 (1 H, m), 3.59 - 3.68 (2 H, m), 3.36 - 3.39 (1 H, m), 3.14 - 3.20 (1 H, m), 1.95 (3 H, s). Mass spectrum m/z 521.3 $(M+H)^+$.

Example 67-2

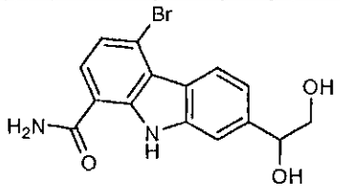
Preparation of racemic 7-(2,3-dihydroxypropoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00482] A solution of racemic 7-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 44-4, 30 mg, 0.052 mmol) in methanol-DMSO was treated with TFA (0.5 mL) and the solution was stirred overnight at rt. The mixture was concentrated and purified by preparative HPLC to provide 7-(2,3-dihydroxypropoxy)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a white solid (9.4 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (1 H, s), 8.16 (1 H, br. s.), 7.94 (1 H, d, J=7.7 Hz), 7.54 - 7.65 (3 H, m), 7.49 (3 H, t, J=7.9 Hz), 7.25 - 7.38 (2 H, m), 6.99 (1 H, d, J=7.7 Hz), 6.92 (1 H, d, J=8.8 Hz), 6.60 (1 H, d, J=1.3 Hz), 4.82 - 5.01 (3 H, m), 4.60 - 4.71 (1 H, m), 3.96 - 4.08 (1 H, m), 3.76 - 3.96 (2 H, m), 3.48 (2 H, t, J=5.6 Hz), 2.44 (3 H, s), 1.77 - 1.88 (3 H, m). Mass spectrum m/z 536.1 $(M+H)^+$.

Example 68-1

Preparation of 4-bromo-7-((RS)-1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide



[00483] Step 1 A solution of potassium *tert*-butoxide (3.40 g, 30.3 mmol) in THF (249 mL) at 0 °C was treated with methyltriphenylphosphonium bromide (8.79 g, 24.60 mmol), forming a bright yellow suspension. After 1 h, 4-bromo-7-formyl-9H-carbazole-1-carboxamide (prepared according to the procedure of Step 1 of Example 41-1, 4 g, 9.46 mmol) was added, and the resulting suspension was warmed to rt and stirred for 3 h. Water was added and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 70:30 hexane-EtOAc to EtOAc). The crude material was suspended in methanol, and the precipitate was collected by filtration and dried. The filtrate was concentrated to provide

additional solid which was collected by filtration, dried and combined with the first crop to provide 4-bromo-7-vinyl-9H-carbazole-1-carboxamide as a light brown solid (1.66 g, ca. 90% purity, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (1 H, s), 8.52 (1 H, d, J=8.3 Hz), 8.06 - 8.29 (1 H, m), 7.79 - 7.88 (2 H, m), 7.58 (1 H, br. s.), 7.35 - 7.45 (2 H, m), 6.78 - 6.98 (1 H, m), 5.88 (1 H, d, J=17.6 Hz), 5.32 (1 H, d). Mass spectrum m/z 344, 346 $(M+H)^+$.

[00484] Step 2 A solution of 4-bromo-7-vinyl-9H-carbazole-1-carboxamide (1.66 g, 4.74 mmol) and 4-methylmopholine N-oxide (0.833 g, 7.11 mmol) in acetone (172 mL) and water (17.2 mL) was treated with osmium tetroxide, 2.5 wt % in *tert*-butanol (0.238 mL, 0.019 mmol). The mixture was stirred at rt overnight, then was treated with additional 4-methylmorpholine N-oxide (0.8 eq., 0.42 g) and osmium tetroxide solution (0.004 eq., 0.2 mL). The mixture was stirred over a weekend, then was treated with sodium sulfite (2.99 g, 23.70 mmol) and stirred for 30 min. The mixture was filtered through a pad of Celite, and the solids were washed with acetone and THF. The filtrates were concentrated and purified by column chromatography (eluting with a gradient from 70:30 EtOAc-hexane to EtOAc, followed by 95:5 EtOAc-methanol) to afford 4-bromo-7-((RS)-1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide as an off-white solid (1.47 g, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (1 H, s), 8.33 (1 H, d, J=8.1 Hz), 8.00 (1 H, br. s.), 7.58 - 7.68 (2 H, m), 7.35 (1 H, br. s.), 7.22 (1 H, d, J=8.1 Hz), 7.07 (1 H, d, J=8.4 Hz), 5.14 (1 H, d, J=4.0 Hz), 4.41 - 4.62 (2 H, m), 3.32 (2 H, t, J=5.7 Hz). Mass spectrum m/z 331, 333 $(M+H-H_2O)^+$.

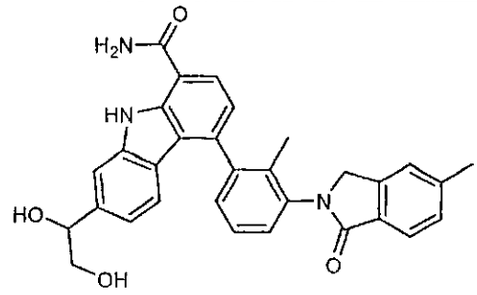
Intermediates 69-1 and 69-2

Preparation of Purified Enantiomers of 4-bromo-7-(1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide

[00485] 4-Bromo-7-((RS)-1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide (Example 68-1, 453 mg) was subjected to chiral supercritical fluid chromatography (WhelkO-1(R,R) 25 x 3 cm, 5 mM column at 35 °C, eluting with 75:25 carbon dioxide-methanol at 180 mL/min) to provide a faster-eluting enantiomer (Intermediate 69-1, 181 mg) and a slower-eluting enantiomer (Intermediate 69-2). Enantiomeric purities were determined to be >99.5% by analytical chiral chromatography. The absolute configurations were not determined.

Example 70-1

Preparation of 7-((R,S)-1,2-dihydroxyethyl)-4-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00486] Using the procedure of Example 3-2, 4-bromo-7-(1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide (Example 68-1, 40 mg, 0.115 mmol) and 5-methyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-18, 41.6 mg, 0.115 mmol) were converted into 7-((RS)-1,2-dihydroxyethyl)-4-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a white solid (30 mg, 49%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.96 (1 H, d, J=7.70 Hz), 7.76 (1 H, d, J=7.70 Hz), 7.66 (1 H, d, J=4.18 Hz), 7.47 - 7.57 (3 H, m), 7.38 - 7.44 (2 H, m), 7.02 - 7.12 (3 H, m), 4.81 - 4.85 (1 H, m), 3.68 - 3.72 (2 H, m), 2.52 (3 H, s), 1.91 (3 H, s). Mass spectrum m/z 488.3 $(M+H)^+$.

[00487] The following compounds were prepared using the procedures demonstrated in Example 70-1 and closely related procedures, using the Intermediates shown in place of Intermediate 50-18.

Example	Starting materials	Compound name	Mass spectrum
70-2	Intermediate 53-1	7-((RS)-1,2-dihydroxyethyl)-4-(3-(4-fluorobenzamido)-2-methylphenyl)-9H-carbazole-1-carboxamide	520.3 $(M+Na)^+$
70-3	Intermediate 50-4	7-((RS)-1,2-dihydroxyethyl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	515.4 $(M+Na)^+$
70-4	Intermediate 50-1	4-(3-amino-2-methylphenyl)-7-((RS)-1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide	376.3 $(M+H)^+$

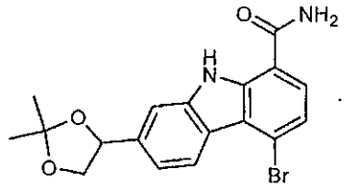
70-5	Intermediate 50-8	7-((RS)-1,2-dihydroxyethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	529.2 $(M+Na)^+$
70-6	Intermediate 50-5	7-((RS)-1,2-dihydroxyethyl)-4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	533.2 $(M+Na)^+$
70-7	Intermediate 50-19	7-((RS)-1,2-dihydroxyethyl)-4-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	492.3 $(M+H-H_2O)^+$
70-8	Intermediate 50-20	7-((RS)-1,2-dihydroxyethyl)-4-(4-methyl-5-(5-methyl-1-oxoisoindolin-2-yl)pyridin-3-yl)-9H-carbazole-1-carboxamide (prepared as the TFA salt)	507.2 $(M+H)^+$
70-9	Intermediate 50-5	7-(1,2-dihydroxyethyl)-4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide[a]	532.2 $(M+Na)^+$
70-10	Intermediate 50-5	7-(1,2-dihydroxyethyl)-4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide[b]	532.2 $(M+Na)^+$
70-11	Intermediate 50-8	7-(1,2-dihydroxyethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide[a]	529.2 $(M+Na)^+$
70-12	Intermediate 50-8	7-(1,2-dihydroxyethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide[b]	529.2 $(M+Na)^+$
70-13	Intermediate 50-27	7-(1,2-dihydroxyethyl)-4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	523.3 $(M+H)^+$
70-14	Intermediate 50-26	4-(3-(6-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide	539.0 $(M+H)^+$

70-15	Intermediate 50-13	7-(1,2-dihydroxyethyl)-4-(2-methyl-3-(1-oxo-4,5,6,7-tetrahydro-1H-isoindol-2(3H)-yl)phenyl)-9H-carbazole-1-carboxamide	478.1 $(M+H-H_2O)^+$
70-16	Intermediate 50-6	7-(1,2-dihydroxyethyl)-4-(3-(5-methoxy-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	504.1 $(M+H-H_2O)^+$
70-17	Intermediate 50-54	7-(1,2-dihydroxyethyl)-4-(2-methyl-3-(quinazolin-4-ylamino)phenyl)-9H-carbazole-1-carboxamide	504.1 $(M+H)^+$

[a] Prepared from Intermediate 69-1 [b] Prepared from Intermediate 69-2

Intermediate 71-1

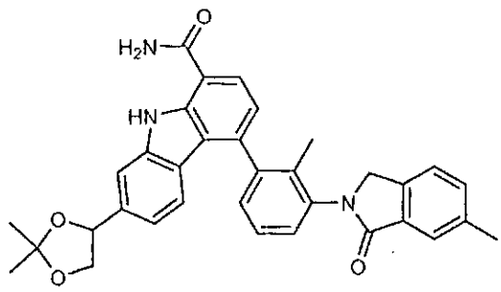
Preparation of 4-bromo-7-(2,2-dimethyl-1,3-dioxolan-4-yl)-9H-carbazole-1-carboxamide



[00488] A mixture of 4-bromo-7-(1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide (Example 68-1, 50 mg, 0.143 mmol) and p-toluenesulfonic acid monohydrate (8.2 mg, 0.043 mmol) in 2,2-dimethoxypropane (1.76 mL, 14.32 mmol) was stirred at rt. DMF (0.5 mL) was added and the mixture was stirred overnight. The mixture was diluted with EtOAc and washed with NaHCO3 (aq) and brine, then dried and concentrated. The residue was purified by column chromatography (eluting with a gradient from 75:25 to 50:50 hexane-EtOAc) to provide 4-bromo-7-(2,2-dimethyl-1,3-dioxolan-4-yl)-9H-carbazole-1-carboxamide as a light yellow solid (40 mg, 75% purity, 54%). Mass spectrum m/z 389, 391 $(M+H)^+$.

Example 72-1

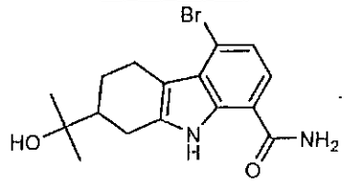
Preparation of 7-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide



[00489] Using the procedure of Example 3-2, 4-bromo-7-(2,2-dimethyl-1,3-dioxolan-4-yl)-9H-carbazole-1-carboxamide (Intermediate 71-1, 40 mg, 0.077 mmol) and 6-methyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-8, 30.8 mg, 0.085 mmol) were converted into 7-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide as a white solid (23 mg, 88% purity, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (1 H, s), 8.21 (1 H, br. s.), 8.03 (1 H, d, J=7.7 Hz), 7.81 (1 H, s), 7.55 - 7.64 (3 H, m), 7.44 - 7.55 (3 H, m), 7.34 (1 H, dd, J=7.5, 1.1 Hz), 6.98 - 7.07 (2 H, m), 6.87 - 6.98 (1 H, m), 5.11 - 5.20 (1 H, m), 4.83 - 4.99 (2 H, m), 4.32 (1 H, ddd, J=8.0, 6.3, 1.5 Hz), 3.56 - 3.67 (1 H, m), 2.44 (3 H, s), 1.83 (3 H, d, J=2.9 Hz), 1.51 (3 H, d, J=3.7 Hz), 1.43 (3 H, s). Mass spectrum m/z 568.2 $(M+Na)^+$.

Example 73-1

Preparation of 5-bromo-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00490] A solution of ethyl 5-bromo-8-carbamoyl-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate (Intermediate 46-1, 2 g, 5.48 mmol) in THF (100 mL) cooled in an ice bath was treated with methyllithium (1.6 M in diethyl ether, 17.11 mL, 27.4 mmol). After 1 h, the mixture was treated slowly with a mixture of 1 M hydrochloric acid (20 mL) and ice (20 g). The organic layer was separated, and the aqueous layer was extracted twice with DCM. The combined organic phases were washed with water and brine, dried and concentrated. The residue was triturated with DCM to provide 5-bromo-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-

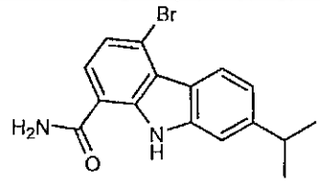
carboxamide as a light yellow solid (1.72 g, 89%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.38 (1 H, d, *J*=8.14 Hz), 7.16 (1 H, d, *J*=8.14 Hz), 3.37 - 3.45 (1 H, m), 2.90 - 2.97 (1 H, m), 2.79 - 2.89 (1 H, m), 2.54 - 2.64 (1 H, m), 2.20 - 2.28 (1 H, m), 1.80 - 1.90 (1 H, m, *J*=11.94, 11.94, 4.95, 2.20 Hz), 1.41 - 1.53 (1 H, m, *J*=12.43, 12.43, 12.32, 5.28 Hz), 1.30 (6 H, s). Mass spectrum m/z 351, 353 $(M+H)^+$.

[00491] The following Intermediate was also prepared using the procedure demonstrated in Example 73-1, substituting Intermediate 48-1 in place of Intermediate 46-1 as starting material.

Intermediate	Compound name	Mass spectrum
73-2	4-bromo-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	329, 331 $(M+H-H_2O)^+$

Intermediate 74-1

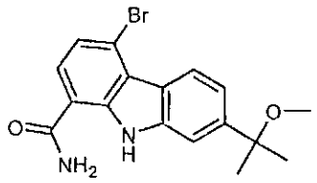
Preparation of 4-bromo-7-isopropyl-9H-carbazole-1-carboxamide



[00492] A suspension of 4-bromo-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide (Intermediate 73-2, 300 mg, 0.864 mmol) in DCM (2 mL) was treated with triethylsilane (1.380 mL, 8.64 mmol) and then slowly with TFA (0.666 mL, 8.64 mmol) and the mixture was stirred at rt for 40 min. The resulting suspension was diluted with DCM and the resulting solution was washed with NaHCO3 (aq). The organic phase was washed with water and brine, and dried and concentrated to give 4-bromo-7-isopropyl-9H-carbazole-1-carboxamide as a white solid (280 mg, 98%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.50 (1 H, br. s.), 8.63 (1 H, d, J=8.1 Hz), 7.32 - 7.40 (3 H, m), 7.22 (1 H, dd, J=8.4, 1.3 Hz), 5.97 (2 H, br. s.), 3.02 - 3.18 (1 H, m), 1.35 (6 H, d, J=6.8 Hz). Mass spectrum m/z 331, 333 $(M+H)^+$.

Intermediate 75-1

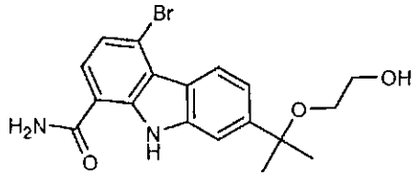
Preparation of 4-bromo-7-(2-methoxypropan-2-yl)-9H-carbazole-1-carboxamide



[00493] A solution of 4-bromo-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide (Intermediate 73-2, 120 mg, 0.346 mmol) and TFA (0.013 mL, 0.173 mmol) in methanol (2 mL) was stirred at rt over a weekend. The mixture was diluted with DCM, washed with 1 M aqueous sodium hydroxide and water, dried and concentrated. The residue was combined with that from another reaction done with 20 mg of Intermediate 73-2, and purified by column chromatography (eluting with hexane-EtOAc) to provide 4-bromo-7-(2-methoxypropan-2-yl)-9H-carbazole-1-carboxamide as a white solid (112 mg, 77%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.53 (1 H, br. s.), 8.68 (1 H, d, J=8.36 Hz), 7.59 (1 H, d, J=1.10 Hz), 7.36 - 7.44 (3 H, m), 3.13 (3 H, s), 1.64 (6 H, s). Mass spectrum m/z 361, 363 $(M+H)^+$.

Intermediate 75-2

Preparation of 4-bromo-7-(2-(2-hydroxyethoxy)propan-2-yl)-9H-carbazole-1-carboxamide



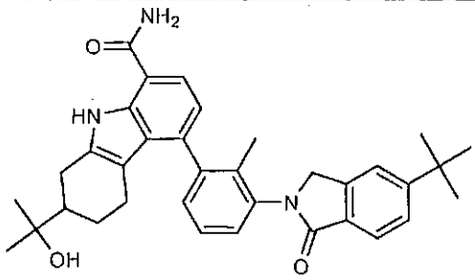
[00494] A mixture of 4-bromo-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide (Intermediate 73-2, 300 mg, 0.864 mmol), p-toluenesulfonic acid monohydrate (8.2 mg, 0.043 mmol) and ethylene glycol (1.45 mL) was stirred at rt overnight. The resulting suspension was treated with NaHCO3 (aq) and diluted with water. The precipitate was collected by filtration, washed with water and dried to provide 4-bromo-7-(2-(2-hydroxyethoxy)propan-2-yl)-9H-carbazole-1-carboxamide as a white solid (324 mg, 96%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.65 (1 H, d, J=8.58 Hz), 7.77 (1 H, d, J=1.10 Hz), 7.75 (1 H, d, J=8.14 Hz), 7.44 (1 H, dd, J=8.36, 1.54 Hz), 7.40 (1 H, d), 3.69 (2 H, t, J=5.17 Hz), 3.32 - 3.34 (2 H, m), 1.68 (6 H, s). Mass spectrum m/z 413, 415 $(M+Na)^+$.

[00495] The following compound was also prepared using the procedures demonstrated in Intermediates 75-1 and 75-2, using Example 70-11 in place of Intermediate 46-1 as starting material.

Example	Compound name	Mass spectrum
75-3	(RS)-7-(2-hydroxy-1-methoxyethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	543.1 $(M+Na)^+$

Example 76-1

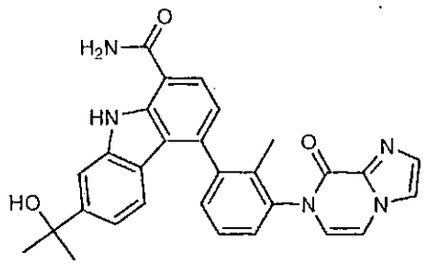
Preparation of 5-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide



[00496] Using the procedure of Example 31-1, 5-bromo-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (Example 73-1, 30 mg, 0.085 mmol) and 5-*tert*-butyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-15, 51.9 mg, 0.128 mmol) were converted into 5-(3-(5-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (25 mg, 51%). ^{1}H NMR (400 MHz, chloroform-d) δ 10.05 (1 H, s), 7.88 (1 H, dd, J=8.35, 2.20 Hz), 7.53 - 7.59 (2 H, m), 7.36 (1 H, dd, J=7.47, 3.95 Hz), 7.28 - 7.33 (2 H, m), 7.26 - 7.28 (1 H, m), 6.90 (1 H, t, J=7.91 Hz), 4.69 - 4.83 (2 H, m), 2.90 (1 H, dd, J=16.04, 5.05 Hz), 2.54 - 2.67 (1 H, m), 1.96 - 2.23 (3 H, m), 1.93 (3 H, d, J=17.14 Hz), 1.74 - 1.89 (1 H, m), 1.58 - 1.68 (1 H, m), 1.39 (9 H, s), 1.31 - 1.37 (1 H, m), 1.23 - 1.26 (6 H, m). Mass spectrum m/z 550.3 $(M+H)^+$.

Example 76-2

Preparation of 7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(8-oxoimidazo[1,2-a]pyrazin-7(8H)-yl)phenyl)-9H-carbazole-1-carboxamide



[00497] Using the procedure of Example 3-2, 4-bromo-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide (Intermediate 73-2, 30 mg, 0.086 mmol) and 7-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)imidazo[1,2-a]pyrazin-8(7H)-one (Intermediate 50-30, 48.6 mg, 0.104 mmol) were converted into 7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(8-oxoimidazo[1,2-a]pyrazin-7(8H)-yl)phenyl)-9H-carbazole-1-carboxamide (4.3 mg, 8.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (1 H, d, J=8.6 Hz), 7.94 (1 H, br. s.), 7.77 (1 H, dd, J=9.7, 7.9 Hz), 7.66 - 7.70 (1 H, m), 7.61 - 7.66 (1 H, m), 7.49 (1 H, dd, J=14.2, 5.8 Hz), 7.28 - 7.36 (3 H, m), 7.15 - 7.29 (2 H, m), 6.93 - 7.00 (1 H, m), 6.85 - 6.90 (1 H, m), 6.79 (1 H, dd, J=15.4, 7.7 Hz), 6.57 (1 H, d, J=8.4 Hz), 4.76 (1 H, d, J=12.5 Hz), 1.52 - 1.60 (3 H, m), 1.21 - 1.30 (6 H, m). Mass spectrum m/z 514.2 $(M+Na)^+$.

[00498] The following compounds were prepared using the procedures demonstrated in Examples 76-1 and 76-2 and closely related procedures, and using the Examples and Intermediates shown as starting materials.

Example	Starting materials	Compound name	Mass spectrum
76-3	Example 73-1, Intermediate 50-14	5-(3-(6-*tert*-butyl-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	550.3 $(M+H)^+$
76-4	Example 73-1, Intermediate 50-5	5-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	512.4 $(M+H)^+$

76-5	Example 73-1, Intermediate 50-8	2-(2-hydroxypropan-2-yl)-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	508.4 $(M+H)^+$
76-6	Example 73-1, Intermediate 50-49	2-(2-hydroxypropan-2-yl)-5-(2-methyl-3-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	495.4 $(M+H)^+$
76-7	Example 73-1, Intermediate 50-50	(Z)-5-(3-(furo[3,4-c]pyridin-3(1H)-ylideneamino)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	495.4 $(M+H)^+$
76-8	Intermediate 74-1, Intermediate 50-49	7-isopropyl-4-(2-methyl-3-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)phenyl)-9H-carbazole-1-carboxamide	475.4 $(M+H)^+$
76-9	Intermediate 74-1, Intermediate 50-50	(Z)-4-(3-(furo[3,4-c]pyridin-3(1H)-ylideneamino)-2-methylphenyl)-7-isopropyl-9H-carbazole-1-carboxamide	475.4 $(M+H)^+$
76-10	Example 73-1, Intermediate 50-23	2-(2-hydroxypropan-2-yl)-5-(2-methyl-3-(2-methyl-4-oxoquinazolin-3(4H)-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	421.4 $(M+H)^+$
76-11	Intermediate 73-2, Intermediate 50-19	4-(3-(5-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	490.3 $(M+H-H_2O)^+$
76-12	Intermediate 73-2, Intermediate 50-4	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	472.3 $(M+H-H_2O)^+$

76-13	Intermediate 73-2, Intermediate 51-2	4-(3-(5-chloro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	506.2 $(M+H-H_2O)^+$
76-14	Intermediate 73-2, Intermediate 50-8	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	486.3 $(M+H-H_2O)^+$
76-15	Intermediate 73-2, Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	530.4 $(M+Na)^+$
76-16	Intermediate 73-2, Intermediate 50-18	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(5-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	486.3 $(M+H-H_2O)^+$
76-17	Intermediate 73-2, Intermediate 50-29	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(1-oxoisoquinolin-2(1H)-yl)phenyl)-9H-carbazole-1-carboxamide	502.4 $(M+H)^+$
76-18	Intermediate 73-2, Intermediate 50-49	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)phenyl)-9H-carbazole-1-carboxamide	491.4 $(M+H)^+$
76-19	Intermediate 73-2, Intermediate 50-50	(Z)-4-(3-(furo[3,4-c]pyridin-3(1H)-ylideneamino)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	491.4 $(M+H)^+$
76-20	Intermediate 73-2, Intermediate 50-7	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(1-oxo-6-(trifluoromethyl)isoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	540.1 $(M+H-H_2O)^+$

76-21	Intermediate 75-1, Intermediate 50-7	7-(2-methoxypropan-2-yl)-4-(2-methyl-3-(1-oxo-6-(trifluoromethyl)isoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	594.2 $(M+Na)^+$
76-22	Intermediate 73-2, Intermediate 50-23	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(2-methyl-4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	517.4 $(M+H)^+$
76-23	Intermediate 73-2, Intermediate 50-17	4-(3-(4-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	490.3 $(M+H-H_2O)^+$
76-24	Intermediate 73-2, Intermediate 50-16	4-(3-(7-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	490.4 $(M+H-H_2O)^+$
76-25	Intermediate 73-2, Intermediate 50-24	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	503.4 $(M+H)^+$
76-26	Intermediate 73-2, Intermediate 50-25	4-(3-(5-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	521.3 $(M+H)^+$
76-27	Intermediate 73-2, Intermediate 50-26	4-(3-(6-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	537.4 $(M+H)^+$
76-28	Intermediate 73-2, Intermediate 50-28	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(6-methyl-4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	517.4 $(M+H)^+$

76-29	Intermediate 74-1, Intermediate 50-16	4-(3-(7-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-isopropyl-9H-carbazole-1-carboxamide	492.4 $(M+H)^+$
76-30	Intermediate 74-1, Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-isopropyl-9H-carbazole-1-carboxamide	492.4 $(M+H)^+$
76-31	Intermediate 74-1, Intermediate 50-7	7-isopropyl-4-(2-methyl-3-(1-oxo-6-(trifluoromethyl)isoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	542.4 $(M+H)^+$
76-32	Intermediate 73-2, Intermediate 50-6	7-(2-hydroxypropan-2-yl)-4-(3-(5-methoxy-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	502.1 $(M+H-H_2O)^+$
76-33	Intermediate 73-2, Intermediate 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	521.4 $(M+H)^+$
76-34	Intermediate 74-1, Intermediate 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-isopropyl-9H-carbazole-1-carboxamide	505.4 $(M+H)^+$
76-35	Example 73-1, Intermediate 50-27	5-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	525.4 $(M+H)^+$
76-36	Intermediate 73-2, Intermediate 50-1	4-(3-amino-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	374.1 $(M+H)^+$

76-37	Intermediate 75-1, Intermediate 50-1	4-(3-amino-2-methylphenyl)-7-(2-methoxypropan-2-yl)-9H-carbazole-1-carboxamide	356.1 (M+H-CH_3OH)$^+$
76-38	Intermediate 73-2, Intermediate 50-12	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(1-oxo-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)phenyl)-9H-carbazole-1-carboxamide	478.1 (M+H-H_2O)$^+$
76-39	Intermediate 73-2, Intermediate 50-13	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(1-oxo-4,5,6,7-tetrahydro-1H-isoindol-2(3H)-yl)phenyl)-9H-carbazole-1-carboxamide	476.2 (M+H-H_2O)$^+$
76-40	Example 73-1, Intermediate 50-24	2-(2-hydroxypropan-2-yl)-5-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	507.4 (M+H)$^+$
76-41	Example 73-1, Intermediate 50-25	5-(3-(5-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	525.4 (M+H)$^+$
76-42	Example 73-1, Intermediate 50-26	5-(3-(6-chloro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	541.4 (M+H)$^+$
76-43	Example 73-1, Intermediate 50-28	2-(2-hydroxypropan-2-yl)-5-(2-methyl-3-(6-methyl-4-oxoquinazolin-3(4H)-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	521.4 (M+H)$^+$
76-44	Example 73-1, Intermediate 50-7	2-(2-hydroxypropan-2-yl)-5-(2-methyl-3-(1-oxo-6-(trifluoromethyl)isoindolin-2-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	562.4 (M+H)$^+$

76-45	Example 73-1, Intermediate 50-12	2-(2-hydroxypropan-2-yl)-5-(2-methyl-3-(1-oxo-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	500.2 $(M+H)^+$
76-46	Example 73-1, Intermediate 50-13	2-(2-hydroxypropan-2-yl)-5-(2-methyl-3-(1-oxo-4,5,6,7-tetrahydro-1H-isoindol-2(3H)-yl)phenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	498.2 $(M+H)^+$
76-47	Example 73-1, Intermediate 50-1	5-(3-amino-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	378.2 $(M+H)^+$
76-48	Intermediate 75-2, Intermediate 50-7	7-(2-(2-hydroxyethoxy)propan-2-yl)-4-(2-methyl-3-(1-oxo-6-(trifluoromethyl)isoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide	624.2 $(M+Na)^+$
76-49	Intermediate 75-2, Intermediate 50-50	(Z)-4-(3-(furo[3,4-c]pyridin-3(1H)-ylideneamino)-2-methylphenyl)-7-(2-(2-hydroxyethoxy)propan-2-yl)-9H-carbazole-1-carboxamide	535.2 $(M+H)^+$
76-50	Intermediate 75-1, Intermediate 50-49	7-(2-methoxypropan-2-yl)-4-(2-methyl-3-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)phenyl)-9H-carbazole-1-carboxamide	473.1 $(M+H-CH_3OH)^+$
76-51	Intermediate 73-2, Intermediate 50-48	4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	521.3 $(M+H)^+$
76-52	Intermediate 75-2, Intermediate 50-24	7-(2-(2-hydroxyethoxy)propan-2-yl)-4-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	569.1 $(M+Na)^+$

76-53	Intermediate 75-1, Intermediate 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(2-methoxypropan-2-yl)-9H-carbazole-1-carboxamide	557.1 $(M+Na)^+$
76-54	Intermediate 75-2, Intermediate 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(2-(2-hydroxyethoxy)propan-2-yl)-9H-carbazole-1-carboxamide	587.1 $(M+Na)^+$
76-55	Intermediate 75-1, Intermediate 50-24	7-(2-methoxypropan-2-yl)-4-(2-methyl-3-(4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	517.1 $(M+H)^+$
76-56	Intermediate 75-1, Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-methoxypropan-2-yl)-9H-carbazole-1-carboxamide	490.0 $(M+H-CH_3OH)^+$
76-57	Intermediate 73-2, Intermediate 50-51	7-(2-hydroxypropan-2-yl)-4-(3-(8-methoxy-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	533.2 $(M+H)^+$
76-58	Intermediate 73-2, Intermediate 50-52	7-(2-hydroxypropan-2-yl)-4-(3-(5-methoxy-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	533.2 $(M+H)^+$
76-59	Intermediate 73-2, Intermediate 50-53	7-(2-hydroxypropan-2-yl)-4-(3-(7-methoxy-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	533.2 $(M+H)^+$
76-60	Example 73-1, Intermediate 50-38	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(4-oxo-6-(trifluoromethoxy)quinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	587.1 $(M+H)^+$

76-61	Intermediate 73-2, Intermediate 50-43	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(2-oxopiperidin-1-yl)phenyl)-9H-carbazole-1-carboxamide	456.2 $(M+H)^+$
76-62	Intermediate 73-2, Intermediate 50-9	4-(3-(6-cyano-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	497.1 $(M+H-H_2O)^+$
76-63	Example 73-1, Intermediate 50-48	5-(3-(8-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	525.2 $(M+H)^+$
76-64	Example 73-1, Intermediate 50-51	2-(2-hydroxypropan-2-yl)-5-(3-(8-methoxy-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide	537.2 $(M+H)^+$
76-65	Intermediate 73-2, Intermediate 50-58	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(8-methyl-4-oxoquinazolin-3(4H)-yl)phenyl)-9H-carbazole-1-carboxamide	517.2 $(M+H)^+$
76-66	Intermediate 73-2, Intermediate 50-59	7-(2-hydroxypropan-2-yl)-4-(3-(6-methoxy-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	533.2 $(M+H)^+$
76-67	Intermediate 73-2, Intermediate 50-60	4-(3-(7-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	521.1 $(M+H)^+$

Example 76-15

[00499] 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 10.60 (1 H, s), 7.70 (1 H, d, *J*=1.10 Hz), 7.63 - 7.68 (2 H, m), 7.52 (1 H, dd, *J*=8.36, 4.40 Hz), 7.44 - 7.48 (2 H,

m), 7.31 - 7.41 (2 H, m), 7.21 (1 H, dd, *J*=8.36, 1.76 Hz), 7.06 - 7.11 (2 H, m), 4.82 (2 H, s), 2.01 (1 H, s), 1.97 (3 H, s), 1.66 (6 H, s).

Example 76-25

[00500] 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 10.57 (1 H, d, *J*=15.19 Hz), 8.38 - 8.43 (1 H, m), 8.15 (1 H, d, *J*=6.60 Hz), 7.78 - 7.84 (2 H, m), 7.68 - 7.72 (1 H, m), 7.66 (1 H, dd, *J*=7.92, 2.20 Hz), 7.42 - 7.60 (4 H, m), 7.27 (1 H, d), 7.12 - 7.16 (1 H, m), 6.90 - 7.08 (1 H, m), 1.91 (3 H, d, *J*=11.88 Hz), 1.63 - 1.67 (6 H, m).

Example 76-32

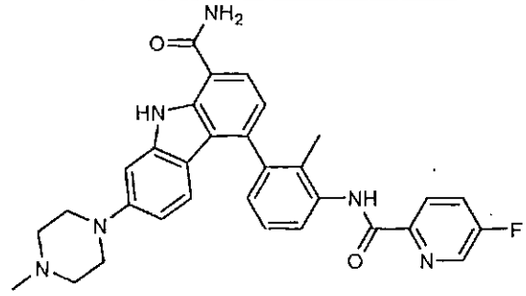
[00501] 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 10.56 (1 H, s), 7.86 (1 H, d, *J*=8.36 Hz), 7.67 (1 H, d, *J*=1.32 Hz), 7.64 (1 H, d, *J*=7.92 Hz), 7.41 - 7.44 (2 H, m), 7.32 - 7.37 (1 H, m), 7.19 (1 H, dd, *J*=8.36, 1.54 Hz), 7.00 - 7.10 (4 H, m), 4.77 (2 H, s), 3.90 (3 H, s), 1.95 (3 H, s), 1.63 (6 H, s)

Example 76-51

[00502] 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 10.59 (1 H, d), 8.18 (2 H, d, *J*=7.26 Hz), 7.71 (1 H, dd, *J*=10.01, 0.99 Hz), 7.65 (1 H, t, *J*=7.70 Hz), 7.41 - 7.59 (5 H, m), 7.20 - 7.29 (1 H, m), 7.07 (1 H, dd, *J*=17.83, 7.70 Hz), 6.87 - 7.15 (1 H, m), 2.00 (1 H, d, *J*=14.97 Hz), 1.89 (3 H, d, *J*=12.54 Hz), 1.64 (6 H, s).

Example 77-1

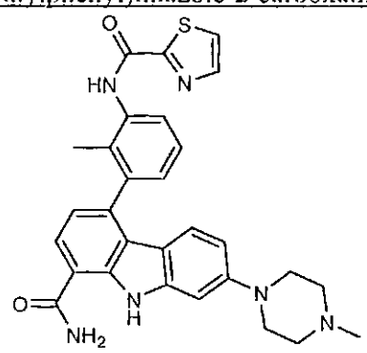
Preparation of 4-(3-(5-fluoropicolinamido)-2-methylphenyl)-7-(4-methylpiperazin-1-yl)-9H-carbazole-1-carboxamide



[00503] A mixture of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazin-1-yl)-9H-carbazole-1-carboxamide, TFA salt (Example 66-3, 40 mg, 0.076 mmol), 5-fluoropicolinic acid (16.1 mg, 0.114 mmol), HOAT (15.5 mg, 0.114 mmol), and EDC (29.1 mg, 0.152 mmol) in acetonitrile (4 mL) was treated with DIEA (0.265 mL, 1.516 mmol). The resulting solution was stirred at rt for 4 h, then was concentrated and purified by preparative HPLC to provide 4-(3-(5-fluoropicolinamido)-2-methylphenyl)-7-(4-methylpiperazin-1-yl)-9H-carbazole-1-carboxamide, TFA salt, as a light brown solid (20 mg, 37%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.47 (1 H, d, J=2.8 Hz), 8.21 (1 H, dd, J=8.8, 4.5 Hz), 7.85 - 7.91 (1 H, m), 7.78 (1 H, d, J=7.8 Hz), 7.72 (1 H, td, J=8.6, 2.9 Hz), 7.33 (1 H, t, J=7.8 Hz), 7.09 - 7.16 (1 H, m), 7.07 (1 H, d, J=2.0 Hz), 6.91 (1 H, d, J=7.8 Hz), 6.81 (1 H, d, J=8.5 Hz), 6.59 (1 H, dd, J=8.8, 2.0 Hz), 3.71 - 3.84 (2 H, m), 3.44 - 3.55 (2 H, m), 3.10 - 3.19 (2 H, m), 2.91 - 3.04 (2 H, m), 2.87 (3 H, s), 1.93 (3 H, s). Mass spectrum m/z 537.1 $(M+H)^+$.

Example 77-2

Preparation of N-(3-(1-carbamoyl-7-(4-methylpiperazin-1-yl)-9H-carbazol-4-yl)-2-methylphenyl)thiazole-2-carboxamide



[00504] A solution of 4-(3-amino-2-methylphenyl)-7-(4-methylpiperazin-1-yl)-9H-carbazole-1-carboxamide, TFA salt (Example 66-3, 30 mg, 0.047 mmol) and TEA (0.026 mL, 0.187 mmol) in DCM-THF (2:1, 3 mL) was treated with thiazole-2-carbonyl chloride, hydrochloric acid salt (8.3 mg, 0.056 mmol) and stirred at rt for 1.5 h. The mixture was concentrated and purified by preparative HPLC to provide N-(3-(1-carbamoyl-7-(4-methylpiperazin-1-yl)-9H-carbazol-4-yl)-2-methylphenyl)thiazole-2-carboxamide, TFA salt, as a white solid (19 mg, 56%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.24 (1 H, s), 10.38 (1 H, s), 8.09 - 8.14 (1 H, m), 8.07 (1 H, d, J=3.1 Hz), 8.04 (1 H, d, J=3.1 Hz), 7.86 (1 H, d, J=8.0 Hz), 7.57 (1 H, d, J=7.5 Hz), 7.41 (1 H, br. s.), 7.34 (1 H, t, J=7.8 Hz), 7.23 (1 H, d, J=1.9 Hz), 7.13 (1 H, d, J=6.7 Hz),

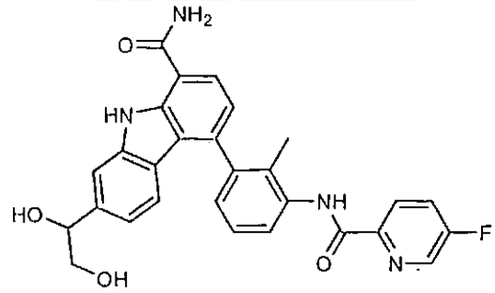
6.87 (1 H, d, J=7.8 Hz), 6.75 (1 H, d, J=8.9 Hz), 6.63 (1 H, dd, J=8.9, 2.2 Hz), 3.69 - 3.79 (2 H, m), 3.43 - 3.50 (2 H, m), 3.06 - 3.18 (2 H, m), 2.87 - 2.97 (2 H, m), 2.79 (3 H, br. s.), 1.87 (3 H, s). Mass spectrum m/z 525.1 $(M+H)^+$.

[00505] The following compound was also prepared using the procedure demonstrated in Example 77-1:

Example	Compound name	Mass spectrum
77-3	N-(3-(1-carbamoyl-7-(4-methylpiperazin-1-yl)-9H-carbazol-4-yl)-2-methylphenyl)-5-methylthiazole-2-carboxamide (prepared as the TFA salt)	539.1 $(M+H)^+$

Example 78-1

Preparation of 7-(1,2-dihydroxyethyl)-4-(3-(5-fluoropicolinamido)-2-methylphenyl)-9H-carbazole-1-carboxamide



[00506] A solution of 4-(3-amino-2-methylphenyl)-7-(1,2-dihydroxyethyl)-9H-carbazole-1-carboxamide (Example 70-4, 28 mg, 0.075 mmol), 5-fluoropicolinic acid (15.8 mg, 0.112 mmol), HOAT (18.3 mg, 0.134 mmol), and EDC (28.6 mg, 0.149 mmol) in acetonitrile-THF (2:1, 3 mL) was treated with DIEA (0.039 mL, 0.224 mmol) and stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC. The residue from concentration of the appropriate effluent fractions was partitioned between NaHCO3 (aq) and EtOAc, and the organic phase was washed with brine, dried and concentrated to provide 7-(1,2-dihydroxyethyl)-4-(3-(5-fluoropicolinamido)-2-methylphenyl)-9H-carbazole-1-carboxamide as an off-white solid (20 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (1 H, s), 10.38 (1 H, s), 8.74 (1 H, d, J=2.6 Hz), 8.28 (1 H, dd, J=8.8, 4.8 Hz), 8.10 - 8.23 (1 H, m), 7.95 - 8.04 (2 H, m), 7.87 - 7.93 (1 H, m), 7.72 (1 H, s), 7.46 - 7.52 (1 H, m), 7.43 (1 H, t, J=7.6 Hz), 7.18 (1 H, d, J=6.6 Hz), 6.97 (1 H, d, J=7.7 Hz), 6.82 - 6.92 (2 H, m), 5.22

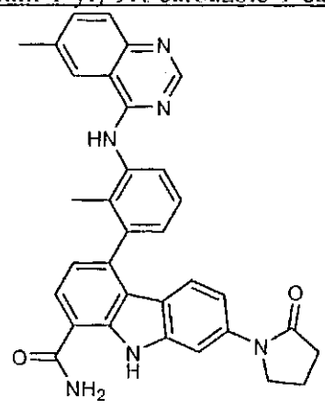
(1 H, t, J=3.5 Hz), 4.66 - 4.72 (1 H, m), 4.56 - 4.64 (1 H, m), 3.44 (2 H, t, J=6.1 Hz), 1.97 (3 H, s). Mass spectrum m/z 521.3 $(M+Na)^+$.

[00507] The following compound was also prepared using the procedure demonstrated in Example 78-1.

Example	Compound name	Mass spectrum
78-2	7-(1,2-dihydroxyethyl)-4-(2-methyl-3-(1-methyl-1H-imidazole-2-carboxamido)phenyl)-9H-carbazole-1-carboxamide	484.4 $(M+H)^+$

Example 79-1

Preparation of 4-(2-methyl-3-(6-methylquinazolin-4-ylamino)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide



[00508] A suspension of 4-chloro-6-methylquinazoline (prepared by the procedure used in Steps 1 and 2 of the preparation of Intermediate 32-1, 16.81 mg, 0.094 mmol) and 4-(3-amino-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide (Intermediate 65-1, 25 mg, 0.063 mmol) in isopropanol (0.75 mL) was treated with hydrogen chloride (4 M in 1,4-dioxane) (0.019 mL, 0.075 mmol) and heated by microwave irradiation in a sealed tube at 140 °C for 45 min. The mixture was concentrated and the residue was purified by preparative HPLC. The residue from concentration of the appropriate effluent fractions was partitioned between NaHCO3 (aq) and EtOAc, and the aqueous phase was extracted twice more with EtOAc. The combined organic phases were dried and concentrated to provide 4-(2-methyl-3-(6-methylquinazolin-4-ylamino)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide as a tan solid (7.4 mg, 20%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.43 (1 H, s), 8.22 (1 H, s), 7.97 (1 H, d, J=7.7 Hz), 7.84 (1 H, d, J=1.3

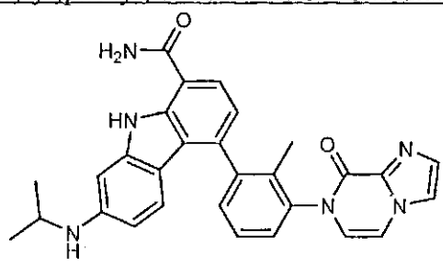
Hz), 7.67 - 7.77 (2 H, m), 7.46 - 7.58 (2 H, m), 7.36 (1 H, dd, J=7.3, 1.5 Hz), 7.21 - 7.30 (2 H, m), 7.13 (1 H, d, J=7.9 Hz), 3.98 - 4.07 (2 H, m), 2.65 (2 H, t, J=8.1 Hz), 2.60 (3 H, s), 2.18 - 2.28 (2 H, m), 1.96 (3 H, s). Mass spectrum m/z 541.5 $(M+H)^+$.

[00509] The following compounds were also prepared using the procedure demonstrated in Example 79-1, using the appropriate chloroquinazoline in place of 4-chloro-6-methylquinazoline.

Example	Compound name	Mass spectrum
79-2	4-(2-methyl-3-(7-methylquinazolin-4-ylamino)phenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	541.5 $(M+H)^+$
79-3	4-(3-(6-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	545.4 $(M+H)^+$
79-4	4-(3-(7-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(2-oxopyrrolidin-1-yl)-9H-carbazole-1-carboxamide	545.4 $(M+H)^+$

Example 80-1

Preparation of 7-(isopropylamino)-4-(2-methyl-3-(8-oxoimidazo[1,2-a]pyrazin-7(8H)-yl)phenyl)-9H-carbazole-1-carboxamide



[00510] Step 1 A solution of tris(dibenzylideneacetone)dipalladium (33 mg, 0.036 mmol) and tricyclohexylphosphine (0.182 mL, 0.173 mmol) in 1,4-dioxane (9 mL), purged with nitrogen, was combined with 4-bromo-7-(isopropylamino)-9H-carbazole-1-carboxamide (Example 61-5, 250 mg, 0.722 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (202 mg, 0.794 mmol) and potassium acetate (142 mg, 1.444 mmol). The mixture was heated with stirring in a sealed tube at 90 °C for 5.5 h. The mixture was cooled to rt and partitioned between water and EtOAc. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried and concentrated. The residue was subjected to column chromatography (eluting with a gradient from 60:40 to 20:80 hexane-EtOAc) to provide 7-(isopropylamino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-carbazole-1-carboxamide as an

impure yellow solid (ca. 35% purity, 170 mg, 21%), used without further purification. Mass spectrum m/z 394.2 $(M+H)^+$.

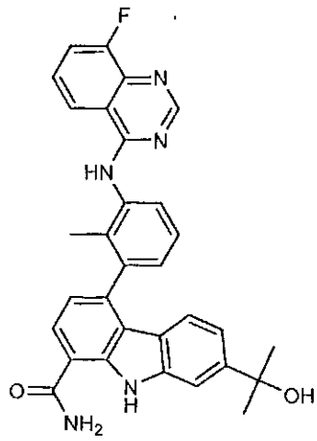
[00511] Step 2 A suspension of impure 7-(isopropylamino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-carbazole-1-carboxamide (60 mg, 0.053 mmol), 7-(3-bromo-2-methylphenyl)imidazo[1,2-a]pyrazin-8(7H)-one TFA salt (Intermediate 11-1, 22.3 mg, 0.053 mmol), tetrakis(triphenylphosphine)palladium (3.1 mg, 0.003 mmol) and 2 M aqueous sodium carbonate (0.080 mL, 0.160 mmol) in toluene-ethanol (4:1, 1.3 mL) was heated under nitrogen at 90 °C overnight. The mixture was concentrated and the residue was purified by preparative HPLC. The appropriate effluent fractions were concentrated and the residue was partitioned between NaHCO3 (aq) and EtOAc. The organic phase was dried and concentrated to provide 7-(isopropylamino)-4-(2-methyl-3-(8-oxoimidazo[1,2-a]pyrazin-7(8H)-yl)phenyl)-9H-carbazole-1-carboxamide as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 - 10.99 (1 H, m), 8.01 (1 H, br. s.), 7.83 (1 H, dd, J=4.5, 1.0 Hz), 7.68 - 7.77 (1 H, m), 7.59 - 7.67 (1 H, m), 7.38 - 7.50 (3 H, m), 7.24 - 7.38 (2 H, m), 7.08 (1 H, dd, J=8.4, 5.9 Hz), 6.76 - 6.87 (1.55 H, m), 6.73 (1 H, dd, J=7.4, 1.9 Hz), 6.48 (0.45 H, d, J=8.8 Hz), 6.13 - 6.29 (1 H, m), 5.44 (1 H, t, J=8.3 Hz), 3.40 - 3.55 (1 H, m), 1.70 (3 H, d, J=11.4 Hz), 1.09 (6 H, td, J=5.8, 3.4 Hz). Mass spectrum m/z 491.3 $(M+H)^+$.

[00512] The following compound was also prepared using procedures demonstrated in Example 80-1, using Intermediate 29-1 in place of Intermediate 11-1.

Example	Compound name	Mass spectrum
80-2	7-(isopropylamino)-4-(2-methyl-3-(2-methyl-8-oxoimidazo[1,2-a]pyrazin-7(8H)-yl)phenyl)-9H-carbazole-1-carboxamide	505.2 $(M+H)^+$

Example 81-1

Preparation of 4-(3-(8-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide



[00513] Step 1 A solution of tris(dibenzylideneacetone)dipalladium (274 mg, 0.30 mmol) and tricyclohexylphosphine (1.51 mL, 1.438 mmol) in 1,4-dioxane (75 mL), purged with nitrogen, was combined with 4-bromo-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide (Example 73-1, 2.08 g, 5.99 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.826 g, 7.19 mmol) and potassium acetate (1.176 g, 11.98 mmol). The mixture was heated with stirring in a sealed tube at 90 °C for 5 h. The mixture was cooled to rt, filtered through Celite and the solids were washed with EtOAc. The filtrate was concentrated and the residue was subjected to column chromatography (eluting with a gradient from 60:40 hexane-EtOAc to EtOAc) to provide 7-(2-hydroxypropan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-carbazole-1-carboxamide as an impure yellow solid (2.03 g, 72%), used without further purification. Mass spectrum m/z 377.2 $(M+H-H_2O)^+$.

[00514] Step 2 A mixture of 7-(2-hydroxypropan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-carbazole-1-carboxamide (ca. 60% purity, 35 mg, 0.053 mmol), N-(3-bromo-2-methylphenyl)-8-fluoroquinazolin-4-amine (Intermediate 32-7, 17.69 mg, 0.053 mmol), and 2 M aqueous sodium carbonate (0.067 mL, 0.133 mmol) in toluene (0.8 mL) and ethanol (0.200 mL) was purged with argon, treated with tetrakis(triphenylphosphine)palladium (3.1 mg, 0.003 mmol) and heated at 90 °C in a sealed tube for 16.5 h. The mixture was cooled to rt and concentrated. The residue was purified by preparative HPLC and the appropriate effluent fractions were treated with NaHCO3 (aq) and partially concentrated at rt. The resulting aqueous suspension was filtered and the precipitate was washed with water and dried to provide 4-(3-(8-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide as a white solid (18.0 mg, 61%). ^{1}H NMR (400 MHz,

DMSO-d_6) δ 11.41 (1 H, s), 10.08 (1 H, s), 8.56 (1 H, s), 8.35 (1 H, d, J=8.4 Hz), 8.16 (1 H, br. s.), 7.99 (1 H, d, J=7.9 Hz), 7.87 (1 H, s), 7.70 (1 H, dd, J=10.2, 8.3 Hz), 7.60 (1 H, td, J=8.1, 5.2 Hz), 7.42 - 7.54 (3 H, m), 7.28 (1 H, dd, J=7.3, 1.3 Hz), 7.11 (2 H, s), 7.01 (1 H, d, J=7.7 Hz), 5.00 (1 H, s), 1.85 (3 H, s), 1.49 (6 H, s). Mass spectrum m/z 520.1 $(M+H)^+$.

[00515] The following compounds were prepared using the procedures demonstrated in Example 81-1 and closely related procedures, and using the Intermediates shown in place of Intermediate 32-7.

Example/ Intermediate	Starting materials	Compound name	Mass spectrum
81-2	Intermediate 29-2	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(2-methyl-8-oxoimidazo[1,2-a]pyrazin-7(8H)-yl)phenyl)-9H-carbazole-1-carboxamide	506.3 $(M+H)^+$
81-3	Intermediate 29-1	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(3-methyl-8-oxoimidazo[1,2-a]pyrazin-7(8H)-yl)phenyl)-9H-carbazole-1-carboxamide	506.3 $(M+H)^+$
81-4	Intermediate 31-1	4-(3-((1H-indazol-1-yl)methyl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	489.3 $(M+H)^+$
81-5	Intermediate 31-2	4-(3-((2H-indazol-2-yl)methyl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	489.3 $(M+H)^+$
81-6	Intermediate 31-3	4-(3-((1H-benzo[d]imidazol-1-yl)methyl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	489.3 $(M+H)^+$
81-7	Intermediate 30-1	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(2-oxo-3-m-tolylimidazolidin-1-yl)phenyl)-9H-carbazole-1-carboxamide	555.3 $(M+Na)^+$

81-8	Intermediate 32-2	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(6-methylquinazolin-4-ylamino)phenyl)-9H-carbazole-1-carboxamide	516.4 $(M+H)^+$
81-9	Intermediate 32-5	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(7-methylquinazolin-4-ylamino)phenyl)-9H-carbazole-1-carboxamide	516.5 $(M+H)^+$
81-10	Intermediate 32-4	4-(3-(6-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	520.4 $(M+H)^+$
81-11	Intermediate 32-3	4-(3-(7-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	520.4 $(M+H)^+$
81-12	Intermediate 32-8	7-(2-hydroxypropan-2-yl)-4-(3-(6-methoxyquinazolin-4-ylamino)-2-methylphenyl)-9H-carbazole-1-carboxamide	532.1 $(M+H)^+$
81-13	Intermediate 32-1	7-(2-hydroxypropan-2-yl)-4-(3-(7-methoxyquinazolin-4-ylamino)-2-methylphenyl)-9H-carbazole-1-carboxamide	532.1 $(M+H)^+$
81-14	Intermediate 32-6	4-(3-(5-fluoroquinazolin-4-ylamino)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	520.1 $(M+H)^+$
81-15	Intermediate 41-2	7-(2-hydroxypropan-2-yl)-4-(3-(6-methoxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	535.2 $(M+H)^+$
81-16	Intermediate 41-4	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-5-yloxy)phenyl)-9H-carbazole-1-carboxamide	502.1 $(M+H-H_2O)^+$

81-17	Intermediate 41-3	4-(3-(5-hydroxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	542.1 $(M+Na)^+$
81-18	Intermediate 41-5	4-(3-(7-chloro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	538.2 $(M+H)^+$
81-19	Intermediate 41-1	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)phenyl)-9H-carbazole-1-carboxamide	504.1 $(M+H)^+$
81-20	Intermediate 41-6	4-(3-(6-fluoro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	522.1 $(M+H)^+$
81-21	Intermediate 41-7	4-(3-(3,4-dimethyl-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	490.1 $(M+Na)^+$
81-22	Intermediate 41-8	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(3-methyl-2-oxopyridin-1(2H)-yl)phenyl)-9H-carbazole-1-carboxamide	466.1 $(M+H)^+$
81-23	Intermediate 41-9	4-(3-(4,4-dimethyl-2-oxopyrrolidin-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	452.1 $(M+H-H_2O)^+$
81-24	Intermediate 42-1	7-(2-hydroxypropan-2-yl)-4-(3-(isobenzofuran-1(3H)-ylidenemethyl)-2-methylphenyl)-9H-carbazole-1-carboxamide	471.0 $(M+H-H_2O)^+$
Intermediate 81-25	2,6-dibromo-toluene	4-(3-bromo-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	419, 421 $(M+H)^+$

81-26	Intermediate 32-9	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(quinazolin-4-ylamino)phenyl)-9H-carbazole-1-carboxamide	502.2 $(M+H)^+$
Intermediate 81-27	Intermediate 41-10	1-(3-(1-carbamoyl-7-(2-hydroxypropan-2-yl)-9H-carbazol-4-yl)-2-methylphenyl)-5-oxopyrrolidine-3-carboxylic acid	468.3 $(M+H-H_2O)^+$
81-28	Intermediate 30-3	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(2-oxo-3-phenylimidazolidin-1-yl)phenyl)-9H-carbazole-1-carboxamide	542.1 $(M+Na)^+$
81-29	Intermediate 30-4	4-(3-(3-tert-butyl-2-oxoimidazolidin-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	521.1 $(M+Na)^+$
81-30	Intermediate 45-1	4-(3-(4-carbamoyl-2-oxopyrrolidin-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	507.0 $(M+Na)^+$
81-31	Intermediate 22-1	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-((2-oxoindolin-3-ylidene)methyl)phenyl)-9H-carbazole-1-carboxamide	484.1 $(M+H-H_2O)^+$
81-32	Intermediate 55-1	4-(3-(5-hydroxy-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	528.0 $(M+Na)^+$
81-33	Intermediate 1-3	7-(2-hydroxypropan-2-yl)-4-(3-(6-methoxy-1-oxoisoindolin-2-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide	502.0 $(M+H-H_2O)^+$
81-34	Intermediate 30-2	4-(3-(3-benzyl-2-oxoimidazolidin-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide	555.2 $(M+Na)^+$
81-35	Intermediate 56-1	7-(2-hydroxypropan-2-yl)-4-(2-methyl-3-(2-oxo-4-phenyl-2,3-dihydro-1H-imidazol-1-yl)phenyl)-9H-carbazole-1-carboxamide	539.1 $(M+Na)^+$

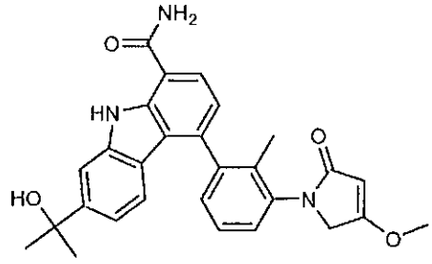
81-36	Intermediate 57-1	benzyl 1-(3-(1-carbamoyl-7-(2-hydroxypropan-2-yl)-9H-carbazol-4-yl)-2-methylphenyl)-2-oxopyrrolidin-3-ylcarbamate	573.2 (M+H-H_2O)$^+$

Example 81-15

[00516] 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.09 - 8.15 (1 H, m), 7.61 - 7.68 (2 H, m), 7.38 - 7.42 (2 H, m), 7.22 - 7.33 (3 H, m), 7.09 - 7.15 (1 H, m), 6.86 - 6.93 (1 H, m), 6.74 (1 H, t), 4.03 - 4.09 (1 H, m), 3.87 (3 H, d, *J*=2.42 Hz), 3.76 - 3.85 (1 H, m), 3.18 - 3.30 (1 H, m), 3.09 (1 H, ddd, *J*=16.29, 5.39, 5.17 Hz), 1.97 - 2.02 (3 H, m), 1.61 - 1.66 (6 H, m).

Example 82-1

Preparation of 7-(2-hydroxypropan-2-yl)-4-(3-(4-methoxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-2-methylphenyl)-9H-carbazole-1-carboxamide

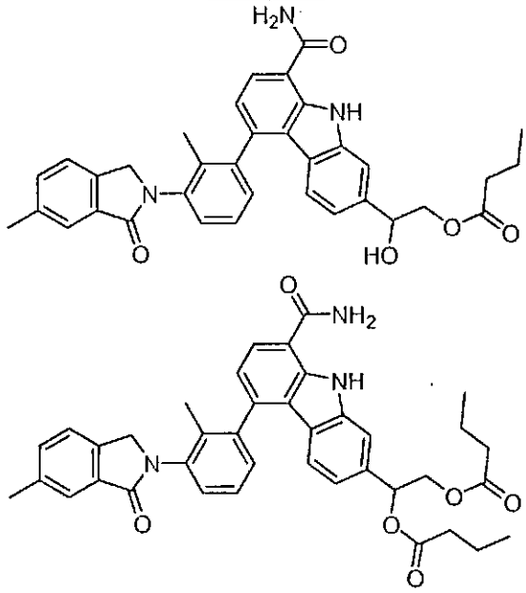


[00517] A mixture of 4-(3-bromo-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide (Intermediate 81-25, 70 mg, 0.160 mmol), 4-methoxy-1H-pyrrol-2(5H)-one (362 mg, 3.20 mmol), cesium carbonate (78 mg, 0.24 mmol), tris(dibenzylideneacetone)dipalladium (14.7 mg, 0.016 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos, 27.8 mg, 0.048 mmol) in 1,4-dioxane (2 mL) was purged with nitrogen and heated via microwave irradiation in a sealed tube at 100 °C for 1 h. The mixture was diluted with DCM, washed with NaHCO3 (aq), dried and concentrated. The residue was purified by preparative HPLC, and the appropriate effluent fractions were treated with NaHCO3 (aq) and extracted with DCM. The combined organic phases were washed with water, dried and concentrated to provide as a white solid (20 mg, 27%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.91 (1 H, d, J=7.70 Hz), 7.73 (1 H, d, J=0.88 Hz), 7.39 - 7.46 (2 H, m), 7.31 - 7.34 (1 H, m), 7.09 (1 H, dd, J=8.47, 1.65 Hz), 7.01 (1 H, d, J=7.70 Hz),

6.98 (1 H, d, J=8.36 Hz), 5.29 (1 H, s), 4.37 - 4.49 (2 H, m), 3.91 (3 H, s), 1.90 (3 H, s), 1.58 (3 H, s), 1.57 (3 H, s). Mass spectrum m/z 492.0 $(M+Na)^+$.

Examples 83-1 and 83-2

Preparation of (RS)-2-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)-2-hydroxyethyl butyrate and (RS)-1-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)ethane-1,2-diyl dibutyrate

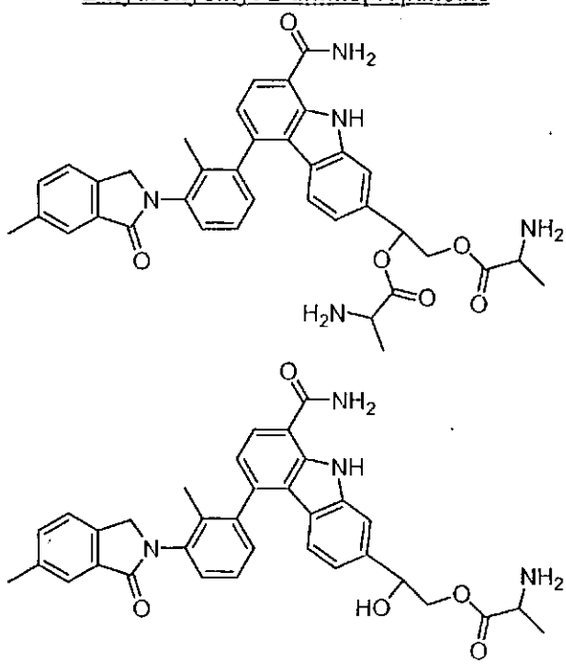


[00518] A solution of 7-(1,2-dihydroxyethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 70-11, 30 mg, 0.059 mmol), butyric anhydride (29 µL, 0.178 mmol), and pyridine (48 µL, 0.593 mmol) in THF-DCM (1:1, 2.4 mL) was stirred at rt overnight. Additional butyric anhydride (0.03 mL, 3 eq.) was added and the mixture was again stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC. The appropriate effluent fractions were partially concentrated and the resulting aqueous suspension was treated with NaHCO3 (aq). The precipitate was collected by filtration, washed with water and dried to provide (RS)-2-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)-2-hydroxyethyl butyrate as a white solid (Example 83-1, 10.5 mg, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (1 H, s), 8.19 (1 H, br. s.), 8.02 (1 H, d, J=7.9 Hz), 7.76 (1 H, d, J=10.1 Hz), 7.54 - 7.64 (3 H, m), 7.50 (3 H, t, J=7.0 Hz), 7.34 (1 H, dd, J=7.7, 1.1 Hz), 6.93 - 7.06 (3 H, m), 5.60 (1 H, dd, J=8.9, 4.3 Hz), 4.89 - 4.94 (2 H, m), 4.82 - 4.89 (1 H, m), 4.05 -

4.13 (2 H, m), 2.44 (3 H, s), 2.27 (2 H, td, J=7.3, 1.1 Hz), 1.83 (3 H, s), 1.51 (2 H, qd, J=7.3, 1.8 Hz), 0.83 (3 H, td, J=7.4, 2.2 Hz). Mass spectrum m/z 599.2 $(M+Na)^+$. Also isolated was (RS)-1-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)ethane-1,2-diyl dibutyrate as a white solid (Example 83-2, 16 mg, 41%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.87 (1 H, d, J=7.7 Hz), 7.57 (2 H, d, J=10.1 Hz), 7.34 - 7.48 (4 H, m), 7.30 (1 H, dd, J=6.9, 1.9 Hz), 6.89 - 7.06 (3 H, m), 5.95 - 6.11 (1 H, m), 4.80 (2 H, s), 4.21 - 4.36 (2 H, m), 2.38 (3 H, s), 2.24 - 2.33 (2 H, m), 2.19 (2 H, td, J=7.3, 1.1 Hz), 1.80 (3 H, s), 1.44 - 1.63 (4 H, m), 0.76 - 0.90 (6 H, m). Mass spectrum m/z 668.3 $(M+Na)^+$.

Example 83-3 and 83-4

Preparation of 1-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)ethane-1,2-diyl bis(2-aminopropanoate) and 2-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)-2-hydroxyethyl 2-aminopropanoate



[00519] A solution of 7-(1,2-dihydroxyethyl)-4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazole-1-carboxamide (Example 70-11, 30 mg, 0.059 mmol), 2-(*tert*-butoxycarbonylamino)propanoic acid (11.8 mg, 0.062 mmol), EDC (34.1 mg, 0.178 mmol), and DMAP (2.2 mg, 0.018 mmol) in DMF (2.4 mL) was stirred at rt overnight. Additional 2-(*tert*-butoxycarbonylamino)propanoic acid

(16 mg) and EDC (17 mg, 1.5 eq.) were added and the mixture was again stirred at rt overnight. TFA (0.3 mL) was added and the mixture was stirred at rt for 1 h, then at 60 °C for 2 h, then at rt overnight. The reaction mixture was concentrated and purified by preparative HPLC. The appropriate effluent fractions were concentrated, treated with hydrogen chloride (4 M in 1,4-dioxane) and water, and the mixture was lyophilized to provide 1-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)ethane-1,2-diyl bis(2-aminopropanoate), hydrochloric acid salt, as a white solid (17 mg, 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 - 11.63 (1 H, m), 8.43 (6 H, br. s.), 8.17 (1 H, br. s.), 7.93 - 8.06 (1 H, m), 7.69 - 7.85 (1 H, m), 7.34 - 7.62 (6 H, m), 7.16 - 7.29 (1 H, m), 6.86 - 7.09 (3 H, m), 5.98 - 6.17 (1 H, m), 4.72 - 4.96 (2 H, m), 4.31 - 4.65 (2 H, m), 3.96 - 4.25 (2 H, m), 2.38 (3 H, s), 1.76 (3 H, s), 1.43 (3 H, dd, J=7.0, 3.7 Hz), 1.24 - 1.38 (3 H, m). Mass spectrum m/z 648.2 $(M+H)^+$. Also isolated was 2-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)-2-hydroxyethyl 2-aminopropanoate, TFA salt, as a white solid (4 mg, 9%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.85 - 7.91 (1 H, m), 7.53 - 7.60 (2 H, m), 7.38 - 7.48 (4 H, m), 7.26 - 7.33 (1 H, m), 7.02 - 7.09 (1 H, m), 6.94 - 7.02 (2 H, m), 5.90 - 5.97 (0.3 H, m), 4.99 (0.7 H, dd, J=7.3, 3.7 Hz), 4.78 - 4.84 (2 H, m), 3.72 - 4.42 (3 H, m), 2.38 (3 H, s), 1.75 - 1.82 (3 H, m), 1.34 - 1.57 (3 H, m). Mass spectrum m/z 577.2 $(M+H)^+$.

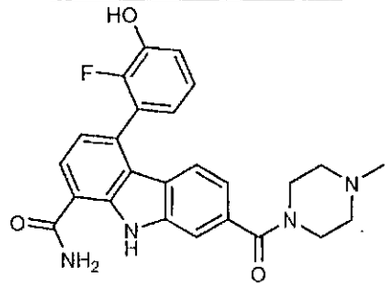
[00520] The following compounds were also prepared using procedures demonstrated in Examples 83-1 through 83-4, using the appropriate acid or acid anhydride.

Example	Compound name	Mass spectrum
83-5	1-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)ethane-1,2-diyl diacetate	612.2 $(M+Na)^+$
83-6	1-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)ethane-1,2-diyl bis(2-amino-3-methylbutanoate) (prepared as the hydrochloric acid salt)	704.2 $(M+H)^+$
83-7	2-(8-carbamoyl-5-(2-methyl-3-(6-methyl-1-	605.1

	oxoisoindolin-2-yl)phenyl)-9H-carbazol-2-yl)-2-hydroxyethyl 2-amino-3-methylbutanoate (prepared as the TFA salt)	$(M+H)^+$

Intermediate 84-1

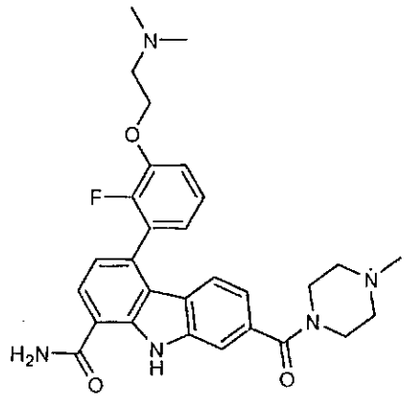
Preparation of 4-(2-fluoro-3-hydroxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00521] A solution of 4-(2-fluoro-3-methoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Example 3-137, 3.6 g, 7.82 mmol) in DCM (42 mL) was stirred at 0 °C and treated with boron tribromide (1 M in DCM, 94 mL, 94 mmol) and the mixture was stirred at rt overnight. The mixture was cooled again to 0 °C and treated slowly with methanol. The mixture was concentrated and purified by column chromatography on neutral alumina (eluting with 90:10 EtOAc-methanol) to provide 4-(2-fluoro-3-hydroxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide as a light colored solid (2.0 g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1 H), 10.08 (s, 1 H), 8.25 (br. s., 1 H), 8.05 (d, J=7.6 Hz, 1 H), 7.81 (s, 1 H), 7.59 (br. s., 1 H), 7.17 (m, 3 H), 7.11 (d, J = 7.6 Hz, 1 H), 6.99 (dd, J = 8.0, 1.2 Hz, 1 H), 6.91 (t, J = 7.2 Hz, 1 H), 3.51 (br. s., 2 H), 3.34 (m, 5 H), 2.34 (br. s., 4 H). Mass spectrum m/z 447.0 $(M+H)^+$.

Example 85-1

Preparation of 4-(3-(2-(dimethylamino)ethoxy)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide



[00522] A mixture of 4-(2-fluoro-3-hydroxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide (Intermediate 84-1, 20 mg, 0.045 mmol) and polymer-supported triphenylphosphine (2.63 mmol/g, 0.358 mmol) in 1,4-dioxane was treated at 0 °C with a solution of diethyl azodicarboxylate (19.5 mg, 0.157 mmol) in THF (0.5 mL), followed after 5 min by a solution of 2-(dimethylamino)ethanol (10 mg, 0.112 mmol) in THF (0.5 mL). The mixture was heated in a sealed tube by microwave irradiation at 90-100 °C for 30 min. The resulting mixture was filtered, the solids were washed with methanol, and the filtrates were concentrated and purified by preparative HPLC to provide 4-(3-(2-(dimethylamino)ethoxy)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide. Mass spectrum m/z 518.2 $(M+H)^+$.

[00523] The following compounds were also prepared using procedures demonstrated in Example 85-1, using the appropriate alcohol in place of 2-(dimethylamino)ethanol.

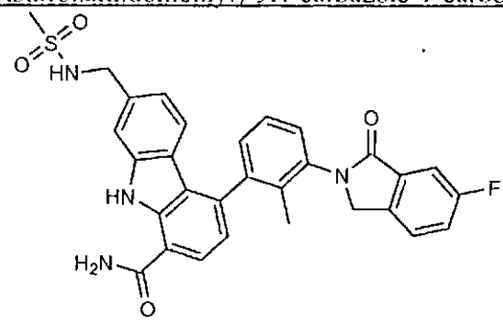
Example	Compound name	Mass spectrum
85-2	4-(2-fluoro-3-phenethoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	551.2 $(M+H)^+$
85-3	4-(2-fluoro-3-(isopentyloxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	517.2 $(M+H)^+$
85-4	4-(2-fluoro-3-propoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	489.2 $(M+H)^+$

85-5	4-(2-fluoro-3-(3-phenylpropoxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	565.2 $(M+H)^+$
85-6	4-(2-fluoro-3-(4-phenylbutoxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	579.2 $(M+H)^+$
85-7	4-(2-fluoro-3-(2-(1-methylpyrrolidin-2-yl)ethoxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	558.2 $(M+H)^+$
85-8	4-(3-ethoxy-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	475.2 $(M+H)^+$
85-9	4-(3-(benzyloxy)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	537.2 $(M+H)^+$
85-10	4-(2-fluoro-3-(4-methoxybenzyloxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	567.2 $(M+H)^+$
85-11	4-(2-fluoro-3-isobutoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	503.2 $(M+H)^+$
85-12	4-(2-fluoro-3-(1-methylpiperidin-4-yloxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	544.2 $(M+H)^+$
85-13	4-(2-fluoro-3-(2-(piperidin-1-yl)ethoxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	558.2 $(M+H)^+$
85-14	4-(2-fluoro-3-isopropoxyphenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	489.2 $(M+H)^+$
85-15	4-(3-(2-(1H-imidazol-1-yl)ethoxy)-2-fluorophenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	541.2 $(M+H)^+$
85-16	4-(2-fluoro-3-(pyrazin-2-ylmethoxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	539.2 $(M+H)^+$

85-17	4-(2-fluoro-3-(thiazol-2-ylmethoxy)phenyl)-7-(4-methylpiperazine-1-carbonyl)-9H-carbazole-1-carboxamide	544.2 $(M+H)^+$

Example 86-1

Preparation of 4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(methylsulfonamidomethyl)-9H-carbazole-1-carboxamide



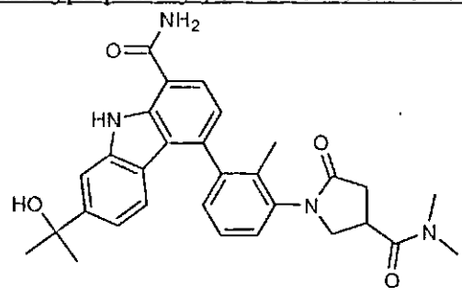
[00524] A suspension of 7-(aminomethyl)-4-bromo-9H-carbazole-1-carboxamide (Step 2 of Example 33-1, 100 mg, 0.314 mmol) and TEA (0.110 mL, 0.786 mmol) in DMF-THF-DCM (25:25:50, 6 mL) was treated dropwise with methanesulfonyl chloride (37 μL, 0.471 mmol) and the resulting mixture was stirred at rt for 3 h. The mixture was partitioned between NaHCO3 (aq) and EtOAc, and the organic phase was washed with brine, dried and concentrated to provide crude 4-bromo-7-(methylsulfonamidomethyl)-9H-carbazole-1-carboxamide as a yellow solid (130 mg, 88%). Without purification, using the procedure of Example 3-2, this material (25 mg, 0.063 mmol) and 6-fluoro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)isoindolin-1-one (Intermediate 50-5, 27.8 mg, 0.076 mmol) were converted into 4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(methylsulfonamidomethyl)-9H-carbazole-1-carboxamide (22 mg, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (1 H, s), 8.20 (1 H, br. s.), 8.03 (1 H, d, J=7.9 Hz), 7.70 - 7.78 (2 H, m), 7.45 - 7.67 (6 H, m), 7.36 (1 H, dd, J=7.7, 1.1 Hz), 7.00 - 7.07 (2 H, m), 6.93 - 7.00 (1 H, m), 4.86 - 5.04 (2 H, m), 4.26 (2 H, d, J=6.2 Hz), 2.87 (3 H, s), 1.84 (3 H, s). Mass spectrum m/z 557.1 $(M+H)^+$.

[00525] The following compounds were also prepared using the procedures demonstrated in Example 86-1 and closely related procedures, and using the Intermediates shown in place of Intermediate 50-5.

Example	Starting materials	Compound name	Mass spectrum
86-2	Intermediate 50-8	4-(2-methyl-3-(6-methyl-1-oxoisoindolin-2-yl)phenyl)-7-(methylsulfonamidomethyl)-9H-carbazole-1-carboxamide	553.1 $(M+H)^+$
86-3	Intermediate 50-51	4-(3-(8-methoxy-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(methylsulfonamidomethyl)-9H-carbazole-1-carboxamide	582.1 $(M+H)^+$
86-4	Intermediate 50-48	4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(methylsulfonamidomethyl)-9H-carbazole-1-carboxamide	570.0 $(M+H)^+$

Example 87-1

Preparation of 4-(3-(4-(dimethylcarbamoyl)-2-oxopyrrolidin-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide

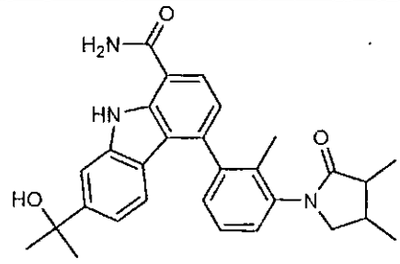


[00526] A solution of 1-(3-(1-carbamoyl-7-(2-hydroxypropan-2-yl)-9H-carbazol-4-yl)-2-methylphenyl)-5-oxopyrrolidine-3-carboxylic acid (Intermediate 81-27, 49 mg, 0.101 mmol), dimethylamine (2 M in THF, 0.252 mL, 0.505 mmol), EDC (38.7 mg, 0.202 mmol) and HOBT (30.9 mg, 0.202 mmol) in THF (2 mL) was stirred at rt overnight. Additional dimethylamine (2 M in THF, 0.252 mL, 0.505 mmol), EDC (38.7 mg, 0.202 mmol) and HOBT (30.9 mg, 0.202 mmol) were added along with DMF (0.5 mL) and the mixture was again stirred overnight. The mixture was diluted with DCM, washed with NaHCO3 (aq), dried and concentrated. The residue was purified by preparative HPLC, and the appropriate effluent fractions were made basic with 1 M aqueous sodium hydroxide and extracted twice with DCM. The organic phase was washed with water, dried and concentrated. The residue was purified by column chromatography (eluting with DCM-methanol-ammonia) to provide 4-(3-(4-(dimethylcarbamoyl)-2-oxopyrrolidin-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide as a white solid (8 mg, 15%). ^{1}H NMR (400 MHz,

methanol-d_4) δ 7.91 (1 H, d, J=7.7 Hz), 7.73 (1 H, d, J=1.1 Hz), 7.40 - 7.49 (2 H, m), 7.33 (1 H, dd, J=6.5, 2.3 Hz), 7.07 (1 H, ddd, J=8.5, 1.4, 1.3 Hz), 7.01 (1 H, d, J=7.9 Hz), 6.94 (1 H, br. s.), 3.84 - 4.13 (3 H, m), 3.13 (3 H, 2 s), 2.97 (3 H, 2 s), 2.85 - 2.94 (1 H, m), 2.74 - 2.83 (1 H, m), 1.93 (3 H, s), 1.57 (6 H, 2 s). Mass spectrum m/z 495.1 $(M+H-H_2O)^+$.

Example 88-1

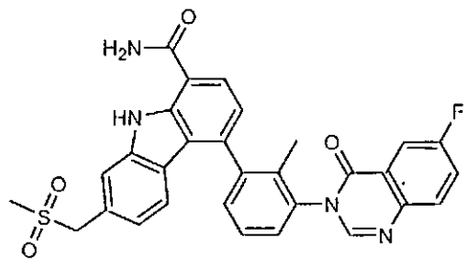
Preparation of 4-(3-(3,4-dimethyl-2-oxopyrrolidin-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide



[00527] A mixture of 4-(3-(3,4-dimethyl-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide (Example 81-21, 20 mg, 0.043 mmol) and ammonium formate (27.0 mg, 0.428 mmol) in methanol (5 mL) was treated with 10% palladium on charcoal (20 mg, 0.019 mmol). The mixture was stirred under nitrogen at rt for 2 h. Additional ammonium formate (27.0 mg, 0.428 mmol) was added and the mixture was stirred at rt overnight. More ammonium formate (57 mg) and 10% palladium on charcoal (40 mg) were added, and after 6 h more additional ammonium formate (57 mg) was added. The mixture was again stirred overnight, then was diluted with DCM and filtered through Celite. The filtrate was washed with water, dried and concentrated. The residue was purified by preparative HPLC and the appropriate effluent fractions were made basic with 1 M aqueous sodium hydroxide and extracted twice with DCM. The combined organic phases were washed with water, dried and concentrated to provide 4-(3-(3,4-dimethyl-2-oxopyrrolidin-1-yl)-2-methylphenyl)-7-(2-hydroxypropan-2-yl)-9H-carbazole-1-carboxamide as a white solid (11 mg, 55%), which was a mixture of diastereomers. Mass spectrum m/z 452.1 $(M+H-H_2O)^+$.

Example 89-1

Preparation of 4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(methylsulfonylmethyl)-9H-carbazole-1-carboxamide



[00528] Step 1 A mixture of 4-bromo-7-(hydroxymethyl)-9H-carbazole-1-carboxamide (Example 30-2, 403 mg, 1.263 mmol), N-chlorosuccinimide (219 mg, 1.642 mmol) and triphenylphosphine (431 mg, 1.642 mmol) in DCM (50 mL) was heated at reflux for 1 h. The mixture was cooled to rt, washed with brine, and the aqueous layer was extracted with DCM. The aqueous layer was filtered and the collected precipitate was washed with water. The organic layers and the collected precipitate were combined and the mixture was concentrated under vacuum. The residue was dissolved in THF (20 mL) and DMSO (5 mL) and the solution was treated with sodium thiomethoxide (115 mg, 1.642 mmol). The mixture was stirred at rt for 30 min, diluted with EtOAc, washed twice with water, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried and concentrated. The residue was purified by column chromatography (eluting with EtOAc-hexane) to provide 4-bromo-7-(methylthiomethyl)-9H-carbazole-1-carboxamide as a white solid (168 mg, 38%) used without further purification. ^{1}H NMR (400 MHz, chloroform-d) δ 8.67 (1 H, d, J=8.1 Hz), 7.46 - 7.52 (2 H, m), 7.36 - 7.41 (1 H, m), 7.26 - 7.29 (1 H, m), 3.87 (2 H, s), 2.03 (3 H, s). Mass spectrum m/z 349, 351 $(M+H)^+$.

[00529] Step 2 A suspension of 4-bromo-7-(methylthiomethyl)-9H-carbazole-1-carboxamide (168 mg, 0.481 mmol) in DCM (10 mL) and THF (2 mL) was treated with 3-chloroperoxybenzoic acid (166 mg, 0.962 mmol) and the mixture was stirred at rt for 30 min. The mixture was treated with NaHCO3 (aq) and the organic phase was separated. The insoluble solid in the aqueous phase was collected by filtration and washed with water. The organic phase and the precipitate were combined and the mixture was concentrated. The residue was triturated with methanol to provide 4-bromo-7-(methylsulfonylmethyl)-9H-carbazole-1-carboxamide as a white solid (180 mg, 98%), used without further purification. ^{1}H NMR (400 MHz, methanol-d_4) δ xx. Mass spectrum m/z 403, 405 $(M+H)^+$.

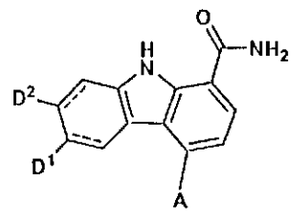
[00530] Step 3 Following the procedure of Example 31-1 but using THF as the solvent instead of toluene-ethanol, 4-bromo-7-(methylsulfonylmethyl)-9H-carbazole-1-carboxamide (50 mg, 0.131 mmol) and 6-fluoro-3-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinazolin-4(3H)-one (Intermediate 50-27, 50 mg, 0.131 mmol) were converted to 4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-yl)-2-methylphenyl)-7-(methylsulfonylmethyl)-9H-carbazole-1-carboxamide as a white solid (16 mg, 22%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 - 8.28 (1 H, m), 7.95 - 8.02 (2 H, m), 7.82 - 7.89 (1 H, m), 7.66 - 7.71 (1 H, m), 7.56 - 7.66 (2 H, m), 7.47 - 7.56 (1 H, m), 6.97 - 7.33 (3 H, m), 4.46 - 4.52 (2 H, m), 2.84 (3 H, s), 1.90 (3 H, s). Mass spectrum m/z 555.0 $(M+H)^+$.

[00531] The following compounds were also prepared using the procedures demonstrated in Example 89-1 and closely related procedures, using the Intermediates shown in place of Intermediate 50-27.

Example	Starting materials	Compound name	Mass spectrum
89-2	Intermediate 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(methylsulfonylmethyl)-9H-carbazole-1-carboxamide	542.1 $(M+H)^+$
89-3	Intermediate 50-6	4-(3-(5-methoxy-1-oxoisoindolin-2-yl)-2-methylphenyl)-7-(methylsulfonylmethyl)-9H-carbazole-1-carboxamide	554.1 $(M+H)^+$

WHAT IS CLAIMED IS:

1. A compound according to formula (I):



(I)

or a salt thereof, wherein

the dashed lines are either single or double bonds;

A is halo, C_{3-10} carbocycle substituted with 0-3 B, C_{6-10} mono- or bicyclic aryl substituted with 0-3 B, a 5-14 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 B, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 B;

B is R^1, halogen, cyano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-N(C(=O)O-R^1)_2$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$,or $-NR^{11}-R^1$;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{1a}, C_{2-6} alkynyl substituted with 0-3 R^{1a}, C_{3-10} cycloalkyl substituted with 0-3 R^{1a}, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

one of D^1 and D^2 is D and the other is H or halo;

D is $-R^2$, halogen, $-(C(R^{11})_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-S(=O)-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$,

$-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, $-NR^{11}-R^2$, $-C(=O)NR^{11}-O-R^2$, $-OC(=O)O-R^2$, $-O^1C(=O)-R^2$, or CH=N-OH;

with the proviso that A is not halo when D is $-C(=O)O-R^2$,

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, C_{2-6} alkynyl substituted with 0-3 R^{2a}, C_{3-10} cycloalkyl substituted with 0-3 R^{2a}, C_{6-10} aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a};

R^{2a} is hydrogen, C=O, F, Cl, Br, OCF_3, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a;

R^{11} is independently hydrogen or C_{1-4} alkyl substituted with 0-1 R^f, CH_2-phenyl, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$,;

alternatively, R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or 4-(C_{1-6} alkyl)piperazinyl;

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, alternatively two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula $-O-(CH_2)_n-O-$, or $-O-CF_2-O-$, wherein n is selected from 1 or 2;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-1 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CH2)_rC(O)R^c$, $-NR^eR^c$, $-NR^eC(O)OR^c$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

R^f is hydrogen, halo, NH_2, OH, or OCH_3 ;

r is 0, 1, 2, 3, or 4; and

p is 0, 1, or 2.

2. A compound according to claim 1:

the dashed lines are either single or double bonds;

A is halo, C_{3-10} cycloalkyl substituted with 0-3 B, C_{6-10} mono- or bicyclic aryl substituted with 0-3 B, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 B, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 B;

B is R^1, halogen, cyano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$,or $-NR^{11}-R^1$;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{1a}, C_{2-6} alkynyl substituted with 0-3 R^{1a}, C_{3-10} cycloalkyl substituted with 0-3 R^{1a}, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $-(CH_2)_r$-3-14 membered carbocycle substituted

with 0-1 R^a, or -$(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

one of D^1 and D^2 is D and the other is H;

D is -R^2, halogen, -$(C(R^{11})_2)_r$-R^2, –O-R^2, –C(=O)-R^2, -C(=O)O-R^2, -C(=O)NR^{11}-R^2, -$S(=O)_2$-R^2, -NR^{11}C(=O)-R^2, -NR^{11}C(=O)NR^{11}-R^2, -NR^{11}C(=O)O-R^2, -$NR^{11}S(=O)_2$-R^2, or -NR^{11}-R^2;

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, C_{2-6} alkynyl substituted with 0-3 R^{2a}, C_{6-10} aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a};

R^{2a} is hydrogen, C=O, F, Cl, Br, OCF_3, CN, NO_2, -$(CH_2)_r$$OR^b$, -$(CH_2)_r$$SR^b$, -$(CH_2)_r$C(O)$R^b$, -$(CH_2)_r$C(O)$OR^b$, -$(CH_2)_r$OC(O)$R^b$, -$(CH_2)_r$$NR^{11}R^{11}$, -$(CH_2)_r$C(O)$NR^{11}R^{11}$, -$(CH_2)_r$$NR^b$C(O)$R^c$, -$(CH_2)_r$$NR^b$C(O)$OR^c$, -$NR^b$C(O)$NR^{11}R^{11}$, -$S(O)_p$$NR^{11}R^{11}$, -$NR^b$$S(O)_p$$R^c$, -S(O)$R^c$, -$S(O)_2$$R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, -$(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or -$(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

R^{11} is independently hydrogen or C_{1-4} alkyl;

alternatively, R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or 4-(C_{1-6} alkyl)piperazinyl;

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, -$(CH_2)_r$$OR^b$, -$(CH_2)_r$$SR^b$, -$(CH_2)_r$C(O)$R^b$, -$(CH_2)_r$C(O)$OR^b$, -$(CH_2)_r$OC(O)$R^b$, -$(CH_2)_r$$NR^{11}R^{11}$, -$(CH_2)_r$C(O)$NR^{11}R^{11}$, -$(CH_2)_r$$NR^b$C(O)$R^c$, -$(CH_2)_r$$NR^b$C(O)$OR^c$, -$NR^b$C(O)$NR^{11}R^{11}$, -$S(O)_p$$NR^{11}R^{11}$, -$NR^b$$S(O)_p$$R^c$, -S(O)$R^c$, -$S(O)_2$$R^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, -$(CH_2)_r$-3-14 membered carbocycle, or -$(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, alternatively two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula –O-$(CH_2)_n$-O-, or –O-CF_2-O-, wherein n is selected from 1 or 2;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^c$, $-(CH2)_rC(O)R^b$, $-NR^cR^c$, $-NR^cC(O)OR^c$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

r is 0, 1, 2, 3, or 4; and

p is 0, 1, or 2.

3. The compound of claim 1, wherein

D is a $-R^2$, $-(CH_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-S(=O)-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, or $-NR^{11}-R^2$;

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, C_{3-10} cycloalkyl substituted with 0-3 R^{2a}, $-C_{6-10}$ aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a};

R^{2a} is hydrogen, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, OR^b, SR^b, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, $-(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, wherein the carbocycle is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a;

r is 0, 1, or 2.

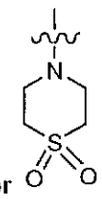
4. The compound of claims 1-2, wherein

A is halo, C_{3-10} carbocycle substituted with 0-3 B C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, a 5-14 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B;

B is R^1, halogen, cyano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$;

R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}.

5. The compound of claims 1-4, wherein

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, ethenyl, C_{3-10} cycloalkyl substituted with 0-3 R^{2a},, C_{6-10} aryl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heterocyclyl is pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl, tetrahydropyranyl, oxazolidinyl (oxazolidin-one), imidazolidinyl (imidazolidin-one), dioxalanyl, or 

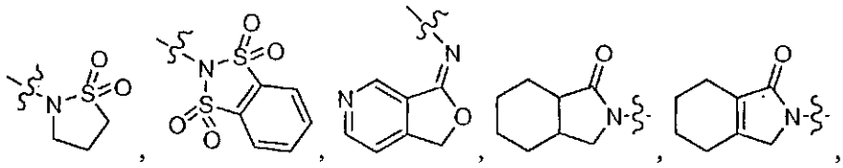
; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heteroaryl is pyrimidinyl, imidazolyl, pyrazinyl, thiadizaolyl, pyridinyl, quinolinyl, isoquinolinyl, or thiazolyl.

6. The compound of claims 1-5, wherein

A is C_6 carbocycle substituted with 0-3 B, C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, a 5-14 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heterocyclyl is chromanyl, 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one, pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heteroaryl is pyridinyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl,, imidazolyl, pyrazolyl, or thiazolyl;

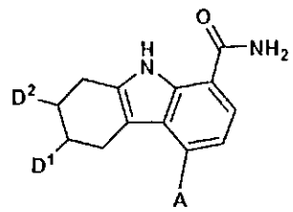
R^1 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{1a}, C_{1-6} haloalkyl, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms

selected from N, O, and S, substituted with 0-3 R^{1a}, wherein the heterocyclyl is 4,5,6,7-tetrahydrobenzo[d]thiazolyl, isoindolinyl, imidazo[1,2-a]pyrazin-8(7H)-one, 1H-pyrrolo[3,4-c]pyridin-3(2H)-one, 1,3-dihydrofuro[3,4-c]pyridine, phthalazine, isoquinolin-1(2H)-one, isoindolinyl, isoindoline-1,3-dione, quinazolin-4(3H)-one,

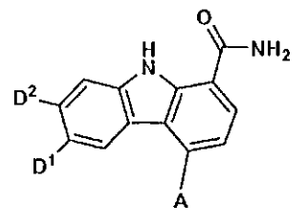


pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a} wherein the heteroaryl is indazolyl, imidazolyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, quinolinyl, quinazolinyl, quinazolin-4(3H)-one pyridinyl or thiazolyl.

7. The compound of claims 1-6, wherein the compound of formula I is a compound of formula (I) is (Ia) or (Ib)



(Ia)



(Ib).

8. The compound of claims 1-7, wherein

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $-(CH_2)_r$-3-6 membered carbocycle, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein the heterocycle is pyrrolidinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, morpholinyl, thiamorpholinyl, triazolyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl,

benzimidazolyl, benzopyranyl, benzofuryl, benzisothiazolyl, benzisoxazolyl, benzodiazinyl, or benzofurazanyl;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-1 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO2, $-OR^e$, $-C(O)R^e$, $-NR^eR^e$, $-NR^eC(O)OR^e$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

R^f is hydrogen, halo, or NH_2;

r is 0 or 1,

9. The compound of claims 1-8, wherein

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-(CH_2)_r$-3-6 membered carbocycle phenyl, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein the heterocycle is thiazolyl, pyridinyl, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, pyrrolidin-one,

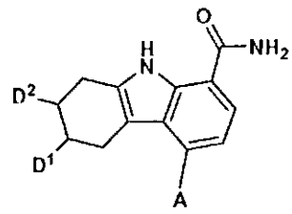
R^b is hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl;

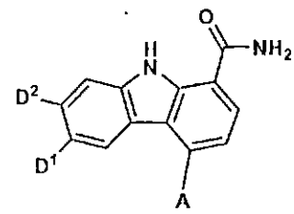
R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO2, $-OR^e$, $-C(O)R^e$, $-NR^eR^e$, $-NR^eC(O)OR^e$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl;

R^e is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl.

10. The compound of claims 1-9, wherein a compound of formula (I) is (Ia) or (Ib)



(Ia)



(Ib)

A is C_{3-10} carbocycle substituted with 0-3 B, wherein the carbocycle is cyclohexyl or cyclohexenyl, C_{6-10} mono- or bicyclic aryl substituted with 0-3 -B, wherein the aryl group is phenyl or naphthyl; a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heterocyclyl group is chromanyl, 3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one, pyrrolidinyl or piperidinyl; or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 -B, wherein the heteroaryl group is pyridinyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, imidazolyl, pyrazolyl or thiazolyl;

B is R^1, halogen, $-C(=O)O-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $N(S(=O)_2-R^1)_2$, or $-NR^{11}-R^1$;

R^1 is hydrogen, trifluoromethyl, C_{1-4} alkyl substituted with 0-1 R^{1a}, phenyl substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, wherein the heteroaryl is pyridyl or thiazolyl;

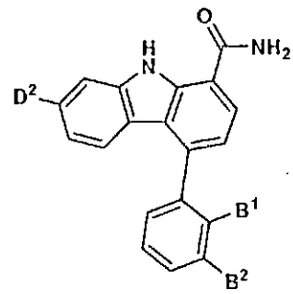
One of D^1 and D^2 is D and the other is hydrogen;

D is R^2, $-C(=O)-R^2$, $-OR^2$, $-C(=O)NR^{11}R^2$, $NR^{11}C(=O)R^2$, $NR^{11}C(=O)NR^{11}-R^2$, $NR^{11}S(=O)_2-R^2$, or $-NR^{11}-R^2$;

R^2 is hydrogen, C_{2-6} alkyl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a} where the heterocyclyl is tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl;

R^{2a} is C_{1-4} alkyl, wherein the alkyl is methyl, ethyl, propyl, i-propyl, butyl, and t-butyl, substituted with 0-1 R^a.

11. A compound according to claim 1, wherein the compound of formula (I) is formula (Ic):

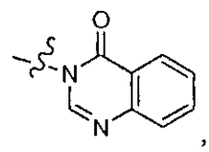
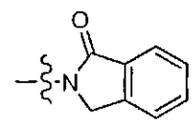
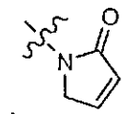
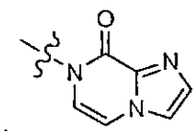
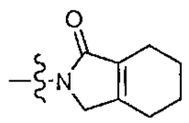
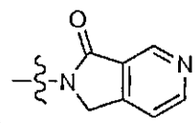
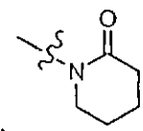
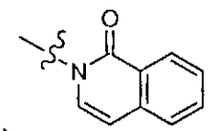
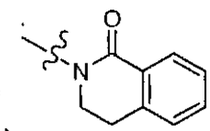
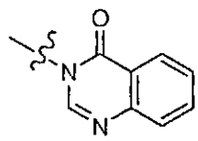
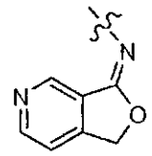


(Ic)

or a salt thereof, wherein

B^1 is methyl or fluorine;

B^2 is R^{1h}, $-NR^{11}C(=O)-R^{1c}$, $-NR^{11}C(=O)NR^{11}-R^{1d}$, or $-NR^{11}-R^{1e}$;

R^{1b} is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , any of which are substituted with 0-3 R^{1a};

R^{1c} is C_{1-6} alkyl, phenyl substituted with 0-2 R^a, cyclopropyl, CH_2-tetrazolyl, or pyridyl, thiazolyl, imidazolyl, benzimidazolyl, pyrimidinyl, any of which are substituted with 0-2 R^a;

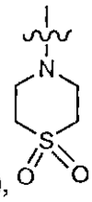
R^{1d} is thiazolyl substituted with 0-1 R^{1a};

R^{1e} is quinazolinyl substituted with 0-1 R^{1a};

R^{1a} is selected from hydrogen, halo, CN, methyl, ethyl, CF_3, OH, O-methyl, CO_2CH_3, $N(CH_3)_2$, $NC(O)CH_3$,

D^2 is $-R^2$, $-(C(R^{11})_2)_r-R^2$, $-OR^2$, $-C(=O)-R^2$, $-C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}-R^2$, - or $-OC(=O)-R^2$;

provided that D^2 is not hydrogen;

R^2 is hydrogen, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{3-10} cyclopropyl substituted with 0-3 R^{2a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heterocyclyl is selected from piperazinyl, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, dioxolanyl, 
piperidinyl, oxazolidinyl (oxazolidin-one), imidazolidinyl (imidazolidin-one), , a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{2a}, wherein the heteroaryl is selected from pyridinyl, imidazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, thiadiazolyl;

R^{2a} is hydrogen, $-(CH_2)_rOR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-NR^bC(O)NR^{11}R^{11}$, $-NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-2 R^a, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a, wherein the heterocycle is selected from pyridinyl, pyrrolidinyl, pyrrolidinonyl, morpholinyl, imidazolyl, piperidinyl;

R^{11} is hydrogen or C_{1-4} alkyl substituted with 0-1 R^f;

R^a is hydrogen, $-OR^b$, $-NR^{11}R^{11}$, or $-(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein the heterocycle is imidazolyl or morpholinyl;

R^b is hydrogen, or C_{1-6} alkyl substituted with 0-2 R^d;

R^c is C_{1-6} alkyl;

R^d is hydrogen, $-OR^e$, or $-NR^eR^e$;

R^e is hydrogen, or C_{1-6} alkyl;

R^f is hydrogen, NH_2, OH, or OCH_3.

12. A compound of claim1, wherein the compound is disclosed in the Examples or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising one or more compounds according to claims 1-11 and a pharmaceutically acceptable carrier or diluent.

14. A method of treating a disease, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound according to

claims 1-11, wherein the disease is systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis (MS), or transplant rejection.

COMPUESTOS DE CARBAZOL CARBOXAMIDA UTILES COMO INHIBIDORES DE CINASA

Campo de la Invención

Esta invención se refiere a compuestos de carbazol carboxamida útiles como inhibidores de cinasa, incluyendo la modulación de tirosina cinasa de Bruton (Btk) y de otras cinasas de la familia Tec tales como Itk. Se proporcionan con la presente invención compuestos heterocíclicos condensados, composiciones que comprenden tales compuestos, y procedimientos para su uso. La invención pertenece adicionalmente a composiciones farmacéuticas que contienen al menos un compuesto de acuerdo con la invención que son útiles para el tratamiento de las afecciones relacionadas con modulación de cinasas y procedimientos de inhibir la actividad de cinasas, incluyendo Btk y otras cinasas de la familia Tec tales como Itk, en un mamífero.

Antecedentes de la Invención

Las proteína cinasas, la familia más grande de enzimas humanas, comprenden bastante más de 500 proteínas. La Btk es un miembro de la familia Tec de tirosina cinasas, y es un regulador del desarrollo temprano de linfocitos B, así como de activación de linfocitos B maduros, de señalización y de supervivencia.

La señalización de linfocitos B a través del

receptor de linfocitos B (BCR) condujo a un amplio intervalo de rendimientos biológicos, que a su vez dependen del estado de desarrollo del linfocito B. La magnitud y duración de las señales de BCR deben regularse con precisión. La señalización mediada por BCR aberrante puede causar activación de linfocitos B con regulación errónea y/o la formación de autoanticuerpos patógenos que conduce a múltiples enfermedades autoinmunes y/o inflamatorias. La mutación de Btk en humanos da como resultado agammaglobulinemia ligada al cromosoma X (XLA). Esta enfermedad está asociada con la maduración dañada de linfocitos B, la producción de inmunoglobulinas disminuida, las respuestas inmunes independientes de linfocitos T comprometidos y la atenuación marcada de la señal de calcio mantenida en estimulación de BCR.

Se ha comprobado evidencia para el papel de Btk en trastornos alérgicos y/o enfermedad autoinmune y/o enfermedad inflamatoria en modelos de ratón deficiente en Btk. Por ejemplo, en modelos preclínicos murinos estándar de lupus eritematoso sistémico (LES), la deficiencia de Btk ha mostrado dar como resultado una mejora marcada en la progresión de la enfermedad. Además, los ratones deficientes en Btk son también resistentes para desarrollar artritis inducida por colágeno y son menos susceptibles a artritis inducida por *Staphylococcus*.

Un gran número de evidencias sostiene el papel de los linfocitos B y el sistema inmune humoral en la patogénesis de enfermedades autoinmunes y/o inflamatorias. Los productos terapéuticos basados en proteínas (tales como Rituxan) desarrollados para disminuir los linfocitos B, representan una aproximación importante para el tratamiento de un número de enfermedades autoinmunes y/o inflamatorias. Debido al papel de la Btk en activación de linfocitos B, los inhibidores de Btk pueden ser útiles como inhibidores de actividad patógena mediada por linfocitos B (tales como una producción de autoanticuerpos).

La Btk se expresa también en células cebadas y en monocitos y ha mostrado ser importante para la función de estas células. Por ejemplo, la deficiencia de Btk en ratones está asociada con activación de células cebadas mediadas por IgE (disminución marcada de TNF-alfa y otra liberación de citocinas inflamatorias), y la deficiencia en Btk en seres humanos está asociada con producción de TNF-alfa grandemente reducida por monocitos activados.

Así, la inhibición de la activación de Btk puede ser útil para el tratamiento de trastornos alérgicos y/o enfermedades autoinmunes y/o inflamatorias incluyendo, pero sin estar limitadas a: SLE, artritis reumatoide, vasculitis múltiples, púrpura trombocitopénica idiopática (ITP), miastenia gravis, rinitis alérgica, esclerosis múltiple (MS),

rechace de transplante, diabetes de tipo I, nefritis membranosa, enfermedad inflamatoria del intestino, anemia hemolítica autoinmune, tiroiditis autoimmune, enfermedades de aglutinina frías y calientes, síndrome de Evan, síndrome urémico hemolítico/púrpura trombocitopenica trombótica (HUS/TTP), sarcoidosis, síndrome de Sjögren, neuropatías periféricas (por ejemplo, síndrome Guillain-Barre), pénfigo vulgar, y asma.

Además, se ha comunicado que la Btk juega un papel en controlar la supervivencia de linfocitos B en ciertos cánceres de linfocitos B. Por ejemplo, se ha mostrado que es importante para la supervivencia de las células de la leucemia linfoblástica aguda de linfocitos B positivos en BCR-Abl. Así la inhibición de la actividad Btk puede ser útil para el tratamiento de linfoma de linfocitos B y de leucemia.

En vista de las numerosas afecciones que se contempla que se benefician por tratamiento que implica modulación de proteína cinasas, es inmediatamente patente que compuestos nuevos capaces de modular proteína cinasas tales como Btk y procedimientos para usar estos compuestos proporcionarían beneficios terapéuticos sustanciales a una amplia diversidad de pacientes.

Se intentan encontrar ampliamente inhibidores de proteína cinasas y una serie de publicaciones informan de

compuestos efectivos en modular proteína cinasas. Por ejemplo, las publicaciones de patentes WO 2005/047290, WO 2005/014599, WO 2005/005429, WO 2006/099075, WO 2006/053121, y US 2006/0183746 dan a conocer ciertos compuestos de imidazopirazina que se dice que inhiben actividad de proteína cinasas, incluyendo actividad de Btk. La publicación de Patente WO 2008/033858 da a conocer procedimientos de inhibir actividad de Btk con diversos compuestos químicos de unión a Btk. La Publicación de Patente US 2006/0084650 describe que los compuestos heterocíclicos condensados ejemplificados por imidazopirimidinas y pirrolotriazinas se pueden usar como inhibidores de proteína cinasas. Además, ciertos compuestos de imidazopiridazina y imidazotriazina se dan a conocer en los documentos WO 2007/038314 (publicado el 5 de abril de 2007) y WO 2008/0045536 (publicado el 21 de febrero de 2008), ambos de los cuales están cedidos al presente cesionario.

La presente invención se refiere a una nueva clase de compuestos heterocíclicos condensados sustituidos que se ha encontrado que son inhibidores efectivos de proteína cinasas incluyendo Btk y cinasas de la otra familia Tec tales como Itk.

Breve Descripción de la Invención

Se proporcionan en el presente documento moduladores de la actividad cinasa que se pueden describir

generalmente como carbazoles sustituidos, tetrahidrocarbazoles, y compuestos relacionados.

La invención se refiere a compuestos de Fórmula I que son útiles como inhibidores de BTK, y son útiles para el tratamiento de enfermedades proliferativas, enfermedades alérgicas, enfermedades autoinmunes y enfermedades inflamatorias, o estereoisómeros, tautómeros, sales farmacéuticamente aceptables, solvatos o profármacos de los mismos.

La presente invención también proporciona procedimientos e intermedios para elaborar los compuestos de la presente invención o estereoiómeros, tautómeros, sales farmacéuticamente aceptables, solvatos o profármacos de los mismos.

La presente invención también proporciona composiciones farmacéuticas que comprenden un portador farmacéuticamente aceptable y al menos de uno de los compuestos de la presente invención o estereoisómeros, tautómeros, sales, solvatos o profármacos farmacéuticamente aceptables de los mismos.

La presente invención también proporciona un procedimiento para inhibición de BTK comprendiendo administrar a un huésped en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención o estereoisómeros,

tautómeros, sales farmacéuticamente aceptables, solvatos o profármacos de los mismos.

La presente invención también proporciona un procedimiento para tratar enfermedades proliferativas, enfermedades alérgicas, enfermedades autoinmunes y enfermedades inflamatorias, comprendiendo administrar a un huésped en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención o estereoisómeros, tautómeros, sales farmacéuticamente aceptables, solvatos o profármacos de los mismos.

La presente invención también proporciona los compuestos de la presente invención o estereoisómeros, tautómeros, sales farmacéuticamente aceptables, solvatos o profármacos de los mismos, para usar en terapia.

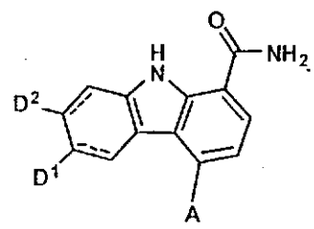
La presente invención también proporciona el uso de los compuestos de la presente invención o estereoisómeros, tautómeros, sales farmacéuticamente aceptables, solvatos o profármacos de los mismos, para la elaboración de un medicamento para el tratamiento de cánceres.

Estas y otras características de la invención se expondrán de forma detallada a lo largo de la descripción.

Descripción Detallada de la Invención

Se proporciona en el presente documento al menos

una entidad química elegida entre compuestos de fórmula (I):



(I)

o un enantiómero, un diastereómero, un profármaco, una sal, o una sal farmacéuticamente aceptable de la misma, en la que

las líneas discontinuas son bien enlaces simples o bien enlaces dobles;

A es halo, carbociclo C_{3-10} sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B;

B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-N(C(=O)O-R^1)_2$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^{1a}, alquinilo C_{2-6} sustituido con 0-3 R^{1a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{1a}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un

heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, substituidos con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituidos con 0-3 R^{1a};

R^{1a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ sustituido con 0-1 R^a;

uno de los D^1 y D^2 es D y el otro es H o halo;

D es $-R^2$, halógeno, $-(C(R^{11})_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, o $-NR^{11}-R^2$, $-C(=O)NR^{11}-O-R^2$, $-OC(=O)O-R^2$, $-O^1C(=O)-R^2$, o CH=N-OH;

a condición de que A no sea halo cuando D sea $-C(=O)O-R^2$,

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, alquinilo C_{2-6} sustituido con 0-3 R^{2a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros

que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituidos con 0-3 R^{2a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituidos con 0-3 R^{2a};

R^{2a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$ sustituido con 0-2 R^a;

R^{11} es independientemente hidrógeno o alquilo C_{1-4} sustituido con 0-1 R^f, CH_2-fenilo, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$;

alternativamente, R^{11} y junto con otro R^{11}, R^1 o R^2 en el mismo átomo de nitrógeno puede unirse para formar un azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, o 4-(alquilo C_{1-6})piperazinilo;

R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, -

$(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-1 R^f, $-(CH_2)_r$-haloalquilo C_{1-6} carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, alternativamente dos R^a en átomos de carbono adyacentes o en el mismo átomo de carbono forman un acetal cíclico de la fórmula $-O-(CH_2)_n-O-$, u $-O-CF_2-O-$, en el que n está seleccionado de 1 ó 2;

R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6} sustituido con 0-1 R^f, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo sustituido con 0-1 R^f;

R^d es hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CH2)_rC(O)R^c$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6}, o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo;

R^f es hidrógeno, halo, NH_2, OH, u OCH_3 ;

r es 0, 1, 2, 3, o 4; y

p es 0, 1, o 2.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que

las líneas discontinuas son bien enlaces simples o

bien enlaces dobles;

A es halo, cicloalquilo C_{3-10} sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B;

B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^{1a}, alquinilo C_{2-6} sustituido con 0-3 R^{1a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{1a}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{1a};

R^{1a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CH_2)_r-$

carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ sustituido con 0-1 R^a;

uno de los D^1 y D^2 es D y el otro es H;

D es $-R^2$, halógeno, $-(C(R^{11})_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, o $-NR^{11}-R^2$;

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, alquinilo C_{2-6} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{2a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{2a};

R^{2a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NRbC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ sustituido con 0-1 R^a;

R^{11} es independientemente hidrógeno o alquilo C_{1-4};

alternativamente, R^{11} y junto con otro R^{11}, R^1, o R^2 en el mismo átomo de nitrógeno pueden unirse formando un acetidinilo, pirrolidinilo, piperidinilo, morfolinilo o 4-(alquilo C_{1-6})piperazinilo;

R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6}, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros , o $-(CH_2)_r$-heterociclo de 5 a 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, alternativamente dos R^a en carbonos adyacentes o en el mismo carbono forman un acetal cíclico de la fórmula $-O-(CH_2)_n-O-$, u $-O-CF_2-O-$, en el que n está seleccionado de 1 ó 2;

R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo;

R^d is hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CH_2)_rC(O)R^b$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6}, o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6}, o

$(CH_2)_r$-fenilo;

r es 0, 1, 2, 3, o 4; y

p es 0, 1, o 2.

En otra modalidad, se proporciona un compuesto de fórmula I en la que

D es un $-R^2$, $-(CH_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, o $-NR^{11}-R^2$;

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, arilo $-C_{6-10}$ sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{2a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{2a};

R^{2a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, OR^b, SR^b, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, siendo el carbociclo ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo; o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ sustituido con 0-1 R^a;

r es 0, 1, o 2.

En otra modalidad, se proporciona un compuesto de fórmula I en la que

A es halo, arilo C_{6-10} mono- o bicíclico sustituido con 0-3 B, un heterociclo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B;

B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{1a}.

En otra modalidad, se proporciona un compuesto de fórmula I en la que

R^2 es hidrógeno, alquilo C_{2-6} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{2a}, siendo el heterociclilo pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos

seleccionados de N, O, y S, sustituido con 0-3 R^{2a}, siendo el heteroarilo piridinilo, quinolinilo, isoquinolinilo, o tiazolilo.

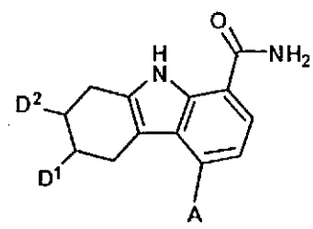
En otra modalidad, se proporciona un compuesto de fórmula I en la que

A es arilo mono- o bicíclico C_{6-10} sustituido con 0-3 -B, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 -B, siendo el heterocíclilo pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 -B, siendo el heteroarilo piridinilo, quinolinilo, isoquinolinilo, indolilo, indazolilo, bencimidazolilo, imidazolilo, pirazolilo, o tiazolilo;

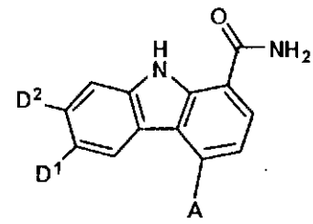
R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{6-10} , arilo C_{6-10} sustituido con 0-3 R^{1a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{1a}, siendo el heterociclilo pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{1a}, siendo el heteroarilo piridinilo o tiazolilo.

En otra modalidad, se proporciona un compuesto de fórmula I, siendo el compuesto de fórmula I un compuesto de fórmula (Ia) o (Ib) o una sal farmacéuticamente aceptable del

mismo.



(Ia)



(Ib).

En otra modalidad, se proporciona un compuesto de fórmula I en la que

R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6}, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-6 miembros , o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, siendo el heterociclo pirrolidinilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furilo, tienilo, piridilo, pirazinilo, pirimidinilo, morfolinilo, tiamorfolinilo, triazolilo, indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, bencimidazolilo, benzopiranilo, benzofurilo, bencisotiazolilo, bencisoxazolilo, benzodiazinilo, o benzofurazanilo;

R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d,

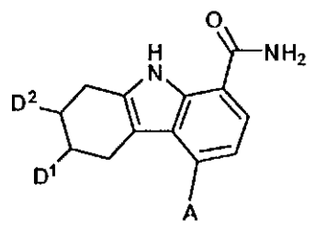
haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo;

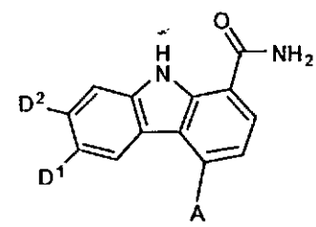
R^d is hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-C(O)R^h$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6}, o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo;

En otra modalidad, se proporciona un compuesto de fórmula I en la que un compuesto de fórmula (I) es (Ia) o (Ib)



(Ia)



(Ib).

A es arilo mono- o bicíclico C_{6-10} sustituido con 0-3 -B, siendo el grupo arilo fenilo o naftilo; un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 -B, siendo el grupo heterociclilo pirrolidinilo o piperidinilo; o un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 -B, siendo el grupo heteroarilo piridinilo, quinolinilo, isoquinolinilo,

indolilo, indazolilo, bencimidazolilo, imidazolilo, pirazolilo o tiazolilo;

B es R^1, halógeno, $-C(=O)O-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$;

R^1 es hidrógeno, trifluorometilo, alquilo C_{1-4} sustituido con 0-1 R^{1a}, fenilo sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{1a}, siendo el heteroarilo piridilo o tiazolilo;

Uno de los D^1 y D^2 es D y el otro es hidrógeno;

D es R^2, $-C(=O)-R^2$, $-C(=O)NR^{11}R^2$, $NR^{11}C(=O)R^2$, $NR^{11}C(=O)NR^{11}-R^2$, $NR^{11}S(=O)_2-R^2$, o $-NR^{11}-R^2$;

R^2 es hidrógeno, alquilo C_{2-6} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{2a}, siendo el heterociclilo pirrolidinilo, piperidinilo, piperazinilo o morfolinilo;

R^{2a} es alquilo C_{1-4}, siendo el alquilo metilo, etilo, propilo, i-propilo, butilo, y t-butilo, sustituido con 0-1 R^a.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que

D es un $-R^2$, $-(CH_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-$

$NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, o $-NR^{11}-R^2$;

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{2a}, -aril C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a};

R^{2a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, OR^b, SR^b, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, en el que el carbociclo es ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo; o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$ sustituido con 0-2 R^a;

r es 0, 1, o 2.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que

A es halo, carbociclo C_{3-10} sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, un

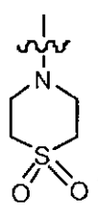
heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B;

B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, etenilo, cicloalquilo C_{3-10} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, en el que el heterociclilo es pirrolidinilo, piperidinilo, morfolinilo o piperazinilo, tetrahidropiranilo, oxazolidinilo (oxazolidin-ona), imidazolidinilo (imidazolidin-ona), dioxalanilo, o



; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{-}

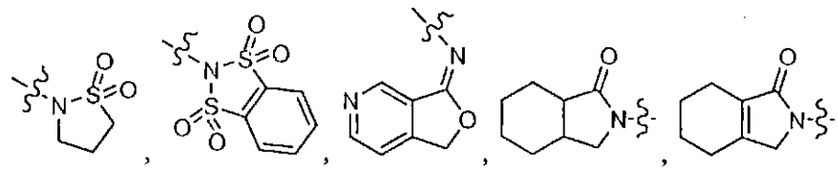
^{2a}, en el que el heteroarilo es pirimidinilo, imidazolilo, pirazinilo, tiadiazolilo, piridinilo, quinolinilo, isoquinolinilo, o tiazolilo.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que

A es carbociclo C_6 sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, en el que el heterociclilo es cromanilo, 3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona, pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, en el que el heteroarilo es piridinilo, quinolinilo, isoquinolinilo, indolilo, indazolilo, benzimidazolilo, furanilo, benzofuranilo, dibenzofuranilo, imidazolilo, pirazolilo o tiazolilo;

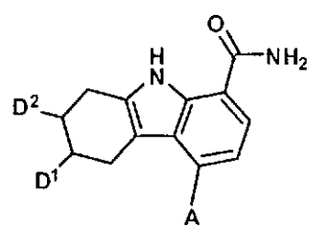
R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, en el que el heterociclilo es 4,5,6,7-tetrahidrobenzo[d]tiazolilo, isoindolinilo, imidazo[1,2-a]pirazin-8(7H)-ona, 1H-pirrolo[3,4-c]piridin-3(2H)-ona, 1,3-dihidrofuro[3,4-c]piridina, ftalazina, isoquinolin-1(2H)-ona, isoindolinilo,

isoindolina-1,3-diona, quinazolin-4(3H)-ona,

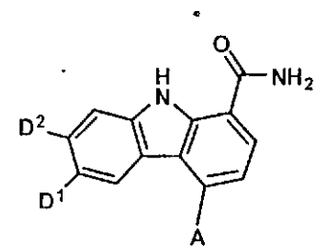


pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a} en el que el heteroarilo es indazolilo, imidazolilo, pirimidinilo, bencimidazolilo, benzotiazolilo, quinolinilo, quinazolinilo, piridinilo de quinazolin-4(3H)-ona o tiazolilo.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que el compuesto de fórmula I es un compuesto de fórmula (Ia) o (Ib)



(Ia)

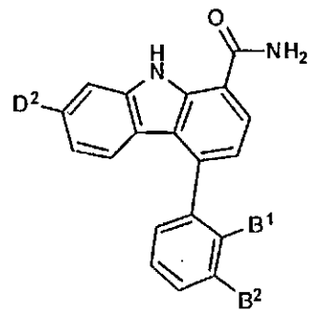


(Ib).

En otra modalidad, se proporciona un compuesto de fórmula I, en el que el compuesto de fórmula I es un compuesto de fórmula (Ic) o (Ib).

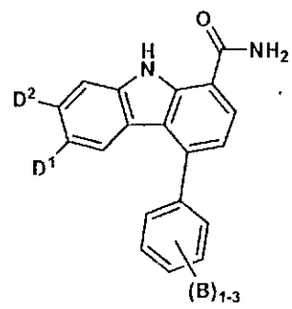
En otra modalidad, se proporciona un compuesto de fórmula I, en el que el compuesto de fórmula I es un

compuesto de fórmula (Ic):



(Ic).

En otra modalidad, se proporciona un compuesto de fórmula I, en el que el compuesto de fórmula I es un compuesto de fórmula (Id):



(Id).

En otra modalidad, se proporciona un compuesto de fórmula I, en el que

R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-1 R^f, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-6 miembros, o $-(CH_2)_r$-heterociclo de 5 a 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados

de N, O, y $S(O)_p$, en el que el heterociclo es pirrolidinilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furilo, tienilo, piridilo, pirazinilo, pirimidinilo, morfolinilo, tiamorfolinilo, triazolilo, indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, benzimidazolilo, benzopiranilo, benzofurilo, benzisotiazolilo, benzisoxazolilo, benzodiazinilo, o benzofurazanilo;

R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6} sustituido con 0-1 R^f, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo sustituido con 0-1 R^f;

R^d es hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-C(O)R^e$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6}, o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo;

R^f es hidrógeno, halo, o NH_2;

r es 0 ó 1.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que

R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$,

$-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6}, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-6 miembros, o $-(CH_2)_r$-heterociclo de 5 a 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$, en el que el heterociclo es tiazolilo, piridinilo, piperidinilo, morfolinilo, piperazinilo, pirrolidinilo, pirrolidinona,

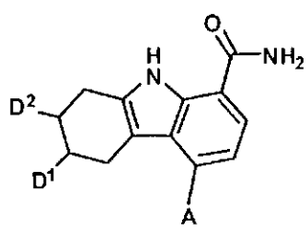
R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo;

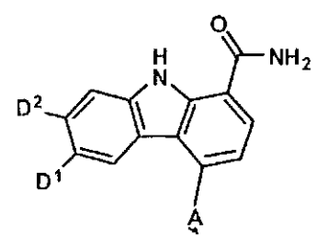
R^d es hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO2, $-OR^e$, $-C(O)R^c$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6}, o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que el compuesto de fórmula (I) es (Ia) o (Ib)



(Ia)



(Ib).

A es carbociclo C_{3-10} sustituido con 0-3 B, en el

que el carbociclo es ciclohexilo o ciclohexenilo, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, en el que el grupo arilo es fenilo o naftilo; un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, en el que el grupo heterocíclico es cromanilo, 3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona, pirrolidinilo o piperidinilo; o un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, en el que el grupo heteroarilo es piridinilo, quinolinilo, isoquinolinilo, indolilo, indazolilo, benzimidazolilo, furanilo, benzofuranilo, dibenzofuranilo, imidazolilo, pirazolilo o tiazolilo;

B es R^1, halógeno, $-C(=O)O-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$;

R^1 es hidrógeno, trifluorometilo, alquilo C_{1-4} sustituido con 0-1 R^{1a}, fenilo sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, en el que el heteroarilo es piridilo o tiazolilo;

Uno de los D^1 y D^2 es D y el otro es hidrógeno;

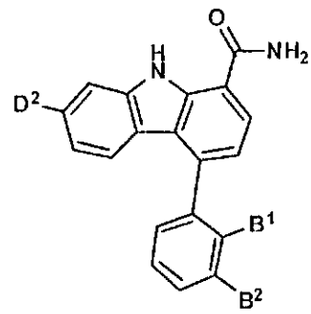
D es R^2, $-C(=O)-R^2$, $-C(=O)NR^{11}R^2$, $NR^{11}C(=O)R^2$, $NR^{11}C(=O)NR^{11}-R^2$, $NR^{11}S(=O)_2-R^2$, o $-NR^{11}-R^2$;

R^2 es hidrógeno, alquilo C_{2-6} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4

heteroátomos seleccionados de N, O, y S, sustituido con 0-3 R^{2a}, siendo el heterociclilo pirrolidinilo, piperidinilo, piperazinilo o morfolinilo;

R^{2a} es alquilo C_{1-4}, siendo el alquilo metilo, etilo, propilo, i-propilo, butilo, y t-butilo, sustituido con 0-1 R^a.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que el compuesto de fórmula (I) es un compuesto de fórmula (Ic):

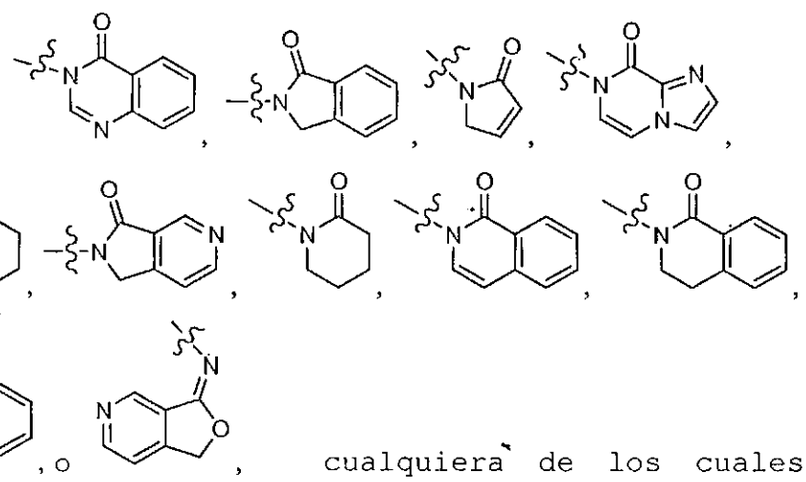


(Ic)

o una sal del mismo, en el que

B^1 es metilo o flúor;

B^2 es R^{1b}, $-NR^{11}C(=O)-R^{1c}$, $-NR^{11}C(=O)NR^{11}-R^{1d}$, o $-NR^{11}-R^{1e}$;

R^{1b} es  , cualquiera de los cuales

está sustituido con 0-3 R^{1a};

R^{1c} es alquilo C_{1-6}, fenilo sustituido con 0-2 R^a, ciclopropilo, CH_2-tetrazolilo, o piridilo, tiazolilo, imidazolilo, benzimidazolilo, pirimidinilo, cualquiera de los cuales está sustituido con 0-2 R^a;

R^{1d} es tiazolilo sustituido con 0-1 R^{1a};

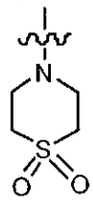
R^{1e} es quinazolinilo sustituido con 0-1 R^{1a};

R^{1a} está seleccionado de hidrógeno, halo, CN, metilo, etilo, CF_3, OH, O-metilo, CO_2CH_3, $N(CH_3)_2$, $NC(O)CH_3$,

D^2 es $-R^2$, $-(C(R^{11})_2)_r-R^2$, $-OR^2$, $-C(=O)-R^2$, $-C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}-R^2$, - o $-OC(=O)-R^2$;

siempre que D^2 no es hidrógeno;

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, ciclopropilo C_{3-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, en el que el heterociclilo está seleccionado de piperazinilo, pirrolidinilo, tetrahidrofuranilo, morfolinilo, dioxolanilo, piperidinilo, oxazolidinilo (oxazolidin-ona), imidazolidinilo (imidazolidin-ona),



, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, en el que el heteroarilo está seleccionado de piridinilo,

imidazolilo, pirazinilo, pirimidinilo, tetrazolilo, tiadiazolilo;

R^{2a} es hidrógeno, $-(CH_2)_rOR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-NR^bC(O)NR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-2 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$ sustituido con 0-2 R^a, en el que el heterociclo está seleccionado de piridinilo, pirrolidinilo, pirrolidinonilo, morfolinilo, imidazolilo, piperidinilo;

R^{11} es hidrógeno o alquilo C_{1-4} sustituido con 0-1 R^f;

R^a es hidrógeno, $-OR^b$, $-NR^{11}R^{11}$, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, en el que el heterociclo es imidazolilo o morfolinilo;

R^b es hidrógeno, o alquilo C_{1-6} sustituido con 0-2 R^d;

R^c es alquilo C_{1-6};

R^d es hidrógeno, $-OR^e$, o $-NR^eR^e$;

R^e es hidrógeno, o alquilo C_{1-6};

R^f es hidrógeno, NH_2, OH, o OCH_3.

En otra modalidad, se proporciona un compuesto de fórmula I en la que D^1 es hidrógeno y D^2 es D.

En otra modalidad, se proporciona un compuesto de

fórmula I en la que D^2 es hidrógeno y D^1 es D.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que el compuesto de fórmula I es un compuesto de fórmula (Ia). En otra modalidad, el compuesto de fórmula (I) es un compuesto de fórmula (Ib). En otra modalidad, el compuesto de fórmula (I) es un compuesto de fórmula (Ic).

En otra modalidad, A es halo, carbociclo C_{3-10} sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que A es carbociclo C_6 sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B, en el que el heterociclilo es, cromanilo, 3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona, pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O, y S, sustituido con 0-3 B, en el que el heteroarilo es piridinilo, quinolinilo, isoquinolinilo, indolilo, indazolilo,

bencimidazolilo, furanilo, benzofuranilo, dibenzofuranilo, imidazolilo, pirazolilo, o tiazolilo.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que A es carbociclo C_{3-10} sustituido con 0-3 B, en el que el carbociclo es ciclohexilo o ciclohexenilo, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, en el que el grupo arilo es fenilo o naftilo; un heterociclilo de 5-10 miembros que contienen 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, en el que el grupo heterociclilo es cromanilo, 3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona, pirrolidinilo o piperidinilo; o un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 -B, en el que el grupo heteroarilo es piridinilo, quinolinilo, isoquinolinilo, indolilo, indazolilo, benzimidazolilo, furanilo, benzofuranilo, dibenzofuranilo, imidazolilo, pirazolilo o tiazolilo.

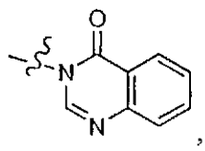
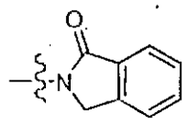
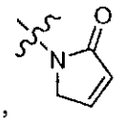
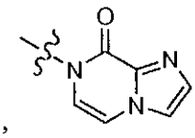
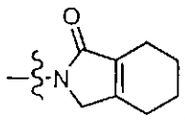
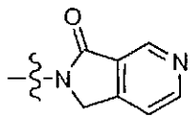
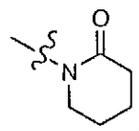
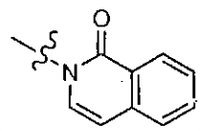
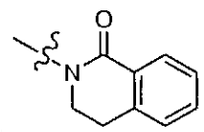
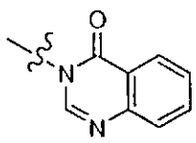
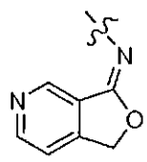
En otra modalidad, se proporciona un compuesto de fórmula I, en el que B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que B es R^1, halógeno, $-C(=O)O-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$;

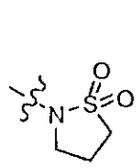
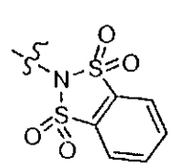
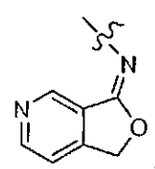
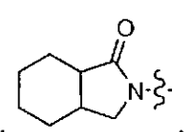
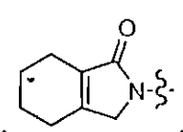
En otra modalidad, se proporciona un compuesto de

fórmula (Ic), en el que B^1 es metilo o flúor;

B^2 es R^{1b}, $-NR^{11}C(=O)-$ R^{1c}, $-NR^{11}C(=O)NR^{11}-$ R^{1d}, o $-NR^{11}-R^{1e}$;

R^{1b} es  ,  ,  ,  ,  ,  ,  ,  ,  ,  , o  , cualquiera de los cuales está sustituido con 0-3 R^{1a}.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, en el que el heterociclilo es 4,5,6,7-tetrahidrobenzo[d]tiazolilo, isindolinilo, imidazo[1,2-a]pirazin-8(7H)-ona, 1H-pirrolo[3,4-c]piridin-3(2H)-ona, 1,3-dihidrofuro[3,4-c]piridina, ftalazina, isoquinolin-1(2H)-ona, isoindolinilo, isoindolina-1,3-diona, quinazolin-4(3H)-ona,

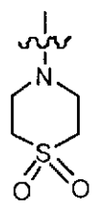
 ,  ,  ,  ,  ,

pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un

heteroarilo de 5-10 miembros heteroarilo que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a} en el que el heteroarilo es indazolilo, imidazolilo, pirimidinilo, bencimidazolilo, benzotiazolilo, quinolinilo, quinazolinilo, quinazolin-4(3H)-ona, piridinilo o tiazolilo.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que R^1 es hidrógeno, trifluorometilo, alquilo C_{1-4} sustituido con 0-1 R^{1a}, fenilo sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, en el que el heteroarilo es piridilo o tiazolilo.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, etenilo, cicloalquilo C_{3-10} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, en el que el heterociclilo es pirrolidinilo, piperidinilo, morfolinilo o piperazinilo, tetrahidropiranilo, oxazolidinilo (oxazolidin-ona), imidazolidinilo (imidazolidin-ona), dioxalanilo, o

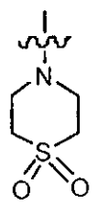


; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{-}

^{2a}, en el que el heteroarilo es pirimidinilo, imidazolilo, pirazinilo, tiadiazolilo, piridinilo, quinolinilo, isoquinolinilo, o tiazolilo.

En otra modalidad, se proporciona un compuesto de fórmula I, en el que R^2 es hidrógeno, alquilo C_{2-6} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a} donde el heterociclilo es tetrazolilo, pirrolidinilo, piperidinilo, piperazinilo o morfolinilo.

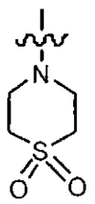
En otra modalidad, se proporciona un compuesto de fórmula I, en el que R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, alquinilo C_{2-6} sustituido con 0-3 R^{2a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, en el que el heterociclilo está seleccionado de piperazinilo, pirrolidinilo, tetrahidrofuranilo, morfolinilo, dioxolanilo, piperidinilo, oxazolidinilo (oxazolidin-ona), imidazolidinilo (imidazolidin-ona),



, un heteroarilo de 5-10 miembros que contienen 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{-}

^{2a}, en el que el heteroarilo está seleccionado de piridinilo, imidazolilo, pirazinilo, tiadiazolilo.

En otra modalidad, se proporciona un compuesto de fórmula (I) en el que R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, ciclopropilo C_{3-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, en el que el heterociclilo está seleccionado de piperazinilo, pirrolidinilo, tetrahidrofuranilo, morfolinilo, dioxolanilo, piperidinilo, oxazolidinilo (oxazolidin-ona), imidazolidinilo (imidazolidin-ona),



, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, en el que el heteroarilo está seleccionado de piridinilo, imidazolilo, pirazinilo, pirimidinilo, tetrazolilo, tiadiazolilo.

En otra modalidad, R^{2a} es hidrógeno, $-(CH_2)_rOR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-NR^bC(O)NR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-2 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$ sustituido con 0-2 R^a, en el que el heterociclo está seleccionado de piridinilo,

pirrolidinilo, pirrolidinonilo, morfolinilo, imidazolilo, piperidinilo.

En otra modalidad, uno de D^1 y D^2 es D y el otro es H; siempre que D no sea hidrógeno.

En otra modalidad, D es un $-R^2$, $-(CH_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, o $-NR^{11}-R^2$.

En otra modalidad, D es R^2, $-C(=O)-R^2$, $-OR^2$, $-C(=O)NR^{11}R^2$, $NR^{11}C(=O)R^2$, $NR^{11}C(=O)NR^{11}-R^2$, $NR^{11}S(=O)_2-R^2$, o $-NR^{11}-R^2$.

En otra modalidad, D^2 es $-R^2$, $-(C(R^{11})_2)_r-R^2$, $-OR^2$, $-C(=O)-R^2$, $-C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}-R^2$, - u $-OC(=O)-R^2$.

En otra modalidad, D^2 es $-R^2$, $-(C(R^{11})_2)_r-R^2$, $-C(=O)-R^2$, $-C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}-R^2$, - u $-OC(=O)-R^2$.

En otra modalidad, se proporciona una composición farmacéutica que comprende uno o más compuestos de fórmula I y un vehículo o diluyente farmacéuticamente aceptable.

La presente invención se refiere también a composiciones farmacéuticas útiles en tratar enfermedades con modulación de cinasas, incluyendo modulación (especialmente inhibición) de Btk y otras cinasas de la familia Tec tales como Itk, que comprenden compuestos de fórmula (I), o sales farmacéuticamente aceptables de las mismas, y vehículos o

diluyentes farmacéuticamente aceptables de las mismas.

La invención se refiere adicionalmente a procedimientos para tratar enfermedades asociadas con la modulación de cinasas, incluyendo la modulación de Btk y de otras cinasas de la familia Tec tales como Itk, que comprenden administrar a un paciente en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de un compuesto de acuerdo con la fórmula (I).

La presente invención proporciona también procedimientos e intermedios para fabricar los compuestos de la presente invención o estereoisómeros, tautómeros, sales farmacéuticamente aceptables, solvatos, o profármacos de los mismos.

La presente invención también proporciona un procedimiento para tratar enfermedades proliferativas, enfermedades alérgicas, enfermedades autoinmunes y enfermedades inflamatorias, que comprende administrar a un huésped en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención o estereoisómeros, tautómeros, sales farmacéuticamente aceptables, solvatos, o profármacos de los mismos.

La presente invención también proporciona un procedimiento para tratar una enfermedad, que comprende administrar a un paciente en necesidad de tal tratamiento una

cantidad terapéuticamente eficaz de un compuesto de la fórmula I, en el que la enfermedad es lupus eritematoso sistémico (LES), artritis reumatoide, esclerosis múltiple (EM) o rechazo de transplante.

La presente invención también proporciona un procedimiento para tratar una afección asociada con una enfermedad proliferativa, una enfermedad alérgica, una enfermedad autoinmune o una enfermedad inflamatoria, que comprende administrar a una paciente en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de un compuesto de fórmula I.

La presente invención también proporciona un procedimiento para tratar una afección que comprende administrar a un paciente en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de un compuesto de la fórmula I, en el que la afección está seleccionada de leucemia mielógena aguda, leucemia mielógena crónica, melanoma metastásico, sarcoma de Kaposi, mieloma múltiple, tumores sólidos, neovascularización ocular, y hemangiomas infantiles, linfoma de linfocitos B, lupus eritematoso sistémico (LES), artritis reumatoide, artritis soriática, vasculitis múltiples, púrpura trombocitopénica idiopática (PTI), miastenia gravis, rinitis alérgica, esclerosis múltiple (EM), rechace de transplantes, diabetes de Tipo I, nefritis membranosa, enfermedad inflamatoria del intestino,

anemia hemolítica autoinmune, tiroiditis autoimmune, enfermedades de aglutininas frías y calientes, síndrome de Evan, síndrome de uremia hemolítica/púrpura trombocitopénica trombótica (SUH/PTI), sarcoidosis, síndrome de Sjogren, neuropatías periféricas, pénfigo vulgar y asma.

La presente invención también proporciona un procedimiento para tratar una artritis reumatoide, que comprende administrar al paciente en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de un compuesto de fórmula I.

La presente invención también proporciona un procedimiento para tratar una enfermedad mediada por linfocitos B, que comprende administrar al paciente en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de un compuesto de fórmula I.

La presente invención también proporciona un procedimiento para tratar una enfermedad mediada por linfocitos B, que comprende administrar al paciente en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de un compuesto de fórmula I, en el que la enfermedad mediada por linfocitos B es una enfermedad modulada por una cinasa seleccionada de Btk, Bmx, Itk, Txk y Tec.

La presente invención también proporciona un procedimiento para tratar enfermedades, que comprende administrar a un paciente en necesidad de tal tratamiento una

cantidad terapéuticamente eficaz de un compuesto de fórmula I, o sal farmacéuticamente aceptable del mismo, en combinación con otros agentes terapéuticos.

La presente invención proporciona también los compuestos de la presente invención o estereoisómeros, tautómeros, sales farmacéuticamente aceptables, solvatos, o profármacos de los mismos, para usar en terapia.

En otra modalidad, los compuestos de la fórmula I se seleccionan de ejemplos ejemplificados o combinaciones de ejemplos ejemplificados u otras modalidades en la presente.

En otra modalidad hay compuestos que tienen una IC_{50} <10 µM en el ensayo Btk descrito abajo.

En otra modalidad hay compuestos que tienen una IC_{50} <=5 nM en el ensayo Btk descrito abajo.

La presente invención también proporciona el uso de los compuestos de la presente invención o de estereoisómeros, tautómeros, sales farmacéuticamente aceptables, solvatos, o profármacos de los mismos, para la elaboración de un medicamento para el tratamiento de cánceres, una enfermedad alérgica, una enfermedad autoinmune o una enfermedad inflamatoria.

La presente invención puede realizarse en otras formas específicas sin apartarse del espíritu o de los atributos esenciales de la misma. Esta invención comprende todas las combinaciones de aspectos preferidos y/o

modalidades preferidas de la invención destacadas en el presente documento. Se entiende que cualquiera y todas las modalidades de la presente invención se pueden tomar en conjunción con cualquier otra modalidad o modalidades para describir modalidades más preferidas adicionales. Se entiende también que cada elemento individual de las modalidades preferidas es por si mismo un elemento independientemente preferido. Además, se quiere decir que cualquier elemento de una modalidad se combina con cualesquiera y con todos los otros elementos de cualquier modalidad para describir una modalidad adicional.

Las siguientes son definiciones de términos usados en esta especificación y en las reivindicaciones adjuntas. La definición inicial proporcionada para un grupo o término en la presente invención se aplica a ese grupo o término en toda la memoria descriptiva y las reivindicaciones, individualmente o como parte de otro grupo, a menos que se indique de otro modo.

Los compuestos de esta invención pueden tener uno o más centros asimétricos. A menos que se indique lo contrario, todas las formas quirales (enantioméricas y diastereoméricas) y racémicas de los compuestos de la presente invención están incluidas en la presente invención. Muchos isómeros geométricos de olefinas, enlaces dobles C=N, y similares pueden estar también presentes en los compuestos,

y todos los isómeros estables tales están contemplados en la presente invención. Se describen isómeros geométricos cis y trans de los compuestos de la presente invención y se pueden aislar como una mezcla de isómeros o de formas isómeras separadas. Los presentes compuestos se pueden aislar en formas ópticamente activas o racémicas. Se conoce bien en la técnica como preparar formas ópticamente activas, tales como por resolución de formas racémicas o por síntesis a partir de materiales de partida ópticamente activos. Se piensa en todas las formas quirales, (enantiómeras y diastereómeras) y todas las formas racémicas y todas las formas isómeras geométricas de una estructura, a menos que la estereoquímica específica o la forma isómera esté específicamente indicada.

Cuando cualquier variable (por ejemplo, R^3) se da más de una vez en cualquier constituyente o fórmula para un compuesto, su definición en cada aparición es independiente de su definición en cualquier otra aparición. Así, por ejemplo, si se muestra que un grupo está sustituido con 0-2 R^3, entonces este grupo puede estar opcionalmente sustituido con hasta dos grupos R^3 y R^3 en cada aparición se selecciona independientemente de la definición de R^3. Además, son permisibles combinaciones de sustituyentes y/o variables sólo si tales combinaciones dan como resultado compuestos estables.

Cuando un enlace a un sustituyente se muestra que cruza un enlace que conecta dos átomos en un anillo, entonces tal sustituyente puede estar enlazado a cualquier átomo en el anillo. Cuando un sustituyente se enumera sin indicar el átomo por medio del que tal sustituyente está unido al resto del compuesto de una fórmula dada, entonces tal sustituyente puede estar unido por medio de un átomo en tal sustituyente. Son permisibles combinaciones de sustituyentes y/o variables sólo si tales combinaciones dan como resultado compuestos estables.

En casos en los que hay átomos de nitrógeno (por ejemplo, aminas) en compuestos de la presente invención, éstos se pueden convertir a N-óxidos mediante tratamiento con un agente oxidante (por ejemplo, MCPBA y/o peróxidos de hidrógeno) para proporcionar otros compuestos de esta invención. Así, todos los átomos de nitrógeno mostrados y reivindicados se considera que cubren tanto el nitrógeno mostrado como su derivado N-óxido (N→O).

De acuerdo con una convención usada en la técnica,



se usa en fórmulas estructurales en el presente documento para representar el enlace que es el punto de unión del resto o sustituyente a la estructura del núcleo o esqueleto.

Un guión "-" que no está entre dos letras o símbolos se usa para indicar un punto de unión para un

sustituyente. Por ejemplo, $-CONH_2$ está unido a través del átomo de carbono.

El término "opcionalmente sustituido" en referencia a un resto particular del compuesto de Fórmula I (*por ejemplo*, un grupo heteroarilo opcionalmente sustituido) hace referencia a un resto que tiene 0, 1, 2, ó más sustituyentes. Por ejemplo, "alquilo opcionalmente sustituido" comprende tanto "alquilo" como "alquilo sustituido" según se define más adelante. Se entenderá por aquellos expertos en la técnica, con respecto a cualquier grupo que contenga uno o más sustituyentes, que tales grupos no están pensados para introducir cualquier sustitución o cualesquiera patrones de sustitución que sean estéricamente no practicables, sintéticamente no factibles y/o inherentemente inestables.

Como se usa en el presente documento, el término "al menos una entidad química" es intercambiable con el término "un compuesto."

Como se usa en el presente documento, el término "alquilo" o "alquileno" está pensado para incluir tanto grupos hidrocarburo alifático saturado de cadena ramificada como grupos hidrocarburo alifático saturado de cadena lineal que tengan el número especificado de átomos de carbono. Por ejemplo, "alquilo C_{1-10}" (o alquileno), está pensado para incluir grupos alquilo de C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, y C_{10}. Adicionalmente, por ejemplo, "alquilo C_1-C_6" designa

alquilo que tiene de 1 a 6 átomos de carbono. Los grupos alquilo pueden estar insustituidos o sustituidos de tal forma que uno o más de sus hidrógenos están reemplazados por otro grupo químico. Los grupos alquilo de ejemplo incluyen, pero no se limitan a, metilo (Me), etilo (Et), propilo (por ejemplo, n-propilo e isopropilo), butilo (por ejemplo, n-butilo, isobutilo, t-butilo), y pentilo (por ejemplo, n-pentilo, isopentilo, neopentilo), y similares.

"Alquenilo" o "alquenileno" están pensados para incluir cadenas de hidrocarburo tanto de configuración lineal como ramificada y que tengan uno o más dobles enlaces carbono-carbono que pueden darse en cualquier punto estable a lo largo de la cadena. Por ejemplo, "alquenilo C_{2-6}" (o alquenileno), está pensado para incluir grupos alquenilo C_2, C_3, C_4, C_5, y C_6. Ejemplos de alquenilo incluyen, pero no se limitan a, etenilo, 1-propenilo, 2-propenilo, 2-butenilo, 3-butenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo, 2-metil-2-propenilo, 4-metil-3-pentenilo, y similares.

"Alquinilo" o "alquinileno" están pensados para incluir cadenas de hidrocarburos tanto de configuración lineal como ramificada y que tengan uno o más enlaces triples carbono-carbono que pueden darse en cualquier punto estable a lo largo de la cadena. Por ejemplo, "alquinilo C_{2-6}" (o alquinileno), está pensado para incluir grupos alquinilo C_2,

C_3, C_4, C_5, y C_6; tales como etinilo, propinilo, butinilo, pentinilo, hexinilo y similares.

Alguien experto en el campo entenderá que, cuando se usa la designación "CO_2" en el presente documento, esto pretende referirse al grupo $-\overset{O}{\overset{\|}{C}}-O-$.

Cuando se usa el termino "alquilo" conjuntamente con otro grupo, tal como en "arilalquilo", esta conjunción define con más especificidad al menos uno de los sustituyentes que contendrá el alquilo sustituido. Por ejemplo, "arilalquilo" hace referencia a un grupo alquilo sustituido según se define anteriormente en el que al menos uno de los sustituyentes es un arilo, tal como un bencilo. Así, el término aril(C_{0-4})alquilo incluye un alquilo inferior sustituido que tiene al menos un sustituyente arilo e incluye también un arilo unido directamente a otro grupo, *es decir*, aril(C_0)alquilo. El término "heteroarilalquilo" hace referencia a un grupo sustituido según se define anteriormente donde al menos uno de los sustituyentes es un heteroarilo.

Cuando se hace referencia a un grupo alquenilo, alquinilo, alquileno, alquenileno, o alquinileno, estos grupos están sustituidos con uno o tres sustituyentes según se definen anteriormente para grupos alquilo sustituidos.

El término "alcoxi" hace referencia a un átomo de oxígeno sustituido con alquilo o alquilo sustituido, según se

definen anteriormente. Por ejemplo, el término "alcoxi" incluye el grupo -O-alquilo C_{1-6} tal como metoxi, etoxi, propoxi, isopropoxi, n-butoxi, sec-butoxi, terc-butoxi, pentoxi, 2-pentiloxi, isopentoxi, neopentoxi, hexoxi, 2-hexoxi, 3-hexoxi, 3-metilpentoxi, y similares. "Alcoxi inferior" hace referencia a grupos alcoxi que tienen uno a cuatro carbonos.

Se entenderá que las selecciones para todos los grupos, incluyendo por ejemplo, alcoxi, tioalquilo, y aminoalquilo, se harán por alguien experto en la técnica para proporcionar compuestos estables.

El término "sustituido", como se usa en el presente documento, quiere decir que uno o más hidrógenos en el átomo o grupo designado están reemplazados por una selección del grupo indicado, siempre que la valencia normal del átomo no se supere. Cuando un sustituyente es oxo, ó ceto, (*es decir*, =O) entonces están reemplazados dos hidrógenos en el átomo. Los sustituyentes ceto no están presentes en restos aromáticos. A menos que se especifique otra cosa, los sustituyentes se nombran en la estructura del núcleo. Por ejemplo, se entenderá que cuando (cicloalquil)alquilo se enumere como un posible sustituyente, el punto de unión de este sustituyente a la estructura del núcleo esté en la parte alquilo. Los enlaces dobles de anillo, como se usan en el presente documento, son dobles enlaces que están formados

entre dos átomos de anillo adyacentes (por ejemplo, C=C, C=N, o N=N).

Las combinaciones de sustituyentes y/o variables son permisibles sólo si tales combinaciones dan como resultado compuestos estables o útiles como intermedios de síntesis. Un compuesto de estructura estable quiere decir que implica un compuesto que es suficientemente fuerte para sobrevivir a aislamiento a partir de una mezcla de reacción a un grado de pureza útil, y a la subsiguiente formulación dentro de un agente terapéutico eficaz. Se prefiere que los compuestos ahora enumerados no contengan un grupo N-halo, $S(O)_2H$, o S(O)H.

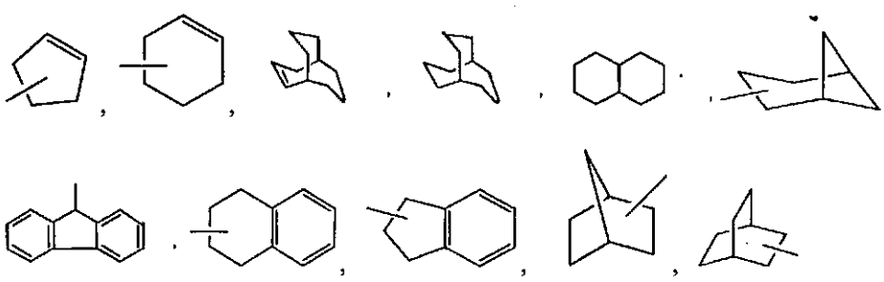
El término "cicloalquilo" hace referencia a grupos alquilo ciclados, incluyendo sistemas de anillos mono, bi o policíclicos. El cicloalquilo C_{3-7} está pensado para incluir grupos cicloalquilo C_3, C_4, C_5, C_6, y C_7. Los grupos cicloalquilo de ejemplo incluyen, pero no están limitados a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, norbornilo, y similares. Como se usa en el presente documento, "carbociclo" o "resto carbocíclico" se pretende que signifique cualquier anillo de 3, 4, 5, 6, o 7 miembros monocíclico o bicíclico estable, o cualquier anillo bicíclico o tricíclico de 7, 8, 9, 10, 11, 12, o 13 miembros estable, cualquiera de los cuales puede ser saturado, parcialmente insaturado, insaturado, o aromático. Ejemplos

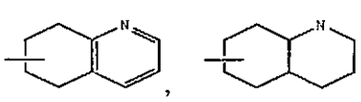
de tales carbociclos incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclobutenilo, ciclopentilo, ciclopentenilo, ciclohexilo, cicloheptenilo, cicloheptilo, cicloheptenilo, adamantilo, ciclooctilo, ciclooctenilo, ciclooctadienilo, [3,3,0]biciclooctano, [4,3,0]biciclononano, [4,4,0]biciclodecano, [2,2,2]biciclooctano, fluorenilo, fenilo, naftilo, indanilo, adamantilo, antracenilo, y tetrahidronaftilo (tetralina). Como se muestra anteriormente, los anillos dotados de puentes están incluidos también en la definición de carbociclo (*por ejemplo*, [2,2,2]biciclooctano). Los carbociclos preferidos, a menos que se especifique otra cosa, son ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y fenilo. Cuando se usa el término "carbociclo", está pensado para incluir "arilo". Un anillo dotado de puentes se da cuando uno o más átomos de carbono enlazan dos átomos no adyacentes. Los puentes preferidos son uno o dos átomos de carbono. Se destaca que un puente siempre convierte un anillo monocíclico en un anillo bicíclico. Cuando un anillo está dotado de puentes, los sustituyentes enumerados para el anillo pueden estar también presentes en el puente.

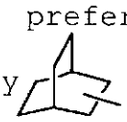
El término "arilo" hace referencia a grupos hidrocarburo aromático monocíclico o bicíclico que tienen 6 a 12 átomos de carbono en la parte de anillo, tal como grupos naftilo y fenilo, cada uno de los cuales puede estar

sustituido.

De acuerdo con ello, en compuestos de fórmula (I), el término "cicloalquilo" incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, biciclooctilo, etc., así como los siguientes sistemas de anillo,





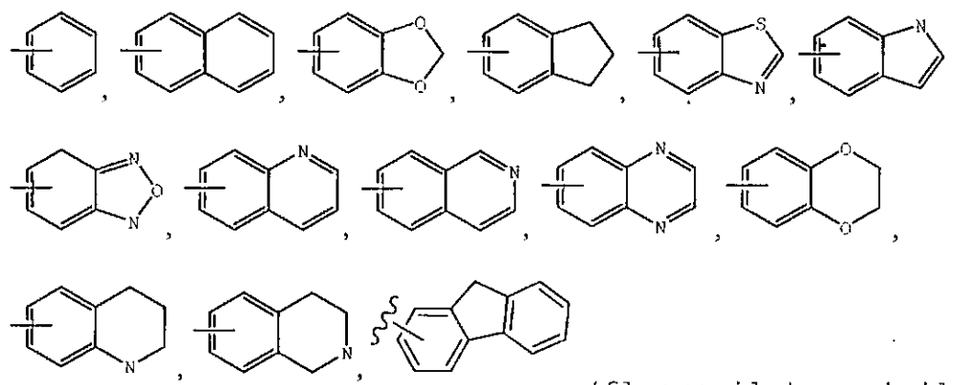
y similares, que pueden estar opcionalmente sustituidos en cualquier átomo disponible del anillo/de los anillos. Los grupos cicloalquilo preferidos incluyen ciclopropilo, ciclopentilo, ciclohexilo, y  .

El término "halo" o "halógeno" hace referencia a cloro, bromo, fluoro y yodo.

El término "haloalquilo" quiere decir un alquilo sustituido que tiene uno o más sustituyentes halo. Por ejemplo, "haloalquilo" incluye mono, bi, y trifluorometilo.

El término "haloalcoxi" quiere decir un grupo alcoxi que tiene uno o más sustituyentes halo. Por ejemplo, "haloalcoxi" incluye OCF_3.

Así, ejemplos de grupos arilo incluyen:

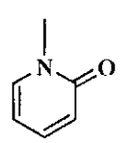
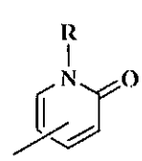
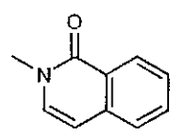
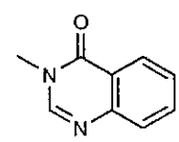


(fluorenilo) y similares, que pueden estar opcionalmente sustituidos en cualquier átomo de carbono o de nitrógeno disponible. Un grupo arilo preferido está opcionalmente sustituido con fenilo.

Los términos "heterocicloalquilo", "heterociclo", "heterocíclico", o "heterociclilo" pueden usarse intercambiablemente y hacen referencia a grupos monocíclicos de 3- a 7- miembros no aromáticos sustituidos e insustituidos, grupos bicíclicos de 7- a 11- miembros, y grupos tricíclicos de 10- a 15- miembros, en los que al menos uno de los anillos tienen al menos un heteroátomo (O, S o N), teniendo este anillo que contiene heteroátomos preferentemente 1, 2, o 3 heteroátomos seleccionados de O, S, y N. Cada anillo de un grupo tal que contiene un heteroátomo puede contener uno o dos átomos de oxígeno o de azufre y/o de uno a cuatro átomos de nitrógeno dado que el número total de heteroátomos en cada anillo es cuatro o menos, y adicionalmente siempre que el anillo contenga al menos un átomo de carbono. Los átomos de nitrógeno y de azufre pueden

estar opcionalmente oxidados y los átomos de nitrógeno pueden estar opcionalmente cuaternizados. Los anillos condensados que completan los grupos bicíclico y tricíclico pueden contener sólo átomos de carbono y pueden ser saturados, parcialmente saturados o insaturados. El grupo heterociclo puede estar unido a un nitrógeno disponible o a un átomo de carbono. El término "heterociclo" incluye grupos "heteroarilo". Según permita la valencia, si este anillo adicional es cicloalquilo o heterociclo está adicionalmente opcionalmente sustituido con =O (oxo).

Los grupos heterocíclicos monocíclicos ejemplares incluyen azetidinilo, pirrolidinilo, oxetanilo, imidazolinilo, oxazolidinilo, isoxazolinilo, tiazolidinilo, isotiazolidinilo, tetrahidrofuranilo, piperidilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidilo, 2-oxopirrolidinilo, 2-oxoazepinilo, azepinilo, 1-piridonilo, 4-piperidonilo, tetrahidropiranilo, morfolinilo, tiamorfolinilo, tiamorfolinilo sulfóxido, tiamorfolinilsulfona, 1,3-dioxolano y tetrahidro-1,1-dioxotienilo y similares. Los grupos heterociclo bicíclicos ejemplares incluyen quinuclidinilo. Los grupos heterociclilo monocíclicos adicionales incluyen

El término "heteroarilo" hace referencia a grupos monocíclicos aromáticos de 5- o 6- miembros sustituidos e insustituidos de sustituidos, grupos bicíclicos de 9- o 10- miembros, y grupos tricíclicos de 11- a 14- miembros que tienen al menos un heteroátomo (O, S o N) en la menos uno de los anillos, teniendo este anillo que contiene heteroátomos preferentemente 1, 2, o 3 heteroátomos seleccionados de O, S, y N. Cada anillo del grupo heterociclo tal que contiene un heteroátomo puede contener uno o dos átomos de oxígeno o de azufre y/o de uno a cuatro átomos de nitrógeno siempre que el número total de heteroátomos en cada anillo sea cuatro o menos y que cada anillo contenga al menos un átomo de carbono. Los anillos condensados que completan los grupos bicíclico y tricíclico pueden contener sólo átomos de carbono y pueden ser saturados, parcialmente saturados o insaturados. Los átomos de nitrógeno y de azufre pueden estar opcionalmente oxidados y los átomos de nitrógeno pueden estar opcionalmente cuaternizados. Los grupos heteroarilo que son bicíclicos o tricíclicos deben incluir al menos un anillo totalmente aromático pero el otro anillo o los otros anillos condensados pueden ser aromáticos o no aromáticos. El grupo heteroarilo puede estar unido en cualquier nitrógeno disponible o en cualquier átomo de carbono de cualquier anillo. Según permita la valencia, si este anillo adicional es cicloalquilo o heterociclo está adicionalmente

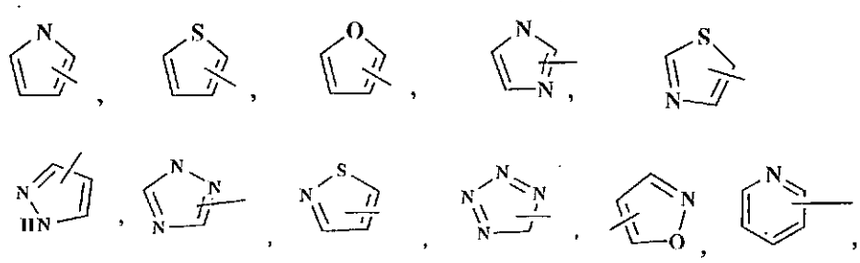
opcionalmente sustituido con =O (oxo).

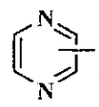
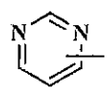
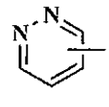
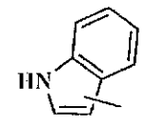
Los grupos heteroarilo monocíclicos ejemplares incluyen pirrolilo, pirazolilo, pirazolinilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, furanilo, tienilo, oxadiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo y similares.

Los grupos heteroarilo bicíclicos ejemplares incluyen indolilo, benzotiazolilo, benzodioxolilo, benzoxazolilo, benzotienilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolilo, bencimidazolilo, benzopiranilo, indolizinilo, benzofuranilo, cromonilo, cumarinilo, benzopiranilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridilo, dihidroisoindolilo, tetrahidroquinolinilo y similares.

Los grupos heteroarilo tricíclicos ejemplares incluyen carbazolilo, bencindolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares.

En compuestos de formula (I), los grupos heteroarilo preferidos incluyen



 ,  ,  , y  , y similares, que pueden estar opcionalmente sustituidos en cualquier átomo de carbono o de nitrógeno disponible.

A menos que se indique de otro modo, cuando se hace alusión a un arilo nombrado específicamente (*por ejemplo*, fenilo), cicloalquilo (*por ejemplo*, ciclohexilo), heterociclo (*por ejemplo*, pirrolidinilo, piperidinilo, y morfolinilo) o heteroarilo (*por ejemplo*, tetrazolilo, imidazolilo, pirazolilo, triazolilo, tiazolilo, y furilo) la alusión está pensada para incluir anillos que tengan 0 a 3, preferentemente 0-2, sustituyentes seleccionados de aquellos enumerados anteriormente para los grupos arilo, cicloalquilo, heterociclo y/o heteroarilo, según sea apropiado.

El término "carbociclilo" o "carbocíclico" hace alusión a un anillo monocíclico o bicíclico en el que todos los átomos de todos los anillos son carbonos. Así, el término incluye anillos cicloalquilo y anillos arilo. Los carbociclos monocíclicos tienen 3 a 6 átomos de carbono, aún más típicamente 5 ó 6 átomos de carbono. Los carbociclos bicíclicos tienen 7 a 12 átomos de carbono, por ejemplo, dispuestas como un sistema [4,5], [5,5], [5,6] o [6,6] biciclo, o 9 ó 10 átomos de carbono dispuestos como un sistema [5,6] o [6,6] biciclo. Ejemplos de carbociclos mono-

y bicíclicos incluyen ciclopropilo, ciclobutilo, ciclopentilo, 1-ciclopent-1-enilo, 1-ciclopent-2-enilo, 1-ciclopent-3-enilo, ciclohexilo, 1-ciclohex-1-enilo, 1-ciclohex-2-enilo, 1-ciclohex-3-enilo, fenilo y naftilo. El anillo carbocíclico puede estar sustituido en cuyo caso los sustituyentes están seleccionados a partir de aquellos enumerados anteriormente por grupos cicloalquilo y arilo.

El término "heteroátomos" incluirá oxígeno, azufre y nitrógeno.

Cuando se usa el término "insaturado" en el presente documento para referirse a un anillo o grupo, el anillo o grupo puede estar totalmente insaturado o parcialmente insaturado.

Por toda la memoria descriptiva, se pueden elegir grupos y sustituyentes de la misma por alguien experto en la técnica para proporcionar restos y compuestos estables y compuestos útiles como compuestos farmacéuticamente aceptables y/o compuestos intermedios útiles en elaborar compuestos farmacéuticamente aceptables.

Los compuestos de fórmula (I) pueden existir en una forma libre (con ninguna ionización) o pueden formar sales que están también dentro del alcance de esta invención. A menos que se indique otra cosa, se entiende que la referencia a un compuesto de la invención incluye referencia a la forma libre y a sales de la misma. El término "sal(es)" indica

sales de ácidos y/o de bases formadas con ácidos o bases inorgánicos y/o orgánicos. Además, el término "sal(es) puede incluir iones híbridos (sales internas), *por ejemplo*, cuando un compuesto de fórmula (I), contiene tanto un resto básico, tal como una amina o piridina o anillo de imidazol, y un resto ácido, tal como un ácido carboxílico. Se prefieren sales farmacéuticamente aceptables (*es decir*, no tóxicas, fisiológicamente aceptables), tales como, por ejemplo, sales metálicas y sales de amina aceptables en las que el catión no contribuya significativamente a la toxicidad o a la actividad biológica de la sal. Sin embargo, pueden ser útiles otras sales, *por ejemplo*, en etapas de aislamiento o purificación que se pueden emplear durante la preparación, y así, se contemplan dentro del alcance de la invención. Se pueden formar sales de los compuestos de la fórmula (I), por ejemplo, haciendo reaccionar un compuesto de la fórmula (I) con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en el que la sal precipita o en un medio acuoso seguido por liofilización.

Las sales de adición de ácidos ejemplares incluyen acetatos (tales como aquellos formados con ácido acético o ácido trihaloacético, por ejemplo, ácido trifluoroacético), adipatos, alginatos, ascorbatos, aspartatos, benzoatos, bencenosulfonatos, bisulfatos, boratos, butiratos, citratos, camforatos, camforsulfonatos, ciclopentanopropionatos,

digluconatos, dodecilsulfatos, etanosulfonatos, fumaratos, glucoheptanoatos, glicerofosfatos, hemisulfatos, heptanoatos, hexanoatos, clorhidratos (formados con ácido clorhídrico), bromhidratos (formados con bromuro de hidrógeno), yodhidratos, 2-hidroxietanosulfonatos, lactatos, maleatos (formados con ácido maleico), metanosulfonatos (formados con ácido metanosulfónico), 2-naftalenosulfonatos, nicotinatos, nitratos, oxalatos, pectinatos, persulfatos, 3-fenilpropionatos, fosfatos, picratos, pivalatos, propionatos, salicilatos, succinatos, sulfatos (tales como aquellos formados con ácido sulfúrico), sulfonatos (tales como aquellos mencionados en el presente documento), tartratos, tiocianatos, toluenosulfonatos tales como tosilatos, undecanoatos, y similares.

Las sales básicas ejemplares incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio, y potasio; sales de metales alcalinotérreos tales como sales de calcio y de magnesio; bario, cinc, y aluminio; sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como trialquilaminas tales como trietilamina, procaína, dibencilamina, N-bencil-β-fenetilamina, 1-efenamina, N,N'-dibenciletileno-diamina, dehidroabietilamina, N-etilpiperidina, bencilamina, diciclohexilamina o aminas y sales farmacéuticamente aceptables similares con aminoácidos tales como arginina, lisina y similares. Los grupos básicos

que contienen nitrógeno se pueden cuaternizar con agentes tales como haluros de alquilo inferior (*por ejemplo,* cloruros, bromuros y yoduros de metilo, etilo, propilo y butilo), dialquilsulfatos (*por ejemplo,* dimetilsulfatos, dietilsulfatos, dibutilsulfatos y diamilsulfatos), haluros de cadena larga (*por ejemplo,* cloruros bromuros y yoduros de decilo, laurilo, miristilo y estearilo), haluros de aralquilo (*por ejemplo,* bromuros de bencilo y fenetilo), y otros. Las sales preferidas incluyen monoclorhidrato, hidrogenosulfato, metanosulfonato, fosfato o nitrato.

La frase "farmacéuticamente aceptable" se emplea en el presente documento para referirse a aquellos compuestos, materiales, composiciones, y/o formas de dosificación que son, dentro del alcance del juicio médico sólido, adecuados para usar en contacto con los tejidos de seres humanos y animales, sin toxicidad excesiva, irritación, respuesta alérgica u otro problema o complicación, proporcional a una relación beneficio/riesgo razonable.

Como se usa en el presente documento, "sales farmacéuticamente aceptables" hace referencia a derivados de los compuestos revelados en los que el compuesto parental está modificado elaborando sales de ácidos o de bases del mismo. Ejemplos de sales farmacéuticamente aceptables incluyen, pero no se limitan a, sales de ácidos minerales u orgánicos de grupos básicos tales como aminas, y a sales

alcalinas y orgánicas de grupos ácidos tales como ácidos carboxílicos. Las sales farmacéuticamente aceptables incluyen las sales no tóxicas convencionales o las sales de amonio cuaternario del compuesto parental formado, por ejemplo, de ácidos inorgánicos u orgánicos no tóxicos. Por ejemplo, tales sales no tóxicas convencionales incluyen aquellas derivadas de ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico, sulfámico, fosfórico, y nítrico; y las sales preparadas de ácidos orgánicos tales como clorhídrico, bromhídrico, sulfúrico, sulfámico, fosfórico, y nítrico; y las sales preparadas a partir de ácidos orgánicos tales como acético, propiónico, succínico, glicólico, esteárico, láctico, málico, tartárico, cítrico, ascórbico, pamoico, maleico, hidroximaleico, fenilacético, glutámico, benzoico, salicílico, sulfanílico, 2-acetoxibenzoico, fumárico, toluenosulfónico, metanosulfónico, etano disulfónico, oxálico, e isetiónico, y similares.

Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir del compuesto parental que contiene un resto básico o ácido por procedimientos químicos convencionales. Generalmente, tales sales se pueden preparar haciendo reaccionar las formas ácidas o básicas libres de estos compuestos con una cantidad estequiométrica de la base o el ácido apropiado en agua o en un disolvente orgánico, o en una mezcla de los dos;

generalmente, se prefieren los medios no acuosos como éter, acetato de etilo, etanol, etanol, isopropanol, o acetonitrilo. Las listas de sales adecuadas se encuentran en *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, **1990**, la revelación del cual se incorpora por la presente mediante referencia.

Están contemplados todos los estereoisómeros de los compuestos de la invención actual, bien en mezcla o bien en forma pura o sustancialmente pura. Los estereoisómeros pueden incluir compuestos que son isómeros ópticos a través de posesión de uno o más átomos quirales, así como compuestos que son isómeros ópticos en virtud de rotación limitada sobre uno o más enlaces (atropisómeros). La definición de los compuestos de acuerdo con la invención abarca todos los estereoiómeros posibles y sus mezclas. Ello abarca particularmente las formas racémicas y los isómeros ópticos aislados que tienen la actividad específica. Las formas racémicas se pueden redisolver por procedimientos físicos, tales como, por ejemplo, cristalización fraccionada, separación, o cristalización de derivados diestereoméricos o separación por cromatografía en columna quiral. Los isómeros ópticos individuales se pueden obtener a partir de los racematos por procedimientos convencionales, tales como, por ejemplo, formación de sales con un ácido ópticamente activo seguida de cristalización.

La presente invención está pensada para incluir todos los isótopos de átomos que aparecen en los presentes compuestos. Los isótopos incluyen aquellos átomos que tienen el mismo número atómico pero diferentes números másicos. A modo de ejemplo general y sin limitación, los isótopos de hidrógeno incluyen deuterio y tritio. Los isótopos de carbono incluyen ^{13}C y ^{14}C. Los compuestos isotópicamente marcados de la invención pueden generalmente prepararse mediante técnicas convencionales conocidas por aquellos expertos en la técnica o mediante procedimientos análogos a aquellos descritos en el presente documento, usando un reactivo isotópicamente marcado en lugar del reactivo no marcado empleado de lo contrario.

Se contemplan también los profármacos y los solvatos de los compuestos de la invención. El término "profármaco" indica un compuesto que, tras administración a un sujeto, sufre conversión por procedimientos metabólicos o químicos proporcionando un compuesto de fórmula (I), y/o una sal y/o solvato del mismo. Cualquier compuesto que se convierta *in vivo* proporcionando el agente bioactivo (*es decir*, un compuesto de fórmula (I)) es un profármaco dentro del alcance y del espíritu de la invención. Por ejemplo, compuestos que contienen un grupo carboxi pueden formar ésteres fisiológicamente hidrolizables que sirven como profármacos hidrolizándose en el cuerpo proporcionando

compuestos de fórmula (I) *per se*. Tales profármacos se administran preferentemente oralmente dado que la hidrólisis en muchos casos tiene lugar principalmente bajo la influencia de las enzimas digestivas. La administración parenteral se puede usar cuando el éster *per se* es activo, o en aquellos casos en que la hidrólisis tiene lugar en la sangre. Ejemplos de ésteres fisiológicamente aceptables de compuestos de fórmula (I) incluyen alquibencilo C_{1-6}, 4-metoxibencilo, indanilo, ftalilo, metoximetilo, alcanoiloxi C_{1-6}-alquilo C_{1-6}, *por ejemplo* acetoximetilo, pivaloiloximetilo o propioniloximetilo, alcoxicarboniloxi C_{1-6}-alquilo C_{1-6}, *por ejemplo* metoxicarbonil-oximetilo o etoxicarboniloximetilo, gliciloximetilo, fenilgliciloximetilo, (5-metil-2-oxo-1,3-dioxolen-4-il)-metilo y otros ésteres fisiológicamente hidrolizables bien conocidos usados, por ejemplo, en las técnicas de las penicilinas y las cefalosporinas. Tales ésteres se pueden preparar mediante técnicas convencionales conocidas en la técnica.

Se conocen bien en la técnica diversas formas de profármacos. Para ejemplos de tales derivados profármacos, véanse:

a) *Design of Prodrugs*, editado por H. Bundgaard, (Elsevier, 1985) y *Methods in Enzymology*, Vol. 112, páginas 309-396, editado por K. Widder, y col. (Academic Press, 1985);

b) *A Textbook of Drug Design and Development*, editado por Krosgaard-Larsen y H. Bundgaard, Capítulo 5, "Design and Application of Prodrugs," por H. Bundgaard, páginas 113-191 (1991); y

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, páginas 1-38 (1992), cada una de las cuales se incorpora en el presente documento mediante referencia.

Los compuestos de la fórmula (I) y las sales de los mismos pueden existir en su forma tautómera, en la que están transpuestos átomos de hidrógeno a otras partes de la molécula y se reordenan los enlaces químicos entre los átomos de las moléculas consecuentemente. Se entenderá que todas las formas tautómeras, en la medida en que ellas puedan existir, están incluidas dentro de la invención. Adicionalmente, los compuestos de la invención tienen isómeros *trans* y *cis*.

Se entenderá adicionalmente que solvatos (*por ejemplo,* hidratos) de los compuestos de Fórmula (I) están también dentro del alcance de la presente invención. Los procedimientos de solvatación se conocen generalmente en la técnica.

Utilidad

Los compuestos de la invención modulan la actividad cinasa, incluyendo la modulación de Btk. Otros tipos de actividad cinasa que se pueden modular por los compuestos de

la presente invención incluyen, pero no se limitan a, la familia Tec de compuestos, tales como Bmx, Btk, Itk, Txk y Tec, y mutantes de los mismos.

De acuerdo con ello, los compuestos de fórmula (I) tienen utilidad en tratar afecciones asociadas con la modulación de actividad cinasa, y particularmente con la inhibición selectiva de actividad de Btk o con la inhibición de Btk y de otras cinasas de la familia Tec tales como Itk. Tales afecciones incluyen enfermedades mediadas por linfocitos B en las que los niveles de citocinas están modulados como una consecuencia de la señalización intracelular. Además, los compuestos de fórmula (I) tienen selectividad ventajosa para actividad de Btk y otras cinasas de la familia Tec tales como Itk sobre la actividad Mk2, preferentemente de al menos 20 veces a aproximadamente 1.000 veces más selectivos.

Como se usan en el presente documento, los términos "tratar" o "tratamiento" comprenden el tratamiento de un estado morboso en un mamífero, particularmente un ser humano, e incluyen: (a) evitar o retardar la aparición del estado morboso en un mamífero, en particular, cuando tal mamífero está predispuesto al estado morboso pero aún no ha sido diagnosticado como que lo tiene; (b) inhibir el estado morboso, es decir, detener su desarrollo; y/o (c) lograr una reducción total o parcial de los síntomas del estado morboso,

y/o aliviar, mejorar, disminuir, o curar la enfermedad o trastorno y/o sus síntomas.

En vista de su actividad como inhibidores selectivos de Btk o Btk y otra cinasa de la familia Tec tal como Itk, los compuestos de Fórmula (I) son útiles en tratar afecciones asociadas con citocinas que incluyen, pero no se limitan a, enfermedades inflamatorias tales como enfermedad de Crohn y colitis ulcerosa, asma, enfermedad de injerto frente a hospedador, enfermedad pulmonar obstructiva crónica; enfermedades autoinmunes tales como enfermedad de Graves, artritis reumatoide, lupus eritematoso sistémico, soriasis; trastornos óseos destructivos tales como enfermedad de resorción ósea, osteoartritis, osteoporosis, trastorno óseo relacionado con mieloma múltiple; trastornos proliferativos tales como leucemia mielógena aguda, leucemia mielógena crónica; trastornos angiogénicos tales como trastornos angiogénicos que incluyen tumores sólidos, neovascularización ocular, y hemangiomas infantiles; enfermedades infecciosas tales como sepsis, choque séptico, y Shigellosis; enfermedades neurodegenerativas tales como enfermedad de Alzheimer, enfermedad de Parkinson, isquemias cerebrales o enfermedad neurodegenerativa causada por daño traumático, enfermedades oncológicas y virales tales como melanoma metastásico, sarcoma de Kaposi, mieloma múltiple, e infección con VIH y retinitis de CMV, SIDA, respectivamente.

Más particularmente, las afecciones o enfermedades específicas que se pueden tratar con los compuestos de la invención incluyen, sin limitación, pancreatitis (aguda o crónica), asma, alergias, síndrome de dificultad respiratoria del adulto, enfermedad pulmonar obstructiva crónica, glomerulonefritis, artritis reumatoide, lupus eritematoso sistémico, escleroderma, tiroiditis crónica, enfermedad de Graves, gastritis autoinmune, diabetes, anemia hemolítica autoinmune, neutropenia autoimnune, trombocitopenia, dermatitis atópica, hepatitis activa crónica, miastenia gravis, esclerosis múltiple, enfermedad inflamatoria del intestino, colitis ulcerosa, enfermedad de Crohn, soriasis, enfermedad de injerto frente a hospedador, reacción inflamatoria inducida por endotoxina, tuberculosis, aterosclerosis, degeneración muscular, caquexia, artritis soriática, síndrome de Reiter, gota, artritis traumática, artritis rubeólica, sinovitis aguda, enfermedad de las células β pancreáticas; enfermedades caracterizadas por infiltración neutrófila masiva; espondilitis reumatoide, artritis gotosa y otras afecciones artríticas, malaria cerebral, enfermedad inflamatoria pulmonar crónica, silicosis, sarcoidosis pulmonar, enfermedad de resorción ósea, rechazos de alotransplantes, fiebre y mialgias debidas a la infección, caquexia secundaria a infección, formación mieloide, formación de tejido de cicatrices, colitis

ulcerosa, piresis, gripe, osteoporosis, osteoartritis, leucemia mielógena aguda, leucemia mielógena crónica, melanoma metastásico, sarcoma de Kaposi, mieloma múltiple, sepsis, choque séptico, y Shigellosis; enfermedad de Alzheimer, enfermedad de Parkinson, isquemias cerebrales o enfermedad neurodegenerativa causada por herida traumática; trastornos angiogénicos incluyendo tumores sólidos, neovascularización ocular y hemangiomas infantiles; enfermedades virales incluyendo infección de hepatitis aguda (incluyendo hepatitis A, hepatitis B y hepatitis C), infección con VIH y retinitis de CMV, SIDA, ARC o malignidad, y herpes; apoplejía, isquemia miocardial, isquemia en ataques cardiacos de infarto, hipoxia de órganos, hiperplasia vascular, reperfusión cardiaca y renal, trombosis, hipertrofia cardiaca, agregación plaquetaria inducida por trombina, endotoxemia y/o síndrome de choque tóxico, afecciones relacionadas con endoperoxidasa sintasa-2 de prostaglandinas, y pénfigo vulgar. Los procedimientos preferidos de tratamiento son aquellos en los que la afección está seleccionada de Crohn y colitis ulcerosa, rechazo de aloinjerto, artritis reumatoide, soriasis, espondilitis anquilosante, artritis soriática, y pénfigo vulgar. Alternativamente los procedimientos preferidos de tratamiento son aquellos en los que la afección está seleccionada de daño por reperfusión isquémica, incluyendo el daño por

reperfusiones de isquemia cerebral que surge de infarto de miocardio. Otro procedimiento preferido de tratamiento es uno en el que la afección es mieloma múltiple.

Además, los inhibidores de cinasa de la presente invención inhiben la expresión de proteínas proinflamatorias inducibles tales como prostaglandina endoperóxido sintasa-2 (PGHS-2), también denominada como ciclooxigenasa-2 (COX-2). De acuerdo con ello, las afecciones asociadas con Btk adicionales incluyen edema, analgesia, fiebre y dolor, tales como dolor neuromuscular, dolor de cabeza, dolor causado por cáncer, dolor dental y dolor de artritis. Los compuestos de la invención también se pueden usar para tratar infecciones virales veterinarias, tales como infecciones por lentivirus, incluyendo, pero no limitadas a virus de infección de anemia equina; o infecciones por retrovirus, incluyendo virus de la inmunodeficiencia felina, virus de la inmunodeficiencia bovina, y virus de la inmunodeficiencia canina.

Cuando los términos "afección asociada con Btk" o "enfermedad o trastorno asociado con Btk" se usan en el presente documento, se pretende que cada uno abarque todas las afecciones identificadas anteriormente como si se repitieran en toda su extensión, así como cualquier otra afección que esté afectada por la actividad de la Btk cinasa.

La presente invención proporciona así procedimientos para tratar tales afecciones, que comprenden

administrar a un sujeto en necesidad de las mismas una cantidad terapéuticamente eficaz de al menos un compuesto de Fórmula (I) o una sal del mismo. "Cantidad terapéuticamente eficaz" está pensada para incluir una cantidad de un compuesto de la presente invención que es eficaz cuando se administra sola o en combinación para inhibir Btk y otras cinasas de la familia Tec y/o para tratar enfermedades.

Los procedimientos para tratar afecciones asociadas con la Btk cinasa pueden comprender administrar compuestos de Fórmula (I) solos o en combinación entre sí y/o con otros agentes terapéuticos adecuados útiles en tratar tales afecciones. De acuerdo con ello, "cantidad terapéuticamente eficaz" está pensada también para incluir una cantidad de la combinación de compuestos reivindicados que es eficaz para inhibir Btk y/o tratar enfermedades asociadas con Btk.

Ejemplos de tales otros agentes terapéuticos incluyen corticosteroides, rolipram, calfostina, fármacos antiinflamatorios supresores de citocinas (CSAID), Interleucina-10, glucocorticoides, salicilatos, óxido nítrico, y otros inmunosupresores; inhibidores de translocación nuclear, tales como deoxispergualina (DSG); fármacos antiinflamatorios no esteroideos (NSAID) tales como ibuprofeno, celecoxib y rofecoxib; esteroides tales como prednisona o dexametasona; agentes antivirales tales como abacavir; agentes antiproliferativos tales como metotrexato,

leflunomida, FK506 (tacrolimus, Prograf); fármacos citotóxicos tales como azatioprina y ciclofosfamida; inhibidores de TNF-α tales como tenidap, anticuerpos anti-TNF o receptor de TNF soluble, y rapamicina (sirolimus o Rapamune) o derivados de los mismos.

Los otros agentes terapéuticos anteriores, cuando se emplean en combinación con los compuestos de la presente invención, se pueden usar, por ejemplo, en aquellas cantidades indicadas en el Vademécum (PDR) o por el contrario como se determina por alguien de experiencia normal en la técnica. En los procedimientos de la presente invención, tal(es) otro(s) agente(s) terapéutico(s) se puede(n) administrar antes de, simultáneamente con, o después de la administración de los compuestos de la invención. La presente invención proporciona también composiciones farmacéuticas capaces de tratar afecciones asociadas a la cinasa Btk, incluyendo afecciones mediadas por IL-1, IL-6, IL-8, IFNγ y TNF-α, como se describe anteriormente.

Las composiciones de la invención pueden contener otros agentes terapéuticos como se describen anteriormente y se pueden formular, por ejemplo, empleando vehículos o diluyentes sólidos o líquidos convencionales, así como aditivos farmacéuticos de un tipo apropiado para el modo de administración deseada (*por ejemplo*, excipientes, aglutinantes, conservantes, estabilizantes, aromas, etc.) de

acuerdo con técnicas tales como aquellas bien conocidas en la técnica de la formulación farmacéutica.

De acuerdo con ello, la presente invención incluye adicionalmente composiciones que comprenden uno o más compuestos de Fórmula (I) y un vehículo farmacéuticamente aceptable.

Un "vehículo farmacéuticamente aceptable se refiere a medios aceptados generalmente en la técnica para la administración de agentes biológicamente activos para animales, en particular mamíferos. Los vehículos farmacéuticamente aceptables se formularon de acuerdo con una serie de factores bien dentro de la competencia de aquellos de experiencia ordinaria en la técnica. Estos incluyen sin limitación el tipo y la naturaleza del agente activo que se está formulando; el sujeto al que se va a administrar la composición que contiene los agentes; la vía de administración deseada de la composición; y la indicación terapéutica que se toma como objetivo. Los vehículos farmacéuticamente aceptables incluyen tanto medios líquidos acuosos como medios líquidos no acuosos, así como una diversidad de formas farmacéuticas sólidas y semisólidas. Tales vehículos pueden incluir una serie de ingredientes y aditivos diferentes además del agente activo, estando tales ingredientes adicionales incluidos en la formulación por una diversidad de razones, *por ejemplo*, estabilización del agente

activo, aglutinantes, etc., bien conocidas por aquellos de experiencia ordinaria en la técnica. Se encuentran descripciones de vehículos farmacéuticamente aceptables adecuados, y de factores implicados en su selección, en una diversidad de fuentes fácilmente disponibles tales como, por ejemplo, *Remington's Pharmaceutical Sciences*, 17ª ed., **1985**, que se incorpora en el presente documento mediante referencia en su totalidad.

Los compuestos de Fórmula (I) pueden administrarse mediante cualesquiera medios adecuados para la afección a tratarse, que pueden depender de la necesidad de tratamiento específico de sitio o de cantidad de fármaco a administrarse. La administración tópica se prefiere generalmente para enfermedades relacionadas con la piel, y se prefiere tratamiento sistémico para afecciones cancerosas o precancerosas, aunque se contemplan otros modos de administración. Por ejemplo, los compuestos se pueden administrar oralmente, tal como en forma de comprimidos, cápsulas, gránulos, polvos, o formulaciones líquidas incluyendo jarabes; tópicamente, tal como en forma de soluciones, suspensiones, geles o pomadas; sublingualmente; bucalmente; parenteralmente, tal como por técnicas de inyección o infusión subcutáneas, intravenosas, intramusculares o intraesternales (*por ejemplo*, como soluciones o suspensiones acuosas o no acuosas inyectables

estériles); nasalmente tal como por pulverizador de inhalación; tópicamente, tal como en forma de una crema o pomada; rectalmente tal como en forma de supositorios; o liposómicamente. Se pueden administrar formulaciones en monodosis que contienen vehículos o diluyentes no tóxicos, farmacéuticamente aceptables. Los compuestos pueden administrarse en una forma adecuada para liberación inmediata o liberación prolongada. La liberación inmediata o la liberación extendida puede lograrse con composiciones farmacéuticas adecuadas o, particularmente en el caso de liberación prolongada, con dispositivos tales como implantes subcutáneos o bombas osmóticas.

Composiciones ejemplares para administración tópica incluyen un vehículo tópico tal como PLASTIBASE® (aceite mineral gelificado con polietileno).

Las composiciones ejemplares para administración oral incluyen suspensiones que pueden contener, por ejemplo, celulosa microcristalina para conferir masa, ácido algínico o alginato de sodio como un agente de suspensión, metilcelulosa como un potenciador de viscosidad, y agentes edulcorantes o aromatizantes tales como aquellos conocidos en la técnica; y comprimidos de liberación inmediata que pueden contener, por ejemplo, celulosa microcristalina, fosfato dicálcico, almidón, estearato de magnesio y/o lactosa y/o otros excipientes, aglutinantes, extensores, disgregantes,

diluyentes y lubricantes tales como aquellos conocidos en la técnica. Los compuestos de la invención pueden también estar administrados oralmente por administración sublingual y/o bucal, *por ejemplo*, con comprimidos moldeados, prensados, o secados en frío. Las composiciones ejemplares pueden incluir diluyentes de disolución rápida tales como manitol, lactosa, sacarosa y/o ciclodextrinas. También pueden estar incluidos en tales formulaciones excipientes de alto peso molecular tales como celulosas (AVICEL®) o polietilenoglicoles (PEG); un excipiente apara ayudar a adhesión mucosa tal como hidroxipropilcelulosa (HPC), hidroxipropilmetilcelulosa (HPMC), celulosa de carboximetil sodio (SCMC), y/o copolímero de anhídrido maleico (*por ejemplo*, GANTREZ®); y agentes para controlar la liberación tales como copolímero poliacrílico (*por ejemplo*, CARBOPOL 934®). Se pueden añadir también lubricantes, agentes deslizantes, aromas, agentes colorantes y estabilizadores para facilidad de fabricación y uso.

Las composiciones ejemplares para aerosol nasal o administración de inhalación incluyen soluciones que pueden contener, por ejemplo, alcohol bencílico u otros conservantes adecuados, promotores de absorción para potenciar la absorción y/o biodisponibilidad, y/o otros agentes solubilizadores o dispersantes tales como aquellos conocidos en la técnica.

Las composiciones ejemplares para administración parenteral incluyen soluciones o suspensiones inyectables que pueden contener, por ejemplo, diluyentes o disolventes parenteralmente aceptables, no tóxicos adecuados, tales como manitol, 1,3-butanodiol, agua, solución de Ringer, una solución de cloruro de sodio isotónica, u otros agentes dispersantes o humectantes y de suspensión adecuados, incluyendo mono- o diglicéridos sintéticos, y ácidos grasos, incluyendo ácido oleico.

Las composiciones ejemplares para administración rectal incluyen supositorios que pueden contener, por ejemplo, excipientes no irritantes adecuados, tales como manteca de cacao, ésteres de glicéridos sintéticos o polietilenoglicoles, que son sólidos a temperaturas ordinarias pero que se licuan y/o disuelven en la cavidad rectal para liberar el fármaco.

La cantidad terapéuticamente aceptable de un compuesto de la presente invención puede determinarse por alguien de experiencia ordinaria en la técnica, e incluye cantidades de dosificación ejemplares para un mamífero de aproximadamente 0.05 a 1000 mg/kg; 1-1000 mg/kg; 1-50 mg/kg; 5-250 mg/kg; 250-1000 mg/kg de peso corporal de compuesto activo por día, que puede

administrarse en una dosis individual o en la forma de dosis divididas individuales, tales como de 1 a 4 veces por día. Se entenderá que el nivel de dosis específico y la frecuencia de dosificación para cualquier sujeto en particular puede variarse y dependerá de una diversidad de factores, incluyendo la actividad del compuesto específico empleado, la estabilidad metabólica y la duración de acción de ese compuesto, la especie, edad, peso corporal, salud general, sexo y dieta del sujeto, el modo y tiempo de administración, velocidad de excreción, combinación de fármacos, y gravedad de la afección particular. Los sujetos preferidos para el tratamiento incluyen animales, lo más preferentemente especies de mamíferos tales como seres humanos, y animales domésticos tales como perros, gatos, caballos, y similares. Así, cuando el término "paciente" se usa en el presente documento, se pretende que este término incluya todos los sujetos, más preferentemente especies de mamíferos, que están afectados por mediación de niveles de enzimas Btk.

Ensayos biológicos

Ensayo de enzima Btk humana recombinante

A placas de 384 pocillos de fondo en V se añadieron compuestos de prueba, Btk humana

recombinante (1 nM, Invitrogen Corporation), péptido marcado con fluoresceína (1.5 μM), ATP (20 μM), y amortiguador de ensayo (HEPES 20 mM a pH 7.4, $MgCl_2$ 10 mM, Brij35 al 0.015% y DTT 4 mM en DMSO al 1.6%), con un volumen final de 30 μl. Después de incubar a temperatura ambiente durante 60 min, la reacción se finalizó añadiendo 45 μl de EDTA 35 mM a cada muestra. La mezcla de reacción se analizó en el Caliper LabChip 3000 (Caliper, Hopkinton, MA) por separación electroforética del sustrato fluorescente y del producto fosforilado. Los datos de inhibición se calcularon por comparación con reacciones sin control enzimático para inhibición del 100% y a controles no inhibidores para inhibición del 0%. Las curvas de respuesta a dosis se generaron para determinar la concentración requerida que inhibe el 50% de la actividad cinasa (CI_{50}). Se disolvieron los compuestos a 10 mM en dimetilsulfóxido (DMSO) y se evaluaron a once concentraciones.

Los ejemplos descritos más adelante tienen una CI_{50} de ≤ 10 μM en el ensayo de BTK descrito anteriormente.

Usando este ensayo, se determinaron los valores de CI_{50} de los siguientes compuestos. Véase Tabla 1.

Tabla 1.

Ejemplo	IC_{50} para Inhibición de Btk, μM
1-3	0.49
2-2	1.3
2-12	0.016
2-13	0.015
2-16	0.016
2-18	0.016
2-24	0.80
2-25	3.1
2-35	0.016
2-43	0.52
3-9	0.017
3-18	2.7
3-19	1.8
3-39	0.016
3-45	0.016
3-48	0.39
3-49	0.69
3-69	0.015
3-75	0.92
3-83	0.94
3-101	0.018
3-114	0.54
3-116	1.6
3-122	0.018
3-124	1.8
3-130	0.002
4-3	0.39

5-2	0.016
5-7	0.018
5-9	0.0019
5-16	0.018
5-19	0.017
5-42	0.015
5-44	0.016
5-58	0.0022
5-62	0.017
5-69	0.002
5-73	0.018
5-86	0.91
8-3	0.016
10-2	4.5
10-3	4.9
10-4	0.017
11-1	0.015
12-1	0.018
17-1	1.1
19-1	0.017
20-1	0.51
24-1	0.017
24-17	0.015
24-33	0.47
24-34	0.41
31-2	0.70
31-3	1.5
33-1	0.0019
34-2	0.0020
38-2	0.0021
38-3	0.0014
39-4	0.0017

41-1	0.016
47-2	4.2
48-2	1.7
50-3	1.3
51-1	0.40
51-4	1.6
52-1	0.52
52-2	0.52
54-7	0.83
57-3	0.0021
57-13	0.015
57-16	0.0021
57-18	0.0022
57-20	0.015
57-37	0.0018
60-1	0.018
61-2	0.0022
66-2	0.016
66-16	0.0020
66-34	0.016
66-37	0.015
67-1	0.0022
70-2	0.0022
70-3	0.0023
70-5	0.0016
70-6	0.00080
70-9	0.0015
70-10	0.0010
70-11	0.0014
70-12	0.0013
70-13	0.00070
70-14	0.00090

73-1	0.54
75-3	0.0011
76-2	0.0013
76-10	0.018
76-15	0.0024
76-18	0.0018
76-25	0.0029
76-32	0.0032
76-41	0.018
76-44	0.018
76-51	0.0014
77-2	0.0019
78-2	0.0016
79-2	0.0169
79-3	0.015
79-4	0.016
80-1	0.0019
81-3	0.0019
81-15	0.0039
81-20	0.0022
82-1	0.0019
83-3	0.0014
83-4	0.0011

Ensayo de proliferación celular de ratón esplénico B

Se molieron bazos de ratones Balb/c (< 12 semanas de edad) a través de tamices y se separaron los eritrocitos de los esplenocitos con amortiguador de lisis RBC (Sigma-

Aldrich Chemical Co, San Luís, MO). Los linfocitos T se redujeron por incubación en columnas de lana de nailon (Wako, Richmond, VA). Los linfocitos B esplénicos resultantes preparados de esta manera fueron rutinariamente $CD19^+$ en más del 90% según se midió por análisis de FACS. Se añadieron linfocitos B (1 X 10^5 células por pocillo) a diluciones en serie de compuestos por triplicado en placas de fondo plano de 96 pocillos en RPMI 1640 (Invitrogen, Grand Island, NY), suplementadas con suero de ternera fetal inactivado por calor al 10% (FCS, Summit Biotechnology, Fort Collins, CO), que contiene L-glutamina al 1% (Invitrogen), 50 µg/ml de gentamicina (Invitrogen) y β-mercaptoetanol 5 X 10^{-5}M (Sigma-Aldrich). Las células se estimularon con 10 µg/ml de fragmento $F(ab')_2$ de IgM anti-IgGβ de ratón de cabra Affinipure (Jackson Immunoresearch, West Grove, PA). Se incubaron los cultivos durante 72 horas, y se sometieron a un pulso durante las últimas 6 horas con un µCi/pocillo de ^{3}[H]-timidina (PerkinElmer, Boston, MA) antes de recoger en un cosechador de células Packard (PerkinElmer), y se contaron por centelleo líquido en un Packard TopCount NXT (PerkinElmer). Se encontró que los análogos más potentes eran activos por debajo de 1 µM.

Ensayo de proliferación de linfocitos B amigdalinos humanos

Se escindieron amígdalas de pacientes que se

sometieron a amigdalectomía rutinaria. El tejido de las amígdalas se picó, se molió a través de tamices y se aislaron las células mononucleares en gradientes de densidad de ficol (Medios de Separación de Linfocitos; Mediatech Inc., Herndon, VA). Se redujeron los linfocitos T de las células mononucleares mediante formación de rosetas con eritrocitos de oveja (SRBC, Colorado Serum Company; Denver, CO). Los linfocitos B amigdalinos preparados por este procedimiento fueron rutinariamente $CD19^+$ en más del 90% según se midió por análisis de FACS. Se añadieron linfocitos B (1 X 10^5 células por pocillo) a diluciones seriadas de compuestos por triplicado en placas de fondo plano de 96 pocillos en RPMI 1640, (Invitrogen, Grand Island, NY), suplementadas con suero de ternera fetal al 10% inactivado con calor (FCS, Summit Biotechnology, Fort Collins, CO), y que contiene antibiótico/antimicótico (Invitrogen, dilución 1:100) y gentamicina (Invitrogen, 5 µg/ml). Las células se estimularon con 40 µg/ml de Fragmento $F(ab')_2$ de IgG + IgM anti-Humano de Cabra Affinipure (Jackson Immunoresearch, West Grove, PA) en un volumen total de 0.2 ml. Se incubaron los cultivos durante 72 horas, y se sometieron a un pulso durante las últimas 6 horas con un µCi/pocillo de ^{3}[H]-timidina (PerkinElmer, Boston, MA) antes de recoger en un cosechador de células Packard (PerkinElmer), y se contaron por centelleo líquido en un Packard TopCount NXT (PerkinElmer).

Ensayo de fosforilación de Btk

Se incubaron células de Ramos (~6 x 10^6 células/ml) en presencia de inhibidores de Btk durante 1 hora a 37°C antes de estimularse con IgM+IgG anti-humano (fragmento $F(ab')_2$, Jackson ImmunoResearch, número de catálogo: 09-006-127) a 50 µg/ml durante exactamente 2 minutos a 37°C. Las células se fijaron inmediatamente añadiendo un volumen igual de amortiguador I BD PhosFlow Fix (BD Biosciences, número de catálogo: 557870) precalentado a la suspensión celular. Después de incubar a 37°C durante 10 minutos, las células se lavaron una vez con 3 ml de amortiguador de lavado de FACS (FBS/PBS al 1%) y se permeabilizaron añadiendo 0.5 ml de amortiguador III BD™ Phosflow Perm (BD Biosciences, número de catálogo 558050) e incubando durante 30 minutos en hielo. Las células se lavaron dos veces adicionales con 3 ml de amortiguador de lavado de FACS, se resuspendieron en 100 µl de amortiguador de lavado de BD FACS, se tiñeron con 20 µl de Alexa647 anti-Btk (pY551) (BD Biosciences, número de catálogo 558134), se incubaron a temperatura ambiente durante 30 minutos en la oscuridad, y se lavaron una vez con 3 ml de amortiguador de lavado de FACS. Las células se resuspendieron en 400 µl de amortiguador de lavado de FACS y se analizaron usando FACSCalibur (BD Biosciences). Los datos de intensidad fluorescente mediana (MFI) en datos de Alexa 647 (FL-4) se recogieron y usaron para cálculos de inhibición.

Ensayo de FLIPR de Ramos

Se añadieron linfocitos B de Ramos RA1 (ATCC CRL-1596) a una densidad de 2 x 10^6 células/ml en RPMI menos rojo fenol (Invitrogen 11835-030) y HEPES 50 mM (Invitrogen 15630-130) conteniendo BSA al 0.1% (Sigma A8577) a una mitad del volumen de amortiguador cargado con calcio (kit de masa de BD para ensayos sensibles a probenecid, número 640177) y se incubaron a temperatura ambiente en la oscuridad durante 1 hora. Se centrifugaron células cargadas con tinción (Beckmann GS-CKR, 1200 rpm, TA, 5 minutos) y se resuspendieron en RPMI a TA menos rojo fenol con HEPES 50 mM y FBS al 10% a una densidad de 1 x 10^6 células/ml. Se aplicaron alícuotas de 150 µl (150.000/pocillo) en placas de ensayo revestidas de poli-D-lisina de 96 pocillos (BD 35 4640) y se centrifugaron brevemente (Beckmann GS-CKR a 800 rpm, 5 minutos, sin freno). Se añadieron 50 µl de diluciones de compuestos en DMSO al 0.4%/RPMI menos rojo fenol + HEPES 50 mM + FBS al 10% a los pocillos y la placa se incubó a TA en la oscuridad durante 1 hora. Las placas de ensayo se centrifugaron brevemente como anteriormente antes de medir niveles de calcio.

Usando el FLIPR1 (Molecular Devices), las células se estimularon añadiendo IgM antihumana de cabra (Invitrogen AHI0601) a 2.5 µg/ml. Se midieron cambios en concentraciones de calcio intracelulares durante 180 segundos y el porcentaje de inhibición se determinó en relación a niveles de calcio

pico en presencia de estimulación solamente. La actividad biológica de ciertos compuestos según se valora usando este ensayo se muestra en la Tabla 2.

Tabla 2.

Ejemplo	IC_{50} para ensayo FLIPR de Inhibición de Ramos, μM
3-61	3.0
3-62	2.9
3-65	1.2
3-66	1.4
3-92	1.4
3-98	1.9
3-120	1.3
3-121	1.5
5-48	1.4
8-1	5.4
11-6	0.28
38-3	0.023
62-1	0.25
66-5	0.26
66-10	0.27
66-14	0.26
66-39	0.26
66-40	0.27
70-13	0.011
70-14	0.014
75-3	0.016
76-7	0.24
76-15	0.048
76-25	0.014

76-26	0.018
76-32	0.038
76-43	0.26
76-49	0.014
76-51	0.017
80-2	0.016
81-1	0.015
81-7	0.26
81-14	0.021
81-15	0.042
82-1	0.017

Ensayo del Indicador NFAT-bla RA1

Los linfocitos B de Ramos que contienen una integración estable de un gen indicador de beta-lactamasa bajo el control de un elemento de respuesta a NFAT (NFAT-*bla* RA1, Invitrogen, K1434) se incubaron a una densidad de 100 x 10^3 células/pocillo con compuestos de prueba a 37°C durante 30 min antes de estimulación con $F(ab')_2$ de IgM antihumano (Jackson ImmunoResearch, 109-006-129) a 2.5µg/ml durante 4.5 horas a 37°C. Después de estimulación, se añadió sustrato LiveBLAzer™-FRET BG (CCF2/AM, o CCF4/AM, Invitrogen) a cada pocillo y se incubó durante 90 min a temperatura ambiente en la oscuridad. Las placas de ensayo se leyeron en un LJL Analyst, con valores de emisión en bruto sustraídos de un sustrato que contiene medios-sólo blanco en medios de ensayo (sin ninguna célula). Se usaron las relaciones de emisión de

460 nm/530 nm (excitación a 405 nm) para calcular la cantidad de estimulación.

Prueba de antígeno KLH y medida de anticuerpos

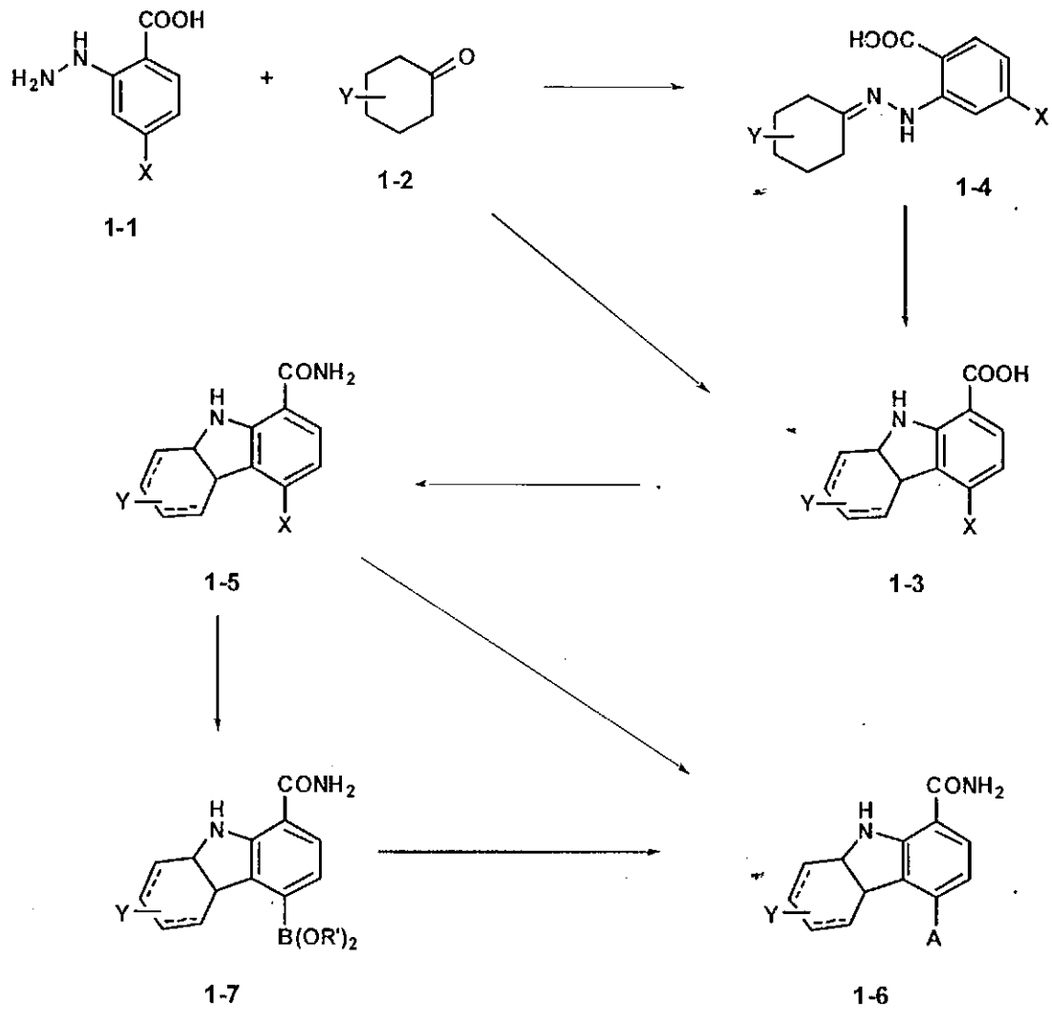
Se inmunizaron intraperitonealmente (IP) ratones BALB/c hembra (6-8 semas de edad) con 250 µg de hemocianina de lapa de California (KLH) (Pierce, Rockford, IL) en medio salino tamponado con fosfato (PBS). Se administró dosis a ratones en grupo apropiados según se indica. Se recogió sangre 14 días tras la inmunización, el suero se separó y se analizó para valoraciones de IgG anti KHL por ELISA. Brevemente, se recubrieron placas de 96 pocillos con KLH en PBS, se bloquearon, y se añadieron diluciones en serie de compuestos de prueba. Los anticuerpos anti-KLH se detectaron usando anticuerpo específico para IgG de ratón conjugado con peroxidasa de rábano picante (Southern Biotechnology Associates, Birmingham, AL) y el sistema de sustrato de peroxidasa TMB (Kirkegaard and Perry Laboratories, Gaithersburg, MD). Se cuantificaron densidades ópticas de placas desarrolladas el un lector de placa de ELISA de SpectraMax Plus (Molecular Devices, Sunnyvale, CA). Cuando se administra dos veces al día, el compuesto de Ejemplos 76-15 inhibió la respuesta de IgG anti-KLH en un 20% y en un 56% a 10 mg/kg y a mg/kg, respectivamente.

Procedimientos de preparación

Los compuestos de Fórmula (I) pueden prepararse por

la ruta esquematizada en el Esquema de reacción 1. Un ácido 2-hidrazinobenzoico **1-1** (donde X bien es el sustituyente A de Fórmula (I) o bien es un precursor adecuado a tal sustituyente, tal como bromo) puede reaccionar con una ciclohexanona adecuada **1-2** (donde Y representa bien el/los sustituyente(s) D_1 y/o D_2 de Fórmula (I) o bien un precursor para tal sustituyente(s)) en un disolvente apropiado con un catalizador adecuado, por ejemplo etanol con ácido clorhídrico, o ácido acético (en cuyo caso el disolvente puede servir también como el catalizador), a una temperatura adecuada (por ejemplo, la temperatura de reflujo del disolvente) para proporcionar el derivado de tetrahidrocarbazol correspondiente **1-3** (donde las líneas discontinuas representan enlaces simples). Esta reacción se conoce comúnmente como la síntesis de indol de Fischer, y se conoce bien en la bibliografía química (por ejemplo, véase J. Kamata y col., Chem. Pharm. Bull. 2004, 52, 1071). Alternativamente, la síntesis de indol de Fischer se puede llevar a cabo en dos etapas consecutivas: **1-1** puede reaccionar con **1-2** según condiciones adecuadas (tales como en un disolvente adecuado tal como etanol o agua, opcionalmente con un catalizador adecuado tal como ácido p-toluenosulfónico) para formar la hidrazona **1-4**, que se puede hacer reaccionar después adicionalmente en condiciones adecuadas (por ejemplo, etanol con ácido clorhídrico, ácido

acético con cloruro de cinc, o ácido trifluoroacético) para formar **1-3** (por ejemplo, véanse J. Lancelot y col., Chem. Pharm. Bull. 1983, 31, 2652; X. Li y R. Vince, Bioorg. Med. Chem. 2006, 14, 2942; o G. Romeo y col., Bioorg. Med. Chem. 2006, 14, 5211).



Esquema de Reacción 1.

Los materiales de partida mostrados en el esquema de reacción 1 pueden prepararse usando procedimientos conocidos en la bibliografía química. Por ejemplo, el

compuesto **1-1** se puede preparar a partir del ácido antranílico correspondiente (véase, por ejemplo, L. Street y col., J. Med. Chem. 1993, 36, 1529). Como otro ejemplo, el compuesto **1-2** donde Y es etoxicarbonilo unido en la posición 3 puede prepararse a partir de 3-hidroxibenzoato de etilo (véase, por ejemplo, J. Hirsch y col., Org. Chem. 1986, 51, 2218.)

Si se desea, el tetrahidrocarbazol **1-3** (donde las líneas discontinuas representan enlaces simples) se puede convertir al carbazol **1-3** (donde las líneas discontinuas representan enlaces dobles) por tratamiento según condiciones oxidantes adecuadas, por ejemplo por tratamiento con 2,3-dicloro-5,6-dicianobenzoquinona en un disolvente adecuado tal como tolueno, a una temperatura adecuada (por ejemplo, véase J. Kamata y col., Chem. Pharm. Bull. 2004, 52, 1071). Esta conversión de un tetrahidrocarbazol en un carbazol se puede llevar a cabo en una secuencia diferente con las otras transformaciones sintéticas esquematizadas en el esquema de reacción 1, por ejemplo en la fase de la estructura 1-5 ó 1-6.

El ácido carboxílico **1-3** se puede convertir en la carboxamida **1-5** usando procedimientos bien conocidos en la bibliografía química, por ejemplo por conversión de **1-3** al ácido clorhídrico por tratamiento con cloruro de oxalilo o cloruro de sulfonilo, seguido por tratamiento con amoniaco; o por tratamiento con amoniaco en presencia de un reactivo de

acoplamiento tal como carbodiimida o clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida y 1-hidroxibenzotriazol o 1-hidroxi-7-azabenzotriazol.

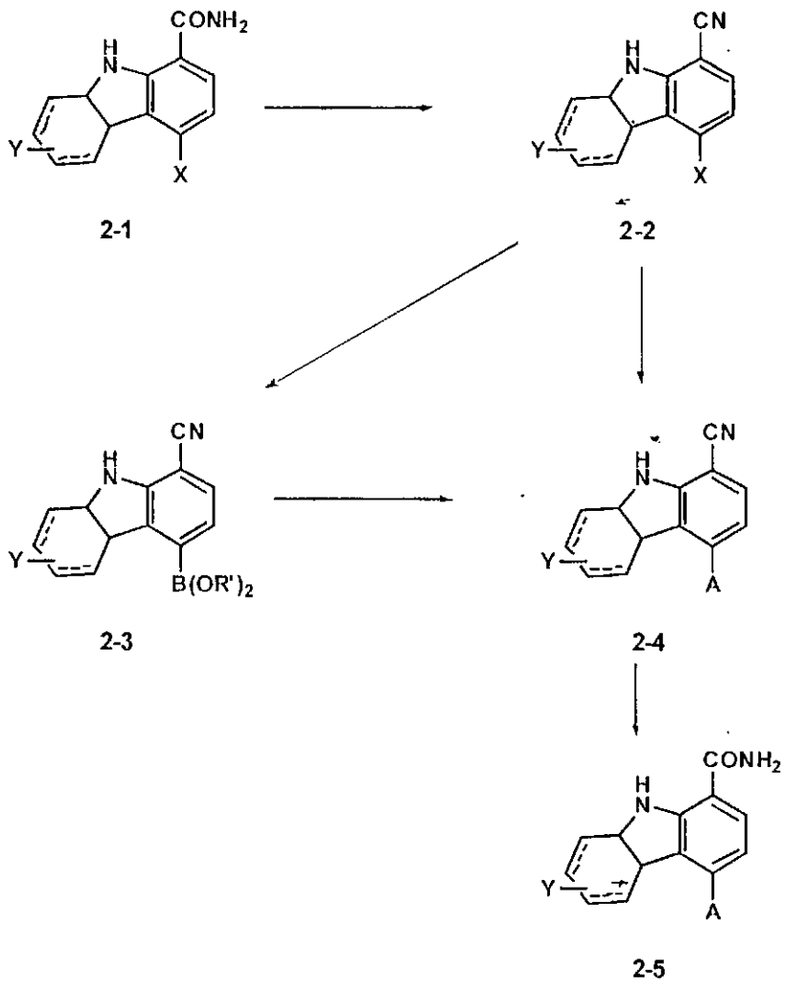
En el caso en que X es un precursor adecuado para A, tal como bromo, **1-5** se puede convertir a **1-6** usado procedimientos conocidos en la bibliografía. Por ejemplo, **1-5** (X = Br) se puede calentar con piperidina para proporcionar **1-6** (A = 1-piperidilo). Además, **1-5** (donde X = Br) se puede convertir a **1-6** (A = por ejemplo, un grupo aromático tal como fenilo, naftilo, piridilo, quinolilo, isoquinolilo opcionalmente sustituidos, o similares) por tratamiento con un ácido arilborónico adecuado o con un éster de ácido arilborónico adecuado en presencia de un catalizador adecuado tal como (1,1'-bis(difenilfosfino)ferroceno)dicloropaladio o tetraquis(trifenilfosfina)paladio, con una base adecuada tal como carbonato de potasio, o fosfato de tripotasio en un disolvente adecuado o en una mezcla de disolventes adecuada, tales como tolueno, 1,4-dioxano, o tolueno-etanol-agua. Esta reacción, conocida comúnmente como el acoplamiento de Suzuki, se conoce bien en la bibliografía química. Alternativamente, el compuesto **1-5** (X = Br) puede convertirse a un éster de boronato **1-7** (donde $B(OR')_2$ es, por ejemplo, 4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-ilo), por ejemplo por tratamiento con 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) en la presencia de una combinación adecuada de catalizador y ligando, tal como tris(dibencilidenoacetona)dipaladio y triciclohexilfosfina, con una

base adecuada tal como acetato de potasio, en un disolvente adecuado tal como 1,4-dioxano (véase, por ejemplo, L. Wang, y col., J. Med. Chem. 2007, 50, 4162). El éster boronato **1-7**, o el ácido borónico derivado **1-7** (R' = H) preparado por hidrólisis del éster boronato usando procedimientos conocidos en la bibliografía, se puede convertir a compuesto **1-6** usando la reacción de acoplamiento de Suzuki o una reacción similar como se describe anteriormente para la conversión directa de **1-5** a **1-6**.

Muchos ácidos borónicos y ésteres boronato adecuados para usar en la conversión de **1-5** a **1-6** (donde A es un grupo arilo o heteroarilo) están disponibles comercialmente, o pueden prepararse a partir de derivados de arilo o de heteroarilo tales como bromuros, cloruros o trifluorometanosulfonatos usando procedimientos conocidos en la bibliografía, por ejemplo como se describe anteriormente para la conversión de **1-5** a **1-7**. Tales bromuros, cloruros o trifluorometanosulfonatos bien están disponibles comercialmente, o bien se conocen en la bibliografía química, o bien se pueden preparar usando transformaciones sintéticas bien conocidas.

En algunos casos puede ser deseable convertir la amida primaria de estructura **1-5** en un grupo funcional diferente, por ejemplo para evitar reacciones indeseadas o para potenciar solubilidad para transformaciones de síntesis subsiguientes. Un ejemplo se muestra el esquema de reacción 2. Se puede convertir el compuesto **2-1** (equivalente al compuesto **1-5** en el esquema de

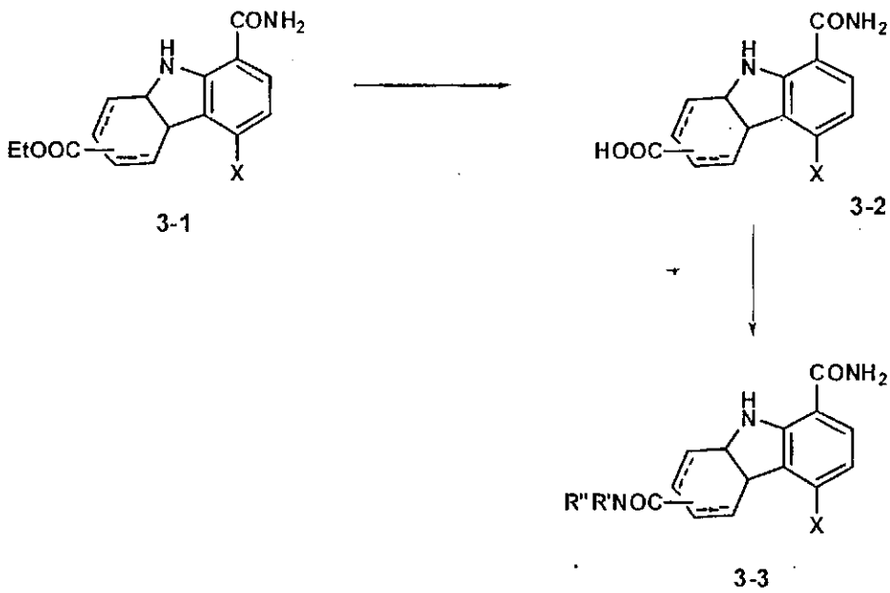
reacción 1) al nitrilo correspondiente **2-2**, por ejemplo por tratamiento según condiciones adecuadas con oxicloruro de fósforo. El compuesto **2-2** (X = Br) puede convertirse después en el compuesto **2-4**, bien directamente o por conversión directa en un éster boronato intermedio o bien en un ácido borónico **2-3**, como se describe anteriormente, seguida por hidrólisis del nitrilo **2-4** a la carboxamida **2-5** usando procedimientos conocidos en la bibliografía química.



2-1 **2-2** **2-3** **2-4** **2-5**

Esquema de reacción 2.

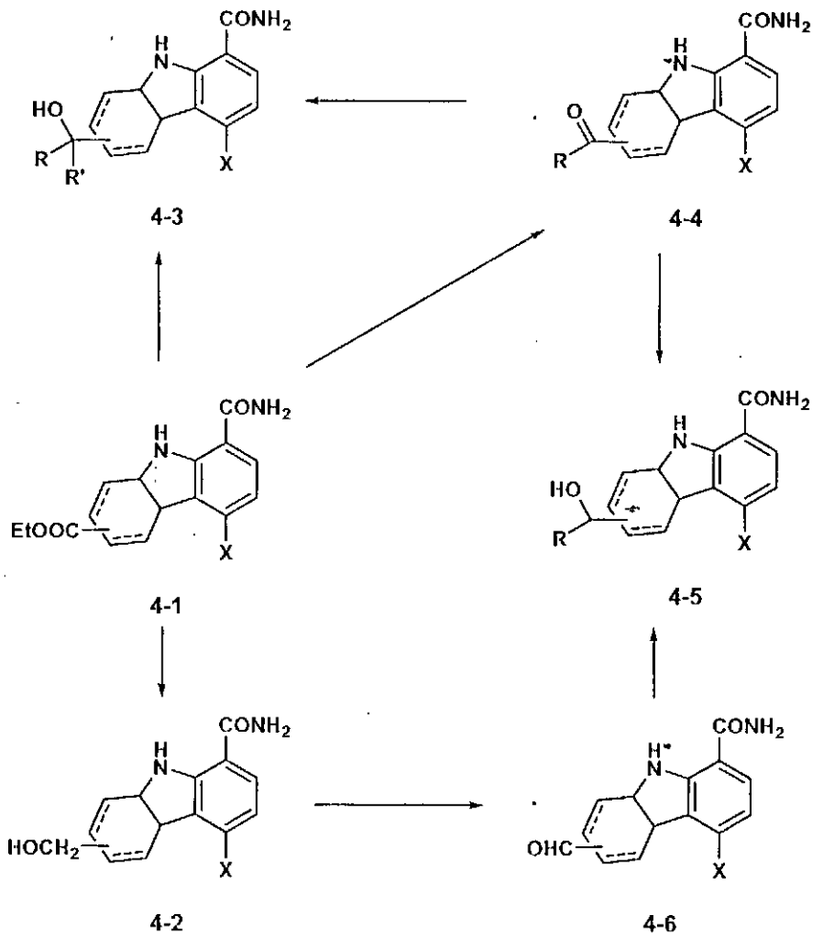
La manipulación de sustituyentes en los compuestos de Fórmula (I) se puede llevar a cabo usando una diversidad de procedimientos que se conocen bien en la bibliografía química. Por ejemplo, como se muestra en el esquema de reacción 3, si el sustituyente Y en compuesto **1-5** (donde X es bien A de Fórmula (I) o bien un precursor para A) es un éster tal como un éster etílico (compuesto **3-1**), este éster se puede convertir en otro sustituyente, por ejemplo por hidrólisis al ácido **3-2** correspondiente, por ejemplo usando una base tal como hidróxido de litio o hidróxido de sodio en agua, seguido por conversión en la amida **3-3** usando cualquiera de una amplia diversidad de procedimientos bien conocidos en la bibliografía química.



Esquema de reacción 3.

Se muestran otros ejemplos de manipulación de un

sustituyente en el esquema de reacción 4. Un éster tal como el éster etílico (compuesto **4-1**) se puede convertir en un alcohol, aldehído ó cetona usando procedimientos de síntesis estándar bien conocidos en la bibliografía. Por ejemplo, el tratamiento del éster con un agente reductor tal como hidruro de litio aluminio puede proporcionar el carbinol primario **4-2**. Alternativamente, el éster se puede convertir en un carbinol terciario **4-3** (donde R y R' son el mismo) por tratamiento con un reactivo organometálico apropiado tal como un haluro de alquilmagnesio o un alquillitio. Alternativamente, el éster se puede convertir a una cetona **4-4**, por ejemplo por hidrólisis al ácido carboxílico, conversión a una N,O-dialquilhidroxamida y tratamiento de este intermedio con un reactivo organometálico apropiado. Una cetona **4-4** se puede convertir a un alcohol terciario **4-3** (donde R y R' son el mismo o diferente) por tratamiento con un reactivo organometálico apropiado, o a un alcohol secundario **4-5** por tratamiento con un agente reductor tal como borohidruro de sodio o hidruro de litio aluminio. Alternativamente, un alcohol primario **4-2** se puede convertir a un aldehído **4-6**, que se puede convertir a un alcohol secundario **4-5** por tratamiento con un reactivo organometálico apropiado.

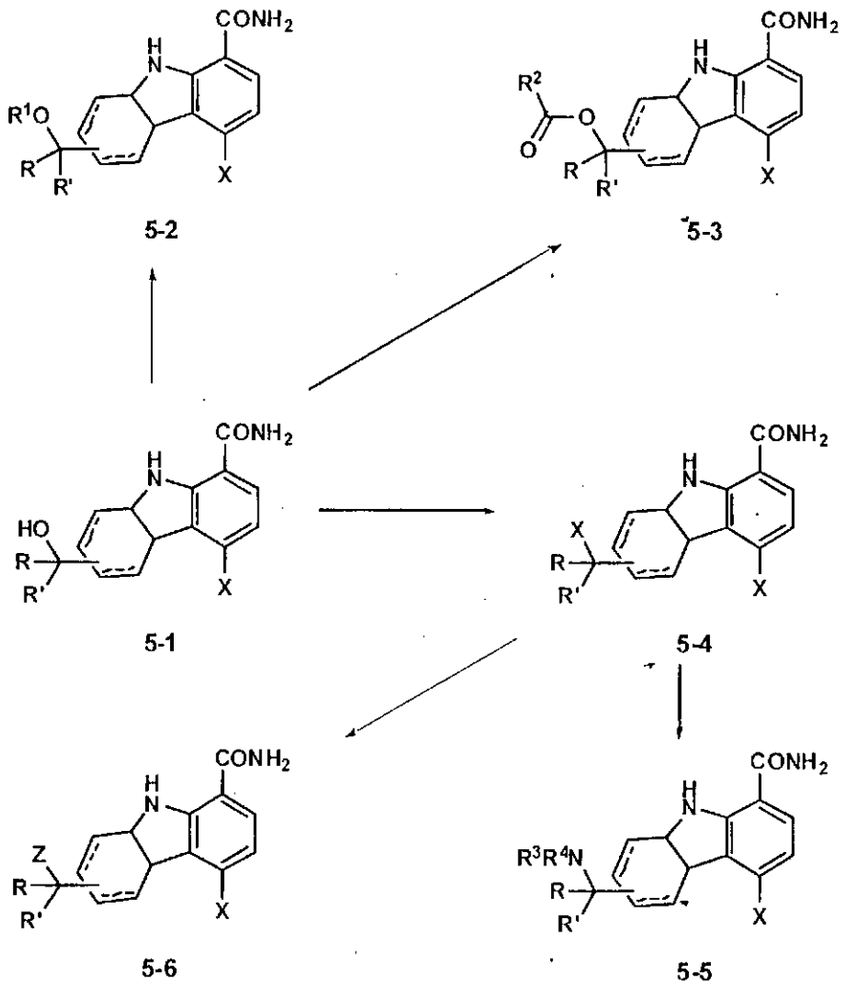


Esquema de reacción 4.

Otros ejemplos de manipulación de un sustituyente se muestran en el esquema de reacción 5, que hacen uso de transformaciones bien conocidas en la bibliografía química. Por ejemplo, un carbinol **5-1** (donde R y R' pueden ser, por ejemplo, hidrógeno o alquilo; derivados de un éster usando las transformaciones ejemplificadas en el esquema de reacción 4) se pueden convertir a un éter **5-2** (R^1 = por ejemplo alquilo) por tratamiento con un agente alquilante tal como un

haluro de alquilo o trifluorometanosulfonato de alquilo en presencia de una base tal como hidruro de sodio, o por tratamiento con un carbinol R^1OH en presencia de un catalizador tal como ácido trifluoroacético. Alternativamente, se puede convertir un carbinol **5-1** en un éster **5-3** (R^2 = por ejemplo alquilo o arilo) o un carbamato **5-3** (R^2 = por ejemplo alquilamino o dialquilamino) por tratamiento con un agente acilante tal como un anhídrido de ácido, cloruro de ácido o cloruro de carbamilo en presencia de una base tal como una trialquilamina o piridina, o por tratamiento con un ácido en presencia de un agente de acoplamiento tal como carbodiimida o clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida, y 1-hidroxibenzotriazol o 1-hidroxi-7-azabenzotriazol. Alternativamente, un carbinol **5-1** se puede convertir en un derivado **5-4**, donde X es un grupo saliente tal como bromuro, metanosulfonato, toluenosulfonato o trifluorometanosulfonato. El compuesto **5-4** puede convertirse después en una amina **5-5** (donde R^3 y R^4 son por ejemplo hidrógeno, alquilo o arilo, o R^3 y R^4 forman un anillo heterocíclico) por tratamiento con una amina HNR^3R^4 apropiada. Alternativamente, el compuesto **5-4** se puede convertir en una amina primaria **5-5** (donde R^3 y R^4 son ambos hidrógeno) por tratamiento con azida de sodio para proporcionar **5-4** (donde X es N_3) seguido por tratamiento con un agente reductor tal como trifenilfosfina en presencia de

agua (comúnmente conocido como reducción de Staudinger). El compuesto **5-4** puede convertirse también en un derivado heterocíclico **5-6**, por ejemplo por tratamiento con un heterociclo ZH bajo condiciones apropiadas. Ejemplos de Z en estructura **5-6** son 2-oxopirrolidin-1-ilo, 2-oxopiperidin-1-ilo, pirazol-1-ilo e imidazol-1-ilo.

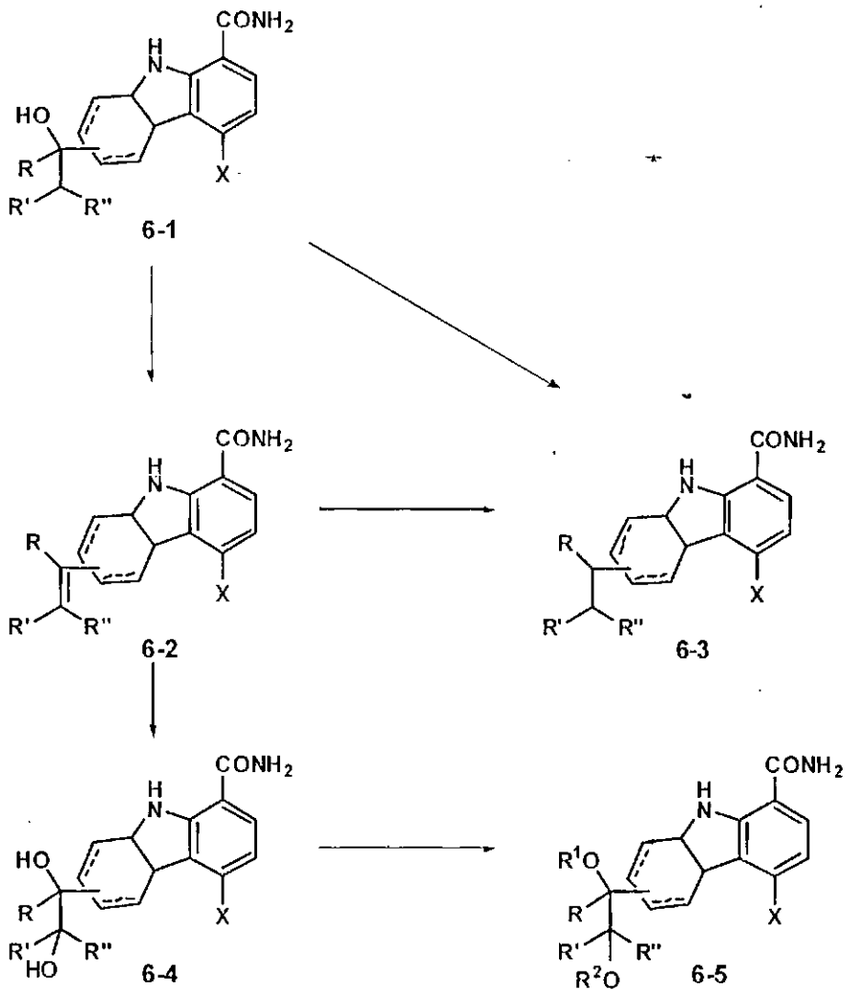


Esquema de reacción 5.

Otros ejemplos de manipulación de un sustituyente se muestran en el esquema de reacción 6, que hace uso de

transformaciones bien conocidas en la bibliografía química. Por ejemplo, un carbinol **6-1** que tiene al menos un hidrógeno beta para el grupo hidroxilo (donde R, R' y R" pueden ser, por ejemplo, hidrógeno o alquilo; preparados por ejemplo usando transformaciones ejemplificadas en el esquema de reacción 4) se puede convertir a un alqueno **6-2**, por ejemplo por deshidratación en presencia de un catalizador ácido, o por conversión del hidroxilo a un grupo saliente tal como metanosulfonato, toluenosulfonato o trifluorometanosulfonato seguido por tratamiento con una base adecuada. Un alqueno **6-2** se puede convertir a **6-3** por reducción del doble enlace, por ejemplo por tratamiento con hidrógeno en presencia de un catalizador adecuado tal como paladio en carbón activo. Alternativamente, un carbinol **6-1** se puede reducir directamente a **6-3**, por ejemplo por tratamiento con un trialquilsilano en presencia de un ácido tal como un ácido trifluoroacético. Alternativamente, un alqueno tal como **6-2** puede convertirse en un diol **6-4**, por ejemplo por tratamiento con N-óxido de 4-metilmorfolina en presencia de peróxido de osmio. Un diol **6-4** se puede convertir en un monoéster o un diéster **6-5** (donde uno o ambos de R^1 y R^2 es/son un grupo arilo), o a un monoéter o un diéter **6-5** (donde uno o ambos de R^1 y R^2 es/son, por ejemplo, un grupo alquilo), o a un monocarbamato o un dicarbamato **6-5** (donde uno o ambos de R^1 y R^2 es/son un grupo carbamilo), o a un compuesto en el que R^1 y

R^2 son independientemente alquilo, acilo o carbamilo, o a un compuesto en el que R^1 y R^2 forman un anillo heterocíclico tal como un 1,3-dioxolano, un 1,3-dioxano, o un 1,3-dioxolan-2-ona, usando procedimientos estándar bien conocidos en la bibliografía química.

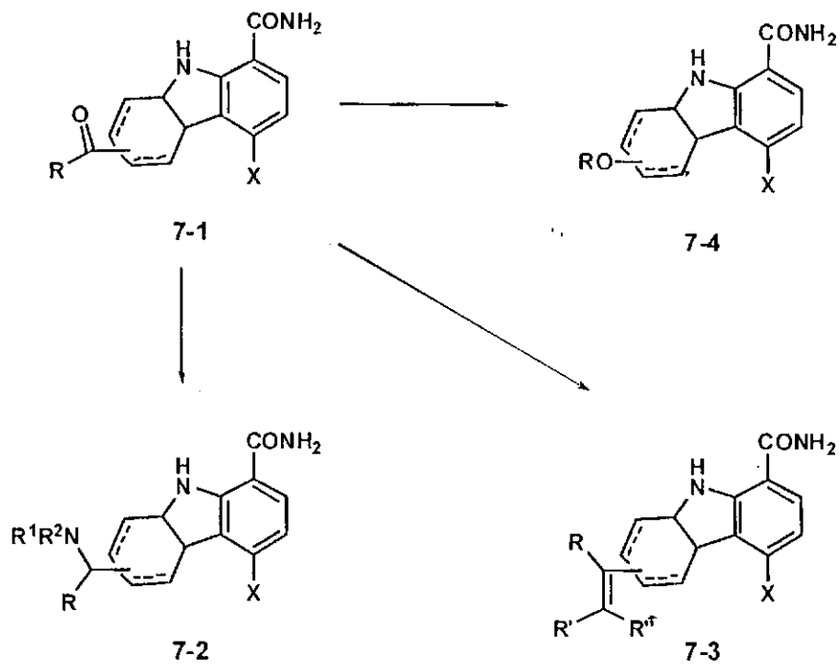


Esquema de reacción 6.

Se muestran otros ejemplos de manipulación de un sustituyente en el esquema de reacción 7, que hacen uso de transformaciones bien conocidas en la bibliografía química.

Por ejemplo, un aldehído o una cetona **7-1** (R = hidrógeno o, por ejemplo, alquilo, respectivamente, preparados por ejemplo usando las transformaciones mostradas en el esquema de reacción 4) se pueden convertir a una amina **7-2** (donde, por ejemplo, R^1 y R^2 son independientemente hidrógeno o alquilo, o R^1 y R^2 conjuntamente para un anillo heterocíclico tal como piperidina, pirrolidina o morfolina) por tratamiento de **7-1** con una amina HNR^1R^2 en presencia de un agente reductor tal como un triacetoxiborohidruro de sodio o cianoborohidruro de sodio, o por tratamiento de **7-1** con una amina HNR^1R^2 con eliminación de agua para formar un intermedio imina seguido por reducción de la imina con un agente reductor adecuado. Alternativamente, **7-1** se puede convertir a una olefina **7-3** por tratamiento con un reactivo adecuado tal como un haluro de alquilltriarilfosfonio o un fosfonato de dialquilo en presencia de una base adecuada, una transformación bien conocida en la bibliografía como la reacción de Wittig. La olefina **7-3** resultante se puede convertir después a una diversidad de otros compuestos, por ejemplo por las transformaciones de **6-2** en el esquema de reacción 6 como se describe anteriormente. Alternativamente, **7-1** se puede convertir a un éster fenólico o a un éster carbinol **7-4** (donde R = formilo o acilo) por tratamiento con un reactivo oxidante tal como ácido 3-cloroperoxibenzoico, ácido peroxiacético, ácido peroxitrifluoroacético o una mezcla de

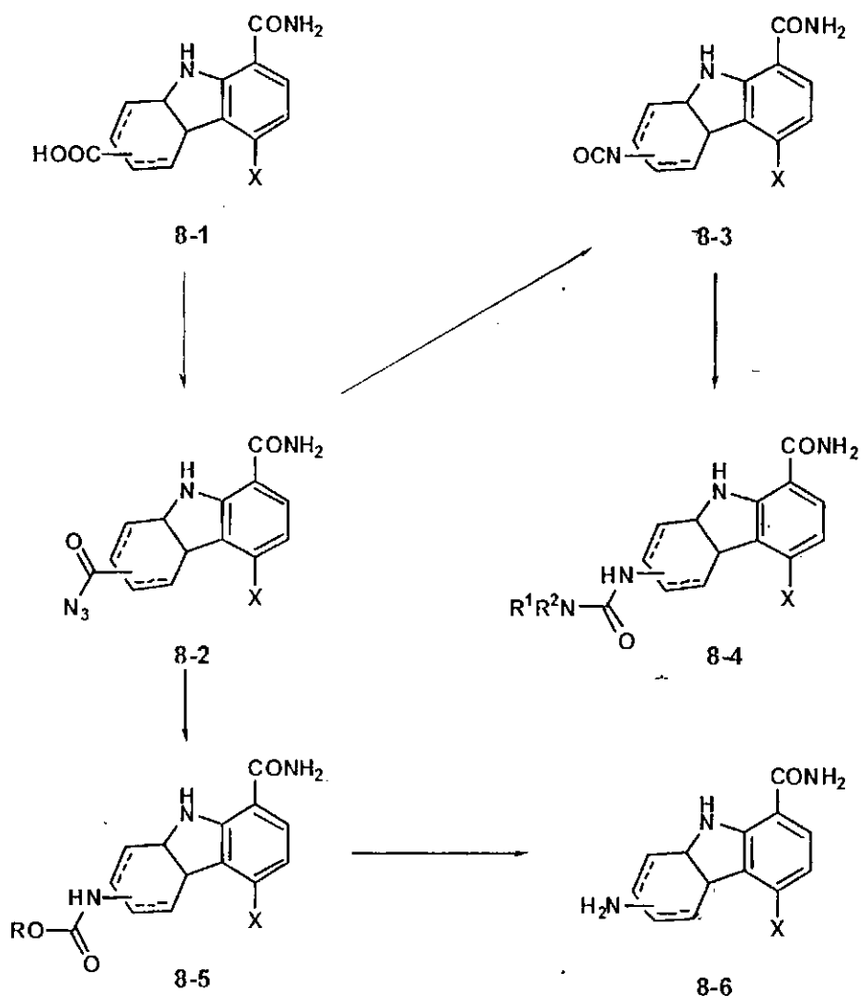
peróxido de hidrógeno y un ácido fuerte tal como ácido sulfúrico, en una reacción bien conocida en la bibliografía química como el reordenamiento de Baeyer-Villiger. Un compuesto **7-4** (R = formilo o acilo) se puede convertir en un fenol o carbinol **7-4** (R = H) por hidrólisis bajo procedimientos bien conocidos. El fenol o carbinol **7-4** se puede convertir después, por ejemplo, a un éster **7-4** (R = acilo), un éter **7-4** (R = por ejemplo alquilo) o carbamato **7-4** (R = carbamilo) usando procedimientos bien conocidos.



Esquema de reacción 7.

Otros ejemplos de manipulación de un sustituyente se muestran en el esquema de reacción 8, que hace uso de transformaciones bien conocidas en la

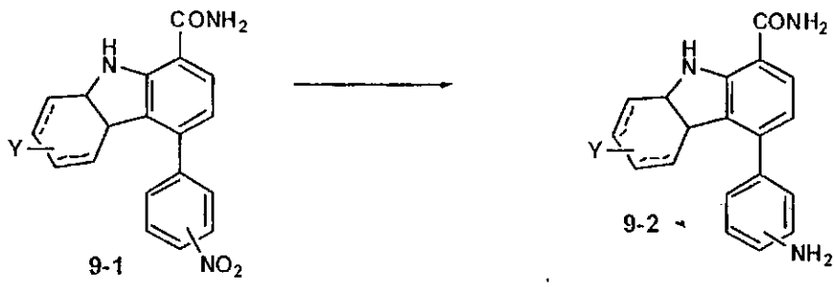
bibliografía química. Un ácido carboxílico **8-1** (preparado, por ejemplo, como se muestra en el esquema de reacción 3) se puede convertir a una acil-azida **8-2**, por ejemplo por tratamiento con fosforazidato de difenilo (difenil-fosforil-azida). La acil-azida se puede convertir sin aislamiento a un isocianato **8-3**, por ejemplo calentando. El isocianato se puede convertir a una urea **8-4** (donde R y R' son independientemente, por ejemplo, hidrógeno o alquilo, o se pueden tomar conjuntamente para formar un anillo tal como piperidina, pirrolidina o morfolina). Alternativamente, la acil-azida **8-2** se puede calendar en presencia de un alcohol para proporcionar un carbamato **8-5** (donde R es, por ejemplo, alquilo o bencilo). El carbamato **8-5** se puede convertir a una amina primaria **8-6** por hidrólisis, o (en el caso donde R es bencilo) por tratamiento con por ejemplo, hidrógeno o formiato de amonio en presencia de un catalizador tal como paladio en carbón activo, o con bromuro de hidrógeno en ácido acético. En estas transformaciones, se puede aislar un intermedio acil-acida **8-2** y/o isocianato **8-3**, o se puede llevar a cabo la secuencia completa de etapas que convierten un ácido **8-1** a una urea **8-4** o un carbamato **8-5** sin aislar las intermedios.



Esquema de reacción 8.

Otro ejemplo de manipulación de un sustituyente se muestra en el esquema de reacción 9. El sustituyente nitro del compuesto **9-1** (donde Y puede representar D^1 y/o D^2 de Fórmula (I) o un precursor para D^1 y/o D^2), preparado por ejemplo por acoplamiento de Suzuki de compuesto **1-5** en el esquema de reacción de reacción 1 con un ácido bencenoborónico nitro-sustituido, se puede reducir usando

procedimientos bien conocidos para proporcionar una anilina **9-2** correspondiente, por ejemplo por tratamiento con hidrógeno en presencia de un catalizador tal como paladio en carbón activo, o por tratamiento con un agente reductor tal como cloruro de cinc o cloruro de estaño (II) en un ácido tal como ácido clorhídrico, o hierro en ácido acético.



Esquema de reacción 9.

Cualquier sustituyente amina (por ejemplo, **5-5** esquemas de reacción 5, **7-2** en Esquema de reacción 7, **8-6** en esquema de reacción 8, o **9-2** en Esquema de reacción 9) en el que la amina es primaria o secundaria se puede convertir a otros sustituyentes usando procedimientos bien conocidos en la bibliografía química. Son ejemplos reacción con un ácido carboxílico, un haluro de ácido carboxílico o un anhídrido de ácido carboxílico para proporcionar una amida; reacción con un isocianato, arilcarbamato o cloruro de carbamilo para proporcionar una urea; reacción con un éster de cloroformiato para proporcionar un carbamato; reacción con un haluro de sulfonilo o un anhídrido sulfónico para proporcionar una sulfonamida o sulfonimida; reacción con un haluro de

sulfamilo para proporcionar una sulfamida; y reacción con un aldehído o cetona en presencia de un agente reductor adecuado para proporcionar una amina alquilada.

Otro ejemplo de transformaciones de un sustituyente de amina tal es reacción con un haluro de arilo o heteroarilo (tales como por ejemplo una 2-cloropiridina, 2-cloroquinolina, 2-cloroisoquinolina o 4-cloroquinazolina), bien en presencia o en ausencia de un catalizador adecuado tal como un catalizador de paladio, para proporcionar una amina arilada. (El caso donde un catalizador de paladio se conoce comúnmente en la bibliografía química como la afinación de Buchwald). Otro ejemplo es reacción con un reactivo bifuncional tal como, por ejemplo, un hidroxiácido o lactona o cloruro de haloacilo o ácido haloalcanoico (para formar una lactama) o una divinilsulfona (para formar un dióxido de tiomorfolina) bajo condiciones adecuadas. En el caso de reacción con un reactivo bifuncional tal, ambas etapas de reacción se pueden lograr en una operación de síntesis, o alternativamente la reacción con una funcionalidad puede estar seguida por aislamiento de un intermedio seguido por la reacción con la otra funcionalidad.

Otro ejemplo de manipulación adicional de un sustituyente es la conversión de un sustituyente adecuado en un grupo arilo (tal como bromo, cloro o trifluorometanosulfonato) a un grupo arilo o heteroarilo, por

ejemplo por medio de acoplamiento de Suzuki como se describe previamente. Otro ejemplo de manipulación adicional de un sustituyente adecuado en un grupo arilo (tal como bromo, cloro o trifluorometanosulfonato) es la conversión de este sustituyente a un sustituyente de amina o de anilina (por tratamiento con una amina o anilina primaria o secundaria bajo condiciones adecuadas, ampliamente comunicadas en la bibliografía química y, cuando se lleva a cabo en presencia de un catalizador adecuado tal como un catalizador de paladio, comúnmente conocido como la aminación de Buchwald). Otro ejemplo de manipulación adicional de un sustituyente adecuado en un grupo arilo (tal como bromo, cloro o trifluorometanosulfonato) es la conversión de este sustituyente en una amida por reacción con una amida primaria o secundaria o una lactama en condiciones adecuadas ampliamente comunicadas en la bibliografía química (por ejemplo, en presencia de una sal de cobre (I) y un ligando de diamina).

La secuencia de transformaciones de síntesis (por ejemplo, el orden de las manipulaciones de los sustituyentes de X e Y y el grupo ácido carboxílico en el compuesto **1-3**) puede variarse dependiendo de la naturaleza del compuesto a preparar, y puede determinarse por alguien experto en la técnica por consideración de las estabilidades de los diversos sustituyentes en las condiciones en las que la reacción se lleva a cabo.

En algunos casos, puede ser deseable para uno o más grupos funcionales en materiales de partida o intermedios estar presentes en una forma protegida. En tales casos, la eliminación del grupo protector se puede llevar a cabo en una etapa adecuada de la secuencia de síntesis, seguida por manipulación adecuada del grupo funcional si se desea. Tales grupos protectores y su uso y eliminación se conocen bien por aquellos expertos en la técnica.

En todas las transformaciones anteriormente descritas, y en las transformaciones relacionadas, se pueden llevar a cabo transformaciones en disolventes relacionados, elegidos por solubilidad de o compatibilidad con los reaccionantes y reactivos o por otras propiedades tales como punto de ebullición o capacidad para facilitar que se lleve a cabo la reacción. Las reacciones se llevan a cabo usualmente a una temperatura elegida para proporcionar una velocidad de reacción conveniente, usualmente desde por debajo de la temperatura de la habitación ambiente a la temperatura de ebullición del disolvente, o por encima del punto de ebullición si la reacción se lleva a cabo en un recipiente cerrado. Las transformaciones descritas se conocen bien generalmente en la bibliografía química, y alguien experto en la técnica de la síntesis orgánica estará familiarizado con disolventes, catalizadores, reactivos, y condiciones adecuados para llevar a cabo las transformaciones deseadas, así como variaciones

deseadas de las secuencias de transformaciones usadas para proporcionar un producto deseado.

En el caso donde las líneas discontinuas de Fórmula (I) representan enlaces simples y están presentes los sustituyentes D^1 y/o D^2, o si los sustituyentes D^1 y/o D^2 llevan un centro quiral, o si el sustituyente A lleva un centro quiral, son posibles enantiómeros. Si las líneas discontinuas representan enlaces simples y adicionalmente uno o más de los sustituyentes A, D^1 y/o D^2 llevan un centro quiral, o si las líneas discontinuas representan enlaces dobles y dos o más de los sustituyentes A, D^1 y/o D^2 llevan centros quirales, son posibles diastereómeros. Adicionalmente, en algunos casos, la rotación restringida sobre ciertos enlaces, particularmente el enlace que une a sustituyente A en Fórmula (I), puede dar lugar a isómeros ópticos, conocidos como atropoisómeros, incluso cuando no está presente ningún átomo quiral. Se puede preparar un compuesto enantioméricamente o diastereoméricamente enriquecido usando un material de partida enantioméricamente o diastereoméricamente enriquecido (por ejemplo, **1-2** para la síntesis esquematizada en el esquema de reacción 1, o acoplamiento de **1-5** ó **1-7** con un reactivo enantioméricamente enriquecido, o acilación de un sustituyente amina o hidroxilo con un agente acilante enantioméricamente enriquecido). Alternativamente, se pueden usar los materiales de partida o

reactivos racémicos, seguido por separación de enantiómeros o diastereómeros, por ejemplo usando HPLC quiral o usando procedimientos químicos bien conocidos en la bibliografía química. Tal separación se puede llevar a cabo en cualquier etapa adecuada en la secuencia de síntesis, o se puede separar el compuesto final de Fórmula (I) en enantiómeros o diastereómeros.

Ejemplos

La preparación de compuestos de Fórmula (I) y los intermedios usados en la preparación de compuestos de Fórmula (I) se puede realizar usando procedimientos mostrados en los siguientes ejemplos y procedimientos relacionados. Los procedimientos y condiciones usadas en estos ejemplos, y los compuestos reales preparados en estos ejemplos, no pretenden ser limitantes, sino que están destinados a demostrar cómo se pueden preparar los compuestos de Fórmula (I). Los materiales de partida y reaccionantes usados en estos ejemplos, cuando no se preparan por un procedimiento descrito en el presente documento, están en general disponibles de forma comercial, o se describen en la bibliografía química, o se pueden preparar usando procedimientos descritos en la bibliografía química.

En los ejemplos, la frase "se seca y se concentra" se refiere en general a secado de una solución en un disolvente orgánico sobre sulfato sódico o sobre sulfato de magnesio, seguido por filtración y eliminación del disolvente

del filtrado (en general a presión reducida y a una temperatura adecuada para la estabilidad del material que se está preparando). La cromatografía en columna se llevó a cabo con cartuchos de gel de sílice rellenos usando un aparato de cromatografía de media presión Isco (Teledyne Corporation), eluyendo con el disolvente o mezcla de disolventes indicado. la cromatografía líquida de alta resolución preparativa (HPLC) se llevó a cabo usando una columna de fase inversa (Waters Sunfire C_{18}, Waters Xbridge C_{18}, Phenomenex Axia C_{18}, YMC S5 ODS o similar) de un tamaño apropiado a la cantidad de material que se está separando, eluyendo por lo general con un gradiente de concentración creciente de metanol o acetonitrilo en agua, que contiene también 0.05% o 0.1% de ácido trifluoracético o acetato amónico 10 mM, a una velocidad de elución adecuada al tamaño de la columna y separación que se pretende conseguir. Los nombres químicos se determinaron usando ChemDraw Ultra, versión 9.0.5 (CambridgeSoft). Se usan las siguientes abreviaturas:

$NaHCO_3$ (ac) - bicarbonato sódico acuoso saturado

salmuera - cloruro sódico acuoso saturado

DCM - diclorometano

DIEA - N,N-diisopropiletilamina

DMAP - 4-(N,N-dimetilamino)piridina

DMF - N,N-dimetilformamida

DMSO - dimetil sulfóxido

EDC - clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida

EtOAc - acetato de etilo

HOAT - 1-hidroxi-7-azabenzotriazol

HOBT - 1-hidroxibenzotriazol hidratado

ta - temperatura ambiente (en general aproximadamente 20-25°C)

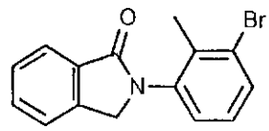
TEA - trietilamina

TFA - ácido trifluoracético

THF - tetrahidrofurano

Intermedio 1-1

Preparación de 2-(3-bromo-2-metilfenil)isoindolin-1-ona

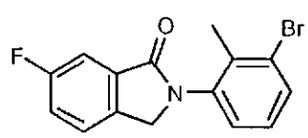


Una solución de 3-bromo-2-metilanilina (10 g, 53.7 mmol) en DCM (200 ml) a 0°C se trató con TEA (14.98 ml, 107 mmol), seguido por la adición gota a gota de cloruro de 2-(clorometil)benzoilo (10.16 g, 53.7 mmol) en DCM (50 ml) durante 1 h. La mezcla se diluyó con DCM (aproximadamente 1 l), se lavó con NaHCO3 (ac) y agua y se concentró para eliminar la mayor parte del disolvente. El precipitado se recogió por filtración y se lavó con DCM (2 x 10 ml) proporcionando N-(3-bromo-2-metilfenil)-2-(clorometil)benzamida como un sólido blanco (8.0 g). El

filtrado se volvió a concentrar, dando lugar a más precipitado que se recogió por filtración y se lavó con DCM (2 x 10 ml) proporcionando más N-(3-bromo-2-metilfenil)-2-(clorometil)benzamida como un sólido blanco (3.06 g), con un rendimiento combinado de 61%. Espectro de masas 338, 340, 342. El filtrado se concentró y se purificó por cromatografía en columna (hexano-EtOAc) proporcionando 2-(3-bromo-2-metilfenil)isoindolin-1-ona como un sólido amarillo (2.0 g, 12%). Una solución de N-(3-bromo-2-metilfenil)-2-(clorometil)benzamida (11.06 g, 32.7 mmol) en DMF (50 ml) se enfrió hasta 0°C y se trató con una mezcla de hidruro sódico (dispersión al 60% en aceite, se lavó con hexano, 1.70 g, 42.4 mmol) y DMF (10 ml). La mezcla se agitó a 0°C durante 1.5 h, luego se trató con agua. El precipitado se recogió por filtración, se secó y se combinó con el material purificado por cromatografía en columna (véase arriba) proporcionando 2-(3-bromo-2-metilfenil)isoindolin-1-ona como un sólido amarillo (9.41 g, 95%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.96 (1 H, d, J=7.5 Hz), 7.58 - 7.67 (2 H, m), 7.49 - 7.57 (2 H, m), 7.20 - 7.25 (1 H, m), 7.15 (1 H, t, J=7.9 Hz), 4.72 (2 H, s), 2.31 (3 H, s). Espectro de masas m/z 302, 304 $(M+H)^+$.

Intermedio 1-2

Preparación de 2-(3-bromo-2-metilfenil)-6-fluoroisoindolin-1-ona



Etapa 1 Se calentó a 78 °C durante 4 horas una suspensión de ácido 5-fluoro-2-metilbenzoico (500 mg, 3.24 mmol), N-bromosuccinimida (606 mg, 3.41 mmol) y peróxido de benzoilo (47 mg, 0.195 mmol) en tetraclorometano (10 ml). La mezcla caliente se filtró y el filtrado se concentró proporcionando ácido 2-(bromometil)-5-fluorobenzoico bruto como un sólido blanco (730 mg), se usó sin purificación posterior. RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.81 (1 H, dd, *J*=9.2, 2.9 Hz), 7.50 (1 H, dd, *J*=8.5, 5.4 Hz), 7.23 - 7.30 (1 H, m), 4.98 (2 H, s).

Etapa 2 Una solución de ácido 2-(bromometil)-5-fluorobenzoico bruto (3.05 g, 13.1 mmol) en DCM (50 ml) se trató con cloruro de oxalilo (1.66 g, 13.1 mmol) y 6 gotas de DMF. La mezcla se agitó a ta durante 1 h, luego se concentró. El residuo se volvió a disolver en DCM (50 ml) y se trató con 3-bromo-2-metilanilina (1.705 g, 9.16 mmol). La mezcla se agitó a ta durante 1 h, luego se añadió en porciones TEA (2.19 ml, 15.7 mmol). La mezcla se agitó a ta durante 2 h, luego se diluyó con DCM (100 ml), se lavó con NaHCO3 (ac) y agua, se secó y se concentró. El residuo se trituró con DCM proporcionando N-(3-bromo-2-metilfenil)-2-(bromometil)-5-fluorobenzamida como un sólido blanco (0.9 g). Las aguas madres se concentraron y el residuo se trituró de nuevo con DCM proporcionando más N-(3-bromo-2-metilfenil)-2-(bromometil)-5-fluorobenzamida como un sólido blanco (0.46

g). Las aguas madres se concentraron y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano hasta EtOAc-hexano 70:30) proporcionando más N-(3-bromo-2-metilfenil)-2-(bromometil)-5-fluorobenzamida como un sólido rosa (1.18 g) para un total de 2.44 g (48%). Espectro de masas m/z 400, 402, 404 $(M+H)^+$.

Etapa 3 Una mezcla de N-(3-bromo-2-metilfenil)-2-(bromometil)-5-fluorobenzamida (2.44 g, 6.33 mmol) y terc-butóxido sódico (0.913 g, 9.50 mmol) en THF (80 ml) se agitó a ta durante 30 min. La mezcla se diluyó con agua y se extrajo dos veces con DCM. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron. El residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc) proporcionando 2-(3-bromo-2-metilfenil)-6-fluoroisoindolin-1-ona como un sólido blanco (1.18 g, 58%). RMN de ^1H (400 MHz, cloroformo-d) δ 7.59 - 7.65 (2 H, m), 7.45 - 7.50 (1 H, m), 7.33 (1 H, td, *J*=8.6, 2.4 Hz), 7.19 - 7.24 (1 H, m), 7.15 (1 H, t, *J*=7.9 Hz), 4.68 (2 H, s), 2.31 (3 H, s). Espectro de masas m/z 320, 322 $(M+H)^+$.

Intermedio 1-3

Preparación de 2-(3-bromo-2-metilfenil)-6-metoxiisondolin-1-ona

Etapa 1 Una suspensión de 5-metoxi-2-metilbenzoato de metilo (1.00 g, 5.55 mmol), N-bromosuccinimida (1.037 g, 5.83 mmol) y peróxido de benzoilo (81 mg, 0.333 mmol) en

tetraclorometano (10 mL) se calentó a 77°C durante 3 horas. La mezcla se diluyó con DCM, se lavó con NaHCO3 (ac), se secó y se concentró para proporcionar 2-(bromometil)-5-metoxibenzoato de metilo crudo como un sólido amarillo claro (1.435 g), usado sin purificación adicional. RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.48 (1 H, d, J=2.64 Hz), 7.37 (1 H, d, J=8.36 Hz), 7.02 (1 H, dd, J=8.58, 2.86 Hz), 4.93 (2 H, s), 3.95 (3 H, s), 3.85 (3 H, s).

Etapa 2 Una mezcla de 2-(bromometil)-5-metoxibenzoato de metilo (1.435 g, 5.54 mmol), 3-bromo-2-metilanilina (1.03 g, 5.54 mmol) y TEA (1.158 mL, 8.31 mmol) en metanol (5 mL) se calentó a 85°C durante 2 horas. La mezcla se diluyó con DCM, se lavó con NaHCO3 (ac), se secó y se concentró. El residuo se purificó mediante cromatografía en columna (eluyendo con EtOAc-hexanó) para proporcionar 2-((3-bromo-2-metilfenilamino)metil)-5-metoxibenzoato de metilo crudo como un aceite amarillo (361 mg, 18%). Espectro de masas m/z 364, 366 $(M+H)^+$.

Etapa 3 Una solución de ((3-bromo-2-metilfenilamino)metil)-5-metoxibenzoato de metilo (360 mg, 0.988 mmol) en THF (10 mL) se trató con ter-butóxido de sodio (142 mg, 1.483 mmol) y se agitó a temperatura ambiente durante la noche. La mezcla se trató con agua y se extrajo dos veces con DCM. Las fases orgánicas combinadas se lavaron con agua, se secaron y se concentraron. El residuo se

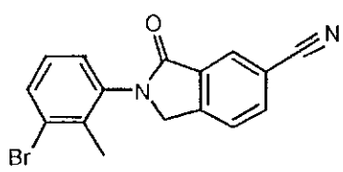
purificó mediante cromatografía en columna (eluyendo con EtOAc-hexano) para proporcionar 2-(3-bromo-2-metilfenil)-6-metoxiisoindol-1-ona como un sólido blanco (246 mg, 75%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.62 (1 H, dd, J=7.9, 1.1 Hz), 7.46 (1 H, d, J=2.4 Hz), 7.42 (1 H, d, J=8.4 Hz), 7.15 - 7.26 (3 H, m), 4.67 (2 H, s), 3.92 (3 H, s), 2.34 (3 H, s). Espectro de masas m/z 332, 334 $(M+H)^+$.

Los siguientes Intermedios se prepararon también usando procedimientos usados para preparar los Intermedios 1-1 a 1-3.

Intermedio	Nombre del compuesto	Espectro de masas
1-4	2-(3-bromo-2-metilfenil)-5-metoxiisoindolin-1-ona	332, 334 $(M+H)^+$
1-5	2-(3-bromo-2-metilfenil)-6-(trifluorometil)isoindolin-1-ona	370, 372 $(M+H)^+$
1-6	2-(3-bromo-2-metilfenil)-6-metilisoindolin-1-ona	316, 318 $(M+H)^+$

Intermedio 2-1

Preparación de 2-(3-bromo-2-metilfenil)-3-oxoisoindolin-5-carbonitrilo



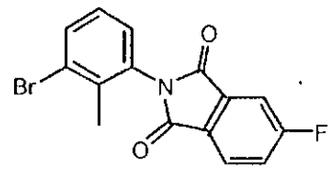
Etapa 1 Una solución de 3-bromo-2-metilanilina (0.67 g, 3.60 mmol) en DCM (18 ml) se trató gota a gota con trimetilaluminio (2 M en tolueno, 1.801 ml, 3.60 mmol) y la solución resultante se agitó a ta durante 30 min. Se añadió una solución de 3-oxo-1,3-dihidroisobenzofuran-5-carbonitrilo (0.573 g, 3.60 mmol) en DCM (18.00 ml) y la mezcla resultante se agitó a ta durante la noche. La mezcla se diluyó con DCM, se lavó con una solución acuosa de tartrato sódico potásico (reaccionante de Fehling II) y agua, luego se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano-EtOAc 80:20 hasta EtOAc) proporcionando N-(3-bromo-2-metilfenil)-5-ciano-2-(hidroximetil)benzamida como un sólido blanco (170 mg, 14%) que se usó sin purificación posterior. Espectro de masas m/z 345, 347 $(M+H)^+$.

Etapa 2 Se trató una solución de N-(3-bromo-2-metilfenil)-5-ciano-2-(hidroximetil)benzamida (170 mg, 0.492 mmol) en THF (20 ml) con azodicarboxilato de di-*terc*-butilo (113 mg, 0.492 mmol) y tributilfosfina (0.119 ml, 0.492 mmol) y se agitó a ta. Después de 2 h la mezcla se concentró y el residuo se sometió a cromatografía en columna (eluyendo con un gradiente de 90:10 a 50:50 de

hexano-EtOAc) proporcionando 2-(3-bromo-2-metilfenil)-3-oxoisoindolin-5-carbonitrilo (100 mg, 62%) como un sólido blanco. RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.07 (1 H, d, *J*=8.1 Hz), 7.82 - 7.89 (2 H, m), 7.64 (1 H, dd, *J*=7.8, 1.4 Hz), 7.13 - 7.25 (2 H, m), 4.78 (2 H, s), 2.30 (3 H, s). Espectro de masas m/z 327, 329 $(M+H)^+$.

Intermedio 3-1

Preparación de 2-(3-bromo-2-metilfenil)-5-fluoroisoindolin-1,3-diona



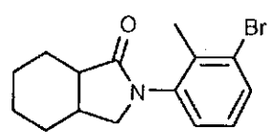
Se calentó a 100°C durante 4.5 horas una mezcla de 3-bromo-2-metilanilina (200 mg, 1.075 mmol) y 5-fluoroisobenzofuran-1,3-diona (179 mg, 1.075 mmol) en ácido acético (2 ml). La mezcla se concentró y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano hasta hexano-EtOAc 60:40) dando 2-(3-bromo-2-metilfenil)-5-fluoroisoindolin-1,3-diona como un sólido blanco (235 mg, 59%). Espectro de masas m/z 334, 336 $(M+H)^+$.

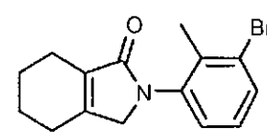
Los siguientes Intermedios también se prepararon usando procedimientos usados para preparar el Intermedio 3-1.

Intermedio	Nombre del compuesto	Espectro de masas
3-2	2-(3-bromo-2-metilfenil)-5-*terc*-butilisoindolin-1,3-diona	372, 374 $(M+H)^+$
3-3	2-(3-bromo-2-metilfenil)-5-cloroisoindolin-1,3-diona	350, 352 $(M+H)^+$
3-4	2-(3-bromo-2-metilfenil)-5-metilisoindolin-1,3-diona	330, 332 $(M+H)^+$
3-5	2-(3-bromo-2-metilfenil)-4-fluoroisoindolin-1,3-diona	334, 336 $(M+H)^+$
3-6	2-(3-bromo-2-metilfenil)hexahidro-1H-isoindol-1,3(2H)-diona	322, 324 $(M+H)^+$
3-7	2-(3-bromo-2-metilfenil)-1H-pirrolo[3,4-c]piridin-1,3(2H)-diona	317, 319 $(M+H)^+$

Intermedios 4-1 y 4-2

Preparación de 2-(3-bromo-2-metilfenil)octahidro-1H-isoindol-1-ona y 2-(3-bromo-2-metilfenil)-2,3,4,5,6,7-hexahidro-1H-isoindol-1-ona





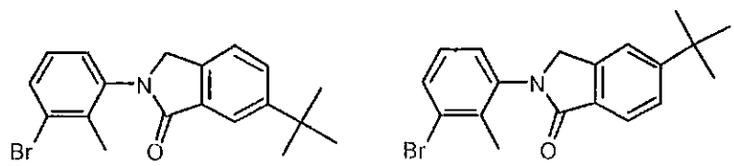
Se trató una suspensión de 2-(3-bromo-2-

metilfenil)hexahidro-1H-isoindol-1,3(2H)-diona (Intermedio 3-6, 4.5 g, 13.97 mmol) en metanol (150 ml), con borohidruro sódico (2.64 g, 69.8 mmol) y se agitó a ta durante 4 h. La mezcla se concentró, y el residuo se disolvió en DCM, se lavó con NaHCO3 (ac) y agua, y se secó y concentró proporcionando 2-(3-bromo-2-metilfenil)-3-hidroxioctahidro-1H-isoindol-1-ona como un sólido amarillo (3.94 g, 87%). Espectro de masas m/z 324, 326 $(M+H)^+$. Sin purificación, se disolvió una porción de este material (1.8 g, 5.55 mmol) en DCM (50 ml) y se trató con trietilsilano (6.46 g, 55.5 mmol). La solución se trató gota a gota a ta con TFA (2.14 ml, 27.8 mmol) y se agitó a ta durante 30 min. La mezcla se concentró y el residuo se disolvió en DCM, se lavó con NaHCO3 (ac) y agua. La fase orgánica se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc) proporcionando 2-(3-bromo-2-metilfenil)octahidro-1H-isoindol-1-ona (Intermedio 4-1, 1.35 g, 79%). RMN de ^1H (400 MHz, cloroformo-d) δ 7.48 - 7.53 (1 H, m), 7.06 - 7.09 (2 H, m), 3.78 (1 H, dd, *J*=9.5, 5.7 Hz), 3.19 (1 H, dd, *J*=9.5, 2.4 Hz), 2.64 - 2.70 (1 H, m), 2.45 - 2.44 (1 H, m), 2.30 (3 H, s), 2.10 - 2.17 (1 H, m), 1.80 - 1.88 (1 H, m), 1.62 - 1.71 (2 H, m), 1.56 - 1.62 (1 H, m), 1.40 - 1.51 (1 H, m), 1.31 (2 H, s). Espectro de masas m/z 308, 310 $(M+H)^+$. También se aisló 2-(3-bromo-2-metilfenil)-2,3,4,5,6,7-hexahidro-1H-isoindol-1-ona (Intermedio 4-2, 224 mg, 13%). RMN de ^1H (400 MHz,

cloroformo-d) δ 7.51 - 7.55 (1 H, m), 7.05 - 7.14 (2 H, m), 4.09 (2 H, t, *J*=1.9 Hz), 2.28 - 2.37 (4 H, m), 2.28 (3 H, s), 1.73 - 1.85 (4 H, m). Espectro de masas m/z 306, 308 $(M+H)^+$.

Intermedios 4-3 y 4-4

Preparación de 2-(3-bromo-2-metilfenil)-6-*terc*-butilisoindolin-1-ona y 2-(3-bromo-2-metilfenil)-5-*terc*-butilisoindolin-1-ona



Se trató una suspensión de 2-(3-bromo-2-metilfenil)-5-*terc*-butilisoindolin-1,3-diona (Intermedio 3-2, 1.0 g, 2.69 mmol) en metanol (20 ml) con borohidruro sódico (203 mg, 5.37 mmol) y se agitó a ta. Después de unos pocos minutos, se añadió más borohidruro sódico (203 mg, 5.37 mmol). Después de 40 min, la mezcla se concentró y el residuo se disolvió en DCM, se lavó con agua y salmuera y se secó y concentró proporcionando un sólido blanco. Este material se disolvió en DCM (10 ml) y se trató con TFA (10 ml) y se agitó durante unos pocos minutos a ta, luego se trató con trietilsilano (6.40 ml, 40.1 mmol) y se agitó a ta durante 2.4 h. La mezcla se concentró y el residuo se disolvió en DCM, se lavó con NaHCO3 (ac) y agua. La fase orgánica se secó y se concentró. El residuo se purificó por cromatografía en

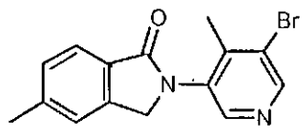
columna (eluyendo con hexano-EtOAc) proporcionando 2-(3-bromo-2-metilfenil)-6-*terc*-butilisoindolin-1-ona (Intermedio 4-3, 134 mg, 28%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.99 (1 H, d, J=1.32 Hz), 7.68 (1 H, dd, J=7.91, 1.76 Hz), 7.60 (1 H, dd, J=7.69, 1.10 Hz), 7.45 (1 H, d, J=7.91 Hz), 7.19 - 7.23 (1 H, m), 7.15 (1 H, t, J=7.69 Hz), 4.68 (2 H, s), 2.31 (3 H, s), 1.39 (9 H, s). Espectro de masas m/z 358, 360 $(M+H)^+$. También se aisló 2-(3-bromo-2-metilfenil)-5-*terc*-butilisoindolin-1-ona (Intermedio 4-4, 250 mg, 52%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.88 (1 H, d, J=7.91 Hz), 7.59 (2 H, dd, J=8.13, 2.86 Hz), 7.53 (1 H, s), 7.20 - 7.23 (1 H, m), 7.12 - 7.17 (1 H, m), 4.69 (2 H, s), 2.31 (3 H, s), 1.40 (9 H, s). Espectro de masas m/z 358, 260 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando procedimientos usados para preparar el Intermedio 4-1 a 4-4.

Intermedio	Nombre del compuesto	Espectro de masas
4-5	2-(3-bromo-2-metilfenil)-7-fluoroisoindolin-1-ona	320, 322 $(M+H)^+$
4-6	2-(3-bromo-2-metilfenil)-4-fluoroisoindolin-1-ona	320, 322 $(M+H)^+$
4-7	2-(3-bromo-2-metilfenil)-5-metilisoindolin-1-ona	316, 318 $(M+H)^+$
4-8	2-(3-bromo-2-metilfenil)-5-fluoroisoindolin-1-ona	320, 322 $(M+H)^+$

Intermedio 5-1

Preparación de 2-(5-bromo-4-metilpiridin-3-il)-5-metilisoindolin-1-ona



Etapa 1 Una mezcla de 5-metilisoindolin-1,3-diona (5.00 g, 31.0 mmol) y virutas de estaño (8.84 g, 74.5 mmol) en ácido acético (30 ml) y ácido clorhídrico concentrado (15 ml) se trató a reflujo durante 3 h. La solución caliente se filtró y las virutas de estaño residuales se lavaron con ácido acético. El filtrado se concentró y el residuo se diluyó con DCM (200 ml), y se lavó con agua (20 ml) y salmuera (20 ml), se secó y se concentró. El precipitado que se formó durante la concentración se recogió por filtración y se lavó con DCM (5 ml) y se secó a vacío dando 5-metilisoindolin-1-ona (2.3 g, 50%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.70 (1 H, d, J=7.77 Hz), 7.43 (1 H, s), 7.35 (1 H, d, J=7.77 Hz), 4.46 (2 H, s), 2.48 (3 H, s). Espectro de masas m/z 148.0 $(M+H)^+$.

Etapa 2 Se calentó una mezcla de 3,5-dibromo-4-metilpiridina (2.00 g, 7.97 mmol), 6-metilisoindolin-1-ona (1.173 g, 7.97 mmol), yoduro de cobre (I) (0.076 g, 0.399 mmol), carbonato potásico (2.203 g, 15.94 mmol) y N^1,N^2-dimetiletano-1,2-diamina (0.070 g, 0.797 mmol) en 1,4-dioxano

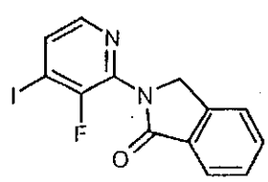
(20 ml) a 100 °C durante 15 h. La mezcla se enfrió hasta ta, se filtró a través de Celite y se lavó con DCM. El filtrado se diluyó con DCM (100 ml) y se lavó con agua (10 ml) y salmuera (10 ml), luego se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano-EtOAc 80:20 hasta EtOAc) dando 2-(5-bromo-4-metilpiridin-3-il)-5-metilisoindolin-1-ona (760 mg, 30%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.68 (1 H, s), 8.42 (1 H, s), 7.84 (1 H, d, *J*=7.77 Hz), 7.37 (1 H, d, *J*=7.77 Hz), 7.34 (1 H, s), 4.73 (2 H, s), 2.40 (3 H, s), 2.35 (3 H, s). Espectro de masas m/z 317, 319 $(M+H)^+$.

El siguiente Intermedio también se preparó usando procedimientos usados para preparar el Intermedio 5-1.

Intermedio	Nombre del compuesto	Espectro de masas
5-2	2-(5-bromo-4-metilpiridin-3-il)isoindolin-1-ona	351.2 $(M+H)^+$

Intermedio 6-1

Preparación de 2-(3-fluoro-4-yodopiridin-2-il)isoindolin-1-ona

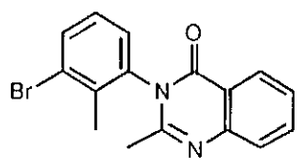


Se calentó una mezcla de 3-fluoro-2,4-

diyodopiridina (300 mg, 0.860 mmol), isoindolin-1-ona (114 mg, 0.860 mmol), yoduro de cobre (I) (8.19 mg, 0.043 mmol), carbonato potásico (238 mg, 1.720 mmol) y N^1,N^2-dimetiletano-1,2-diamina (7.58 mg, 0.086 mmol) en 1,4-dioxano (5 ml) a 110 °C en un tubo sellado durante 15 h. La mezcla se enfrió hasta ta, se filtró a través de Celite y se lavó con DCM. El filtrado se concentró y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano-EtOAc 80:20 hasta EtOAc) dando 2-(3-fluoro-4-yodopiridin-2-il)isoindolin-1-ona (125 mg, 41%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.86 - 8.06 (2 H, m), 7.41 - 7.71 (4 H, m), 5.04 (2 H, s). Espectro de masas m/z 354.9 $(M+H)^+$.

Intermedio 7-1

Preparación de 3-(3-bromo-2-metilfenil)-2-metilquinazolin-4(3H)-ona

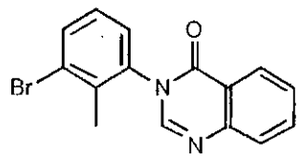


Una solución de 2-metil-4H-benzo[d][1,3]oxazin-4-ona (300 mg, 1.862 mmol), 3-bromo-2-metilanilina (346 mg, 1.862 mmol) y trietoximetano (276 mg, 1.862 mmol) en THF (2 ml) se calentó durante la noche en un tubo sellado a 100°C. La mezcla se enfrió hasta ta y se diluyó con DCM. La solución se lavó con agua y NaHCO3 (ac) y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo

con un gradiente de 90:10 a 50:50 de hexano-EtOAc) y el producto bruto se trituró en hexano dando 3-(3-bromo-2-metilfenil)-2-metilquinazolin-4(3H)-ona como un sólido blanquecino (120 mg, 20%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.28 (1 H, dd, J=7.92, 1.10 Hz), 7.77 - 7.82 (1 H, m), 7.68 - 7.73 (2 H, m), 7.47 - 7.52 (1 H, m), 7.22 - 7.25 (1 H, m), 7.13 - 7.17 (1 H, m), 2.20 (6 H, s). Espectro de masas m/z 329, 331 $(M+H)^+$.

Intermedio 8-1

Preparación de 3-(3-bromo-2-metilfenil)quinazolin-4(3H)-ona



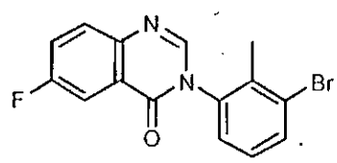
Una mezcla de 1H-benzo[d][1,3]oxazin-2,4-diona (200 mg, 1.226 mmol), 3-bromo-2-metilanilina (228 mg, 1.226 mmol), y trimetoximetano (390 mg, 3.68 mmol) en THF (2 ml) se calentó durante la noche en un tubo sellado a 100°C. La mezcla se enfrió hasta ta y se concentró, y el residuo se purificó por cromatografía en columna (eluyendo con 90:10 a 50:50 de hexano-EtOAc) dando 3-(3-bromo-2-metilfenil)quinazolin-4(3H)-ona (140 mg, 36%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.37 (1 H, dd, *J*=8.3, 1.2 Hz), 7.97 (1 H, s), 7.76 - 7.86 (2 H, m), 7.72 (1 H, t, *J*=4.6 Hz), 7.57 (1 H, ddd, *J*=8.0, 6.7, 1.5 Hz), 7.21 - 7.28 (2 H, m), 2.26 (3 H, s). Espectro de masas m/z 315, 317 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando procedimientos usados para preparar el Intermedio 8-1.

Intermedio	Nombre del compuesto	Espectro de masas
8-2	3-(3-bromo-2-metilfenil)-5-fluoroquinazolin-4(3H)-ona	333, 335 $(M+H)^+$
8-3	3-(3-bromo-2-metilfenil)-6-cloroquinazolin-4(3H)-ona	349, 351, 353 $(M+H)^+$

Intermedio 9-1

Preparación de 3-(3-bromo-2-metilfenil)-6-fluoroquinazolin-4(3H)-ona



Una mezcla de ácido 2-amino-5-fluorobenzoico (1.00 g, 6.45 mmol), 3-bromo-2-metilanilina (1.199 g, 6.45 mmol) y trietoximetano (0.955 g, 6.45 mmol) en THF (2 ml) se calentó a 110°C durante la noche en un tubo sellado. La mezcla se enfrió hasta ta y se diluyó con EtOAc. La solución se lavó con NaHCO3 (ac) y agua, luego se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 80:20 a 70:30 de hexano-EtOAc) dando 3-(3-bromo-2-metilfenil)-6-fluoroquinazolin-4(3H)-ona como un sólido blanco (1.2g, 56%). RMN de ^1H (400 MHz, cloroformo-d) δ 8.00 (1 H, dd, J=8.4, 3.1 Hz), 7.93 (1 H, s), 7.81 (1 H, dd, J=9.0, 4.8 Hz), 7.74 (1 H, dd, J=6.9, 2.3

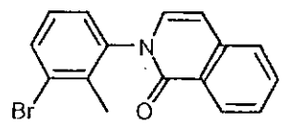
Hz), 7.50 - 7.58 (1 H, m), 7.21 - 7.26 (2 H, m), 2.25 (3 H, s). Espectro de masas m/z 333, 335 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando procedimientos usados para preparar el Intermedio 9-1.

Intermedio	Nombre del compuesto	Espectro de masas
9-2	3-(3-bromo-2-metilfenil)-6-metilquinazolin-4(3H)-ona	329, 331 $(M+H)^+$
9-3	3-(3-bromo-2-metilfenil)-8-fluoroquinazolin-4(3H)-ona	333, 335 $(M+H)^+$
9-4	3-(3-bromo-2-metilfenil)-8-metoxiquinazolin-4(3H)-ona	345, 347 $(M+H)^+$
9-5	3-(3-bromo-2-metilfenil)-5-metoxiquinazolin-4(3H)-ona	345, 347 $(M+H)^+$
9-6	3-(3-bromo-2-metilfenil)-7-metoxiquinazolin-4(3H)-ona	345, 347 $(M+H)^+$
9-7	3-(3-bromo-2-metilfenil)-6-(trifluorometoxi)quinazolin-4(3H)-ona	399, 401 $(M+H)^+$
9-8	3-(3-bromo-2-metilfenil)-8-metilquinazolin-4(3H)-ona	329, 331 $(M+H)^+$
9-9	3-(3-bromo-2-metilfenil)-6-metoxiquinazolin-4(3H)-ona	329, 331 $(M+H)^+$
9-10	3-(3-bromo-2-metilfenil)-7-fluoroquinazolin-4(3H)-ona	329, 331 $(M+H)^+$

Intermedio 10-1

Preparación de 2-(3-bromo-2-metilfenil)isoquinolin-1(2H)-ona



Etapa 1 Una mezcla de 3-bromo-2-metilanilina (1 g, 5.37 mmol) y isocroman-1,3-diona (0.872 g, 5.37 mmol) en ácido acético (15 ml) se calentó durante la noche a 100°C en un tubo sellado. La mezcla se enfrió hasta ta y se concentró, y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano-EtOAc 80:20 hasta EtOAc) dando 2-(3-bromo-2-metilfenil)isoquinolïn-1,3(2H,4H)-diona como un sólido color castaño (630 mg, 36%). Espectro de masas m/z 330, 332 $(M+H)^+$.

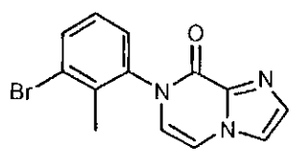
Etapa 2 Se trató una suspensión de 2-(3-bromo-2-metilfenil)isoquinolin-1,3(2H,4H)-diona (630 mg, 1.908 mmol) en metanol (100 ml) con borohidruro sódico (217 mg, 5.72 mmol) a ta. Después de 1.5 h, se añadió más borohidruro sódico (120 mg). Después de 7 h, la mezcla se concentró y el residuo se repartió entre agua y DCM. La fase orgánica se secó y se concentró dando 2-(3-bromo-2-metilfenil)-3-hidroxi-3,4-dihidroisoquinolin-1(2H)-ona como una espuma amarillo claro (600 mg, 95%), se usó sin purificación posterior. Espectro de masas m/z 332, 334 $(M+H)^+$.

Etapa 3 Se trató una solución de 2-(3-bromo-2-metilfenil)-3-hidroxi-3,4-dihidroisoquinolin-1(2H)-ona bruta

(600 mg, 1.806 mmol) en DCM (30 ml) con trietilsilano (15 ml, 94 mmol) y la mezcla resultante se trató lentamente con TFA (1.392 ml, 18.06 mmol). La mezcla se agitó a ta durante 2 h, luego se concentró y el residuo se disolvió en DCM. La solución se lavó con NaHCO3 (ac) y agua, luego se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 80:20 hasta hexano-EtOAc 60:40) dando 2-(3-bromo-2-metilfenil)isoquinolin-1(2H)-ona como un sólido blanco (380 mg, 67%). Espectro de masas m/z 314, 316 $(M+H)^+$.

Intermedio 11-1

Preparación de (3-bromo-2-metilfenil)imidazo[1,2-a]pirazin-8(7H)-ona



Etapa 1 Se trató una solución de 3-bromo-2-metilanilina (0.63g, 3.39 mmol), ácido 1H-imidazol-2-carboxílico (0.455 g, 4.06 mmol), HOAT (0.830 g, 6.10 mmol) y EDC (1.298 g, 6.77 mmol) en DCM-THF 2:1 (100 ml) con DIEA (1.774 ml, 10.16 mmol) y se agitó a ta durante la noche. Se añadieron más ácido 1H-imidazol-2-carboxílico (0.6 eq, 0.228 g), EDC (0.64 g), HOAT (0.41 g) y DIEA (0.8 ml) y la mezcla se agitó a ta durante 6 días. La mezcla se repartió entre NaHCO3 (ac) y DCM, y la fase orgánica se lavó con salmuera,

se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de DCM hasta DCM-metanol 94:6) proporcionando N-(3-bromo-2-metilfenil)-1H-imidazol-2-carboxamida como un sólido (80% de pureza, 0.76 g, 64%). Espectro de masas m/z 280, 282 $(M+H)^+$.

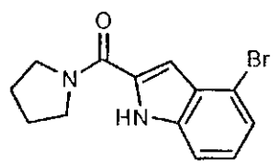
Etapa 2 Se trató una solución de N-(3-bromo-2-metilfenil)-1H-imidazol-2-carboxamida (0.70 g, 2.499 mmol) en DMF (12.4 ml) con carbonato potásico (0.794 g, 5.75 mmol) y 2-bromo-1,1-dietoxietano (0.395 ml, 2.62 mmol). La suspensión se calentó a 100°C durante la noche. La mezcla se enfrió hasta ta, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 85:15 a 20:80 de hexano-EtOAc) proporcionando N-(3-bromo-2-metilfenil)-1-(2,2-dietoxietil)-1H-imidazol-2-carboxamida como un sólido blanco (0.81 g, 82%). RMN de ^1H (400 MHz, DMSO-d_6) δ 10.17 (1 H, s), 7.51 (1 H, d, J=2.6 Hz), 7.49 (1 H, d, J=2.6 Hz), 7.44 (1 H, d, J=1.1 Hz), 7.18 (1 H, t, J=8.0 Hz), 7.10 (1 H, d, J=1.1 Hz), 4.75 (1 H, t, J=5.4 Hz), 4.52 (2 H, d, J=5.3 Hz), 3.63 (2 H, dq, J=9.7, 7.0 Hz), 3.35 - 3.44 (2 H, m), 2.31 (3 H, s), 1.05 (6 H, t, J=7.0 Hz). Espectro de masas m/z 396, 398 $(M+H)^+$.

Etapa 3 Se trató una suspensión de N-(3-bromo-2-metilfenil)-1-(2,2-dietoxietil)-1H-imidazol-2-carboxamida (0.81 g, 2.044 mmol) en agua (10.2 ml) con ácido clorhídrico

1 M (8.2 ml, 8.2 mmol) y la mezcla se calentó a reflujo durante la noche. La mezcla se enfrió hasta ta, se trató con NaHCO3 (ac) y se extrajo con EtOAc. Se recogió un precipitado por filtración proporcionando un sólido blanco (0.33 g), que era una mezcla (aproximadamente 1:1) de 7-(3-bromo-2-metilfenil)imidazo[1,2-a]pirazin-8(7H)-ona y 7-(3-bromo-2-metilfenil)-6-hidroxi-6,7-dihidroimidazo[1,2-a]pirazin-8(5H)-ona (Espectro de masas m/z 322, 324 $(M+H)^+$). El filtrado se secó y se concentró proporcionando 7-(3-bromo-2-metilfenil)imidazo[1,2-a]pirazin-8(7H)-ona como un sólido blanco (0.34 g, 66%) contaminada con una pequeña cantidad de 7-(3-bromo-2-metilfenil)-6-hidroxi-6,7-dihidroimidazo[1,2-a]pirazin-8(5H)-ona. Espectro de masas m/z 304, 306 $(M+H)^+$. Las mezclas podían convertirse en 7-(3-bromo-2-metilfenil)imidazo[1,2-a]pirazin-8(7H)-ona, sal TFA, calentando con TFA a reflujo durante 2 h.

Intermedio 12-1

Preparación de (4-bromo-1H-indol-2-il)(pirrolidin-1-il)metanona



Se trató una mezcla de ácido 4-bromo-1H-indol-2-carboxílico (250 mg, 1.04 mmol), pirrolidina (0.129 ml, 1.56 mmol) y HOAT (213 mg, 1.56 mmol) en acetonitrilo (5 ml) con

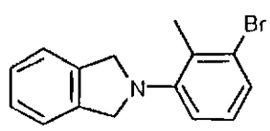
DIEA (0.364 ml, 2.08 mmol) y EDC (399 mg, 2.08 mmol) y la mezcla se agitó a ta. Después de 18.25 h, la mezcla se diluyó con EtOAc, se filtró para eliminar algo de sólido color castaño y se lavó secuencialmente con ácido clorhídrico 1 M y NaHCO3 (ac) y se secó y concentró proporcionando (4-bromo-1H-indol-2-il)(pirrolidin-1-il)metanona como un sólido color castaño (205 mg, 67%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.96 (s, 1 H) 7.46 (d, J=7.9 Hz, 1 H) 7.27 (d, J=7.5 Hz, 1 H) 7.06 - 7.17 (m, 1 H) 6.82 (s, 1 H) 3.85 (t, J=6.8 Hz, 2 H) 3.55 (t, J=6.8 Hz, 2 H) 1.93 - 2.04 (m, 2 H) 1.81 - 1.92 (m, 2 H). Espectro de masas m/z 293, 295 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando procedimientos usados para preparar el Intermedio 12-1.

Intermedio	Nombre del compuesto	Espectro de masas
12-2	4-bromo-N-etil-1H-indol-2-carboxamida	267, 269 $(M+H)^+$
12-3	4-bromo-N-(4-fluorofenil)-1H-indol-2-carboxamida	333, 335 $(M+H)^+$

Intermedio 13-1

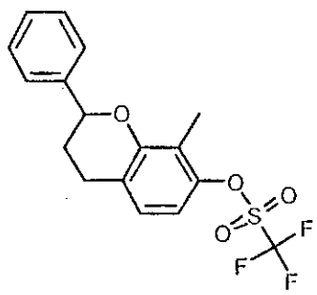
Preparación de 2-(3-bromo-2-metilfenil)isoindolina



Una mezcla de 3-bromo-2-metilanilina (372 mg, 2.00 mmol), 1,2-bis(clorometil)benceno (385 mg, 2.20 mmol) y carbonato potásico (304 mg, 2.20 mmol) en agua (2 ml) se calentó mediante radiación en microondas en un tubo sellado a 120 °C durante 25 min. La mezcla se extrajo con EtOAc y la fase orgánica se lavó con agua, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano hasta EtOAc-hexano 30:70) proporcionando 2-(3-bromo-2-metilfenil)isoindolina como un aceite amarillo claro (360 mg, 63%). Espectro de masas m/z 288, 290 $(M+H)^+$.

Intermedio 14-1

Preparación de trifluorometanosulfonato de 8-metil-2-fenilcroman-7-ilo



Etapa 1 Se trató una suspensión de (E)-3-fenilprop-2-en-1-ol (2.22 g, 16.51 mmol) y 2-metilbenceno-1,3-diol (2.05 g, 16.51 mmol) en 1,2-dicloroetano (100 ml) con ácido p-toluenosulfónico monohidratado (0.157 g, 0.826 mmol) y la mezcla se trató a reflujo durante 1 h. La mezcla se enfrió hasta ta y se concentró, y el residuo se sometió a

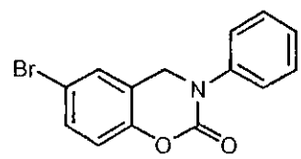
cromatografía en columna (eluyendo con un gradiente de 90:10 a 75:25 de hexano-EtOAc) proporcionando una mezcla de 4-cinamil-2-metilbenceno-1,3-diol y 4,6-dicinamil-2-metilbenceno-1,3-diol (2:1, 1.97 g). Este material (1.89 g) se disolvió en tolueno (60 ml) y se trató con ácido p-toluenosulfónico monohidratado (299 mg, 1.57 mmol) y se calentó a reflujo durante 6 h. La mezcla se enfrió hasta ta, se diluyó con EtOAc (100 ml), se lavó con NaHCO3 (ac) (2x30 ml), agua (30 ml) y salmuera (30 ml), se secó y se concentró. La cromatografía en columna (eluyendo con un gradiente de 95:5 a 70:30 de hexano-EtOAc) proporcionó 8-metil-2-fenilcroman-7-ol como un líquido marrón (aproximadamente 85% de pureza, 672 mg, 17%) que se usó sin purificación posterior. RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.35 - 7.50 (4 H, m), 7.27 - 7.35 (1 H, m), 6.79 (1 H, d, J=8.36 Hz), 6.38 (1 H, d, J=8.14 Hz), 5.07 (1 H, dd, J=10.12, 2.42 Hz), 4.64 (1 H, s), 2.83 - 3.02 (1 H, m), 2.71 (1 H, ddd, J=16.01, 4.90, 3.74 Hz), 2.16 - 2.27 (1 H, m), 2.14 (3 H, s), 1.86 - 2.04 (1 H, m). Espectro de masas m/z 241.0 $(M+H)^+$.

Etapa 2 Se añadió anhídrido trifluorometanosulfónico (0.613 ml, 3.63 mmol) gota a gota a una solución de 8-metil-2-fenilcroman-7-ol (671 mg, 2.79 mmol) en DCM (10 ml) y piridina (10 ml) a 0°C. Después de 30 min, la mezcla se diluyó con EtOAc (70 ml), se lavó con agua (2x30 ml) y salmuera (30 ml), se secó y se concentró. El

residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 95:5 a 85:15 de hexano-EtOAc) dando trifluorometanosulfonato de 8-metil-2-fenilcroman-7-ilo como líquido incoloro (925 mg, 89%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.28 - 7.61 (5 H, m), 6.97 (1 H, d, J=8.58 Hz), 6.79 (1 H, d, J=8.58 Hz), 5.11 (1 H, dd, J=10.23, 2.31 Hz), 2.99 (1 H, ddd, J=16.73, 11.11, 5.83 Hz), 2.68 - 2.88 (1 H, m), 2.17 - 2.32 (4 H, m), 1.88 - 2.12 (1 H, m). Espectro de masas m/z 390.0 $(M+H)^+$.

Intermedio 15-1

Preparación de 6-bromo-3-fenil-3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona



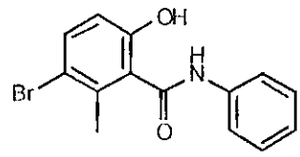
Etapa 1 Se añadió anilina (1.50 ml, 16.42 mmol) a una solución de 5-bromo-2-hidroxibenzaldehído (3.00 g, 14.92 mmol) en 1,2-dicloroetano (100 ml). Después de 10 min a ta, se añadió triacetoxiborohidruro sódico (4.74 g, 22.39 mmol). La mezcla se agitó a ta. Después de cuatro días, se añadieron más anilina (1.50 ml, 16.42 mmol) y triacetoxiborohidruro sódico (4.74 g, 22.39 mmol). Después de dos días más; se añadió cloruro amónico acuoso saturado (200 ml). La mezcla se agitó a ta durante 3 h. Se separaron las fases y la fase acuosa se extrajo con DCM (2x50 ml). Las fases orgánicas

reunidas se secaron y concentraron. El residuo se trató con tolueno (25 ml) y hexanos (25 ml) y la mezcla se agitó durante 30 min. El precipitado se lavó con mezcla 1:1 de tolueno-hexanos (3 ml) y se secó a vacío dando 4-bromo-2-((fenilamino)metil)fenol como un sólido blanco (2.64 g, 64%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 8.70 (1 H, s ancho), 7.18 - 7.46 (4 H, m), 6.95 (1 H, t, J=7.48 Hz), 6.80 - 6.90 (2 H, m), 6.77 (1 H, d, J=8.58 Hz), 4.39 (2 H, s), 3.98 (1 H, s ancho). Espectro de masas m/z 278, 280 $(M+H)^+$.

Etapa 2 Se añadieron carbonildiimidazol (0.874 g, 5.39 mmol) y DMAP (0.088 g, 0.719 mmol) a una solución de 4-bromo-2-((fenilamino)metil)fenol (1.00 g, 3.60 mmol) en DCM (100 ml) y la mezcla resultante se agitó a ta durante 60 h. La mezcla se diluyó con hexanos (100 ml), se lavó con NaHCO3 (ac) (2x25 ml), ácido clorhídrico 1 M (25 ml) y salmuera (25 ml), se secó y se filtró a través de una almohadilla de gel de sílice. Los sólidos se aclararon con EtOAc-hexano 1:1 y el filtrado se concentró dando 6-bromo-3-fenil-3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona como un sólido blanco (1.09 g, 100%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 7.41 - 7.56 (3 H, m), 7.30 - 7.41 (3 H, m), 7.21 - 7.29 (1 H, m), 7.01 (1 H, d, J=8.80 Hz), 4.80 (2 H, s). Espectro de masas m/z 304, 306 $(M+H)^+$.

Intermedio 16-1

Preparación de 3-bromo-6-hidroxi-2-metil-N-fenilbenzamida



Etapa 1 Se trató una solución de 2-hidroxi-6-metilbenzoato de etilo (2.04 g, 11.32 mmol) en metanol (25 ml) a ta con hidróxido sódico acuoso 1 M (45.3 ml, 45.3 mmol) y la mezcla se trató a reflujo durante 6 h. La mezcla se enfrió hasta ta y el metanol se eliminó a vacío. El residuo acuoso se trató con ácido clorhídrico 1 M hasta pH aproximadamente 1. El precipitado se recogió por filtración, se lavó con agua y se secó a vacío dando ácido 2-hidroxi-6-metilbenzoico como un sólido blanco (1.62 g, 94%). RMN de ^1H (400 MHz, metanol-d_4). δ 7.26 (1 H, t, J=7.92 Hz), 6.75 (2 H, t, J=7.92 Hz), 2.45 (3 H, s). Espectro de masas m/z 153.1 $(M+H)^+$.

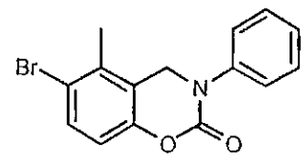
Etapa 2 Se trató una suspensión de ácido 2-hidroxi-6-metilbenzoico (1.32 g, 8.68 mmol) en acetonitrilo (20 ml) a -20 °C se trató con complejo de éter dimetílico y ácido tetrafluorobórico (1.109 ml, 9.11 mmol), seguido por la adición en varias porciones de N-bromosuccinimida (1.699 g, 9.54 mmol) durante 30 min. La mezcla se calentó hasta 0 °C y se agitó durante 1 h, luego se trató con bisulfito sódico acuoso al 40% (10 ml). El

acetonitrilo se eliminó a vacío y el residuo acuoso se extrajo con EtOAc (3x40 ml). Las fases orgánicas reunidas se lavaron con agua y salmuera, se secaron y se concentraron dando ácido 3-bromo-6-hidroxi-2-metilbenzoico como un sólido blanco (1.60 g, 80%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.47 (1 H, d, J=8.80 Hz), 6.67 (1 H, d, J=8.80 Hz), 2.40 (3 H, s). Espectro de masas m/z 231, 233 $(M-H)^-$.

Etapa 3 Se añadió cloruro de tionilo (0.111 ml, 1.524 mmol) a una solución de benzotriazol (594 mg, 4.99 mmol) en DCM (8 ml) a ta y la mezcla se agitó durante 30 min. Se añadió una solución de ácido 3-bromo-6-hidroxi-2-metilbenzoico (320 mg, 1.385 mmol) en THF (8.00 ml) y la mezcla se agitó a ta durante 2 horas. La mezcla se filtró y el sólido se lavó con DCM (3 ml). El filtrado se concentró, y el residuo se disolvió en anilina (2 g, 21.48 mmol) y calentó en un tubo sellado por radiación en microondas a 150 °C durante 10 min. La mezcla se diluyó con EtOAc (100 ml) y se lavó con ácido clorhídrico 2 M (20 ml), agua (10 ml) y salmuera (10 ml), se secó y se concentró. El residuo se trituró con DCM (4 ml) dando la 3-bromo-6-hidroxi-2-metil-N-fenilbenzamida como sólido color claro (290 mg, 68%). Espectro de masas m/z 306, 308 $(M+H)^+$.

Intermedio 17-1

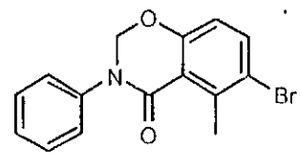
Preparación de 6-bromo-5-metil-3-fenil-3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona



Se trató una solución de 3-bromo-6-hidroxi-2-metil-N-fenilbenzamida (Intermedio 16-1, 50 mg, 0.163 mmol) en THF (2 ml) a ta con hidruro de litio y aluminio (50 mg, 1.317 mmol) y la mezcla se trató a reflujo durante 2 h. Se enfrió hasta ta y se trató cuidadosamente con cloruro amónico acuoso saturado (2 ml).La mezcla se diluyó con DCM (60 ml) y se lavó con agua (5 ml) y salmuera (5 ml), se secó y se concentró dando el 4-bromo-3-metil-2-((fenilamino)metil)fenol (45 mg). Sin purificación, este material se disolvió en DCM (3 ml) y se trató con carbonildiimidazol (30.5 mg, 0.188 mmol) y DMAP (2.091 mg, 0.017 mmol) a ta y la mezcla se agitó durante 1 h. La mezcla se diluyó con DCM (60 ml) y se lavó con NaHCO3 (ac) (5 ml) y salmuera (5 ml), se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 95:5 a 50:50 de hexano-EtOAc) dando 6-bromo-5-metil-3-fenil-3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona (25 mg). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.33 - 7.57 (6 H, m), 6.88 (1 H, d, J=8.88 Hz), 4.82 (2 H, s), 2.30 (3 H, s). Espectro de masas m/z 318, 320 $(M+H)^+$.

Intermedio 18-1

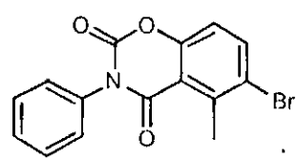
Preparación de 6-bromo-5-metil-3-fenil-2H-benzo[e][1,3]oxazin-4(3H)-ona



Una mezcla de 3-bromo-6-hidroxi-2-metil-N-fenilbenzamida (Intermedio 16-1, 40 mg, 0.131 mmol) y paraformaldehído (11.77 mg, 0.392 mmol) en TFA (1 ml) se calentó a 100 °C durante 4 h. El TFA se eliminó a vacío, y el residuo se diluyó con EtOAc (80 ml), se lavó con NaHCO3 (ac) (10 ml), agua (10 ml) y salmuera (10 ml) y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 95:5 a 70:30 de hexano-EtOAc) dando 6-bromo-5-metil-3-fenil-2H-benzo[e][1,3]oxazin-4(3H)-ona (25 mg, 45%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.63 (1 H, d, J=8.80 Hz), 7.37 - 7.50 (3 H, m), 7.29 - 7.35 (2 H, m), 6.81 (1 H, d, J=8.80 Hz), 5.48 (2 H, s), 2.80 (3 H, s). Espectro de masas m/z 318, 320 $(M+H)^+$.

Intermedio 19-1

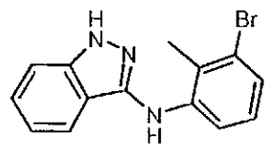
Preparación de 6-bromo-5-metil-3-fenil-2H-benzo[e][1,3]oxazin-2,4(3H)-diona



Etapa 1 Se trató una solución de 3-bromo-6-hidroxi-2-metil-N-fenilbenzamida (Intermedio 16-1, 40 mg, 0.131 mmol) en piridina (1 ml) con cloroformiato de etilo (0.015 ml, 0.157 mmol) a ta y la mezcla se calentó hasta 100 °C durante 2 h. Se añadió más cloroformiato de etilo (0.015 ml, 0.157 mmol) y la mezcla se agitó a 100 °C durante 15 h. La mezcla se enfrió y se diluyó con EtOAc (80 ml), y la solución se lavó con NaHCO3 (ac) (10 ml), agua (2x10 ml) y salmuera (10 ml) y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 95:5 a 70:30 de hexano-EtOAc) dando 6-bromo-5-metil-3-fenil-2H-benzo[e][1,3]oxazin-2,4(3H)-diona (19 mg, 44%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.90 (1 H, d, J=9.02 Hz), 7.43 - 7.68 (3 H, m), 7.27 - 7.40 (2 H, m), 7.12 (1 H, d, J=8.80 Hz), 2.90 (3 H, s). Espectro de masas m/z 332, 334 $(M+H)^+$.

Intermedio 20-1

Preparación de N-(3-bromo-2-metilfenil)-1H-indazol-3-amina



Etapa 1 Se trató una mezcla de 3-bromo-2-metilanilina (1.66 ml, 13.4 mmol), ácido 2-fluorobenzoico (1.883 g, 13.4 mmol) y HOAT (2.74 g, 20.2 mmol) en EtOAc (60 ml) con DIEA (4.7 ml, 26.9 mmol) y EDC (5.15 g, 26.9 mmol) y la mezcla se agitó a ta. Después de 19 h, la mezcla se diluyó

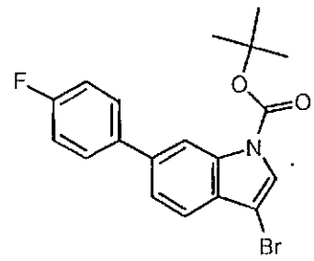
con EtOAc y se lavó con agua, ácido clorhídrico 1 M (dos veces), NaHCO3 (ac) (dos veces) y salmuera, se secó y se concentró proporcionando N-(3-bromo-2-metilfenil)-2-fluorobenzamida como agujas esponjosas de color castaño (4.11 g, 99%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.34 - 8.50 (1 H, m), 8.20 (1 H, td, J=7.9, 1.8 Hz), 7.96 (1 H, d, J=8.1 Hz), 7.50 - 7.59 (1 H, m), 7.44 (1 H, dd, J=8.0, 0.8 Hz), 7.30 - 7.37 (1 H, m), 7.21 (1 H, dd, J=12.8, 7.9 Hz), 7.12 (1 H, t, J=8.0 Hz), 2.45 (3 H, s). Espectro de masas m/z 308, 310 $(M+H)^+$.

Etapa 2 Se calentó a reflujo una mezcla de N-(3-bromo-2-metilfenil)-2-fluorobenzamida (2.00 g, 6.49 mmol) y 2,4-disulfuro de 2,4-bis-(4-metoxifenil)-1,3-ditia-2,4-difosfetano (reactivo de Lawesson, 1.575 g, 3.89 mmol) en tolueno (25 ml). Después de 3.5 h, la solución se enfrió hasta ta y se concentró proporcionando un sólido amarillo oscuro. Este se purificó por cromatografía en columna (eluyendo con un gradiente de 95:5 a 90:10 de hexano-EtOAc) proporcionando N-(3-bromo-2-metilfenil)-2-fluorobenzotioamida como un sólido amarillo (1.892 g, 90%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 9.18 (1 H, d, J=7.7 Hz), 8.23 (1 H, td, J=8.0, 1.8 Hz), 7.60 (1 H, d, J=7.9 Hz), 7.45 - 7.52 (1 H, m), 7.43 (1 H, d, J=7.7 Hz), 7.23 - 7.30 (1 H, m), 7.11 - 7.21 (2 H, m), 2.41 (3 H, s). Espectro de masas m/z 324, 326 $(M+H)^+$.

Etapa 3 Se trató una solución amarilla de N-(3-bromo-2-metilfenil)-2-fluorobenzotioamida (500 mg, 1.542 mmol) en DMSO (5 ml) con hidrazina anhidra (0.484 ml, 15.42 mmol) y se calentó a 150°C. Después de 2 h 20 min la solución se enfrió hasta ta, se diluyó con NaHCO3 (ac) y se extrajo dos veces con EtOAc. Las fases orgánicas reunidas se lavaron dos veces con agua y una vez con salmuera, se secaron y se concentraron. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 85:15 a 50:50 de hexano-EtOAc) proporcionando N-(3-bromo-2-metilfenil)-1H-indazol-3-amina como un sólido céreo color castaño (162 mg, 35%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 9.38 (1 H, s ancho), 7.49 (1 H, d, J=8.1 Hz), 7.45 (1 H, d, J=7.9 Hz), 7.40 (2 H, d, J=3.5 Hz), 7.19 (1 H, dd, J=7.9, 0.9 Hz), 7.10 (1 H, dt, J=8.1, 4.0 Hz), 6.98 (1 H, t, J=8.1 Hz), 6.10 (1 H, s), 2.49 (3 H, s). Espectro de masas m/z 302, 304 $(M+H)^+$.

Intermedio 21-1

Preparación de 3-bromo-6-(4-fluorofenil)-1H-indol-1-carboxilato de terc-butilo



Etapa 1 Se purgó una mezcla de 6-bromo-1H-indol (0.25 g, 1.275 mmol), ácido 4-fluorofenilborónico (0.178 g,

1.275 mmol) y carbonato sódico acuoso 2 M (2.0 ml, 4.00 mmol) en tolueno (10 ml) y etanol (2.400 ml) con argón y se trató con tetraquis(trifenilfosfina)paladio (0.074 g, 0.064 mmol). La mezcla se calentó a 90°C. Después de 17 h, la mezcla se enfrió hasta ta y se repartió entre agua y EtOAc. La fase orgánica se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 95:5 hasta 60:40 de hexano-EtOAc) proporcionando 6-(4-fluorofenil)-1H-indol como un sólido blanco (175.5 mg, 65%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.17 (1 H, s ancho), 7.65 - 7.71 (2 H, m), 7.56 - 7.62 (2 H, m), 7.37 (1 H, t, J=2.9 Hz), 7.22 - 7.31 (3 H, m), 6.44 (1 H, t, J=2.0 Hz). Espectro de masas m/z 212.2 $(M+H)^+$.

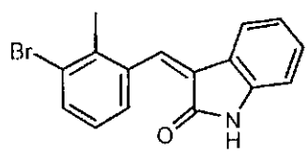
Etapa 2 Se trató una solución de 6-(4-fluorofenil)-1H-indol (172 mg, 0.814 mmol) en THF (5 ml) con dicarbonato de di-*terc*-butilo (213 mg, 0.977 mmol) y DMAP (24.87 mg, 0.204 mmol) y se agitó a ta. Después de 21 h, la mezcla se concentró y el residuo se disolvió en EtOAc y se lavó con ácido clorhídrico 0.2 M. La fase orgánica se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 95:5 a 50:50 de hexano-EtOAc) proporcionando 6-(4-fluorofenil)-1H-indol-1-carboxilato de terc-butilo como una goma incolora (199.7 mg, 79%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.39 (1 H, s ancho), 7.54 - 7.67 (4 H, m), 7.43 (1 H, dd, J=8.1, 1.5 Hz),

7.13 (2 H, t, J=8.6 Hz), 6.58 (1 H, d, J=3.5 Hz), 1.68 (9 H, s). Espectro de masas m/z 312.2 $(M+H)^+$.

Etapa 3 Se trató una solución de 6-(4-fluorofenil)-1H-indol-1-carboxilato de terc-butilo (187.8 mg, 0.603 mmol) en THF (4 ml) con N-bromosuccinimida (118 mg, 0.663 mmol) y se agitó a ta. Después de 18 h, la solución se diluyó con éter, se lavó con 2 x 10 ml de bisulfito sódico acuoso (aproximadamente 1.5 M), luego con NaHCO3 (ac), se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano a 90:10 de hexano-EtOAc) proporcionando 3-bromo-6-(4-fluorofenil)-1H-indol-1-carboxilato de terc-butilo como una espuma vítrea blanca (134 mg, 57%). RMN de ^1H (400 MHz, cloroformo-d) δ 8.39 (1 H, s ancho), 7.59 - 7.68 (3 H, m), 7.54 - 7.59 (1 H, m), 7.48 - 7.53 (1 H, m), 7.14 (2 H, t, J=8.7 Hz), 1.67 (9 H, s).

Intermedio 22-1

Preparación de 3-(3-bromo-2-metilbenciliden)indolin-2-ona



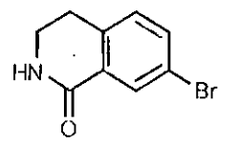
Etapa 1 Una mezcla de (3-bromo-2-metilfenil)metanol (preparado de acuerdo con los procedimientos expuestos en la solicitud de patente de Estados Unidos 2006/0173183, 500 mg, 2.49 mmol) en THF (20 ml) se agitó a ta y se trató con 1,1,1-tris(acetiloxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona

(peryodinano de Dess-Martin, 1.58 g, 3.73 mmol). Después de 2 h, la mezcla se diluyó con éter (aproximadamente 100 ml) y se lavó con bisulfito sódico acuoso al 5%, NaHCO3 (ac) y salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano a 55:45 de hexano-EtOAc) proporcionando 3-bromo-2-metilbenzaldehído como un aceite incoloro (343 mg, 70%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.26 (1 H, s), 7.78 (2 H, ddd, J=9.7, 8.0, 1.2 Hz), 7.20 - 7.27 (1 H, m), 2.75 (3 H, s).

Etapa 2 Se trató una solución de 3-bromo-2-metilbenzaldehído (200 mg, 1.01 mmol) e indolin-2-ona (134 mg, 1.01 mmol) en etanol (10 ml) con piperidina (0.099 ml, 1.01 mmol) y se calentó a 80-85°C. Después de 15.25 h, la solución se enfrió hasta ta y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 80:20 a 30:70 de hexano-acetato de etilo) proporcionando 3-(3-bromo-2-metilbenciliden)indolin-2-ona como un sólido amarillo brillante (94.9 mg, 30%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.89 (1 H, s ancho), 7.85 (1 H, s), 7.64 (1 H, d, J=7.9 Hz), 7.47 (1 H, d, J=7.7 Hz), 7.20 (1 H, td, J=7.7, 1.1 Hz), 7.07 - 7.16 (2 H, m), 6.87 (1 H, d, J=7.9 Hz), 6.81 (1 H, td, J=7.6, 1.0 Hz), 2.43 (3 H, s). Espectro de masas m/z 314, 316 $(M+H)^+$.

Intermedio 23-1

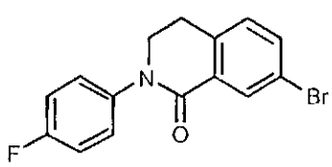
Preparación de 7-bromo-3,4-dihidroisoquinolin-1(2H)-ona



Se añadió azida de sodio (0.431 g, 6.63 mmol) lentamente a una mezcla de 6-bromo-2,3-dihidro-1H-inden-1-ona (1 g, 4.74 mmol) y ácido metanosulfónico (15 ml, 231 mmol) en DCM (30 ml) a 0°C. La mezcla se agitó a ta durante 15 horas, luego se inactivó cuidadosamente con hidróxido sódico acuoso 1 M (50 ml). La fase acuosa se extrajo con DCM (3x50 ml), y las fases orgánicas reunidas se lavaron con agua (20 ml) y salmuera (20 ml), se secaron y se concentraron. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 90:10 de hexano-EtOAc hasta EtOAc) dando 7-bromo-3,4-dihidroisoquinolin-1(2H)-ona como sólido blanco (650 mg, 61%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.35 (1 H, s ancho), 7.08 - 7.17 (1 H, m), 6.98 - 7.06 (1 H, m), 6.95 (1 H, d, J=1.98 Hz), 2.93 (2 H, t, J=7.59 Hz), 2.49 - 2.68 (2 H, m). Espectro de masas m/z 226, 228 $(M+H)^+$.

Intermedio 24-1

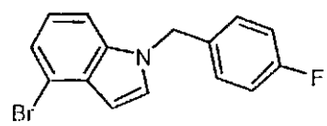
Preparación de 7-bromo-2-(4-fluorofenil)-3,4-dihidroisoquinolin-1(2H)-ona



Una mezcla de 7-bromo-3,4-dihidroisoquinolin-1(2H)-ona (Intermedio 23-1, 60 mg, 0.265 mmol), 1-fluoro-4-yodobenceno (118 mg, 0.531 mmol), carbonato potásico (36.7 mg, 0.265 mmol) y yoduro de cobre (I) (10.11 mg, 0.053 mmol) en DMF (1.000 ml) se calentó a 130 °C durante 5 h. La mezcla se enfrió hasta ta y se filtró a través de una almohadilla de Celite, y los sólidos se lavaron con EtOAc. El filtrado se lavó con agua y salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 90:10 hasta 60:40 de hexano-EtOAc) dando 7-bromo-2-(4-fluorofenil)-3,4-dihidroisoquinolin-1(2H)-ona (40 mg, 47%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.15 - 7.27 (4 H, m), 7.04 - 7.13 (2 H, m), 6.48 (1 H, d, J=1.94 Hz), 2.96 - 3.08 (2 H, m), 2.73 - 2.84 (2 H, m). Espectro de masas m/z 320, 322 $(M+H)^+$.

Intermedio 25-1

Preparación de 4-bromo-1-(4-fluorobencil)-1H-indol

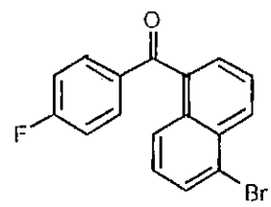


Se agitó una suspensión de hidruro sódico (dispersión al 60% en aceite, 112 mg, 2.81 mmol) en THF (12 ml) a ta y se trató con una solución de 4-bromo-1H-indol (500 mg, 2.45 mmol) en THF (3 ml). Después de 1-2 min, la mezcla se trató con bromuro de 4-fluorobencilo (0.318 ml, 2.45 mmol)

y se agitó la solución ligeramente turbia a ta. Después de 20 h, la mezcla se concentró. El residuo se repartió entre EtOAc y ácido clorhídrico 0.1 M y la fase acuosa se extrajo de nuevo con EtOAc. Las fases orgánicas reunidas se lavaron con salmuera, se secaron y se concentraron. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 90:10 a 50:50 de hexano-EtOAc) proporcionando 4-bromo-1-(4-fluorobencil)-1H-indol como un aceite incoloro (461.4 mg, 85% de pureza, 51%) contaminado con aproximadamente 15% en peso de 4-bromo-1,3-bis(4-fluorobencil)-1H-indol. RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.28 (1 H, dd, J=7.6, 0.8 Hz), 7.19 (1 H, d, J=8.4 Hz), 7.16 (1 H, d, J=3.3 Hz), 6.94 - 7.09 (5 H, m), 6.60 (1 H, dd, J=3.1, 0.9 Hz), 5.28 (2 H, s). Espectro de masas m/z 304, 306 $(M+H)^+$.

Intermedio 26-1

Preparación de (5-bromonaftalen-1-il)(4-fluorofenil)metanona



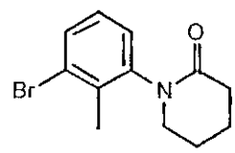
Etapa 1 Se trató una solución de ácido 5-bromo-1-naftoico (preparado de acuerdo con el procedimiento de Hausamann, *Chem. Ber.*, 1876, 9, 1519; 2.00 g, 7.97 mmol) en THF (50 ml) con TEA (2.22 ml, 15.93 mmol), luego con

cloroformiato de isobutilo (1.088 g, 7.97 mmol) y la suspensión resultante se agitó a ta. Después de 25 min, la mezcla se trató con más TEA (2.22 ml, 15.93 mmol), luego con una solución de sal clorhidrato de N,O-dimetilhidroxilamina (0.777 g, 7.97 mmol) en agua (5 ml) y la mezcla se agitó a ta. Después de 2.4 h, la mezcla se concentró y el residuo se recogió en EtOAc y agua. La mezcla se filtró, se separaron las fases y la fase orgánica se lavó con NaHCO3 (ac), se secó y se concentró proporcionando 5-bromo-N-metoxi-N-metil-1-naftamida como un sólido pastoso (1.03 g, 30%) contaminado con aproximadamente 30% de 5-bromo-1-naftoato de isobutilo. Espectro de masas m/z 294, 296 $(M+H)^+$. Sin purificación posterior, se agitó una solución de este material (1.01 g, 2.404 mmol) en THF (15 ml) en hielo y se trató con bromuro (4-fluorofenil)magnesio, 2M en éter (7.21 ml, 14.42 mmol). La solución se agitó en hielo y se dejó calentar lentamente hasta ta. Después de 16 h, la mezcla se trató con ácido clorhídrico 1 M y se extrajo dos veces con EtOAc. Las fases orgánicas reunidas se secaron y concentraron. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano a 85:15 de hexano-EtOAc) proporcionando (5-bromonaftalen-1-il)(4-fluorofenil)metanona como un aceite viscoso amarillo pálido (658 mg, 83%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.49 (1 H, d, J=8.6 Hz), 7.95 (1 H, d, J=8.6 Hz), 7.86 - 7.93 (3 H, m), 7.74 (1 H, dd, J=8.5, 7.2 Hz),

7.64 - 7.68 (1 H, m), 7.40 (1 H, dd, J=8.5, 7.6 Hz), 7.25 (2 H, t, J=8.8 Hz). Espectro de masas m/z 329, 331 $(M+H)^+$.

Intermedio 27-1

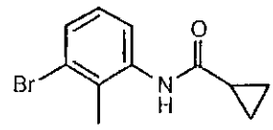
Preparación de 1-(3-bromo-2-metilfenil)piperidin-2-ona



Se trató una solución de 3-bromo-2-metilanilina (1 g, 5.37 mmol) en DCM (15 ml) con TEA (0.749 ml, 5.37 mmol) y luego gota a gota con una solución de cloruro de 5-bromopentanoilo (1.072 g, 5.37 mmol) en DCM (4 ml). La mezcla se agitó a ta durante 30 min, luego se diluyó con DCM, se lavó con agua y salmuera y se secó y concentró. El residuo se disolvió en THF (100 ml) y se añadió a una suspensión de hidruro sódico (dispersión al 60% en aceite, se lavó con hexano, 0.430 g, 10.75 mmol) en THF (50 ml). La mezcla resultante se agitó durante la noche a ta. La mezcla se concentró y el residuo se acidificó con ácido clorhídrico 1 M. La mezcla se extrajo con DCM y la fase orgánica se lavó con agua, se secó y se concentró dando 1-(3-bromo-2-metilfenil)piperidin-2-ona como un aceite color castaño (1.4 g, 97%). RMN de ^1H (400 MHz, cloroformo-d) δ 7.49 - 7.54 (1 H, m), 7.07 - 7.13 (2 H, m), 3.38 - 3.60 (2 H, m), 2.44 - 2.49 (2 H, m), 2.26 (3 H, s), 1.91 - 2.02 (4 H, m). Espectro de masas m/z 268, 270 $(M+H)^+$.

Intermedio 28-1

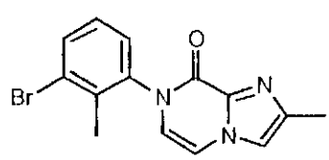
Preparación de N-(3-bromo-2-metilfenil)ciclopropanocarboxamida

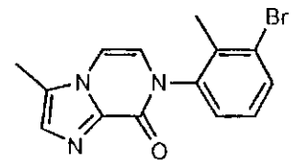


Se trató una solución de 3-bromo-2-metilanilina (2.00 g, 10.75 mmol) en DCM (20 ml) con TEA (3.00 ml, 21.50 mmol) y luego con una solución de cloruro de 4-bromobutanoilo (2.392 g, 12.90 mmol) en DCM (10 ml), y la mezcla resultante se agitó a ta. Después de 2.4 h, la mezcla se diluyó con DCM, se lavó con NaHCO3 (ac) y agua y se secó y concentró. El residuo se disolvió en THF (20 ml) y se trató con hexano-lavó con hidruro sódico (dispersión al 60% en aceite, 0.860 g, 21.50 mmol). La mezcla se agitó a ta durante 1.5 h, luego se concentró. El residuo se disolvió en DCM, se lavó con agua, ácido clorhídrico 1 M y salmuera y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano-EtOAc 80:20 hasta EtOAc) proporcionando N-(3-bromo-2-metilfenil)ciclopropanocarboxamida (900 mg, 33%) como un sólido blanco. Espectro de masas m/z 254, 256 $(M+H)^+$.

Intermedio 29-1 y 29-2

Preparación de 7-(3-bromo-2-metilfenil)-2-metilimidazo[1,2-a]pirazin-8(7H)-ona y 7-(3-bromo-2-metilfenil)-3-metilimidazo[1,2-a]pirazin-8(7H)-ona

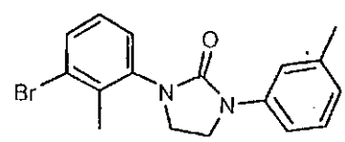




Siguiendo los procedimientos usados para preparar el Intermedio 11-1 pero sustituyendo ácido 1H-imidazol-2-carboxílico por ácido 4-metil-1H-imidazol-2-carboxílico, se preparó una mezcla de 7-(3-bromo-2-metilfenil)-2-metilimidazo[1,2-a]pirazin-8(7H)-ona y 7-(3-bromo-2-metilfenil)-3-metilimidazo[1,2-a]pirazin-8(7H)-ona con un rendimiento total de 5%. Espectro de masas m/z 318, 320 $(M+H)^+$.

Intermedio 30-1

Preparación de 1-(3-bromo-2-metilfenil)-3-m-tolilimidazolidin-2-ona

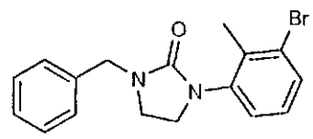


Una suspensión de 1,3-dibromo-2-metilbenceno (185 mg, 0.740 mmol), 1-m-tolilimidazolidin-2-ona (50 mg, 0.284 mmol), yoduro de cobre (I) (5.40 mg, 0.028 mmol), trifosfato potásico (120 mg, 0.567 mmol) y (+/-)-*trans*-1,2-

diaminociclohexano (3.4 µl, 0.028 mmol) en 1,4-dioxano (1 ml) se purgó con nitrógeno y se calentó a 120°C en un tubo sellado. Después de 21.5 h, la mezcla se concentró y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano a 50:50 de hexano-EtOAc) proporcionando 1-(3-bromo-2-metilfenil)-3-m-tolilimidazolidin-2-ona como un sólido blanco (70 mg, 70%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.51 - 7.54 (1 H, m), 7.49 (1 H, s), 7.34 (1 H, dd, J=8.05, 1.94 Hz), 7.24 (2 H, d, J=8.05 Hz), 7.11 (1 H, t, J=7.91 Hz), 6.90 (1 H, d, J=7.49 Hz), 3.98 - 4.04 (2 H, m), 3.81 - 3.87 (2 H, m), 2.38 (3 H, s), 2.36 (3 H, s). Espectro de masas m/z 345, 347 $(M+H)^+$.

Intermedio 30-2

Preparación de 1-bencil-3-(3-bromo-2-metilfenil)imidazolidin-2-ona



Etapa 1 Una solución de imidazolidin-2-ona (500 mg, 5.81 mmol) en DMF (30 mL) se agitó en hielo y se trató con hidruro de sodio, dispersión en aceite al 60% (264 mg, 6.60 mmol). La mezcla se agitó a ta durante 50 minutos, luego se trató con (bromometil)benceno (0.691 mL, 5.81 mmol). Después de dos horas, la mezcla se vertió en agua y se extrajo tres veces con EtOAc. Las capas orgánicas combinadas se secaron y

concentraron, y el residuo se purificó mediante cromatografía en columna (eluyendo con EtOAc) para proporcionar 1-bencilimidazolidin-2-ona como un sólido blanco (160 mg, 16%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.22 - 7.39 (5 H, m), 4.53 (1 H, br. s), 4.37 (2 H, s), 3.25 - 3.46 (4 H, m).

Etapa 2 Una mezcla de 1,3-dibromo-2-metilbenceno (0.147 mL, 1.064 mmol), 1-bencilimidazolidin-2-ona (75 mg, 0.426 mmol), yoduro de cobre (I) (8.11 mg, 0.043 mmol), (+/-)-*trans*-1,2-diaminociclohexano (5.1 µl, 0.043 mmol) y trifosfato potásico (181 mg, 0.851 mmol)en dioxano (2 ml) se sonificó mientras se burbujeaba con argón durante 1 minuto. La mezcla se calentó en un tubo sellado a 120°C. Después de 18.25 horas, la mezcla se enfrió a ta, se diluyó con EtOAc y se filtró a través de Celite. El filtrado se concentró y el residuo se purificó mediante cromatografía en columna (eluyendo con un gradiente de 20:80 de EtOAc-hexano a EtOAc) para proporcionar 1-bencil-3-(3-bromo-2-metilfenil)imidazolidin-2-ona como un sólido blanco ceroso (36 mg, 25%). RMN de ^{1}H (400 MHz, cloroformo-d) δ7.49 (1 H, dd, J=7.9, 0.9 Hz), 7.28 - 7.40 (5 H, m), 7.19 (1 H, dd, J=7.8, 1.0 Hz), 7.08 (1 H, t, J=7.9 Hz), 4.46 (2 H, s), 3.64 (2 H, dd, J=8.8, 6.8 Hz), 3.37 (2 H, dd, J=8.8, 7.0 Hz), 2.36 (3 H, s). Espectro de masas m/z 346.8 $(M+H)^+$.

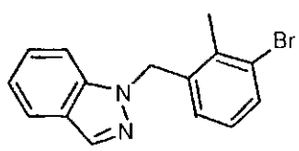
Los siguientes intermedios también se prepararon usando procedimientos usados para preparar los Intermedios

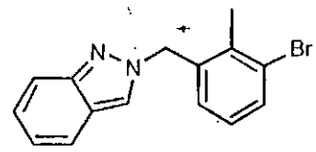
30-1 y 30-2.

Intermedio	Nombre del compuesto	Espectro de masas
30-3	1-(3-bromo-2-metilfenil)-3-fenilimidazolidin-2-ona	331, 333 $(M+H)^+$
30-4	1-(3-bromo-2-metilfenil)-3-terc-butilimidazolidin-2-ona	311, 313 $(M+H)^+$

Intermedios 31-1 y 31-2

Preparación de 1-(3-bromo-2-metilbencil)-1H-indazol y 2-(3-bromo-2-metilbencil)-2H-indazol



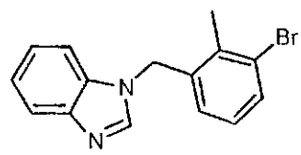


Se calentó con agitación a 80°C una mezcla de 1-bromo-3-(bromometil)-2-metilbenceno (preparado de acuerdo con los procedimientos expuestos en la solicitud de patente de Estados Unidos 2006/0173183, 250 mg, 0.947 mmol), 1H-indazol (112 mg, 0.947 mmol) y carbonato potásico (131 mg, 0.947 mmol) en acetonitrilo (5 ml). Después de 18.25 h, la mezcla se enfrió hasta ta, se diluyó con agua y se extrajo tres veces con EtOAc. Las fases orgánicas reunidas se secaron y concentraron. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 95:5 a 65:35 de hexano-EtOAc) proporcionando 1-(3-bromo-2-metilbencil)-1H-indazol

como un aceite que cristalizó en reposo (Intermedio 31-1, 74 mg, 26%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.06 (1 H, d, J=0.9 Hz), 7.76 (1 H, dt, J=8.1, 1.0 Hz), 7.48 (1 H, d, J=7.9 Hz), 7.30 - 7.37 (1 H, m), 7.26 - 7.30 (1 H, m), 7.16 (1 H, ddd, J=8.0, 6.8, 1.0 Hz), 6.93 (1 H, t, J=7.8 Hz), 6.70 (1 H, d, J=7.7 Hz), 5.61 (2 H, s), 2.45 (3 H, s). Espectro de masas m/z 301, 303 $(M+H)^+$. También se obtuvo 2-(3-bromo-2-metilbencil)-2H-indazol como una goma amarillo pálido (Intermedio 31-2, 164 mg, 58%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.68 - 7.76 (2 H, m), 7.54 - 7.63 (2 H, m), 7.28 (1 H, ddd, J=8.2, 7.2, 1.1 Hz), 6.97 - 7.10 (3 H, m), 5.63 (2 H, s), 2.37 (3 H, s). Espectro de masas m/z 301, 303 $(M+H)^+$.

Intermedio 31-3

Preparación de 1-(3-bromo-2-metilbencil)-1H-benzo[d]imidazol

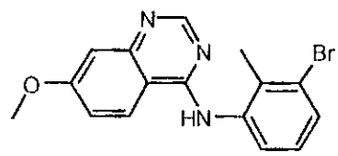


Se agitó a ta durante 5 h una mezcla de 1-bromo-3-(bromometil)-2-metilbenceno (250 mg, 0.947 mmol), 1H-benzo[d]imidazol (336 mg, 2.84 mmol) y carbonato potásico (131 mg, 0.947 mmol) en acetonitrilo (5 ml), la mezcla se diluyó con EtOAc y se filtró y el sólido se lavó con EtOAc. El filtrado se lavó con agua, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo

con un gradiente de 60:40 de hexano-EtOAc hasta EtOAc), proporcionando 1-(3-bromo-2-metilbencil)-1H-benzo[d]imidazol como un sólido blanco (233 mg, 82%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.14 (1 H, s), 7.68 - 7.78 (1 H, m), 7.56 (1 H, d, J=7.9 Hz), 7.36 - 7.44 (1 H, m), 7.25 - 7.34 (2 H, m), 7.03 (1 H, t, J=7.8 Hz), 6.82 (1 H, d, J=7.7 Hz), 5.58 (2 H, s), 2.45 (3 H, s). Espectro de masas m/z 301, 303 $(M+H)^+$.

Intermedio 32-1

Preparación de N-(3-bromo-2-metilfenil)-7-metoxiquinazolin-4-amina



Etapa 1 Se calentó a 130°C una mezcla de ácido 2-amino-4-metoxibenzoico (0.5 g, 2.99 mmol) y acetato de formamidina (0.623 g, 5.98 mmol) en 2-metoxietanol (4 ml). Después de 15.25 h, la mezcla se enfrió hasta ta. El precipitado resultante se recogió por filtración, se lavó con metanol y se secó proporcionando 7-metoxiquinazolin-4-ol como un sólido color castaño (473 mg, 90%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.08 (1 H, s ancho), 8.06 (1 H, s), 8.03 (1 H, d, J=9.5 Hz), 7.03 - 7.14 (2 H, m), 3.90 (3 H, s).

Etapa 2 Se trató una suspensión de 7-metoxiquinazolin-4-ol (400 mg, 2.271 mmol) en oxicloruro de fósforo (7 ml, 75 mmol) a reflujo durante 3 h. La solución se

concentró y el residuo se suspendió en EtOAc y se agitó en un baño de hielo con NaHCO3 (ac) hasta que se disolvió todo el sólido y cesó la generación de gas. Se separaron las fases y la fase orgánica se secó y se concentró proporcionando 4-cloro-7-metoxiquinazolina como un sólido de color amarillo claro-castaño (438 mg, 99%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.94 (1 H, s), 8.15 (1 H, d, J=9.7 Hz), 7.29 - 7.37 (2 H, m), 4.00 (3 H, s).

Etapa 3 Se trató una mezcla de 4-cloro-7-metoxiquinazolina (200 mg, 1.028 mmol) y 3-bromo-2-metilanilina (0.253 ml, 2.055 mmol) en isopropanol (11 ml) con cloruro de hidrógeno (4 M en 1,4-dioxano, 0.385 ml, 1.541 mmol) y se calentó en un tubo sellado por radiación en microondas a 140°C durante 45 min. Al enfriarse se formó un precipitado que se recogió por filtración y se secó a vacío proporcionando la sal clorhidrato de N-(3-bromo-2-metilfenil)-7-metoxiquinazolin-4-amina como un sólido color castaño (281 mg, 68%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.65 (1 H, s), 8.48 (1 H, d, J=9.2 Hz), 7.69 (1 H, dd, J=8.0, 1.0 Hz), 7.51 (1 H, dd, J=9.4, 2.4 Hz), 7.37 (1 H, dd, J=7.9, 0.9 Hz), 7.26 - 7.30 (1 H, m), 7.24 (1 H, d, J=2.4 Hz), 4.08 (3 H, s), 2.36 (3 H, s). Espectro de masas m/z 344, 346 $(M+H)^+$. El filtrado se concentró y el residuo se repartió entre NaHCO3 (ac) y EtOAc. La fase orgánica se secó y se concentró, y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 75:25 a 25:75 de hexano-EtOAc) proporcionando N-(3-bromo-2-metilfenil)-7-metoxiquinazolin-4-amina como un sólido blanquecino (61 mg, 17%). RMN de ^{1}H (400 MHz, cloroformo-d) δ

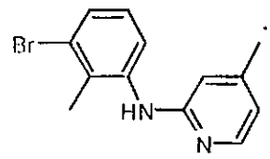
8.64 (1 H, s), 7.76 (1 H, d, J=9.0 Hz), 7.62 (1 H, dd, J=8.0, 0.8 Hz), 7.51 (1 H, dd, J=8.1, 0.9 Hz), 7.08 - 7.20 (3 H, m), 5.30 (1 H, s), 3.96 (3 H, s), 2.41 (3 H, s). Espectro de masas m/z 344, 346 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando procedimientos usados para preparar el Intermedio 32-1.

Intermedio	Nombre del compuesto	Espectro de masas
32-2	N-(3-bromo-2-metilfenil)-6-metilquinazolin-4-amina	328, 330 $(M+H)^+$
32-3	N-(3-bromo-2-metilfenil)-7-fluoroquinazolin-4-amina	332, 334 $(M+H)^+$
32-4	N-(3-bromo-2-metilfenil)-6-fluoroquinazolin-4-amina	332, 334 $(M+H)^+$
32-5	N-(3-bromo-2-metilfenil)-7-metilquinazolin-4-amina	328, 330 $(M+H)^+$
32-6	N-(3-bromo-2-metilfenil)-5-fluoroquinazolin-4-amina	332, 334 $(M+H)^+$
32-7	N-(3-bromo-2-metilfenil)-8-fluoroquinazolin-4-amina	332, 334 $(M+H)^+$
32-8	N-(3-bromo-2-metilfenil)-6-metoxiquinazolin-4-amina	344, 346 $(M+H)^+$
32-9	N-(3-bromo-2-metilfenil)quinazolin-4-amina	314, 316 $(M+H)^+$

Intermedio 33-1

Preparación de N-(3-bromo-2-metilfenil)-4-metilpiridin-2-amina



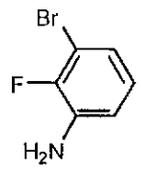
Se calentó una mezcla de 3-bromo-2-metilanilina (200 mg, 1.075 mmol), 2-fluoro-4-metilpiridina (155 mg, 1.397 mmol) y terc-butóxido potásico (193 mg, 1.72 mmol) en DMSO (4 ml) en un tubo sellado mediante radiación en microondas a 190°C durante 40 min. La mezcla se repartió entre EtOAc y agua, y la fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano hasta 85:15 de hexano-EtOAc) proporcionando N-(3-bromo-2-metilfenil)-4-metilpiridin-2-amina como un sólido amarillo (100 mg, 34%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.05 (1 H, d, *J*=5.3 Hz), 7.38 (2 H, d, *J*=8.1 Hz), 7.06 (1 H, t, *J*=8.0 Hz), 6.58 (1 H, d, *J*=5.3 Hz), 6.40 (1 H, s), 6.23 (1 H, s ancho), 2.37 (3 H, s), 2.23 (3 H, s). Espectro de masas m/z 277, 279 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando procedimientos usados para preparar el Intermedio 33-1.

Intermedio	Nombre del compuesto	Espectro de masas
33-2	N-(3-bromo-2-metilfenil)-5-metilpiridin-2-amina	277, 279 $(M+H)^+$
33-3	N-(3-bromo-2-metilfenil)piridin-2-amina	263, 265 $(M+H)^+$
33-4	N-(3-bromo-2-metilfenil)-3-metilpiridin-2-amina	277, 279 $(M+H)^+$

Intermedio 34-1

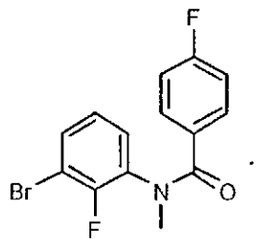
Preparación de 3-bromo-2-fluoroanilina



Se trató una solución de 1-bromo-2-fluoro-3-nitrobenceno (1.10 g, 5.00 mmol) en etanol-ácido acético-agua (2:2:1) (25 ml) con polvo de hierro (1.396 g, 25.0 mmol) y la mezcla se trató a reflujo durante 1 h. La mezcla se enfrió hasta ta y se filtró a través de una almohadilla de Celite. El filtrado se concentró y el residuo se repartió entre EtOAc y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se secó y se concentró proporcionando 3-bromo-2-fluoroanilina como un aceite marrón (880 mg, 93%). RMN de ^1H (400 MHz, cloroformo-d) δ 6.85 - 6.92 (1 H, m), 6.80 (1 H, td, J=8.0, 1.2 Hz), 6.66 - 6.73 (1 H, m), 3.81 (2 H, s ancho).

Intermedio 35-1

Preparación de N-(3-bromo-2-fluorofenil)-4-fluoro-N-metilbenzamida



Etapa 1 Se calentó una solución de Intermedio 34-1 (205 mg, 1.079 mmol) en ácido fórmico (0.611 ml, 16.18 mmol) a 90°C durante 5.5 h. La mezcla se concentró y se repartió entre EtOAc y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se secó y se concentró, y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 85:15 a 70:30 de hexano-EtOAc) proporcionando N-(3-bromo-2-fluorofenil)formamida como un sólido blanquecino (216 mg, 92%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.49 (1 H, s), 8.27 - 8.37 (1 H, m), 7.44 (1 H, s ancho), 7.30 (1 H, ddd, *J*=8.1, 6.6, 1.5 Hz), 7.04 (1 H, td, *J*=8.2, 1.5 Hz), 1.58 (3 H, s). Espectro de masas m/z 218, 220 $(M+H)^+$.

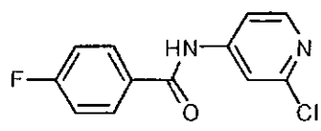
Etapa 2 Se trató una suspensión de N-(3-bromo-2-fluorofenil)formamida (216 mg, 0.991 mmol) en THF (8 ml) con complejo de borano-sulfuro de metilo (2.0 M en THF, 1.486 ml, 2.97 mmol) y la mezcla resultante se trató a reflujo durante 2 h. Se añadió ácido clorhídrico 1 M y la mezcla se calentó de nuevo a reflujo durante 1 h. La mezcla se enfrió hasta ta

y se concentró y el residuo se repartió entre NaHCO3 (ac) y EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró proporcionando 3-bromo-2-fluoro-N-metilanilina como un aceite amarillo claro (60 mg, 30%). Espectro de masas m/z 204, 206 $(M+H)^+$.

Etapa 3 Se trató una solución de 3-bromo-2-fluoro-N-metilanilina (32 mg, 0.157 mmol) y diisopropilamina (0.055 ml, 0.314 mmol) en DCM (2 ml) con cloruro de 4-fluorobenzoilo (0.028 ml, 0.235 mmol) y la mezcla se agitó a ta durante 2 h. La mezcla se repartió entre DCM y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 90:10 a 80:20 de hexano-EtOAc) proporcionando N-(3-bromo-2-fluorofenil)-4-fluoro-N-metilbenzamida como un sólido blanco (35 mg, 68%). Espectro de masas m/z 326, 328 $(M+H)^+$.

Intermedio 35-2

Preparación de N-(2-cloropiridin-4-il)-4-fluorobenzamida

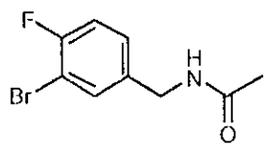


Una solución de 2-bromopiridin-4-amina (500 mg, 2.89 mmol) en piridina (8 ml) se agitó en hielo y se trató con cloruro de 4-fluorobenzoilo (0.376 ml, 3.18 mmol). La solución resultante se agitó a ta durante 20.25 h, luego se

concentró y el residuo se repartió entre EtOAc y agua. La fase orgánica se lavó con NaHCO3 (ac) y agua, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 80:20 a 20:80 de hexano-EtOAc) proporcionando N-(2-cloropiridin-4-il)-4-fluorobenzamida como un sólido vítreo blanco (532 mg, 73%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.29 (d, J=5.5 Hz, 1 H) 8.14 (s ancho,1 H) 7.89 (dd, J=8.8, 5.1 Hz, 2 H) 7.77 (d, J=2.0 Hz, 1 H) 7.48 (dd, J=5.7, 2.0 Hz, 1 H) 7.18 (t, J=8.6 Hz, 2 H). Espectro de masas m/z 251, 253 $(M+H)^+$.

Intermedio 35-3

Preparación de N-(3-bromo-4-fluorobencil)acetamida

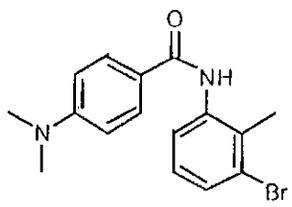


Una solución de sal clorhidrato de (3-bromo-4-fluorofenil)metanamina (500 mg, 2.079 mmol) en piridina (6 ml) se agitó en hielo y se trató con anhídrido acético (0.235 ml, 2.495 mmol). La solución resultante se agitó a ta durante 17 h, luego se concentró. El residuo se agitó en ácido clorhídrico 1 M, formando un precipitado que se recogió por filtración, se aclaró con agua y se secó proporcionando N-(3-bromo-4-fluorobencil)acetamida como un sólido blanco (435 mg, 85%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.47 (dd, J=6.6, 2.2 Hz, 1 H) 7.20 (ddd, J=8.6, 4.6, 2.2 Hz, 1 H) 7.07 (t,

J=8.3 Hz, 1 H) 5.84 (s ancho,1 H) 4.38 (d, J=5.9 Hz, 2 H) 2.04 (s, 3 H). Espectro de masas m/z 246, 248 $(M+H)^+$.

Intermedio 35-4

Preparación de N-(3-bromo-2-metilfenil)-4-(dimetilamino)benzamida



Se trató una suspensión de ácido 4-(dimetilamino)benzoico (100 mg, 0.605 mmol) en DCM (3 ml) con 1-cloro-N,N,2-trimetilprop-1-en-1-amina (0.120 ml, 0.908 mmol) y la solución resultante se agitó a ta durante 1.5 h. Se añadió 3-bromo-2-metilanilina (0.053 ml, 0.432 mmol), seguido por DIEA (0.264 ml, 1.513 mmol). La mezcla se agitó a ta durante 1 h, luego se diluyó con DCM y NaHCO3 (ac). Se separaron las fases y la fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 85:15 a 65:35 de hexano-EtOAc) proporcionando N-(3-bromo-2-metilfenil)-4-(dimetilamino)benzamida como un sólido amarillo claro (77 mg, 53%). RMN de ^1H (400 MHz, DMSO-d_6) δ 9.75 (s, 1 H) 7.85 (d, J=9.0 Hz, 2 H) 7.49 (dd, J=8.0, 1.0 Hz, 1 H) 7.30 (dd, J=7.9, 0.9 Hz, 1 H) 7.15 (t, J=7.9 Hz, 1 H) 6.75 (d, J=9.0 Hz, 2 H) 2.99 (s, 6 H) 2.25 (s, 3 H). Espectro de masas

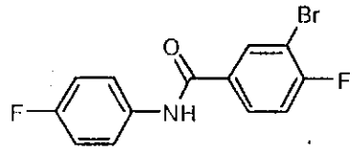
m/z 331, 333 $(M-H)^-$.

Los siguientes Intermedios se prepararon también usando procedimientos usados para preparar los Intermedios 35-1 a 35-4.

Intermedio	Nombre del compuesto	Espectro de masas
35-5	N-(3-bromo-4-fluorofenil)acetamida	232, 234 $(M+H)^+$
35-6	N-(3-bromofenil)-4-fluorobenzamida	294, 296 $(M+H)^+$
35-7	N-(3-bromo-2-fluorofenil)-4-fluorobenzamida	312, 314 $(M+H)^+$
35-8	N-(3-bromo-2-fluorofenil)-4-(dimetilamino)benzamida	337, 339 $(M+H)^+$
35-9	N-(3-bromofenil)-4-fluoro-N-metilbenzamida	308, 310 $(M+H)^+$
35-10	N-(5-bromo-2-fluorofenil)-4-fluorobenzamida	312, 314 $(M+H)^+$
35-11	N-(3-bromo-4-fluorofenil)-4-fluorobenzamida	312, 314 $(M+H)^+$
35-12	N-(3-bromo-4-fluorobencil)-4-fluorobenzamida	326, 328 $(M+H)^+$
35-13	N-(3-bromo-2-fluorofenil)acetamida	232, 234 $(M+H)^+$

Intermedio 36-1

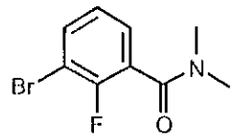
Preparación de 3-bromo-4-fluoro-N-(4-fluorofenil)benzamida



Una solución de ácido 3-bromo-4-fluorobenzoico (976 mg, 4.46 mmol) en DCM (25 ml) se agitó a ta y se trató con cloruro de oxalilo (1.950 ml, 22.28 mmol), seguido por una gota de DMF, provocando el comienzo de generación de gas. Después de 2.4 h, la solución se calentó hasta ebullición durante 1-2 minutos y se dejó enfriar hasta ta. Después de 3 h en total, la solución se concentró proporcionando cloruro de 3-bromo-4-fluorobenzoilo como un sólido blanco (1.00 g, 94%). Una parte de este material (200 mg, 0.842 mmol) se añadió a una solución enfriada en hielo de 4-fluoroanilina (0.081 ml, 0.842 mmol) en piridina (4 ml), y la solución se agitó a ta durante 65 h. La solución se concentró y el residuo se agitó en ácido clorhídrico 1 M, formando un precipitado que se recogió por filtración, se lavó con agua y se secó proporcionando 3-bromo-4-fluoro-N-(4-fluorofenil)benzamida como un sólido blanquecino (227.5 mg, 80%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 10.38 (s, 1 H) 8.29 (dd, J=6.7, 2.1 Hz, 1 H) 8.01 (ddd, J=8.6, 4.8, 2.2 Hz, 1 H) 7.75 (dd, J=9.0, 5.1 Hz, 2 H) 7.55 (t, J=8.6 Hz, 1 H) 7.20 (t, J=8.9 Hz, 2 H). Espectro de masas m/z 312, 314 $(M+H)^+$.

Intermedio 36-2

Preparación de 3-bromo-2-fluoro-N,N-dimetilbenzamida



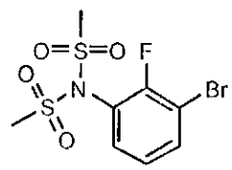
Una suspensión de ácido 3-bromo-2-fluorobenzoico (1.009 g, 4.61 mmol) en DCM (25 ml) se agitó a ta y se trató con cloruro de oxalilo (2.016 ml, 23.04 mmol), seguido por una gota de DMF, provocando el comienzo de generación de gas. Después de 2.4 h, la solución se calentó hasta ebullición durante 1-2 min y se dejó enfriar hasta ta. Después de 3 h en total, la solución se concentró proporcionando cloruro de 3-bromo-2-fluorobenzoilo como un líquido amarillo oscuro (1.078 g, 99%). Una parte de este (200 mg, 0.842 mmol) se disolvió en THF (1.5 ml) y se añadió a una solución de dimetilamina (2 M en metanol, 2.0 ml, 4.00 mmol) en THF (2 ml). La mezcla se agitó a ta durante 18 h, luego se concentró. El residuo se disolvió en EtOAc, se lavó secuencialmente con ácido clorhídrico 1 M, NaHCO3 (ac) y salmuera, y se secó y concentró proporcionando 3-bromo-2-fluoro-N,N-dimetilbenzamida como un aceite amarillo claro (192 mg, 93%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.60 (ddd, J=8.1, 6.5, 1.6 Hz, 1 H) 7.32 (ddd, J=7.6, 5.9, 1.6 Hz, 1 H) 7.09 (td, J=7.8, 0.7 Hz, 1 H) 3.14 (s, 3 H) 2.93 (d, J=1.5 Hz, 3 H). Espectro de masas m/z 246, 248 $(M+H)^+$.

Los siguientes Intermedios se prepararon también usando procedimientos usados para preparar los Intermedios 36-1 y 36-2.

Intermedio	Nombre del compuesto	Espectro de masas
36-3	3-bromo-2-fluoro-N-(4-fluorofenil)benzamida	312, 314 $(M+H)^+$
36-4	3-bromo-4-fluorobenzamida	218, 220 $(M+H)^+$
36-5	3-bromo-2-fluorobenzamida	218, 220 $(M+H)^+$
36-6	3-bromo-2-fluoro-N-metilbenzamida	232, 234 $(M+H)^+$
36-7	3-bromo-4-fluoro-N,N-dimetilbenzamida	246, 248 $(M+H)^+$

Intermedio 37-1

Preparación de N-(3-bromo-2-fluorofenil)-N-(metilsulfonil)metanosulfonamida

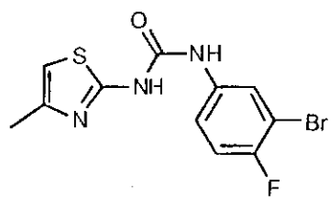


Una solución de 3-bromo-2-fluoroanilina (Intermedio 34-1, 160 mg, 0.842 mmol) y DIEA (0.368 ml, 2.105 mmol) en DCM (3 ml) se agitó a aproximadamente -5°C y se trató con

cloruro de metanosulfonilo (0.098 ml, 1.263 mmol) y se agitó a esta temperatura durante 2 h. La mezcla se repartió entre DCM y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se secó y se concentró proporcionando N-(3-bromo-2-fluorofenil)-N-(metilsulfonil)metanosulfonamida como un sólido amarillo (308 mg, cuantitativo), que se usó sin purificación posterior. RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.70 (1 H, ddd, *J*=8.1, 6.4, 1.5 Hz), 7.33 (1 H, ddd, *J*=8.1, 6.5, 1.6 Hz), 7.15 (1 H, td, *J*=8.1, 1.4 Hz), 3.46 (6 H, s). Espectro de masas m/z 363, 365 $(M+NH_4)^+$.

Intermedio 38-1

Preparación de 1-(3-bromo-4-fluorofenil)-3-(4-metiltiazol-2-il)urea



Etapa 1 Una solución de 2-amino-4-metiltiazol (11.42 g, 0.10 mol) en DCM se enfrió hasta 0 °C y se trató con TEA (12.1 g, 0.12 mol), luego se añadió gota a gota con agitación cloroformiato de fenilo (15.6 g, 0.10 mol). La mezcla se agitó durante 10 minutos, luego se lavó con NaHCO3 (ac), agua y salmuera y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo con 60:40 de hexano-EtOAc) dando 4-metiltiazol-2-ilcarbamato de fenilo

como un sólido blanco (12 g, 51%). RMN de ^{1}H (300 MHz, cloroformo-d) δ 12.38 (s ancho, 1 H) 7.47-7.40 (m, 2 H) 7.30-7.19 (m, 3 H) 6.52 (d, J = 1.1 Hz, 1 H) 2.41 (d, J = 0.8 Hz, 3 H).

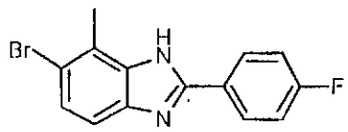
Etapa 2 Una solución de 3-bromo-4-fluoroanilina (250 mg, 1.316 mmol) en THF (6 ml) se agitó en hielo y se trató con TEA (0.367 ml, 2.63 mmol), luego con 4-metiltiazol-2-ilcarbamato de fenilo (308 mg, 1.316 mmol) y la solución resultante se agitó a ta durante 70 h. La mezcla se concentró y el residuo se agitó en ácido clorhídrico 1 M, formando un precipitado que se recogió por filtración, se aclaró con agua y se secó a vacío proporcionando 1-(3-bromo-4-fluorofenil)-3-(4-metiltiazol-2-il)urea como un sólido blanquecino (400 mg, 92%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 9.62 (s, 1 H) 7.94 (dd, J=6.3, 2.4 Hz, 1 H) 7.37 - 7.45 (m, 1 H) 7.32 (t, J=8.7 Hz, 1 H) 6.67 (d, J=1.1 Hz, 1 H) 2.23 (d, J=1.1 Hz, 3 H). Espectro de masas m/z 330, 332 $(M+H)^+$.

El siguiente Intermedio también se preparó usando procedimientos usados para preparar el Intermedio 38-1.

Intermedio	Nombre del compuesto	Espectro de masas
38-2	1-(3-bromo-4-fluorobencil)-3-(4-metiltiazol-2-il)urea	344, 346 $(M+H)^+$

Intermedio 39-1

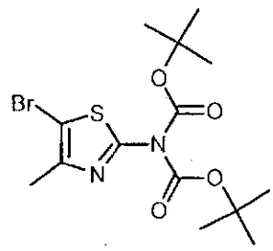
Preparación de 6-bromo-2-(4-fluorofenil)-7-metil-1H-benzo[d]imidazol



Se trató una solución de 4-bromo-3-metilbenceno-1,2-diamina (preparado de acuerdo con el procedimiento de la solicitud de patente PCT WO 2008/021851, (400 mg, 1.989 mmol) en DCM (10 ml) con TEA (0.693 ml, 4.97 mmol), luego se trató gota a gota con cloruro de 4-fluorobenzoilo (0.282 ml, 2.387 mmol). La mezcla se agitó a ta durante 70 min, luego se concentró. El residuo se suspendió en etanol (25 ml), se trató con ácido clorhídrico concentrado (3 ml, 36.5 mmol) y se calentó a 90-95°C. Después de 42.4 h, la mezcla se enfrió hasta ta y el etanol se eliminó a vacío. La pasta residual se suspendió en agua y se ajustó el pH a aproximadamente 8 con NaHCO3 (ac). El precipitado se recogió por filtración, se lavó con agua y se secó a vacío proporcionando 6-bromo-2-(4-fluorofenil)-7-metil-1H-benzo[d]imidazol como un sólido rosa pálido (636 mg, 95%). RMN de ^1H (400 MHz, DMSO-d_6) δ 8.24 (2 H, dd, J=8.9, 5.4 Hz), 7.33 - 7.45 (4 H, m), 2.47 (3 H, s). Espectro de masas m/z 305, 307 $(M+H)^+$.

Intermedio 40-1

Preparación de N,N-bis(*terc*-butiloxicarbonil)-5-bromo-4-metiltiazol-2-ilamina



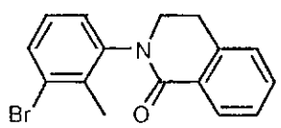
Etapa 1 Se trató una solución de 5-bromo-4-metiltiazol-2-amina (2.00 g, 10.36 mmol) en piridina (10 ml) en varias porciones a ta con dicarbonato de di-*terc*-butilo (2.487 g, 11.40 mmol). Después de agitar a ta durante la noche quedaba bastante material de partida. La mezcla se enfrió hasta 0°C y se trató con hexametildisilazida de litio (1 M en THF, 25.9 ml, 25.9 mmol) seguido por dicarbonato de di-*terc*-butilo (2.487 g, 11.40 mmol). La mezcla se calentó hasta ta durante 1 h, luego se diluyó con EtOAc, se lavó dos veces con ácido clorhídrico 0.5 M, luego con hidróxido sódico acuoso 1 M, se secó y se concentró. La purificación del residuo por cromatografía en columna (elución con hexano-EtOAc) proporcionó 5-bromo-4-metiltiazol-2-ilcarbamato de terc-butilo (814 mg, 27%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 2.27 (3 H, s), 1.53 (9 H, s). Espectro de masas m/z 293, 295 $(M+H)^+$.

Etapa 2 Una mezcla de dicarbonato de di-terc-butilo (667 mg, 3.05 mmol), 5-bromo-4-metiltiazol-2-ilcarbamato de

terc-butilo (814 mg, 2.78 mmol) y DMAP (339 mg, 2.78 mmol) en DCM (10 ml) se agitó a ta durante la noche. La mezcla se concentró y el residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc) proporcionando N,N-bis(*terc*-butiloxicarbonil)-5-bromo-4-metiltiazol-2-ilamina. Espectro de masas m/z 393, 395 $(M+H)^+$.

Intermedio 41-1

Preparación de 2-(3-bromo-2-metilfenil)-3,4-dihidroisoquinolin-1(2H)-ona



Etapa 1 Se trató una solución de 2,3-dihidro-1H-inden-1-ona (1 g, 7.57 mmol) en DCM (10 ml) con ácido metanosulfónico (10 ml) y se enfrió hasta 0°C. Se añadió azida de sodio (0.984 g, 15.13 mmol) y la mezcla se agitó a 0°C durante 2 h, luego a ta durante la noche. La mezcla se basificó con hidróxido sódico acuoso al 20% y se extrajo con DCM. La fase orgánica se lavó con agua, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc) proporcionando 3,4-dihidroquinolin-2(1H)-ona como un sólido blanco (655 mg, 60%). RMN de ^1H (400 MHz, metanol-d_4) δ 7.08 - 7.19 (2 H, m), 6.92 - 6.99 (1 H, m), 6.85 (1 H, d, J=7.9 Hz), 5.47 (1 H, s), 2.92 (2 H, t, J=7.6 Hz), 2.49 - 2.48 (2 H, m). Espectro de masas m/z 148.1 $(M+H)^+$. También se obtuvo 3,4-

dihidroisoquinolin-1(2H)-ona como un aceite incoloro (162 mg, 15%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.93 (1 H, dd, J=7.8, 1.0 Hz), 7.44 - 7.52 (1 H, m), 7.35 (1 H, td, J=7.6, 1.2 Hz), 7.29 (1 H, d, J=7.7 Hz), 3.50 (2 H, t, J=6.6 Hz), 2.98 (2 H, t, J=6.7 Hz). Espectro de masas m/z 148.1 $(M+H)^+$.

Etapa 2 Se purgó con nitrógeno una mezcla de 1,3-dibromo-2-metilbenceno (340 mg, 1.359 mmol), 3,4-dihidroisoquinolin-1(2H)-ona (100 mg, 0.679 mmol) y carbonato potásico (94 mg, 0.679 mmol) en DMSO (2 ml), se trató con yoduro de cobre (I) (25.9 mg, 0.136 mmol) y se calentó a 150°C durante 3.5 h. La mezcla se combinó con la de una segunda reacción usando 1,3-dibromo-2-metilbenceno (2.49 g, 10.36 mmol) y 3,4-dihidroisoquinolin-1(2H)-ona (508 mg, 3.45 mmol), se diluyó con DCM y se filtró a través de Celite. El filtrado se lavó con hidróxido amónico acuoso al 5%, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc) proporcionando 2-(3-bromo-2-metilfenil)-3,4-dihidroisoquinolin-1(2H)-ona como un sólido amarillo (142 mg, 11%),RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.15 (1 H, dd, J=7.70, 1.10 Hz), 7.55 (1 H, dd, J=7.92, 1.10 Hz), 7.46 - 7.51 (1 H, m), 7.37 - 7.42 (1 H, m), 7.24 - 7.28 (1 H, m), 7.17 - 7.21 (1 H, m), 7.09 - 7.16 (1 H,

m), 3.95 (1 H, ddd, J=12.21, 10.12, 4.73 Hz), 3.73 (1 H, ddd, J=11.94, 6.33, 5.28 Hz), 3.26 (1 H, ddd, J=15.74, 10.23, 5.28 Hz), 3.06 - 3.14 (1 H, m), 2.36 (3 H, s). Espectro de masas m/z 316, 318 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando procedimientos usados para preparar el Intermedio 41-1.

Intermedio	Nombre del compuesto	Espectro de masas
41-2	2-(3-bromo-2-metilfenil)-6-metoxi-3,4-dihidroisoquinolin-1(2H)-ona	346, 348 $(M+H)^+$
41-3	2-(3-bromo-2-metilfenil)-5-hidroxi-3,4-dihidroisoquinolin-1(2H)-ona	332, 334 $(M+H)^+$
41-4[a]	5-(3-bromo-2-metilfenoxi)-3,4-dihidroisoquinolin-1(2H)-ona	332, 334 $(M+H)^+$
41-5	2-(3-bromo-2-metilfenil)-7-cloro-3,4-dihidroisoquinolin-1(2H)-ona	350, 352 $(M+H)^+$
41-6	2-(3-bromo-2-metilfenil)-6-fluoro-3,4-dihidroisoquinolin-1(2H)-ona	334, 336 $(M+H)^+$

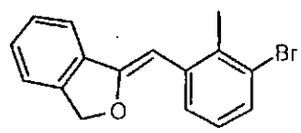
[a] Obtenido a partir de la misma reacción usada para preparar el Intermedio 41-3

Los siguientes intermedios también se prepararon usando procedimientos de la Etapa 2 usados para preparar el Intermedio 41-1.

Intermedio	Nombre del compuesto	Espectro de masas
41-7	1-(3-bromo-2-metilfenil)-3,4-dimetil-1H-pirrol-2(5H)-ona	280, 282 $(M+H)^+$
41-8	1-(3-bromo-2-metilfenil)-3-metilpiridin-2(1H)-ona	278, 280 $(M+H)^+$
41-9	1-(3-bromo-2-metilfenil)-4.4-dimetilpirrolidin-2-ona	282, 284 $(M+H)^+$
41-10	ácido 1-(3-bromo-2-metilfenil)-5-oxopirrolidin-3-carboxílico	298, 300 $(M+H)^+$

Intermedio 42-1

Preparación de 1-(3-bromo-2-metilbenciliden)-1,3-dihidroisobenzofurano



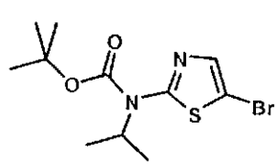
Etapa 1 Se purgó con nitrógeno una mezcla de (2-etinilfenil)metanol (100 mg, 0.757 mmol), 1,3-dibromo-2-metilbenceno (189 mg, 0.757 mmol) y TEA (0.211 ml, 1.513 mmol) en THF (2 ml) y se trató con yoduro de cobre (I) (2.88 mg, 0.015 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (26.6 mg, 0.038 mmol). La mezcla se calentó en un tubo sellado a 60°C durante 1.5 h. La mezcla se filtró, el filtrado se lavó con NaHCO3 (ac) y agua y se secó y

concentró. El residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc) proporcionando (2-((3-bromo-2-metilfenil)etinil)fenil)metanol como un sólido blanco (130 mg., 57%). RMN de ^{1}H (400 MHz, cloróformo-d) δ 7.44 - 7.58 (4 H, m), 7.39 (1 H, td, J=7.54, 1.43 Hz), 7.27 - 7.34 (1 H, m), 7.00 - 7.09 (1 H, m), 4.93 (2 H, d, J=6.38 Hz), 2.64 (3 H, s). Espectro de masas m/z 323, 325 $(M+Na)^+$.

Etapa 2 Se calentó una solución de (2-((3-bromo-2-metilfenil)etinil)fenil)-metanol (50 mg, 0.166 mmol) y fluoruro de tetrabutilamonio, 1.0 M en THF (0.332 ml, 0.332 mmol) en THF (0.5 ml) a 67°C durante 2 h. La mezcla se diluyó con EtOAc, se lavó dos veces con agua y una vez con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano hasta 80:20 de EtOAc-hexano) proporcionando 1-(3-bromo-2-metilbenciliden)-1,3-dihidroisobenzofuran como un sólido amarillo claro (36 mg, 72%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 8.00 - 8.06 (1 H, m), 7.58 - 7.64 (1 H, m), 7.32 - 7.41 (4 H, m), 7.04 (1 H, t, J=7.92 Hz), 6.07 (1 H, s), 5.49 (2 H, s), 2.41 (3 H, s). Espectro de masas m/z 301, 303 $(M+H)^+$.

Intermedio 43-1

Preparación de 5-bromotiazol-2-il(isopropil)carbamato de terc-butilo



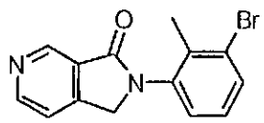
Etapa 1 Se añadió dicarbonato de di-terc-butilo (28.90 g, 132.4 mmol) en varias porciones a una suspensión de bromhidrato de 2-amino-5-bromotiazol (28.64 g, 110.3 mmol) en piridina (100 ml) durante 20 min a ta. La mezcla se agitó a ta durante la noche, luego se concentró. El residuo se repartió entre ácido clorhídrico 0.5 M (200 ml) y EtOAc (200 ml). La fase orgánica se secó y se concentró, y el residuo se filtró a través de una almohadilla de gel de sílice usando hexano-EtOAc 90:10. El filtrado se concentró dando 5-bromotiazol-2-ilcarbamato de terc-butilo como un sólido blanco (19.5 g, 63%). RMN de ^1H (400 MHz, cloroformo-d) δ 7.27 (s, 1 H) 1.60 (s, 9 H). Espectro de masas m/z 223, 225 $(M+H)^+$.

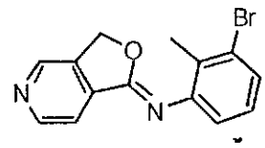
Etapa 2 Se trató una solución de 5-bromotiazol-2-ilcarbamato de terc-butilo (3 g, 10.7 mmol), isopropanol (6.40 g, 107.4 mmol) y trifenilfosfina (5.63 g, 21.5 mmol) en THF (30 ml) con azodicarboxilato de dietilo (3.74 g, 21.5 mmol) gota a gota a 0°C y se agitó durante la noche mientras se calentaba lentamente hasta ta. La mezcla se concentró y el residuo se disolvió en DCM (20 ml), se filtró para eliminar el sólido sin disolver y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con hexano) dando 5-bromotiazol-2-il(isopropil)carbamato de terc-butilo como un aceite amarillo claro (3.10 g, 90%). RMN de ^1H (400 MHz, cloroformo-d) δ 7.34 (s, 1 H), 5.29 (m, 1 H) 1.59 (s, 9 H)

1.45 (d, 6.8 Hz, 6 H). Espectro de masas m/z 265, 267 $(M+H-C_4H_9)^+$.

Intermedios 44-1 y 44-2

Preparación de 2-(3-bromo-2-metilfenil)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-1-ona y (Z)-3-bromo-N-(furo[3,4-c]piridin-1(3H)-iliden)-2-metilanilina



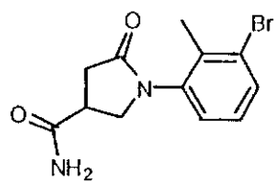


Se trató una suspensión de 2-(3-bromo-2-metilfenil)-1H-pirrolo[3,4-c]piridin-1,3(2H)-diona (4.7 g, 14.82 mmol) en metanol (200 ml) con borohidruro sódico (2 g, 52.9 mmol) y se agitó a ta durante 1 h. La mezcla se concentró y el residuo se trató con NaHCO3 (ac). La mezcla se extrajo varias veces con una mezcla de DCM y metanol. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron dando una mezcla de N-(3-bromo-2-metilfenil)-4-(hidroximetil)-nicotinamida y N-(3-bromo-2-metilfenil)-3-(hidroximetil)isonicotinamida como un sólido blanquecino. Espectro de masas m/z 321, 323 $(M+H)^+$. Sin purificación, este material se suspendió en THF (250 ml) y se trató con trifenilfosfina (soportada en polímero, 3 mmol P/g de resina, 18.44 g, 54.8 mmol) y azodicarboxilato de dietilo (6.45 g, 37.1 mmol) y la mezcla se agitó a ta durante 4 h. La mezcla se filtró y se concentró, y el residuo se disolvió en DCM, se

lavó con agua, NaHCO3 (ac) y salmuera y se secó y concentró. El residuo se sometió a cromatografía en columna (eluyendo con EtOAc) proporcionando 2-(3-bromo-2-metilfenil)-2,3-dihidro-1H-pirrolo[3,4-c]piridin-1-ona como un sólido blanco (Intermedio 44-1, 2.7 g, 60%), RMN de ^{1}H (400 MHz, cloroformo-d) δ 9.21 (1 H, d, J=0.88 Hz), 8.84 (1 H, d, J=5.06 Hz), 7.63 (1 H, dd, J=7.70, 1.32 Hz), 7.51 (1 H, dd, J=5.06, 0.88 Hz), 7.22 (1 H, dt, J=7.70, 1.32 Hz), 7.17 (1 H, d, J=7.92 Hz), 4.76 (2 H, s), 2.31 (3 H, s). Espectro de masas m/z 303, 305 $(M+H)^+$. También se obtuvo (Z)-3-bromo-N-(furo[3,4-c]piridin-1(3H)-iliden)-2-metilanilina como un sólido blanco (Intermedio 44-2, 760 mg, 17%), que también contenía la (Z)-3-bromo-N-(furo[3,4-c]piridin-3(1H)-iliden)-2-metilanilina isomérica. RMN de ^{1}H (400 MHz, cloroformo-d) δ 9.26 (1 H, s), 8.80 (1 H, d, J=5.06 Hz), 7.42 (1 H, dd, J=5.06, 0.88 Hz), 7.31 - 7.35 (1 H, m), 7.02 - 7.08 (2 H, m), 5.39 (2 H, s), 2.35 (3 H, s). Espectro de masas m/z 303, 305 $(M+H)^+$.

Intermedio 45-1

Preparación de 1-(3-bromo-2-metilfenil)-5-oxopirrolidin-3-carboxamida

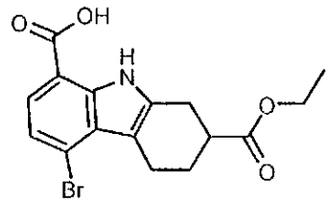


Se agitó a ta durante 5 horas una mezcla de ácido 1-(3-bromo-2-metilfenil)-5-oxopirrolidin-3-carboxílico

(Intermedio 41-10, 100 mg, 0.335 mmol), EDC (129 mg, 0.671 mmol), HOBT (103 mg, 0.671 mmol) y amoníaco acuoso al 28% en THF (2 ml). La mezcla se diluyó con acetato de etilo, se lavó con NaHCO3 (ac) y agua y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo con DCM-metanol 90:10) proporcionando 1-(3-bromo-2-metilfenil)-5-oxopirrolidin-3-carboxamida como un sólido blanco (26 mg, 26%). Espectro de masas m/z 297, 299 $(M+H)^+$.

Intermedio 46-1

Preparación de ácido 5-bromo-2-(etoxicarbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico



Etapa 1 Se añadió una solución de nitrito sódico (2.448 g, 35.5 mmol) en agua (12 ml) gota a gota a una suspensión de ácido 2-amino-4-bromobenzoico (7.30 g, 33.8 mmol) en ácido clorhídrico concentrado (34 ml) a -5°C, a una velocidad tal que la temperatura no superó 0°C. La suspensión resultante se agitó a -5°C durante 10 min y luego se añadió gota a gota a una solución agitada rápidamente de cloruro de estaño (II) (13.46 g, 71.0 mmol) en ácido clorhídrico concentrado (10 ml) a -5°C, a una velocidad tal que la temperatura no superó 0°C. La suspensión resultante se

calentó hasta ta y se agitó durante 1 h. El precipitado se recogió por filtración, se lavó con agua y se secó proporcionando sal clorhidrato del ácido 4-bromo-2-hidrazinilbenzoico como un sólido castaño pálido (7.79 g, 86%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 9.14 (s ancho,1 H) 7.79 (d, J=8.35 Hz, 1 H) 7.34 (d, J=1.76 Hz, 1 H) 7.13 (dd, J=8.35, 1.76 Hz, 1 H). Espectro de masas m/z 231, 233 $(M+H)^+$.

Etapa 2 Se trató una suspensión agitada de sal clorhidrato del ácido 4-bromo-2-hidrazinilbenzoico (16.35 g, 58.1 mmol) en ácido acético (171 ml) con 3-oxociclohexanocarboxilato de etilo (9.88 g, 58.1 mmol) a ta. La mezcla se agitó a reflujo durante 2.4 h, luego se enfrió hasta ta y se concentró proporcionando un sólido marrón. Este se suspendió en EtOAc (20 ml) y el precipitado se recogió por filtración, se lavó con EtOAc y se secó al aire proporcionando ácido 5-bromo-2-(etoxicarbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico (11.46 g). El filtrado se concentró y el residuo se volvió a suspender en EtOAc, el precipitado se recogió por filtración y se secó proporcionando más producto (0.82 g) para dar un total de 12.28 g (58%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 13.10 (s ancho,1 H) 11.06 (s, 1 H) 7.50 (d, J=8.13 Hz, 1 H) 7.19 (d, J=8.13 Hz, 1 H) 4.07 - 4.15 (m, 2 H) 3.08 - 3.19 (m, 1 H) 2.99 - 3.08 (m, 1 H) 2.89 - 2.99 (m, 2 H) 2.79 - 2.89 (m, 1 H) 2.09 - 2.22 (m, 1 H) 1.75 - 1.89 (m, 1 H) 1.20 (t, J=7.14 Hz, 3

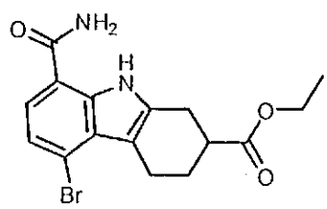
H). Espectro de masas m/z 366.0, 368.0 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando los procedimientos usados para preparar el Intermedio 46-1 pero usando la cetona apropiada en lugar de 3-oxociclohexanocarboxilato de etilo.

Intermedio	Nombre del compuesto	Espectro de masas
46-2	ácido 5-bromo-3-(etoxicarbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico	366, 368 $(M+H)^+$
46-3	ácido 5-bromo-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico	294, 296 $(M+H)^+$

Intermedio 47-1

Preparación de 5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-carboxilato de etilo



Se trató una suspensión de ácido 5-bromo-2-(etoxicarbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico (Intermedio 46-1, 12.28 g, 33.5 mmol), EDC (7.71 g, 40.2 mmol) y HOBT (6.16 g, 40.2 mmol) en THF-DCM (4:1, 335 ml) con hidróxido amónico acuoso al 28% (7.83 ml, 201 mmol) y la

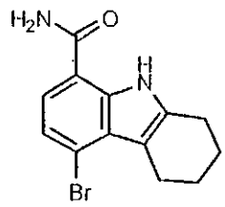
suspensión resultante se agitó a ta durante la noche. La mezcla se concentró y el residuo se suspendió en agua. El precipitado se recogió por filtración, se lavó con agua y EtOAc y se secó dando 5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-carboxilato de etilo (8.92 g). El filtrado se concentró y el residuo se suspendió en metanol. Se recogió un sólido por filtración, se lavó con metanol y se secó al aire proporcionando más producto (0.39 g) para un total de 9.31 g (76%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.08 (s, 1 H) 8.02 (s ancho,1 H) 7.43 (d, J=8.13 Hz, 1 H) 7.39 (s ancho,1 H) 7.14 (d, J=8.13 Hz, 1 H) 4.02 - 4.17 (m, 2 H) 3.07 - 3.18 (m, 1 H) 2.97 - 3.06 (m, 1 H) 2.86 - 2.98 (m, 2 H) 2.77 - 2.86 (m, 1 H) 2.09 - 2.19 (m, 1 H) 1.72 - 1.86 (m, 1 H) 1.20 (t, J=7.14 Hz, 3 H). Espectro de masas m/z 365, 367 $(M+H)^+$.

El siguiente Intermedio también se preparó usando el procedimiento usado para preparar el Intermedio 47-1 pero usando el Intermedio 46-2 en lugar del Intermedio 46-1.

Intermedio	Nombre del compuesto	Espectro de masas
47-2	5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-3-carboxilato de etilo	365, 367 $(M+H)^+$

Intermedio 47-3

Preparación de 5-bromo-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida

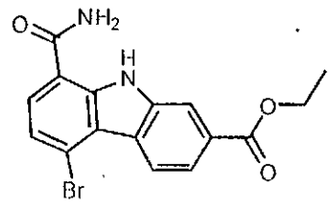


Una mezcla de ácido 5-bromo-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico (Intermedio 46-3, 70% de pureza, mezclada con Intermedio 47-3 de una reacción incompleta realizada de acuerdo con el procedimiento usado para preparar el Intermedio 47-1; 3 g, 7.14 mmol) en THF (80 ml) y DCM (20 ml) se trató con HOAT (1.166 g, 8.57 mmol) y EDC (1.642 g, 8.57 mmol). La mezcla se agitó a ta durante 2.4 h, luego se trató con amoníaco gas anhidro durante aproximadamente 2 minutos, formando una suspensión muy espesa. La mezcla se agitó durante 30 min, luego se trató de nuevo con amoníaco gas durante aproximadamente 1 min. Después de agitar durante otra hora, la mezcla se diluyó con agua y EtOAc (disolviendo el sólido). Se separaron las fases y la fase acuosa se extrajo de nuevo con EtOAc. Las fases orgánicas reunidas se lavaron dos veces con hidróxido sódico acuoso 0.1 M, luego con ácido clorhídrico 1 M y salmuera, se secó y se concentró proporcionando 5-bromo-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido color naranja pálido-castaño (2.47

g, 84%, incluyendo el producto de la reacción incompleta que proporciona el material de partida). RMN de ^1H (400 MHz, DMSO-d_6) δ 10.95 (1 H, s), 8.02 (1 H, s ancho), 7.44 (1 H, d, J=7.9 Hz), 7.38 (1 H, s ancho), 7.14 (1 H, d, J=8.1 Hz), 2.99 (2 H, s ancho), 2.75 (2 H, s ancho), 1.78 (4 H, s ancho). Espectro de masas m/z 293, 295 $(M+H)^+$.

Intermedio 48-1

Preparación de 5-bromo-8-carbamoil-9H-carbazol-2-carboxilato de etilo



Se trató una suspensión agitada de 5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-carboxilato de etilo (Intermedio 47-1, 9.31 g, 25.5 mmol) y 2,3-dicloro-5,6-diciano-1,4-benzoquinona (12.73 g, 56.1 mmol) en tolueno (127 ml) a reflujo durante 3 h. La mezcla se enfrió hasta ta y el precipitado se recogió por filtración, se lavó con tolueno y agua y se secó al aire. El sólido se suspendió en metanol y el precipitado se recogió por filtración, se lavó con metanol y se secó al aire proporcionando 5-bromo-8-carbamoil-9H-carbazol-2-carboxilato de etilo (7.68 g). El filtrado se concentró y el residuo se suspendió en metanol. El precipitado se recogió por filtración, se lavó con metanol y

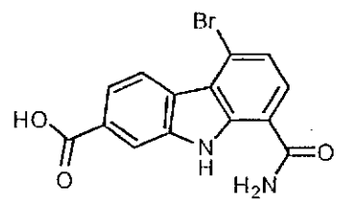
se secó al aire proporcionando más producto (0.60 g) para un total de 8.28 g (90%). RMN de ^1H (400 MHz, DMSO-d_6) δ 12.03 (s, 1 H) 8.69 (d, J=8.57 Hz, 1 H) 8.51 (d, J=1.10 Hz, 1 H) 8.26 (s ancho,1 H) 7.93 (d, J=8.13 Hz, 1 H) 7.87 (dd, J=8.57, 1.54 Hz, 1 H) 7.63 (s ancho,1 H) 7.50 (d, J=8.13 Hz, 1 H) 4.37 (q, J=7.03 Hz, 2 H) 1.37 (t, J=7.14 Hz, 3 H). Espectro de masas m/z 361, 363 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando el procedimiento usado para preparar el Intermedio 48-1 pero usando el material apropiado en lugar del Intermedio 47-1.

Intermedio	Nombre del compuesto	Espectro de masas
48-2	5-bromo-8-carbamoil-9H-carbazol-3-carboxilato de etilo	361, 363 $(M+H)^+$
48-3	4-bromo-9H-carbazol-1-carboxamida	289, 291 $(M+H)^+$

Intermedio 49-1

Preparación de ácido 5-bromo-8-carbamoil-9H-carbazol-2-carboxílico



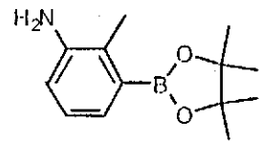
Se trató una suspensión de 5-bromo-8-carbamoil-9H-carbazol-2-carboxilato de etilo (Intermedio 48-1, 1.81 g, 5.01 mmol) e hidróxido de litio monohidratado (0.601 g, 15.03 mmol) en THF-etanol-agua (3:1:1, 50 ml) a reflujo durante 2 h. La mezcla se enfrió hasta ta y se concentró. El residuo se agitó en agua y se trató con ácido clorhídrico 1 M hasta pH 1-2. El precipitado se recogió por filtración, se lavó con agua y se secó proporcionando ácido 5-bromo-8-carbamoil-9H-carbazol-2-carboxílico como un sólido marrón claro (1.84 g, aproximadamente 90% de pureza, 99%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.95 (s ancho,1 H) 12.02 (s, 1 H) 8.69 (d, J=8.53 Hz, 1 H) 8.47 (s, 1 H) 8.28 (s ancho,1 H) 7.94 (d, J=8.28 Hz, 2 H) 7.87 (d, J=8.28 Hz, 1 H) 7.65 (s ancho,1 H) 7.51 (d, J=8.03 Hz, 1 H). Espectro de masas m/z 331, 333 $(M-H)^-$.

Los siguientes intermedios también se prepararon usando el procedimiento usado para preparar el Intermedio 49-1 pero usando el material apropiado en lugar del Intermedio 48-1.

Intermedio	Nombre del compuesto	Espectro de masas
49-2	ácido 5-bromo-8-carbamoil-9H-carbazol-3-carboxílico	331, 333 $(M-H)^-$
49-3	ácido 5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-carboxílico	335, 337 $(M-H)^-$

Intermedio 50-1

Preparación de 2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina



Se purgó una mezcla de 3-bromo-2-metilanilina (4.00 g, 21.5 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (6.55 g, 25.8 mmol) y acetato potásico (4.22 g, 43.0 mmol) en 1,4-dioxano (44.8 ml) y DMSO (9.0 ml) con nitrógeno durante 10 min. Se añadió aducto de [1,1'-bis(difenilfosfino)ferroceno]-dicloropaladio y DCM (0.527 g, 0.645 mmol), la mezcla se purgó durante otros 5 minutos y luego se trató a reflujo durante 2 h. La mezcla se enfrió y se filtró a través de Celite. Los sólidos se lavaron con EtOAc, y los filtrados reunidos se lavaron con agua y salmuera y se secaron y concentraron. El residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc usando un gradiente desde 95:5 a 85:15) proporcionando 2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina como un sólido céreo amarillo claro (4.4 g, 88%), que se usó sin purificación posterior. RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.21 (1 H, dd, J=7.3, 1.0 Hz), 7.02 (1 H, t, J=7.7 Hz), 6.75 (1 H, dd, J=7.8, 1.0 Hz), 3.54 (2 H, "s ancho), 2.37 (3 H, s), 1.34 (12 H, s). Espectro de masas m/z 233.3, 234.3,

235.3 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando el procedimiento usado para preparar el Intermedio 50-1 o procedimientos relacionados parecidos.

Intermedio	Material de partida[a]	Nombre del compuesto	Espectro de masas
50-2		2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzonitrilo	[b]
50-3		3.5-difluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina	256.3 $(M+H)^+$
50-4	Intermedio 1-1	2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	350.3 $(M+H)^+$
50-5	Intermedio 1-2	6-fluoro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	368.1 $(M+H)^+$

50-6	Intermedio 1-3	5-metoxi-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	380.1 $(M+H)^+$
50-7	Intermedio 1-4	2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-6-(trifluorometil)isoindolin-1-ona	418.1 $(M+H)^+$
50-8	Intermedio 1-5	6-metil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	364.0 $(M+H)^+$
50-9	Intermedio 2-1	2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-3-oxoisoindolin-5-carbonitrilo	375.3 $(M+H)^+$
50-10	Intermedio 3-1	5-fluoro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1.3-diona	382.1 $(M+H)^+$

50-11	Intermedio 3-2	5-*terc*-butil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1.3-diona	420.2 $(M+H)^+$
50-12	Intermedio 4-1	2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)octahidro-1H-isoindol-1-ona	356.1 $(M+H)^+$
50-13	Intermedio 4-2	2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-2,3,4,5,6,7-hexahidro-1H-isoindol-1-ona	354.2 $(M+H)^+$
50-14	Intermedio 4-3	6-*terc*-butil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	406.2 $(M+H)^+$
50-15	Intermedio 4-4	5-*terc*-butil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	406.2 $(M+H)^+$

50-16	Intermedio 4-5	7-fluoro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	368.3 $(M+H)^+$
50-17	Intermedio 4-6	4-fluoro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	368.3 $(M+H)^+$
50-18	Intermedio 4-7	5-metil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	364.2 $(M+H)^+$
50-19	Intermedio 4-8	5-fluoro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona	368.2 $(M+H)^+$
50-20	Intermedio 5-1	5-metil-2-(4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-3-il)isoindolin-1-ona	365.2 $(M+H)^+$
50-21	Intermedio 5-2	2-(4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-3-il)isoindolin-1-ona	351.2 $(M+H)^+$

50-22	Intermedio 6-1	2-(3-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il)isoindolin-1-ona	355 $(M+H)^+$
50-23	Intermedio 7-1	2-metil-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	377.3 $(M+H)^+$
50-24	Intermedio 8-1	3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	363.3 $(M+H)^+$
50-25	Intermedio 8-2	5-fluoro-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	381.3 $(M+H)^+$
50-26	Intermedio 8-3	6-cloro-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	397, 399 $(M+H)^+$

50-27	Intermedio 9-1	6-fluoro-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	381.3 $(M+H)^+$
50-28	Intermedio 9-2	6-metil-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	377.3 $(M+H)^+$
50-29	Intermedio 10-1	2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoquinolin-1(2H)-ona	362.3 $(M+H)^+$
50-30	Intermedio 11-1	7-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)imidazo[1.2-a]pirazin-8(7H)-ona	352.1 $(M+H)^+$
50-31	Intermedio 12-1	pirrolidin-1-il(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indol-2-il)metanona	341.1 $(M+H)^+$

50-32	Intermedio 13-1	2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolina	336.2 $(M+H)^+$
50-33	Intermedio 17-1	5-metil-3-fenil-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3.4-dihidro-2H-benzo[e][1,3]oxazin-2-ona	366.1 $(M+H)^+$
50-34	Intermedio 18-1	5-metil-3-fenil-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2H-benzo[e][1,3]oxazin-4(3H)-ona	366.1 $(M+H)^+$
50-35	Intermedio 19-1	5-metil-3-fenil-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2H-benzo[e][1,3]oxazin-2.4(3H)-diona	380.1 $(M+H)^+$
50-36	Intermedio 20-1	N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-indazol-3-amina	350.3 $(M+H)^+$

50-37	Intermedio 21-1	6-(4-fluorofenil)-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indol-1-carboxilato de terc-butilo	438.2 $(M+H)^+$
50-38	Intermedio 9-7	3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-6-(trifluorometoxi)quinazolin-4(3H)-ona	447.1 $(M+H)^+$
50-39	Intermedio 23-1	7-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3.4-dihidroisoquinolin-1(2H)-ona	274.1 $(M+H)^+$
50-40	Intermedio 24-1	2-(4-fluorofenil)-7-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3.4-dihidroisoquinolin-1(2H)-ona	368.1 $(M+H)^+$
50-41	Intermedio 25-1	1-(4-fluorobencil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indol	352.2 $(M+H)^+$
50-42	Intermedio 26-1	(4-fluorofenil)(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-1-il)metanona	377.24 $(M+H)^+$

50-43	Intermedio 27-1	1-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)piperidin-2-ona	316.3 $(M+H)^+$
50-44	Intermedio 28-1	N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)ciclopropanocarboxamida	302.2 $(M+H)^+$
50-45	Intermedio 34-1	2-fluoro-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina	238.1 $(M+H)^+$
50-46	Intermedio 39-1	2-(4-fluorofenil)-7-metil-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol	353.2 $(M+H)^+$
50-47	Intermedio 40-1	N,N-bis(*terc*-butiloxicarbonil)-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-4-metiltiazol-2-ilamina	441.2 $(M+H)^+$

50-48	Intermedio 9-3	8-fluoro-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	381.2 $(M+H)^+$
50-49	Intermedio 44-1	2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-pirrolo[3.4-c]piridin-3(2H)-ona	351.5 $(M+H)^+$
50-50	Intermedio 44-2	(Z)-N-(furo[3.4-c]piridin-1(3H)-iliden)-2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina	351.3 $(M+H)^+$
50-51	Intermedio 9-4	8-metoxi-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	393.1 $(M+H)^+$
50-52	Intermedio 9-5	5-metoxi-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	393.1 $(M+H)^+$

50-53	Intermedio 9-6	7-metoxi-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	393.1 $(M+H)^+$
50-54	Intermedio 32-9	N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4-amina	362.0 $(M+H)^+$
50-55	Intermedio 32-6	5-fluoro-N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4-amina	379.9 $(M+H)^+$
50-56	Intermedio 32-3	7-fluoro-N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4-amina	380.0 $(M+H)^+$
50-57	Intermedio 32-7	8-fluoro-N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4-amina	380.0 $(M+H)^+$

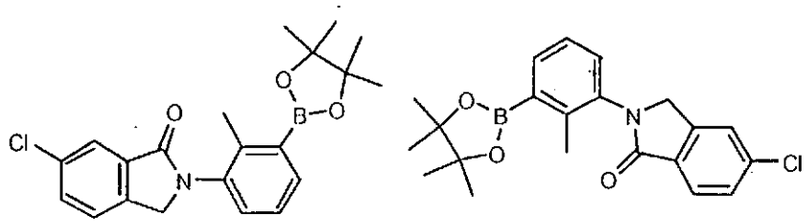
50-58	Intermedio 9-8	8-metil-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	377.1 $(M+H)^+$
50-59	Intermedio 9-9	6-metoxi-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	393.1 $(M+H)^+$
50-60	Intermedio 9-10	7-fluoro-3-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona	381.1 $(M+H)^+$

[a] No se indica si los materiales de partida están disponibles comercialmente.

[b] RMN de ^1H (400 MHz, metanol-d_4) δ 7.96 (1 H, dd, J=7.59, 1.21 Hz), 7.72 (1 H, dd, J=7.70, 1.32 Hz), 7.33 (1 H, t, J=7.37 Hz), 2.72 (3 H, s), 1.37 (12 H, s).

Intermedios 51-1 y 51-2

Preparación de 6-cloro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona y 5-cloro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona

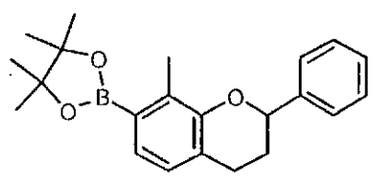


Se trató una suspensión de 2-(3-bromo-2-metilfenil)-5-cloroisoindolin-1,3-diona bruta (Intermedio 3-3, 3.77 g, 10.75 mmol) en metanol (100 ml) con borohidruro sódico (1.017 g, 26.9 mmol) y se agitó a ta durante 2 h. La mezcla se concentró dando un sólido que se suspendió en DCM (20 ml) y se trató con trietilsilano (18.12 ml, 113 mmol) y se agitó a ta. Después de unos pocos minutos, la mezcla se trató lentamente con TFA (4.37 ml, 56.7 mmol) y se agitó durante 10 min. Se añadió más TFA (4.37 ml, 56.7 mmol) y la solución se agitó a ta durante 1.5 h. La mezcla se concentró y el residuo se disolvió en DCM. La solución se lavó con NaHCO3 (ac) y agua y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo con EtOAc-hexano 25:75) dando un sólido que contenía tanto 2-(3-bromo-2-metilfenil)-6-cloroisoindolin-1-ona como 2-(3-bromo-2-metilfenil)-5-cloroisoindolin-1-ona. Usando el procedimiento

usado para preparar el Intermedio 50-1, este material (0.85 g, 2.43 mmol) se convirtió en una mezcla de 6-cloro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona y 5-cloro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona que se separó por cromatografía en columna (eluyendo con un gradiente de 95:5 a 75:25 de hexano-EtOAc). 6-cloro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 51-1, 126 mg, 13%): RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.94 (1 H, d, J=1.9 Hz), 7.83 (1 H, dd, J=7.1, 1.8 Hz), 7.57 (1 H, dd, J=8.0, 1.9 Hz), 7.44 (1 H, d, J=8.0 Hz), 7.27 - 7.33 (2 H, m), 4.66 (2 H, s), 2.41 (3 H, s), 1.35 (12 H, s). Espectro de masas m/z 384, 386 $(M+H)^+$. 5-cloro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 51-2, 315 mg, 33%): RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.88 (1 H, d, J=8.6 Hz), 7.82 (1 H, dd, J=7.1, 1.8 Hz), 7.48 - 7.54 (2 H, m), 7.27 - 7.32 (2 H, m), 4.66 (2 H, s), 2.41 (3 H, s), 1.35 (12 H, s). Espectro de masas m/z 384, 386 $(M+H)^+$.

Intermedio 52-1

Preparación de 4,4,5,5-tetrametil-2-(8-metil-2-fenilcroman-7-il)-1,3,2-dioxaborolano



Una mezcla de trifluorometanosulfonato de 8-

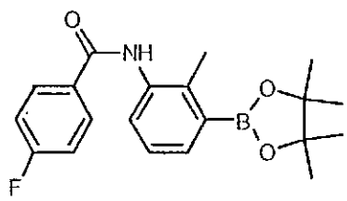
metil-2-fenilcroman-7-ilo (Intermedio 14-1, 0.300 g, 0.806 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (0.246 g, 0.967 mmol), aducto de [1,1'-bis(difenilfosfino)ferroceno]-dicloropaladio y DCM (0.066 g, 0.081 mmol), difenilfosforilferroceno (0.045 g, 0.081 mmol) y fosfato tripotásico (0.342 g, 1.611 mmol) en DMF se calentó en un tubo sellado en nitrógeno a 80°C durante 15 h. La mezcla se enfrió y se diluyó con EtOAc (30 ml), se lavó con cloruro amónico acuoso saturado (10 ml), agua (10 ml) y salmuera (10 ml), se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 97.5:2.4 a 95:5 de hexano-EtOAc) dando 4,4,5,5-tetrametil-2-(8-metil-2-fenilcroman-7-il)-1,3,2-dioxaborolano como líquido incoloro (aproximadamente 85% de pureza). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.35 - 7.46 (4 H, m), 7.26 - 7.35 (2 H, m), 6.92 (1 H, d, J=7.48 Hz), 5.11 (1 H, dd, J=9.79, 2.31 Hz), 2.98 (1 H, ddd, J=16.84, 11.11, 6.16 Hz), 2.70 - 2.83 (1 H, m), 2.40 - 2.44 (3 H, m), 2.15 - 2.30 (1 H, m), 1.92 - 2.04 (1 H, m), 1.34 (12 H, s). Espectro de masas m/z 351.1 $(M+H)^+$.

Los siguientes intermedios también se prepararon usando el procedimiento usado para preparar el Intermedio 52-1.

Intermedio	Material de partida	Nombre del compuesto	Espectro de masas
52-2	Intermedio 15-1	3-fenil-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona	352.3 $(M+H)^+$

Intermedio 53-1

Preparación de 4-fluoro-N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)benzamida

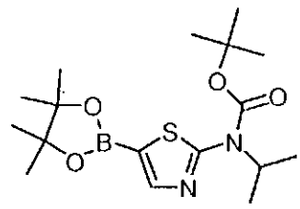


Se trató una solución de 2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (Intermedio 50-1, 1.10 g, 4.72 mmol) en EtOAc (25 ml) con TEA (0.789 ml, 5.66 mmol), luego con cloruro de 4-fluorobenzoilo (0.577 ml, 4.81 mmol) y la mezcla se agitó a ta. Después de 22 h, la mezcla se diluyó con EtOAc, se lavó dos veces con agua, luego con salmuera, y se secó y concentró proporcionando 4-fluoro-N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)benzamida como una espuma vítrea (1.705 g,

aproximadamente 90% de pureza, 92%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.96 (d, J=7.5 Hz, 1 H) 7.90 (dd, J=8.6, 5.3 Hz, 2 H) 7.66 (dd, J=7.4, 1.2 Hz, 1 H) 7.63 (s ancho,1 H) 7.22 - 7.29 (m, 1 H) 7.18 (t, J=8.6 Hz, 2 H) 2.43 (s, 3 H) 1.36 (s, 12 H). Espectro de masas m/z 356.1 $(M+H)^+$.

Intermedio 54-1

Preparación de (5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)tiazol-2-il)carbamato de *terc*-butil-isopropilo

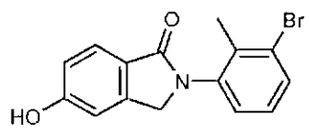


Se trató una solución de 5-bromotiazol-2-il(isopropil)carbamato de terc-butilo (Intermedio 43-1, 7.5 g, 23.3 mmol) en THF (50 ml) se trató con n-butil litio (1.6 M en hexano, 21.8 ml, 34.88 mmol) gota a gota a -78°c. La solución resultante se agitó a -78°c durante 10 min, luego se trató gota a gota con 2-isopropoxi-4,4,5,5-tetrametil-1,3,2-dioxaborolano (6.49 g, 34.9 mmol). La mezcla se agitó a -78°c durante 2 h, luego se calentó hasta ta y se trató con cloruro amónico acuoso al 50% (50 ml). La mezcla se extrajo con EtOAc (100 ml) y la fase orgánica se lavó con agua y salmuera y se secó y concentró. El residuo se suspendió en hexano (30 ml) y el precipitado se recogió por filtración, se lavó con hexano (20 ml) y se secó dando (5-(4,4,5,5-tetrametil-1,3,2-

dioxaborolan-2-il)tiazol-2-il)carbamato de *terc*-butil-isopropilo como un sólido amarillo (4.17 g, 48%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.95 (s, 1 H) 5.37 (m, 1 H) 1.60 (s, 9 H) 1.44 (d, 6.7 Hz, 6 H) 1.34 (s, 12 H).

Intermedio 55-1

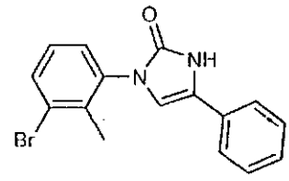
Preparación de 2-(3-bromo-2-metilfenil)-5-hidroxiisoindolin-1-ona



Una mezcla de 2-(3-bromo-2-metilfenil)-5-metoxiisoindolin-1-ona (Intermedio 1-4, 100 mg, 0.30 mmol) y tribromuro de boro 1.0 M en DCM (900 µL, 0.90 mmol) se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se diluyó con DCM, se lavó con NaHCO3 (ac) y se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con AcOEt-hexano) para proporcionar 2-(3-bromo-2-metilfenil)-5-hidroxiisoindolin-1-ona en forma de un sólido blanco (62 mg, 65%). ^{1}H RMN (400 MHz, cloroformo-d) δ 10.27 (1 H, br. s), 7.64 (1H, dd, J = 7.9, 0.9 Hz), 7.59 (1H, d, J = 8.4 Hz), 7.44 (1H, d, J = 7.3 Hz), 7.25 (1H, t, J = 7.9 Hz), 6.98 (1H, d, J = I 5 Hz), 6.93 (1H, dd, J = 8.3, 2.1 Hz), 4.77 (2 H, s), 2.20 (3H, s). Espectro de masas m/z 318, 320 $(M+H)^+$.

Intermedio 56-1

Preparación de 1-(3-bromo-2-metilfenil)-4-fenil-1H-imidazol-2(3H)-ona



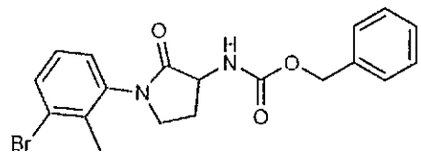
Etapa 1 Una mezcla de 3-bromo-2-metilanilina (0.620 ml, 5.03 mmol) y bicarbonato de sodio (565 mg, 6.73 mmol) en acetonitrilo (4.5 mL) fue tratada con 2-bromo-1-feniletanona (500 mg, 2.51 mmol) y la mezcla se agitó a temperatura ambiente. Después de 24 h, la suspensión se filtró y el precipitado se suspendió y se sonificó en agua, se recogió de nuevo por filtración, se lavó con agua y se secó para suministrar 2-(3-bromo-2-metilfenilamino)-1-feniletanona como un sólido blanquecino (508 mg, 67%). ^{1}H RMN (400 MHz, cloroformo-d) δ 8.00 a 8.06 (2 H, m), 7.61 - 7.68 (1H, m), 7.53 (2 H, t, J = 7.6 Hz), 6.94 - 7.01 (2 H, m), 6.51 - 6.58 (1H, m), 5.06 (1H, t, J = 4.1 Hz), 4.62 (2 H, d, J = 4.4 Hz), 2.40 (3H, s). Espectro de masas m/z 304, 306 $(M+H)^+$.

Etapa 2 Siguiendo el procedimiento de Congiu et al. (Bioorg. Med. Chem. Lett, 2008, 989), 2-(3-bromo-2-metilfenilamino)-1-feniletanona (250 mg, 0.822 mmol) se convirtió, después de la purificación por cromatografía en columna (eluyendo con un gradiente de 25:75 de EtOAc-hexano a EtOAc) 1-(3-bromo-2-metilfenil)-4-fenil-1H-imidazol-2(3H)-ona

como un sólido blanco (59 mg, 22%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 11.00 (1H, s), 7.70 (1H, dd, J = 8.0, 1.0 Hz), 7.59 (2 H, d, J = 7.3 Hz), 7.34 - 7.43 (3 H, m), 7.21 - 7.32 (3 H, m), 2.27 (3H, s). Espectro de masas m/z 329, 331 $(M+H)^+$.

Intermedio 57-1

Preparación de 1-(3-bromo-2-metilfenil)-2-oxopirrolidin-3-ilcarbamato de bencilo racémico



Etapa 1 Una solución de 3-bromo-2-metilanilina (0.662 mL, 5,37 mmol) y ácido 2-(benciloxicarbonilamino)-4-(metiltio)butanoico racémico (1.523 g, 5.37 mmol) en acetonitrilo (25 mL) fue tratada con 1-hidroxi-7-azabenzotriazol (0.878 g, 6.45 mmol), diisopropiletilamina (1.877 ml, 10.75 mmol) y EDC (1.236 g, 6.45 mmol) y se agitó a temperatura ambiente. Después de 20.5 h, la mezcla se diluyó con agua y acetato de etilo. La fase orgánica se separó, se lavó con HCl acuoso 1 M y NaHCO3 (ac) y se filtró para eliminar un sólido blanco floculante. El filtrado se secó y se concentró, y el residuo se recristalizó de etanol para dar 1-(3-bromo-2-metilfenilamino)-4-(metiltio)-1-oxobutan-2-ilcarbamato de bencilo racémico como un sólido marrón (1.33 g, 69%). ^{1}H RMN (400 MHz, cloroformo-d) δ 8.08 (1H, br. s), 7.68 (1H, d, J = 7.9 Hz), 7.39 (1H, d, J = 7.9

Hz), 7.34 (5 H, s), 7.04 (1H, t, J = 8.0 Hz), 5.58 (1H, d, J = 7.9 Hz), 5.14 (2 H, s), 4.53 (1 H, q, J = 7.0 Hz), 2.55 - 2.72 (2 H, m), 2.28 (3H, br s.), 2.17 - 2.27 (1H, m), 2.12 (3H, s), 2.01 - 2.10 (1H, m). Espectro de masas m/z 451, 453 $(M+H)^+$.

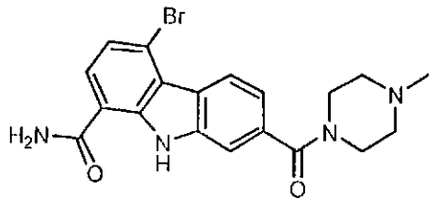
Etapa 2 Una mezcla 1-(3-bromo-2-metilfenilamino)-4-(metiltio)-1-oxobutan-2-ilcarbamato de bencilo racémico (1.31 g, 2.90 mmol) y DCM (4 mL) se diluyó con yodometano (7.5 ml, 120 mmol) y la mezcla se agitó a temperatura ambiente. Después de 24.5 horas, la mezcla (una solución con un aceite rojizo insoluble) se concentró al vacío. El residuo se trató tres veces con DCM y se concentró al vacío para proporcionar yoduro de (3-(benciloxicarbonilamino)-4-(3-bromo-2-metilfenilamino)-4-oxobutil)dimetilsulfonio racémico como una espuma vidriosa de color amarillo anaranjado (1.75 g, 97%). ^1H RMN (400 MHz, cloroformo-d) 89.16 (1 H, br. S.), 7.28 - 7.46 (7 H, m), 6.99 (1H, t, J = 8.0 Hz), 6.71 (1H, d, J = 6.8 Hz), 5.11 (2 H, s), 4.84 (1 H, br. s.), 3.75 (1H, br. s.), 3.54 (1H, br. s.), 3.14 (3 H, br. s.), 2.96 (3H, s), 2.75 (1H, br s.), 2.33 - 2.41 (1H, m), 2.30 (3H, br s.). Espectro de masas m/z 465, 467 $(M)^+$.

Etapa 3 Una solución de yoduro de (3-(benciloxicarbonilamino)-4-(3-bromo-2-metilfenilamino)-4-oxobutil)dimetilsulfonio racémico (1.96 g, 3.30 mmol) en DMSO anhidro (33 mL) se agitó a temperatura ambiente y se trató

con carbonato de cesio (2.69 g, 8.26 mmol) en 3 porciones más de 25 min. Después de 4.5 h, la mezcla se diluyó con AcOEt, se lavó tres veces con agua y dos veces con salmuera, se secó y se concentró para proporcionar 1-(3-bromo-2-metilfenil)-2-oxopirrolidin-3-ilcarbamato de bencilo racémico como un sólido de color canela (1.248 g, 94%). ^{1}H RMN (400 MHz, cloroformo-d) δ 7.52 - 7.58 (1H, m), 7.30 - 7.40 (5 H, m), 7.10 (2 H, d, J = 5.1 Hz), 5.47 (1H, br. s.), 5.15 (2 H, s), 4.39 (1H, ddd, J = 10.6, 8.3, 5.2 Hz), 3.72 (1H, td, J = 9.9, 6.4 Hz), 3.60 (1H, t, J = 9.4 Hz), 2.27 (3H, s), 2.11 - 2.26 (2 H, m). Espectro de masas m/z 425, 427 $(M+Na)^+$.

Ejemplo 1-1

Preparación de 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Se trató una suspensión de ácido 5-bromo-8-carbamoil-9H-carbazol-2-carboxílico (Intermedio 49-1, 1.84 g, 4.97 mmol), EDC (1.334 g, 6.96 mmol), y HOBT (1.066 g, 6.96 mmol) en THF-DCM-DMF (4:1:1) (124 ml) con 1-metilpiperazina (1.656 ml, 14.91 mmol) y la mezcla se agitó a ta durante 3 días. La mezcla se concentró y el residuo se repartió entre DCM y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se

secó y se concentró proporcionando un aceite. Este se purificó por cromatografía en columna (DCM-amoníaco metanólico 2 M, 100:0 hasta 95:5 hasta 92.4:7.5). El sólido resultante se suspendió en EtOAc, se recogió por filtración y se secó proporcionando 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (1.57 g, 76%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.83 (s, 1 H) 8.57 (d, J=8.13 Hz, 1 H) 8.20 (s ancho,1 H) 7.84 (d, J=8.35 Hz, 1 H) 7.79 (s, 1 H) 7.56 (s ancho,1 H) 7.42 (d, J=8.13 Hz, 1 H) 7.22 (d, J=8.13 Hz, 1 H) 3.30 - 3.70 (m, 4 H) 2.19 - 2.39 (m, 4 H) 2.16 (s, 3 H). Espectro de masas m/z 415, 417 $(M+H)^+$.

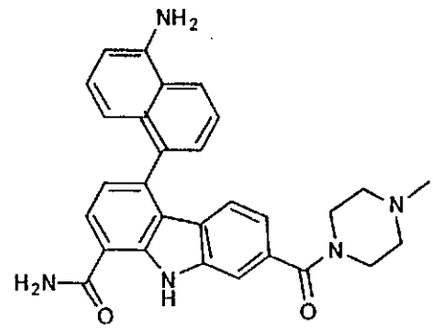
Los siguientes Ejemplos también se prepararon usando los procedimientos usados para preparar el Ejemplo 1-1, o procedimientos relacionados parecidos.

Ejemplo/ Interme-dio	Material de partida	Nombre del compuesto	Espectro de masas
1-2	Intermedio 49-2	4-bromo-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	415, 417 $(M+H)^+$
1-3	Intermedio 49-3	5-bromo-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	419, 421 $(M+H)^+$

1-4(a)	Intermedio 49-1	4-bromo-7-(morfolin-4-carbonil)-9H-carbazol-1-carboxamida	402, 404 $(M+H)^+$
1-5(a)	Intermedio 49-3	5-bromo-N^2-(3-(dimetilamino)propil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	421, 423 $(M+H)^+$
1-6(a)	Intermedio 49-3	5-bromo-N^2-(4-(dimetilamino)butil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	435, 437 $(M+H)^+$
1-7(a)	Intermedio 49-3	5-bromo-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	420, 422 $(M+H)^+$
1-8(a)	Intermedio 49-3	5-bromo-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	433, 435 $(M+H)^+$
1-9(a)	Intermedio 49-3	5-bromo-N^2-metil-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	447, 449 $(M+H)^+$
1-10(a)	Intermedio 49-1	4-bromo-N^7,N^7-dimetil-9H-carbazol-1,7-dicarboxamida	360, 362 $(M+H)^+$

Ejemplo 2-1

Preparación de 4-(5-aminonaftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Etapa 1 Una solución de tris(dibencilidenoacetona)dipaladio (27.6 mg, 0.031 mmol) y triciclohexilfosfina (1.0 M en tolueno, 0.144 ml, 0.144 mmol) en 1,4-dioxano (8 ml) se purgó con argon durante 10 min. Se añadieron 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-1, 500 mg, 1.204 mmol), 4.4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (336 mg, 1.324 mmol) y acetato potásico (177 mg, 1.806 mmol), se continuó burbujeando durante otros 5 minutos y la mezcla se calentó en un tubo sellado con agitación a 85-90°C durante 18 h. La mezcla se enfrió hasta ta y se diluyó con agua y EtOAc y se separaron las fases. La fase acuosa se extrajo dos veces con EtOAc, y las fases orgánicas reunidas se secaron y concentraron. El residuo se recogió en acetonitrilo, se filtró y el filtrado se concentró dando 7-(4-metilpiperazin-1-carbonil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-

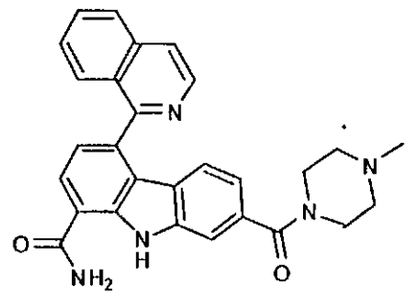
9H-carbazol-1-carboxamida como una espuma vítrea color amarillo-castaño (602 mg) que se usó sin purificación posterior. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.65 (s, 1 H) 8.86 (d, J=8.3 Hz, 1 H) 8.25 (s ancho,1 H) 7.95 (d, J=7.7 Hz, 1 H) 7.90 - 7.94 (m, 2 H) 7.58 (d, J=7.5 Hz, 1 H) 7.16 (d, J=6.8 Hz, 1 H) 3.36 - 3.72 (m, 4 H) 2.34 (s ancho,4 H) 2.21 (s, 3 H) 1.43 (s, 12 H); se observaron impurezas alifáticas. Espectro de masas m/z 463.34 $(M+H)^+$.

Etapa 2 Se trató una mezcla de 7-(4-metilpiperazin-1-carbonil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-9H-carbazol-1-carboxamida (el producto bruto preparado de acuerdo con la Etapa 1, 40 mg, 0.065 mmol), 5-bromonaftalen-1-amina (21.61 mg, 0.097 mmol) y carbonato potásico (13.45 mg, 0.097 mmol) en tolueno (1.5 ml) y etanol (0.75 ml) con complejo de [1,1'-bis(difenilfosfino)-ferroceno]dicloropaladio(II) y DCM (5.3 mg, 0.007 mmol) y se purgó con argon durante aproximadamente 5 min. La mezcla se calentó a 90°C durante 19 h, luego se enfrió hasta ta y se concentró. El residuo se purificó por HPLC preparativa, luego se repartió entre EtOAc y NaHCO3 (ac), se extrajo de nuevo la fase acuosa con EtOAc, y las fases orgánicas reunidas se secaron y concentraron proporcionando 4-(5-aminonaftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido amarillo claro (13.1 mg, 42%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.71 (s, 1 H) 8.22 - 8.27 (m, 2 H) 8.07 (d,

J=7.7 Hz, 1 H) 7.73 (s, 1 H) 7.55 (s ancho,1 H) 7.52 (dd, J=8.6, 6.8 Hz, 1 H) 7.42 (dd, J=6.9, 1.0 Hz, 1 H) 7.09 (d, J=7.7 Hz, 1 H) 6.96 (dd, J=8.2, 7.6 Hz, 1 H) 6.64 - 6.70 (m, 2 H) 6.49 (d, J=8.3 Hz, 1 H) 6.38 (d, J=8.1 Hz, 1 H) 5.85 (s, 2 H) 3.48 - 3.59 (m, 4 H) 2.17 - 2.37 (m, 4 H) 2.14 (s, 3 H). Espectro de masas m/z 478.10 $(M+H)^+$.

Ejemplo 2-2

Preparación de 4-(isoquinolin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

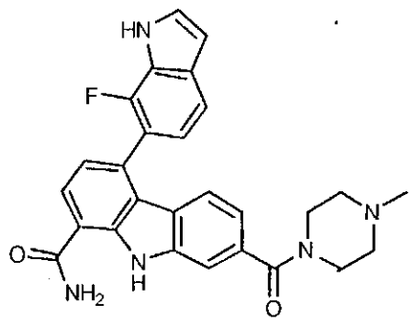


Usando el procedimiento de la Etapa 2 del Ejemplo 2-1, 7-(4-metilpiperazin-1-carbonil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-9H-carbazol-1-carboxamida (el producto bruto preparado de acuerdo con la Etapa 1 del Ejemplo 2-1, 40 mg, 0.065 mmol) y 1-cloroisoquinolina (15.92 mg, 0.097 mmol) se convirtieron en 4-(isoquinolin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (6 mg, 20%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.82 (s, 1 H) 8.71 (d, J=5.5 Hz, 1 H) 8.32 (s ancho,1 H) 8.15 (d, J=7.7 Hz, 2 H) 8.06 (d, J=5.3 Hz, 1 H) 7.80 (ddd, J=8.2, 6.5, 1.5 Hz, 1 H) 7.77 (s, 1 H) 7.63 (s ancho,1 H) 7.46 - 7.55 (m, 2 H) 7.25

(d, J=7.9 Hz, 1 H) 6.71 (dd, J=8.2, 1.4 Hz, 1 H) 6.24 (d, J=8.1 Hz, 1 H) 3.46 - 3.62 (m, 4 H) 2.18 - 2.34 (m, 4 H) 2.16 (s, 3 H). Espectro de masas m/z 464.3 $(M+H)^+$.

Ejemplo 2-3

Preparación de 4-(7-fluoro-1H-indol-6-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

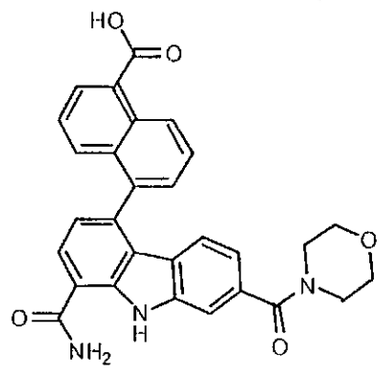


Se purgó una mezcla de 7-(4-metilpiperazin-1-carbonil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-9H-carbazol-1-carboxamida (preparada de acuerdo con el procedimiento de Etapa 1 del Ejemplo 2-1, 75 mg, 0.065 mmol), 6-bromo-7-fluoro-1H-indol (preparado de acuerdo con la solicitud de patente de Estados Unidos 2007/112005, 18.7 mg, 0.087 mmol), y carbonato sódico acuoso 2 M (0.081 ml, 0.162 mmol) en tolueno (0.8 ml) y etanol (0.2 ml) con argon, se trató con tetraquis(trifenilfosfina)paladio (7.5 mg, 0.007 mmol) y se calentó a 90°C. Después de 16 h, la mezcla se enfrió hasta ta. El residuo se purificó por HPLC preparativa. La sal TFA resultante se repartió entre $NaHCO_3$ (ac) y EtOAc, y los extractos orgánicos se secaron y se concentraron

proporcionando 4-(7-fluoro-1H-indol-6-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido blanquecino (9 mg, 30%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.99 (d, J=7.5 Hz, 1 H) 7.68 (d, J=0.9 Hz, 1 H) 7.52 (d, J=7.9 Hz, 1 H) 7.39 (d, J=3.5 Hz, 1 H) 7.25 (dd, J=8.1, 1.1 Hz, 1 H) 7.21 (d, J=7.5 Hz, 1 H) 7.08 (dd, J=8.1, 6.4 Hz, 1 H) 6.92 (dd, J=8.1, 1.5 Hz, 1 H) 6.63 (t, J=3.3 Hz, 1 H) 3.77 (s ancho,2 H) 3.49 (s ancho,2 H) 2.41 (s ancho,2 H) 2.39 (s ancho,2 H) 2.30 (s, 3 H). Espectro de masas m/z 470.1 $(M+H)^+$.

Ejemplo 2-4

Preparación de ácido 5-(1-carbamoil-7-(morfolin-4-carbonil)-9H-carbazol-4-il)-1-naftoico



Usando los procedimientos del Ejemplo 2-1, se convirtieron 4-bromo-7-(morfolin-4-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-4) y ácido 4-bromo-1-naftoico (preparado de acuerdo con el procedimiento de Hausamann, *Chem. Ber.*, 1876, 9, 1519) en ácido 5-(1-carbamoil-7-(morfolin-4-carbonil)-9H-carbazol-4-il)-1-naftoico con un 42%

de rendimiento total. RMN de ^1H (400 MHz, metanol-d_4) δ 13.32 (s ancho,1 H) 11.80 (s, 1 H) 9.03 (d, J=9.0 Hz, 1 H) 8.29 (s ancho,1 H) 8.08 - 8.17 (m, 2 H) 7.82 (dd, J=8.7, 7.1 Hz, 1 H) 7.78 (s, 1 H) 7.64 (d, J=6.4 Hz, 1 H) 7.61 (s ancho,1 H) 7.55 (d, J=8.3 Hz, 1 H) 7.37 (dd, J=8.3, 7.3 Hz, 1 H) 7.16 (d, J=7.7 Hz, 1 H) 6.72 (dd, J=8.3, 1.3 Hz, 1 H) 6.28 (d, J=8.3 Hz, 1 H) 3.53 (s ancho,8 H). Espectro de masas m/z 494.3 $(M+H)^+$.

Los Ejemplos de la tabla siguiente también se prepararon usando los procedimientos usados para preparar los Ejemplos 2-1 a 2-4, o procedimientos relacionados parecidos.

Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
2-5	Ejemplo 1-1 [a]	ácido 3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-fluorobenzoico (preparado como la sal TFA)	475.3 $(M+H)^+$
2-6	Ejemplo 1-1 [a]	ácido 2-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-4-fluorofenil)acético (preparado como la sal TFA)	489.3 $(M+H)^+$

2-7	Ejemplo 1-1 [a]	4-(5-amino-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	446.3 $(M+H)^+$
2-8	Ejemplo 1-1 [a]	4-(2-fluoro-5-(trifluorometil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	499.3 $(M+H)^+$
2-9	Ejemplo 1-1 [a]	4-(2-fluoro-5-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	445.3 $(M+H)^+$
2-10	Ejemplo 1-1 [a]	4-(5-ciano-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	456.3 $(M+H)^+$
2-11	Ejemplo 1-1 [a]	4-(5-acetil-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	473.3 $(M+H)^+$
2-12	Ejemplo 1-1 [a]	4-(2,4-difluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	449.2 $(M+H)^+$
2-13	Ejemplo 1-1 [a]	4-(5-cloro-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	465, 467 $(M+H)^+$

2-14	Ejemplo 1-1 [a]	4-(2,6-difluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	449.2 (M+H)+
2-15	Ejemplo 1-1 [a]	4-(5-acetamidoisoquinolin-8-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	521.4 $(M+H)^+$
2-16	Ejemplo 1-4 [a]	ácido 3-(1-carbamoil-7-(morfolin-4-carbonil)-9H-carbazol-4-il)-4-fluorobenzoico	462.2 $(M+H)^+$
2-17	Ejemplo 1-4 [a]	ácido 2-(3-(1-carbamoil-7-(morfolin-4-carbonil)-9H-carbazol-4-il)-4-fluorofenil)acético	476.2 $(M+H)^+$
2-18	Ejemplo 1-2 [a]	4-(2-fluorofenil)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	431.2 $(M+H)^+$
2-19	Ejemplo 1-1 [a]	4-(1H-indazol-6-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	453.1 $(M+H)^+$
2-20	Ejemplo 1-1 [a]	4-(4-amino-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	446.1 $(M+H)^+$

2-21	Ejemplo 1-1 [a]	4-(4-acetamido-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	488.1 $(M+H)^+$
2-22	Ejemplo 1-1 [a]	4-(isoquinolin-8-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	464.3 $(M+H)^+$
2-23	Ejemplo 1-1 [a]	ácido 3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-4-fluorobenzoico (preparado como la sal TFA)	475.3 $(M+H)^+$
2-24	Ejemplo 1-1, Intermedio 12-2	4-(2-(etilcarbamoil)-1H-indol-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	523.2 $(M+H)^+$
2-25	Ejemplo 1-1, Intermedio 12-3	4-(2-(4-fluorofenilcarbamoil)-1H-indol-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	589.2 $(M+H)^+$
2-26	Ejemplo 1-1, Intermedio 30-1	4-(2-metil-3-(2-oxo-3-m-tolilimidazolidin-1-il)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	601.5 $(M+H)^+$

2-27	Ejemplo 1-1, Intermedio 6-1	4-(3-fluoro-2-(1-oxoisoindolin-2-il)piridin-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	563.3 $(M+H)^+$
2-28	Ejemplo 1-1 [b]	ácido 5-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-1-naftoico (preparado como la sal TFA)	507.3 $(M+H)^+$
2-29	Ejemplo 1-1 [a]	ácido 4-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-3-fluorobenzoico (preparado como la sal TFA)	475.3 $(M+H)^+$
2-30	Ejemplo 1-1, Intermedio 33-1	4-(2-metil-3-(4-metilpiridin-2-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	533.3 $(M+H)^+$
2-31	Ejemplo 1-1, Intermedio 33-2	4-(2-metil-3-(5-metilpiridin-2-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	533.3 $(M+H)^+$

2-32	Ejemplo 1-1, Intermedio 33-3	4-(2-metil-3-(piridin-2-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	519.3 $(M+H)^+$
2-33	Ejemplo 1-1, Intermedio 33-4	4-(2-metil-3-(3-metilpiridin-2-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	519.3 $(M+H)^+$
2-34	Ejemplo 1-1, Intermedio 35-4	4-(3-(4-(dimetilamino)benzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	589.4 $(M+H)^+$
2-35	Ejemplo 1-1, Intermedio 35-5	4-(5-acetamido-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	488.3 $(M+H)^+$
2-36	Ejemplo 1-1, Intermedio 35-6	4-(3-(4-fluorobenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	550.3 $(M+H)^+$

2-37	Ejemplo 1-1, Intermedio 35-3	4-(5-(acetamidometil)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	502.3 $(M+H)^+$
2-38	Ejemplo 1-1, Intermedio 35-7	4-(2-fluoro-3-(4-fluorobenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	568.2 $(M+H)^+$
2-39	Ejemplo 1-1, Intermedio 35-8	4-(3-(4-(dimetilamino)benzamido)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	593.3 $(M+H)^+$
2-40	Ejemplo 1-1, Intermedio 35-1	4-(2-fluoro-3-(4-fluoro-N-metilbenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	582.3 $(M+H)^+$
2-41	Ejemplo 1-1, Intermedio 35-9	4-(3-(4-fluoro-N-metilbenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	564.1 $(M+H)^+$

2-42	Ejemplo 1-1, Intermedio 35-10	4-(4-fluoro-3-(4-fluorobenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	568.1 $(M+H)^+$
2-43	Ejemplo 1-1, Intermedio 35-2	4-(4-(4-fluorobenzamido)piridin-2-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	551.3 $(M+H)^+$
2-44	Ejemplo 1-1, Intermedio 35-11	4-(2-fluoro-5-(4-fluorobenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	568.1 $(M+H)^+$
2-45	Ejemplo 1-1, Intermedio 35-12	4-(2-fluoro-5-((4-fluorobenzamido)metil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	582.1 $(M+H)^+$
2-46	Ejemplo 1-1, Intermedio 35-13	4-(3-acetamido-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	488.3 $(M+H)^+$

2-47	Ejemplo 1-1, Intermedio 36-1	4-(2-fluoro-5-(4-fluorofenilcarbamoil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	568.2 $(M+H)^+$
2-48	Ejemplo 1-1, Intermedio 36-3	4-(2-fluoro-3-(4-fluorofenilcarbamoil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	568.2 $(M+H)^+$
2-49	Ejemplo 1-1, Intermedio 36-4	4-(5-carbamoil-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	474.2 $(M+H)^+$
2-50	Ejemplo 1-1, Intermedio 36-5	4-(3-carbamoil-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, (preparado como la sal TFA)	474.2 $(M+H)^+$
2-51	Ejemplo 1-1, Intermedio 36-6	4-(2-fluoro-3-(metilcarbamoil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	488.2 $(M+H)^+$

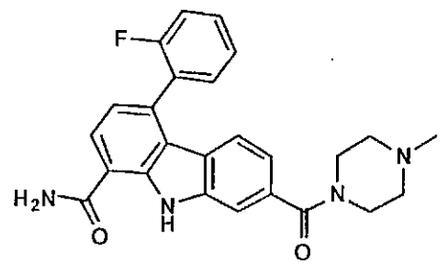
2-52	Ejemplo 1-1, Intermedio 36-7	4-(5-(dimetilcarbamoil)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	502.2 $(M+H)^+$
2-53	Ejemplo 1-1, Intermedio 36-2	4-(3-(dimetilcarbamoil)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	502.2 $(M+H)^+$
2-54	Ejemplo 1-1, Intermedio 37-1	4-(2-fluoro-3-(metilsulfonamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	524.1 $(M+H)^+$
2-55	Ejemplo 1-1, Intermedio 38-1	4-(2-fluoro-5-(3-(4-metiltiazol-2-il)ureido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	586.1 $(M+H)^+$
2-56	Ejemplo 1-1, Intermedio 38-2	4-(2-fluoro-5-((3-(4-metiltiazol-2-il)ureido)metil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	600.1 $(M+H)^+$

[a] Haluro de arilo disponible comercialmente.

[b] ácido 4-bromo-1-naftoico (preparado de acuerdo con el procedimiento de Hausamann, *Chem. Ber.*, 1876, 9, 1519.

Ejemplo 3-1

Preparación de 4-(2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

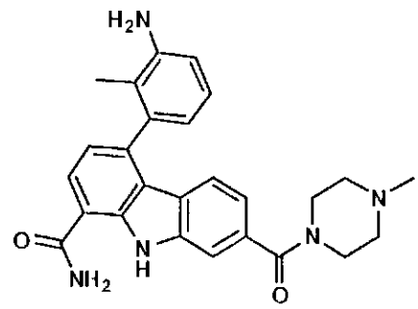


Se purgó con nitrógeno durante 5 minutos una suspensión de 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-1, 25 mg, 0.06 mmol), ácido 2-fluorofenil-borónico (0.17 mg, 0.12 mmol), carbonato potásico (21 mg, 0.15 mmol), y [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (5 mg, 0.006 mmol) en tolueno-etanol (2:1, 2.4 ml), luego se calentó a 90°C durante la noche. La mezcla se concentró y purificó por HPLC preparativa proporcionando 4-(2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (23 mg, 70%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.79 (s, 1 H) 8.26 (s ancho,1 H) 8.06 (d, J=7.91 Hz, 1 H) 7.86 (s, 1 H) 7.57 - 7.67 (m, 2 H) 7.55 (td, J=7.58, 1.76 Hz, 1 H) 7.39 - 7.49 (m, 2 H) 7.13 (d, J=7.69 Hz, 1 H)

7.07 - 7.11 (m, 1 H) 7.02 - 7.07 (m, 1 H) 3.81 (s ancho,4 H) 3.10 - 3.30 (m, 4 H) 2.79 (s, 3 H). Espectro de masas m/z 431.2 $(M+H)^+$.

Ejemplo 3-2

Preparación de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

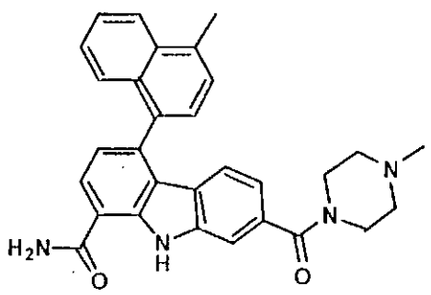


Se purgó con nitrógeno durante 5 minutos una suspensión de 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-1, 300 mg, 0.722 mmol), tetraquis-(trifenilfosfina)paladio (33.4 mg, 0.029 mmol), carbonato sódico acuoso 2 M (0.9 ml, 1.806 mmol) y 2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (Intermedio 50-1, 253 mg, 1.084 mmol) en tolueno-etanol (4:1, 15 ml) y luego se calentó a reflujo durante 7.5 h. La mezcla se concentró y el residuo se repartió entre cloroformo y agua. La fase acuosa se extrajo con cloroformo y las fases orgánicas reunidas se lavaron con salmuera, se secaron y se concentraron. El residuo se purificó por cromatografía en columna (eluyendo con DCM-amoníaco metanólico 2 M, gradiente desde 100:0 hasta 95:5) proporcionando 4-(3-amino-2-

metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido blanco (207 mg, 65%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.65 (s, 1 H) 8.16 (s ancho,1 H) 7.97 (d, J=7.91 Hz, 1 H) 7.78 (s, 1 H) 7.48 (s ancho,1 H) 7.08 (t, J=7.80 Hz, 1 H) 6.81 - 6.97 (m, 4 H) 6.49 - 6.65 (m, 1 H) 3.12 - 3.25 (m, 4 H) 2.92 - 3.10 (m, 4 H) 2.76 (s, 3 H) 1.70 (s, 3 H). Espectro de masas m/z 442.2 $(M+H)^+$.

Ejemplo 3-3

Preparación de 4-(4-metilnaftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

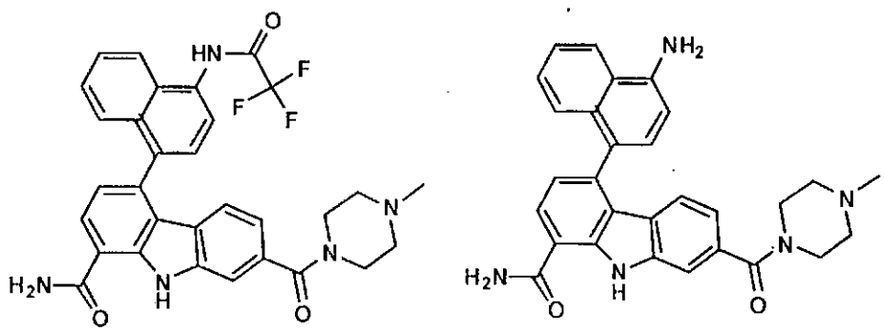


Usando el procedimiento del Ejemplo 3-1, se convirtieron 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-1, 25 mg, 0.06 mmol) y ácido 4-metilnaftalenoborónico (23 mg, 0.12 mmol) en 4-(4-metilnaftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, aislada como la sal TFA después de purificación por HPLC. Este material se repartió entre EtOAc y NaHCO3 (ac), y la fase acuosa se extrajo dos veces con EtOAc. Las fases orgánicas reunidas se secaron y concentraron proporcionando 4-(4-metilnaftalen-1-il)-7-(4-metilpiperazin-

1-carbonil)-9H-carbazol-1-carboxamida (23 mg, 79%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.76 (s, 1 H) 8.26 (s ancho,1 H) 8.16 (d, J=8.3 Hz, 1 H) 8.10 (d, J=7.7 Hz, 1 H) 7.75 (s, 1 H) 7.52 - 7.62 (m, 3 H) 7.45 (d, J=7.0 Hz, 1 H) 7.28 - 7.38 (m, 2 H) 7.11 (d, J=7.7 Hz, 1 H) 6.67 (dd, J=8.2, 1.4 Hz, 1 H) 6.37 (d, J=8.1 Hz, 1 H) 3.32 - 3.67 (m, 4 H) 2.80 (s, 3 H) 2.16 - 2.35 (m, 4 H) 2.14 (s, 3 H). Espectro de masas m/z 477.3 $(M+H)^+$.

Ejemplos 3-4 y 3-5

Preparación de 7-(4-metilpiperazin-1-carbonil)-4-(4-(2.2,2-trifluoroacetamido)naftalen-1-il)-9H-carbazol-1-carboxamida y 4-(4-aminonaftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

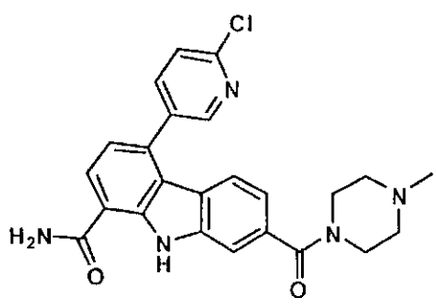


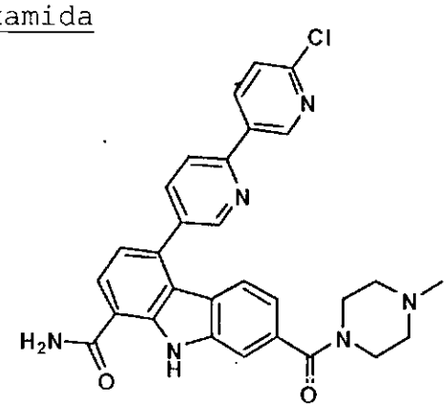
Usando el procedimiento del Ejemplo 3-3, se convirtieron 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-1, 25 mg, 0.06 mmol) y ácido 4-(2.2,2-trifluoroacetamido)naftalen-1-ilborónico (34 mg, 0.12 mmol) en 7-(4-metilpiperazin-1-carbonil)-4-(4-(2.2,2-trifluoroacetamido)naftalen-1-il)-9H-carbazol-1-

carboxamida (9.7 mg, 28%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.76 (s, 1 H) 11.63 (s ancho,1 H) 8.25 (s ancho,1 H) 8.09 (d, J=7.7 Hz, 1 H) 8.04 (d, J=8.3 Hz, 1 H) 7.75 (d, J=7.5 Hz, 1 H) 7.73 (d, J=0.7 Hz, 1 H) 7.54 - 7.61 (m, 3 H) 7.31 - 7.38 (m, 2 H) 7.14 (d, J=7.7 Hz, 1 H) 6.63 (dd, J=8.1, 1.5 Hz, 1 H) 6.33 (d, J=8.1 Hz, 1 H) 3.44 - 3.56 (m, 4 H) 2.14 - 2.31 (m, 4 H) 2.11 (s, 3 H). Espectro de masas m/z 574.3 $(M+H)^+$. También se obtuvo 4-(4-aminonaftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (14 mg, 50%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.63 (s, 1 H) 8.15 (d, J=8.3 Hz, 2 H) 8.01 (d, J=7.5 Hz, 1 H) 7.68 (s, 1 H) 7.48 (s ancho,1 H) 7.32 (t, J=7.3 Hz, 1 H) 7.11 - 7.23 (m, 3 H) 7.03 (d, J=7.7 Hz, 1 H) 6.79 (d, J=7.7 Hz, 1 H) 6.64 (d, J=8.3 Hz, 1 H) 6.49 (d, J=7.9 Hz, 1 H) 5.93 (s, 2 H) 3.34 - 3.60 (m, 4 H) 2.13 - 2.31 (m, 4 H) 2.10 (s, 3 H). Espectro de masas m/z 478.3 $(M+H)^+$.

Ejemplos 3-6 y 3-7

Preparación de 4-(6-cloropiridin-3-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida y 4-(6'-cloro-2,3'-bipiridin-5-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



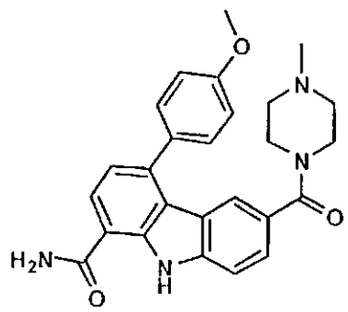


Usando el procedimiento del Ejemplo 3-2, se

convirtió 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-1, 25 mg, 0.060 mmol) y ácido 6-cloropiridin-3-ilborónico (19 mg, 0.120 mmol) en 4-(6-cloropiridin-3-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido amarillo claro (11 mg, 26%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.87 (s, 1 H) 9.85 (s ancho,1 H) 8.65 (d, J=2.0 Hz, 1 H) 8.29 (s ancho,1 H) 8.13 (dd, J=8.2, 2.4 Hz, 1 H) 8.09 (d, J=7.9 Hz, 1 H) 7.90 (s, 1 H) 7.77 (d, J=8.3 Hz, 1 H) 7.62 (s ancho,1 H) 7.30 (d, J=8.3 Hz, 1 H) 7.16 (d, J=7.9 Hz, 1 H) 7.10 (dd, J=8.2, 1.4 Hz, 1 H) 3.03 - 3.27 (m, 8 H) 2.82 (s, 3 H). Espectro de masas m/z 448.1 $(M+H)^+$. También se aisló 4-(6'-cloro-2,3'-bipiridin-5-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido amarillo (6 mg, 11%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.89 (s, 1 H) 9.99 (s ancho,1 H) 9.26 (d, J=2.4 Hz, 1 H) 8.96 (d, J=2.2 Hz, 1 H) 8.66 (dd, J=8.3, 2.4 Hz, 1 H) 8.35 (d, J=8.1 Hz, 1 H) 8.30 (s ancho,1 H) 8.22 (dd, J=8.1, 2.2 Hz, 1 H) 8.12 (d, J=7.9 Hz, 1 H) 7.92 (s, 1 H) 7.72 (d, J=8.6 Hz, 1 H) 7.62 (s ancho,1 H) 7.41 (d, J=8.3 Hz, 1 H) 7.22 (d, J=7.7 Hz, 1 H) 7.09 (dd, J=8.2, 1.4 Hz, 1 H) 3.02 - 3.53 (m, 8 H) 2.82 (s, 3 H). Espectro de masas m/z 525.2 $(M+H)^+$.

Ejemplo 3-8

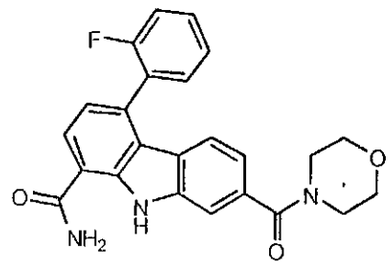
Preparación de 4-(4-metoxifenil)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 3-1, se convirtieron 4-bromo-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-2, 25 mg, 0.06 mmol) y ácido 4-metoxifenilborónico (14 mg, 0.09 mmol) en 4-(4-metoxifenil)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, (8 mg, 22%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.84 (s, 1 H) 8.22 (s ancho,1 H) 8.03 (d, *J*=7.69 Hz, 1 H) 7.83 (d, *J*=8.35 Hz, 1 H) 7.53 - 7.62 (m, 4 H) 7.51 (dd, *J*=8.57, 1.54 Hz, 1 H) 7.14 (d, *J*=8.79 Hz, 2 H) 7.06 (d, *J*=7.69 Hz, 1 H) 4.11 - 4.38 (m, 2 H) 3.88 (s, 3H) 3.10 - 3.28 (m, 4 H) 2.87 - 3.04 (m, 2 H) 2.81 (s, 3 H). Espectro de masas m/z 443.3 $(M+H)^+$.

Ejemplo 3-9

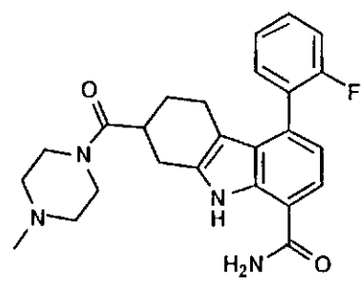
Preparación de 4-(2-fluorofenil)-7-(morfolin-4-carbonil)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 3-1, se convirtieron 4-bromo-7-(morfolin-4-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-4, 25 mg, 0.06 mmol) y ácido 2-fluorofenilborónico (17.4 mg, 0.124 mmol) en 4-(2-fluorofenil)-7-(morfolin-4-carbonil)-9H-carbazol-1-carboxamida (15.9 mg, 61%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.76 (s, 1 H) 8.25 (s ancho,1 H) 8.06 (d, J=7.9 Hz, 1 H) 7.82 (s, 1 H) 7.53 - 7.66 (m, 3 H) 7.40 - 7.48 (m, 2 H) 7.12 (d, J=7.7 Hz, 1 H) 7.09 (dd, J=8.2, 0.8 Hz, 1 H) 6.99 (dd, J=8.2, 1.0 Hz, 1 H) 3.59 (s ancho,8 H). Espectro de masas m/z 418.2 $(M+H)^+$.

Ejemplo 3-10

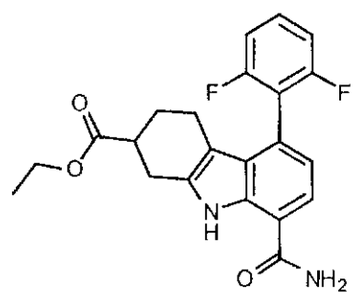
Preparación de 5-(2-fluorofenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida



Siguiendo el procedimiento del Ejemplo 3-1, se convirtieron 5-bromo-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Ejemplo 1-3, 30 mg, 0.072 mmol) y ácido 2-fluorofenilborónico (20 mg, 0.143 mmol) en 5-(2-fluorofenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida, sal TFA, como sólido blanco (25 mg, 62%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 10.92 (d, 1 H) 8.04 (s ancho,1 H) 7.62 (d, J=7.47 Hz, 1 H) 7.42 - 7.50 (m, 1 H) 7.17 - 7.41 (m, 4 H) 6.76 - 6.89 (m, 1 H) 4.37 - 4.57 (m, 1 H) 4.09 - 4.29 (m, 2 H) 3.46 - 3.62 (m, 2 H) 2.83 - 3.15 (m, 6 H) 2.80 (s, 3 H) 2.10 - 2.42 (m, 1 H) 1.86 - 2.07 (m, 1 H) 1.68 - 1.84 (m, 1 H) 1.27 - 1.60 (m, 1 H). Espectro de masas m/z 435.3 $(M+H)^+$.

Ejemplo 3-11

Preparación de 8-carbamoil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-2-carboxilato de etilo

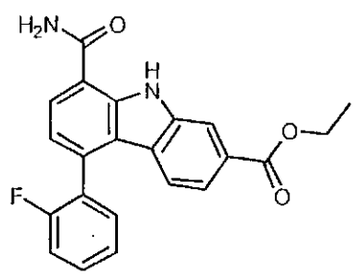


Se purgó con nitrógeno durante 2 minutos una mezcla de 5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-carboxilato de etilo (Intermedio 47-1, 20 mg, 0.055 mmol), ácido 2,6-difluorofenilborónico (17.3 mg, 0.110 mmol),

diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (4.5 mg, 11.0 mmol), carbonato potásico (15.1 mg, 0.110 mmol) y tris(dibencilidenoacetona)dipaladio (5.0 mg, 0.005 mmol) en THF (2 ml), luego se calentó en un tubo sellado durante la noche. La mezcla se filtró y se concentró, y el residuo se purificó por HPLC preparativa. Las fracciones de efluente apropiadas se basificaron con hidróxido sódico acuoso 1 M y se extrajeron dos veces con DCM. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron proporcionando 8-carbamoil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-2-carboxilato de etilo como un sólido amarillo claro (10 mg, 44%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.10 (1 H, s ancho), 7.31 - 7.44 (2 H, m), 6.95 - 7.06 (3 H, m), 4.10 - 4.22 (2 H, m), 2.96 - 3.12 (2 H, m), 2.80 (1 H, dddd, J=17.52, 5.99, 3.08, 2.86 Hz), 2.27 - 2.41 (1 H, m), 2.15 - 2.27 (1 H, m), 2.04 - 2.14 (1 H, m), 1.69 - 1.85 (1 H, m), 1.26 (3 H, t, J=7.25 Hz). Espectro de masas m/z 399.1 $(M+H)^+$.

Ejemplo 3-12

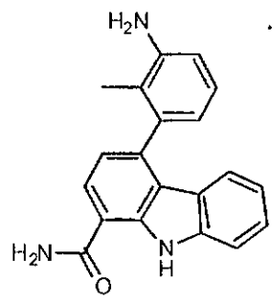
Preparación de 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-carboxilato de etilo



Siguiendo el procedimiento del Ejemplo 3-1, se convirtieron 5-bromo-8-carbamoil-9H-carbazol-2-carboxilato de etilo (Intermedio 48-1, 1.00 g, 2.35 mmol) y ácido 2-fluorofenilborónico (395 mg, 2.82 mmol) en 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-carboxilato de etilo como sólido blanco (72%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.91 (1 H, s), 8.46 (1 H, s), 8.26 (1 H, s ancho), 8.09 (1 H, d, J=7.7 Hz), 7.52 - 7.68 (4 H, m), 7.39 - 7.49 (2 H, m), 7.15 (2 H, d, J=7.9 Hz), 4.32 (2 H, q, J=7.0 Hz), 1.33 (3 H, t, J=7.1 Hz). Espectro de masas m/z 377.1 $(M+H)^+$.

Ejemplo 3-13

Preparación de 4-(3-amino-2-metilfenil)-9H-carbazol-1-carboxamida

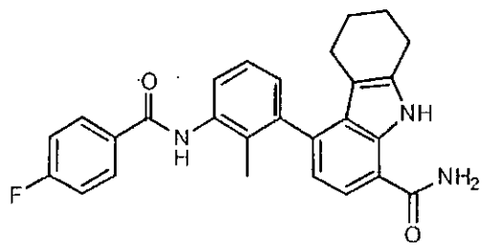


Usando el procedimiento del Ejemplo 3-2, se convirtió 4-bromo-9H-carbazol-1-carboxamida (Intermedio 48-3, 100 mg, 0.35 mmol) en 4-(3-amino-2-metilfenil)-9H-carbazol-1-carboxamida como un sólido blanquecino (109 mg, 64%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 7.93 (1 H, d, J=7.7 Hz), 7.57 (1 H, d, J=8.1 Hz), 7.33 (1 H, ddd, J=8.2, 7.1, 1.2 Hz), 7.16 (1 H, t, J=7.8 Hz), 6.98 - 7.02 (2 H, m), 6.95 (1 H, dd, J=7.9, 0.9

Hz), 6.87 - 6.93 (1 H, m), 6.72 (1 H, dd, J=7.5, 0.9 Hz), 1.85 (3 H, s). Espectro de masas m/z 316.2 $(M+H)^+$.

Ejemplo 3-14

Preparación de 5-(3-(4-fluorobenzamido)-2-metilfenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida



Usando el procedimiento del Ejemplo 3-2, se convirtieron 5-bromo-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Intermedio 47-3, 30 mg, 0.102 mmol) y 4-fluoro-N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)benzamida (Intermedio 53-1, 36.3 mg, 0.102 mmol) en 5-(3-(4-fluorobenzamido)-2-metilfenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido blanquecino (5.7 mg, 12%). RMN de ^1H (400 MHz, DMSO-d_6) δ 8.04 - 8.15 (2 H, m), 7.62 (1 H, d, J=7.5 Hz), 7.32 - 7.43 (3 H, m), 7.27 (1 H, t, J=7.6 Hz), 7.09 (1 H, d, J=7.3 Hz), 6.73 (1 H, d, J=7.7 Hz), 4.06 (2 H, s), 2.74 (2 H, s ancho), 1.89 (3 H, s), 1.65 - 1.75 (2 H, m), 1.48 - 1.60 (2 H, m). Espectro de masas m/z 442.3 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 3-1 a 3-14 y procedimientos similares.

Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
3-15	Ejemplo 1-1 [a]	4-(2.3-difluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	449.2 $(M+H)^+$
3-16	Ejemplo 1-1 [a]	4-(2.3-diclorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	481.1 $(M+H)^+$
3-17	Ejemplo 1-1 [a]	4-(2,4-diclorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	481.1 $(M+H)^+$
3-18	Ejemplo 1-1 [a]	4-(2-etoxinaftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	507.4 $(M+H)^+$
3-19	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(quinolin-8-il)-9H-carbazol-1-carboxamida	464.3 $(M+H)^+$
3-20	Ejemplo 1-1 [a]	4-(isoquinolin-5-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	464.3 $(M+H)^+$

3-21	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(quinolin-5-il)-9H-carbazol-1-carboxamida	464.3 $(M+H)^+$
3-22	Ejemplo 1-1 [a]	4-(isoquinolin-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	464.3 $(M+H)^+$
3-23	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(quinolin-4-il)-9H-carbazol-1-carboxamida	464.3 $(M+H)^+$
3-24	Ejemplo 1-1 [a]	4-(4-aminofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	428.2 $(M+H)^+$
3-25	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(piridin-3-il)-9H-carbazol-1-carboxamida, sal TFA	414.2 $(M+H)^+$
3-26	Ejemplo 1-1 [a]	4-(4-hidroxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	429.2 $(M+H)^+$
3-27	Ejemplo 1-2 [a]	4-(3-metoxifenil)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	443.3 $(M+H)^+$

3-28	Ejemplo 1-2 [a]	4-(4-acetamidofenil)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	470.3 $(M+H)^+$
3-29	Ejemplo 1-2 [a]	4-(3-acetamidofenil)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	470.3 $(M+H)^+$
3-30	Ejemplo 1-2 [a]	6-(4-metilpiperazin-1-carbonil)-4-(naftalen-1-il)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	463.3 $(M+H)^+$
3-31	Ejemplo 1-1 [a]	4-(1H-indol-6-il)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	452.2 $(M+H)^+$
3-32	Ejemplo 1-1 [a]	4-(1H-indol-4-il)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	452.2 $(M+H)^+$
3-33	Ejemplo 1-1 [a]	4-(3-fluoropiridin-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	432.1 $(M+H)^+$
3-34	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(3-metilpiridin-4-il)-9H-carbazol-1-carboxamida	428.1 $(M+H)^+$

3-35	Ejemplo 1-1 [a]	4-(3-clorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	447.2 $(M+H)^+$
3-36	Ejemplo 1-1 [a]	4-(4-clorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida(preparado como la sal TFA)	447.2 $(M+H)^+$
3-37	Ejemplo 1-1, Intermedio 50-45	4-(3-amino-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	446.1 $(M+H)^+$
3-38	Ejemplo 1-1 [a]	4-(2-fluoro-5-metoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	461.2 $(M+H)^+$
3-39	Ejemplo 1-1 [a]	4-(5-etoxi-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	475.1 $(M+H)^+$
3-40	Ejemplo 1-1 [a]	4-(2-fluoro-5-(hidroximetil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	461.1 $(M+H)^+$

3-41	Ejemplo 1-1 [a]	4-(4-metil-2-(4-(trifluorometil)fenil)tiazol-5-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	578.2 $(M+H)^+$
3-42	Ejemplo 1-1 [a]	4-(2-etilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	441.2 $(M+H)^+$
3-43	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(2-(trifluorometil)fenil)-9H-carbazol-1-carboxamida	481.2 $(M+H)^+$
3-44	Ejemplo 1-1 [a]	4-(2,6-dimetilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	441.2 $(M+H)^+$
3-45	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-fenil-9H-carbazol-1-carboxamida (preparada como la sal TFA)	413.1 $(M+H)^+$
3-46	Ejemplo 1-1 [a]	4-(5-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	442.2 $(M+H)^+$
3-47	Ejemplo 1-1 [a]	4-(1H-indol-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	452.2 $(M+H)^+$

3-48	Ejemplo 1-1 [a]	4-(bifenil-3-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	489.4 $(M+H)^+$
3-49	Ejemplo 1-1 [a]	4-(dibenzo[b,d]furan-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	503.4 $(M+H)^+$
3-50	Ejemplo 1-1, Intermedio 50-2	4-(3-ciano-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	452.3 $(M+H)^+$
3-51	Ejemplo 1-1, Intermedio 50-3	4-(4-amino-2,6-difluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	464.3 $(M+H)^+$
3-52	Ejemplo 1-1 [a]	4-(4-metoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	443.3 $(M+H)^+$
3-53	Ejemplo 1-1 [a]	4-(3-metoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	443.3 $(M+H)^+$

3-54	Ejemplo 1-1 [a]	4-(2,4-difluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida(preparado como la sal TFA)	449.3 $(M+H)^+$
3-55	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(4-fenoxifenil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	505.3 $(M+H)^+$
3-56	Ejemplo 1-1 [a]	4-(3,4-diclorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	481.2 $(M+H)^+$
3-57	Ejemplo 1-1 [a]	ácido 4-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)benzoico (preparado como la sal TFA)	457.3 $(M+H)^+$
3-58	Ejemplo 1-1 [a]	ácido 3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)benzoico (preparado como la sal TFA)	457.3 $(M+H)^+$
3-59	Ejemplo 1-1 [a]	4-(4-acetamidofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	470.3 $(M+H)^+$

3-60	Ejemplo 1-1 [a]	4-(3-acetamidofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	470.4 $(M+H)^+$
3-61	Ejemplo 1-1 [a]	4-(4-(metilcarbamoil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	470.3 $(M+H)^+$
3-62	Ejemplo 1-1 [a]	4-(3-(metilcarbamoil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	470.4 $(M+H)^+$
3-63	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(naftalen-2-il)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	463.3 $(M+H)^+$
3-64	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(naftalen-1-il)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	463.3 $(M+H)^+$
3-65	Ejemplo 1-1 [a]	4-(4-*terc*-butilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	469.4 $(M+H)^+$

3-66	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-(3-(metilsulfonamido)fenil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	506.3 $(M+H)^+$
3-67	Ejemplo 1-1 [a]	7-(4-metilpiperazin-1-carbonil)-4-o-tolil-9H-carbazol-1-carboxamida (preparada como la sal TFA)	427.4 $(M+H)^+$
3-68	Ejemplo 1-1 [a]	4-(3-cloro-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	461.2 $(M+H)^+$
3-69	Ejemplo 1-1 [a]	4-(2-clorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	447.2 $(M+H)^+$
3-70	Ejemplo 1-1 [a]	4-(2-metoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	443.2 $(M+H)^+$

3-71	Ejemplo 1-3 [a]	5-(2,4-difluorofenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como la sal TFA)	453.2 $(M+H)^+$
3-72	Ejemplo 1-3 [a]	5-(2.3-difluorofenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como la sal TFA)	453.2 $(M+H)^+$
3-73	Ejemplo 1-3 [a]	5-(4-acetamidofenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como la sal TFA)	474.3 $(M+H)^+$
3-74	Ejemplo 1-3 [a]	2-(4-metilpiperazin-1-carbonil)-5-(naftalen-1-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como la sal TFA)	467.3 $(M+H)^+$

3-75	Ejemplo 1-1, Intermedio 50-31	7-(4-metilpiperazin-1-carbonil)-4-(2-(pirrolidin-1-carbonil)-1H-indol-4-il)-9H-carbazol-1-carboxamida	549.2 $(M+H)^+$
3-76	Ejemplo 1-1, Intermedio 50-4	4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	558.2 $(M+H)^+$
3-77	Ejemplo 1-1, Intermedio 50-32	4-(3-(isoindolin-2-il)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	544.3 $(M+H)^+$
3-78	Ejemplo 1-1, Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	576.3 $(M+H)^+$

3-79	Ejemplo 1-1, Intermedio 50-15	4-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	614.4 $(M+H)^+$
3-80	Intermedio 48-3, Intermedio 50-4	4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	432.2 $(M+H)^+$
3-81	Ejemplo 1-1, Intermedio 52-1	4-(8-metil-2-fenilcroman-7-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	559.2 $(M+H)^+$
3-82	Ejemplo 1-1, Intermedio 50-33	7-(4-metilpiperazin-1-carbonil)-4-(2-oxo-3-fenil-3,4-dihidro-2H-benzo[e][1,3]oxazin-6-il)-9H-carbazol-1-carboxamida	560.4 $(M+H)^+$

3-83	Ejemplo 1-1, Intermedio 50-37	4-(6-(4-fluorofenil)-1H-indol-3-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	546.3 $(M+H)^+$
3-84	Intermedio 48-1, Intermedio 50-4	8-carbamoil-5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-carboxilato de etilo	526.1 $(M+Na)^+$
3-85	Ejemplo 1-1, Intermedio 50-46	4-(2-(4-fluorofenil)-7-metil-1H-benzo[d]imidazol-6-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	561.2 $(M+H)^+$
3-86	Ejemplo 1-1, Intermedio 50-39	7-(4-metilpiperazin-1-carbonil)-4-(1-oxo-1.2.3,4-tetrahidroisoquinolin-7-il)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	482.2 $(M+H)^+$

3-87	Ejemplo 1-1, Intermedio 50-40	4-(2-(4-fluorofenil)-1-oxo-1.2.3,4-tetrahidroisoquinolin-7-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	576.3 $(M+H)^+$
3-88	Ejemplo 1-1, Intermedio 50-41	4-(1-(4-fluorobencil)-1H-indol-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	560.3 $(M+H)^+$
3-89	Ejemplo 1-1, Intermedio 50-33	4-(5-metil-2-oxo-3-fenil-3,4-dihidro-2H-benzo[e][1,3]oxazin-6-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	574.3 $(M+H)^+$
3-90	Ejemplo 1-1, Intermedio 50-34	4-(5-metil-4-oxo-3-fenil-3,4-dihidro-2H-benzo[e][1,3]oxazin-6-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	574.3 $(M+H)^+$

3-91	Ejemplo 1-1, Intermedio 50-35	4-(4-hidroxi-2-metil-3-(fenilcarbamoil)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	562.3 $(M+H)^+$
3-92	Ejemplo 1-1, Intermedio 50-21	4-(4-metil-5-(1-oxoisoindolin-2-il)piridin-3-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	559.4 $(M+H)^+$
3-93	Ejemplo 1-4, Intermedio 50-21	4-(4-metil-5-(1-oxoisoindolin-2-il)piridin-3-il)-7-(morfolin-4-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	546.4 $(M+H)^+$
3-94	Ejemplo 1-1, Intermedio 50-20	4-(4-metil-5-(5-metil-1-oxoisoindolin-2-il)piridin-3-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	573.4 $(M+H)^+$

3-95	Ejemplo 1-4, Intermedio 50-20	4-(4-metil-5-(5-metil-1-oxoisoindolin-2-il)piridin-3-il)-7-(morfolin-4-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	560.3 $(M+H)^+$
3-96	Ejemplo 1-1, Intermedio 50-42	4-(5-(4-fluorobenzoil)naftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	585.4 $(M+H)^+$
3-97	Intermedio 48-3, Intermedio 53-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	438.2 $(M+H)^+$
3-98	Ejemplo 1-1, Intermedio 50-36	4-(3-(1H-indazol-3-ilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	558.5 $(M+H)^+$

3-99	Intermedio 47-3, Intermedio 50-4	5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	436.3 $(M+H)^+$
3-100	Intermedio 48-1, Intermedio 53-1	8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxilato de etilo	510.13 $(M+H)^+$
3-101	Ejemplo 1-5, Intermedio 50-4	N^2-(3-(dimetilamino)propil)-5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	564.2 $(M+H)^+$
3-102	Ejemplo 1-6, Intermedio 50-4	N^2-(4-(dimetilamino)butil)-5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	578.2 $(M+H)^+$

3-103	Ejemplo 1-5 [a]	N^2-(3-(dimetilamino)propil)-5-(2-fluoro-5-metoxifenil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	467.2 $(M+H)^+$
3-104	Ejemplo 1-5 [a]	N^2-(3-(dimetilamino)propil)-5-(5-etoxi-2-fluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	481.2 $(M+H)^+$
3-105	Ejemplo 1-5 [a]	N^2-(3-(dimetilamino)propil)-5-(2-fluoro-5-(hidroximetil)fenil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	467.2 $(M+H)^+$
3-106	Ejemplo 1-7, Intermedio 50-4	5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	563.2 $(M+H)^+$
3-107	Ejemplo 1-7, Intermedio 50-32	5-(3-(isoindolin-2-il)-2-metilfenil)-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	549.3 $(M+H)^+$

3-108	Ejemplo 1-8, Intermedio 53-1	5-(3-(4-fluorobenzamido)-2-metilfenil)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	582.3 $(M+H)^+$
3-109	Ejemplo 1-8 [a]	5-(2,4-dimetiltiazol-5-il)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	466.2 $(M+H)^+$
3-110	Ejemplo 1-8, Intermedio 50-4	5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	576.3 $(M+H)^+$
3-111	Ejemplo 1-8, Intermedio 54-1	5-(8-carbamoil-2-(1-metilpiperidin-4-ilcarbamoil)-2,3,4,9-tetrahidro-1H-carbazol-5-il)tiazol-2-il(isopropil)carbamato de terc-butilo	595.3 $(M+H)^+$
3-112	Ejemplo 1-8, [a]	5-(furan-3-il)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	421.1 $(M+H)^+$

3-113	Ejemplo 1-8, [a]	5-(benzofuran-2-il)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	471.2 $(M+H)^+$
3-114	Ejemplo 1-7, [a]	5-(3-formilfuran-2-il)-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	436.1 $(M+H)^+$
3-115	Ejemplo 1-7, [a]	5-(1-metil-1H-pirazol-5-il)-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	422.2 $(M+H)^+$
3-116	Ejemplo 1-7, [a]	4-(8-carbamoil-2-(tetrahidro-2H-piran-4-ilcarbamoil)-2,3,4,9-tetrahidro-1H-carbazol-5-il)-1H-pirazol-1-carboxilato de terc-butilo	408.2 (M+H-Boc)$^+$
3-117	Ejemplo 1-7, [a]	5-ciclohexenil-N2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	422.3 $(M+H)^+$

3-118	Ejemplo 1-3, Intermedio 50-19	5-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	580.4 $(M+H)^+$
3-119	Ejemplo 1-3, Intermedio 50-5	5-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	580.4 $(M+H)^+$
3-120	Ejemplo 1-3, Intermedio 50-18	5-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	576.4 $(M+H)^+$
3-121	Ejemplo 1-3, Intermedio 50-8	5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	576.4 $(M+H)^+$

3-122	Ejemplo 1-3, Intermedio 50-4	5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	562.4 $(M+H)^+$
3-123	Ejemplo 1-3, Intermedio 50-43	5-(2-metil-3-(2-oxopiperidin-1-il)fenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	528.4 $(M+H)^+$
3-124	Ejemplo 1-7, Intermedio 50-47	5-(2-(N,N-bis(*terc*-butoxicarbonil)amino)-4-metiltiazol-5-il)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	654.4 $(M+H)^+$
3-125	Ejemplo 1-9, Intermedio 50-4	N^2-metil-5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	590.4 $(M+H)^+$

3-126	Ejemplo 1-9, Intermedio 50-19	5-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-N^2-metil-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	608.4 $(M+H)^+$
3-127	Ejemplo 1-9, Intermedio 50-18	N^2-metil-5-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	604.5 $(M+H)^+$
3-128	Ejemplo 1-9, Intermedio 50-29	N^2-metil-5-(2-metil-3-(1-oxoisoquinolin-2(1H)-il)fenil)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	602.4 $(M+H)^+$
3-129	Ejemplo 1-9, Intermedio 50-9	5-(3-(6-ciano-1-oxoisoindolin-2-il)-2-metilfenil)-N^2-metil-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	615.5 $(M+H)^+$

3-130	Ejemplo 1-9, Intermedio 50-7	N^2-metil-5-(2-metil-3-(1-oxo-6-(trifluorometil)isoindolin-2-il)fenil)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	658.3 $(M+H)^+$
3-131	Ejemplo 1-3, Intermedio 50-20	5-(4-metil-5-(5-metil-1-oxoisoindolin-2-il)piridin-3-il)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como la sal TFA)	577.3 $(M+H)^+$
3-132	Intermedio 48-1, Intermedio 50-24	8-carbamoil-5-(2-metil-3-(4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-2-carboxilato de etilo	517.0 $(M+H)^+$
3-133	Intermedio 48-1, Intermedio 50-48	8-carbamoil-5-(3-(8-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-2-carboxilato de etilo	535.1 $(M+H)^+$

3-134	Intermedio 48-1, Intermedio 50-27	8-carbamoil-5-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-2-carboxilato de etilo	535.3 $(M+H)^+$
3-135	Intermedio 48-1, Intermedio 50-29	8-carbamoil-5-(2-metil-3-(6-metil-4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-2-carboxilato de etilo	531.3 $(M+H)^+$
3-136	Ejemplo 1-7, Intermedio 50-10	4-(3-(5-fluoro-1,3-dioxoisoindolin-2-il)-2-metilfenil)-N^7-(tetrahidro-2H-piran-4-il)-9H-carbazol-1.7-dicarboxamida[b]	591.3 $(M+H)^+$
3-137	Ejemplo 1-1 [a]	4-(2-fluoro-3-metoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	461.2 $(M+H)^+$

3-138	Intermedio 48-1, Intermedio 50-8	8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-carboxilato de etilo	518.1 $(M+H)^+$
3-139	Intermedio 48-1, Intermedio 50-5	8-carbamoil-5-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-2-carboxilato de etilo	544.1 $(M+Na)^+$
3-140	Intermedio 48-1, Intermedio 50-17	8-carbamoil-5-(3-(4-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-2-carboxilato de etilo	544.1 $(M+Na)^+$
3-141	Intermedio 48-3, Intermedio 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	463.1 $(M+H)^+$

3-142	Intermedio 48-3, Intermedio 50-24	4-(2-metil-3-(4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	445.1 $(M+H)^+$
3-143	Intermedio 1-10(a), Intermedio 50-5	4-(3-(6-fluoro-1-oxoindolin-2-il)-2-metilfenil)-N^7,N^7-dimetil-9H-carbazol-1,7-dicarboxamida	521.0 $(M+H)^+$
3-144	Intermedio 1-10(a), Intermedio 50-24	N^7,N^7-dimetil-4-(2-metil-3-(4-oxaquinazolin-3(4H)-il)fenil)-9H-carbazol-1,7-dicarboxamida	516.0 $(M+H)^+$
3-145	Intermedio 1-10(a), Intermedio 50-8	N^7,N^7-dimetil-4-(2-metil-3-(6-metil-1-oxoindolin-2-il)fenil)-9H-carbazol-1,7-dicarboxamida	517.1 $(M+H)^+$

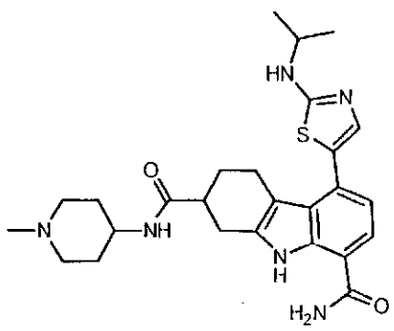
3-146	Intermedio 48-3, Intermedio 50-48	4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	463.1 $(M+H)^+$

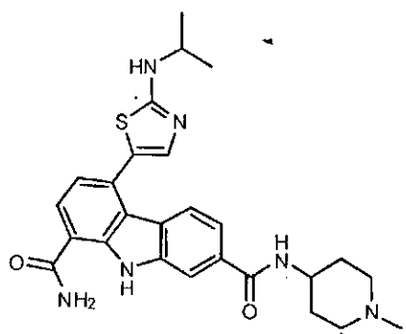
[a] Ácido borónico o éster boronato disponible comercialmente.

[b] Obtenido como subproducto de la reacción de 5-fluoro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1,3-diona (Intermedio 50-10) con 5-bromo-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida (Ejemplo 1-7(a)).

Ejemplos 4-1 y 4-2

Preparación de 5-(2-(isopropilamino)tiazol-5-il)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida y 4-(2-(isopropilamino)tiazol-5-il)-N^7-(1-metilpiperidin-4-il)-9H-carbazol-1,7-dicarboxamida





Se agitó a ta durante 2 h una solución de 5-(8-carbamoil-2-(1-metilpiperidin-4-ilcarbamoil)-2,3,4,9-tetrahidro-1H-carbazol-5-il)tiazol-2-il(isopropil)carbamato de terc-butilo (Ejemplo 3-111, 35 mg, 0.059 mmol) en DCM (1 ml) y TFA (1 ml). La solución se concentró y el residuo se repartió entre DCM y bicarbonato sódico acuoso 1 M. La fase orgánica se concentró y el residuo se purificó por HPLC preparativa. Las fracciones de efluente apropiadas se basificaron con hidróxido sódico acuoso 1 M, se extrajeron dos veces con DCM y las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron proporcionando 5-(2-(isopropilamino)tiazol-5-il)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida (Ejemplo 4-1, 18 mg, 61%) como un sólido blanco. RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.51 (1 H, d, *J*=7.91 Hz), 6.95 (1 H, d, *J*=7.91 Hz), 6.89 (1 H, s), 3.81 - 3.89 (1 H, m), 3.64 - 3.73 (1 H, m), 2.79 - 3.07 (4 H, m), 2.49 - 2.75 (3 H, m), 2.27 (3 H, s), 2.09 - 2.18 (2 H, m), 1.97 - 2.06 (1 H, m), 1.84 - 1.92 (2 H, m), 1.70 - 1.83 (1 H, m), 1.48 - 1.61 (2 H, m), 1.27 (6 H, d, *J*=6.15 Hz). Espectro de masas m/z 495.2 $(M+H)^+$. También se obtuvo 4-(2-(isopropilamino)tiazol-5-il)-N^7-(1-metilpiperidin-4-il)-9H-carbazol-1,7-dicarboxamida como un sólido blanco (Ejemplo 4-2, 5.2 mg, 18%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.04 - 8.10 (2 H, m), 7.88 - 7.93 (1 H, m), 7.52 - 7.58 (1 H, m), 7.25 (1 H, s), 7.14 - 7.20 (1 H, m),

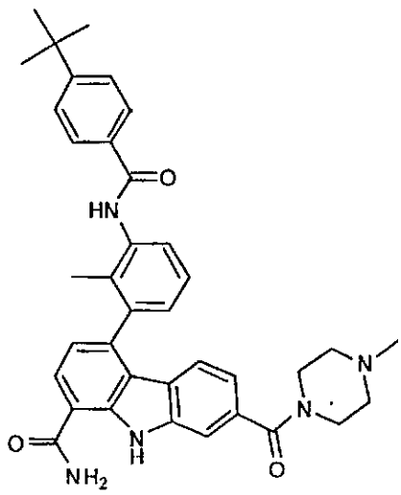
3.87 - 3.98 (2 H, m), 2.88 - 2.97 (2 H, m), 2.31 (3 H, s), 2.15 - 2.24 (2 H, m), 1.95 - 2.03 (2 H, m), 1.64 - 1.79 (2 H, m), 1.32 (6 H, d, J=6.59 Hz). Espectro de masas m/z 491.2 $(M+H)^+$.

El siguiente compuesto se preparó también a partir del Ejemplo 3-124 usando procedimientos usados para preparar el Ejemplo 4-1:

Ejemplo	Nombre del compuesto	Espectro de masas
4-3	5-(2-amino-4-metiltiazol-5-il)-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	454.2 $(M+H)^+$

Ejemplo 5-1

Preparación de 4-(3-(4-*terc*-butilbenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

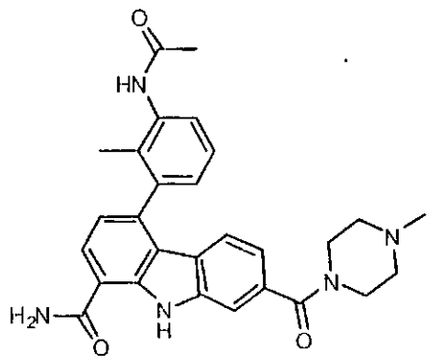


Se trató una solución de 4-(3-amino-2-metilfenil)-

7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-2, 40 mg, 0.045 mmol) y TEA (0.013 ml, 0.091 mmol) en THF (2 ml) con cloruro de 4-*terc*-butilbenzoilo (0.016 ml, 0.091 mmol). La mezcla se agitó a ta durante 1 h, luego se concentró y purificó por HPLC preparativa proporcionando 4-(3-(4-*terc*-butilbenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (22 mg, 65%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.76 (s, 1 H) 10.03 (s, 1 H) 8.25 (s ancho,1 H) 8.08 (d, J=7.69 Hz, 1 H) 7.94 (d, J=8.57 Hz, 2 H) 7.85 (s, 1 H) 7.47 - 7.61 (m, 4 H) 7.41 (t, J=7.69 Hz, 1 H) 7.20 (d, J=7.03 Hz, 1 H) 6.98 - 7.07 (m, 3 H) 2.93 - 3.50 (m, 8 H) 2.81 (s, 3 H) 1.90 (s, 3 H) 1.30 (s, 9 H). Espectro de masas m/z 602.4 $(M+H)^+$.

Ejemplo 5-2

Preparación de 4-(3-acetamido-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

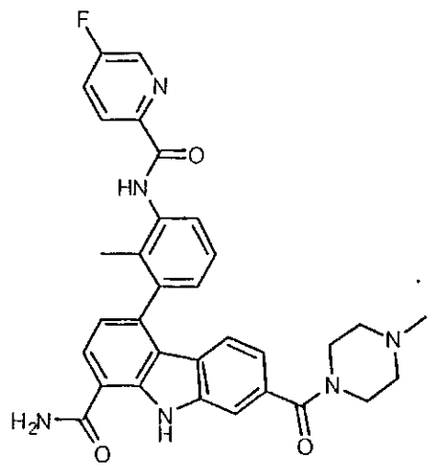


Se trató una solución de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

(Ejemplo 3-2, 20 mg, 0.045 mmol) y DIEA (0.024 ml, 0.136 mmol) en DCM (2 ml) con cloruro de acetilo (4 µl, 0.054 mmol). La mezcla se agitó a ta durante 2 h, luego se concentró y purificó por HPLC preparativa proporcionando 4-(3-acetamido-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (18 mg, 66%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.69 (1 H, s), 9.44 (1 H, s), 8.18 (1 H, s ancho), 8.00 (1 H, d, J=7.7 Hz), 7.78 (1 H, s), 7.50 (2 H, d, J=7.3 Hz), 7.28 (1 H, t, J=7.7 Hz), 7.05 (1 H, d, J=7.3 Hz), 6.88 - 6.98 (2 H, m), 6.83 (1 H, d, J=8.1 Hz), 2.86 - 3.11 (4 H, m), 2.75 (3 H, s), 2.02 (3 H, s), 1.80 (3 H, s). Espectro de masas m/z 484.3 $(M+H)^+$.

Ejemplo 5-3

Preparación de 4-(3-(5-fluoropicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Se trató una mezcla de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

(Ejemplo 3-2, 100 mg, 0.204 mmol), ácido 5-fluoropicolínico (43.1 mg, 0.306 mmol) y HOAT (41.6 mg, 0.306 mmol) en acetonitrilo (2 ml) con DIEA (0.053 ml, 0.306 mmol) y EDC (78 mg, 0.408 mmol) y la mezcla se agitó a ta. Después de 18 h, la mezcla se diluyó con metanol y purificó por HPLC preparativa. El residuo acuoso de la concentración de las fracciones de efluente apropiadas se basificó con NaHCO3 (ac) y se extrajo tres veces con EtOAc. Las fases orgánicas reunidas se secaron y concentraron proporcionando 4-(3-(5-fluoropicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un polvo gris claro (111.5 mg, 92%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.58 (d, J=3.1 Hz, 1 H) 8.31 (dd, J=8.8, 4.8 Hz, 1 H) 7.96 - 8.03 (m, 2 H) 7.82 (td, J=8.6, 2.6 Hz, 1 H) 7.68 (d, J=0.9 Hz, 1 H) 7.45 (t, J=7.9 Hz, 1 H) 7.23 (dd, J=7.5, 0.9 Hz, 1 H) 7.09 (d, J=7.9 Hz, 1 H) 7.03 - 7.08 (m, 1 H) 6.95 - 7.00 (m, 1 H) 3.78 (s ancho,2 H) 3.49 (s ancho,2 H) 2.42 (s ancho,2 H) 2.40 (s ancho,2 H) 2.31 (s, 3 H) 2.04 (s, 3 H). Espectro de masas m/z 565.2 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 5-1 a 5-3 y procedimientos similares. En esta tabla, "material de partida" se refiere a la amina que reacciona con el ácido carboxílico o cloruro de ácido disponible comercialmente apropiado.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
5-4	Ejemplo 3-2	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	564.3 $(M+H)^+$
5-5	Ejemplo 3-2	4-(2-metil-3-(picolinamido)fenil)-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	547.2 $(M+H)^+$
5-6	Ejemplo 3-2	N-(3-(1-carbamoil-6-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenil)tiazol-2-carboxamida	553.2 $(M+H)^+$
5-7	Ejemplo 3-2	4-(2-metil-3-(nicotinamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	547.2 $(M+H)^+$
5-8	Ejemplo 3-2	4-(3-(isonicotinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	547.2 $(M+H)^+$

5-9	Ejemplo 3-2	4-(3-(1H-imidazol-2-carboxamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	536.3 $(M+H)^+$
5-10	Ejemplo 3-2	4-(2-metil-3-(pirimidin-4-carboxamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	548.2 $(M+H)^+$
5-11	Ejemplo 3-2	4-(3-(1H-benzo[d]imidazol-2-carboxamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	586.2 $(M+H)^+$
5-12	Ejemplo 3-2	4-(2-fluoro-4-(4-fluorobenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	568.1 $(M+H)^+$
5-13	Ejemplo 3-2	4-(3-(5-etilpicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	575.2 $(M+H)^+$
5-14	Ejemplo 3-2	4-(3-(5-butilpicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	603.3 $(M+H)^+$

5-15	Ejemplo 3-2	4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	550.2 $(M+H)^+$
5-16	Ejemplo 3-2	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenil)-4-isopropiltiazol-2-carboxamida	595.2 $(M+H)^+$
5-17	Ejemplo 3-2	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenil)-4,5,6,7-tetrahidrobenzo[d]tiazol-2-carboxamida	607.2 $(M+H)^+$
5-18	Ejemplo 3-2	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenil)-5-metiltiazol-2-carboxamida	567.2 $(M+H)^+$
5-19	Ejemplo 3-2	4-(3-(3-hidroxipicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	563.2 $(M+H)^+$

5-20	Ejemplo 3-2	4-(2-metil-3-(pirimidin-2-carboxamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	548.2 $(M+H)^+$
5-21	Ejemplo 3-2	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenil)benzo[d]tiazol-2-carboxamida	603.2 $(M+H)^+$
5-22	Ejemplo 3-2	4-(2-metil-3-(1-metil-1H-benzo[d]imidazol-2-carboxamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	600.2 $(M+H)^+$
5-23	Ejemplo 3-2	4-(3-(5-cloropicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	581.2 $(M+H)^+$
5-24	Ejemplo 3-2	4-(3-(5-bromopicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	625, 627 $(M+H)^+$

5-25	Ejemplo 3-2	4-(2-metil-3-(5-(trifluorometil)picolinamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	615.2 $(M+H)^+$
5-26	Ejemplo 3-2	4-(3-(6-hidroxipicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	563.2 $(M+H)^+$
5-27	Ejemplo 3-2	4-(3-(5-hidroxipicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	563.2 $(M+H)^+$
5-28	Ejemplo 3-2	4-(2-metil-3-(5-metilpicolinamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	561.3 $(M+H)^+$
5-29	Ejemplo 3-2	4-(3-(5-bromopirimidin-2-carboxamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	626, 628 $(M+H)^+$

5-30	Ejemplo 3-2	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenil)-2-clorotiazol-5-carboxamida	587.1 $(M+H)^+$
5-31	Ejemplo 3-2	4-(3-(5-cianopicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	572.2 $(M+H)^+$
5-32	Ejemplo 3-2	4-(2-metil-3-(5-(pirrolidin-1-il)picolinamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	616.3 $(M+H)^+$
5-33	Ejemplo 3-37	4-(2-fluoro-3-(picolinamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	551.2 $(M+H)^+$
5-34	Ejemplo 3-37	4-(2-fluoro-3-(5-fluoropicolinamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	569.2 $(M+H)^+$
5-35	Ejemplo 3-37	4-(3-(5-cianopicolinamido)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	576.2 $(M+H)^+$

5-36	Ejemplo 3-37	4-(2-fluoro-3-(5-(pirrolidin-1-il)picolinamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	620.3 $(M+H)^+$
5-37	Ejemplo 3-37	4-(2-fluoro-3-(pirimidin-4-carboxamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	552.2 $(M+H)^+$
5-38	Ejemplo 3-37	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-fluorofenil)tiazol-2-carboxamida	557.1 $(M+H)^+$
5-39	Ejemplo 3-37	4-(2-fluoro-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	554.2 $(M+H)^+$
5-40	Ejemplo 3-2	4-(2-metil-3-(2-(piridin-2-il)acetamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	561.2 $(M+H)^+$
5-41	Ejemplo 3-2	4-(2-metil-3-(1-(piridin-2-il)ciclopropanocarboxamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	587.3 $(M+H)^+$

5-42	Ejemplo 3-2	4-(3-(1-(4-fluorofenil)ciclopropanocarboxamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	604.2 $(M+H)^+$
5-43	Ejemplo 3-2	4-(3-(1-(4-fluorofenil)ciclobutanocarboxamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	618.2 $(M+H)^+$
5-44	Ejemplo 3-2	4-(3-(2-(4-clorofenil)-2-metilpropanamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	622.2 $(M+H)^+$
5-45	Ejemplo 3-2	4-(3-benzamido-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	546.3 $(M+H)^+$
5-46	Ejemplo 3-13	4-(2-metil-3-(1-metil-1H-benzo[d]imidazol-2-carboxamido)fenil)-9H-carbazol-1-carboxamida	474.4 $(M+H)^+$
5-47	Ejemplo 3-13	4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-9H-carbazol-1-carboxamida	424.3 $(M+H)^+$

5-48	Ejemplo 3-51	4-(2,6-difluoro-4-(4-fluorobenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	586.4 $(M+H)^+$
5-49	Ejemplo 3-2	4-(3-(ciclopropanocarboxamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	509.9 $(M+H)^+$
5-50	Ejemplo 3-2	4-(3-(ciclohexanocarboxamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	551.9 $(M+H)^+$
5-51	Ejemplo 3-2	4-(3-(2-clorobenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	579.8 $(M+H)^+$
5-52	Ejemplo 3-2	4-(3-(3-clorobenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	579.8 $(M+H)^+$

5-53	Ejemplo 3-2	4-(3-(3-(dimetilamino)benzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	588.9 $(M+H)^+$
5-54	Ejemplo 3-2	4-(3-(4-cianobenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	570.8 $(M+H)^+$
5-55	Ejemplo 3-2	4-(3-(4-clorobenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	579.8 $(M+H)^+$
5-56	Ejemplo 3-2	4-(3-(4-acetamidobenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	602.8 $(M+H)^+$

5-57	Ejemplo 3-2	4-(3-(4-metoxibenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	575.8 $(M+H)^+$
5-58	Ejemplo 3-2	4-(2-metil-3-(4-metilbenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	559.8 $(M+H)^+$
5-59	Ejemplo 3-2	4-(3-isobutiramido-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	511.9 $(M+H)^+$
5-60	Ejemplo 3-2	4-(3-(2-cianoacetamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	508.8 $(M+H)^+$
5-61	Ejemplo 3-2	4-(3-(3,3-dimetilbutanamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	539.9 $(M+H)^+$

5-62	Ejemplo 3-2	4-(2-metil-3-(3-metilbutanamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	525.8 $(M+H)^+$
5-63	Ejemplo 3-2	4-(2-metil-3-(4-metilpentanamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	539.9 $(M+H)^+$
5-64	Ejemplo 3-2	4-(2-metil-3-pivalamidofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	525.9 $(M+H)^+$
5-65	Ejemplo 3-2	4-(3-(2-(dimetilamino)acetamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	526.9 $(M+H)^+$
5-66	Ejemplo 3-2	4-(2-metil-3-(2-fenilacetamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	559.8 $(M+H)^+$

5-67	Ejemplo 3-2	4-(2-metil-3-pent-4-inamidofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	521.9 $(M+H)^+$
5-68	Ejemplo 3-2	4-(2-metil-3-pentanamidofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	525.9 $(M+H)^+$
5-69	Ejemplo 3-2	4-(2-metil-3-(4-sulfamoilbenzamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	624.8 $(M+H)^+$
5-70	Ejemplo 3-2	4-(2-metil-3-(2-metil-2-fenilpropanamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	587.9 $(M+H)^+$
5-71	Ejemplo 3-2	4-(3-(2-(dimetilamino)benzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	588.8 $(M+H)^+$

5-72	Ejemplo 3-2	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenil)-2-feniltiazol-4-carboxamida (preparada como la sal TFA)	628.8 $(M+H)^+$
5-73	Ejemplo 3-2	4-(3-(1-cianociclopropanocarboxamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	534.8 $(M+H)^+$
5-74	Ejemplo 3-2	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenil)tiazol-4-carboxamida (preparada como la sal TFA)	552.8 $(M+H)^+$
5-75	Ejemplo 3-2	4-(2-metil-3-(3-morfolinopropanamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	582.9 $(M+H)^+$

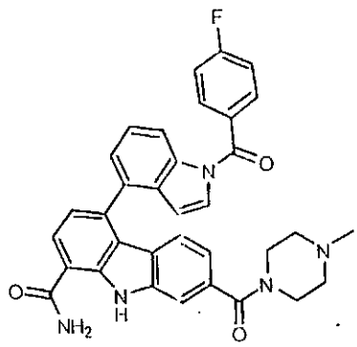
5-76	Ejemplo 3-2	4-(3-(3-(1H-imidazol-1-il)propanamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	563.8 $(M+H)^+$
5-77	Ejemplo 3-2	4-(3-(2-(1H-tetrazol-5-il)acetamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	551.8 $(M+H)^+$
5-78	Ejemplo 3-2	4-(2-metil-3-(3-(2-oxopirrolidin-1-il)propanamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	580.8 $(M+H)^+$
5-79	Ejemplo 3-2	4-(2-metil-3-(2-(pirazin-2-il)acetamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	561.8 $(M+H)^+$

5-80	Ejemplo 3-2	4-(3-bifenil-4-ilcarboxamido-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	622.0 $(M+H)^+$
5-81	Ejemplo 3-2	4-(3-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)-2-metilfenilcarbamoil)benzoato de metilo (preparado como la sal TFA)	603.9 $(M+H)^+$
5-82	Ejemplo 3-2	4-(2-metil-3-(3-fenilpropanamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	573.9 $(M+H)^+$
5-83	Ejemplo 3-46	4-(2-metil-5-(1-metil-1H-imidazol-2-carboxamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	550.2 $(M+H)^+$
5-84	Ejemplo 3-46	4-(5-(4-fluorobenzamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	564.2 $(M+H)^+$

5-85	Ejemplo 4-1	5-(2-(N-isopropilacetamido)tiazol-5-il)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	495.2 $(M+H)^+$
5-86	Ejemplo 4-3	5-(2-benzamido-4-metiltiazol-5-il)-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida	558.1 $(M+H)^+$

Ejemplo 6-1

Preparación de 4-(1-(4-fluorobenzoil)-1H-indol-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

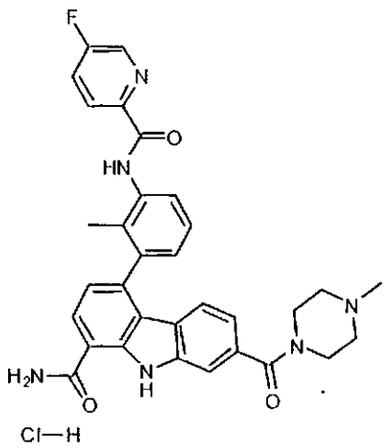


Se trató una solución de 4-(1H-indol-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-47, 50 mg, 0.100 mmol) en DCM (1 ml) secuencialmente con DMAP (3.7 mg, 0.030 mmol), TEA (0.028 ml, 0.199 mmol) y cloruro de 4-fluorobenzoilo (0.013 ml, 0.110 mmol). La mezcla se agitó a ta durante 17 h, luego se trató con más cloruro de 4-fluorobenzoilo (0.013 ml, 0.110 mmol) y TEA (0.028 ml, 0.199 mmol) y se continuó agitando durante 111 h. La mezcla se

concentró y el residuo se disolvió en metanol y purificó por HPLC preparativa. Las fracciones de efluente apropiadas se repartieron entre NaHCO3 (ac) y EtOAc y la fase acuosa se extrajo dos veces más con EtOAc. Las fases orgánicas reunidas se secaron y concentraron proporcionando 4-(1-(4-fluorobenzoil)-1H-indol-4-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido amarillo (19.5 mg, 31%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.51 (1 H, d, J=8.3 Hz), 8.03 (1 H, d, J=7.9 Hz), 7.84 (2 H, dd, J=8.8, 5.3 Hz), 7.68 (1 H, s), 7.57 (1 H, t, J=7.7 Hz), 7.46 (1 H, d, J=7.5 Hz), 7.26 - 7.36 (3 H, m), 7.20 (1 H, d, J=7.9 Hz), 6.96 (1 H, d, J=7.9 Hz), 6.86 (1 H, dd, J=8.3, 1.3 Hz), 6.19 (1 H, d, J=4.0 Hz), 3.77 (2 H, s ancho), 3.46 (2 H, s ancho), 2.41 (2 H, s ancho), 2.38 (2 H, s ancho), 2.30 (3 H, s). Espectro de masas m/z 574.3 $(M+H)^+$.

Ejemplo 7-1

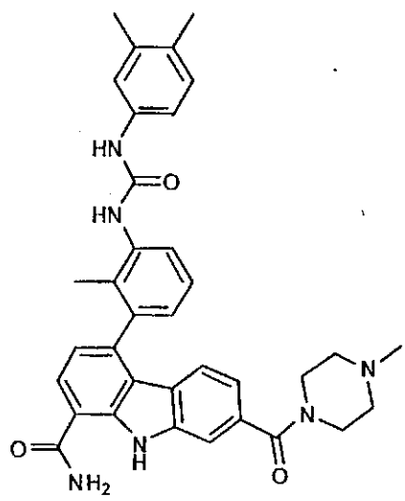
Preparación de 4-(3-(5-fluoropicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como la sal clorhidrato



Se trató una solución de 4-(3-(5-fluoropicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 5-3, 32.7 mg, 0.058 mmol) en EtOAc (1 ml) s con cloruro de hidrógeno, 4 M en 1,4-dioxano (0.1 ml, 0.400 mmol). El sólido resultante se suspendió en más EtOAc con tratamiento en ultrasonidos, y el precipitado se recogió por filtración, se aclaró con EtOAc y se secó proporcionando la sal clorhidrato de 4-(3-(5-fluoropicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un polvo blanquecino (30.5 mg, 88%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.58 (d, J=2.6 Hz, 1 H) 8.31 (dd, J=8.8, 4.4 Hz, 1 H) 8.03 (d, J=7.5 Hz, 1 H) 7.99 (d, J=8.3 Hz, 1 H) 7.82 (td, J=8.6, 2.6 Hz, 1 H) 7.76 (s, 1 H) 7.46 (t, J=7.7 Hz, 1 H) 7.23 (d, J=7.5 Hz, 1 H) 7.10 (s, 3 H) 3.32 - 3.61 (m, 4 H) 3.09 - 3.24 (m, 2 H) 2.94 (s, 3 H) 2.03 (s, 3 H). Espectro de masas m/z 565.2 $(M+H)^+$.

Ejemplo 8-1

Preparación de 4-(3-(3-(3,4-dimetilfenil)ureido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

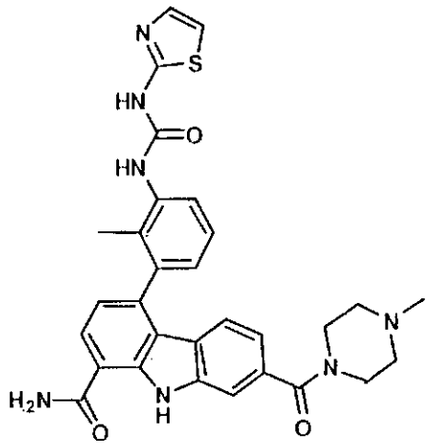


Se trató una solución de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-2, 25 mg, 0.028 mmol) y TEA (8 µl, 0.057 mmol) en DCM (2 ml) con 4-isocianato-1,2-dimetilbenceno (8.33 mg, 0.057 mmol) y la mezcla se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa proporcionando 4-(3-(3-(3,4-dimetilfenil)ureido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (11 mg, 53%). RMN de ^{1}H (400 MHz, DMSO-d6) δ 11.70 (s, 1 H) 8.87 (s, 1 H) 8.19 (s ancho,1 H) 8.00 (t, J=7.40 Hz, 3 H) 7.78 (s, 1 H) 7.51 (s ancho,1 H) 7.27 (t, J=7.78 Hz, 1 H) 7.19 (s, 1 H) 7.13 (d, J=6.78 Hz, 1 H) 6.87 - 7.00 (m, 4 H) 6.81 (d, J=8.03 Hz, 1 H)

3.34 - 3.57 (m, 4 H) 2.97 - 3.17 (m, 4 H) 2.69 (s ancho,3 H) 2.13 (s, 3 H) 2.09 (s, 3 H) 1.85 (s, 3 H). Espectro de masas m/z 589.4 $(M+H)^+$.

Ejemplo 8-2

Preparación de 4-(2-metil-3-(3-tiazol-2-ilureido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Se trató una solución de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-2, 25 mg, 0.028 mmol) y TEA (8 µl, 0.057 mmol) en DCM (2 ml) con tiazol-2-ilcarbamato de fenilo (12.47 mg, 0.057 mmol) y se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa proporcionando 4-(2-metil-3-(3-tiazol-2-ilureido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (10 mg, 45%) contaminado con aproximadamente 15% de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida. RMN de ^1H (400 MHz, DMSO-d_6) δ 11.80

(s, 1 H) 8.58 (s ancho,1 H) 8.28 (s ancho,1 H) 8.08 (t, *J*=7.40 Hz, 2 H) 7.87 (s, 1 H) 7.60 (s ancho,1 H) 7.36 - 7.44 (m, 2 H) 7.15 (d, *J*=3.51 Hz, 1 H) 7.00 - 7.10 (m, 4 H) 6.88 (d, *J*=8.28 Hz, 1 H) 2.98 - 3.56 (m, 8 H) 2.83 (s ancho,3 H) 1.94 (s, 3 H). Espectro de masas m/z 568.3 $(M+H)^+$.

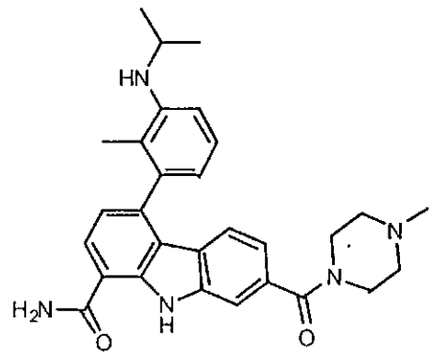
Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 8-1 a 8-2 y procedimientos similares. En esta tabla, "material de partida" se refiere a la amina que reacciona con el reaccionante formador de urea apropiado.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
8-3	Ejemplo 3-2	4-(2-metil-3-(3-fenilureido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	560.8 $(M+H)^+$
8-4	Ejemplo 3-2	4-(3-(3-(4-clorofenil)ureido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	594.8 $(M+H)^+$

8-5	Ejemplo 3-2	4-(3-(3-(4-metoxifenil)ureido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	590.8 $(M+H)^+$

Ejemplo 9-1

Preparación de 4-(3-(isopropilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Se añadió triacetoxiborohidruro sódico (41 mg, 0.193 mmol) a una solución de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-2, 30 mg, 0.068 mmol), ácido acético (0.03 ml, 0.524 mmol) y acetona (0.170 ml, 2.315 mmol) en DCM (0.3 ml) y la mezcla se agitó a ta durante 4 h. El disolvente se evaporó y el residuo se disolvió en agua y purificó por HPLC preparativa y liofilización proporcionando 4-(3-(isopropilamino)-2-metilfenil)-7-(4-metilpiperazin-1-

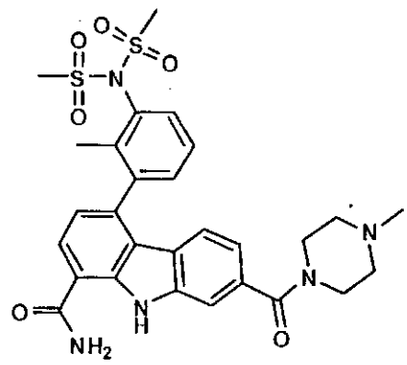
carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un polvo blanco (31.7 mg, 56%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.07 (1 H, d, J=7.70 Hz), 7.79 (1 H, s), 7.58 - 7.66 (2 H, m), 7.50 - 7.54 (1 H, m), 7.11 (1 H, d, J=7.70 Hz), 7.03 (1 H, dd, J=8.14, 1.54 Hz), 6.82 (1 H, d, J=7.92 Hz), 3.84 (1 H, dt, J=13.04, 6.57 Hz), 3.37 - 3.69 (4 H, m), 3.05 - 3.27 (4 H, m), 2.94 (3 H, s), 2.11 (3 H, s), 1.50 (3 H, d, J=6.38 Hz), 1.45 (3 H, d, J=6.60 Hz). Espectro de masas m/z 484.2 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 9-1 y procedimientos similares, sustituyendo el aldehído o cetona apropiado por acetona.

Ejemplo	Nombre del compuesto	Espectro de masas
9-2	4-(3-(4-fluorobencilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	550.2 $(M+H)^+$
9-3	4-(3-(1-(4-fluorofenil)etilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	564.3 $(M+H)^+$

Ejemplo 10-1

Preparación de 4-(2-metil-3-(N-(metilsulfonil)metilsulfonamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

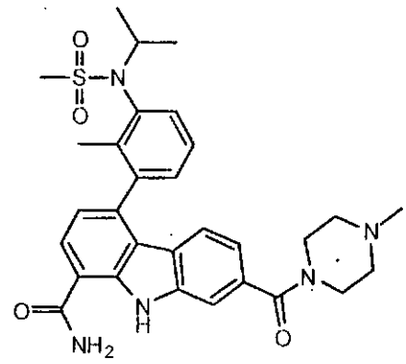


Se trató una solución de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-2, 20 mg, 0.045 mmol) y DIEA (0.024 ml, 0.136 mmol) en DCM (2 ml) con cloruro de metanosulfonilo (4 µl, 0.054 mmol) y se agitó a ta durante 2 h. Se añadió más cloruro de metanosulfonilo y la mezcla se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa proporcionando 4-(2-metil-3-(N-(metilsulfonil)metilsulfonamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (16 mg, 46%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.72 (s, 1 H) 8.21 (s ancho,1 H) 8.04 (d, *J*=7.9 Hz, 1 H) 7.77 (s, 1 H) 7.63 (dd, *J*=7.9, 1.1 Hz, 1 H) 7.53 (s ancho,1 H) 7.45 (t, *J*=7.8 Hz, 1 H) 7.37 (d, *J*=8.6 Hz, 1 H) 7.03 (d, *J*=7.7 Hz, 1 H) 6.83 - 6.88 (m, 1 H) 6.76 - 6.83 (m, 1 H) 3.53 (s, 6 H)

2.93 - 3.20 (m, 8 H) 2.75 (s, 3 H) 1.97 (s, 3 H). Espectro de masas m/z 598.2 $(M+H)^+$.

Ejemplos 10-2 y 10-3

Preparación de dos isómeros rotacionales de 4-(3-(N-isopropilmetilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

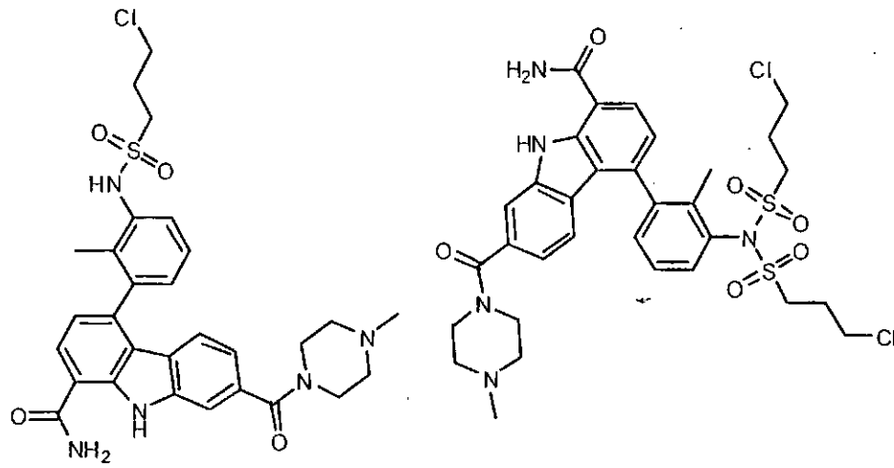


Se añadió cloruro de metanosulfonilo (1.3 µl, 0.016 mmol) a una solución agitada de 4-(3-(isopropilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA (Ejemplo 9-1, 13 mg, 0.016 mmol) en piridina (0.2 ml) a ta. Después de 30 min, se añadió más cloruro de metanosulfonilo (2.4 µl) y la mezcla se agitó durante la noche. La mezcla se trató con ácido clorhídrico 1 M (0.56 ml), se disolvió en metanol y purificó por HPLC preparativa proporcionando dos isómeros rotacionales de 4-(3-(N-isopropilmetilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, aislados por separado como sales TFA después de liofilización. Isómero A (3.3 mg, 31%) RMN de ^1H (400 MHz,

cloroformo-d) δ 9.58 (1 H, s), 7.81 (1 H, d, J=7.70 Hz), 7.68 (1 H, s), 7.41 - 7.47 (1 H, m), 7.32 - 7.37 (2 H, m), 7.11 (1 H, d, J=7.70 Hz), 7.05 (1 H, d, J=8.14 Hz), 6.86 (1 H, d, J=8.14 Hz), 4.60 - 4.72 (1 H, m), 3.66 (3 H, s ancho), 3.05 (8 H, s ancho), 2.90 (3 H, s), 1.91 (3 H, s), 1.40 (3 H, d, J=6.60 Hz), 1.12 (3 H, d, J=6.82 Hz). Espectro de masas m/z 562.1 $(M+H)^+$. Isómero B (2.9 mg; 27%) RMN de ^1H (400 MHz, cloroformo-d) δ 9.41 (1 H, s ancho), 7.84 (1 H, d, J=7.70 Hz), 7.69 (1 H, s), 7.46 (1 H, t, J=7.81 Hz), 7.36 (2 H, t, J=8.25 Hz), 7.13 (1 H, d, J=7.70 Hz), 7.05 (1 H, dd, J=8.25, 1.21 Hz), 6.92 (1 H, d, J=8.36 Hz), 4.71 - 4.82 (1 H, m), 3.67 (3 H, s ancho), 2.49 - 3.07 (11 H, m), 1.90 (3 H, s), 1.43 (3 H, d, J=6.60 Hz), 1.10 (3 H, d, J=6.60 Hz). Espectro de masas m/z 562.2 $(M+H)^+$.

Ejemplos 10-4 y 10-5

Preparación de 4-(3-(3-cloropropilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida y 4-(3-(3-cloro-N-(3-cloropropilsulfonil)propilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Usando el procedimiento de los Ejemplos 10-2 y 10-3, se convirtió 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-2, 33.5 mg, 0.076 mmol) en 4-(3-(3-cloropropilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 10-4, 12.6 mg, 24%), aislada como sal TFA después de Purificación por HPLC y liofilización. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.77 (1 H, s), 9.79 (1 H, s ancho), 9.41 (1 H, s), 8.26 (1 H, s ancho), 8.07 (1 H, d, J=7.92 Hz), 7.85 (1 H, s), 7.53 - 7.62 (1 H, m), 7.47 - 7.51 (1 H, m), 7.41 (1 H, t, J=7.70 Hz), 7.21 (1 H, dd, J=7.48, 1.10 Hz), 7.03 (1 H, d, J=7.70 Hz), 6.97 (1 H, dd, J=8.14, 1.32 Hz), 6.83 (1 H, d, J=8.14 Hz), 3.80 (2 H, t, J=6.49 Hz), 3.36 - 3.64 (8 H, m), 3.30 - 3.36 (2 H, m), 2.82 (3 H, s ancho), 2.18 - 2.29 (2 H, m), 2.00 (3 H, s). Espectro de masas m/z 582.1 $(M+H)^+$. También se aisló como la sal TFA 4-(3-(3-cloro-N-(3-cloropropilsulfonil)propilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un polvo blanco (Ejemplo 10-5, 3.7 mg, 6%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.79 (1 H, s), 9.85 (1 H, s ancho), 8.28 (1 H, s ancho), 8.11 (1 H, d, J=7.92 Hz), 7.84 (1 H, s), 7.70 (1 H, dd, J=7.92, 1.10 Hz), 7.58 - 7.63 (1 H, m), 7.55 (1 H, t, J=7.81 Hz), 7.45 (1 H, dd, J=7.59, 0.99

Hz), 7.09 (1 H, d, J=7.70 Hz), 6.92 (1 H, dd, J=8.14, 1.54 Hz), 6.83 (1 H, d, J=8.14 Hz), 3.76 - 4.04 (10 H, m), 2.96 - 3.66 (5 H, m), 2.81 (3 H, s ancho), 2.23 - 2.35 (4 H, m), 2.06 (3 H, s). Espectro de masas m/z 722.0 $(M+H)^+$.

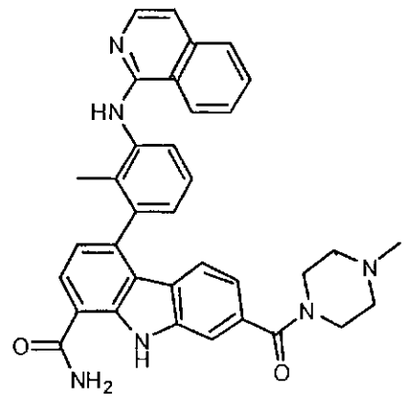
Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 10-1 a 10-5, usando el cloruro de sulfonilo apropiado.

Ejemplo	Nombre del compuesto	Espectro de masas
10-6	4-(2-metil-3-(fenilsulfonamido)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	581.8 $(M+H)^+$
10-7	4-(3-(4-clorofenilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	615.7 $(M+H)^+$
10-8	4-(3-(4-metoxifenilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	611.8 $(M+H)^+$

10-9	4-(3-(1,1,3,3,-tetraoxobenzo[d][1,3,2]ditiazol-2-il)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	644.0 $(M+H)^+$

Ejemplo 11-1

Preparación de 4-(3-(isoquinolin-1-ilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

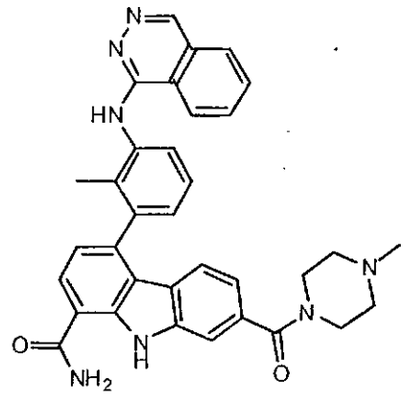


Se trató una suspensión de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-2, 35 mg, 0.079 mmol) y 1-cloroisoquinolina (19.45 mg, 0.119 mmol) en isopropanol (0.5 ml) con cloruro de hidrógeno 4M en 1,4-dioxano (3 gotas) y la mezcla se calentó en un tubo sellado por radiación en microondas a 140°C durante 45 min. Se añadió más cloruro de hidrógeno 4 M en 1,4-dioxano (1 gota) y la mezcla se calentó de nuevo en un tubo sellado por radiación en microondas a

140°C durante 60 min. La mezcla se concentró y el residuo se purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron y el residuo se repartió entre NaHCO3 (ac) y EtOAc, y la fase acuosa se extrajo dos veces más con EtOAc. Las fases orgánicas reunidas se secaron y concentraron proporcionando 4-(3-(isoquinolin-1-ilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido blanco (16 mg, 32%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.28 (1 H, d, J=8.3 Hz), 7.91 (1 H, d, J=7.8 Hz), 7.72 (1 H, d, J=6.1 Hz), 7.66 (1 H, d, J=8.3 Hz), 7.56 - 7.61 (2 H, m), 7.48 (1 H, ddd, J=8.0, 7.2, 0.8 Hz), 7.44 (1 H, d, J=7.5 Hz), 7.34 (1 H, t, J=7.8 Hz), 7.22 (1 H, d, J=8.0 Hz), 7.14 (1 H, d, J=6.7 Hz), 7.06 (1 H, d, J=7.8 Hz), 6.97 (1 H, d, J=6.1 Hz), 6.94 (1 H, dd, J=8.2, 1.5 Hz), 3.71 (2 H, s ancho), 3.42 (2 H, s ancho), 2.45 (2 H, s ancho), 2.32 (2 H, s ancho), 2.23 (3 H, s), 1.81 (3 H, s). Espectro de masas m/z 569.4 $(M+H)^+$.

Ejemplo 11-2

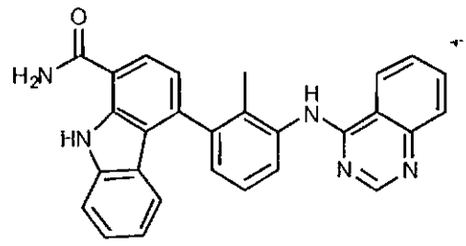
Preparación de 4-(2-metil-3-(ftalazin-1-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 11-1 pero calentando solo a 140°C durante 45 min, se convirtieron 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-2, 35 mg, 0.079 mmol) y 1-cloroftalazina (19.57 mg, 0.119 mmol) en 4-(2-metil-3-(ftalazin-1-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido amarillo claro (7.3 mg, 15%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.88 (1 H, s ancho), 8.47 (1 H, d, J=7.0 Hz), 8.03 (1 H, d, J=7.7 Hz), 7.91 - 8.01 (3 H, m), 7.70 (1 H, s), 7.51 - 7.59 (1 H, m), 7.47 (1 H, t, J=7.7 Hz), 7.24 - 7.34 (2 H, m), 7.18 (1 H, d, J=7.9 Hz), 7.09 (1 H, dd, J=8.1, 1.3 Hz), 3.83 (2 H, s ancho), 3.54 (2 H, s ancho), 2.47 (2 H, s ancho), 2.44 (2 H, s ancho), 2.35 (3 H, s), 1.96 (3 H, s). Espectro de masas m/z 570.4 $(M+H)^+$.

Ejemplo 11-3

Preparación de 4-(2-metil-3-(quinazolin-4-ilamino)fenil)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 11-1 pero

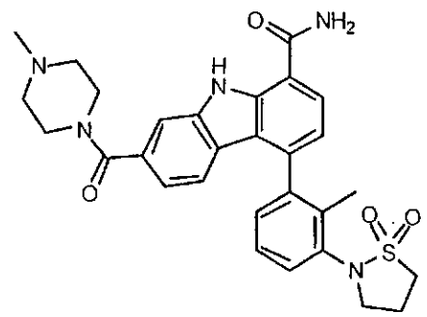
calentando a 140°C dos veces durante 30 min y una vez durante 45 min, se convirtieron 4-(3-amino-2-metilfenil)-9H-carbazol-1-carboxamida (Ejemplo 3-13, 26.4 mg, 0.084 mmol) y 4-cloroquinazolina (20.67 mg, 0.126 mmol) en 4-(2-metil-3-(quinazolin-4-ilamino)fenil)-9H-carbazol-1-carboxamida como un sólido blanco (8.0 mg, 20%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.37 (1 H, s), 8.31 (1 H, dd, J=8.4, 0.9 Hz), 7.86 (1 H, d, J=7.9 Hz), 7.75 - 7.83 (1 H, m), 7.66 - 7.73 (1 H, m), 7.56 (1 H, ddd, J=8.3, 7.0, 1.2 Hz), 7.49 (1 H, d, J=8.4 Hz), 7.35 - 7.46 (2 H, m), 7.22 - 7.31 (2 H, m), 7.12 (1 H, d, J=7.7 Hz), 7.00 (1 H, d, J=7.9 Hz), 6.84 - 6.92 (1 H, m), 1.84 (3 H, s). Espectro de masas m/z 444.2 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 11-1 a 11-3, partiendo del Ejemplo 3-2 y la cloroquinazolina sustituida apropiada (preparada de acuerdo con los procedimientos de las Etapas 1 y 2 del Intermedio 32-1).

Ejemplo	Nombre del compuesto	Espectro de masas
11-4	4-(2-metil-3-(quinazolin-4-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	570.4 $(M+H)^+$
11-5	4-(3-(6-cloroquinazolin-4-ilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	604.4 $(M+H)^+$
11-6	4-(3-(7-cloroquinazolin-4-ilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	604.5 $(M+H)^+$
11-7	4-(3-(7-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	588.5 $(M+H)^+$
11-8	4-(3-(6-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	588.5 $(M+H)^+$
11-9	4-(2-metil-3-(7-metilquinazolin-4-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	584.5 $(M+H)^+$
11-10	4-(2-metil-3-(6-metilquinazolin-4-ilamino)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	584.5 $(M+H)^+$

Ejemplo 12-1

Preparación de 4-(3-(1,1-dioxoisotiazolidin-2-il)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

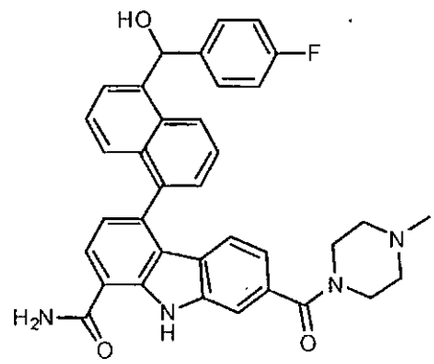


Se trató una solución de 4-(3-(3-cloropropilsulfonamido)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA (Ejemplo 10-4, 10.7 mg, 0.015 mmol) en THF (0.5 ml) con una solución de hexametildisilazida de litio (1 M en THF, 0.092 ml, 0.092 mmol) a ta. Después de calentar hasta 60°C y añadir DMF (0.2 ml) y agitar durante 5 h, la mezcla se concentró y el residuo se purificó por HPLC preparativa proporcionando 4-(3-(1,1-dioxoisotiazolidin-2-il)-2-metilfenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, aislada como la sal TFA (3.5 mg, 34%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.77 (1 H, s), 9.85 (1 H, s ancho), 8.26 (1 H, s ancho), 8.08 (1 H, d, J=7.70 Hz), 7.85 (1 H, s), 7.61 (1 H, dd, J=8.03, 0.99 Hz), 7.48 (1 H, t, J=7.70 Hz), 7.30 - 7.34 (1 H, m), 7.06 (1 H, d, J=7.70 Hz), 6.97 (1 H, dd, J=8.25, 1.43 Hz), 6.86 (1 H, d,

J=8.14 Hz), 3.69 - 3.76 (2 H, m), 3.29 - 3.64 (10 H, m), 2.82 (3 H, s), 2.42 - 2.48 (2 H, m), 2.00 (3 H, s). Espectro de masas m/z 546.1 $(M+H)^+$.

Ejemplos 13-1 y 13-2

Preparación de dos diastereómeros de 4-(5-((4-fluorofenil)(hidroxi)metil)naftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

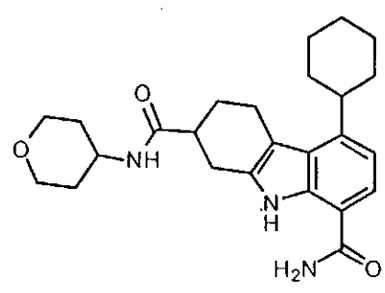


Se trató una solución de 4-(5-(4-fluorobenzoil)naftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-96, 30 mg, 0.051 mmol) en etanol (0.5 ml) con un par de gránulos de borohidruro sódico y se agitó a ta. Después de 90 min, la mezcla se trató con 2 gotas de ácido clorhídrico 1 M y purificó por HPLC preparativa proporcionando dos diastereómeros de 4-(5-((4-fluorofenil)(hidroxi)metil)naftalen-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida. El diastereómero 1 (Ejemplo 13-1) se aisló como un polvo blanco (10.4 mg, 31%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.23 (1 H, d, J=8.6 Hz), 7.99 (1 H, d, J=7.7 Hz), 7.48 - 7.61 (3 H, m),

7.36 - 7.46 (3 H, m), 7.31 (1 H, d, J=8.4 Hz), 7.19 (1 H, dd, J=8.4, 7.0 Hz), 7.12 (1 H, d, J=7.7 Hz), 7.02 (2 H, t, J=8.8 Hz), 6.59 (1 H, dd, J=8.1, 1.5 Hz), 6.51 (1 H, s), 6.31 (1 H, d, J=8.1 Hz), 3.68 (2 H, s ancho), 3.35 (2 H, s ancho), 2.43 (2 H, s ancho), 2.28 (2 H, s ancho), 2.23 (3 H, s). Espectro de masas m/z 587.4 $(M+H)^+$. El diastereómero 2 (Ejemplo 13-2) se aisló como un polvo blanco (8 mg, 23%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.19 (1 H, d, J=8.6 Hz), 7.99 (1 H, d, J=7.9 Hz), 7.61 (1 H, d, J=6.8 Hz), 7.59 (1 H, s), 7.49 - 7.56 (1 H, m), 7.43 (1 H, dd, J=6.8, 0.7 Hz), 7.38 (2 H, dd, J=8.5, 5.4 Hz), 7.26 - 7.32 (1 H, m), 7.16 - 7.24 (1 H, m), 7.11 (1 H, d, J=7.7 Hz), 7.00 (2 H, t, J=8.8 Hz), 6.61 (1 H, dd, J=8.1, 1.3 Hz), 6.58 (1 H, s), 6.36 (1 H, d, J=8.1 Hz), 3.68 (2 H, s ancho), 3.35 (2 H, s ancho), 2.43 (2 H, s ancho), 2.28 (2 H, s ancho), 2.22 (3 H, s). Espectro de masas m/z 587.4 $(M+H)^+$.

Ejemplo 14-1

Preparación de 5-ciclohexil-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida

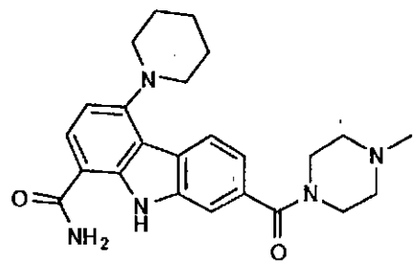


Una solución de 5-ciclohexenil-N^2-(tetrahidro-2H-

piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida (Ejemplo 3-117, 28 mg, 0.066 mmol) en metanol (10 ml) se combinó con paladio al 10% sobre carbón (80 mg) y se agitó en una atmósfera de hidrógeno (310 kPa) durante 1 h. La mezcla se filtró, el sólido se aclaró con metanol y se concentraron los filtrados proporcionando 5-ciclohexil-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida como un sólido blanquecino (28 mg, cuantitativo). RMN de ^1H (400 MHz, metanol-d_4) δ 7.46 - 7.50 (1 H, m), 6.91 (1 H, d, *J*=8.05 Hz), 3.89 - 3.98 (3 H, m), 3.46 - 3.54 (2 H, m), 3.13 (1 H, dd, *J*=14.43, 4.16 Hz), 2.95 - 3.06 (2 H, m), 2.87 - 2.94 (1 H, m), 2.65 - 2.73 (1 H, m), 2.15 (1 H, dd, *J*=11.10, 3.05 Hz), 1.77 - 1.99 (8 H, m), 1.47 - 1.61 (6 H, m), 1.26 - 1.40 (2 H, m). Espectro de masas m/z 424.3 $(M+H)^+$.

Ejemplo 15-1

Preparación de 7-(4-metilpiperazin-1-carbonil)-4-(piperidin-1-il)-9H-carbazol-1-carboxamida

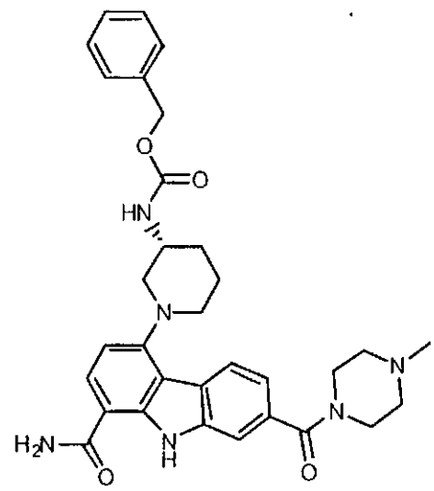


Se calentó una mezcla de 4-bromo-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-1, 30 mg, 0.072 mmol) y piperidina (1 ml) durante la noche

mediante radiación en microondas a 170°C en un tubo sellado. La mezcla se enfrió hasta ta y purificó por HPLC preparativa proporcionando 7-(4-metilpiperazin-1-carbonil)-4-(piperidin-1-il)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (22 mg, 56%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.61 (s, 1 H) 8.05 (d, J=8.35 Hz, 2 H) 7.95 (d, J=8.13 Hz, 1 H) 7.85 (d, J=1.32 Hz, 1 H) 7.32 (dd, J=8.13, 1.54 Hz, 2 H) 6.82 (d, J=8.35 Hz, 1 H) 3.92 - 4.13 (m, 4 H) 3.21 - 3.57 (m, 6 H) 3.14 (d, J=13.40 Hz, 6 H) 2.84 (s, 3 H) 1.66 (s ancho,2 H). Espectro de masas m/z 420.3 $(M+H)^+$.

Ejemplo 16-1

Preparación de 1-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)piperidin-3-ilcarbamato de (R)-bencilo



Etapa 1 Se calentó a 105 °C durante 1 hora una suspensión de 5-bromo-8-carbamoil-9H-carbazol-2-carboxilato

de etilo (Intermedio 48-1, 2.2g, 6.09 mmol) en oxicloruro de fósforo (45.4 ml, 487 mmol). La suspensión se enfrió hasta ta y se concentró dando un sólido marrón, que se suspendió en agua. El precipitado se recogió por filtración, se lavó con agua y se secó proporcionando 5-bromo-8-ciano-9H-carbazol-2-carboxilato de etilo (2.05 g, 98%) como sólido marrón claro. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.78 (s, 1 H) 8.71 (d, *J*=8.57 Hz, 1 H) 8.24 (s, 1 H) 7.95 (d, *J*=8.57 Hz, 1 H) 7.89 (d, *J*=8.13 Hz, 1 H) 7.61 (d, *J*=8.13 Hz, 1 H) 4.39 (q, *J*=7.10 Hz, 2 H) 1.37 (t, 2 H). Espectro de masas m/z 360, 362 $(M+NH_4)^+$.

Etapa 2 Una mezcla de carbonato de cesio (0.960 g, 2.95 mmol), (RS)-2,2'-bis(difenilfosfino)-1,1'-binaftaleno (0.059 g, 0.095 mmol), tris(dibencilidenoacetona)dipaladio (0.058 g, 0.063 mmol), 5-bromo-8-ciano-9H-carbazol-2-carboxilato de etilo (0.85 g, 2.105 mmol) y piperidin-3-ilcarbamato de (R)-bencilo (0.493 g, 2.105 mmol) se suspendió en 1,4-dioxano (70 ml). La mezcla se purgó con nitrógeno y se calentó a 100 °C durante 18 h. La mezcla se enfrió hasta ta y se concentró. El residuo se repartió entre EtOAc y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 80:20 hasta 60:40 de hexano-EtOAc) proporcionando 5-(3-(benciloxicarbonilamino)piperidin-1-il)-8-ciano-9H-carbazol-2-carboxilato de (R)-etilo como un sólido marrón (0.68 g, 70%

de pureza, 37% de rendimiento), que se usó sin purificación posterior. Espectro de masas m/z 497.2 $(M+H)^+$.

Etapa 3 Una solución de 5-(3-(benciloxicarbonilamino)piperidin-1-il)-8-ciano-9H-carbazol-2-carboxilato de (R)-etilo (0.67 g, 1.349 mmol) e hidróxido potásico (0.379 g, 6.75 mmol) en etanol-agua 10:1 (33 ml) se calentó a 85 °C durante 2 h. La mezcla se enfrió hasta ta y el precipitado se recogió por filtración, se lavó con etanol y se secó proporcionando ácido (R)-5-(3-(benciloxicarbonilamino)piperidin-1-il)-8-ciano-9H-carbazol-2-carboxílico como un sólido amarillo (130 mg, 21%). Espectro de masas m/z 469.1 $(M+H)^+$. También se aisló de los filtrados ácido (R)-5-(3-aminopiperidin-1-il)-8-ciano-9H-carbazol-2-carboxílico (150 mg, 33%). Espectro de masas m/z 335.2 $(M+H)^+$.

Etapa 4 Una solución de ácido (R)-5-(3-(benciloxicarbonilamino)piperidin-1-il)-8-ciano-9H-carbazol-2-carboxílico (130 mg, 0.277 mmol), EDC (74.5 mg, 0.388 mmol), HOBT (59.5 mg, 0.388 mmol) y 1-metilpiperazina (0.092 ml, 0.832 mmol) en THF-DCM-DMF (4:1:1, 6 ml) se agitó a ta durante un fin de semana. La mezcla se concentró y se repartió entre EtOAc y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 100:0 a 92.4:7.5 de DCM-amoníaco metanólico 2 M)

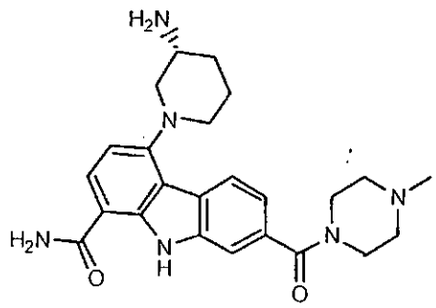
proporcionando 1-(1-ciano-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)piperidin-3-ilcarbamato.de (R)-bencilo como un sólido amarillo (60 mg). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.31 (s, 1 H) 8.09 (d, *J*=8.13 Hz, 1 H) 7.82 (d, *J*=8.35 Hz, 1 H) 7.64 (s, 1 H) 7.49 (d, *J*=7.69 Hz, 1 H) 7.24 - 7.40 (m, 6 H) 6.93 (d, *J*=8.35 Hz, 1 H) 4.87 - 5.11 (m, 2 H) 3.00 - 3.96 (m, 12 H) 2.83 (s, 3 H) 2.45 - 2.70 (m, 1 H) 1.73 - 2.08 (m, 3 H) 1.34 - 1.57 (m, 1 H).). Espectro de masas m/z 551.2 $(M+H)^+$.

Etapa 5 Se trató una solución de 1-(1-ciano-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)piperidin-3-ilcarbamato de (R)-bencilo (108 mg, 0.196 mmol) en DMSO (2 ml) con hidróxido potásico acuoso al 22% (0.208 ml, 0.981 mmol), y luego gota a gota con una solución de peróxido de hidrógeno acuoso al 30% (0.200 ml, 1.961 mmol). La mezcla se agitó a ta durante 2.4 h. Se añadió agua, la suspensión resultante se agitó a ta durante 15 min, y el sólido se recogió por filtración, se lavó con agua y se secó proporcionando 1-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)piperidin-3-ilcarbamato de (R)-bencilo como un sólido blanquecino (89 mg, 80%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.17 (d, *J*=8.13 Hz, 1 H) 7.81 (d, *J*=8.35 Hz, 1 H) 7.66 (s, 1 H) 7.30 (d, *J*=7.91 Hz, 1 H) 7.09 - 7.26 (m, 5 H) 6.82 (d, *J*=8.35 Hz, 1 H) 4.90 - 5.03 (m, 2 H) 3.87 - 3.99 (m, 1 H) 3.57 - 3.68 (m, 1 H) 3.27 - 3.54 (m, 5 H) 3.06 - 3.19 (m, 4 H) 2.69 - 2.82 (m, 1 H) 2.47 - 2.65 (m,

1 H) 1.98 - 2.11 (m, 1 H) 1.83 - 1.97 (m, 2 H) 1.32 - 1.53 (m, 1 H). Espectro de masas m/z 569.3 $(M+H)^+$.

Ejemplo 17-1

Preparación de (R)-4-(3-aminopiperidin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

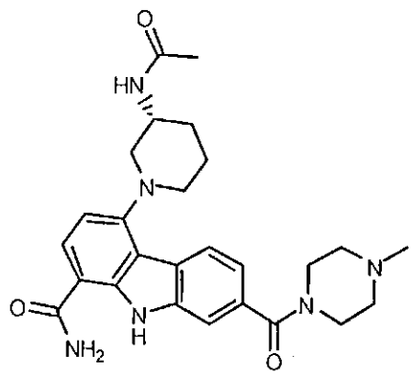


En una mezcla de 1-(1-carbamoil-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-4-il)piperidin-3-ilcarbamato de (R)-bencilo (Ejemplo 16-1, 80 mg, 0.141 mmol), paladio al 10% sobre carbón (14.97 mg, 0.014 mmol) y formiato amónico (53.2 mg, 0.844 mmol) en metanol (8 ml) se inyectó nitrógeno y se calentó a 75 °C durante 1 h. La mezcla se enfrió hasta ta, se diluyó con metanol y se filtró a través de una almohadilla de Celite. El filtrado se concentró proporcionando (R)-4-(3-aminopiperidin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido blanco (75 mg, 98%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.13 (d, J=8.13 Hz, 1 H) 7.86 (d, J=8.35 Hz, 1 H) 7.68 (s, 1 H) 7.29 (d, J=9.67 Hz, 1 H) 6.86 (d, J=8.35 Hz, 1 H) 3.54 - 3.72 (m, 2 H) 3.24 - 3.53 (m, 5 H) 2.88 (s, 3 H) 2.11 - 2.29 (m, 1 H) 1.92 - 2.11 (m, 2 H) 1.44 - 1.73 (m, 1 H). Espectro

de masas m/z 435.2 $(M+H)^+$.

Ejemplo 18-1

Preparación de (R)-4-(3-acetamidopiperidin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Se trató una solución de (R)-4-(3-aminopiperidin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 17-1, 25 mg, 0.058 mmol) y TEA (0.016 ml, 0.115 mmol) en DCM-THF (2:1, 3 ml) con cloruro de acetilo (4.9 µl, 0.069 mmol). La mezcla se agitó a ta durante 1.5 h, luego se concentró y el residuo se purificó por HPLC preparativa. El producto, aislado como la sal TFA, se repartió entre DCM y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se secó y se concentró proporcionando (R)-4-(3-acetamidopiperidin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido blanco (12 mg, 39%). RMN de ^1H (500 MHz, etanol-d_6) δ 8.24 (d, *J*=7.97 Hz, 1 H) 7.89 (d, *J*=8.52 Hz, 1 H) 7.69 (s, 1 H) 7.32 (d, *J*=9.35 Hz, 1 H) 6.90 (d, *J*=8.52 Hz, 1 H) 4.21 - 4.32 (m, 1 H) 3.73 - 3.93 (m, 2 H) 3.42 - 3.72

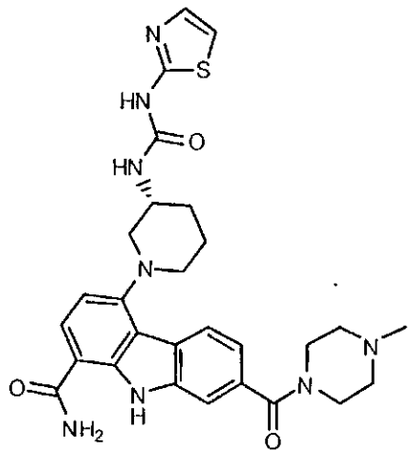
(m, 5 H) 2.96 - 3.11 (m, 1 H) 2.39 - 2.63 (m, 4 H) 2.35 (s, 3 H) 2.06 - 2.15 (m, 1 H) 1.97 - 2.06 (m, 2 H) 1.95 (s, 3 H) 1.48 - 1.59 (m, 1H). Espectro de masas m/z 477.3 $(M+H)^+$.

El siguiente compuesto también se preparó usando el procedimiento mostrado en el Ejemplo 18-1, sustituyendo cloruro de acetilo por cloruro de benzoilo.

Ejemplo	Nombre del compuesto	Espectro de masas
18-2	(R)-4-(3-benzamidopiperidin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	539.3 $(M+H)^+$

Ejemplo 19-1

Preparación de (R)-7-(4-metilpiperazin-1-carbonil)-4-(3-(3-tiazol-2-ilureido)piperidin-1-il)-9H-carbazol-1-carboxamida

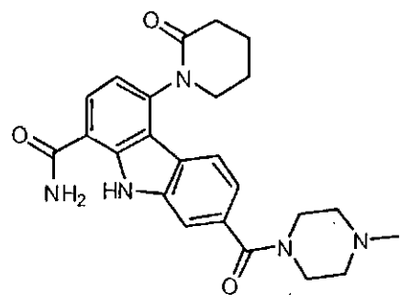


Se trató una solución de (R)-4-(3-aminopiperidin-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida

(Ejemplo 17-1, 23 mg, 0.053 mmol) y TEA (0.015 ml, 0.106 mmol) en THF (3 ml) con tiazol-2-ilcarbamato de fenilo (17.49 mg, 0.079 mmol). La mezcla se agitó a 60°C durante 1.5 h, luego a 70°C durante 2 h, luego se concentró y purificó por HPLC preparativa. La sal TFA aislada se repartió entre DCM y NaHCO3 (ac) y la fase orgánica se secó y se concentró proporcionando (R)-7-(4-metilpiperazin-1-carbonil)-4-(3-(3-tiazol-2-ilureido)piperidin-1-il)-9H-carbazol-1-carboxamida como un sólido blanco (14 mg, 43%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.27 (1 H, d, J=7.9 Hz), 7.87 (1 H, d, J=8.3 Hz), 7.68 (1 H, d, J=1.1 Hz), 7.28 (1 H, d, J=7.9 Hz), 7.18 (1 H, s ancho), 6.93 (1 H, d, J=3.7 Hz), 6.87 (1 H, d, J=8.3 Hz), 4.25 (1 H, ancho), 3.82 (2 H, ancho), 3.41 - 3.68 (3 H, m), 3.19 (3 H, ancho), 2.36 - 2.63 (4 H, m), 2.33 (3H, s), 1.84 - 2.20 (3 H, m), 1.71 (1 H, s ancho). Espectro de masas m/z 561.3 $(M+H)^+$.

Ejemplo 20-1

Preparación de 7-(4-metilpiperazin-1-carbonil)-4-(2-oxopiperidin-1-il)-9H-carbazol-1-carboxamida



Etapa 1 Una mezcla de 4-bromo-7-(4-metilpiperazin-

1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 1-1, 118.1 mg, 0.284 mmol), azida de sodio (37.0 mg, 0.569 mmol), yoduro de cobre (I) (36.4 mg, 0.191 mmol), (RS)-prolina (24.6 mg, 0.214 mmol), hidróxido sódico acuoso 1 M (0.191 ml, 0.191 mmol), etanol (1.5 ml) y agua (0.191 ml) se purgó con argon y se calentó a 95°C en un tubo sellado. Después de 17.5 h, la mezcla se enfrió hasta ta, se filtró a través de una almohadilla de gel de sílice, y los sólidos se aclararon con metanol. El filtrado se concentró y se trató con ácido clorhídrico 1 M, y el precipitado resultante se recogió por filtración y se secó proporcionando 4-azido-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida impura, sal clorhidrato, como un sólido marrón claro (31.8 mg, 27%). El filtrado se purificó por HPLC preparativa proporcionando 4-azido-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido marrón (20.7 mg, 15%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.37 (1 H, d, J=8.14 Hz), 7.97 (1 H, d, J=8.14 Hz), 7.73 (1 H, s), 7.33 (1 H, dd, J=8.14, 1.32 Hz), 7.06 (1 H, d, J=8.36 Hz), 3.34 - 3.72 (6 H, m), 3.26 (2 H, s ancho), 2.96 (3 H, s). Espectro de masas m/z 378.2 $(M+H)^+$.

Etapa 2 Una suspensión de 4-azido-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida impura, sal clorhidrato (31.8 mg, 0.060 mmol), cloruro de amonio (25 mg, 0.467 mmol) y polvo de cinc (60 mg, 0.918 mmol) en

metanol (1 ml) y THF (1 ml) se agitó a ta. Después de 1 h, la mezcla se purificó por cromatografía en columna (eluyendo con un gradiente de DCM hasta DCM-metanol 80:20) proporcionando 4-amino-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido amarillo claro (11.8 mg, 56%). Espectro de masas m/z 352.3 $(M+H)^+$.

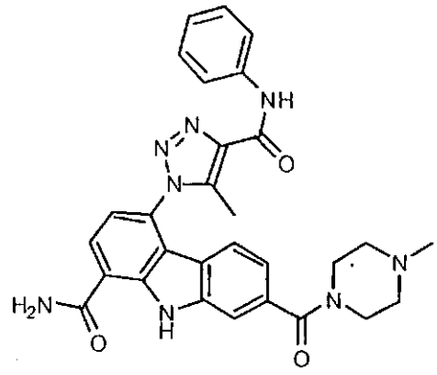
Etapa 3 Se trató una solución de 4-amino-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (11.8 mg, 0.034 mmol) y TEA (0.047 ml, 0.336 mmol) en DCM (0.5 ml) y DMF (0.25 ml) con cloruro de 5-cloropentanoilo (0.017 ml, 0.134 mmol) y se agitó a ta. Se añadió más cloruro de 5-cloropentanoilo (0.017 ml, 0.134 mmol) después de 3 h y la mezcla se agitó a ta durante la noche. La mezcla se concentró y se repartió entre EtOAc y cloruro amónico acuoso saturado. La fase acuosa se purificó por HPLC preparativa proporcionando 4-(5-cloropentanamido)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido amarillo claro (6.6 mg, 34%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.15 (1 H, d, J=8.14 Hz), 7.96 (1 H, d, J=8.14 Hz), 7.77 (1 H, d, J=0.88 Hz), 7.27 - 7.38 (2 H, m), 3.68 (2 H, s ancho), 3.33 - 3.63 (4 H, m), 3.12 - 3.29 (2 H, m), 2.97 (3 H, s), 2.68 (2 H, s ancho), 1.98 (4 H, s ancho). Espectro de masas m/z 470.4 $(M+H)^+$.

Etapa 4 Se trató una solución de 4-(5-cloropentanamido)-7-(4-metilpiperazin-1-carbonil)-9H-

carbazol-1-carboxamida, sal TFA (6.6 mg, 0.011 mmol) en DMF (0.5 ml) con hidruro sódico (dispersión al 60% en aceite, 12.7 mg, 0.318 mmol) y la mezcla se agitó a ta durante 35 min. La mezcla se concentró, se recogió en cloruro amónico acuoso saturado y purificó por HPLC preparativa proporcionando 7-(4-metilpiperazin-1-carbonil)-4-(2-oxopiperidin-1-il)-9H-carbazol-1-carboxamida, aislada como la sal TFA, como un polvo blanco después de liofilización (4.3 mg, 69%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.03 (1 H, d, J=7.92 Hz), 7.96 (1 H, d, J=8.14 Hz), 7.79 (1 H, d, J=0.88 Hz), 7.36 (1 H, dd, J=8.03, 1.43 Hz), 7.17 (1 H, d, J=7.92 Hz), 3.84 - 3.93 (1 H, m), 3.73 - 3.82 (1 H, m), 3.34 - 3.64 (4-H, m), 3.13 - 3.27 (2 H, m), 2.97 (3 H, s), 2.60 - 2.82 (2 H, m), 2.08 - 2.25 (4 H, m). Espectro de masas m/z 434.4 $(M+H)^+$.

Ejemplo 21-1

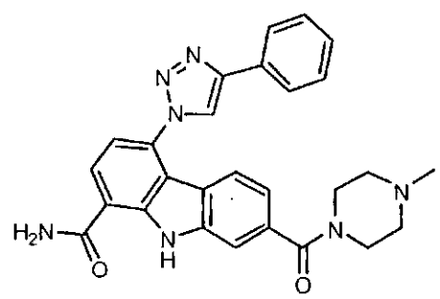
Preparación de 4-(5-metil-4-(fenilcarbamoil)-1H-1,2,3-triazol-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Una solución de 4-azido-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (base libre, preparada a partir del material preparado de acuerdo con la Etapa 1 del Ejemplo 20-1, 24.1 mg, 0.036 mmol) y 3-oxo-N-fenilbutanamida (17.5 mg, 0.099 mmol) en etanol (0.5 ml) y THF (0.5 ml) se añadió a 0°C a una solución de etóxido sódico preparada a partir de sodio (6.7 mg, 0.291 mmol) y etanol (0.5 ml). Después de 2 h, la mezcla se calentó hasta ta y se agitó durante la noche. La mezcla se concentró y el residuo se purificó por HPLC preparativa proporcionando 4-(5-metil-4-(fenilcarbamoil)-1H-1,2,3-triazol-1-il)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida, sal TFA, como un polvo amarillo claro después de liofilización (2.6 mg, 10%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.19 (1 H, d, J=7.92 Hz), 7.85 (1 H, s), 7.77 - 7.82 (2 H, m), 7.41 (3 H, t, J=7.70 Hz), 7.17 - 7.23 (2 H, m), 6.75 (1 H, d, J=8.14 Hz), 3.34 - 3.64 (4 H, m), 3.09 - 3.27 (2 H, m), 2.95 (3 H, s), 2.48 (3 H, s). Espectro de masas m/z 537.3 $(M+H)^+$.

Ejemplo 22-1

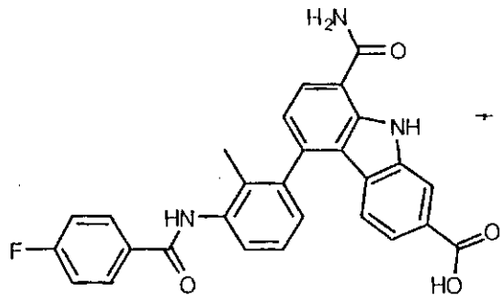
Preparación de 7-(4-metilpiperazin-1-carbonil)-4-(4-fenil-1H-1,2,3-triazol-1-il)-9H-carbazol-1-carboxamida



Una solución de 4-azido-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (base libre, preparada a partir del material preparado de acuerdo con la Etapa 1 del Ejemplo 20-1, 10 mg, 0.026 mmol), etinilbenceno (3.2 µl, 0.029 mmol), sulfato de cobre (II) (0.42 mg, 0.003 mmol) y l-ascorbato sódico (1.1 mg, 0.005 mmol) en THF (0.5 ml) y agua (0.1 ml) se agitó a 45°C durante la noche. La reacción no fue completa, por lo que la mezcla se agitó a 45°C durante 4.5 h, luego a 95°C durante la noche. La mezcla se concentró y el residuo se disolvió en una mezcla de metanol y ácido clorhídrico 1 M (2:1), se filtró y purificó por HPLC preparativa y liofilización proporcionando 7-(4-metilpiperazin-1-carbonil)-4-(4-fenil-1H-1,2,3-triazol-1-il)-9H-carbazol-1-carboxamida, sal TFA, como un polvo blanco (5.2 mg, 33%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.90 (1 H, s), 8.16 (1 H, d, J=7.92 Hz), 8.00 - 8.04 (2 H, m), 7.84 (1 H, s), 7.50 - 7.55 (2 H, m), 7.48 (1 H, d, J=7.92 Hz), 7.40 - 7.46 (1 H, m), 7.36 (1 H, d, J=8.80 Hz), 7.20 (1 H, dd, J=8.25, 1.43 Hz), 3.33 - 3.68 (4 H, m), 3.10 - 3.28 (2 H, m), 2.95 (3 H, s). Espectro de masas m/z 480.3 $(M+H)^+$.

Ejemplo 23-1

Preparación de ácido 8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxílico

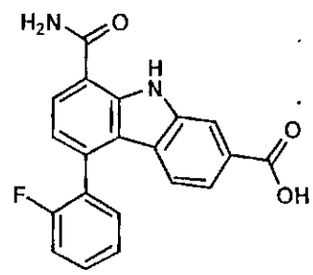


Se trató una suspensión de 8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxilato de etilo (Ejemplo 3-100, 1.63 g, 3.20 mmol) en etanol (12 ml) con hidróxido sódico acuoso 1 M (1.5 ml, 1.500 mmol), formando una suspensión amarilla que se calentó a 90-95°C durante 30 min. La mezcla se enfrió hasta ta y se acidificó con ácido clorhídrico 1 M. El precipitado se recogió por filtración, se lavó con agua y se secó proporcionando ácido 8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxílico como un sólido blanquecino (1.496 g, 92%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.76 (s ancho,1 H) 11.84 (s, 1 H) 10.15 (s, 1 H) 8.38 (s, 1 H) 8.24 (s ancho,1 H) 8.03 - 8.13 (m, 3 H) 7.56 (s ancho,1 H) 7.46 - 7.54 (m, 2 H) 7.42 (t, J=7.7 Hz, 1 H) 7.35 (t, J=9.0 Hz, 2 H) 7.23 (dd, J=7.5, 1.3 Hz, 1 H) 7.04 (d, J=7.5 Hz, 1 H) 7.01 (d, J=8.3 Hz, 1 H) 1.88 (s, 3 H). Espectro de masas m/z 482.1 $(M+H)^+$.

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Ejemplo 23-2

Preparación de ácido 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-carboxílico



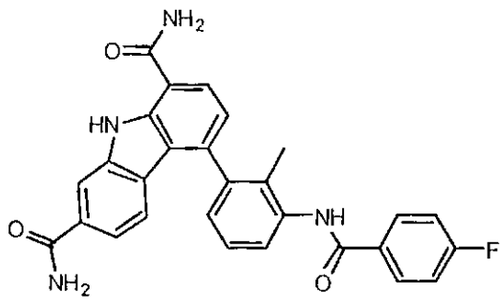
Se trató una suspensión de 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-carboxilato de etilo (Ejemplo 3-12, 0.8 g, 2.126 mmol) e hidróxido de litio monohidratado (0.255 g, 6.38 mmol) en THF-etanol-agua (3:1:1) (25.0 ml) a reflujo durante 4 h. La mezcla se concentró y el residuo se suspendió en agua. El pH se ajustó a 1-2 por adición de ácido clorhídrico 1 M. El precipitado se recogió por filtración, se lavó con agua y se secó proporcionando ácido 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-carboxílico como un sólido amarillo (520 mg, 71%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.77 (s ancho,1 H) 11.87 (s, 1 H) 8.41 (m, 1 H) 8.26 (s ancho,1 H) 8.08 (d, J=7.69 Hz, 1 H) 7.50 - 7.67 (m, 4 H) 7.40 - 7.49 (m, 2 H) 7.09 - 7.17 (m, 2 H). Espectro de masas m/z 349.1 $(M+H)^+$.

El siguiente compuesto también se preparó usando procedimientos mostrados en el Ejemplo 23-1, usando

	Material de partida	Nombre del compuesto	Espectro de masas
23-3	Ejemplo 3-11	ácido 8-carbamoil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-2-carboxílico	371.1 $(M+H)^+$

Ejemplo 24-1

Preparación de 4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1,7-dicarboxamida

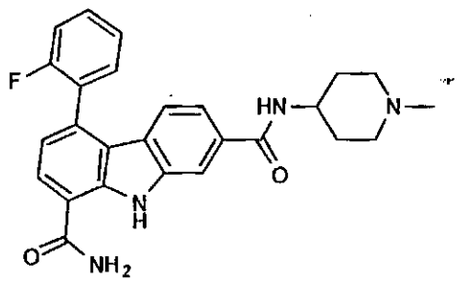


Se trató una mezcla de ácido 8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxílico (Ejemplo 23-1, 30 mg, 0.062 mmol) y HOAT (12.72 mg, 0.093 mmol) en THF (0.4 ml) con hidróxido amónico acuoso al 28% (0.052 ml, 0.374 mmol) y EDC (23.89 mg, 0.125 mmol) y la mezcla se agitó a ta. Después de 22.4 h, la mezcla se concentró y purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron y el residuo se trató con NaHCO3 (ac) y se extrajo tres veces con EtOAc. Las fases

orgánicas reunidas se secaron y concentraron proporcionando 4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1,7-dicarboxamida como un sólido blanquecino (9.6 mg, 29%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.11 (d, J=1.3 Hz, 1 H) 8.03 - 8.08 (m, 2 H) 8.01 (d, J=7.9 Hz, 1 H) 7.51 - 7.55 (m, 1 H) 7.41 - 7.48 (m, 2 H) 7.29 (dd, J=7.5, 1.3 Hz, 1 H) 7.24 (t, J=8.8 Hz, 2 H) 7.08 - 7.12 (m, 2 H) 1.98 (s, 3 H). Espectro de masas m/z 481.1 $(M+H)^+$.

Ejemplo 24-2

Preparación de 4-(2-fluorofenil)-N^7-(1-metilpiperidin-4-il)-9H-carbazol-1,7-dicarboxamida

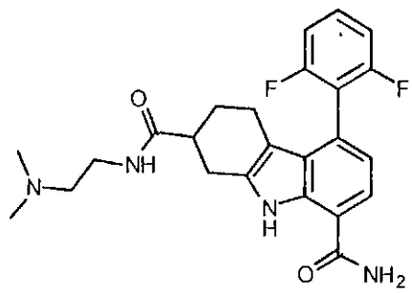


Una mezcla de ácido 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-carboxílico (Ejemplo 23-2, 30 mg, 0.086 mmol), EDC (23.11 mg, 0.121 mmol), HOBT (18.46 mg, 0.121 mmol), DIEA (30 µl, 0.172 mmol), y 1-metilpiperidin-4-amina (9.83 mg, 0.086 mmol) en THF y DMF (4:1, 2 ml) se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa. El producto aislado se repartió entre DCM y NaHCO3 (ac). La fase orgánica se secó y se concentró proporcionando 4-(2-fluorofenil)-N^7-(1-metilpiperidin-4-il)-

9H-carbazol-1,7-dicarboxamida como un sólido blanco (25 mg, 62%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.75 (s, 1 H) 8.24 (s ancho,1 H) 8.20 (s, 1 H) 8.13 (d, *J*=7.69 Hz, 1 H) 8.05 (d, *J*=7.91 Hz, 1 H) 7.52 - 7.68 (m, 3 H) 7.33 - 7.48 (m, 3 H) 7.13 (d, *J*=7.69 Hz, 1 H) 7.05 (d, *J*=8.35 Hz, 1 H) 3.64 - 3.80 (m, 1 H) 2.69 - 2.79 (m, 2 H) 1.87 - 2.00 (m, 2 H) 1.70 - 1.80 (m, 2 H) 1.48 - 1.65 (m, 2 H). Espectro de masas m/z 445.2 $(M+H)^+$.

Ejemplo 24-3

Preparación de 5-(2,6-difluorofenil)-N^2-(2-(dimetilamino)etil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida



Usando el procedimiento del Ejemplo 24-2, se convirtieron ácido 8-carbamoil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-2-carboxílico (Ejemplo 23-3, 20 mg, 0.054 mmol) y N^1,N^1-dimetiletano-1,2-diamina (7.1 mg, 0.081 mmol) en 5-(2,6-difluorofenil)-N^2-(2-(dimetilamino)etil)-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida (25 mg, 62%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.08 (1 H, s ancho), 7.35 - 7.39 (2 H, m), 6.99 (3 H, d, J=8.35 Hz), 6.20

(2 H, s ancho), 3.28 - 3.43 (3 H, m), 2.84 - 3.13 (2 H, m), 2.44 - 2.62 (1 H, m), 2.27 - 2.45 (3 H, m), 2.18 (6 H, s), 1.91 - 2.03 (1 H, m), 1.74 - 1.86 (1 H, m). Espectro de masas m/z 441.1 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 24-1 a 24-3, partiendo del ácido carboxílico apropiado (preparado de acuerdo con los Ejemplos 23-1 a 23-3) y la amina apropiada.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
24-4	Ejemplo 23-2	N^7-(2-(dimetilamino)etil)-4-(2-fluorofenil)-N^7-metil-9H-carbazol-1,7-dicarboxamida	432.9 $(M+H)^+$
24-5	Ejemplo 23-2	4-(2-fluorofenil)-7-(4-(2-metoxietil)piperazin-1-carbonil)-9H-carbazol-1-carboxamida	475.2 $(M+H)^+$
24-6	Ejemplo 23-2	4-(2-fluorofenil)-7-(4-(3-metoxipropil)piperazin-1-carbonil)-9H-carbazol-1-carboxamida	489.3 $(M+H)^+$

24-7	Ejemplo 23-2	7-(4-(dimetilamino)piperidin-1-carbonil)-4-(2-fluorofenil)-9H-carbazol-1-carboxamida	459.2 $(M+H)^+$
24-8	Ejemplo 23-2	4-(2-fluorofenil)-N^7-metil-N^7-(2-(metilsulfonil)etil)-9H-carbazol-1,7-dicarboxamida	468.1 $(M+H)^+$
24-9	Ejemplo 23-2	7-((S)-3-(dimetilamino)pirrolidin-1-carbonil)-4-(2-fluorofenil)-9H-carbazol-1-carboxamida	445.5 $(M+H)^+$
24-10	Ejemplo 23-2	7-((R)-3-(dimetilamino)pirrolidin-1-carbonil)-4-(2-fluorofenil)-9H-carbazol-1-carboxamida	445.5 $(M+H)^+$
24-11	Ejemplo 23-3	5-(2,6-difluorofenil)-N^2-(4-(dimetilamino)butil)-2,3,4,9-tetrahidro-1H-carbazol-2.8-dicarboxamida	469.2 $(M+H)^+$
24-12	Ejemplo 23-3	5-(2,6-difluorofenil)-2-(4-metilpiperazin-1-carbonil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	453.2 $(M+H)^+$
24-13	Ejemplo 23-3	5-(2,6-difluorofenil)-N^2-(3-(dimetilamino)propil)-2,3,4,9-tetrahidro-1H-carbazol-2.8-dicarboxamida	455.1 $(M+H)^+$

24-14	Ejemplo 23-3	5-(2,6-difluorofenil)-N^2-(1-metilpiperidin-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2.8-dicarboxamida	467.2 $(M+H)^+$
24-15	Ejemplo 23-3	5-(2,6-difluorofenil)-N^2-(tetrahidro-2H-piran-4-il)-2,3,4,9-tetrahidro-1H-carbazol-2.8-dicarboxamida	454.2 $(M+H)^+$
24-16	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(2-(1-(RS)-metilpirrolidin-2-il)etil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	592.0 $(M+H)^+$
24-17	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(4-(2-hidroxietil)piperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	594.0 $(M+H)^+$
24-18	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(2-morfolinoetil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	594.0 $(M+H)^+$

24-19	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(piridin-3-ilmetil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	572.0 $(M+H)^+$
24-20	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(piridin-4-ilmetil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	572.0 $(M+H)^+$
24-21	Ejemplo 23-1	N^7-(3-(1H-imidazol-1-il)propil)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	589.0 $(M+H)^+$
24-22	Ejemplo 23-1	7-(4-(dimetilamino)piperidin-1-carbonil)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	592.0 $(M+H)^+$

24-23	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-metil-N^7-(piridin-3-ilmetil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	586.1 $(M+H)^+$
24-24	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-metil-N^7-(1-(RS)-metilpirrolidin-3-il)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	578.0 $(M+H)^+$
24-25	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(2-fenilpropan-2-il)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	599.0 $(M+H)^+$
24-26	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(piridin-3-il)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	557.9 $(M+H)^+$
24-27	Ejemplo 23-1	N^7-(3-(dimetilamino)fenil)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	600.0 $(M+H)^+$

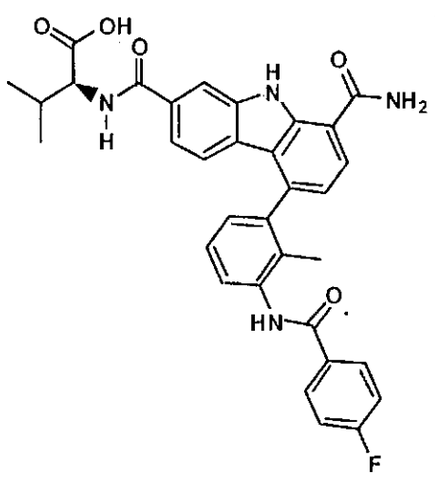
24-28	Ejemplo 23-1	N^7-(2-amino-2-oxoetil)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	537.9 $(M+H)^+$
24-29	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(4-(hidroximetil)piperidin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	580.0 $(M+H)^+$
24-30	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(3-hidroxibencil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	586.9 $(M+H)^+$
24-31	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-oxopiperazin-1-carbonil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	563.9 $(M+H)^+$
24-32	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(tiazol-2-il)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	563.9 $(M+H)^+$

24-33	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(3-metoxifenil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	586.9 $(M+H)^+$
24-34	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(4-fluorofenil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	575.0 $(M+H)^+$
24-35	Ejemplo 23-1	N^7-*terc*-butil-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	537.0 $(M+H)^+$
24-36	Ejemplo 23-1	N^7-bencil-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	571.0 $(M+H)^+$
24-37	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-metil-N^7-fenil-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	571.0 $(M+H)^+$
24-38	Ejemplo 23-1	N^7-ciclopropil-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	520.9 $(M+H)^+$

24-39	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(piridin-2-il)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	558.0 $(M+H)^+$
24-40	Ejemplo 23-1	4-(3-(4-fluorobenzamido)-2-metilfenil)-N^7-(piridin-2-ilmetil)-9H-carbazol-1,7-dicarboxamida (preparada como la sal TFA)	572.1 $(M+H)^+$

Ejemplo 25-1

Preparación de ácido (2S)-2-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxamido)-3-metilbutanoico



Se agitó a ta durante 21 horas una mezcla de ácido 8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxílico (Ejemplo 23-1, 19.3 mg, 0.04 mmol),

EDC (9.6 mg, 0.05 mmol), HOBT (7.7 mg, 0.0.05 mmol), DIEA (25.8 mg, 0.20 mmol) y 2-amino-3-metilbutanoato de (S)-*terc*-butilo, sal clorhidrato (10.5 mg, 0.05 mmol) en DMF (0.36 ml). La mezcla se concentró y el residuo se agitó en DCM (0.5 ml) y TFA (0.5 ml) durante 2 h. La mezcla se concentró y el residuo se purificó por HPLC preparativa proporcionando ácido (2S)-2-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxamido)-3-metilbutanoico, sal TFA (15.3 mg, 55%). Espectro de masas m/z 581.0 $(M+H)^+$.

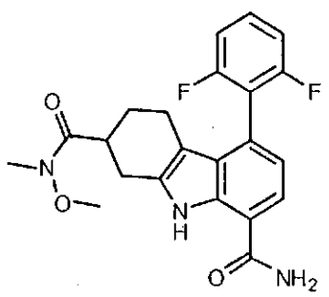
Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 25-1.

Ejemplo	Nombre del compuesto	Espectro de masas
25-2	ácido (2S,3S)-2-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxamido)-3-metilpentanoico (preparado como la sal TFA)	595.0 $(M+H)^+$
25-3	ácido 2-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carboxamido)acético (preparado como la sal TFA)	538.9 $(M+H)^+$

25-4	ácido (2R)-1-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carbonil)pirrolidin-2-carboxílico (preparado como la sal TFA)	579.0 $(M+H)^+$
25-5	ácido (2S)-1-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-carbonil)pirrolidin-2-carboxílico (preparado como la sal TFA)	578.9 $(M+H)^+$

Ejemplo 26-1

Preparación de 5-(2,6-difluorofenil)-N^2-metoxi-N^2-metil-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida

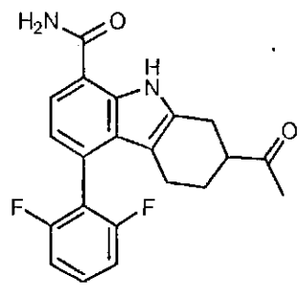


Se trató una solución de ácido 8-carbamoil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-2-carboxílico (Ejemplo 23-3, 720 mg, 1.944 mmol) y TEA (1.084 ml, 7.78 mmol) en THF (5 ml) con cloroformiato de isobutilo (266 mg, 1.944 mmol) a 0°C. Después de agitar durante 10 min, se añadió una solución de sal clorhidrato de N,O-

dimetilhidroxilamina (190 mg, 1.944 mmol) en THF (2 ml) y agua (0.5 ml). La mezcla se agitó durante 30 min, luego se diluyó con DCM, se lavó con NaHCO3 (ac) y agua y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo con EtOAc) proporcionando 5-(2,6-difluorofenil)-N^2-metoxi-N^2-metil-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida como un sólido blanco (802 mg, 93%). RMN de ^1H (400 MHz, cloroformo-d) δ 1.70 - 1.82 (m, 1 H) 1.90 - 1.99 (m, 1 H) 2.19 - 2.25 (m, 2 H) 2.32 - 2.42 (m, 1 H) 2.84 - 2.92 (m, 1 H) 3.05 - 3.19 (m, 1 H) 3.23 (s, 3 H) 3.70 (s, 3 H) 6.98 - 7.06 (m, 3 H) 7.35 - 7.42 (m, 2 H) 10.10 (s, 1 H). Espectro de masas m/z 414.2 $(M+H)^+$.

Ejemplo 27-1

Preparación de 2-acetil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida

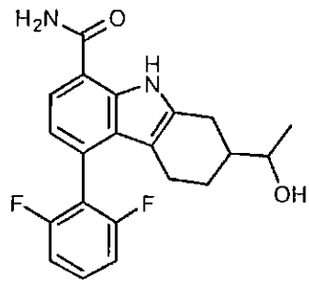


Se trató una solución de 5-(2,6-difluorofenil)-N^2-metoxi-N^2-metil-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida (Ejemplo 26-1, 719 mg, 1.739 mmol) en THF (1 ml) con bromuro de metilmagnesio (3 M en éter dietílico, 2.90 ml, 8.70 mmol) a 0°C. Después de 20 min, se añadió más

bromuro de metilmagnesio (2.90 ml, 8.70 mmol) y se continuó agitando durante 30 min more. La mezcla se trató con ácido clorhídrico 1 M y se extrajo cuatro veces con DCM. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron. El residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc) y el material resultante se trituró con DCM proporcionando 2-acetil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido blanquecino (210 mg, 33%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.59 (1 H, d, J=7.91 Hz), 7.39 - 7.49 (2 H, m), 7.01 - 7.09 (3 H, m), 6.90 (1 H, d, J=7.91 Hz), 2.86 - 2.97 (3 H, m), 2.24 - 2.33 (1 H, m), 2.22 (3 H, s), 2.01 - 2.18 (2 H, m), 1.54 - 1.66 (1 H, m). Espectro de masas m/z 369.1 $(M+H)^+$.

Ejemplos 28-1 y 28-2

Preparación de dos diastereómeros de 5-(2,6-difluorofenil)-2-(1-hidroxietil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida

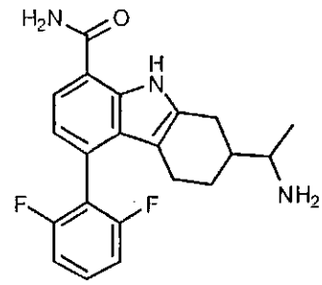


Una suspensión de 2-acetil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Ejemplo 27-1, 30 mg, 0.081 mmol) y borohidruro sódico (6.2 mg, 0.163 mmol)

en metanol (1 ml) se agitó a ta durante 1 h. La mezcla se diluyó con DCM, se lavó con NaHCO3 (ac) y agua y se secó y concentró. El residuo se purificó por HPLC preparativa proporcionando dos diastereómeros de 5-(2,6-difluorofenil)-2-(1-hidroxietil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida. Cada uno se repartió entre hidróxido sódico acuoso 1 M y DCM, seguido por secado y concentración, proporcionando los diastereómeros racémicos separados de 5-(2,6-difluorofenil)-2-(1-hidroxietil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida. El diastereómero más polar (Ejemplo 28-1) era un sólido blanco (10 mg, 33%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 1.26 (d, J=6.59 Hz, 3 H) 1.30 - 1.43 (m, 1 H) 1.78 - 1.89 (m, 1 H) 1.97 - 2.05 (m, J=12.74 Hz, 1 H) 2.14 - 2.22 (m, 1 H) 2.24 - 2.35 (m, 1 H) 2.47 (dd, J=16.04, 10.77 Hz, 1 H) 2.81 (dd, J=16.48, 5.05 Hz, 1 H) 3.70 - 3.79 (m, 1 H) 6.96 - 7.04 (m, 3 H) 7.32 - 7.41 (m, 2 H) 10.05 (s, 1 H). Espectro de masas m/z 371.1 $(M+H)^+$. El diastereómero menos polar (Ejemplo 28-2) era un sólido blanco (8 mg, 27%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 1.26 (d, J=6.15 Hz, 3 H) 1.34 - 1.40 (m, 1 H) 1.42 - 1.53 (m, 1 H) 1.75 - 1.90 (m, 2 H) 2.24 - 2.35 (m, 1 H) 2.68 (dd, J=16.26, 10.11 Hz, 1 H) 2.94 (dd, J=16.26, 5.27 Hz, 1 H) 3.80 (s, 1 H) 6.96 - 7.05 (m, 3 H) 7.34 - 7.40 (m, 2 H) 10.05 (s, 1 H). Espectro de masas m/z 371.1 $(M+H)^+$.

Ejemplo 29-1

Preparación de 2-(1-aminoetil)-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida



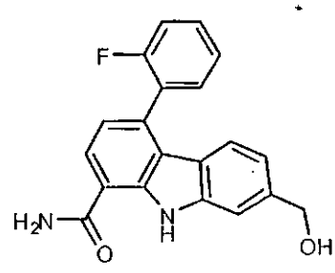
Una suspensión de 2-acetil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Ejemplo 27-1, 30 mg, 0.081 mmol), acetato amónico (25.1 mg, 0.326 mmol) y triacetoxiborohidruro sódico (25.9 mg, 0.122 mmol) en DCM (1 ml) se calentó a 50°C durante 1 h. La mezcla se enfrió, se diluyó con DCM, se lavó con NaHCO3 (ac) y agua y se secó y concentró. El residuo se purificó por HPLC preparativa, y las fracciones de efluente apropiadas se basificaron con hidróxido sódico acuoso 1 M y se extrajeron dos veces con DCM. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron proporcionando una mezcla de diastereómeros de 2-(1-aminoetil)-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido blanco (20 mg, 67%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.59 (1 H, d, J=7.47 Hz), 7.39 - 7.49 (1 H, m), 7.01 - 7.09 (2 H, m), 6.89 (1 H, d), 2.78 - 2.94 (2 H, m), 2.46 - 2.61 (1 H, m), 2.06 - 2.28 (2 H, m), 1.77 - 1.94 (1 H, m), 1.62 - 1.74 (1 H, m), 1.26 - 1.40 (1 H, m), 1.13 (3 H, d, J=6.59 Hz). Espectro de masas m/z 370.1 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 29-1, usando la amina apropiada en lugar de acetato amónico.

Ejemplo	Nombre del compuesto	Espectro de masas
29-2	5-(2,6-difluorofenil)-2-(1-(1-metilpiperidin-4-ilamino)etil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como una mezcla de diastereómeros)	467.2 $(M+H)^+$
29-3	5-(2,6-difluorofenil)-2-(1-morfolinoetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como una mezcla de diastereómeros)	440.2 $(M+H)^+$

Ejemplo 30-1

Preparación de 4-(2-fluorofenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida



Se trató una solución de 8-carbamoil-5-(2-

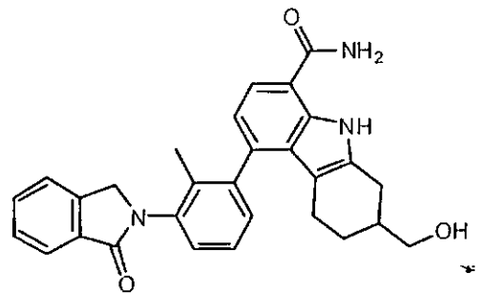
fluorofenil)-9H-carbazol-2-carboxilato de etilo (Ejemplo 3-12, 0.81g, 2.152 mmol) en THF (26.9 ml) a 0°C con hidruro de litio y aluminio (1.0 M en THF, 3.01 ml, 3.01 mmol), y la mezcla se agitó a ta durante 5 h. Se añadió más hidruro de litio y aluminio (1.3 ml, 1.3 mmol) y la mezcla se agitó a ta durante la noche. La mezcla se trató con metanol y TFA y se diluyó con EtOAc, se lavó con salmuera, se secó y se concentró proporcionando 4-(2-fluorofenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida impura (0.78 g) contaminada con material de partida. Se purificó una pequeña cantidad por HPLC preparativa proporcionando 4-(2-fluorofenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida, aislada como la sal TFA. RMN de ^{1}H (500 MHz, metanol-d_4) δ 7.82 (1 H, d, J=7.8 Hz), 7.51 (1 H, s), 7.44 - 7.50 (1 H, m), 7.42 (1 H, td, J=7.5, 1.9 Hz), 7.25 - 7.30 (1 H, m), 7.22 (1 H, t, J=9.2 Hz), 7.05 (1 H, d, J=8.3 Hz), 6.99 (1 H, d, J=7.8 Hz), 6.85 (1 H, dd, J=8.0, 1.4 Hz), 4.62 (2 H, s). Espectro de masas m/z 334.9 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 30-1.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
30-2	Intermedio 48-1	4-bromo-7-(hidroximetil)-9H-carbazol-1-carboxamida	319, 321 $(M+H)^+$
30-3(a)	Intermedio 47-1	5-bromo-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	323, 325 $(M+H)^+$

Ejemplo 31-1

Preparación de 2-(hidroximetil)-5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida

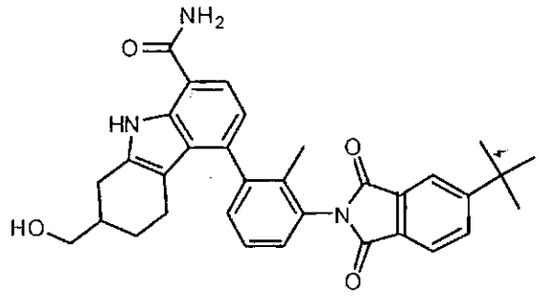


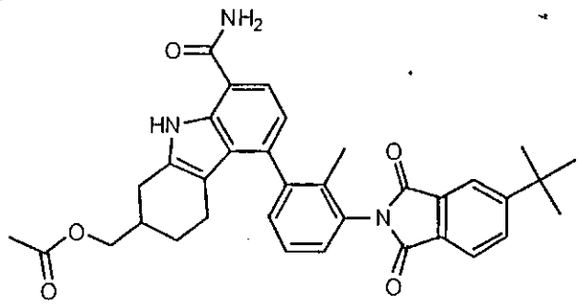
Una mezcla de 5-bromo-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Ejemplo 30-3, 80 mg, 0.248 mmol), 2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-4, 130 mg, 0.371 mmol), fosfato tripotásico acuoso 2 M (0.371 ml, 0.743 mmol), y tetraquis(trifenilfosfina)paladio (14.30 mg, 0.012 mmol) en tolueno (3 ml) y etanol (1 ml) se selló en un vial y se calentó a 100°C durante 6 horas. La mezcla se

enfrió y se diluyó con EtOAc, y la solución se lavó con agua, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de DCM hasta 96:3.6:0.4 de DCM-metanol-hidróxido amónico acuoso al 28%) proporcionando 2-(hidroximetil)-5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido amarillo claro (68 mg, 53%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 7.79 (1 H, d, J=7.91 Hz), 7.46 - 7.53 (1 H, m), 7.38 - 7.44 (2 H, m), 7.30 (1 H, dd, J=7.91, 3.08 Hz), 7.14 - 7.26 (3 H, m), 6.77 (1 H, dd, J=7.69, 2.86 Hz), 4.59 - 4.74 (2 H, m), 3.39 - 3.54 (3 H, m), 2.72 - 2.80 (2 H, m), 2.30 - 2.44 (2 H, m), 1.80 - 2.10 (3 H, m), 1.75 (3 H, d, J=8.35 Hz). Espectro de masas m/z 466.1 $(M+H)^+$.

Ejemplos 31-2 y 31-3

Preparación de 5-(3-(5-*terc*-butil-1,3-dioxoisoindolin-2-il)-2-metilfenil)-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida y (5-(3-(5-*terc*-butil-1,3-dioxoisoindolin-2-il)-2-metilfenil)-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-il)mEtOAc



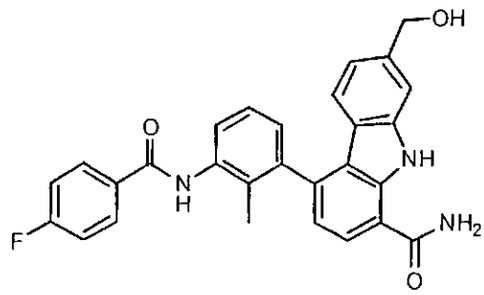


Se calentó a 100 °C en un tubo sellado durante la noche una mezcla de 5-bromo-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Ejemplo 30-3, 50 mg, 0.155 mmol), 5-*terc*-butil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1,3-diona (Intermedio 50-11, 97 mg, 0.232 mmol), fosfato tripotásico acuoso 2 M (0.232 ml, 0.464 mmol), y tetraquis(trifenilfosfina)paladio (8.9 mg, 7.7 µmol) en tolueno (3 ml) y etanol (1 ml). La mezcla se enfrió hasta ta, se trató con ácido clorhídrico 1 M, se extrajo con EtOAc, y la fase orgánica se secó y se concentró proporcionando ácido 5-*terc*-butil-2-(3-(8-carbamoil-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-5-il)-2-metilfenilcarbamoil)benzoico (Espectro de masas m/z 554.4 $(M+H)^+$). Sin purificación, Este material se disolvió en ácido acético (4 ml) y se calentó a 100°C durante 2 h, luego se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de DCM hasta 90:9:1 de DCM-metanol-hidróxido amónico acuoso al 28%), seguido por purificación por HPLC preparativa. Las

fracciones de efluente apropiadas se basificaron con NaHCO3 (ac) y se extrajeron con DCM, se secaron y se concentraron proporcionando 5-(3-(5-*terc*-butil-1,3-dioxoisoindolin-2-il)-2-metilfenil)-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Ejemplo 31-2) como un sólido amarillo claro (18 mg, 18%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.05 (1 H, s), 7.98 - 8.02 (1 H, m), 7.86 - 7.91 (1 H; m), 7.79 - 7.84 (1 H, m), 7.33 - 7.45 (4 H, m), 7.24 - 7.28 (2 H, m), 6.89 - 6.94 (1 H, m), 3.56 - 3.71 (2 H, m), 2.91 (1 H, dd, J=16.70, 4.83 Hz), 2.48 - 2.61 (1 H, m), 1.99 - 2.10 (2 H, m), 1.88 - 1.99 (2 H, m), 1.86 (3 H, s), 1.43 - 1.55 (2 H, m), 1.41 (9 H, s). Espectro de masas m/z 536.3 $(M+H)^+$. También se obtuvo (5-(3-(5-*terc*-butil-1,3-dioxoisoindolin-2-il)-2-metilfenil)-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-il)mEtOAc (Ejemplo 31-3) como un sólido amarillo claro (15 mg, 14%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.05 (1 H, s), 7.97 - 8.05 (1 H, m), 7.86 - 7.91 (1 H, m), 7.79 - 7.84 (1 H, m), 7.33 - 7.41 (3 H, m), 7.26 - 7.28 (1 H, m), 4.00 - 4.13 (2 H, m), 2.90 (2 H, td, J=10.88, 5.05 Hz), 2.46 - 2.71 (2 H, m), 2.12 - 2.34 (2 H, m), 2.08 (4 H, s), 1.87 (3 H, d, J=7.03 Hz), 1.45 - 1.54 (1 H, m), 1.41 (9 H, s). Espectro de masas m/z 578.3 $(M+H)^+$.

Ejemplo 31-4

Preparación de 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 3-2, 4-bromo-7-(hidroximetil)-9H-carbazol-1-carboxamida (Ejemplo 30-2, 800 mg, 2.41 mmol) y 4-fluoro-N-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)benzamida (Intermedio 53-1, 979 mg, 2.76 mmol) se convirtieron en 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida (550 mg, 47%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.50 (1 H, s), 10.15 (1 H, s), 8.21 (1 H, s ancho), 8.05 - 8.15 (2 H, m), 7.99 (1 H, d, J=7.9 Hz), 7.70 (1 H, s), 7.46 - 7.57 (2 H, m), 7.32 - 7.46 (3 H, m), 7.22 (1 H, dd, J=7.6, 1.0 Hz), 6.97 (1 H, d, J=7.7 Hz), 6.80 - 6.93 (2 H, m), 5.18 (1 H, t, J=5.7 Hz), 4.58 (2 H, d, J=5.5 Hz), 1.90 (3 H, s). Espectro de masas m/z 466.3 $(M-H)^-$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 31-1 a 31-4, a partir de los materiales de partida indicados.

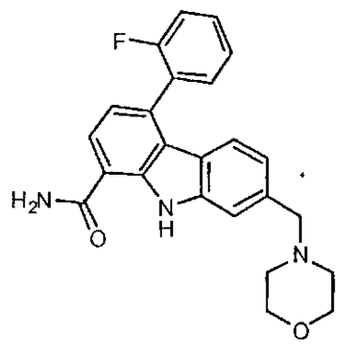
Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
31-5	Ejemplo 30-3(a), Intermedio 50-15	5-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	522.3 $(M+H)^+$
31-6	Ejemplo 30-3(a), Intermedio 50-14	5-(3-(6-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	522.3 $(M+H)^+$
31-7	Ejemplo 30-3(a), Intermedio 50-19	5-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-2-(hidroximetil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	484.2 $(M+H)^+$
31-8	Ejemplo 30-3(a), Intermedio 50-18	2-(hidroximetil)-5-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	480.2 $(M+H)^+$

31-9	Ejemplo 30-2, Intermedio 50-24	7-(hidroximetil)-4-(2-metil-3-(4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	475.0 $(M+H)^+$
31-10	Ejemplo 30-2, Intermedio 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida	493.0 $(M+H)^+$
31-11	Ejemplo 30-2, Intermedio 50-8	7-(hidroximetil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	458.0 $(M+H-H_2O)^+$
31-12	Ejemplo 30-2, Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida	462.1 $(M+H-H_2O)^+$
31-13	Ejemplo 30-2, Intermedio 50-38	7-(hidroximetil)-4-(2-metil-3-(4-oxo-6-(trifluorometoxi)quinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	541.0 $(M+H-H_2O)^+$

31-14	Ejemplo 30-2, Intermedio 50-48	4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida	475.1 (M+H-H_2O)$^+$
31-15	Ejemplo 30-2, Intermedio 50-54	7-(hidroximetil)-4-(2-metil-3-(quinazolin-4-ilamino)fenil)-9H-carbazol-1-carboxamida	474.0 (M+H)$^+$
31-16	Ejemplo 30-2, Intermedio 50-55	4-(3-(5-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida	492.1 (M+H)$^+$
31-17	Ejemplo 30-2, Intermedio 50-56	4-(3-(7-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida	492.1 (M+H)$^+$
31-18	Ejemplo 30-2, Intermedio 50-57	4-(3-(8-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida	492.1 (M+H)$^+$

Ejemplo 32-1

Preparación de 4-(2-fluorofenil)-7-(morfolinometil)-9H-carbazol-1-carboxamida



Se trató una solución de 4-(2-fluorofenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida (Ejemplo 30-1, 223 mg, 0.667 mmol) y TEA (0.279 ml, 2.001 mmol) en THF (8 ml) con cloruro de metanosulfonilo (0.104 ml, 1.334 mmol). La suspensión resultante se agitó a ta durante 15 min. La mezcla se diluyó con EtOAc, se lavó con agua y salmuera, y se secó y concentró proporcionando metanosulfonato de (8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-il)metilo bruto como una espuma vítrea amarilla (300 mg, aproximadamente 50% de pureza). Una parte de este material (80 mg, 0.097 mmol) se disolvió en DMF (1 ml), se trató con morfolina (84 mg, 0.970 mmol) y se calentó a 45°C durante 3 días. La mezcla se purificó por HPLC preparativa proporcionando 4-(2-fluorofenil)-7-(morfolinometil)-9H-carbazol-1-carboxamida (9.6 mg, 23%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.94 (1 H, d, J=7.8 Hz), 7.59 (1 H, s), 7.52 - 7.58 (1 H, m), 7.48 - 7.52 (1 H, m), 7.33 -

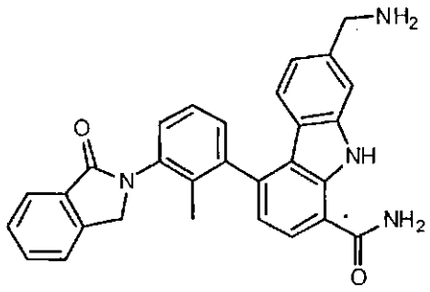
7.39 (1 H, m), 7.30 (1 H, t, J=9.0 Hz), 7.21 (1 H, d, J=8.3 Hz), 7.14 (1 H, d, J=7.8 Hz), 6.99 (1 H, dd, J=8.3, 1.5 Hz), 3.81 (2 H, s), 3.71 - 3.77 (4 H, m), 2.66 (4 H, s ancho). Espectro de masas m/z 404.2 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 32-1, usando la amina apropiada en lugar de morfolina.

Ejemplo	Nombre del compuesto	Espectro de masas
32-2	4-(2-fluorofenil)-7-((4-metilpiperazin-1-il)metil)-9H-carbazol-1-carboxamida	417.2 $(M+H)^+$
32-3	4-(2-fluorofenil)-7-(piperidin-1-ilmetil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	402.2 $(M+H)^+$

Ejemplo 33-1

Preparación de 7-(aminometil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Etapa 1 Se trató una suspensión de 4-bromo-7-

(hidroximetil)-9H-carbazol-1-carboxamida (Ejemplo 30-2, 300 mg, 0.940 mmol) y TEA (0.262 ml, 1.880 mmol) en THF (9.4 ml) gota a gota con cloruro de metanosulfonilo (0.077 ml, 0.987 mmol) y la mezcla se agitó a ta durante 1 h. Se trató con NaHCO3 (ac) y se extrajo con EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró proporcionando metanosulfonato de (5-bromo-8-carbamoil-9H-carbazol-2-il)metilo bruto como un sólido amarillo claro (390 mg, 89%). Este material se suspendió en DMF (8.3 ml) y se trató con azida de sodio (271 mg, 4.17 mmol). Después de agitarse durante la noche a ta, la mezcla se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró proporcionando 7-(azidometil)-4-bromo-9H-carbazol-1-carboxamida bruta como un sólido amarillo claro (350 mg, 97%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.80 (1 H, s), 8.62 (1 H, d, J=8.4 Hz), 8.22 (1 H, s ancho), 7.88 (1 H, d, J=8.1 Hz), 7.83 (1 H, s), 7.58 (1 H, s ancho), 7.46 (1 H, d, J=8.4 Hz), 7.28 (1 H, dd, J=8.1, 1.5 Hz), 4.63 (2 H, s).

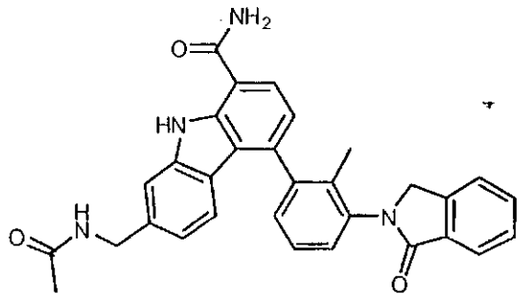
Etapa 2 Una mezcla de 7-(azidometil)-4-bromo-9H-carbazol-1-carboxamida (350 mg, 0.814 mmol), trifenilfosfina (427 mg, 1.627 mmol) y agua (18 µl, 0.976 mmol) en THF (10 ml) se calentó a 70°C durante 3.5 h. La mezcla se enfrió hasta ta y se repartió entre EtOAc y ácido clorhídrico 1 M. El pH de la fase acuosa se elevó hasta 8-9 con lentejas de

hidróxido sódico, y luego se extrajo con EtOAc. La fase orgánica se secó y se concentró proporcionando 7-(aminometil)-4-bromo-9H-carbazol-1-carboxamida bruta como una espuma vítrea amarilla (320 mg, 99%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.61 (1 H, ancho), 8.47 - 8.55 (1 H, m), 8.19 (1 H, s ancho), 7.81 - 7.84 (1 H, m), 7.76 (1 H, s), 7.63 - 7.66 (1 H, m), 7.53 - 7.59 (2 H, m), 7.41 (1 H, d, J=8.1 Hz), 7.27 (1 H, dd, J=8.4, 1.3 Hz), 3.90 (2 H, s).

Etapa 3 Usando el procedimiento del Ejemplo 3-2, se convirtieron 7-(aminometil)-4-bromo-9H-carbazol-1-carboxamida bruta (320 mg, 0.;805 mmol) e Intermedio 50-4 (309 mg, 0.885 mmol) en 7-(aminometil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida bruta como un sólido amarillo claro (aproximadamente 50% puro, 570 mg, 77%). Se purificó una pequeña cantidad por HPLC preparativa proporcionando la sal TFA. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.64 (1 H, s), 8.11 (3 H, ancho), 7.98 (1 H, d, J=7.9 Hz), 7.68 - 7.74 (2 H, m), 7.62 (2 H, d, J=4.0 Hz), 7.57 (1 H, dd, J=7.9, 1.1 Hz), 7.51 (1 H, dd, J=7.8, 3.6 Hz), 7.44 (2 H, t, J=7.6 Hz), 7.27 (1 H, dd, J=7.6, 1.0 Hz), 6.96 - 7.08 (3 H, m), 4.78 - 5.00 (2 H, m), 4.06 (2 H, d, J=5.3 Hz), 1.76 (3 H, s). Espectro de masas m/z 483.2 $(M+Na)^+$.

Ejemplo 34-1

Preparación de 7-(acetamidometil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida

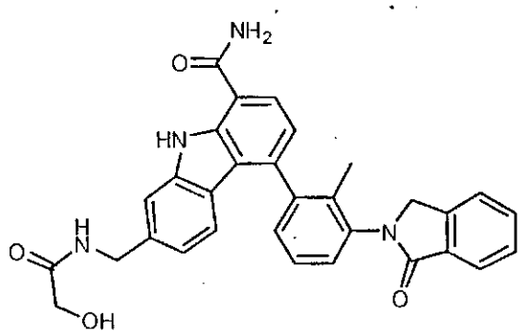


Se trató una solución de 7-(aminometil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida bruta (Ejemplo 33-1, 60 mg, 0.065 mmol) y TEA (23 µl, 0.163 mmol) en THF (1.3 ml) con anhídrido acético (7.4 µl, 0.078 mmol) y la mezcla se agitó a ta durante la noche. La mezcla se concentró y el residuo se purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron y el residuo se repartió entre NaHCO3 (ac) y EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró proporcionando 7-(acetamidometil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido blanquecino (12 mg, 36%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.51 (1 H, s), 8.29 - 8.45 (1 H, m), 8.18 (1 H, s ancho), 8.01 (1 H, d, J=7.9 Hz), 7.81 (1 H, d, J=7.5 Hz), 7.69 (2 H, d, J=4.0 Hz), 7.60 - 7.65 (2 H, m), 7.57 (1 H, ddd, J=7.9, 4.2, 4.0 Hz), 7.50 (2 H, t, J=7.8 Hz), 7.34 (1 H, dd, J=7.7, 1.1 Hz), 6.94 - 7.06 (2 H, m), 6.87 (1 H, dd, J=8.3, 1.4 Hz),

4.90 - 5.04 (2 H, m), 4.35 (2 H, t, J=5.2 Hz), 1.89 (3 H, s), 1.84 (3 H, s). Espectro de masas m/z 503.2 $(M+H)^+$.

Ejemplo 34-2

Preparación de 7-((2-hidroxiacetamido)metil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Se trató una solución de 7-(aminometil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida bruta (Ejemplo 33-1, 25 mg, 0.054 mmol), ácido glicólico (8.26 mg, 0.109 mmol), HOAT (13.30 mg, 0.098 mmol) y EDC (20.81 mg, 0.109 mmol) en acetonitrilo-THF (2:1) (5 ml) con DIEA (0.028 ml, 0.163 mmol) y se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron proporcionando una suspensión acuosa, que se trató con NaHCO3 (ac). El precipitado se recogió por filtración, se lavó con agua y se secó proporcionando 7-((2-hidroxiacetamido)metil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (17 mg, 59%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.49 (1 H, s), 8.22 - 8.28 (1 H, m), 8.17 (1 H, s ancho), 7.97 - 8.05 (1 H, m), 7.81 (1 H, d, J=7.5 Hz), 7.69 (2 H, d, J=3.7

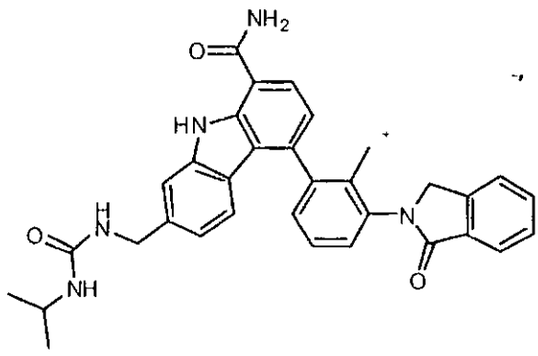
Hz), 7.54 - 7.66 (3 H, m), 7.42 - 7.54 (2 H, m), 7.28 - 7.38 (1 H, m), 7.03 (1 H, d, J=7.9 Hz), 6.94 - 7.00 (1 H, m), 6.86 - 6.94 (1 H, m), 5.45 (1H, ancho), 4.88 - 5.05 (2 H, m), 4.33 - 4.48 (2 H, m), 3.88 (2 H, s), 1.83 (3 H, s). Espectro de masas m/z 519.2 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 34-1, usando anhídridos de ácido o cloruros de ácido apropiados.

Ejemplo	Nombre del compuesto	Espectro de masas
34-3	4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-(pivalamidometil)-9H-carbazol-1-carboxamida	545.3 $(M+H)^+$
34-4	7-(isobutiramidometil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	531.3 $(M+H)^+$

Ejemplo 35-1

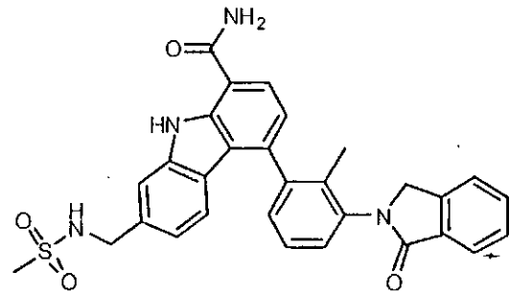
Preparación de 7-((3-isopropilureido)metil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Una solución de 7-(aminometil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 33-1, 30 mg, 0.065 mmol) y 2-isocianatopropano (0.019 ml, 0.195 mmol) en THF (3 ml) se agitó a 40°C durante la noche. La mezcla se concentró y purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron y se repartieron entre EtOAc y NaHCO3 (ac). La fase orgánica se secó y se concentró proporcionando 7-((3-isopropilureido)metil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido blanco (5.8 mg, 14%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.84 (1 H, d, J=7.7 Hz), 7.77 (1 H, d, J=7.5 Hz), 7.53 - 7.63 (2 H, m), 7.38 - 7.51 (4 H, m), 7.30 (1 H, dd, J=7.2, 1.7 Hz), 6.93 - 6.99 (2 H, m), 6.85 (1 H, dd, J=8.3, 1.4 Hz), 4.79 - 4.91 (2 H, m), 4.33 (2 H, s), 3.69 - 3.78 (1 H, m), 1.79 (3 H, s), 1.03 (6 H, d, J=6.4 Hz). Espectro de masas m/z 546.3 $(M+H)^+$.

Ejemplo 36-1

Preparación de 4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-(metilsulfonamidometil)-9H-carbazol-1-carboxamida

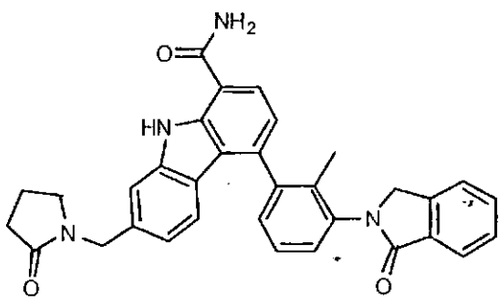


Se trató una solución de 7-(aminometil)-4-(2-metil-

3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 33-1, 60 mg, 0.065 mmol) y TEA (23 µl, 0.163 mmol) en THF (1.3 ml) con cloruro de metanosulfonilo (5.6 µl, 0.072 mmol) y la mezcla se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron y se repartieron entre EtOAc y $NaHCO_3$ (ac). La fase orgánica se secó y se concentró, y el residuo se purificó otra vez por cromatografía en columna (eluyendo con un gradiente de 40:60 de hexano-EtOAc hasta EtOAc) proporcionando 4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-(metilsulfonamidometil)-9H-carbazol-1-carboxamida como un sólido blanquecino (7 mg, 18%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.57 (1 H, s), 8.19 (1 H, s ancho), 8.02 (1 H, d, J=7.7 Hz), 7.81 (1 H, d, J=7.7 Hz), 7.73 (1 H, s), 7.69 (2 H, d, J=3.7 Hz), 7.61 - 7.65 (1 H, m), 7.54 - 7.61 (2 H, m), 7.51 (2 H, t, J=7.7 Hz), 7.35 (1 H, dd, J=7.5, 1.1 Hz), 7.00 - 7.08 (2 H, m), 6.93 - 6.99 (1 H, m), 4.88 - 5.05 (2 H, m), 4.26 (2 H, d, J=5.9 Hz), 2.87 (3 H, s), 1.84 (3 H, s). Espectro de masas m/z 539.2 $(M+H)^+$.

Ejemplo 37-1

Preparación de 4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-((2-oxopirrolidin-1-il)metil)-9H-carbazol-1-carboxamida

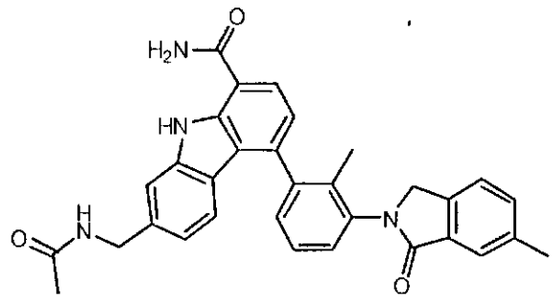


Se trató una solución de 7-(aminometil)-4-(2-

metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 33-1, 80 mg, 0.087 mmol) en THF (3 ml) con DIEA (0.030 ml, 0.174 mmol) y una solución de cloruro de 4-bromobutanoilo (10 µl, 0.087 mmol) en DCM (1 ml) y la mezcla se agitó a ta durante 35 min. La mezcla de reacción se diluyó con EtOAc, se lavó con NaHCO3 (ac) y salmuera y se secó y concentró. El residuo se disolvió en THF (6 ml) y se trató con hidruro sódico (dispersión al 60% en aceite, 24.32 mg, 0.608 mmol). La mezcla resultante se agitó a 50°C durante 2 h, luego se diluyó con agua y se extrajo con EtOAc. La fase orgánica se secó y se concentró y el residuo se purificó por HPLC preparativa proporcionando 4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-((2-oxopirrolidin-1-il)metil)-9H-carbazol-1-carboxamida como un sólido blanco (2 mg, 3%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.44 (1 H, s), 8.11 (1 H, s ancho), 7.95 (1 H, d, J=7.9 Hz), 7.73 (1 H, d, J=7.5 Hz), 7.62 (2 H, d, J=3.7 Hz), 7.46 - 7.57 (3 H, m), 7.42 (2 H, t, J=7.7 Hz), 7.23 - 7.29 (1 H, m), 6.90 - 6.99 (2 H, m), 6.74 (1 H, dd, J=8.1, 1.5 Hz), 4.79 - 5.00 (2 H, m), 4.25 - 4.51 (2 H, m), 3.11 - 3.22 (2 H, m), 2.19 - 2.29 (2 H, m), 1.80 - 1.93 (2 H, m), 1.77 (3 H, s). Espectro de masas m/z 529.2 $(M+H)^+$.

Ejemplo 38-1

Preparación de 7-(acetamidometil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Etapa 1 Se trató una suspensión de 7-(aminometil)-4-bromo-9H-carbazol-1-carboxamida (preparada de acuerdo con la Etapa 2 del Ejemplo 33-1, 168 mg, 0.528 mmol) y TEA (0.184 ml, 1.320 mmol) en THF (18 ml) con anhídrido acético (0.080 ml, 0.845 mmol). La mezcla se agitó a ta durante 2 h, luego se repartió entre EtOAc y ácido clorhídrico 1 M. La fase orgánica se lavó con NaHCO3 (ac) y salmuera, se secó y se concentró proporcionando 7-(acetamidometil)-4-bromo-9H-carbazol-1-carboxamida como un sólido blanquecino. Espectro de masas m/z 359.9 $(M+H)^+$.

Etapa 2 Usando el procedimiento del Ejemplo 3-2, se convirtieron 7-(acetamidometil)-4-bromo-9H-carbazol-1-carboxamida (25 mg, 0.069 mmol) y Intermedio 50-8 (30.3 mg, 0.083 mmol) en 7-(acetamidometil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida, obtenida como un sólido blanco (19 mg, 52%) RMN de ^1H (400 MHz, DMSO-d_6) δ 11.51 (1 H, s), 8.36 (1 H, t, J=5.8 Hz), 8.18 (1 H, s

ancho), 8.01 (1 H, d, J=7.7 Hz), 7.54 - 7.66 (4 H, m), 7.49 (3 H, t, J=7.6 Hz), 7.33 (1 H, dd, J=7.7, 1.1 Hz), 6.93 - 7.07 (2 H, m), 6.87 (1 H, dd, J=8.1, 1.3 Hz), 4.83 - 4.99 (2 H, m), 4.27 - 4.43 (2 H, m), 2.44 (3 H, s), 1.89 (3 H, s), 1.83 (3 H, s). Espectro de masas m/z 517.2 $(M+H)^+$.

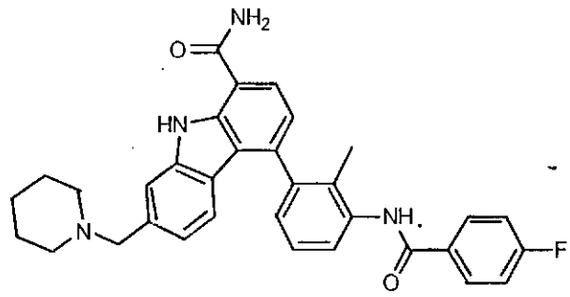
Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 38-1 y procedimientos similares, usando los materiales de partida mostrados en lugar del Intermedio 50-8.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
38-2	Intermedio 50-5	7-(acetamidometil)-4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida	521.2 $(M+H)^+$
38-3	Intermedio 50-27	7-(acetamidometil)-4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	534.1 $(M+H)^+$
38-4	Intermedio 50-24	7-(acetamidometil)-4-(2-metil-3-(4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	516.1 $(M+H)^+$

38-5	Intermedio 50-48	7-(acetamidometil)-4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	534.1 $(M+H)^+$
38-6	Intermedio 50-51	7-(acetamidometil)-4-(3-(8-metoxi-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	546.1 $(M+H)^+$

Ejemplo 39-1

Preparación de 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(piperidin-1-ilmetil)-9H-carbazol-1-carboxamida



Etapa 1 Se trató una solución de 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida (Ejemplo 31-4, 0.54 g, 1.155 mmol) en THF (38.5 ml) con 1.1,1-tris(acetiloxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona (peryodinano de Dess-Martin, 0.784 g, 1.848 mmol) a ta y la mezcla se agitó durante 2 h. La mezcla se repartió entre NaHCO3 (ac) y EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se trituró con

metanol y el sólido se recogió por filtración y se secó proporcionando 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-formil-9H-carbazol-1-carboxamida como un sólido naranja (458 mg, 85%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.98 (1 H, s), 10.16 (1 H, s), 10.03 (1 H, s), 8.23 - 8.32 (2 H, m), 8.05 - 8.14 (3 H, m), 7.60 (1 H, s ancho), 7.49 - 7.55 (1 H, m), 7.39 - 7.49 (2 H, m), 7.32 - 7.39 (2 H, m), 7.21 - 7.27 (1 H, m), 7.09 (2 H, t, J=8.1 Hz), 1.88 (3 H, s). Espectro de masas m/z 466.3 $(M+H)^+$.

Etapa 2 Se trató una suspensión de 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-formil-9H-carbazol-1-carboxamida (30 mg, 0.064 mmol) en THF (3 ml) con piperidina (16.46 mg, 0.193 mmol) y triacetoxiborohidruro sódico (34.1 mg, 0.161 mmol). La mezcla se agitó a ta durante 3.5 h, luego se trató de nuevo con más piperidina (16.5 mg, 0.193 mmol) y triacetoxiborohidruro sódico (20 mg). Después de agitar durante la noche, la mezcla se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por HPLC preparativa proporcionando 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(piperidin-1-ilmetil)-9H-carbazol-1-carboxamida (14 mg, 39%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.06 (2 H, dd, J=8.7, 5.4 Hz), 7.98 (1 H, d, J=7.8 Hz), 7.63 (1 H, s), 7.52 (1 H, d, J=7.3 Hz), 7.44 (1 H, t, J=7.8 Hz), 7.18 - 7.31 (3 H, m), 7.07 (2 H, d, J=7.5 Hz), 6.96 - 7.02 (1 H, m), 3.96 (2 H, s),

2.72 - 2.88 (4 H, m), 1.99 (3 H, s), 1.63 - 1.75 (4 H, m), 1.48 - 1.60 (2 H, m). Espectro de masas m/z 535.2 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 39-1, usando la amina apropiada en lugar de piperidina.

Ejemplo	Nombre del compuesto	Espectro de masas
39-2	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(morfolinometil)-9H-carbazol-1-carboxamida	537.1 $(M+H)^+$
39-3	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-((4-metilpiperazin-1-il)metil)-9H-carbazol-1-carboxamida	550.1 $(M+H)^+$
39-4	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(pirrolidin-1-ilmetil)-9H-carbazol-1-carboxamida	521.1 $(M+H)^+$
39-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-((2-hidroxietilamino)metil)-9H-carbazol-1-carboxamida	511.0 $(M+H)^+$

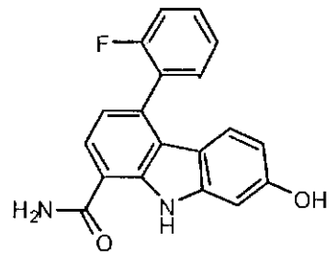
39-6	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-((2-metoxietilamino)metil)-9H-carbazol-1-carboxamida	525.1 $(M+H)^+$
39-7	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(((RS)-3-hidroxipirrolidin-1-il)metil)-9H-carbazol-1-carboxamida	537.1 $(M+H)^+$
39-8	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(((2-hidroxietil)(metil)amino)metil)-9H-carbazol-1-carboxamida	524.9 $(M+H)^+$
39-9	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(((RS)-2-(hidroximetil)morfolino)metil)-9H-carbazol-1-carboxamida	567.2 $(M+H)^+$
39-10	7-(ciclobutilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	507.3 $(M+H)^+$
39-11	7-(ciclopentilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	520.9 $(M+H)^+$

39-12	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(neopentilamino)-9H-carbazol-1-carboxamida	522.9 $(M+H)^+$
39-13	7-(ciclopropilmetilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	506.8 $(M+H)^+$
39-14	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(tetrahidro-2H-piran-4-ilamino)-9H-carbazol-1-carboxamida	536.8 $(M+H)^+$
39-15	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-((1-metil-1H-imidazol-2-il)metilamino)-9H-carbazol-1-carboxamida	546.8 $(M+H)^+$
39-16	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-((1-metilpiperidin-4-il)metilamino)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	563.9 $(M+H)^+$
39-17	7-(ciclopentilmetilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	534.9 $(M+H)^+$

39-18	7-(ciclohexilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	534.9 $(M+H)^+$

Ejemplo 40-1

Preparación de 4-(2-fluorofenil)-7-hidroxi-9H-carbazol-1-carboxamida



Etapa 1 Se trató una solución de 4-(2-fluorofenil)-7-(hidroximetil)-9H-carbazol-1-carboxamida (Ejemplo 30-1, 147 mg, 0.440 mmol) en DCM (3 ml), acetonitrilo (5 ml) y THF (3 ml) con 1,1,1-tris(acetiloxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona (Peryodinano de Dess-Martin, 373 mg, 0.879 mmol). Después de 30 min a ta, la mezcla se diluyó con EtOAc (30 ml), se lavó dos veces con sulfito sódico acuoso 1 M y salmuera, se secó y se concentró dando 4-(2-fluorofenil)-7-formil-9H-carbazol-1-carboxamida como un sólido color castaño (aproximadamente 80% de pureza, 163 mg, 87%), usada sin purificación. Espectro de masas m/z 333.1 $(M+H)^+$.

Etapa 2 Se trató una solución de 4-(2-fluorofenil)-7-formil-9H-carbazol-1-carboxamida bruta (25.2 mg, 0.076 mmol) en metanol (2 ml) a 0°C con peróxido de hidrógeno acuoso

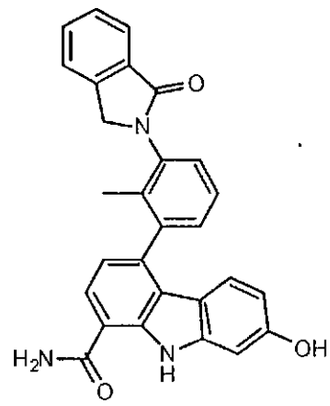
al 30% (0.039 ml, 0.379 mmol) y ácido sulfúrico (0.020 ml, 0.379 mmol). Después de 1.5 h, se añadieron más peróxido de hidrógeno (0.100 ml) y ácido sulfúrico (0.050 ml) y la mezcla se agitó a ta durante la noche. Después de 16 h, se añadió hidróxido sódico acuoso 1 M (2 ml) y la mezcla se agitó durante 1 h. El pH se ajustó a aproximadamente 4 y el disolvente orgánico se eliminó a vacío. El residuo acuoso se diluyó con agua y el precipitado se recogió por filtración, se lavó con agua y se secó. El residuo se purificó por HPLC preparativa proporcionando 4-(2-fluorofenil)-7-hidroxi-9H-carbazol-1-carboxamida como sólido color castaño después de liofilización (5.1 mg, 21%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.81 (1 H, d, *J*=7.70 Hz), 7.45 - 7.64 (2 H, m), 7.21 - 7.42 (2 H, m), 7.03 (1 H, d, *J*=7.92 Hz), 6.90 - 6.99 (2 H, m), 6.45 (1 H, dd, *J*=8.58, 2.20 Hz). Espectro de masas m/z 321.0 $(M+H)^+$.

El siguiente compuesto también se preparó usando los procedimientos mostrados en el Ejemplo 40-1, sustituyendo el Ejemplo 31-11 en lugar del Ejemplo 30-1 como material de partida:

Ejemplo	Nombre del compuesto	Espectro de masas
40-2	7-hidroxi-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	462.0 $(M+H)^+$

Ejemplo 41-1

Preparación de 7-hidroxi-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Etapa 1 Se agitó a ta una solución parcial de 4-bromo-7-(hidroximetil)-9H-carbazol-1-carboxamida (Ejemplo 30-2, 1.00 g, 3.13 mmol) en THF (75 ml) y se trató con 1.1,1-tris(acetiloxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona (peryodinano de Dess-Martin, 1.993 g, 4.70 mmol). Después de 45 min, la solución se diluyó con EtOAc y se lavó con sulfito sódico acuoso al 5%, NaHCO3 (ac) y salmuera, luego se secó y se concentró. El residuo se trituró con metanol y el precipitado se recogió por filtración, se lavó con metanol y se secó proporcionando 4-bromo-7-formil-9H-carbazol-1-carboxamida como un polvo color castaño (aproximadamente 85% de pureza, 948 mg, 81%) que se usó sin purificación. RMN de ^1H (400 MHz, DMSO-d_6) δ 12.13 (1 H, s), 10.14 (1 H, s), 8.80 (1 H, d, J=8.1 Hz), 8.38 (1 H, d, J=0.9 Hz), 8.28 (1 H, s ancho), 7.97 (1 H, d, J=8.1 Hz), 7.83 (1 H, dd, J=8.3, 1.4

Hz), 7.64 (1 H, s ancho), 7.54 (1 H, d, J=8.1 Hz). Espectro de masas m/z 317, 319 $(M+H)^+$.

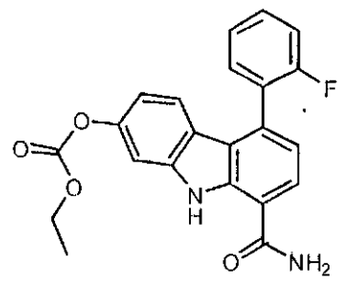
Etapa 2 Usando el procedimiento del Ejemplo 3-2, se convirtieron 4-bromo-7-formil-9H-carbazol-1-carboxamida (75 mg, 0.236 mmol) y 2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-4, 83 mg, 0.236 mmol) en 7-formil-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un polvo gris-verde (aproximadamente 90% de pureza, 97 mg, 89%), que se usó sin purificación posterior. Espectro de masas m/z 460.2 $(M+H)^+$.

Etapa 3 Se trató una suspensión de 7-formil-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (30 mg, 0.052 mmol) en metanol (1 ml) con ácido sulfúrico (4.2 µl, 0.078 mmol) seguido por peróxido de hidrógeno acuoso al 30% (0.032 ml, 0.313 mmol) y se agitó a ta durante 23 h, la mezcla se trató con hidróxido sódico acuoso 1 M (200 µl) y se agitó durante 1 h. La mezcla se diluyó con agua y el precipitado se recogió por filtración, se lavó con agua y se secó. El residuo se purificó por HPLC preparativa proporcionando 7-hidroxi-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un polvo color castaño (3.6 mg, 15%). RMN de ^1H (400 MHz, metanol-d_4) δ 7.90 (1 H, d, J=7.5 Hz), 7.86 (1 H, d, J=7.9 Hz), 7.65 - 7.76 (2 H, m), 7.48 - 7.63 (3 H, m), 7.42 (1 H, d, J=6.6 Hz), 7.03 (1 H, d, J=7.9 Hz), 6.98 (1 H, s), 6.92 (1

H, d, J=8.8 Hz), 6.54 (1 H, d, J=9.0 Hz), 4.97 (2 H, s), 1.94 (3 H, s). Espectro de masas m/z 448.1 $(M+H)^+$.

Ejemplo 42-1

Preparación de etil carbonato de 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-ilo

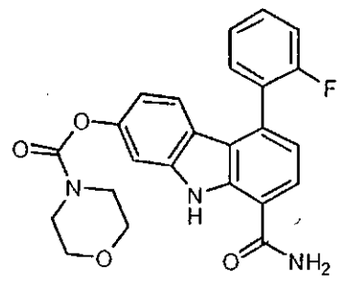


Se añadió cloroformiato de etilo (8.19 mg, 0.075 mmol) a una solución de 4-(2-fluorofenil)-7-hidroxi-9H-carbazol-1-carboxamida (Ejemplo 40-1, 18.6 mg, 0.058 mmol) en piridina (1 ml). Después de 17 h, se añadió más cloroformiato de etilo (8.19 mg, 0.075 mmol). Después de 5 h más, se añadió más cloroformiato de etilo (0.05 ml). Después de 15 h más, la mezcla se diluyó con EtOAc (30 ml), se lavó con agua (10 ml) y salmuera (5 ml), se secó y se concentró. El residuo se purificó por HPLC preparativa proporcionando etil carbamato de 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-ilo como un sólido blanco (7.0 mg, 28%). RMN de ^1H (400 MHz, cloroformo-d) δ 10.44 (1 H, s ancho), 7.62 (1 H, dd, J=7.92, 1.98 Hz), 7.41 - 7.57 (2 H, m), 7.20 - 7.40 (4 H, m), 7.16 (1 H, dd, J=7.81, 1.65 Hz), 6.79 - 6.92 (1 H, m), 6.60 (2 H, s ancho), 4.34 (2 H, q, J=7.26 Hz), 1.41 (3 H, t, J=7.15 Hz). Espectro

de masas m/z 393.0 $(M+H)^+$.

Ejemplo 43-1

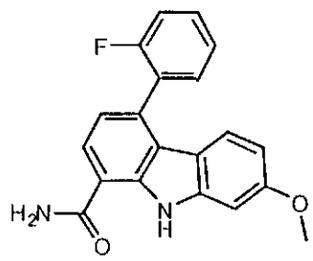
Preparación de morfolin-4-carboxilato de 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-ilo



Se añadió cloruro de morfolin-4-carbonilo (11.29 mg, 0.075 mmol) a una solución de 4-(2-fluorofenil)-7-hidroxi-9H-carbazol-1-carboxamida (Ejemplo 40-1, 18.6 mg, 0.058 mmol) en piridina (1 ml). Después de 22 h a ta, se añadió más cloruro de morfolin-4-carbonilo (11.29 mg, 0.075 mmol). Después de 15 h, la mezcla se diluyó con EtOAc (30 ml), se lavó con agua (10 ml) y salmuera (5 ml) y se secó y concentró. El residuo se purificó por HPLC preparativa proporcionando morfolin-4-carboxilato de 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-ilo como un sólido blanco (7.9 mg, 27%). RMN de ^1H (400 MHz, cloroformo-d) δ 9.94 (1 H, s ancho), 7.41 - 7.65 (3 H, m), 7.33 (2 H, t, J=8.14 Hz), 7.20 (1 H, d, J=8.58 Hz), 6.92 - 7.15 (4 H, m), 6.73 (1 H, dd, J=8.58, 1.98 Hz), 3.80 (4 H, t, J=4.62 Hz), 3.67 - 3.76 (2 H, m), 3.62 (2 H, s ancho). Espectro de masas m/z 434.0 $(M+H)^+$.

Ejemplo 44-1

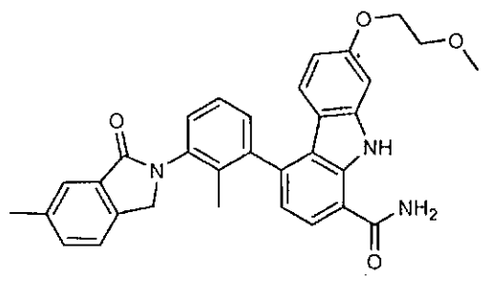
Preparación de 4-(2-fluorofenil)-7-metoxi-9H-carbazol-1-carboxamida



Se añadieron carbonato potásico (25.1 mg, 0.182 mmol) y yodometano (4.9 µl, 0.079 mmol) a una solución de 4-(2-fluorofenil)-7-hidroxi-9H-carbazol-1-carboxamida (Ejemplo 40-1, 19.4 mg, 0.061 mmol) en DMSO (1 ml) y la mezcla se agitó a ta. Después de 17 h, la mezcla se diluyó con EtOAc (30 ml), se lavó con cloruro amónico acuoso saturado (5 ml), agua (2x5 ml), y salmuera (5 ml), se secó y se concentró. El residuo se purificó por HPLC preparativa proporcionando 4-(2-fluorofenil)-7-metoxi-9H-carbazol-1-carboxamida (1.9 mg, 9%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.39 (1 H, s ancho), 7.58 (1 H, d, J=7.70 Hz), 7.44 - 7.55 (2 H, m), 7.28 - 7.39 (2 H, m), 7.07 - 7.22 (2 H, m), 7.00 (1 H, d, J=2.20 Hz), 6.65 (1 H, dd, J=8.80, 2.42 Hz), 6.57 (2 H, s ancho), 3.88 (3 H, s). Espectro de masas m/z 335.0 $(M+H)^+$.

Ejemplo 44-2

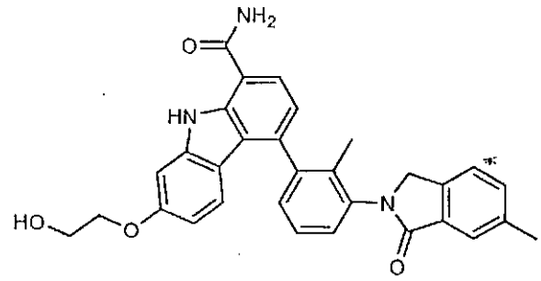
Preparación de 7-(2-metoxietoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Una mezcla de 7-hidroxi-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 40-2, 30 mg, 0.065 mmol) y carbonato de potasio (18 mg, 0.130 mmol) en DMF (1.0 mL) se agitó a temperatura ambiente durante 30 minutos, luego se trató con 1-bromo-2-metoxietano (14 mg, 0.098 mmol). La mezcla se calentó a 90°C durante 4 h, se enfrió a ta y se concentró al vacío. El residuo se purificó por HPLC preparativa para proporcionar 7-(2-metoxietoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido blanco (12.5 mg, 35%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 11.39 (1 H, s), 8.17 (1 H, br. s.), 7.95 (1 H, d, J = 7.9 Hz), 7.54 - 7.64 (3 H, m), 7.49 (3 H, t, J = 8.0 Hz), 7.27 - 7.38 (2 H, m), 7.00 (1 H, d, J = 7.9 Hz), 6.91 (1 H, Hz = 8.8 d, J), 6.59 (1 H, dd, J = 8.8, 2.4 Hz), 4.91 (2 H, d, J = 3.3 Hz), 4.12 (2 H, dd, J = 5.5, 3.1 Hz), 3.63 - 3.75 (2 H, m), 3.33 (3 H, s), 2.44 (3 H, s), 1.83 (3 H, s). Espectro de masas m/z 520.1 $(M+H)^+$.

Ejemplo 44-3

Preparación de 7-(2-hidroxietoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida

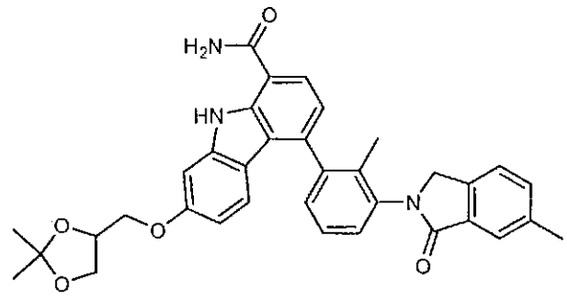


Una mezcla de 7-hidroxi-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 40-2, 30 mg, 0.065 mmol) y carbonato de potasio (36 mg, 0.260 mmol) en DMF (1.0 mL) se agitó a temperatura ambiente durante 30 minutos, luego se trató con (2-bromoetoxi)(*terc*-butil)dimetilsilano (62.2 mg, 0.260 mmol) y se calentó a 90°C durante 4 horas. La mezcla se filtró, el filtrado se trató con cloruro de hidrógeno (4 M en dioxano, 1 mL) y la solución se agitó a temperatura ambiente durante la noche. La solución se concentró al vacío y el residuo se purificó por HPLC preparativa para proporcionar 7-(2-hidroxietoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como fuera de sólido blanco (16.5 mg, 45%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 11.39 (1 H, s), 8.17 (1 H, br. s.), 7.94 (1 H, d, J = 7.9 Hz), 7.53 - 7.65 (3 H, m), 7.49 (3 H, t, J = 7.8 Hz), 7.27 - 7.39 (2 H, m), 6.99 (1 H, d, J = 7.7 Hz), 6.92 (1 H, Hz = 8.8 d, J), 6.59 (1 H, dd, J = 8.8, 2.4

Hz), 4.75 - 4.98 (3 H, m), 3.95 - 4.07 (2 H, m), 3.69 - 3.80 (2 H, m), 2.44 (3 H, s). Espectro de masas m/z 506.0 $(M+H)^+$.

Ejemplo 44-4

Preparación de 7-((2,2-dimetil-1,3-dioxolan-4-il)metoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida racémica

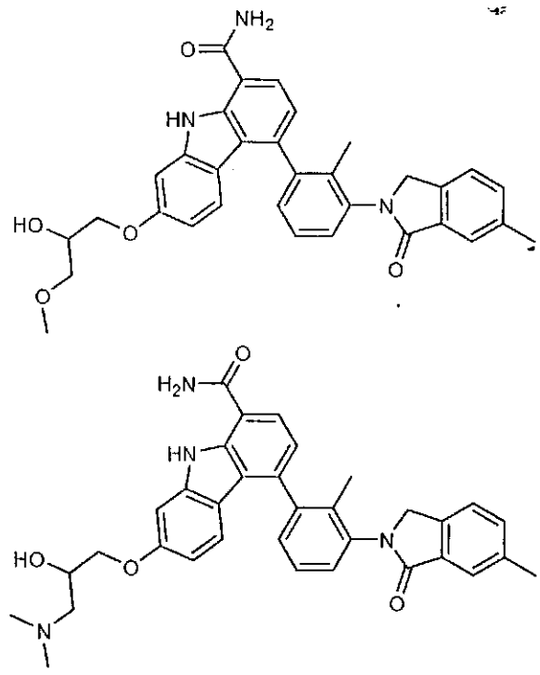


Una mezcla de 7-hidroxi-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 40-2, 50 mg, 0.108 mmol) y carbonato de potasio (30 mg, 0.217 mmol) en DMF (1.7 mL) se agitó a temperatura ambiente durante 30 minutos, luego se trató con 4-metilbenzenesulfonato de (4,4-dimetil-1,3-dioxolan-2-il)metilo racémico (46.5 mg, 0.163 mmol). La mezcla resultante se calentó a 80°C durante la noche. La mezcla se enfrió hasta la temperatura ambiente, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 50:50 a 80:20 de EtOAc-hexano) para proporcionar 7-((2,2-dimetil-1,3-dioxolan-4-il)metoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida

racémica como un sólido amarillo claro (30 mg, 48%). Espectro de masas m/z 576.1 $(M+H)^+$.

Ejemplos 44-5 y 44-6

Preparación de 7-(2-hidroxi-3-metoxipropoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida y 7-(3-(dimetilamino)-2-hidroxipropoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Una mezcla de 7-hidroxi-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 40-2, 30 mg, 0.065 mmol) y carbonato de potasio (36 mg, 0.260 mmol) en DMF (1.0 mL) se agitó a temperatura ambiente durante 30 minutos, luego se trató con 2-(brómometil)oxirano (27 mg, 0.195 mmol). La mezcla resultante se calienta a 90°C durante 3.5 h, se enfrió a ta y se filtró. El filtrado fue tratado

con metanol, se agitó a temperatura ambiente durante 2 h, luego se calentó a 90°C durante 1 h. La mezcla se concentró al vacío y se purificó por HPLC preparativa para proporcionar 7-(2-hidroxi-3-metoxipropoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 44-5, 4.7 mg, 13%). ^{1}H RMN (400 MHz, metanol-d_4) δ 7.83 (1 H, d, J = 7.9 Hz), 7.72 (1 H, d, J = 0.7 Hz), 7.46 - 7.52 (4 H, m), 7.38 - 7.45 (1 H, m), 7.04 - 7.12 (2 H, m), 6.99 (1 H, d, J = 8.8 Hz), 6.70 (1 H, dd, J = 8.7, 2.3 Hz), 4.86 (2 H, d, J = 1.8 Hz), 4.03 - 4.22 (3 H, m), 3.53 - 3.65 (2 H, m), 3.42 (3 H, s), 2.50 (3 H, s), 1.93 (3 H, s). Espectro de masas m/z 550.1 $(M+H)^+$. También se aisló 7-(3-(dimetilamino)-2-hidroxipropoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 44-6, 2.0 mg, 5%). Espectro de masas m/z 563.1 $(M+H)^+$.

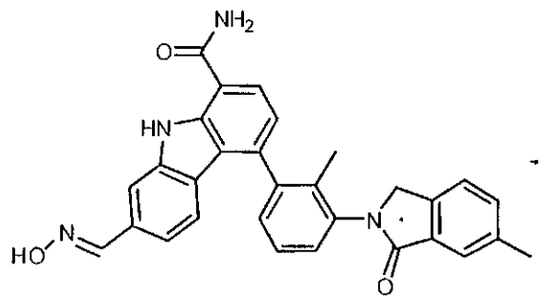
Los siguientes compuestos se prepararon mediante los procedimientos demostrados en el ejemplo 44-2:

Ejemplo	Nombre del compuesto	Espectro de masas
44-7	7-(fluoroetoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	508.1 $(M+H)^+$

Ejemplo	Nombre del compuesto	Espectro de masas
40-8	7-(2-hidroxipropoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	520.1 $(M+H)^+$

Ejemplo 45-1

Preparación de (E)-7-((hidroxiimino)metil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



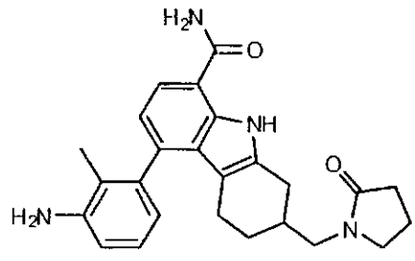
Etapa 1 Se trató una mezcla de 4-bromo-7-formil-9H-carbazol-1-carboxamida (preparada de acuerdo con la Etapa 1 del Ejemplo 41-1, 200 mg, 0.631 mmol) y sal clorhidrato de hidroxilamina (65.7 mg, 0.946 mmol) en etanol (3 ml) con carbonato sódico acuoso 2 M (0.236 ml, 0.473 mmol) y se calentó a 80-90°C. Después de 17.5 h, la mezcla se enfrió hasta ta y se repartió entre EtOAc y agua. La fase orgánica se secó y se concentró y el residuo se trituró con metanol, y el precipitado se recogió por filtración, se aclaró con metanol y se secó proporcionando (E)-4-bromo-7-

((hidroxiimino)metil)-9H-carbazol-1-carboxamida como un sólido gris-castaño (110 mg, 53%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.87 (1 H, s), 11.33 (1 H, s), 8.65 (1 H, d, J=8.4 Hz), 8.32 (1 H, s), 8.28 (1 H, s ancho), 8.09 (1 H, s), 7.92 (1 H, d, J=8.1 Hz), 7.64 (1 H, s ancho), 7.58 (1 H, d, J=8.6 Hz), 7.51 (1 H, d, J=8.1 Hz). Espectro de masas m/z 332, 334 $(M+H)^+$.

Etapa 2 Usando el procedimiento del Ejemplo 3-2, se convirtieron (E)-4-bromo-7-((hidroxiimino)metil)-9H-carbazol-1-carboxamida (82 mg, 0.247 mmol) y 6-metil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-8, 90 mg, 0.247 mmol) en (E)-7-((hidroxiimino)metil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido rosa pálido (52 mg, 40%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.20 (1 H, s), 8.00 (1 H, d, J=7.7 Hz), 7.82 (1 H, s), 7.70 (1 H, s), 7.49 - 7.59 (4 H, m), 7.43 (1 H, dd, J=6.7, 2.1 Hz), 7.31 (1 H, dd, J=8.3, 1.2 Hz), 7.11 (2 H, d, J=7.7 Hz), 4.92 (2 H, s), 2.40 (3 H, s), 1.92 (3 H, s). Espectro de masas m/z 489.3 $(M+H)^+$.

Ejemplo 46-1

Preparación de 5-(3-amino-2-metilfenil)-2-((2-oxopirrolidin-1-il)metil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida



Etapa 1 Se trató una solución de ácido 5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-carboxílico (Intermedio 49-3, 2 g, 5.93 mmol) y TEA (2.067 ml, 14.83 mmol) en THF (20 ml) con cloroformiato de isobutilo (0.810 g, 5.93 mmol) a 0°C. La mezcla se agitó durante 10 min, luego se trató con una solución de sal clorhidrato de N,O-dimetilhidroxilamina (0.579 g, 5.93 mmol) en THF (2 ml) y agua (1 ml). La mezcla se agitó a 0°C durante 1 h, luego se diluyó con DCM, se lavó con NaHCO3 (ac) y agua, se secó y se concentró. El residuo se trituró con DCM proporcionando 5-bromo-N^2-metoxi-N^2-metil-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida como un sólido amarillo claro (1.73 g, 77%). Espectro de masas m/z 380, 382 $(M+H)^+$.

Etapa 2 Se trató una suspensión de 5-bromo-N^2-metoxi-N^2-metil-2,3,4,9-tetrahidro-1H-carbazol-2,8-dicarboxamida (1.73 g, 4.55 mmol) en THF (40 ml) con hidruro de litio y aluminio (0.259 g, 6.82 mmol) en varias porciones durante 30 min a 0°C. Después de 20 min, se añadió en varias porciones más hidruro de litio y aluminio (120 mg) y la mezcla se agitó a ta durante 20 min. La mezcla de reacción se enfrió hasta 0°C y se trató gota a gota con ácido clorhídrico 0.5 M y la mezcla resultante se extrajo tres veces con DCM. Las fases orgánicas reunidas se lavaron con NaHCO3 (ac) y agua, se secaron y se concentraron proporcionando 5-bromo-2-formil-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un

sólido amarillo (1.31 g, 90%), se usó sin purificación posterior. Espectro de masas m/z 321, 323 $(M+H)^+$.

Etapa 3 Se trató una solución de 5-bromo-2-formil-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida bruta (1 g, 3.11 mmol) en DCM (20 ml) con acetato amónico (3.60 g, 46.7 mmol) y triacetoxiborohidruro sódico (0.990 g, 4.67 mmol) a ta y se agitó durante 10 min. Se añadió THF (2 ml) para intentar disolver el material de partida, pero no se observó reacción después de 1 h. La mezcla se concentró y el residuo se disolvió en DMSO (10 ml). Se añadió más triacetoxiborohidruro sódico (500 mg) y la mezcla se agitó a ta durante la noche. La mezcla se diluyó con agua y el precipitado se separó por filtración. El filtrado se trató con hidróxido sódico acuoso 1 M y se extrajo tres veces con EtOAc. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron proporcionando 2-(aminometil)-5-bromo-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido blanco (130 mg, 13%), que se usó sin purificación posterior. Espectro de masas m/z 322, 324 $(M+H)^+$.

Etapa 4 Se trató una suspensión de 2-(aminometil)-5-bromo-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (130 mg, 0.403 mmol) y TEA (0.067 ml, 0.484 mmol) en THF (2 ml) con cloruro de 4-bromobutanoilo (74.8 mg, 0.403 mmol). La mezcla se agitó a ta durante 20 min, se diluyó con DCM, se lavó con NaHCO3 (ac), se secó y se concentró. El residuo se purificó

por cromatografía en columna (eluyendo con EtOAc) proporcionando 5-bromo-2-((4-bromobutanamido)metil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido blanco (80 mg, 42%). Espectro de masas m/z 470, 472, 474 $(M+H)^+$.

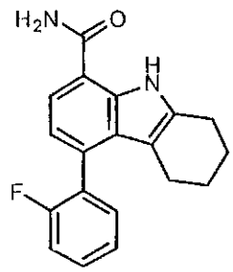
Etapa 5 Se trató una solución de 5-bromo-2-((4-bromobutanamido)metil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (80 mg, 0.170 mmol) en DMF (1 ml) con NaH (60% en aceite mineral, se lavó previamente con hexano, 34 mg, 0.849 mmol). La mezcla se agitó a ta durante 30 min, se diluyó con agua y se extrajo tres veces con DCM. Las fases orgánicas reunidas se secaron y se concentraron y el residuo se purificó por cromatografía en columna (eluyendo con hidróxido amónico acuoso al 5%-metanol-DCM) proporcionando 5-bromo-2-((2-oxopirrolidin-1-il)metil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido amarillo claro, se usó sin purificación posterior (40 mg, 60%). Espectro de masas m/z 390, 392 $(M+H)^+$.

Etapa 6 Usando el procedimiento del Ejemplo 3-2, se convirtieron 5-bromo-2-((2-oxopirrolidin-1-il)metil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (40 mg, 0.102 mmol) e Intermedio 50-1 (22.4 mg, 0.102 mmol) en 5-(3-amino-2-metilfenil)-2-((2-oxopirrolidin-1-il)metil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido blanco (2 mg, 5%). RMN de ^1H (400 MHz, metanol-d_4) δ 7.51 - 7.56 (1 H, m), 6.94 - 7.01 (1 H, m), 6.72 - 6.81 (2 H, m), 6.57 (1 H, t,

J=6.59 Hz), 3.44 - 3.53 (2 H, m), 3.28 - 3.32 (7 H, m), 2.84 (1 H, dd, J=16.70, 4.83 Hz), 2.36 - 2.40 (3 H, m), 2.11 - 2.22 (1 H, m), 1.96 - 2.10 (4 H, m), 1.77 - 1.85 (3 H, m), 1.65 (1 H, sextuplete), 1.20 - 1.37 (2 H, m). Espectro de masas m/z 417.3 $(M+H)^+$.

Ejemplo 47-1

Preparación de 5-(2-fluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida



Etapa 1 Una mezcla de 2-amino-4-bromobenzoato de metilo (3.06 g, 13.3 mmol), ácido 2-fluorofenilborónico (2.23 g, 16.0 mmol), tetraquis(trifenilfosfina)paladio (1.54 g, 1.33 mmol) y carbonato sódico acuoso 1 M (16.6 ml, 16.6 mmol) en 1,2-dimetoxietano (66.5 ml) se agitó a 90°C durante la noche. La mezcla se enfrió hasta ta, se filtró a través de una almohadilla de Celite y los sólidos se aclararon con EtOAc. El filtrado se lavó con agua y salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de hexano hasta hexano-EtOAc 90:10) proporcionando 3-amino-2'-fluorobifenil-4-carboxilato de metilo (2.63 g, 81 %) como un sólido blanco.

RMN de ^1H (400 MHz, cloroformo-d) δ 7.90 (d, J = 8.25 Hz, 1H), 7.38-7.46 (m, 1H), 7.27-7.35 (m, 1H), 7.08-7.22 (m, 2H), 6.85 (s, 1H), 6.82 (d, J = 8.25 Hz, 1H), 5.83 (s ancho, 1H), 3.88 (s, 3H). Espectro de masas m/z 246.1 $(M+H)^+$.

Etapa 2 Una solución de 3-amino-2'-fluorobifenil-4-carboxilato de metilo (0.425 g, 1.73 mmol) en hidróxido sódico acuoso 1 M (6.9 ml, 6.9 mmol) y THF (3.5 ml) se calentó a reflujo durante la noche. La mezcla se enfrió hasta ta y se concentró casi hasta sequedad. Se añadió ácido clorhídrico 6 M (0.1 ml) a la solución a 0 °C y el precipitado se recogió por filtración, se lavó con agua y se secó dando ácido 3-amino-2'-fluorobifenil-4-carboxílico (0.338 g, 84 %) como un sólido blanco. RMN de ^1H (400 MHz, DMSO-d_6) δ 7.87, d, 8.25, 1H), 7.50 (t, J = 7.97, 1H), 7.47-7.55 (m, 1H), 7.25-7.36 (m, 2H), 6.92 (s ancho, 1H), 6.76 (s, 1H), 6.59 (d, J = 7.70, 1H). Espectro de masas m/z 232.1 $(M+H)^+$.

Etapa 3 Se trató una solución de ácido 3-amino-2'-fluorobifenil-4-carboxílico (0.104 g, 0.452 mmol) en ácido clorhídrico concentrado (1.13 ml) a -10°C con una solución de nitrito sódico (0.037 g, 0.542 mmol) en agua (1.13 ml). La mezcla se mantuvo a aproximadamente 0 °C durante 30 min, luego se trató con una solución fría de cloruro de estaño (II) dihidratado (0.306 g, 1.355 mmol) en agua (1.13 ml) mientras se mantenía la temperatura de 0-3 °C. La mezcla se

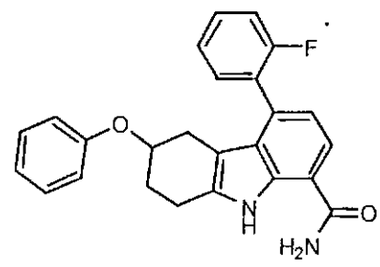
agitó mientras se calentaba hasta temperatura ambiente durante la noche. El precipitado se recogió por filtración, se lavó con agua y éter y se secó dando ácido 2'-fluoro-3-hidrazinilbifenil-4-carboxílico como la sal clorhidrato (0.068 g, 48 %) como un sólido blanco. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 9.09 (s ancho, 1H), 7.91 (d, J = 8.25 Hz, 1H), 7.58 (t, J = 7.15 Hz, 1H), 7.38-7.49 (m, 1H), 7.19-7.33 (m, 3H), 7.12 (d, J = 8.25 Hz, 1H). Espectro de masas m/z 247.1 $(M+H)^+$.

Etapa 4 Una solución de ácido 2'-fluoro-3-hidrazinilbifenil-4-carboxílico (0.306 g, 1.24 mmol) y ciclohexanona (0.183 g, 1.86 mmol) en ácido acético (6.2 ml) se calentó a reflujo en nitrógeno durante 2 h. La mezcla se enfrió hasta ta y se concentró. El residuo se repartió entre EtOAc y ácido clorhídrico 1 M. La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se trituró con EtOAc y DCM dando ácido 5-(2-fluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico (0.132 g) como un sólido blanco. El filtrado se purificó por cromatografía en columna (eluyendo con un gradiente de hexano hasta EtOAc-hexano 50:50) dando más producto (0.029 g, 41% total). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.95 (s ancho, 1H), 10.79 (s, 1H), 7.68 (d, J = 7.15, 1H), 7.42-7.51 (m, 1H), 7.24-7.34 (m, 3H), 6.87 (d, J = 7.15, 1H), 2.67-2.82 (m, 2H), 1.89-2.10 (m, 2H), 1.65-1.81 (m, 2H), 1.44-1.63 (m, 2H). Espectro de masas m/z 310.1 $(M+H)^+$.

Etapa 5 Se trató una solución de ácido 5-(2-fluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico (0.097 g, 0.314 mmol), EDC (0.072 g, 0.376 mmol) y HOBT (0.058 g, 0.376 mmol) en THF (2.4 ml) y DCM (0.6 ml) con hidróxido amónico acuoso al 28% (0.073 ml, 1.88 mmol). La mezcla se agitó durante la noche. Se añadieron más EDC (0.072 g, 0.376 mmol), HOBT (0.058 g, 0.376 mmol) y hidróxido amónico acuoso al 28% (0.073 ml, 1.88 mmol), y la mezcla se calentó a 50°C en un tubo sellado durante 2 días. La mezcla se enfrió hasta ta, se disolvió en EtOAc, se lavó con NaHCO3 (ac) y salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de DCM hasta DCM-metanol 98:2) dando 5-(2-fluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (0.030 g, 30 %) como un sólido blanquecino. Espectro de masas m/z 309.0 $(M+H)^+$.

Ejemplo 47-2

Preparación de 5-(2-fluorofenil)-3-fenoxi-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida



Etapa 1 Se trató una solución de 1,4-

dioxaspiro[4,5]decan-8-ol (1.00 g, 6.32 mmol), fenol (0.714 g, 7.59 mmol) y trifenilfosfina (1.824 g, 6.95 mmol) en DCM (21.07 ml) con azodicarboxilato de diisopropilo (1.48 ml, 7.59 mmol) y la mezcla se agitó a ta durante 5 días. La mezcla se concentró y el residuo se purificó por cromatografía en columna, eluyendo con un gradiente de hexano hasta hexano-EtOAc 80:20). El producto bruto se disolvió en EtOAc y la solución se lavó dos veces con hidróxido sódico acuoso 1 M y salmuera, se secó y se concentró proporcionando 8-fenoxi-1,4-dioxaspiro[4,5]decano como un líquido incoloro (0.468 g, 32%). RMN de ^{1}H (500 MHz, cloroformo-d) δ 7.16 - 7.24 (2 H, m), 6.81 - 6.89 (3 H, m), 4.30 - 4.38 (1 H, m), 3.85 - 3.93 (4 H, m), 1.80 - 1.90 (6 H, m), 1.50 - 1.59 (2 H, m).

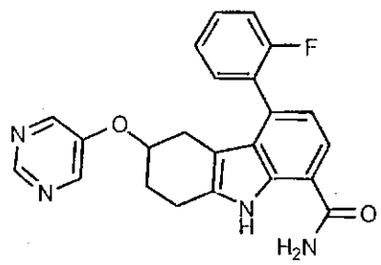
Etapa 2 Una solución de 8-fenoxi-1,4-dioxaspiro[4,5]decano (0.460 g, 1.963 mmol) en THF (5.0 ml) y ácido clorhídrico 3 M (5 ml) se agitó a ta durante 2 días. La mezcla se extrajo con EtOAc y la fase orgánica se lavó con salmuera, se secó y se concentró proporcionando 4-fenoxiciclohexanona como un aceite incoloro (0.344 g, 92%). RMN de ^{1}H (500 MHz, cloroformo-d) δ 7.22 - 7.27 (2 H, m), 6.87 - 6.94 (3 H, m), 4.62 - 4.66 (1 H, m), 2.49 - 2.68 (2 H, m), 2.19 - 2.30 (4 H, m), 1.96 - 2.04 (2 H, m). Espectro de masas m/z 191.1 $(M+H)^+$.

Etapa 3 Usando los procedimientos del Ejemplo 47-1

Etapas 4 y 5, se convirtió 4-fenoxiciclohexanona en 5-(2-fluorofenil)-3-fenoxi-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida con un 2.1% de rendimiento total. RMN de ^{1}H (500 MHz, DMSO-d_6) δ 11.06 (1 H, s), 8.13 (1 H, s ancho), 7.71 (1 H, d, J=7.1 Hz), 7.26 - 7.53 (7 H, m), 6.89 - 6.97 (4 H, m), 4.65 - 4.78 (1 H, m), 2.95 (2 H, t, J=6.3 Hz), 2.48 (1 H, dd, J=15.4, 3.8 Hz), 2.24 - 2.41 (1 H, m), 2.13 (1 H, s ancho), 1.91 - 2.04 (1 H, m). Espectro de masas m/z 401.2 $(M+H)^+$.

Ejemplo 47-3(a)

Preparación de 5-(2-fluorofenil)-3-(pirimidin-5-iloxi)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida



Etapa 1 Usando el procedimiento del Ejemplo 47-1 Etapa 4, se convirtieron ácido 2'-fluoro-3-hidrazinilbifenil-4-carboxílico (0.190 g, 0.770 mmol) y 4-hidroxiciclohexanona (0.132 g, 1.154 mmol) en ácido 5-(2-fluorofenil)-3-hidroxi-2,3,4,9-tetrahidro-1H-carbazol-8-carboxílico como un sólido amarillo claro (0.089 g, 36%). Espectro de masas m/z 326.1 $(M+H)^+$.

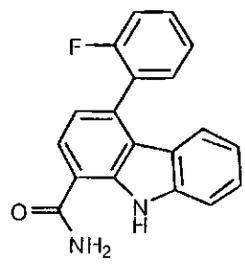
Etapa 2 Se trató una solución de ácido 5-(2-fluorofenil)-3-hidroxi-2,3,4,9-tetrahidro-1H-carbazol-8-

carboxílico (0.069 g, 0.213 mmol) en DMF (1.07 ml) con cloruro amónico (0.023 g, 0.427 mmol), HOAT (0.058 g, 0.427 mmol), EDC (0.082 g, 0.427 mmol) y DIEA (0.149 ml, 0.853 mmol) y se agitó durante un fin de semana. La mezcla se diluyó con DCM, se lavó con ácido clorhídrico al 5%, NaHCO3 (ac), salmuera y cloruro de litio acuoso al 10%, se secó y se concentró dando 5-(2-fluorofenil)-3-hidroxi-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como una espuma amarillo claro (0.045 g, 65%). Espectro de masas m/z 325.1 $(M+H)^+$.

Etapa 3 Usando el procedimiento del Ejemplo 47-2 Etapa 1, se convirtieron 5-(2-fluorofenil)-3-hidroxi-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (0.099 g, 0.306 mmol) y pirimidin-5-ol (0.035 g, 0.368 mmol) en 5-(2-fluorofenil)-3-(pirimidin-5-iloxi)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como una espuma amarillo claro (0.054 g, 34%). Espectro de masas m/z 403.1 $(M+H)^+$.

Ejemplo 48-1

Preparación de 4-(2-fluorofenil)-9H-carbazol-1-carboxamida



Se trató una solución de 5-(2-fluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Ejemplo 47-1, 0.024 g,

0.078 mmol) en tolueno (0.39 ml) con 2,3-dicloro-5,6-diciano-1,4-benzoquinona (0.039 g, 0.171 mmol) y la mezcla se calentó hasta reflujo. Después de 4 h, la mezcla se enfrió hasta ta. El sólido se separó por filtración y se aclaró con EtOAc. El filtrado se concentró, se diluyó con metanol y se sometió a HPLC preparativa. El efluente que contenía producto se trató con NaHCO3 (ac) y se concentró. El residuo se extrajo tres veces con DCM y las fases orgánicas reunidas se secaron y se concentraron dando 4-(2-fluorofenil)-9H-carbazol-1-carboxamida (0.0045 g, 19%) como un sólido castaño claro. Espectro de masas m/z 305.0 $(M+H)^+$.

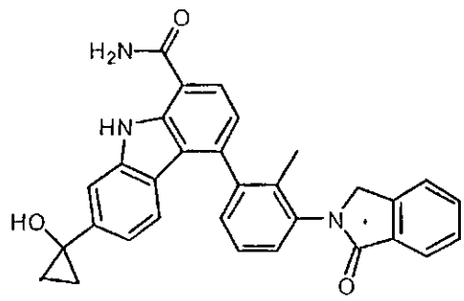
Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 48-1.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
48-2	Ejemplo 47-2	4-(2-fluorofenil)-6-fenoxi-9H-carbazol-1-carboxamida	397.0 $(M+H)^+$
48-3	Ejemplo 47-3	4-(2-fluorofenil)-6-(pirimidin-5-iloxi)-9H-carbazol-1-carboxamida	399.0 $(M+H)^+$
48-4	Ejemplo 24-15	4-(2,6-difluorofenil)-N'-(tetrahidro-2H-piran-4-il)-9H-carbazol-1,7-dicarboxamida	450.2 $(M+H)^+$

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Ejemplo 49-1

Preparación de 7-(1-hidroxiciclopropil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Etapa 1 Se trató una solución de 5-bromo-8-carbamoil-9H-carbazol-2-carboxilato de etilo (Intermedio 48-1, 0.275 g, 0.761 mmol) con isopropóxido de titanio (IV) (0.31 ml, 1.07 mmol), seguido por cloruro de etil magnesio (2 M en THF, 3.81 ml, 7.61 mmol). La mezcla se agitó a ta durante 1 h, luego se enfrió en hielo y se trató con agua (10 ml). Después de 30 min, el sólido se separó por filtración y se aclaró con éter (150 ml). La fase orgánica se secó y se concentró dando 4-bromo-7-(1-hidroxiciclopropil)-9H-carbazol-1-carboxamida como un sólido amarillo (0.220 g, 79%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.65 (1 H, s), 8.52 (1 H, d, J=8.4 Hz), 8.25 (1 H, s ancho), 7.84 - 7.89 (2 H, m), 7.61 (1 H, s ancho), 7.45 (1 H, d, J=8.1 Hz), 7.13 (1 H, dd, J=8.5, 1.7 Hz), 6.11 (1 H, s), 1.21 - 1.27 (2 H, m), 1.06 - 1.11 (2 H, m).

Etapa 2 Una solución de 4-bromo-7-(1-hidroxiciclopropil)-9H-carbazol-1-carboxamida (0.151 g, 0.436

mmol), *terc*-butilclorodimetilsilano (0.079 g, 0.524 mmol) e imidazol (0.074 g, 1.091 mmol) en DMF (2.2 ml) se agitó a ta durante 18 h. Se añadieron más *terc*-butilclorodimetilsilano (0.079 g, 0.524 mmol) e imidazol (0.074 g, 1.091 mmol) y se continuó agitando durante 1 h. La mezcla se diluyó con EtOAc (75 ml) y se lavó siete veces con salmuera. La fase orgánica se secó y se concentró y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 90:10 a 50:50 de hexano-EtOAc) dando 4-bromo-7-(1-(*terc*-butildimetilsililoxi)ciclopropil)-9H-carbazol-1-carboxamida (0.144 g, 67%).

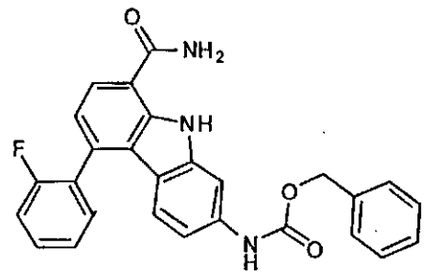
Etapa 3 Usando el procedimiento del Ejemplo 31-1, se convirtieron 4-bromo-7-(1-(*terc*-butildimetilsililoxi)ciclopropil)-9H-carbazol-1-carboxamida (0.059 g, 0.129 mmol) y 2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-4, 0.054 g, 0.154 mmol) en 7-(1-(*terc*-butildimetilsililoxi)ciclopropil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (0.048 g, 60%).

Etapa 4 Se trató una solución de 7-(1-(*terc*-butildimetilsililoxi)ciclopropil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (0.039 g, 0.065 mmol) en THF (0.66 ml) con fluoruro de tetra-n-butilamonio (1 M en THF, 0.098 ml, 0.098 mmol). Después de 10

min, la mezcla se combinó con una mezcla idéntica realizada al 22% de la escala descrita y la mezcla se concentró. El residuo se purificó por HPLC preparativa. Las fracciones de efluente apropiadas se trataron con $NaHCO_3$ (ac) y se concentraron parcialmente. El residuo acuoso se extrajo tres veces con DCM y las fases orgánicas reunidas se secaron y concentraron dando 7-(1-hidroxiciclopropil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido blanco (23.3 mg, 60%). RMN de ^1H (500 MHz, DMSO-d_6) δ 11.42 (1 H, s), 8.18 (1 H, s ancho), 7.98 (1 H, d, J=7.7 Hz), 7.80 (1 H, d, J=7.7 Hz), 7.72 (1 H, s), 7.68 (2 H, d, J=3.8 Hz), 7.60 (1 H, d, J=7.7 Hz), 7.56 (1 H, ddd, J=7.8, 4.1, 4.0 Hz), 7.49 (2 H, t, J=7.7 Hz), 7.33 (1 H, d, J=7.1 Hz), 7.01 (1 H, d, J=7.7 Hz), 6.95 (1 H, d, J=8.2 Hz), 6.79 (1 H, d, J=8.2 Hz), 5.95 (1 H, s), 4.90 - 5.02 (2 H, m), 1.84 (3 H, s), 1.07 - 1.15 (2 H, m), 0.91 - 1.00 (2 H, m). Espectro de masas m/z 488.3 $(M+H)^+$.

Ejemplo 50-1

Preparación de 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-ilcarbamato de bencilo



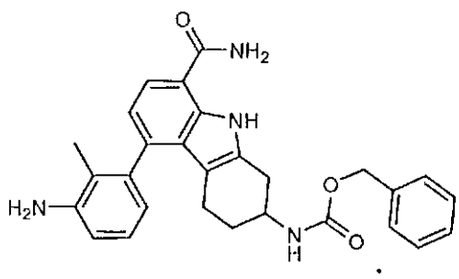
Se trató una suspensión de ácido 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-carboxílico (Ejemplo 23-2, 320 mg, 0.919 mmol) y tamices moleculares de 4Å (60 mg) en 1,4-dioxano (15 ml) a 50°C con TEA (0.316 ml, 2.269 mmol) y azida de difenilfosforilo (0.491 ml, 2.269 mmol). La mezcla se agitó a 50°C durante 1.5 h, seguido por adición de fenilmetanol (0.951 ml, 9.19 mmol). La mezcla se agitó entonces a 80°C durante 18 h. Se repartió la mezcla enfriada entre EtOAc y NaHCO3 (ac). La fase orgánica se lavó con salmuera, se secó y se concentró el residuo se purificó por cromatografía en columna (eluyendo con hexano-EtOAc 35:65). El residuo después de concentración se suspendió en hexano y el precipitado se recogió por filtración proporcionando 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-ilcarbamato de bencilo como un sólido blanquecino (400 mg, 83%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.50 (s, 1 H) 9.83 (s, 1 H) 8.15 (s ancho,1 H) 8.00 (s, 1 H) 7.91 (d, *J*=7.69 Hz, 1 H) 7.45 - 7.64 (m, 3 H) 7.32 - 7.46 (m, 7 H) 7.03 (d, *J*=7.91 Hz, 1 H) 6.87 - 6.98 (m, 2 H) 5.15 (s, 2 H). Espectro de masas m/z 454.1 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 50-1.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
Intermedio 50-2(a)	Ejemplo 23-3	8-carbamoil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo	476.1 $(M+H)^+$
50-3	Intermedio 49-1	5-bromo-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo	438, 440 $(M+H)^+$
Intermedio 50-4(a)	Intermedio 49-3	5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo	442, 444 $(M+H)^+$

Ejemplo 51-1

Preparación de 5-(3-amino-2-metilfenil)-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo

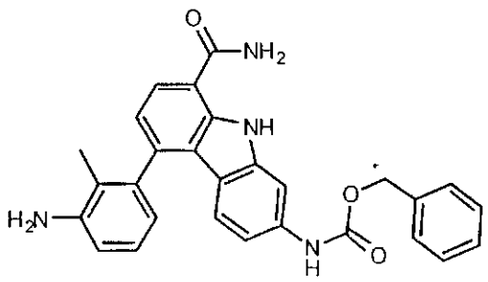


Usando el procedimiento del Ejemplo 3-2, se convirtieron 5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo (Ejemplo 50-4, 300 mg, 0.678 mmol) y 2-metil-3-(4,4,5,5-tetrametil-1,3,2-

dioxaborolan-2-il)anilina (Intermedio 50-1, 237 mg, 1.017 mmol) en 5-(3-amino-2-metilfenil)-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo, sal TFA, aislado como un sólido blanco después de purificación por HPLC preparativa (60 mg, 15%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.63 (1 H, dd, J=7.7, 2.9 Hz), 7.18 - 7.46 (8 H, m), 6.82 (1 H, dd, J=7.5, 2.8 Hz), 5.10 (2 H, s), 3.90 (1 H, s ancho), 3.14 (1 H, d, J=4.8 Hz), 2.72 (1 H, s ancho), 1.77 - 2.19 (6 H, m), 1.51 - 1.68 (1 H, m). Espectro de masas m/z 469.3 $(M+H)^+$.

Ejemplo 51-2

Preparación de 5-(3-amino-2-metilfenil)-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo

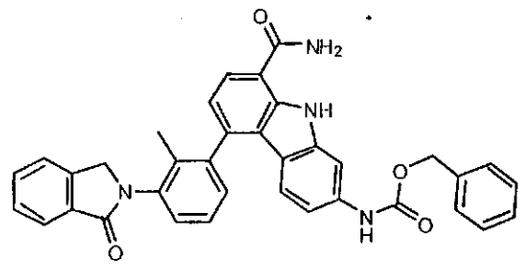


Usando el procedimiento del Ejemplo 3-2, se convirtieron 5-bromo-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo (Ejemplo 50-3, 1.00 g, 2.28 mmol) y 2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (Intermedio 50-1, 638 mg, 2.74 mmol) en 5-(3-amino-2-metilfenil)-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo aislado como un sólido blanquecino después de triturar en

metanol (aproximadamente 80-85% de pureza, 860 mg, 65%). Se purificó una porción por HPLC preparativa proporcionando la sal TFA. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.45 (1 H, s), 9.81 (1 H, s), 8.13 (1 H, s ancho), 7.95 (1 H, s), 7.89 (1 H, d, J=7.5 Hz), 7.29 - 7.51 (6 H, m), 7.25 (1 H, d, J=7.9 Hz), 7.16 (1 H, d, J=7.5 Hz), 6.81 - 6.96 (3 H, m), 6.65 (1 H, d, J=8.8 Hz), 5.14 (2 H, s), 1.83 (3 H, s). Espectro de masas m/z 465.1 $(M+H)^+$.

Ejemplo 51-3

Preparación de 8-carbamoil-5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-ilcarbamato de bencilo



Usando el procedimiento del Ejemplo 31-1, se convirtieron 5-bromo-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo (Ejemplo 50-3, 400 mg, 0.913 mmol) y 2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-4, 414 mg, 1.19 mmol) en 8-carbamoil-5-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-ilcarbamato de bencilo como un sólido blanco (90% de pureza, 530 mg, 90%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.58 (1 H, s), 7.96 (1 H, d, J=7.91 Hz), 7.85 (1 H, s ancho), 7.61 (2 H,

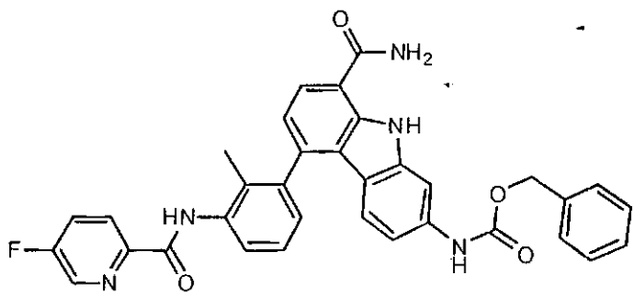
d, J=7.47 Hz), 7.54 (2 H, d, J=4.83 Hz), 7.33 - 7.45 (7 H, m), 7.06 (2 H, dd, J=12.42, 8.13 Hz), 6.93 (1 H, s), 6.84 - 6.88 (1 H, m), 5.22 (2 H, s), 4.82 (2 H, s), 1.94 (3 H, s). Espectro de masas m/z 581.3 $(M+H)^+$.

El siguiente compuesto también se preparó usando procedimientos mostrados en el Ejemplo 51-3, usando el Intermedio 50-15 en lugar del Intermedio 50-4.

Ejemplo	Nombre del compuesto	Espectro de masas
51-4	5-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo	637.2 $(M+H)^+$

Ejemplo 52-1

Preparación de 8-carbamoil-5-(3-(5-fluoropicolinamido)-2-metilfenil)-9H-carbazol-2-ilcarbamato de bencilo

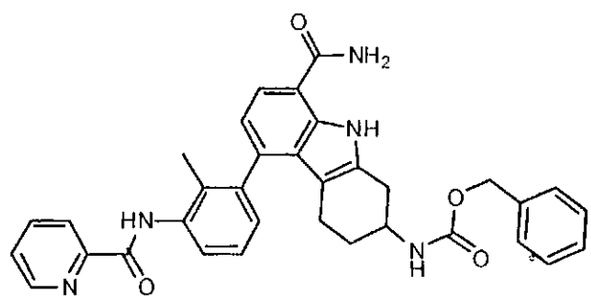


Se trató una mezcla de 5-(3-amino-2-metilfenil)-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo (Ejemplo 51-2, 100 mg, 0.215 mmol), ácido 5-fluoropicolínico (45.6 mg, 0.323 mmol), HOAT (44.0 mg, 0.323 mmol) y EDC (83 mg, 0.431 mmol)

en DCM-THF (80:20, 12 ml) con DIEA (0.150 ml, 0.861 mmol) y la solución se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa proporcionando 8-carbamoil-5-(3-(5-fluoropicolinamido)-2-metilfenil)-9H-carbazol-2-ilcarbamato de bencilo como un sólido blanco (47 mg, 36%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.48 (1 H, s), 10.41 (1 H, s), 9.83 (1 H, s), 8.74 (1 H, d, J=3.0 Hz), 8.27 (1 H, dd, J=8.8, 4.8 Hz), 8.09 - 8.21 (1 H, m), 7.96 - 8.03 (2 H, m), 7.94 (1 H, d, J=7.8 Hz), 7.85 (1 H, d, J=7.5 Hz), 7.29 - 7.51 (7 H, m), 7.15 - 7.21 (1 H, m), 6.91 - 6.98 (2 H, m), 6.79 (1 H, d, J=8.8 Hz), 5.16 (2 H, s), 1.96 (3 H, s). Espectro de masas m/z 588.1 $(M+H)^+$.

Ejemplo 52-2

Preparación de 8-carbamoil-5-(2-metil-3-(picolinamido)fenil)-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo



Una solución de 5-(3-amino-2-metilfenil)-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo, sal TFA (Ejemplo 51-1, 55 mg, 0.094 mmol), TEA (0.066 ml, 0.472 mmol) y sal clorhidrato de cloruro de picolinoilo (50.4 mg, 0.283 mmol) en DCM (8 ml) se agitó a ta

durante la noche. La mezcla se concentró y purificó por HPLC preparativa proporcionando 8-carbamoil-5-(2-metil-3-(picolinamido)fenil)-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo, aislado como la sal TFA, como un sólido blanco (26 mg, 39%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.59 (1 H, t, J=4.8 Hz), 8.14 (1 H, d, J=8.3 Hz), 7.89 - 7.99 (1 H, m), 7.85 (1 H, dd, J=9.9, 8.1 Hz), 7.50 (2 H, dd, J=7.7, 2.0 Hz), 7.11 - 7.32 (6 H, m), 7.01 (1 H, d, J=7.9 Hz), 6.74 (1 H, d, J=7.5 Hz), 4.96 (2 H, s), 3.68 - 3.87 (1 H, m), 2.96 - 3.10 (1 H, m), 2.49 - 2.66 (1 H, m), 1.82 - 2.11 (5 H, m), 1.73 (1 H, s ancho), 1.34 - 1.62 (1 H, m). Espectro de masas m/z 575.1 $(M+H)^+$.

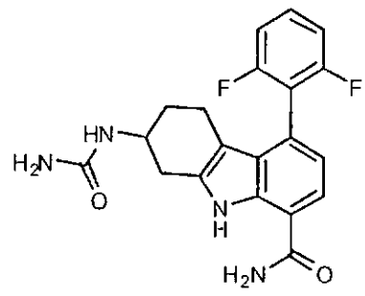
Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 52-1 y 52-2, usando el ácido carboxílico o cloruro de ácido carboxílico apropiado.

Ejemplo/Intermedio	Nombre del compuesto	Espectro de masas
52-3	8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-ilcarbamato de bencilo	585.4 $(M-H)^-$

52-4	8-carbamoil-5-(2-metil-3-(picolinamido)fenil)-9H-carbazol-2-ilcarbamato de bencilo (preparado como la sal TFA)	570.0 $(M+H)^+$
Intermedio 52-5	8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-2,3,4,9-tetrahidro-1H-carbazol-2-ilcarbamato de bencilo	591.3 $(M+H)^+$
Intermedio 52-6	8-carbamoil-5-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-9H-carbazol-2-ilcarbamato de bencilo	573.4 $(M+H)^+$

Ejemplo 53-1

Preparación de 5-(2,6-difluorofenil)-2-ureido-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida

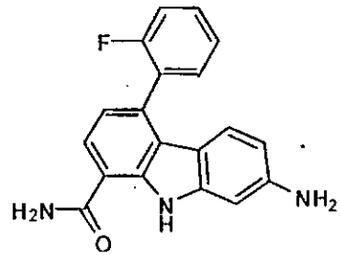


Una solución de ácido 8-carbamoil-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-2-carboxílico (Ejemplo 23-3, 30 mg, 0.081 mmol), fosforazidato de difenilo (55.7 mg, 0.203 mmol) y TEA (0.028 ml, 0.203 mmol) en 1,4-dioxano (2 ml) se calentó a 50°C durante 2 h. La mezcla se

enfrió hasta ta y se trató con hidróxido amónico acuoso al 28% (2 ml). Después de 20 min la mezcla se diluyó con DCM, se lavó con agua, se secó y se concentró, y el residuo se purificó por HPLC preparativa. Las fracciones de efluente apropiadas se basificaron con hidróxido sódico acuoso 1 M y se extrajo dos veces con DCM. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron proporcionando 5-(2,6-difluorofenil)-2-ureido-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido blanco (9 mg, 28%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 1.60 - 1.72 (m, 1 H) 1.79 - 1.89 (m, 1 H) 2.13 - 2.32 (m, 2 H) 2.68 (dd, *J*=16.48, 7.25 Hz, 1 H) 3.13 (dd, *J*=16.70, 5.27 Hz, 1 H) 3.98 - 4.09 (m, *J*=6.15 Hz, 1 H) 4.58 (s, 1 H) 6.91 (d, *J*=7.91 Hz, 1 H) 7.05 (t, *J*=8.13 Hz, 2 H) 7.38 - 7.50 (m, 1 H) 7.60 (d, *J*=7.91 Hz, 1 H). Espectro de masas m/z 385.1 $(M+H)^+$.

Ejemplo 54-1

Preparación de 7-amino-4-(2-fluorofenil)-9H-carbazol-1-carboxamida

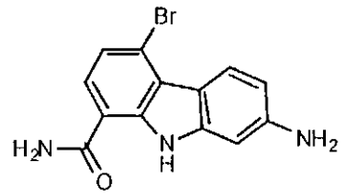


Se trató una mezcla de 8-carbamoil-5-(2-fluorofenil)-9H-carbazol-2-ilcarbamato de bencilo (Ejemplo

50-1, 400 mg, 0.882 mmol), paladio al 10% sobre carbón (94 mg, 0.088 mmol) y formiato amónico (334 mg, 5.29 mmol) en metanol (20 ml) a reflujo durante 1 h. La mezcla se enfrió hasta ta, se diluyó con metanol y se filtró a través de una almohadilla de Celite. El filtrado se concentró dando 7-amino-4-(2-fluorofenil)-9H-carbazol-1-carboxamida con rendimiento cuantitativo. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.07 (s, 1 H) 8.11 (s ancho,1 H) 7.78 (d, *J*=7.78 Hz, 1 H) 7.51 (d, *J*=2.01 Hz, 2 H) 7.35 - 7.47 (m, 3 H) 6.93 (d, *J*=7.78 Hz, 1 H) 6.79 - 6.84 (m, 1 H) 6.72 (d, *J*=8.03 Hz, 1 H) 6.24 (dd, *J*=8.41, 1.88 Hz, 1 H) 5.22 (s, 2 H). Espectro de masas m/z 320.1 $(M+H)^+$.

Ejemplo 54-2

Preparación de 7-amino-4-bromo-9H-carbazol-1-carboxamida

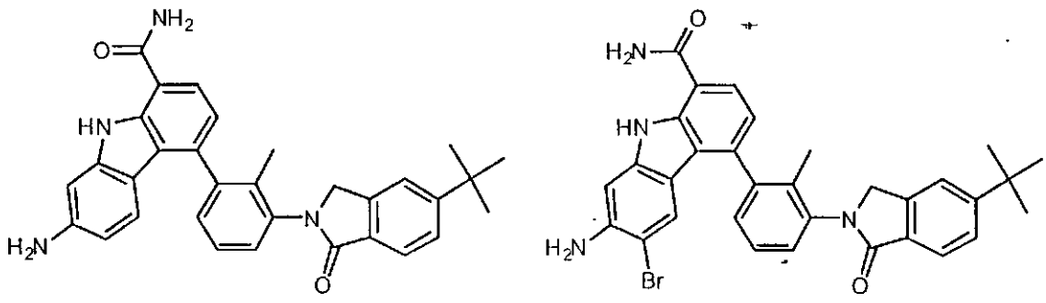


Una suspensión de 5-bromo-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo (Ejemplo 50-3, 2.18 g, 4.97 mmol) en bromuro de hidrógeno (30-35% en ácido acético, 11.9 ml, 59.7 mmol) se agitó a ta durante 30 min. La mezcla se diluyó con éter (100 ml) y el precipitado se recogió por filtración, se lavó con éter y se secó proporcionando 7-amino-4-bromo-9H-carbazol-1-carboxamida, sal bromhidrato, como un sólido amarillo claro (2.20 g). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.02

(1 H, s), 8.69 (1 H, d, J=8.5 Hz), 8.28 (1 H, s ancho), 7.91 (1 H, d, J=8.0 Hz), 7.84 (1 H, d, J=1.8 Hz), 7.65 (1 H, s ancho), 7.51 (1 H, d, J=8.3 Hz), 7.25 (1 H, dd, J=8.4, 1.9 Hz). Espectro de masas m/z 304, 306 $(M+H)^+$. La sal se repartió entre EtOAc y NaHCO3 (ac). Se recogió sólido residual por filtración, se lavó con EtOAc y agua y se secó. La fase orgánica del filtrado se separó, se lavó con salmuera y se secó y concentró. El residuo sólido se combinó con el sólido filtrado, se disolvió en acetona, se filtró para separar el sólido sin disolver y el filtrado se concentró proporcionando 7-amino-4-bromo-9H-carbazol-1-carboxamida, sal bromhidrato, como un sólido amarillo claro (1.62 g, 96%).

Ejemplos 54-3 y 54-4

Preparación de 7-amino-4-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida y 7-amino-6-bromo-4-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida



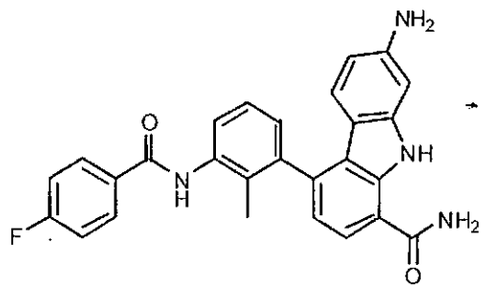
Una solución de 5-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-8-carbamoil-9H-carbazol-2-ilcarbamato de bencilo (Ejemplo 51-4, 65 mg, 0.102 mmol) en bromuro de

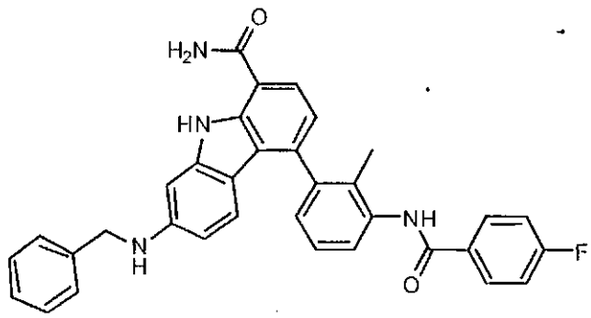
hidrógeno (30-35% en ácido acético, 5 ml, 27.6 mmol) se agitó a ta durante 1.5 h. La mezcla se diluyó con DCM y se concentró. El residuo se disolvió en DCM, que contenía una pequeña cantidad de metanol y la solución se mezcló con hidróxido sódico acuoso 1 M. La fase orgánica se separó, se lavó con agua, se secó y se concentró y el residuo se trituró con hexano. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 97:2.7:0.3 hasta 90:9:1 de DCM-metanol-hidróxido amónico acuoso al 28%) proporcionando 7-amino-4-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida como un sólido blanco (Ejemplo 54-3, 45 mg, 88%) como un sólido blanco. RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.32 (1 H, s), 7.89 (1 H, d, J=8.35 Hz), 7.57 (1 H, d, J=7.91 Hz), 7.49 - 7.55 (2 H, m), 7.35 - 7.47 (3 H, m), 7.04 (1 H, d, J=7.47 Hz), 6.93 (1 H, d, J=8.35 Hz), 6.74 (1 H, d, J=1.76 Hz), 6.46 (1 H, dd, J=8.57, 1.98 Hz), 4.79 (2 H, d, J=2.20 Hz), 3.84 (2 H, s ancho), 1.96 (3 H, s), 1.40 (9 H, s). Espectro de masas m/z 503.3 $(M+H)^+$. También se obtuvo 7-amino-6-bromo-4-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida como un sólido blanco (Ejemplo 54-4, 5 mg, 8%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.34 (1 H, s), 7.89 (1 H, d, J=7.91 Hz), 7.53 - 7.59 (3 H, m), 7.44 - 7.48 (2 H, m), 7.35 (1 H, dd, J=5.71, 3.08 Hz), 7.05 - 7.08 (2 H, m), 6.84 (1 H, s), 4.83 (2 H, s), 4.22 (2 H, s ancho), 1.95 (3 H, s), 1.40

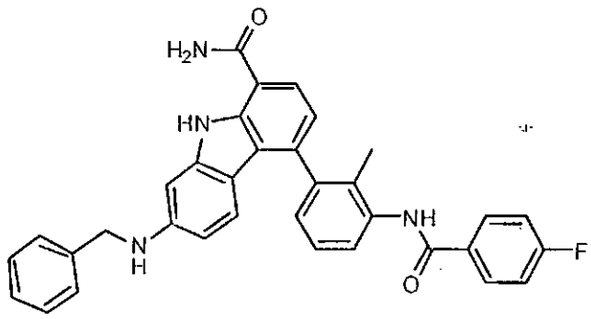
(9 H, s). Espectro de masas m/z 581, 583 $(M+H)^+$.

Ejemplo 54-5, 54-6 y 54-7

Preparación de 7-amino-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida, 7-(bencilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida y 7-(dibencilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida







Usando el procedimiento de los Ejemplos 54-3 y 54-4, se convirtió 8-carbamoil-5-(3-(4-fluorobenzamido)-2-

metilfenil)-9H-carbazol-2-ilcarbamato de bencilo (Ejemplo 52-3, 720 mg, 1.227 mmol) en 7-amino-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida, se purificó por HPLC preparativa y se convirtió en la base libre (Ejemplo 54-5, 330 mg, 59%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.02 (1 H, s), 10.10 (1 H, s), 8.00 - 8.17 (3 H, m), 7.77 (1 H, d, J=7.9 Hz), 7.43 - 7.48 (1 H, m), 7.29 - 7.42 (4 H, m), 7.17 (1 H, d, J=6.6 Hz), 6.73 - 6.86 (2 H, m), 6.60 (1 H, d, J=8.8 Hz), 6.21 (1 H, dd, J=8.6, 2.0 Hz), 5.17 (2 H, s), 1.90 (3 H, s). Espectro de masas m/z 453.0 $(M+H)^+$. También se obtuvo 7-(bencilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (Ejemplo 54-6, 4.1 mg, 0.6%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.08 (1 H, s ancho), 10.09 (1 H, s), 8.02 - 8.12 (3 H, m), 7.79 (1 H, d, J=7.5 Hz), 7.43 - 7.48 (1 H, m), 7.25 - 7.41 (8 H, m), 7.18 - 7.24 (1 H, m), 7.16 (1 H, d, J=6.2 Hz), 6.84 (2 H, d, J=7.9 Hz), 6.61 (1 H, d, J=8.3 Hz), 6.28 - 6.36 (1 H, m), 4.29 (2 H, s), 1.89 (3 H, s). Espectro de masas m/z 543.0 $(M+H)^+$. También se obtuvo 7-(dibencilamino)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (Ejemplo 54-7, 4.2 mg, 0.5%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.09 (1 H, s), 10.04 (1 H, s), 8.05 (3 H, dd, J=8.8, 5.3 Hz), 7.79 (1 H, d, J=7.9 Hz), 7.16 - 7.45 (15 H, m), 7.12 (1 H, d, J=6.2 Hz), 7.04 (1 H, d, J=2.2 Hz), 6.83 (1 H, d, J=7.5 Hz), 6.57 (1 H, d, J=8.8 Hz), 6.33 (1 H, dd, J=8.8, 2.2 Hz), 4.71 (4 H, s), 1.88 (3 H, s).

Espectro de masas m/z 633.1 $(M+H)^+$.

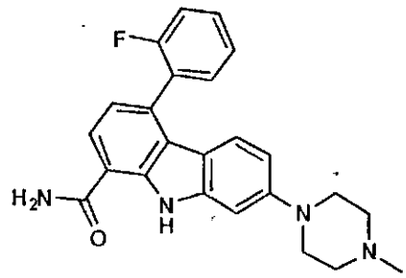
Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 54-1 a 54-7.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
54-8	Ejemplo 52-4	7-amino-4-(2-metil-3-(picolinamido)fenil)-9H-carbazol-1-carboxamida (preparada como la sal bis TFA)	436.1 $(M+H)^+$
54-9	Ejemplo 52-5	2-amino-5-(3-(4-fluorobenzamido)-2-metilfenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como la sal TFA)	457.2 $(M+H)^+$
54-10	Ejemplo 51-2	7-amino-4-(3-amino-2-metilfenil)-9H-carbazol-1-carboxamida	331.2 $(M+H)^+$
54-11	Ejemplo 52-1	7-amino-4-(3-(5-fluoropicolinamido)-2-metilfenil)-9H-carbazol-1-carboxamida	450.0 $(M+H)^+$

54-12	Ejemplo 52-1	7-(bencilamino)-4-(3-(5-fluoropicolinamido)-2-metilfenil)-9H-carbazol-1-carboxamida	544.0 $(M+H)^+$
54-13	Ejemplo 52-2	2-amino-5-(2-metil-3-(picolinamido)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (preparada como la sal bis TFA)	440.1 $(M+H)^+$
54-14	Ejemplo 51-3	7-amino-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	447.2 $(M+H)^+$
54-15	Ejemplo 52-6	7-amino-4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-9H-carbazol-1-carboxamida	439.2 $(M+H)^+$
54-16	Ejemplo 50-2(a)	2-amino-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	342.1 $(M+H)^+$

Ejemplo 55-1

Preparación de 4-(2-fluorofenil)-7-(4-metilpiperazin-1-il)-9H-carbazol-1-carboxamida



Una mezcla de 7-amino-4-(2-fluorofenil)-9H-carbazol-1-carboxamida (Ejemplo 54-1, 30 mg, 0.094 mmol), sal clorhidrato de 2-cloro-N-(2-cloroetil)-N-metiletanamina (27.1 mg, 0.141 mmol) y carbonato sódico (49.8 mg, 0.470 mmol) en *terc*-butanol (2 ml) se calentó a reflujo durante la noche. La mezcla se enfrió hasta ta y se concentró. El residuo se purificó por HPLC preparativa proporcionando 4-(2-fluorofenil)-7-(4-metilpiperazin-1-il)-9H-carbazol-1-carboxamida, sal TFA, como un sólido amarillo claro (11 mg, 20%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.28 (s, 1 H) 8.13 (s ancho,1 H) 7.85 (d, *J*=7.91 Hz, 1 H) 7.41 - 7.59 (m, 3 H) 7.30 - 7.41 (m, 2 H) 7.25 (d, *J*=2.20 Hz, 1 H) 6.97 (d, *J*=7.91 Hz, 1 H) 6.89 (d, *J*=0.88 Hz, 1 H) 6.67 (d, *J*=2.20 Hz, 1 H) 3.70 - 3.82 (m, 2 H) 3.43 - 3.52 (m, 2 H) 3.08 - 3.19 (m, 2 H) 2.86 - 2.99 (m, 2 H) 2.80 (s, 3 H). Espectro de masas m/z 403.2 $(M+H)^+$.

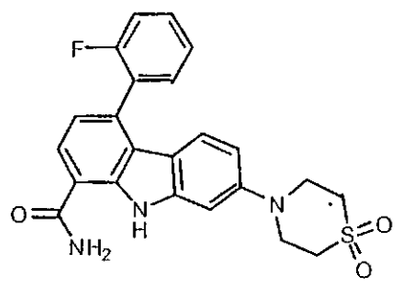
Los siguientes compuestos también se prepararon

usando procedimientos mostrados en el Ejemplo 55-1, usando (en el caso del Ejemplo 55-2) 1-cloro-2-(2-cloroetoxi)etano en lugar de sal clorhidrato de 2-cloro-N-(2-cloroetil)-N-metiletanamina.

Ejemplo /Intermedio	Material de partida	Nombre del compuesto	Espectro de masas
55-2	Ejemplo 54-1	4-(2-fluorofenil)-7-morfolino-9H-carbazol-1-carboxamida, (preparada como la sal de ácido trifluroacético)	390.1 $(M+H)^+$
Intermedio 55-3	Ejemplo 54-2	4-bromo-7-(4-metilpiperazin-1-il)-9H-carbazol-1-carboxamida	387, 389 $(M+H)^+$

Ejemplo 56-1

Preparación de 4-(2-fluorofenil)-7-(1,1-dioxotiomorfolino)-9H-carbazol-1-carboxamida



Se trató una suspensión de 7-amino-4-(2-

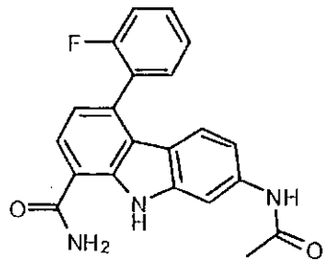
fluorofenil)-9H-carbazol-1-carboxamida (Ejemplo 54-1, 36 mg, 0.113 mmol) en 2-propanol (1.0 ml) con vinilsulfonileteno (20 µl, 0.199 mmol) a ta. La mezcla de reacción se calentó a 100°C durante 26 h. La mezcla se enfrió hasta ta, se concentró y el residuo se purificó por HPLC preparativa proporcionando 4-(2-fluorofenil)-7-(1,1-dioxotiomorfolino)-9H-carbazol-1-carboxamida como un sólido amarillo (14 mg, 28%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.26 (1 H, s), 8.17 (1 H, s ancho), 7.90 (1 H, d, *J*=7.9 Hz), 7.47 - 7.62 (3 H, m), 7.37 - 7.46 (2 H, m), 7.35 (1 H, d, *J*=1.8 Hz), 7.01 (1 H, d, *J*=7.9 Hz), 6.93 (1 H, d, *J*=8.3 Hz), 6.74 (1 H, dd, *J*=9.0, 2.4 Hz), 3.77 - 3.81 (4 H, m), 3.08 - 3.19 (4 H, m). Espectro de masas m/z 438.1 $(M+H)^+$.

El siguiente compuesto también se preparó usando procedimientos mostrados en el Ejemplo 56-1, usando el Ejemplo 54-5 en lugar del Ejemplo 54-1 como material de partida.

Ejemplo	Nombre del compuesto	Espectro de masas
56-2	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(1.1-dioxotiomorfolino)-9H-carbazol-1-carboxamida	571.3 $(M-H)^-$

Ejemplo 57-1

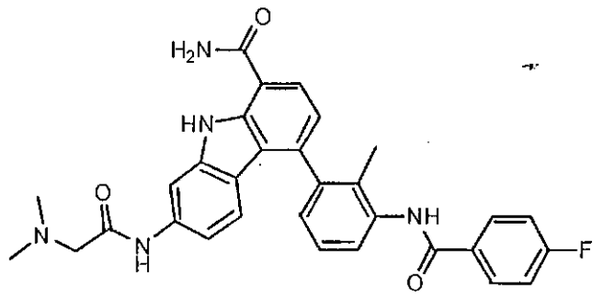
Preparación de 7-acetamido-4-(2-fluorofenil)-9H-carbazol-1-carboxamida



Se trató una solución de 7-amino-4-(2-fluorofenil)-9H-carbazol-1-carboxamida (Ejemplo 54-1, 25 mg, 0.078 mmol) y TEA (0.022 ml, 0.157 mmol) en DCM-THF (2:1, 3 ml) con cloruro de acetilo (6.7 µl, 0.094 mmol). La mezcla se agitó a ta. durante 1 h, luego se concentró. El residuo se purificó por HPLC preparativa proporcionando 7-acetamido-4-(2-fluorofenil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (13 mg, 45%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.95 (s, 1 H) 7.79 (d, *J*=7.91 Hz, 1 H) 7.36 - 7.53 (m, 2 H) 7.13 - 7.33 (m, 2 H) 6.98 (d, *J*=7.69 Hz, 2 H) 6.85 (d, *J*=10.33 Hz, 1 H) 2.05 (s, 3 H). Espectro de masas m/z 360.3 $(M+H)^+$.

Ejemplo 57-2

Preparación de 7-(2-(dimetilamino)acetamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida

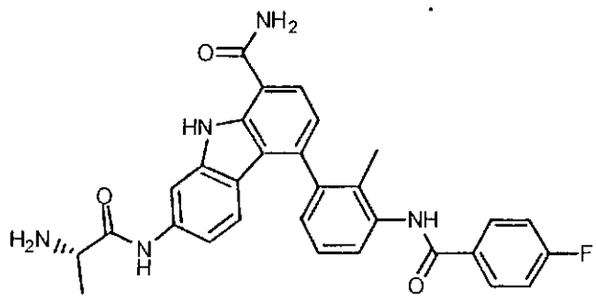


Una solución de 7-amino-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (Ejemplo 54-5, 30 mg, 0.066 mmol), sal clorhidrato del ácido 2-(dimetilamino)acético (13.9 mg, 0.099 mmol), HOAT (18.1 mg, 0.133 mmol), EDC (31.8 mg, 0.166 mmol) y TEA (0.037 ml, 0.265 mmol) en DCM-THF (2:1, 3 ml) se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa proporcionando 7-(2-(dimetilamino)acetamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida, sal TFA, como un sólido blanco (22 mg, 50%). RMN de ^{1}H (500 MHz, metanol-d_4) δ 8.02 (1 H, d, J=1.1 Hz), 7.96 (2 H, dd, J=8.7, 5.4 Hz), 7.84 (1 H, d, J=7.8 Hz), 7.42 (1 H, d, J=7.2 Hz), 7.34 (1 H, t, J=7.6 Hz), 7.12 - 7.21 (3 H, m), 6.95 (1 H, d, J=7.8 Hz), 6.86 - 6.94 (2 H, m), 4.04 (2 H, s), 2.91 (s, 6H), 1.90 (3 H, s). Espectro

de masas m/z 538.1 $(M+H)^+$.

Ejemplo 57-3

Preparación de 7-((S)-2-aminopropanamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida



Una solución de 7-amino-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (Ejemplo 54-5, 21.8 mg, 0.049 mmol), ácido (S)-2-(*terc*-butoxicarbonilamino)propanoico (10.6 mg, 0.056 mmol), HOBT (8.6 mg, 0.056 mmol), EDC (10.8 mg, 0.056 mmol) y DIEA (0.043 ml, 0.250 mmol) en DMF (0.675 ml) se agitó a ta durante la noche. La mezcla se concentró y se trató con TFA (0.5 ml) y DCM (0.5 ml). Después de 2 h, la solución se concentró y el residuo se purificó por HPLC preparativa proporcionando 7-((S)-2-aminopropanamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida, sal TFA (5.7 mg, 15%). Espectro de masas m/z 523.9 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 57-1 a 57-3, usando el ácido o cloruro de ácido apropiado.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
57-4	Ejemplo 54-16	2-acetamido-5-(2,6-difluorofenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	384.2 $(M+H)^+$
57-5	Ejemplo 54-5	7-acetamido-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	495.2 $(M+H)^+$
57-6	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(nicotinamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	558.1 $(M+H)^+$
57-7	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(isonicotinamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	558.1 $(M+H)^+$

57-8	Ejemplo 54-5	7-(3-(dimetilamino)propanamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	552.1 $(M+H)^+$
57-9	Ejemplo 54-5	7-(ciclopropanocarboxamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	521.0 $(M+H)^+$
57-10	Ejemplo 54-1	7-acrilamido-4-(2-fluorofenil)-9H-carbazol-1-carboxamida	374.0 $(M+H)^+$
57-11	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-(4-hidroxifenil)propanamido)-9H-carbazol-1-carboxamida	600.9 $(M+H)^+$
57-12	Ejemplo 54-5	2-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-ilamino)-2-oxoEtOAc	552.9 $(M+H)^+$

57-13	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(2-(piridin-4-il)acetamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	571.9 $(M+H)^+$
57-14	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-hidroxipropanamido)-9H-carbazol-1-carboxamida	524.9 $(M+H)^+$
57-15	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(2-(piridin-3-il)acetamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	571.9 $(M+H)^+$
57-16	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(4-morfolinobutanamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	608.0 $(M+H)^+$
57-17	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(1-metil-1H-imidazol-2-carboxamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	560.9 $(M+H)^+$

57-18	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-morfolinopropanamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	594.0 $(M+H)^+$
57-19	Ejemplo 54-5	7-(4-clorobenzamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	590.9 $(M+H)^+$
57-20	Ejemplo 54-5	7-(4-cianobenzamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	581.9 $(M+H)^+$
57-21	Ejemplo 54-5	7-(4-(dimetilamino)benzamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	599.9 $(M+H)^+$
57-22	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(4-metoxibenzamido)-9H-carbazol-1-carboxamida	586.9 $(M+H)^+$
57-23	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-isobutiramido-9H-carbazol-1-carboxamida	522.9 $(M+H)^+$

57-24	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-pivalamido-9H-carbazol-1-carboxamida	537.0 $(M+H)^+$
57-25	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(2-fenilacetamido)-9H-carbazol-1-carboxamida	570.9 $(M+H)^+$
57-26	Ejemplo 54-5	N-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-il)-1,2,3-tiadiazol-4-carboxamida	564.8 $(M+H)^+$
57-27	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(2-hidroxi-2-fenilacetamido)-9H-carbazol-1-carboxamida	586.9 $(M+H)^+$
57-28	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(pirimidin-5-carboxamido)-9H-carbazol-1-carboxamida	558.9 $(M+H)^+$
57-29	Ejemplo 54-5	7-(2-cianoacetamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	519.9 $(M+H)^+$

57-30	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-metoxipropanamido)-9H-carbazol-1-carboxamida	538.9 $(M+H)^+$
57-31	Ejemplo 54-5	7-(2-(1H-tetrazol-5-il)acetamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	562.8 $(M+H)^+$
57-32	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-(2-oxopirrolidin-1-il)propanamido)-9H-carbazol-1-carboxamida	591.9 $(M+H)^+$
57-33	Ejemplo 54-5	7-(3-(1H-imidazol-1-il)propanamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	574.9 $(M+H)^+$
57-34	Ejemplo 54-5	N-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-il)morfolin-2-carboxamida (preparada como la sal TFA)	565.9 $(M+H)^+$

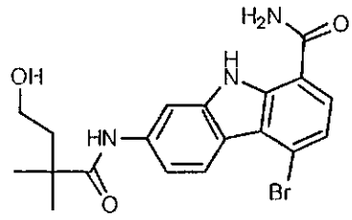
57-35	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(piperidin-3-carboxamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	564.0 $(M+H)^+$
57-36	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-((R)-piperidin-2-carboxamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	564.0 $(M+H)^+$
57-37	Ejemplo 54-5	7-(2-aminoacetamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	509.9 $(M+H)^+$
57-38	Ejemplo 54-5	7-(3-clorobenzamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	590.8 $(M+H)^+$
57-39	Ejemplo 54-5	7-benzamido-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	556.9 $(M+H)^+$
57-40	Ejemplo 54-5	7-(2-clorobenzamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	590.8 $(M+H)^+$

57-41	Ejemplo 54-5	7-(4-acetamidobenzamido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	613.9 $(M+H)^+$
57-42	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-metilbutanamido)-9H-carbazol-1-carboxamida	536.9 $(M+H)^+$
57-43	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(pirazin-2-carboxamido)-9H-carbazol-1-carboxamida	558.9 $(M+H)^+$
57-44	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(picolinamido)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	557.9 $(M+H)^+$
57-45	Ejemplo 54-5	N-(8-carbamoil-5-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-2-il)tiazol-4-carboxamida	563.8 $(M+H)^+$
57-46	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(2-(pirazin-2-il)acetamido)-9H-carbazol-1-carboxamida	572.9 $(M+H)^+$

57-47	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(2-(piridin-2-il)acetamido)-9H-carbazol-1-carboxamida	571.9 $(M+H)^+$
57-48	Ejemplo 54-14	7-isobutiramido-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	517.3 $(M+H)^+$
57-49	Ejemplo 54-14	4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-pivalamido-9H-carbazol-1-carboxamida	531.3 $(M+H)^+$
57-50	Ejemplo 54-15	4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-7-pivalamido-9H-carbazol-1-carboxamida (preparada como la sal TFA)	523.4 $(M+H)^+$
57-51	Ejemplo 54-2	4-bromo-7-pivalamido-9H-carbazol-1-carboxamida	388, 390 $(M+H)^+$
57-52	Ejemplo 54-2	4-bromo-7-(ciclopropanocarboxamido)-9H-carbazol-1-carboxamida	372, 374 $(M+H)^+$

Ejemplo 58-1

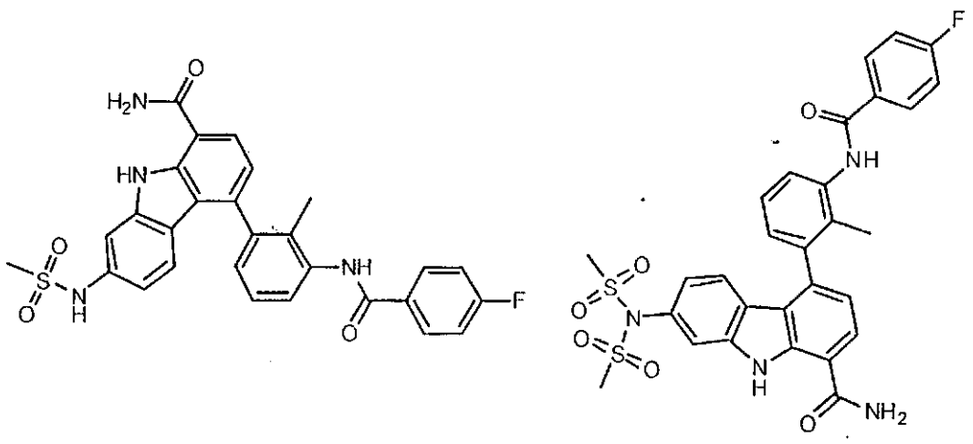
Preparación de 4-bromo-7-(4-hidroxi-2,2-dimetilbutanamido)-9H-carbazol-1-carboxamida



Una mezcla de bromhidrato de 7-amino-4-bromo-9H-carbazol-1-carboxamida (Ejemplo 54-2, 500 mg, 1.299 mmol) y 3,3-dimetildihidrofuran-2(3H)-ona (222 mg, 1.948 mmol) en THF (10 ml) se trató con trimetilaluminio (2 M en tolueno, 562 mg, 7.79 mmol) gota a gota a ta. La mezcla se calentó a 50°C durante 1.5 h, se enfrió hasta ta y se trató con agua. La mezcla se filtró a través de Celite y los sólidos se lavaron cuidadosamente con DCM y metanol. El filtrado se lavó con agua, se secó y se concentró y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de DCM hasta amoníaco al 10%-metanol-DCM) proporcionando 4-bromo-7-(4-hidroxi-2,2-dimetilbutanamido)-9H-carbazol-1-carboxamida como un sólido amarillo (250 mg, 46%). Espectro de masas m/z 418, 420 $(M+H)^+$.

Ejemplos 59-1 y 59-2

Preparación de 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(metilsulfonamido)-9H-carbazol-1-carboxamida y 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(N-(metilsulfonil)metilsulfonamido)-9H-carbazol-1-carboxamida



Se trató una solución de 7-amino-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (Ejemplo 54-5, 30 mg, 0.066 mmol) y TEA (0.018 ml, 0.133 mmol) en DCM-THF (2:1, 3 ml) con cloruro de metanosulfonilo (10 µl, 0.133 mmol). La mezcla se agitó a ta durante 1.5 h y se concentró y purificó por HPLC preparativa proporcionando 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(metilsulfonamido)-9H-carbazol-1-carboxamida como un sólido blanco (Ejemplo 59-1, 3.5 mg, 9%). RMN de ^{1}H (500 MHz, metanol-d_4) δ 7.91 - 8.01 (2 H, m), 7.83 (1 H, d, J=7.8 Hz), 7.45 (1 H, d, J=1.7 Hz), 7.42 (1 H, d, J=7.8 Hz), 7.34 (1 H, t, J=7.8 Hz), 7.12 - 7.20 (3 H, m), 6.95 (1 H, d, J=7.8 Hz), 6.88 (1 H, d, J=8.6 Hz), 6.73 (1 H, dd, J=8.5, 2.1 Hz), 2.85 (3 H, s), 1.90 (3 H, s).

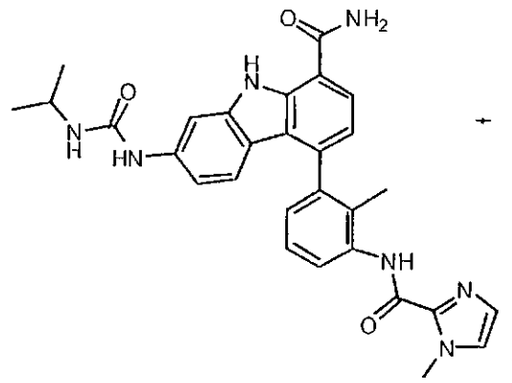
Espectro de masas m/z 531.0 $(M+H)^+$. También se obtuvo 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(N-(metilsulfonil)metilsulfonamido)-9H-carbazol-1-carboxamida como un sólido blanco (Ejemplo 59-2, 14 mg, 28%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.67 (1 H, s), 10.08 (1 H, s), 8.21 (1 H, s ancho), 7.97 - 8.08 (3 H, m), 7.79 (1 H, d, J=1.8 Hz), 7.53 (1 H, s ancho), 7.48 (1 H, d, J=7.3 Hz), 7.26 - 7.39 (3 H, m), 7.15 (1 H, d, J=6.5 Hz), 6.93 - 7.03 (2 H, m), 6.86 (1 H, d, J=8.3 Hz), 3.46 (6 H, d, J=9.0 Hz), 1.86 (3 H, s). Espectro de masas m/z 607.2 $(M-H)^-$.

El siguiente compuesto también se preparó usando el procedimiento mostrado en los Ejemplos 59-1 y 59-2, sustituyendo el Ejemplo 54-1 en lugar del Ejemplo 54-5 como material de partida:

Ejemplo	Nombre del compuesto	Espectro de masas
59-3	4-(2-fluorofenil)-7-(metilsulfonamido)-9H-carbazol-1-carboxamida	398.1 $(M+H)^+$

Ejemplo 60-1

Preparación de 7-(3-isopropilureido)-4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-9H-carbazol-1-carboxamida



Una solución de 7-amino-4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-9H-carbazol-1-carboxamida (Ejemplo 54-15, 29 mg, 0.066 mmol) y 2-isocianatopropano (0.019 ml, 0.198 mmol) en 1,2-dicloroetano (3 ml) se agitó a ta durante 2.4 h, luego a 50°C durante 2 h. Se añadió más 2-isocianatopropano y la mezcla se agitó a 40°C durante 16 h. La mezcla se concentró y purificó por HPLC. Las fracciones de efluente apropiadas se concentraron parcialmente, se trataron con NaHCO3 (ac) y se extrajeron con EtOAc. La fase orgánica se secó y se concentró proporcionando 7-(3-isopropilureido)-4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-9H-carbazol-1-carboxamida como un sólido rosa pálido (15 mg, 43%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.32 (1 H, s), 9.97 (1 H, s), 8.37 (1 H, s), 8.13 (1 H, s ancho), 7.88 (1 H, d, J=7.9 Hz), 7.81 (1 H, d, J=1.8 Hz), 7.76 (1 H, d, J=7.9 Hz), 7.40 - 7.48 (2 H, m), 7.38 (1 H, t, J=7.7 Hz), 7.13 (1 H, d,

J=7.5 Hz), 7.06 (1 H, s), 6.82 - 6.92 (2 H, m), 6.73 (1 H, d, J=8.3 Hz), 5.98 (1 H, d, J=7.5 Hz), 4.01 (3 H, s), 3.68 - 3.81 (1 H, m), 1.89 - 1.95 (3 H, m), 1.07 (6 H, d). Espectro de masas m/z 524.3 $(M+H)^+$.

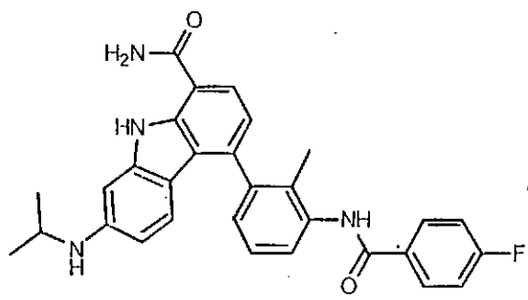
Los siguientes compuestos también se prepararon usando el procedimiento mostrado en el Ejemplo 60-1, sustituyendo el Ejemplo 54-5 en lugar del Ejemplo 54-15 como material de partida y usando el isocianato apropiado en lugar de 2-isocianatopropano.

Ejemplo	Nombre del compuesto	Espectro de masas
60-2	7-(3-(4-clorofenil)ureido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	605.8 $(M+H)^+$
60-3	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-fenilureido)-9H-carbazol-1-carboxamida	571.9 $(M+H)^+$
60-4	7-(3-etilureido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	523.9 $(M+H)^+$
60-5	7-(3-*terc*-butilureido)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	551.9 $(M+H)^+$

60-6	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(3-isopropilureido)-9H-carbazol-1-carboxamida	537.9 $(M+H)^+$

Ejemplo 61-1

Preparación de 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(isopropilamino)-9H-carbazol-1-carboxamida



Se trató una suspensión de 7-amino-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida (Ejemplo 54-5, 1 g, 2.210 mmol), acetona (3.4 ml, 20 eq.) y ácido acético (0.443 ml, 7.74 mmol) en 1,2-dicloroetano (220 ml) con triacetoxiborohidruro sódico (1.639 g, 7.74 mmol) y se agitó a 40°C durante 4 h. Se añadieron más triacetoxiborohidruro sódico (520 mg, 1.1 eq) y ácido acético (0.19 ml, 1.5 eq) y la mezcla se agitó durante la noche. La mezcla se trató con NaHCO3 (ac) y la fase orgánica se separó, se lavó con salmuera, se secó y se concentró. El residuo se purificó por HPLC preparativa. Las fracciones de efluente apropiadas se basificaron con NaHCO3 (ac) y se extrajeron con EtOAc. La fase orgánica se lavó con salmuera, se secó y se

concentró. El residuo se trituró con metanol proporcionando 4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(isopropilamino)-9H-carbazol-1-carboxamida como un sólido blanquecino (520 mg, 48%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.01 (1 H, s), 10.09 (1 H, s), 8.07 (3 H, dd, J=8.8, 5.3 Hz), 7.77 (1 H, d, J=7.9 Hz), 7.27 - 7.51 (5 H, m), 7.17 (1 H, d, J=6.2 Hz), 6.73 - 6.88 (2 H, m), 6.60 (1 H, d, J=8.3 Hz), 6.23 (1 H, dd, J=8.8, 2.2 Hz), 5.49 (1 H, d, J=7.9 Hz), 3.53 (1 H, dd, J=13.8, 6.4 Hz), 1.90 (3 H, s), 1.04 - 1.21 (6 H, m). Espectro de masas m/z 495.1 $(M+H)^+$.

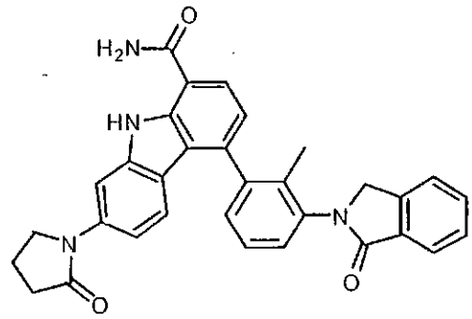
Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 61-1, usando el aldehído o cetona apropiados en lugar de acetona.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
61-2	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(1-metilpiperidin-4-ilamino)-9H-carbazol-1-carboxamida	550.1 $(M+H)^+$
61-3	Ejemplo 54-14	7-(isopropilamino)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	489.3 $(M+H)^+$

61-4	Ejemplo 54-15	7-(isopropilamino)-4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-9H-carbazol-1-carboxamida	481.2 $(M+H)^+$
61-5	Ejemplo 54-2	4-bromo-7-(isopropilamino)-9H-carbazol-1-carboxamida	346, 348 $(M+H)^+$
61-6	Ejemplo 54-2	(S)-4-bromo-7-((2,2-dimetil-1,3-dioxolan-4-ilmetil)amino)-9H-carbazol-1-carboxamida	418, 420 $(M+H)^+$

Ejemplo 62-1

Preparación de 4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida



Se trató una solución de 7-amino-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 54-14, 60 mg, 0.134 mmol) en THF (3 ml) con TEA (0.019 ml, 0.134 mmol) y una solución de cloruro de 4-bromobutanoilo (24.92 mg, 0.134 mmol) en DCM (1 ml). La mezcla se agitó a ta durante 40 min, luego se diluyó con DCM, se lavó con agua, se

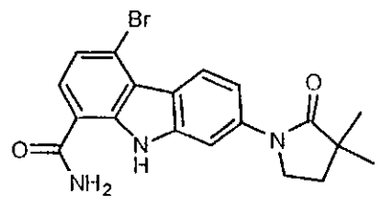
secó y se concentró. El residuo se disolvió en THF (5 ml) y se añadió a una suspensión de hidruro sódico (dispersión al 60% en aceite, 40 mg, 1.000 mmol, se lavó previamente con hexano) en THF (5 ml). La mezcla se agitó a ta durante la noche, luego se calentó a 65°C durante 30 min. La mezcla se enfrió hasta ta, se vertió en agua y se extrajo con EtOAc. La fase orgánica se secó y se concentró, y el residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 99:0.9:0.1 a 90:9:1 de DCM-metanol-hidróxido amónico acuoso al 28%) proporcionando 4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida (50 mg, 66%) como un sólido blanco. RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.67 (1 H, s), 7.96 (1 H, d, J=7.47 Hz), 7.91 (1 H, s), 7.74 (1 H, d, J=7.91 Hz), 7.62 - 7.67 (1 H, m), 7.52 - 7.58 (2 H, m), 7.45 - 7.48 (2 H, m), 7.38 - 7.42 (1 H, m), 7.22 (1 H, dd, J=8.79, 1.76 Hz), 7.11 (2 H, d, J=7.91 Hz), 4.86 (2 H, s), 3.90 - 4.02 (2 H, m), 2.66 (2 H, t, J=8.13 Hz), 2.16 - 2.25 (2 H, m), 1.94 (3 H, s). Espectro de masas m/z 515.3 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en el Ejemplo 62-1.

Ejemplo	Material de partida	Nombre del compuesto	Espectro de masas
62-2	Ejemplo 54-5	4-(3-(4-fluorobenzamido)-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	521.1 $(M+H)^+$
62-3	Ejemplo 54-15	4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	507.1 $(M+H)^+$
62-4	Ejemplo 54-2	4-bromo-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	372, 374 $(M+H)^+$

Ejemplo 63-1

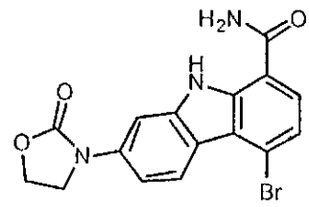
Preparación de 4-bromo-7-(3,3-dimetil-2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida



Una solución de 4-bromo-7-(4-hidroxi-2,2-dimetilbutanamido)-9H-carbazol-1-carboxamida (Ejemplo 58-1, 89 mg, 0.213 mmol), azodicarboxilato de dietilo (0.051 ml, 0.319 mmol) y trifenilfosfina (84 mg, 0.319 mmol) en THF (1 ml) se agitó a ta durante 1 h. Se añadieron más azodicarboxilato de dietilo (0.051 ml, 0.319 mmol) y trifenilfosfina (84 mg, 0.319 mmol), y se repitieron de nuevo estas condiciones después de 1 h más. La mezcla se diluyó con DCM, se lavó con NaHCO3 (ac) y agua y se secó y concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de DCM hasta 90:9:1 de DCM-metanol-hidróxido amónico acuoso al 28%), luego por HPLC preparativa. Las fracciones de efluente apropiadas se basificaron con hidróxido sódico acuoso 1 M y se extrajo dos veces con DCM. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron proporcionando 4-bromo-7-(3,3-dimetil-2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida como un sólido amarillo (44 mg, 52%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.66 (1 H, d, J=8.58 Hz), 7.94 (1 H, d, J=1.54 Hz), 7.73 (1 H, d, J=8.36 Hz), 7.55 (1 H, dd, J=8.80, 1.98 Hz), 7.39 (1 H, d, J=8.14 Hz), 3.97 (2 H, t, J=6.93 Hz), 2.11 (2 H, t, J=6.93 Hz), 1.28 (6 H, s). Espectro de masas m/z 400, 402 $(M+H)^+$.

Ejemplo 64-1

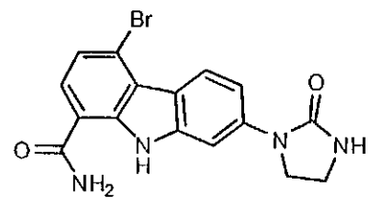
Preparación de 4-bromo-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 62-1, se convirtieron 7-amino-4-bromo-9H-carbazol-1-carboxamida (Ejemplo 54-2, 650 mg, 2.14 mmol) y cloroformiato de 2-bromoetilo (534 mg, 2.46 mmol) en 4-bromo-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida como un sólido amarillo claro (688 mg, 71%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.72 (1 H, s), 8.55 (1 H, d, J=8.88 Hz), 8.20 (1 H, s ancho), 8.02 (1 H, d, J=2.22 Hz), 7.82 (1 H, d, J=8.32 Hz), 7.52 - 7.60 (2 H, m), 7.42 (1 H, d, J=8.05 Hz), 4.47 - 4.52 (2 H, m), 4.14 - 4.20 (2 H, m). Espectro de masas m/z 374, 376 $(M+H)^+$.

Ejemplo 65-1

Preparación de 4-bromo-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida

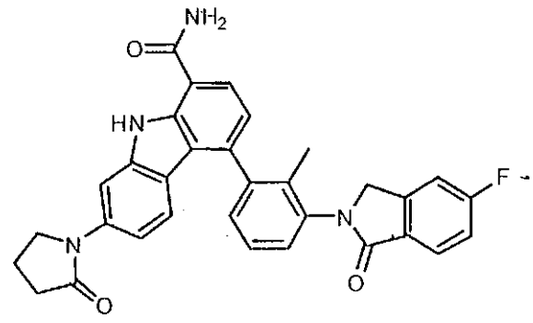


Se trató una solución de bromhidrato de 7-amino-4-

bromo-9H-carbazol-1-carboxamida (Ejemplo 54-2, 700 mg, 1.818 mmol) y DIEA (0.381 ml, 2.182 mmol) en DMF (5 ml) con 1-cloro-2-isocianatoetano (230 mg, 2.182 mmol). Después de 2 h, la mezcla se trató con NaH (60% en aceite mineral, 582 mg, 14.54 mmol). Después de 10 min, la mezcla se diluyó con agua. El precipitado se recogió por filtración, se secó, se trituró con metanol, se recogió de nuevo por filtración y se secó proporcionando 4-bromo-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida como un sólido amarillo claro (410 mg, 60%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.55 (1 H, s), 8.46 (1 H, d, J=8.80 Hz), 8.16 (1 H, s ancho), 7.92 (1 H, s), 7.77 (1 H, d, J=8.14 Hz), 7.63 - 7.68 (1 H, m), 7.52 (1 H, s ancho), 7.36 - 7.41 (1 H, m), 6.99 (1 H, s), 3.92 - 3.98 (2 H, m), 3.43 - 3.50 (2 H, m). Espectro de masas m/z 373, 375 $(M+H)^+$.

Ejemplo 66-1

Preparación de 4-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida

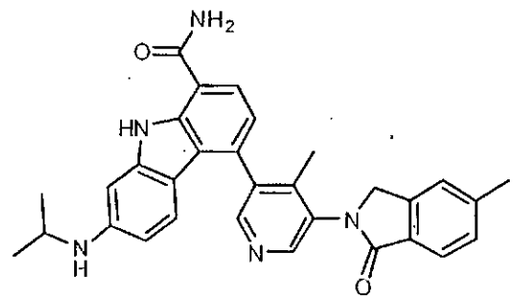


Usando el procedimiento del Ejemplo 31-1, se

convirtieron 4-bromo-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida (Ejemplo 62-4, 40 mg, 0.107 mmol) y 5-fluoro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-19, 51.3 mg, 0.140 mmol) en 4-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida (30 mg, 52%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.86 - 7.96 (3 H, m), 7.46 - 7.53 (2 H, m), 7.40 - 7.45 (1 H, m), 7.35 (1 H, dd, J=8.03, 2.01 Hz), 7.25 - 7.32 (1 H, m), 7.20 (1 H, dd, J=8.53, 2.01 Hz), 7.07 - 7.13 (2 H, m), 4.92 (2 H, s), 3.97 - 4.06 (2 H, m), 2.66 (2 H, t, J=8.03 Hz), 2.18 - 2.29 (2 H, m), 1.94 (3 H, s). Espectro de masas m/z 533.1 $(M+H)^+$.

Ejemplo 66-2

Preparación de 7-(isopropilamino)-4-(4-metil-5-(5-metil-1-oxoisoindolin-2-il)piridin-3-il)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 3-2, se convirtieron 4-bromo-7-(isopropilamino)-9H-carbazol-1-carboxamida (Ejemplo 61-5, 19.01 mg, 0.055 mmol) y 5-metil-2-(4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-3-il)isoindolin-1-ona (Intermedio 50-20, 20 mg,

0.055 mmol) en 7-(isopropilamino)-4-(4-metil-5-(5-metil-1-oxoisoindolin-2-il)piridin-3-il)-9H-carbazol-1-carboxamida (18 mg, 65%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.65 (1 H, s), 8.46 (1 H, s), 7.79 (1 H, d, J=7.92 Hz), 7.73 (1 H, d, J=7.70 Hz), 7.40 (1 H, s), 7.36 (1 H, d, J=7.70 Hz), 6.96 (1 H, d, J=7.92 Hz), 6.80 (1 H, d, J=8.58 Hz), 6.74 (1 H, d, J=1.98 Hz), 6.35 - 6.54 (1 H, m), 4.81 - 4.97 (2 H, m), 3.53 - 3.82 (1 H, m), 2.45 (3 H, s), 1.97 (3 H, s), 1.06 - 1.24 (6 H, m). Espectro de masas m/z 504.3 $(M+H)^+$.

Los siguientes compuestos se prepararon usando los procedimientos mostrados en los Ejemplos 66-1 y 66-2 y procedimientos estrechamente relacionados y usando los Ejemplos e Intermedios mostrados como materiales de partida.

Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
66-3	Ejemplo 55-3, Intermedio 50-1	4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-il)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	414.2 $(M+H)^+$
66-4	Ejemplo 61-5, Intermedio 50-1	4-(3-amino-2-metilfenil)-7-(isopropilamino)-9H-carbazol-1-carboxamida	373.3 $(M+H)^+$

66-5	Ejemplo 62-4, Intermedio 50-18	4-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	529.3 $(M+H)^+$
66-6	Ejemplo 62-4, Intermedio 51-2	4-(3-(5-cloro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	549.2 $(M+H)^+$
66-7	Ejemplo 62-4, Intermedio 50-1	4-(3-amino-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	399.1 $(M+H)^+$
66-8	Ejemplo 64-1, Intermedio 50-18	4-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	531.3 $(M+H)^+$
66-9	Ejemplo 64-1, Intermedio 51-2	4-(3-(5-cloro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	551.2 $(M+H)^+$
66-10	Ejemplo 64-1, Intermedio 50-4	4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	517.3 $(M+H)^+$

66-11	Ejemplo 65-1, Intermedio 50-4	4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	516.3 $(M+H)^+$
66-12	Ejemplo 65-1, Intermedio 50-18	4-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	530.3 $(M+H)^+$
66-13	Ejemplo 65-1, Intermedio 51-2	4-(3-(5-cloro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	550.3 $(M+H)^+$
66-14	Ejemplo 65-1, Intermedio 50-19	4-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	534.3 $(M+H)^+$
66-15	Ejemplo 61-6, Intermedio 50-4	7-(((S)-2,2-dimetil-1,3-dioxolan-4-il)metilamino)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	561.3 $(M+H)^+$

66-16	Ejemplo 62-4, Intermedio 50-8	4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	529.3 $(M+H)^+$
66-17	Ejemplo 62-4, Intermedio 50-44	4-(3-(ciclopropanocarboxamido)-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	467.2 $(M+H)^+$
66-18	Ejemplo 62-4, Intermedio 50-43	4-(2-metil-3-(2-oxopiperidin-1-il)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	481.3 $(M+H)^+$
66-19	Ejemplo 62-4, Intermedio 50-29	4-(2-metil-3-(1-oxoisoquinolin-2(1H)-il)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	527.4 $(M+H)^+$
66-20	Ejemplo 62-4, Intermedio 50-9	4-(3-(6-ciano-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	540.4 $(M+H)^+$
66-21	Ejemplo 64-1, Intermedio 50-44	4-(3-(ciclopropanocarboxamido)-2-metilfenil)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	469.2 $(M+H)^+$

66-22	Ejemplo 64-1, Intermedio 50-19	4-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	535.1 $(M+H)^+$
66-23	Ejemplo 64-1, Intermedio 50-29	4-(2-metil-3-(1-oxoisoquinolin-2(1H)-il)fenil)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	529.3 $(M+H)^+$
66-24	Ejemplo 65-1, Intermedio 50-29	4-(2-metil-3-(1-oxoisoquinolin-2(1H)-il)fenil)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	528.3 $(M+H)^+$
66-25	Ejemplo 64-1, Intermedio 51-1	4-(3-(6-cloro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	551.1 $(M+H)^+$
66-26	Ejemplo 64-1, Intermedio 50-8	4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	531.2 $(M+H)^+$
66-27	Ejemplo 65-1, Intermedio 50-8	4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	530.1 $(M+H)^+$

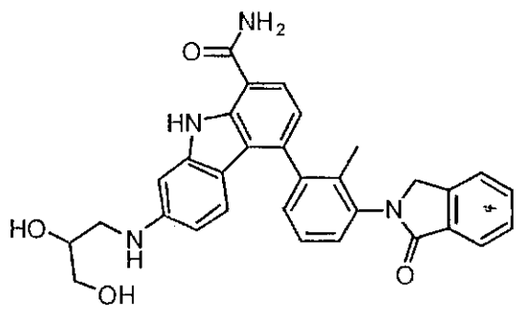
66-28	Ejemplo 65-1, Intermedio 51-1	4-(3-(6-cloro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	550.1 $(M+H)^+$
66-29	Ejemplo 65-1, Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	534.2 $(M+H)^+$
66-30	Ejemplo 57-51, Intermedio 50-8	4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-7-pivalamido-9H-carbazol-1-carboxamida	545.2 $(M+H)^+$
66-31	Ejemplo 57-51, Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-pivalamido-9H-carbazol-1-carboxamida	549.2 $(M+H)^+$
66-32	Ejemplo 57-51, Intermedio 50-18	4-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-7-pivalamido-9H-carbazol-1-carboxamida	545.2 $(M+H)^+$
66-33	Ejemplo 57-51, Intermedio 51-2	4-(3-(5-cloro-1-oxoisoindolin-2-il)-2-metilfenil)-7-pivalamido-9H-carbazol-1-carboxamida	565.2 $(M+H)^+$

66-34	Ejemplo 57-51, Intermedio 50-19	4-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-pivalamido-9H-carbazol-1-carboxamida	549.3 $(M+H)^+$
66-35	Ejemplo 58-1, Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(4-hidroxi-2,2-dimetilbutanamido)-9H-carbazol-1-carboxamida	579.4 $(M+H)^+$
66-36	Ejemplo 58-1, Intermedio 50-8	7-(4-hidroxi-2,2-dimetilbutanamido)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	575.2 $(M+H)^+$
66-37	Ejemplo 63-1, Intermedio 50-8	7-(3,3-dimetil-2-oxopirrolidin-1-il)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	557.4 $(M+H)^+$
66-38	Ejemplo 63-1, Intermedio 50-5	7-(3,3-dimetil-2-oxopirrolidin-1-il)-4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida	561.4 $(M+H)^+$

66-39	Ejemplo 57-52, Intermedio 50-4	7-(ciclopropanocarboxamido)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	515.1 $(M+H)^+$
66-40	Ejemplo 64-1, Intermedio 50-20	4-(4-metil-5-(5-metil-1-oxoisoindolin-2-il)piridin-3-il)-7-(2-oxooxazolidin-3-il)-9H-carbazol-1-carboxamida	532.2 $(M+H)^+$
66-41	Ejemplo 65-1, Intermedio 50-20	4-(4-metil-5-(5-metil-1-oxoisoindolin-2-il)piridin-3-il)-7-(2-oxoimidazolidin-1-il)-9H-carbazol-1-carboxamida	531.3 $(M+H)^+$

Ejemplo 67-1

Preparación de 7-(2,3-dihidroxipropilamino)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida

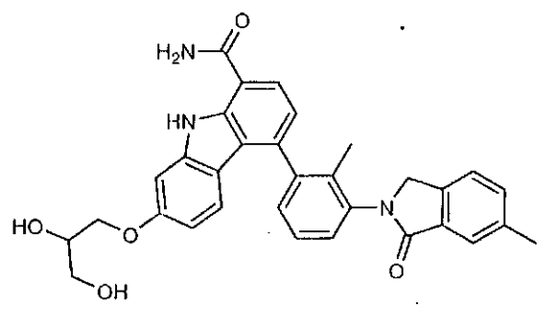


Se trató una solución de 7-(((S)-2,2-dimetil-1,3-dioxolan-4-il)metilamino)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 66-15, 50 mg, 0.089 mmol) en THF (1 ml) con ácido clorhídrico 2 M (4.46 ml,

8.92 mmol) y la mezcla se agitó a ta durante 1 h. La mezcla se basificó con hidróxido sódico acuoso 1 M y se extrajo dos veces con DCM. Las fases orgánicas reunidas, junto con algo de precipitado insoluble, se secaron y concentraron. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de DCM hasta 90:9:1 de DCM-metanol-hidróxido amónico acuoso al 28%) proporcionando 7-(2,3-dihidroxipropilamino)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido naranja (20 mg, 39%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.90 (1 H, d, J=7.49 Hz), 7.79 (1 H, d, J=7.77 Hz), 7.67 - 7.74 (2 H, m), 7.58 - 7.62 (1 H, m), 7.49 - 7.55 (2 H, m), 7.42 (1 H, dd, J=6.94, 1.94 Hz), 6.99 (1 H, d, J=7.77 Hz), 6.86 (1 H, d, J=8.32 Hz), 6.81 (1 H, d, J=1.94 Hz), 6.45 (1 H, dd, J=8.74, 1.80 Hz), 4.97 (2 H, s), 3.88 - 3.93 (1 H, m), 3.59 - 3.68 (2 H, m), 3.36 - 3.39 (1 H, m), 3.14 - 3.20 (1 H, m), 1.95 (3 H, s). Espectro de masas m/z 521.3 $(M+H)^+$.

Ejemplo 67-2

Preparación de 7-(2,3-dihidroxipropoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida racémica

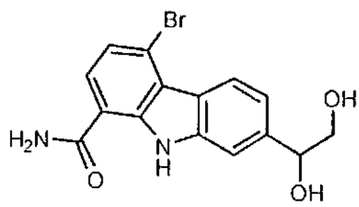


Una solución de 7-((2,2-dimetil-1,3-dioxolan-4-

il)metoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 44-4, 30 mg, 0.052 mmol) en metanol-DMSO se trató con TFA (0.5 ml) y la solución se agitó durante la noche a temperatura ambiente. La mezcla se concentró y se purificó por HPLC preparativa para proporcionar 7-(2,3-dihidroxipropoxi)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido blanco (9.4 mg, 32%). ^{1}H RMN (400 MHz, DMSO-d6) δ 11.39 (1H, s), 8.16 (1H, br. s.), 7.94 (1H, d, J = 7.7 Hz), 7.54 - 7.65 (3H, m), 7.49 (3H, t, J = 7.9 Hz), 7.25 - 7.38 (2 H, m), 6.99 (1H, d, J = 7.7 Hz), 6.92 (1H, d, J = 8.8 Hz), 6.60 (1H, d, J = 1.3 Hz), 4.82 - 5.01 (3 H, m), 4.60 - 4.71 (1H, m), 3.96 - 4.08 (1H, m), 3.76 - 3.96 (2 H, m), 3.48 (2 H, t, J = 5.6 Hz), 2.44 (3H, s), 1.77 - 1.88 (3 H, m). Espectro de masas m/z 536.1 $(M+H)^+$.

Ejemplo 68-1

Preparación de 4-bromo-7-((RS)-1,2-dihidroxietil)-9H-carbazol-1-carboxamida



Etapa 1 Se trató una solución de terc-butóxido potásico (3.40 g, 30.3 mmol) en THF (249 ml) a 0°C con bromuro de metiltrifenilfosfonio (8.79 g, 24.60 mmol),

formando una suspensión amarillo brillante. Después de 1 h, se añadió 4-bromo-7-formil-9H-carbazol-1-carboxamida (preparada de acuerdo con el procedimiento de Etapa 1 del Ejemplo 41-1, 4 g, 9.46 mmol), y la suspensión resultante se calentó hasta ta y se agitó durante 3 h. Se añadió agua y la mezcla se extrajo con EtOAc. La fase orgánica se lavó con salmuera, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con un gradiente de 70:30 de hexano-EtOAc hasta EtOAc). El material bruto se suspendió en metanol y el precipitado se recogió por filtración y se secó. El filtrado se concentró proporcionando más sólido que se recogió por filtración, se secó y se combinó con la primera tanda proporcionando 4-bromo-7-vinil-9H-carbazol-1-carboxamida como un sólido marrón claro (1.66 g, aproximadamente 90% de pureza, 50%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.68 (1 H, s), 8.52 (1 H, d, J=8.3 Hz), 8.06 - 8.29 (1 H, m), 7.79 - 7.88 (2 H, m), 7.58 (1 H, s ancho), 7.35 - 7.45 (2 H, m), 6.78 - 6.98 (1 H, m), 5.88 (1 H, d, J=17.6 Hz), 5.32 (1 H, d). Espectro de masas m/z 344, 346 $(M+H)^+$.

Etapa 2 Se trató una solución de 4-bromo-7-vinil-9H-carbazol-1-carboxamida (1.66 g, 4.74 mmol) y N-óxido de 4-metilmorfolina (0.833 g, 7.11 mmol) en acetona (172 ml) y agua (17.2 ml) con tetraóxido de osmio, 2.4% en peso en *terc*-butanol (0.238 ml, 0.019 mmol). La mezcla se agitó a ta

durante la noche, luego se trató con más N-óxido de 4-metilmorfolina (0.8 eq., 0.42 g) y solución de tetraóxido de osmio (0.004 eq., 0.2 ml). La mezcla se agitó durante un fin de semana, luego se trató con sulfito sódico (2.99 g, 23.70 mmol) y se agitó durante 30 min. La mezcla se filtró a través de una almohadilla de Celite y los sólidos se lavaron con acetona y THF. El filtrados se concentraron y se purificó por cromatografía en columna (eluyendo con un gradiente de 70:30 de EtOAc-hexano hasta EtOAc, seguido por 95:5 de EtOAc-metanol) proporcionando 4-bromo-7-((RS)-1,2-dihidroxietil)-9H-carbazol-1-carboxamida como un sólido blanquecino (1.47 g, 86%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.45 (1 H, s), 8.33 (1 H, d, J=8.1 Hz), 8.00 (1 H, s ancho), 7.58 - 7.68 (2 H, m), 7.35 (1 H, s ancho), 7.22 (1 H, d, J=8.1 Hz), 7.07 (1 H, d, J=8.4 Hz), 5.14 (1 H, d, J=4.0 Hz), 4.41 - 4.62 (2 H, m), 3.32 (2 H, t, J=5.7 Hz). Espectro de masas m/z 331, 333 $(M+H-H_2O)^+$.

Ejemplos 69-1 y 69-2

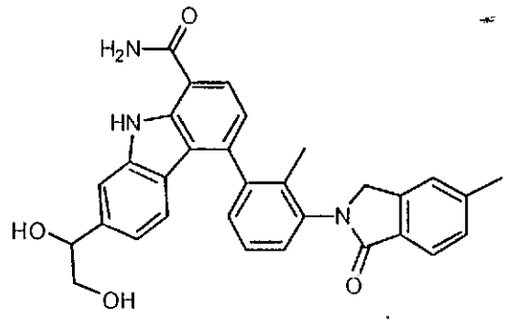
Preparación de enantiómeros purificados de 4-bromo-7-(1,2-dihidroxietil)-9H-carbazol-1-carboxamida

Se sometió 4-bromo-7-((RS)-1,2-dihidroxietil)-9H-carbazol-1-carboxamida (Ejemplo 68-1, 453 mg) a cromatografía quiral en fluido supercrítico (columna WhelkO-1(R,R) 25 x 3 cm, 5 mM a 35°C, eluyendo con dióxido de carbono-metanol 75:25 a 180 ml/min) proporcionando un enantiómero que eluye

más rápido (Ejemplo 69-1, 181 mg) y un enantiómero que eluye más lento (Ejemplo 69-2). Se determinó que las purezas enantioméricas eran >99.5% por cromatografía quiral analítica. No se determinaron las configuraciones absolutas.

Ejemplo 70-1

Preparación de 7-((R,S)-1,2-dihidroxietil)-4-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 3-2, se convirtieron 4-bromo-7-(1,2-dihidroxietil)-9H-carbazol-1-carboxamida (Ejemplo 68-1, 40 mg, 0.115 mmol) y 5-metil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-18, 41.6 mg, 0.115 mmol) en 7-((RS)-1,2-dihidroxietil)-4-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido blanco (30 mg, 49%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.96 (1 H, d, J=7.70 Hz), 7.76 (1 H, d, J=7.70 Hz), 7.66 (1 H, d, J=4.18 Hz), 7.47 - 7.57 (3 H, m), 7.38 - 7.44 (2 H, m), 7.02 - 7.12 (3 H, m), 4.81 - 4.85 (1 H, m), 3.68 - 3.72 (2 H, m), 2.42 (3 H, s), 1.91 (3 H, s). Espectro de masas m/z 488.3 $(M+H)^+$.

Los siguientes compuestos se prepararon usando los procedimientos mostrados en el Ejemplo 70-1 y procedimientos estrechamente relacionados, usando los Intermedios mostrados en lugar del Intermedio 50-18.

Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
70-2	Intermedio 53-1	7-((RS)-1,2-dihidroxietil)-4-(3-(4-fluorobenzamido)-2-metilfenil)-9H-carbazol-1-carboxamida	520.3 $(M+Na)^+$
70-3	Intermedio 50-4	7-((RS)-1,2-dihidroxietil)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	515.4 $(M+Na)^+$
70-4	Intermedio 50-1	4-(3-amino-2-metilfenil)-7-((RS)-1,2-dihidroxietil)-9H-carbazol-1-carboxamida	376.3 $(M+H)^+$
70-5	Intermedio 50-8	7-((RS)-1,2-dihidroxietil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	529.2 $(M+Na)^+$

70-6	Intermedio 50-5	7-((RS)-1,2-dihidroxietil)-4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida	533.2 $(M+Na)^+$
70-7	Intermedio 50-19	7-((RS)-1,2-dihidroxietil)-4-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida	492.3 $(M+H-H_2O)^+$
70-8	Intermedio 50-20	7-((RS)-1,2-dihidroxietil)-4-(4-metil-5-(5-metil-1-oxoisoindolin-2-il)piridin-3-il)-9H-carbazol-1-carboxamida (preparada como la sal TFA)	507.2 $(M+H)^+$
70-9	Intermedio 50-5	7-(1,2-dihidroxietil)-4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida[a]	532.2 $(M+Na)^+$
70-10	Intermedio 50-5	7-(1,2-dihidroxietil)-4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida[b]	532.2 $(M+Na)^+$

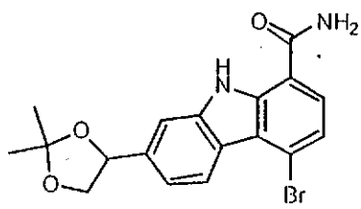
70-11	Intermedio 50-8	7-(1,2-dihidroxietil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida[a]	529.2 $(M+Na)^+$
70-12	Intermedio 50-8	7-(1,2-dihidroxietil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida[b]	529.2 $(M+Na)^+$
70-13	Intermedio 50-27	7-(1,2-dihidroxietil)-4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	523.3 $(M+H)^+$
70-14	Intermedio 50-26	4-(3-(6-cloro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(1,2-dihidroxietil)-9H-carbazol-1-carboxamida	539.0 $(M+H)^+$
70-15	Intermedio 50-13	7-(1,2-dihidroxietil)-4-(2-metil-3-(1-oxo-4,5,6,7-tetrahidro-1H-isoindol-2(3H)-il)fenil)-9H-carbazol-1-carboxamida	478.1 $(M+H-H_2O)^+$

70-16	Intermedio 50-6	7-(1,2-dihidroxietil)-4-(3-(5-metoxi-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida	504.1 (M+H-H_2O)$^+$
70-17	Intermedio 50-54	7-(1,2-dihidroxietil)-4-(2-metil-3-(quinazolin-4-ilamino)fenil)-9H-carbazol-1-carboxamida	504.1 (M+H)$^+$

[a] Preparado a partir del Ejemplo 69-1 [b] Preparado a partir del Ejemplo 69-2

Ejemplo 71-1

Preparación de 4-bromo-7-(2,2-dimetil-1,3-dioxolan-4-il)-9H-carbazol-1-carboxamida

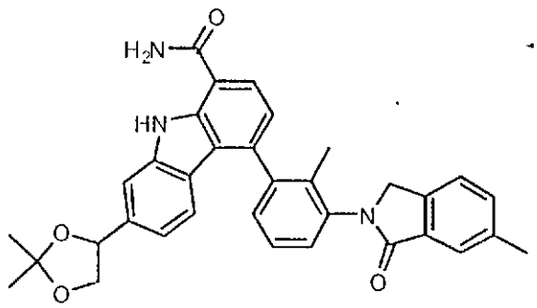


Se agitó a ta una mezcla de 4-bromo-7-(1,2-dihidroxietil)-9H-carbazol-1-carboxamida (Ejemplo 68-1, 50 mg, 0.143 mmol) y ácido p-toluenosulfónico monohidratado (8.2 mg, 0.043 mmol) en 2,2-dimetoxipropano (1.76 ml, 14.32 mmol). Se añadió DMF (0.5 ml) y la mezcla se agitó durante la noche. La mezcla se diluyó con EtOAc y se lavó con NaHCO3 (ac) y salmuera, luego se secó y concentró. El residuo se purificó

por cromatografía en columna (eluyendo con un gradiente de 75:25 hasta 50:50 de hexano-EtOAc) proporcionando 4-bromo-7-(2,2-dimetil-1,3-dioxolan-4-il)-9H-carbazol-1-carboxamida como un sólido amarillo claro (40 mg, 75% de pureza, 54%). Espectro de masas m/z 389, 391 $(M+H)^+$.

Ejemplo 72-1

Preparación de 7-(2,2-dimetil-1,3-dioxolan-4-il)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida

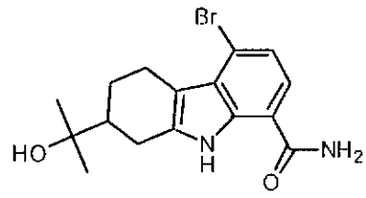


Usando el procedimiento del Ejemplo 3-2, se convirtieron 4-bromo-7-(2,2-dimetil-1,3-dioxolan-4-il)-9H-carbazol-1-carboxamida (Ejemplo 71-1, 40 mg, 0.077 mmol) y 6-metil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-8, 30.8 mg, 0.085 mmol) en 7-(2,2-dimetil-1,3-dioxolan-4-il)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida como un sólido blanco (23 mg, 88% de pureza, 43%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.60 (1 H, s), 8.21 (1 H, s ancho), 8.03 (1 H, d, J=7.7 Hz), 7.81 (1 H, s), 7.55 - 7.64 (3 H, m), 7.44 - 7.55 (3 H, m), 7.34 (1 H, dd, J=7.5, 1.1 Hz), 6.98 -

7.07 (2 H, m), 6.87 - 6.98 (1 H, m), 5.11 - 5.20 (1 H, m), 4.83 - 4.99 (2 H, m), 4.32 (1 H, ddd, J=8.0, 6.3, 1.5 Hz), 3.56 - 3.67 (1 H, m), 2.44 (3 H, s), 1.83 (3 H, d, J=2.9 Hz), 1.51 (3 H, d, J=3.7 Hz), 1.43 (3 H, s). Espectro de masas m/z 568.2 $(M+Na)^+$.

Ejemplo 73-1

Preparación de 5-bromo-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida



Se trató una solución de 5-bromo-8-carbamoil-2,3,4,9-tetrahidro-1H-carbazol-2-carboxilato de etilo (Intermedio 46-1, 2 g, 5.48 mmol) en THF (100 ml) enfriado en un baño de hielo con metil litio (1.6 M en éter dietílico, 17.11 ml, 27.4 mmol). Después de 1 h, la mezcla se trató lentamente con una mezcla de ácido clorhídrico 1 M (20 ml) y hielo (20 g). La fase orgánica se separó y la fase acuosa se extrajo dos veces con DCM. Las fases orgánicas reunidas se lavaron con agua y salmuera, se secaron y se concentraron. El residuo se trituró con DCM proporcionando 5-bromo-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida como un sólido amarillo claro (1.72 g, 89%). RMN de ^1H (400 MHz, metanol-d_4) δ 7.38 (1 H, d, J=8.14 Hz), 7.16

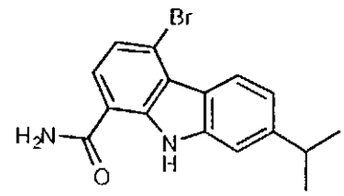
(1 H, d, J=8.14 Hz), 3.37 - 3.45 (1 H, m), 2.90 - 2.97 (1 H, m), 2.79 - 2.89 (1 H, m), 2.44 - 2.64 (1 H, m), 2.20 - 2.28 (1 H, m), 1.80 - 1.90 (1 H, m, J=11.94, 11.94, 4.95, 2.20 Hz), 1.41 - 1.53 (1 H, m, J=12.43, 12.43, 12.32, 5.28 Hz), 1.30 (6 H, s). Espectro de masas m/z 351, 353 $(M+H)^+$.

El siguiente compuesto también se preparó usando el procedimiento mostrado en el Ejemplo 73-1, sustituyendo el Intermedio 48-1 en lugar del Intermedio 46-1 como material de partida.

Ejemplo	Nombre del compuesto	Espectro de masas
73-2	4-bromo-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	329, 331 $(M+H-H_2O)^+$

Ejemplo 74-1

Preparación de 4-bromo-7-isopropil-9H-carbazol-1-carboxamida

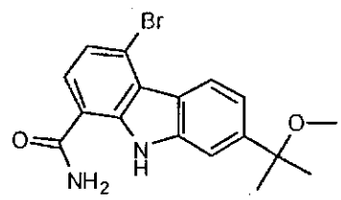


Se trató una suspensión de 4-bromo-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida (Ejemplo 73-2, 300 mg, 0.864 mmol) en DCM (2 ml) con trietilsilano (1.380 ml, 8.64 mmol) y luego lentamente con TFA (0.666 ml, 8.64

mmol) y la mezcla se agitó a ta durante 40 min. La suspensión resultante se diluyó con DCM y la solución resultante se lavó con NaHCO3 (ac). La fase orgánica se lavó con agua y salmuera y se secó y concentró dando 4-bromo-7-isopropil-9H-carbazol-1-carboxamida como un sólido blanco (280 mg, 98%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.50 (1 H, s ancho), 8.63 (1 H, d, J=8.1 Hz), 7.32 - 7.40 (3 H, m), 7.22 (1 H, dd, J=8.4, 1.3 Hz), 5.97 (2 H, s ancho), 3.02 - 3.18 (1 H, m), 1.35 (6 H, d, J=6.8 Hz). Espectro de masas m/z 331, 333 $(M+H)^+$.

Ejemplo 75-1

Preparación de 4-bromo-7-(2-metoxipropan-2-il)-9H-carbazol-1-carboxamida

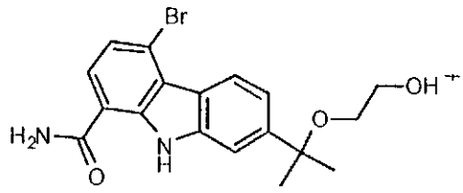


Se agitó a ta durante un fin de semana una solución de 4-bromo-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida (Ejemplo 73-2, 120 mg, 0.346 mmol) y TFA (0.013 ml, 0.173 mmol) en metanol (2 ml). La mezcla se diluyó con DCM, se lavó con hidróxido sódico acuoso 1 M y agua, se secó y se concentró. El residuo se combinó con el de otra reacción realizada con 20 mg del Ejemplo 73-2, y se purificó por cromatografía en columna (eluyendo con hexano-EtOAc) proporcionando 4-bromo-7-(2-metoxipropan-2-il)-9H-carbazol-1-

carboxamida como un sólido blanco (112 mg, 77%). RMN de ^1H (400 MHz, cloroformo-d) δ 10.53 (1 H, s ancho), 8.68 (1 H, d, J=8.36 Hz), 7.59 (1 H, d, J=1.10 Hz), 7.36 - 7.44 (3 H, m), 3.13 (3 H, s), 1.64 (6 H, s). Espectro de masas m/z 361, 363 $(M+H)^+$.

Ejemplo 75-2

Preparación de 4-bromo-7-(2-(2-hidroxietoxi)propan-2-il)-9H-carbazol-1-carboxamida



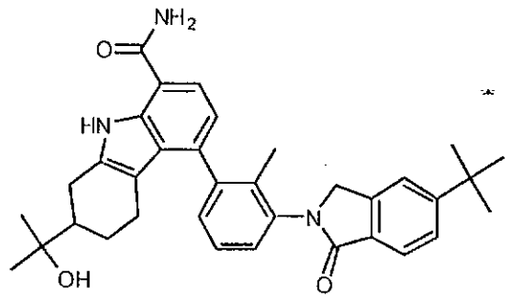
Se agitó a ta durante la noche una mezcla de 4-bromo-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida (Ejemplo 73-2, 300 mg, 0.864 mmol), ácido p-toluenosulfónico monohidratado (8.2 mg, 0.043 mmol) y etilenglicol (1.45 ml). La suspensión resultante se trató con NaHCO3 (ac) y se diluyó con agua. El precipitado se recogió por filtración, se lavó con agua y se secó proporcionando 4-bromo-7-(2-(2-hidroxietoxi)propan-2-il)-9H-carbazol-1-carboxamida como un sólido blanco (324 mg, 96%). RMN de ^1H (400 MHz, metanol-d_4) δ 8.65 (1 H, d, J=8.58 Hz), 7.77 (1 H, d, J=1.10 Hz), 7.75 (1 H, d, J=8.14 Hz), 7.44 (1 H, dd, J=8.36, 1.54 Hz), 7.40 (1 H, d), 3.69 (2 H, t, J=5.17 Hz), 3.32 - 3.34 (2 H, m), 1.68 (6 H, s). Espectro de masas m/z 413, 415 $(M+Na)^+$.

El siguiente compuesto también se preparó usando los procedimientos mostrados en los Ejemplos 75-1 y 75-2, usando el Ejemplo 70-11 en lugar del Intermedio 46-1 como material de partida.

Ejemplo	Nombre del compuesto	Espectro de masas
75-3	(RS)-7-(2-hidroxi-1-metoxietil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	543.1 $(M+Na)^+$

Ejemplo 76-1

Preparación de 5-(3-(5-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida

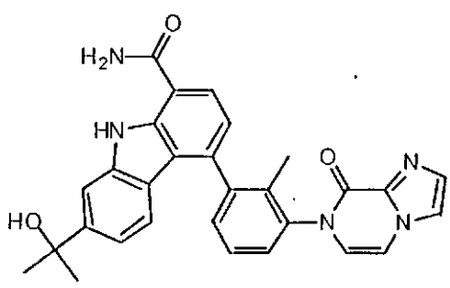


Usando el procedimiento del Ejemplo 31-1, se convirtieron 5-bromo-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (Ejemplo 73-1, 30 mg, 0.085 mmol) y 5-*terc*-butil-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-15, 51.9 mg, 0.128 mmol) en 5-(3-(5-*terc*-butil-1-

oxoisoindolin-2-il)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida (25 mg, 51%). RMN de ^{1}H (400 MHz, cloroformo-d) δ 10.05 (1 H, s), 7.88 (1 H, dd, J=8.35, 2.20 Hz), 7.53 - 7.59 (2 H, m), 7.36 (1 H, dd, J=7.47, 3.95 Hz), 7.28 - 7.33 (2 H, m), 7.26 - 7.28 (1 H, m), 6.90 (1 H, t, J=7.91 Hz), 4.69 - 4.83 (2 H, m), 2.90 (1 H, dd, J=16.04, 5.05 Hz), 2.44 - 2.67 (1 H, m), 1.96 - 2.23 (3 H, m), 1.93 (3 H, d, J=17.14 Hz), 1.74 - 1.89 (1 H, m), 1.58 - 1.68 (1 H, m), 1.39 (9 H, s), 1.31 - 1.37 (1 H, m), 1.23 - 1.26 (6 H, m). Espectro de masas m/z 550.3 $(M+H)^+$.

Ejemplo 76-2

Preparación de 7-(2-hidroxipropan-2-il)-4-(2-metil-3-(8-oxoimidazo[1,2-a]pirazin-7(8H)-il)fenil)-9H-carbazol-1-carboxamida



Usando el procedimiento del Ejemplo 3-2, se convirtieron 4-bromo-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida (Ejemplo 73-2, 30 mg, 0.086 mmol) y 7-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)imidazo[1,2-a]pirazin-8(7H)-ona (Intermedio 50-30, 48.6 mg, 0.104 mmol) en 7-(2-hidroxipropan-2-il)-4-(2-metil-

3-(8-oxoimidazo[1,2-a]pirazin-7(8H)-il)fenil)-9H-carbazol-1-carboxamida (4.3 mg, 8.5%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.20 (1 H, d, J=8.6 Hz), 7.94 (1 H, s ancho), 7.77 (1 H, dd, J=9.7, 7.9 Hz), 7.66 - 7.70 (1 H, m), 7.61 - 7.66 (1 H, m), 7.49 (1 H, dd, J=14.2, 5.8 Hz), 7.28 - 7.36 (3 H, m), 7.15 - 7.29 (2 H, m), 6.93 - 7.00 (1 H, m), 6.85 - 6.90 (1 H, m), 6.79 (1 H, dd, J=15.4, 7.7 Hz), 6.57 (1 H, d, J=8.4 Hz), 4.76 (1 H, d, J=12.4 Hz), 1.52 - 1.60 (3 H, m), 1.21 - 1.30 (6 H, m). Espectro de masas m/z 514.2 $(M+Na)^+$.

Los siguientes compuestos se prepararon usando los procedimientos mostrados en los Ejemplos 76-1 y 76-2 y procedimientos estrechamente relacionados, y usando los Ejemplos e Intermedios mostrados como materiales de partida.

Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
76-3	Ejemplo 73-1, Intermedio 50-14	5-(3-(6-*terc*-butil-1-oxoisoindolin-2-il)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	550.3 $(M+H)^+$
76-4	Ejemplo 73-1, Intermedio 50-5	5-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	512.4 $(M+H)^+$

76-5	Ejemplo 73-1, Intermedio 50-8	2-(2-hidroxipropan-2-il)-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	508.4 $(M+H)^+$
76-6	Ejemplo 73-1, Intermedio 50-49	2-(2-hidroxipropan-2-il)-5-(2-metil-3-(3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	495.4 $(M+H)^+$
76-7	Ejemplo 73-1, Intermedio 50-50	(Z)-5-(3-(furo[3,4-c]piridin-3(1H)-ilidenamino)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	495.4 $(M+H)^+$
76-8	Ejemplo 74-1, Intermedio 50-49	7-isopropil-4-(2-metil-3-(3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-il)fenil)-9H-carbazol-1-carboxamida	475.4 $(M+H)^+$
76-9	Ejemplo 74-1, Intermedio 50-50	(Z)-4-(3-(furo[3,4-c]piridin-3(1H)-ilidenamino)-2-metilfenil)-7-isopropil-9H-carbazol-1-carboxamida	475.4 $(M+H)^+$

76-10	Ejemplo 73-1, Intermedio 50-23	2-(2-hidroxipropan-2-il)-5-(2-metil-3-(2-metil-4-oxoquinazolin-3(4H)-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	421.4 $(M+H)^+$
76-11	Ejemplo 73-2, Intermedio 50-19	4-(3-(5-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	490.3 $(M+H-H_2O)^+$
76-12	Ejemplo 73-2, Intermedio 50-4	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	472.3 $(M+H-H_2O)^+$
76-13	Ejemplo 73-2, Intermedio 51-2	4-(3-(5-cloro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	506.2 $(M+H-H_2O)^+$
76-14	Ejemplo 73-2, Intermedio 50-8	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	486.3 $(M+H-H_2O)^+$

76-15	Ejemplo 73-2, Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	530.4 $(M+Na)^+$
76-16	Ejemplo 73-2, Intermedio 50-18	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(5-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	486.3 $(M+H-H_2O)^+$
76-17	Ejemplo 73-2, Intermedio 50-29	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(1-oxoisoquinolin-2(1H)-il)fenil)-9H-carbazol-1-carboxamida	502.4 $(M+H)^+$
76-18	Ejemplo 73-2, Intermedio 50-49	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-il)fenil)-9H-carbazol-1-carboxamida	491.4 $(M+H)^+$
76-19	Ejemplo 73-2, Intermedio 50-50	(Z)-4-(3-(furo[3,4-c]piridin-3(1H)-ilidenamino)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	491.4 $(M+H)^+$

76-20	Ejemplo 73-2, Intermedio 50-7	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(1-oxo-6-(trifluorometil)isoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	540.1 (M+H-H_2O)$^+$
76-21	Ejemplo 75-1, Intermedio 50-7	7-(2-metoxipropan-2-il)-4-(2-metil-3-(1-oxo-6-(trifluorometil)isoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	594.2 (M+Na)$^+$
76-22	Ejemplo 73-2, Intermedio 50-23	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(2-metil-4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	517.4 (M+H)$^+$
76-23	Ejemplo 73-2, Intermedio 50-17	4-(3-(4-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	490.3 (M+H-H_2O)$^+$
76-24	Ejemplo 73-2, Intermedio 50-16	4-(3-(7-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	490.4 (M+H-H_2O)$^+$

76-25	Ejemplo 73-2, Intermedio 50-24	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	503.4 $(M+H)^+$
76-26	Ejemplo 73-2, Intermedio 50-25	4-(3-(5-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	521.3 $(M+H)^+$
76-27	Ejemplo 73-2, Intermedio 50-26	4-(3-(6-cloro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	537.4 $(M+H)^+$
76-28	Ejemplo 73-2, Intermedio 50-28	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(6-metil-4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	517.4 $(M+H)^+$
76-29	Ejemplo 74-1, Intermedio 50-16	4-(3-(7-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-isopropil-9H-carbazol-1-carboxamida	492.4 $(M+H)^+$
76-30	Ejemplo 74-1, Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-isopropil-9H-carbazol-1-carboxamida	492.4 $(M+H)^+$

76-31	Ejemplo 74-1, Intermedio 50-7	7-isopropil-4-(2-metil-3-(1-oxo-6-(trifluorometil)isoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	542.4 $(M+H)^+$
76-32	Ejemplo 73-2, Intermedio 50-6	7-(2-hidroxipropan-2-il)-4-(3-(5-metoxi-1-oxoisoindolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida	502.1 $(M+H-H_2O)^+$
76-33	Ejemplo 73-2, Intermedio 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	521.4 $(M+H)^+$
76-34	Ejemplo 74-1, Intermedio 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-isopropil-9H-carbazol-1-carboxamida	505.4 $(M+H)^+$
76-35	Ejemplo 73-1, Intermedio 50-27	5-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	525.4 $(M+H)^+$

76-36	Ejemplo 73-2, Intermedio 50-1	4-(3-amino-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	374.1 $(M+H)^+$
76-37	Ejemplo 75-1, Intermedio 50-1	4-(3-amino-2-metilfenil)-7-(2-metoxipropan-2-il)-9H-carbazol-1-carboxamida	356.1 $(M+H-CH_3OH)^+$
76-38	Ejemplo 73-2, Intermedio 50-12	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(1-oxo-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-il)fenil)-9H-carbazol-1-carboxamida	478.1 $(M+H-H_2O)^+$
76-39	Ejemplo 73-2, Intermedio 50-13	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(1-oxo-4,5,6,7-tetrahidro-1H-isoindol-2(3H)-il)fenil)-9H-carbazol-1-carboxamida	476.2 $(M+H-H_2O)^+$
76-40	Ejemplo 73-1, Intermedio 50-24	2-(2-hidroxipropan-2-il)-5-(2-metil-3-(4-oxoquinazolin-3(4H)-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	507.4 $(M+H)^+$

76-41	Ejemplo 73-1, Intermedio 50-25	5-(3-(5-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	525.4 $(M+H)^+$
76-42	Ejemplo 73-1, Intermedio 50-26	5-(3-(6-cloro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	541.4 $(M+H)^+$
76-43	Ejemplo 73-1, Intermedio 50-28	2-(2-hidroxipropan-2-il)-5-(2-metil-3-(6-metil-4-oxoquinazolin-3(4H)-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	521.4 $(M+H)^+$
76-44	Ejemplo 73-1, Intermedio 50-7	2-(2-hidroxipropan-2-il)-5-(2-metil-3-(1-oxo-6-(trifluorometil)isoindolin-2-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	562.4 $(M+H)^+$

76-45	Ejemplo 73-1, Intermedio 50-12	2-(2-hidroxipropan-2-il)-5-(2-metil-3-(1-oxo-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	500.2 $(M+H)^+$
76-46	Ejemplo 73-1, Intermedio 50-13	2-(2-hidroxipropan-2-il)-5-(2-metil-3-(1-oxo-4,5,6,7-tetrahidro-1H-isoindol-2(3H)-il)fenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	498.2 $(M+H)^+$
76-47	Ejemplo 73-1, Intermedio 50-1	5-(3-amino-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	378.2 $(M+H)^+$
76-48	Ejemplo 75-2, Intermedio 50-7	7-(2-(2-hidroxietoxi)propan-2-il)-4-(2-metil-3-(1-oxo-6-(trifluorometil)isoindolin-2-il)fenil)-9H-carbazol-1-carboxamida	624.2 $(M+Na)^+$
76-49	Ejemplo 75-2, Intermedio 50-50	(Z)-4-(3-(furo[3,4-c]piridin-3(1H)-ilidenamino)-2-metilfenil)-7-(2-(2-hidroxietoxi)propan-2-il)-9H-carbazol-1-carboxamida	535.2 $(M+H)^+$

76-50	Ejemplo 75-1, Intermedio 50-49	7-(2-metoxipropan-2-il)-4-(2-metil-3-(3-oxo-1H-pirrolo[3,4-c]piridin-2(3H)-il)fenil)-9H-carbazol-1-carboxamida	473.1 (M+H-CH_3OH)$^+$
76-51	Ejemplo 73-2, Intermedio 50-48	4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	521.3 (M+H)$^+$
76-52	Ejemplo 75-2, Intermedio 50-24	7-(2-(2-hidroxietoxi)propan-2-il)-4-(2-metil-3-(4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	569.1 (M+Na)$^+$
76-53	Ejemplo 75-1, Intermedio 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(2-metoxipropan-2-il)-9H-carbazol-1-carboxamida	557.1 (M+Na)$^+$
76-54	Ejemplo 75-2, Intermedio 50-27	4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(2-(2-hidroxietoxi)propan-2-il)-9H-carbazol-1-carboxamida	587.1 (M+Na)$^+$

76-55	Ejemplo 75-1, Intermedio 50-24	7-(2-metoxipropan-2-il)-4-(2-metil-3-(4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	517.1 $(M+H)^+$
76-56	Ejemplo 75-1, Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-metoxipropan-2-il)-9H-carbazol-1-carboxamida	490.0 $(M+H-CH_3OH)^+$
76-57	Ejemplo 73-1, Intermedio 50-51	7-(2-hidroxipropan-2-il)-4-(3-(8-metoxi-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	533.2 $(M+H)^+$
76-58	Ejemplo 73-1, Intermedio 50-52	7-(2-hidroxipropan-2-il)-4-(3-(5-metoxi-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	533.2 $(M+H)^+$
76-59	Ejemplo 73-1, Intermedio 50-53	7-(2-hidroxipropan-2-il)-4-(3-(7-metoxi-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	533.2 $(M+H)^+$

76-60	Ejemplo 73-1, Intermedio 50-38	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(4-oxo-6-(trifluorometoxi)quinazolin-3(4H)-il)fenil)-9H-carbazol-1-carboxamida	587.1 $(M+H)^+$
76-61	Ejemplo 73-1, Intermedio 50-43	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(2-oxopiperidin-1-il)fenil)-9H-carbazol-1-carboxamida	456.2 $(M+H)^+$
76-62	Intermedio 73-2, Intermedio 50-9	4-(3-(6-ciano-1-oxoisoindoli-2-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	497.1 $(M+H-H_2O)^+$
76-63	Intermedio 73-1, Intermedio 50-48	5-(3-(8-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-2-(2-hidroxipropan-2-il)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	525.2 $(M+H)^+$
76-64	Intermedio 73-1, Intermedio 50-51	2-(2-hidroxipropan-2-il)-5-(3-(8-metoxi-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-2,3,4,9-tetrahidro-1H-carbazol-8-carboxamida	537.2 $(M+H)^+$

76-65	Intermedio 73-2, Intermedio 50-58	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(8-metil-4-oxoquinazolin-3(4H)-il)fenil)-9H-carbazol-8-carboxamida	517.2 $(M+H)^+$
76-66	Intermedio 73-2, Intermedio 50-59	7-(2-hidroxipropan-2-il)-4-(3-(6-metoxi-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-9H-carbazol-8-carboxamida	533.2 $(M+H)^+$
76-67	Intermedio 73-2, Intermedio 50-60	4-(3-(7-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-8-carboxamida	521.1 $(M+H)^+$

Ejemplo 76-15

^{1}H RMN (400 MHz, *CLOROFORMO-d*) δ ppm 10.60 (1 H, s), 7.70 (1 H, d, J=L lO Hz), 7.63 - 7.68 (2 H, m), 7.52 (1 H, dd, J=8.36, 4.40 Hz), 7.44 - 7.48 (2 H, m), 7.31 - 7.41 (2 H, m), 7.21 (1 H, dd, J=8.36, 1.76 Hz), 7.06 - 7.11 (2 H, m), 4.82 (2 H, s), 2.01 (1 H, s), 1.97 (3 H, s), 1.66 (6 H, s).

Ejemplo 76-25

^{1}H RMN (400 MHz, *CLOROFORMO-d*) δ ppm 10.57 (1 H, d, J=15.19 Hz), 8.38 - 8.43 (1 H, m), 8.15 (1 H, d, J=6.60 Hz), 7.78 - 7.84 (2 H, m), 7.68 - 7.72 (1 H, m), 7.66 (1 H, dd, J=7.92, 2.20 Hz), 7.42 - 7.60 (4 H, m), 7.27 (1 H, d), 7.12 - 7.16 (1 H, m), 6.90 - 7.08 (1 H, m), 1.91 (3 H, d, J=I 1.88

Hz), 1.63 - 1.67 (6 H, m).

Ejemplo 76-32

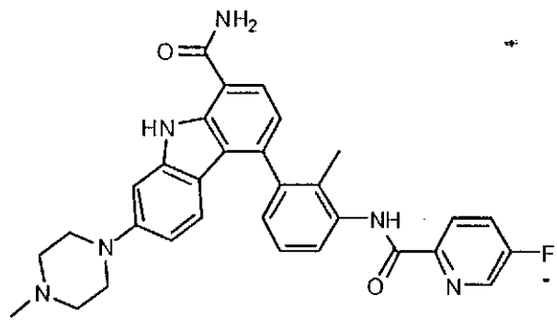
^{1}H RMN (400 MHz, *CLOROFORMO-d*) δ ppm 10.56 (1 H, s), 7.86 (1 H, d, J=8.36 Hz), 7.67 (1 H, d, J=I.32 Hz), 7.64 (1 H, d, J=7.92 Hz), 7.41 - 7.44 (2 H, m), 7.32 - 7.37 (1 H, m), 7.19 (1 H, dd, J=8.36, 1.54 Hz), 7.00 - 7.10 (4 H, m), 4.77 (2 H, s), 3.90 (3 H, s), 1.95 (3 H, s), 1.63 (6 H, s)

Ejemplo 76-51

^{1}H RMN (400 MHz, *CLOROFORMO-d*) δ ppm 10.59 (1 H, d), 8.18 (2 H, d, J=7.26 Hz), 7.71 (1 H, dd, J=10.01, 0.99 Hz), 7.65 (1 H, t, J=7.70 Hz), 7.41 - 7.59 (5 H, m), 7.20 - 7.29 (1 H, m), 7.07 (1 H, dd, J=17.83, 7.70 Hz), 6.87 - 7.15 (1 H, m), 2.00 (1 H, d, J=14.97 Hz), 1.89 (3 H, d, J=12.54 Hz), 1.64 (6 H, s).

Ejemplo 77-1

Preparación de 4-(3-(5-fluoropicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-il)-9H-carbazol-1-carboxamida

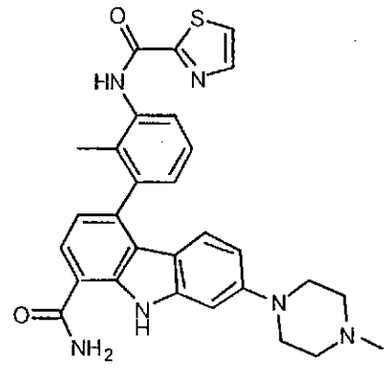


Se trató una mezcla de 4-(3-amino-2-metilfenil)-7-(4-metilpiperazin-1-il)-9H-carbazol-1-carboxamida, sal TFA (Ejemplo 66-3, 40 mg, 0.076 mmol), ácido 5-fluoropicolínico

(16.1 mg, 0.114 mmol), HOAT (15.5 mg, 0.114 mmol), y EDC (29.1 mg, 0.152 mmol) en acetonitrilo (4 ml) con DIEA (0.265 ml, 1.516 mmol). La solución resultante se agitó a ta durante 4 h, luego se concentró y purificó por HPLC preparativa proporcionando 4-(3-(5-fluoropicolinamido)-2-metilfenil)-7-(4-metilpiperazin-1-il)-9H-carbazol-1-carboxamida, sal TFA, como un sólido marrón claro (20 mg, 37%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.47 (1 H, d, J=2.8 Hz), 8.21 (1 H, dd, J=8.8, 4.5 Hz), 7.85 - 7.91 (1 H, m), 7.78 (1 H, d, J=7.8 Hz), 7.72 (1 H, td, J=8.6, 2.9 Hz), 7.33 (1 H, t, J=7.8 Hz), 7.09 - 7.16 (1 H, m), 7.07 (1 H, d, J=2.0 Hz), 6.91 (1 H, d, J=7.8 Hz), 6.81 (1 H, d, J=8.5 Hz), 6.59 (1 H, dd, J=8.8, 2.0 Hz), 3.71 - 3.84 (2 H, m), 3.44 - 3.55 (2 H, m), 3.10 - 3.19 (2 H, m), 2.91 - 3.04 (2 H, m), 2.87 (3 H, s), 1.93 (3 H, s). Espectro de masas m/z 537.1 $(M+H)^+$.

Ejemplo 77-2

Preparación de N-(3-(1-carbamoil-7-(4-metilpiperazin-1-il)-9H-carbazol-4-il)-2-metilfenil)tiazol-2-carboxamida



Se trató una solución de 4-(3-amino-2-metilfenil)-

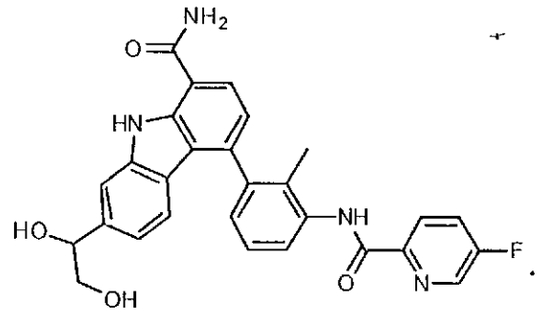
7-(4-metilpiperazin-1-il)-9H-carbazol-1-carboxamida, sal TFA (Ejemplo 66-3, 30 mg, 0.047 mmol) y TEA (0.026 ml, 0.187 mmol) en DCM-THF (2:1, 3 ml) con cloruro de tiazol-2-carbonilo, sal clorhidrato (8.3 mg, 0.056 mmol) y se agitó a ta durante 1.5 h. La mezcla se concentró y purificó por HPLC preparativa proporcionando N-(3-(1-carbamoil-7-(4-metilpiperazin-1-il)-9H-carbazol-4-il)-2-metilfenil)tiazol-2-carboxamida, sal TFA, como un sólido blanco (19 mg, 56%). RMN de ^1H (500 MHz, DMSO-d_6) δ 11.24 (1 H, s), 10.38 (1 H, s), 8.09 - 8.14 (1 H, m), 8.07 (1 H, d, J=3.1 Hz), 8.04 (1 H, d, J=3.1 Hz), 7.86 (1 H, d, J=8.0 Hz), 7.57 (1 H, d, J=7.5 Hz), 7.41 (1 H, s ancho), 7.34 (1 H, t, J=7.8 Hz), 7.23 (1 H, d, J=1.9 Hz), 7.13 (1 H, d, J=6.7 Hz), 6.87 (1 H, d, J=7.8 Hz), 6.75 (1 H, d, J=8.9 Hz), 6.63 (1 H, dd, J=8.9, 2.2 Hz), 3.69 - 3.79 (2 H, m), 3.43 - 3.50 (2 H, m), 3.06 - 3.18 (2 H, m), 2.87 - 2.97 (2 H, m), 2.79 (3 H, s ancho), 1.87 (3 H, s). Espectro de masas m/z 525.1 $(M+H)^+$.

El siguiente compuesto también se preparó usando el procedimiento mostrado en el Ejemplo 77-1:

Ejemplo	Nombre del compuesto	Espectro de masas
77-3	N-(3-(1-carbamoil-7-(4-metilpiperazin-1-il)-9H-carbazol-4-il)-2-metilfenil)-5-metiltiazol-2-carboxamida (preparada como la sal TFA)	539.1 $(M+H)^+$

Ejemplo 78-1

Preparación de 7-(1,2-dihidroxietil)-4-(3-(5-fluoropicolinamido)-2-metilfenil)-9H-carbazol-1-carboxamida



Se trató una solución de 4-(3-amino-2-metilfenil)-7-(1,2-dihidroxietil)-9H-carbazol-1-carboxamida (Ejemplo 70-4, 28 mg, 0.075 mmol), ácido 5-fluoropicolínico (15.8 mg, 0.112 mmol), HOAT (18.3 mg, 0.134 mmol) y EDC (28.6 mg, 0.149 mmol) en acetonitrilo-THF (2:1, 3 ml) con DIEA (0.039 ml, 0.224 mmol) y se agitó a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa. El residuo de la concentración de las fracciones de efluente apropiadas se repartieron entre NaHCO3 (ac) y EtOAc y la fase orgánica se lavó con salmuera, se secó y se concentró proporcionando 7-(1,2-dihidroxietil)-4-(3-(5-fluoropicolinamido)-2-metilfenil)-9H-carbazol-1-carboxamida como un sólido blanquecino (20 mg, 53%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.47 (1 H, s), 10.38 (1 H, s), 8.74 (1 H, d, J=2.6 Hz), 8.28 (1 H, dd, J=8.8, 4.8 Hz), 8.10 - 8.23 (1 H, m), 7.95 - 8.04 (2 H, m), 7.87 - 7.93 (1 H, m), 7.72 (1 H, s), 7.46 - 7.52 (1 H,

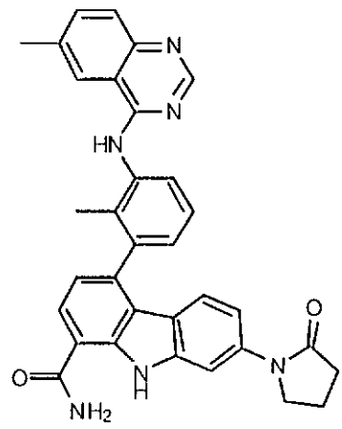
m), 7.43 (1 H, t, J=7.6 Hz), 7.18 (1 H, d, J=6.6 Hz), 6.97 (1 H, d, J=7.7 Hz), 6.82 - 6.92 (2 H, m), 5.22 (1 H, t, J=3.5 Hz), 4.66 - 4.72 (1 H, m), 4.56 - 4.64 (1 H, m), 3.44 (2 H, t, J=6.1 Hz), 1.97 (3 H, s). Espectro de masas m/z 521.3 $(M+Na)^+$.

El siguiente compuesto también se preparó usando el procedimiento mostrado en el Ejemplo 78-1.

Ejemplo	Nombre del compuesto	Espectro de masas
78-2	7-(1,2-dihidroxietil)-4-(2-metil-3-(1-metil-1H-imidazol-2-carboxamido)fenil)-9H-carbazol-1-carboxamida	484.4 $(M+H)^+$

Ejemplo 79-1

Preparación de 4-(2-metil-3-(6-metilquinazolin-4-ilamino)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida



Una suspensión de 4-cloro-6-metilquinazolina

(preparada por el procedimiento usado en las Etapas 1 y 2 de la preparación del Intermedio 32-1, 16.81 mg, 0.094 mmol) y 4-(3-amino-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida (Ejemplo 65-1, 25 mg, 0.063 mmol) en isopropanol (0.75 ml) se trató con cloruro de hidrógeno (4 M en 1,4-dioxano) (0.019 ml, 0.075 mmol) y se calentó por radiación en microondas en un tubo sellado a 140°C durante 45 min. La mezcla se concentró y el residuo se purificó por HPLC preparativa. El residuo de la concentración de las fracciones de efluente apropiadas se repartió entre NaHCO3 (ac) y EtOAc, y la fase acuosa se extrajo dos veces más con EtOAc. Las fases orgánicas reunidas se secaron y concentraron proporcionando 4-(2-metil-3-(6-metilquinazolin-4-ilamino)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida como un sólido color castaño (7.4 mg, 20%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 8.43 (1 H, s), 8.22 (1 H, s), 7.97 (1 H, d, J=7.7 Hz), 7.84 (1 H, d, J=1.3 Hz), 7.67 - 7.77 (2 H, m), 7.46 - 7.58 (2 H, m), 7.36 (1 H, dd, J=7.3, 1.5 Hz), 7.21 - 7.30 (2 H, m), 7.13 (1 H, d, J=7.9 Hz), 3.98 - 4.07 (2 H, m), 2.65 (2 H, t, J=8.1 Hz), 2.60 (3 H, s), 2.18 - 2.28 (2 H, m), 1.96 (3 H, s). Espectro de masas m/z 541.5 $(M+H)^+$.

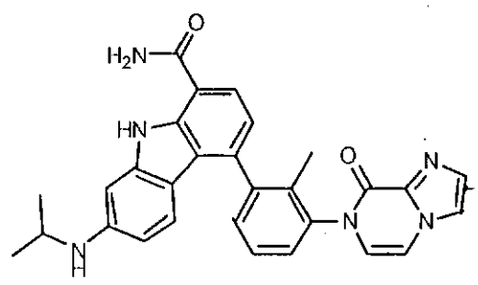
Los siguientes compuestos también se prepararon usando el procedimiento mostrado en el Ejemplo 79-1, usando la cloroquinazolina apropiada en lugar de 4-cloro-6-

metilquinazolina.

Ejemplo	Nombre del compuesto	Espectro de masas
79-2	4-(2-metil-3-(7-metilquinazolin-4-ilamino)fenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	541.5 $(M+H)^+$
79-3	4-(3-(6-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	545.4 $(M+H)^+$
79-4	4-(3-(7-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(2-oxopirrolidin-1-il)-9H-carbazol-1-carboxamida	545.4 $(M+H)^+$

Ejemplo 80-1

Preparación de 7-(isopropilamino)-4-(2-metil-3-(8-oxoimidazo[1,2-a]pirazin-7(8H)-il)fenil)-9H-carbazol-1-carboxamida



Etapa 1 Una solución de

tris(dibencilidenoacetona)dipaladio (33 mg, 0.036 mmol) y triciclohexilfosfina (0.182 ml, 0.173 mmol) en 1,4-dioxano (9 ml), purgada con nitrógeno, se combinó con 4-bromo-7-(isopropilamino)-9H-carbazol-1-carboxamida (Ejemplo 61-5, 250 mg, 0.722 mmol), 4.4,4',4',5.5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (202 mg, 0.794 mmol) y acetato potásico (142 mg, 1.444 mmol). La mezcla se calentó con agitación en un tubo sellado a 90°C durante 5.5 h. La mezcla se enfrió hasta ta y se repartió entre agua y EtOAc. La fase acuosa se extrajo dós veces con EtOAc, y las fases orgánicas reunidas se secaron y concentraron. El residuo se sometió a cromatografía en columna (eluyendo con un gradiente de 60:40 hasta 20:80 de hexano-EtOAc) proporcionando 7-(isopropilamino)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-9H-carbazol-1-carboxamida como un sólido amarillo impuro (aproximadamente 35% de pureza, 170 mg, 21%), que se usó sin purificación posterior. Espectro de masas m/z 394.2 $(M+H)^+$.

Etapa 2 Una suspensión de 7-(isopropilamino)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-9H-carbazol-1-carboxamida impura (60 mg, 0.053 mmol), sal TFA de 7-(3-bromo-2-metilfenil)imidazo[1,2-a]pirazin-8(7H)-ona (Intermedio 11-1, 22.3 mg, 0.053 mmol), tetraquis(trifenilfosfina)paladio (3.1 mg, 0.003 mmol) y carbonato sódico acuoso 2 M (0.080 ml, 0.160 mmol) en tolueno-etanol (4:1, 1.3 ml) se calentó en nitrógeno a 90 °C

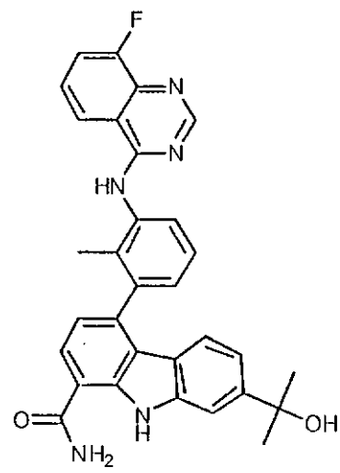
durante la noche. La mezcla se concentró y el residuo se purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron y el residuo se repartió entre NaHCO3 (ac) y EtOAc. La fase orgánica se secó y se concentró proporcionando 7-(isopropilamino)-4-(2-metil-3-(8-oxoimidazo[1,2-a]pirazin-7(8H)-il)fenil)-9H-carbazol-1-carboxamida como un sólido amarillo claro. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 10.83 - 10.99 (1 H, m), 8.01 (1 H, s ancho), 7.83 (1 H, dd, J=4.5, 1.0 Hz), 7.68 - 7.77 (1 H, m), 7.59 - 7.67 (1 H, m), 7.38 - 7.50 (3 H, m), 7.24 - 7.38 (2 H, m), 7.08 (1 H, dd, J=8.4, 5.9 Hz), 6.76 - 6.87 (1.55 H, m), 6.73 (1 H, dd, J=7.4, 1.9 Hz), 6.48 (0.45 H, d, J=8.8 Hz), 6.13 - 6.29 (1 H, m), 5.44 (1 H, t, J=8.3 Hz), 3.40 - 3.55 (1 H, m), 1.70 (3 H, d, J=11.4 Hz), 1.09 (6 H, td, J=5.8, 3.4 Hz). Espectro de masas m/z 491.3 $(M+H)^+$.

El siguiente compuesto también se preparó usando procedimientos mostrados en el Ejemplo 80-1, usando el Intermedio 29-1 en lugar del Intermedio 11-1.

Ejemplo	Nombre del compuesto	Espectro de masas
80-2	7-(isopropilamino)-4-(2-metil-3-(2-metil-8-oxoimidazo[1,2-a]pirazin-7(8H)-il)fenil)-9H-carbazol-1-carboxamida	505.2 $(M+H)^+$

Ejemplo 81-1

Preparación de 4-(3-(8-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida



Etapa 1 Una solución de tris(dibencilidenoacetona)dipaladio (274 mg, 0.30 mmol) y triciclohexilfosfina (1.51 ml, 1.438 mmol) en 1,4-dioxano (75 ml), se purgó con nitrógeno, se combinó con 4-bromo-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida (Ejemplo 73-1, 2.08 g, 5.99 mmol), 4.4,4',4',5.5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (1.826 g, 7.19 mmol) y acetato potásico (1.176 g, 11.98 mmol). La mezcla se calentó con agitación en un tubo sellado a 90°C durante 5 h. La mezcla se enfrió hasta ta, se filtró a través de Celite y los sólidos se lavaron con EtOAc. El filtrado se concentró y el residuo se sometió a cromatografía en columna (eluyendo con un gradiente de 60:40 de hexano-EtOAc hasta EtOAc)

proporcionando 7-(2-hidroxipropan-2-il)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-9H-carbazol-1-carboxamida como un sólido amarillo impuro (2.03 g, 72%), que se usó sin purificación posterior. Espectro de masas m/z 377.2 $(M+H-H_2O)^+$.

Etapa 2 Una mezcla de 7-(2-hidroxipropan-2-il)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-9H-carbazol-1-carboxamida (aproximadamente 60% de pureza, 35 mg, 0.053 mmol), N-(3-bromo-2-metilfenil)-8-fluoroquinazolin-4-amina (Intermedio 32-7, 17.69 mg, 0.053 mmol) y carbonato sódico acuoso 2 M (0.067 ml, 0.133 mmol) en tolueno (0.8 ml) y etanol (0.200 ml) se purgó con argon, se trató con tetraquis(trifenilfosfina)paladio (3.1 mg, 0.003 mmol) y se calentó a 90°C en un tubo sellado durante 16.5 h. La mezcla se enfrió hasta ta y se concentró. El residuo se purificó por HPLC preparativa y las fracciones de efluente apropiadas se trataron con NaHCO3 (ac) y se concentraron parcialmente a ta. La suspensión acuosa resultante se filtró y el precipitado se lavó con agua y se secó proporcionando 4-(3-(8-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida como un sólido blanco (18.0 mg, 61%). RMN de ^1H (400 MHz, DMSO-d_6) δ 11.41 (1 H, s), 10.08 (1 H, s), 8.56 (1 H, s), 8.35 (1 H, d, J=8.4 Hz), 8.16 (1 H, s ancho), 7.99 (1 H, d, J=7.9 Hz), 7.87 (1 H, s), 7.70 (1 H, dd, J=10.2, 8.3 Hz), 7.60 (1 H, td, J=8.1, 5.2 Hz), 7.42 - 7.54 (3 H, m), 7.28 (1 H, dd, J=7.3, 1.3 Hz), 7.11 (2

H, s), 7.01 (1 H, d, J=7.7 Hz), 5.00 (1 H, s), 1.85 (3 H, s), 1.49 (6 H, s). Espectro de masas m/z 520.1 $(M+H)^+$.

Los siguientes compuestos se prepararon usando los procedimientos mostrados en el Ejemplo 81-1 y procedimientos estrechamente relacionados, y usando los Intermedios mostrados en lugar del Intermedio 32-7.

Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
81-2	Intermedio 29-2	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(2-metil-8-oxoimidazo[1,2-a]pirazin-7(8H)-il)fenil)-9H-carbazol-1-carboxamida	506.3 $(M+H)^+$
81-3	Intermedio 29-1	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(3-metil-8-oxoimidazo[1,2-a]pirazin-7(8H)-il)fenil)-9H-carbazol-1-carboxamida	506.3 $(M+H)^+$
81-4	Intermedio 31-1	4-(3-((1H-indazol-1-il)metil)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	489.3 $(M+H)^+$
81-5	Intermedio 31-2	4-(3-((2H-indazol-2-il)metil)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	489.3 $(M+H)^+$

81-6	Intermedio 31-3	4-(3-((1H-benzo[d]imidazol-1-il)metil)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	489.3 $(M+H)^+$
81-7	Intermedio 30-1	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(2-oxo-3-m-tolilimidazolidin-1-il)fenil)-9H-carbazol-1-carboxamida	555.3 $(M+Na)^+$
81-8	Intermedio 32-2	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(6-metilquinazolin-4-ilamino)fenil)-9H-carbazol-1-carboxamida	516.4 $(M+H)^+$
81-9	Intermedio 32-5	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(7-metilquinazolin-4-ilamino)fenil)-9H-carbazol-1-carboxamida	516.5 $(M+H)^+$
81-10	Intermedio 32-4	4-(3-(6-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	520.4 $(M+H)^+$
81-11	Intermedio 32-3	4-(3-(7-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	520.4 $(M+H)^+$

81-12	Intermedio 32-8	7-(2-hidroxipropan-2-il)-4-(3-(6-metoxiquinazolin-4-ilamino)-2-metilfenil)-9H-carbazol-1-carboxamida	532.1 $(M+H)^+$
81-13	Intermedio 32-1	7-(2-hidroxipropan-2-il)-4-(3-(7-metoxiquinazolin-4-ilamino)-2-metilfenil)-9H-carbazol-1-carboxamida	532.1 $(M+H)^+$
81-14	Intermedio 32-6	4-(3-(5-fluoroquinazolin-4-ilamino)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	520.1 $(M+H)^+$
81-15	Intermedio 41-2	7-(2-hidroxipropan-2-il)-4-(3-(6-metoxi-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)-2-metilfenil)-9H-carbazol-1-carboxamida	535.2 $(M+H)^+$
81-16	Intermedio 41-4	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(1-oxo-1,2,3,4-tetrahidroisoquinolin-5-iloxi)fenil)-9H-carbazol-1-carboxamida	502.1 $(M+H-H_2O)^+$

81-17	Intermedio 41-3	4-(3-(5-hidroxi-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	542.1 $(M+Na)^+$
81-18	Intermedio 41-5	4-(3-(7-cloro-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	538.2 $(M+H)^+$
81-19	Intermedio 41-1	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(1-oxo-3,4-dihidroisoquinolin-2(1H)-il)fenil)-9H-carbazol-1-carboxamida	504.1 $(M+H)^+$
81-20	Intermedio 41-6	4-(3-(6-fluoro-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	522.1 $(M+H)^+$
81-21	Intermedio 41-7	4-(3-(3,4-dimetil-2-oxo-2,4-dihidro-1H-pirrol-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	490.1 $(M+Na)^+$

81-22	Intermedio 41-8	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(3-metil-2-oxopiridin-1(2H)-il)fenil)-9H-carbazol-1-carboxamida	466.1 $(M+H)^+$
81-23	Intermedio 41-9	4-(3-(4,4-dimetil-2-oxopirrolidin-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	452.1 $(M+H-H_2O)^+$
81-24	Intermedio 42-1	7-(2-hidroxipropan-2-il)-4-(3-(isobenzofuran-1(3H)-ilidenometil)-2-metilfenil)-9H-carbazol-1-carboxamida	471.0 $(M+H-H_2O)^+$
81-25	2,6-dibromo-tolueno	4-(3-bromo-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	419, 421 $(M+H)^+$
81-26	Intermedio 32-9	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(quinazolin-4-ilamino)fenil)-9H-carbazol-1-carboxamida	502.2 $(M+H)^+$
81-27	Intermedio 41-10	ácido 1-(3-(1-carbamoil-7-(2-hidroxipropan-2-il)-9H-carbazol-4-il)-2-metilfenil)-5-oxopirrolidin-3-carboxílico	468.3 $(M+H-H_2O)^+$

81-28	Intermedio 30-2	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(2-oxo-3-fenilimidazolidin-1-il)fenil)-9H-carbazol-1-carboxamida	542.1 $(M+Na)^+$
81-29	Intermedio 30-3	4-(3-(3-terc-butil-2-oxoimidazolidin-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	521.1 $(M+Na)^+$
81-30	Intermedio 45-1	4-(3-(4-carbamoil-2-oxopirrolidin-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	507.0 $(M+Na)^+$
81-31	Intermedio 22-1	7-(2-hidroxipropan-2-il)-4-(2-metil-3-((2-oxoindolin-3-iliden)metil)fenil)-9H-carbazol-1-carboxamida	484.1 $(M+H-H_2O)^+$
81-32	Intermedio 55-1	4-(3-(5-hidroxi-1-oxoisoindolin-2-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	528.0 $(M+Na)^+$
81-33	Intermedio 1-3	7-(2-hidroxipropan-2-il)-4-(3-(6-metoxi-1-oxoisondolin-2-il)-2-metilfenil)-9H-carbazol-1-carboxamida	502.0 $(M+H-H_2O)^+$

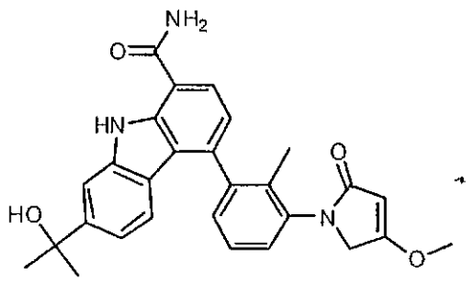
81-34	Intermedio 30-2	4-(3-(3-bencil-2-oxoimidazolin-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida	555.2 $(M+Na)^+$
81-35	Intermedio 56-1	7-(2-hidroxipropan-2-il)-4-(2-metil-3-(2-oxo-4-fenil-2,3-dihidro-1H-imidazol-1-il)fenil)-9H-carbazol-1-carboxamida	539.1 $(M+Na)^+$
81-36	Intermedio 57-1	carbamato de 1-(3-(1-carbamoil-7-(2-hidroxipropan-2-il)-9H-carbazol-4-il)-2-metilfenil)-2-oxopirrolidin-3-ilo	573.2 $(M+H-H_2O)^+$

Ejemplo 81-15

^{1}H RMN (400 MHz, *CLOROFORMO-d*) δ ppm 8.09 - 8.15 (1 H, m), 7.61 - 7.68 (2 H, m), 7.38 - 7.42 (2 H, m), 7.22 - 7.33 (3 H, m), 7.09 - 7.15 (1 H, m), 6.86 - 6.93 (1 H, m), 6.74 (1 H, t), 4.03 - 4.09 (1 H, m), 3.87 (3 H, d, J=2.42 Hz), 3.76 - 3.85 (1 H, m), 3.18 - 3.30 (1 H, m), 3.09 (1 H, ddd, J=16.29, 5.39, 5.17 Hz), 1.97 - 2.02 (3 H, m), 1.61 - 1.66 (6 H, m).

Ejemplo 82-1

Preparación de 7-(2-hidroxipropan-2-il)-4-(3-(4-metoxi-2-oxo-2,4-dihidro-1H-pirrol-1-il)-2-metilfenil)-9H-carbazol-1-carboxamida

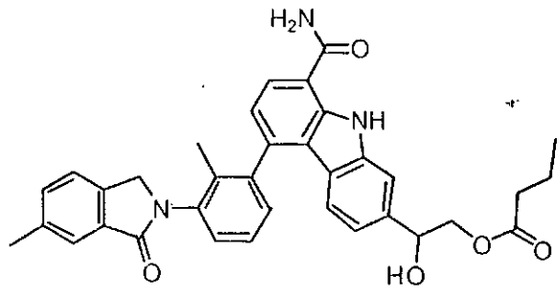


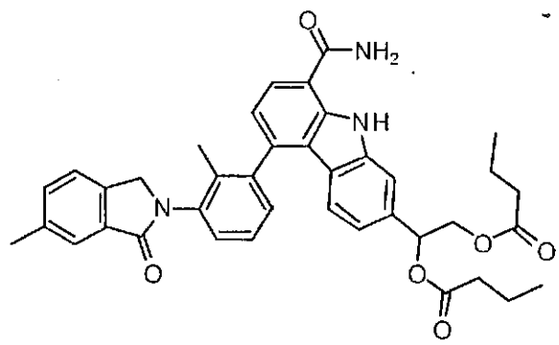
Una mezcla de 4-(3-bromo-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida (Ejemplo 81-25, 70 mg, 0.160 mmol), 4-metoxi-1H-pirrol-2(5H)-ona (362 mg, 3.20 mmol), carbonato de cesio (78 mg, 0.24 mmol), tris(dibencilidenoacetona)dipaladio (14.7 mg, 0.016 mmol) y 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (xantphos, 27.8 mg, 0.048 mmol) en 1,4-dioxano (2 ml) se purgó con nitrógeno y se calentó mediante radiación en microondas en un tubo sellado a 100°C durante 1 h. La mezcla se diluyó con DCM, se lavó con NaHCO3 (ac), se secó y se concentró. El residuo se purificó por HPLC preparativa, y las fracciones de efluente apropiadas se trataron con NaHCO3 (ac) y se extrajeron con DCM. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron proporcionando como un sólido blanco (20 mg, 27%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.91 (1 H, d, J=7.70 Hz), 7.73 (1 H, d, J=0.88 Hz), 7.39 - 7.46 (2 H,

m), 7.31 - 7.34 (1 H, m), 7.09 (1 H, dd, J=8.47, 1.65 Hz), 7.01 (1 H, d, J=7.70 Hz), 6.98 (1 H, d, J=8.36 Hz), 5.29 (1 H, s), 4.37 - 4.49 (2 H, m), 3.91 (3 H, s), 1.90 (3 H, s), 1.58 (3 H, s), 1.57 (3 H, s). Espectro de masas m/z 492.0 $(M+Na)^+$.

Ejemplos 83-1 y 83-2

Preparación de butirato de (RS)-2-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)-2-hidroxietilo y dibutirato de (RS)-1-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)etano-1,2-diilo





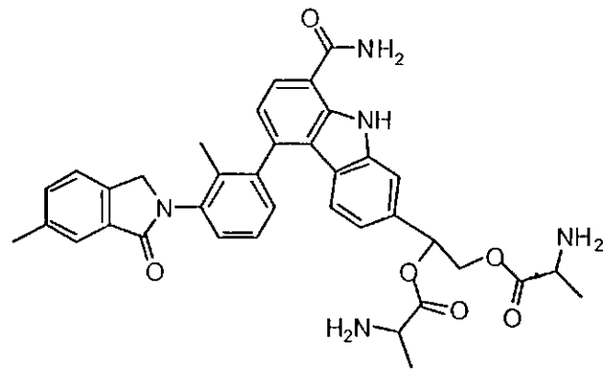
Una solución de 7-(1,2-dihidroxietil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 70-11, 30 mg, 0.059 mmol), anhídrido

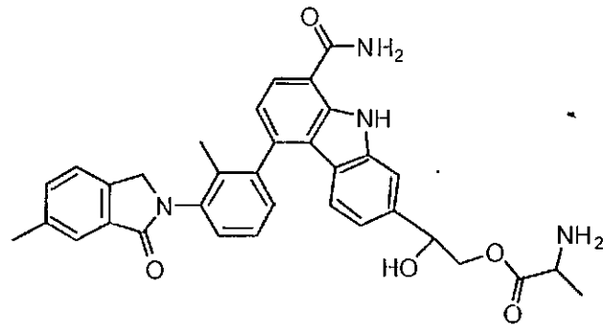
butírico (29 µl, 0.178 mmol) y piridina (48 µl, 0.593 mmol) en THF-DCM (1:1, 2.4 ml) se agitó a ta durante la noche. Se añadió más anhídrido butírico (0.03 ml, 3 eq.) y la mezcla se agitó de nuevo a ta durante la noche. La mezcla se concentró y purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron parcialmente y la suspensión acuosa resultante se trató con NaHCO3 (ac). El precipitado se recogió por filtración, se lavó con agua y se secó proporcionando butirato de (RS)-2-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)-2-hidroxietilo como un sólido blanco (Ejemplo 83-1, 10.5 mg, 28%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.53 (1 H, s), 8.19 (1 H, s ancho), 8.02 (1 H, d, J=7.9 Hz), 7.76 (1 H, d, J=10.1 Hz), 7.54 - 7.64 (3 H, m), 7.50 (3 H, t, J=7.0 Hz), 7.34 (1 H, dd, J=7.7, 1.1 Hz), 6.93 - 7.06 (3 H, m), 5.60 (1 H, dd, J=8.9, 4.3 Hz), 4.89 - 4.94 (2 H, m), 4.82 - 4.89 (1 H, m), 4.05 - 4.13 (2 H, m), 2.44 (3 H, s), 2.27 (2 H, td, J=7.3, 1.1 Hz), 1.83 (3 H, s), 1.51 (2 H, qd, J=7.3, 1.8 Hz), 0.83 (3 H, td, J=7.4, 2.2 Hz). Espectro de masas m/z 599.2 $(M+Na)^+$. También se aisló dibutirato de (RS)-1-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)etano-1,2-diilo como un sólido blanco (Ejemplo 83-2, 16 mg, 41%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.87 (1 H, d, J=7.7 Hz), 7.57 (2 H, d, J=10.1 Hz), 7.34 - 7.48 (4 H, m), 7.30 (1 H, dd, J=6.9, 1.9 Hz), 6.89 - 7.06 (3 H, m), 5.95

- 6.11 (1 H, m), 4.80 (2 H, s), 4.21 - 4.36 (2 H, m), 2.38 (3 H, s), 2.24 - 2.33 (2 H, m), 2.19 (2 H, td, J=7.3, 1.1 Hz), 1.80 (3 H, s), 1.44 - 1.63 (4 H, m), 0.76 - 0.90 (6 H, m). Espectro de masas m/z 668.3 $(M+Na)^+$.

Ejemplo 83-3 y 83-4

Preparación de bis(2-aminopropanoato) de 1-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)etano-1,2-diilo y 2-aminopropanoato de 2-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)-2-hidroxietilo





Una solución de 7-(1,2-dihidroxietil)-4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-1-carboxamida (Ejemplo 70-11, 30 mg, 0.059 mmol), ácido 2-

(*terc*-butoxicarbonilamino)propanoico (11.8 mg, 0.062 mmol), EDC (34.1 mg, 0.178 mmol) y DMAP (2.2 mg, 0.018 mmol) en DMF (2.4 ml) se agitó a ta durante la noche. Se añadieron más ácido 2-(*terc*-butoxicarbonilamino)propanoico (16 mg) y EDC (17 mg, 1.5 eq.) y la mezcla se agitó de nuevo a ta durante la noche. Se añadió TFA (0.3 ml) y la mezcla se agitó a ta durante 1 h, luego a 60°C durante 2 h, luego a ta durante la noche. La mezcla de reacción se concentró y purificó por HPLC preparativa. Las fracciones de efluente apropiadas se concentraron, se trataron con cloruro de hidrógeno (4 M en 1,4-dioxano) y agua y la mezcla se liofilizó proporcionando bis(2-aminopropanoato) de 1-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)etano-1,2-diilo, sal clorhidrato, como un sólido blanco (17 mg, 37%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.44 - 11.63 (1 H, m), 8.43 (6 H, s ancho), 8.17 (1 H, s ancho), 7.93 - 8.06 (1 H, m), 7.69 - 7.85 (1 H, m), 7.34 - 7.62 (6 H, m), 7.16 - 7.29 (1 H, m), 6.86 - 7.09 (3 H, m), 5.98 - 6.17 (1 H, m), 4.72 - 4.96 (2 H, m), 4.31 - 4.65 (2 H, m), 3.96 - 4.25 (2 H, m), 2.38 (3 H, s), 1.76 (3 H, s), 1.43 (3 H, dd, J=7.0, 3.7 Hz), 1.24 - 1.38 (3 H, m). Espectro de masas m/z 648.2 $(M+H)^+$. También se aisló 2-aminopropanoato de 2-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)-2-hidroxietilo, sal TFA, como un sólido blanco (4 mg, 9%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.85 - 7.91 (1 H, m), 7.53 - 7.60 (2 H, m), 7.38 - 7.48 (4 H, m), 7.26 -

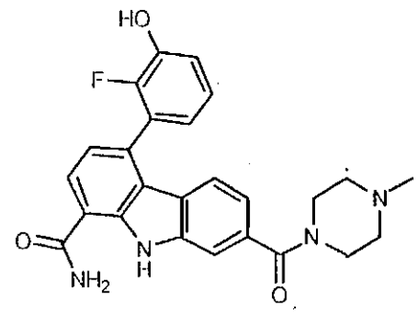
7.33 (1 H, m), 7.02 - 7.09 (1 H, m), 6.94 - 7.02 (2 H, m), 5.90 - 5.97 (0.3 H, m), 4.99 (0.7 H, dd, J=7.3, 3.7 Hz), 4.78 - 4.84 (2 H, m), 3.72 - 4.42 (3 H, m), 2.38 (3 H, s), 1.75 - 1.82 (3 H, m), 1.34 - 1.57 (3 H, m). Espectro de masas m/z 577.2 $(M+H)^+$.

Los siguientes compuestos también se prepararon usando procedimientos mostrados en los Ejemplos 83-1 a 83-4, usando el ácido o anhídrido de ácido apropiado.

Ejemplo	Nombre del compuesto	Espectro de masas
83-5	diacetato de 1-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)etano-1,2-diilo	612.2 $(M+Na)^+$
83-6	bis(2-amino-3-metilbutanoato) de 1-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)etano-1,2-diilo (preparado como la sal clorhidrato)	704.2 $(M+H)^+$
83-7	2-amino-3-metilbutanoato de 2-(8-carbamoil-5-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-9H-carbazol-2-il)-2-hidroxietilo (preparado como la sal TFA)	605.1 $(M+H)^+$

Ejemplo 84-1

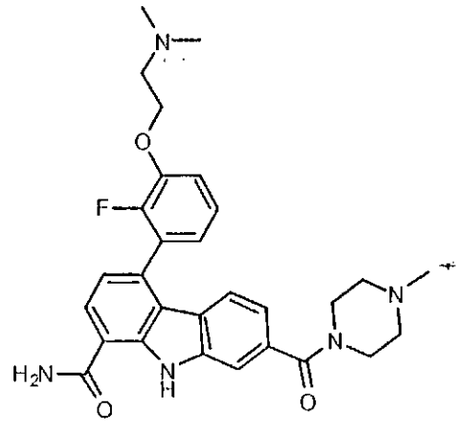
Preparación de 4-(2-fluoro-3-hidroxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Se agitó a 0°C una solución de 4-(2-fluoro-3-metoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 3-137, 3.6 g, 7.82 mmol) en DCM (42 ml) se agitó a 0 °C y se trató con tribromuro de boro (1 M en DCM, 94 ml, 94 mmol) y la mezcla se agitó a ta durante la noche. La mezcla se enfrió de nuevo hasta 0°C y se trató lentamente con metanol. La mezcla se concentró y se purificó por cromatografía en columna en alúmina neutra (eluyendo con EtOAc-metanol 90:10) proporcionando 4-(2-fluoro-3-hidroxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida como un sólido color claro (2.0 g, 57%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.75 (s, 1 H), 10.08 (s, 1 H), 8.25 (s ancho,1 H), 8.05 (d, J=7.6 Hz, 1 H), 7.81 (s, 1 H), 7.59 (s ancho,1 H), 7.17 (m, 3 H), 7.11 (d, J = 7.6 Hz, 1 H), 6.99 (dd, J = 8.0, 1.2 Hz, 1 H), 6.91 (t, J = 7.2 Hz, 1 H), 3.51 (s ancho,2 H), 3.34 (m, 5 H), 2.34 (s ancho,4 H). Espectro de masas m/z 447.0 $(M+H)^+$.

Ejemplo 85-1

Preparación de 4-(3-(2-(dimetilamino)etoxi)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida



Una mezcla de 4-(2-fluoro-3-hidroxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida (Ejemplo 84-1, 20 mg, 0.045 mmol) y trifenilfosfina soportada en polímero (2.63 mmol/g, 0.358 mmol) en 1,4-dioxano se trató a 0 °C con una solución de azodicarboxilato de dietilo (19.5 mg, 0.157 mmol) en THF (0.5 ml), seguido después de 5 min por una solución de 2-(dimetilamino)etanol (10 mg, 0.112 mmol) en THF (0.5 ml). La mezcla se calentó en un tubo sellado por radiación en microondas a 90-100°C durante 30 min. La mezcla resultante se filtró, los sólidos se lavaron con metanol, y se concentraron los filtrados y purificaron por HPLC preparativa proporcionando 4-(3-(2-(dimetilamino)etoxi)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida. Espectro de masas m/z 518.2 $(M+H)^+$.

Los siguientes compuestos también se prepararon

usando procedimientos mostrados en el Ejemplo 85-1, usando el alcohol apropiado en lugar de 2-(dimetilamino)etanol.

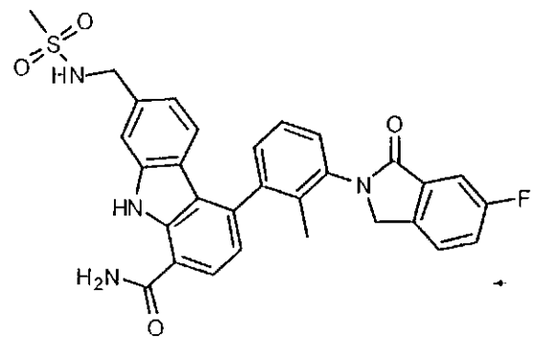
Ejemplo	Nombre del compuesto	Espectro de masas
85-2	4-(2-fluoro-3-fenetoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	551.2 $(M+H)^+$
85-3	4-(2-fluoro-3-(isopentiloxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	517.2 $(M+H)^+$
85-4	4-(2-fluoro-3-propoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	489.2 $(M+H)^+$
85-5	4-(2-fluoro-3-(3-fenilpropoxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	565.2 $(M+H)^+$
85-6	4-(2-fluoro-3-(4-fenilbutoxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	579.2 $(M+H)^+$

85-7	4-(2-fluoro-3-(2-(1-metilpirrolidin-2-il)etoxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	558.2 $(M+H)^+$
85-8	4-(3-etoxi-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	475.2 $(M+H)^+$
85-9	4-(3-(benciloxi)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	537.2 $(M+H)^+$
85-10	4-(2-fluoro-3-(4-metoxibenciloxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	567.2 $(M+H)^+$
85-11	4-(2-fluoro-3-isobutoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	503.2 $(M+H)^+$
85-12	4-(2-fluoro-3-(1-metilpiperidin-4-iloxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	544.2 $(M+H)^+$

85-13	4-(2-fluoro-3-(2-(piperidin-1-il)etoxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	558.2 $(M+H)^+$
85-14	4-(2-fluoro-3-isopropoxifenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida.	489.2 $(M+H)^+$
85-15	4-(3-(2-(1H-imidazol-1-il)etoxi)-2-fluorofenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	541.2 $(M+H)^+$
85-16	4-(2-fluoro-3-(pirazin-2-ilmetoxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	539.2 $(M+H)^+$
85-17	4-(2-fluoro-3-(tiazol-2-ilmetoxi)fenil)-7-(4-metilpiperazin-1-carbonil)-9H-carbazol-1-carboxamida	544.2 $(M+H)^+$

Ejemplo 86-1

Preparación de 4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(metilsulfonamidometil)-9H-carbazol-1-carboxamida



Una suspensión de 7-(aminometil)-4-bromo-9H-carbazol-1-carboxamida (Etapa 2 del Ejemplo 33-1, 100 mg, 0.314 mmol) y TEA (0.110 ml, 0.786 mmol) en DMF-THF-DCM (25:25:50, 6 ml) se trató gota a gota con cloruro de metanosulfonilo (37 µl, 0.471 mmol) y la mezcla resultante se agitó a ta durante 3 h. La mezcla se repartió entre NaHCO3 (ac) y EtOAc y la fase orgánica se lavó con salmuera, se secó y se concentró proporcionando 4-bromo-7-(metilsulfonamidometil)-9H-carbazol-1-carboxamida bruta como un sólido amarillo (130 mg, 88%). Sin purificación, usando el procedimiento del Ejemplo 3-2, se convirtieron este material (25 mg, 0.063 mmol) y 6-fluoro-2-(2-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)isoindolin-1-ona (Intermedio 50-5, 27.8 mg, 0.076 mmol) en 4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(metilsulfonamidometil)-

9H-carbazol-1-carboxamida (22 mg, 58%). RMN de ^{1}H (400 MHz, DMSO-d_6) δ 11.58 (1 H, s), 8.20 (1 H, s ancho), 8.03 (1 H, d, J=7.9 Hz), 7.70 - 7.78 (2 H, m), 7.45 - 7.67 (6 H, m), 7.36 (1 H, dd, J=7.7, 1.1 Hz), 7.00 - 7.07 (2 H, m), 6.93 - 7.00 (1 H, m), 4.86 - 5.04 (2 H, m), 4.26 (2 H, d, J=6.2 Hz), 2.87 (3 H, s), 1.84 (3 H, s). Espectro de masas m/z 557.1 $(M+H)^+$.

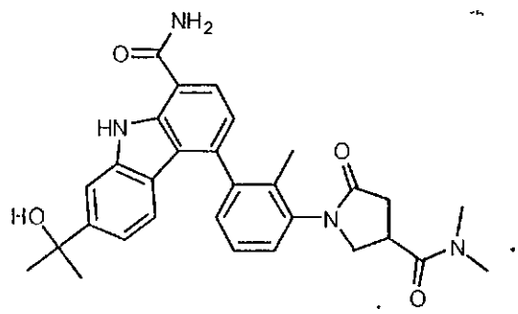
Los siguientes compuestos también se prepararon usando los procedimientos mostrados en el Ejemplo 86-1 y procedimientos estrechamente relacionados, y usando los Intermedios mostrados en lugar del Intermedio 50-5.

Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
86-2	Intermedio 50-8	4-(2-metil-3-(6-metil-1-oxoisoindolin-2-il)fenil)-7-(metilsulfonamidometil)-9H-carbazol-1-carboxamida	553.1 $(M+H)^+$
86-3	Intermedio 50-51	4-(3-(8-metoxi-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(metilsulfonamidometil)-9H-carbazol-1-carboxamida	582.1 $(M+H)^+$

86-4	Intermedio 50-48	4-(3-(8-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(metilsulfonamidometil)-9H-carbazol-1-carboxamida	570.0 $(M+H)^+$

Ejemplo 87-1

Preparación de 4-(3-(4-(dimetilcarbamoil)-2-oxopirrolidin-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida

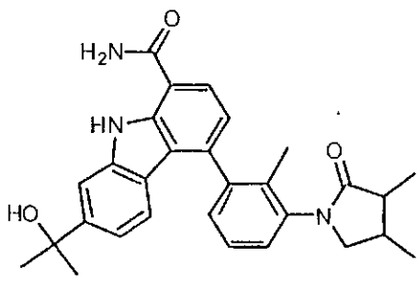


Una solución de ácido 1-(3-(1-carbamoil-7-(2-hidroxipropan-2-il)-9H-carbazol-4-il)-2-metilfenil)-5-oxopirrolidin-3-carboxílico (Ejemplo 81-27, 49 mg, 0.101 mmol), dimetilamina (2 M en THF, 0.252 ml, 0.505 mmol), EDC (38.7 mg, 0.202 mmol) y HOBT (30.9 mg, 0.202 mmol) en THF (2 ml) se agitó a ta durante la noche. Se añadieron más dimetilamina (2 M en THF, 0.252 ml, 0.505 mmol), EDC (38.7 mg, 0.202 mmol) y HOBT (30.9 mg, 0.202 mmol) junto con DMF (0.5 ml) y la mezcla se agitó de nuevo durante la noche. La mezcla se diluyó con DCMe, se lavó con $NaHCO_3$ (ac), se secó y

se concentró. El residuo se purificó por HPLC preparativa y las fracciones de efluente apropiadas se basificaron con hidróxido sódico acuoso 1 M y se extrajeron dos veces con DCM. La fase orgánica se lavó con agua, se secó y se concentró. El residuo se purificó por cromatografía en columna (eluyendo con DCM-metanol-amoníaco), proporcionando 4-(3-(4-(dimetilcarbamoil)-2-oxopirrolidin-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida como un sólido blanco (8 mg, 15%). RMN de ^{1}H (400 MHz, metanol-d_4) δ 7.91 (1 H, d, J=7.7 Hz), 7.73 (1 H, d, J=1.1 Hz), 7.40 - 7.49 (2 H, m), 7.33 (1 H, dd, J=6.5, 2.3 Hz), 7.07 (1 H, ddd, J=8.5, 1.4, 1.3 Hz), 7.01 (1 H, d, J=7.9 Hz), 6.94 (1 H, s ancho), 3.84 - 4.13 (3 H, m), 3.13 (3 H, 2 s), 2.97 (3 H, 2 s), 2.85 - 2.94 (1 H, m), 2.74 - 2.83 (1 H, m), 1.93 (3 H, s), 1.57 (6 H, 2 s). Espectro de masas m/z 495.1 $(M+H-H_2O)^+$.

Ejemplo 88-1

Preparación de 4-(3-(3,4-dimetil-2-oxopirrolidin-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida

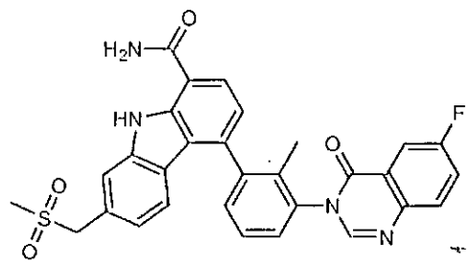


Se trató una mezcla de 4-(3-(3,4-dimetil-2-oxo-2,4-

dihidro-1H-pirrol-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida (Ejemplo 81-21, 20 mg, 0.043 mmol) y formiato amónico (27.0 mg, 0.428 mmol) en metanol (5 ml) con paladio al 10% sobre carbón (20 mg, 0.019 mmol). La mezcla se agitó en nitrógeno a ta durante 2 h. Se añadió más formiato amónico (27.0 mg, 0.428 mmol) y la mezcla se agitó a ta durante la noche. Se añadieron más formiato amónico (57 mg) y paladio al 10% sobre carbón (40 mg) y después de 6 h se añadió más formiato amónico (57 mg). La mezcla se agitó de nuevo durante la noche, luego se diluyó con DCM y se filtró a través de Celite. El filtrado se lavó con agua, se secó y se concentró. El residuo se purificó por HPLC preparativa y las fracciones de efluente apropiadas se basificaron con hidróxido sódico acuoso 1 M y se extrajeron dos veces con DCM. Las fases orgánicas reunidas se lavaron con agua, se secaron y se concentraron proporcionando 4-(3-(3,4-dimetil-2-oxopirrolidin-1-il)-2-metilfenil)-7-(2-hidroxipropan-2-il)-9H-carbazol-1-carboxamida como un sólido blanco (11 mg, 55%), que era una mezcla de diastereómeros. Espectro de masas m/z 452.1 $(M+H-H_2O)^+$.

Ejemplo 89-1

Preparación de 4-(3-(6-fluoro-4-oxoquinazolin-3 (4H)-il)-2-metilfenil)-7-(metilsulfonilmetil)-9H-carbazol-1-carboxamida



Etapa 1 Una mezcla de 4-bromo-7-(hidroximetil)-9H-carbazol-1-carboxamida (Ejemplo 30-2, 403 mg, 1.263 mmol), N-clorosuccinimida (219 mg, 1.642 mmol) y trifenilfosfina (431 mg, 1.642 mmol) en DCM (50 mL) se calentó a reflujo durante 1 h. La mezcla se enfrió hasta la temperatura ambiente, se lavó con salmuera, y la capa acuosa se extrajo con DCM. La capa acuosa se filtró y el precipitado recogido se lavó con agua. Las capas orgánicas y el precipitado recogido se combinaron y la mezcla se concentró al vacío. El residuo se disolvió en THF (20 ml) y DMSO (5 mL) y la solución fue tratada con tiometóxido de sodio (115 mg, 1.642 mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos, se diluyó con EtOAc, se lavó dos veces con agua, y la fase acuosa se extrajo con EtOAc. Las fases orgánicas combinadas se secaron y se concentraron. El residuo se purificó por cromatografía en columna (eluyendo con EtOAc-hexano) para proporcionar 4-bromo-7-(metiltiometil)-9H-carbazol-1-carboxamida como un

sólido blanco (168 mg, 38%) usada sin purificación adicional. ^{1}H RMN (400 MHz, cloroformo-d) δ 8.67 (1H, d, J = 8,1 Hz), 7.46 - 7.52 (2 H, m), 7.36 - 7.41 (1H, m), 7.26 - 7.29 (1 H, m), 3.87 (2 H, s), 2.03 (3H, s). Espectro de masas m/z 349, 351 $(M+H)^+$.

Etapa 2 Una suspensión de 4-bromo-7-(metiltiometil)-9H-carbazol-1-carboxamida (168 mg, 0.481 mmol) en DCM (10 mL) y THF (2 mL) se trató con ácido 3-cloroperoxibenzoico (166 mg, 0.962 mmol) y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla fue tratada con NaHCO3 (ac) y la fase orgánica se separó. Los sólidos insolubles en la fase acuosa se recogieron por filtración y se lavaron con agua. La fase orgánica y el precipitado se combinaron y la mezcla se concentró. El residuo se trituró con metanol para proporcionar 4-bromo-7-(metilsulfonilmetil)-9H-carbazol-1-carboxamida como un sólido blanco (180 mg, 98%), usado sin purificación adicional. ^{1}H RMN (400 MHz, metanol-d_4) δ xx. Espectro de masas m/z 403, 405 $(M+H)^+$.

Etapa 3 Siguiendo el procedimiento del ejemplo 31-1, pero usando THF como el solvente en lugar de tolueno-etanol, 4-bromo-7-(metilsulfonilmetil)-9H-carbazol-1-carboxamida (50 mg, 0.131 mmol) y 6-fluoro-3-(2-metil-3-(4,4,5,5-tetrametil-1;3,2-dioxaborolan-2-il)fenil)quinazolin-4(3H)-ona (Intermedio 50-27, 50 mg, 0.131 mmol) se convierteron en 4-(3-(6-fluoro-4-oxoquinazolin-3(4H)-il)-2-metilfenil)-7-(metilsulfonilmetil)-9H-carbazol-1-carboxamida como un sólido blanco (16 mg, 22%). ^{1}H RMN (400 MHz, metanol-d_4) δ 8.20 - 8.28 (1H, m), 7.95 - 8.02 (2 H, m), 7.82 - 7.89 (1H, m), 7.66 - 7.71 (1H,

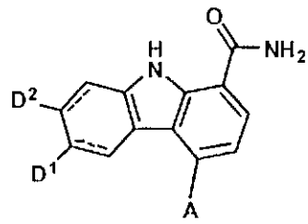
m), 7.56 - 7.66 (2 H, m), 7.47 - 7.56 (1H, m), 6.97 - 7.33 (3 H, m), 4.46 - 4.52 (2 H, m), 2.84 (3H, s), 1.90 (3H, s). Espectro de masas m/z 555.0 $(M+H)^+$.

Los siguientes compuestos se prepararon usando los procedimientos demostrados en el Ejemplo 89-1 y procedimientos estrechamente relacionados, usando los Intermedios mostrados en lugar del Intermedio 50-27.

Ejemplo	Materiales de partida	Nombre del compuesto	Espectro de masas
89-2	Intermedio 50-5	4-(3-(6-fluoro-1-oxoisoindolin-2-il)-2-metilfenil)-7-(metilsulfonilmetil)-9H-carbazol-1-carboxamida	542.1 $(M+H)^+$
89-3	Intermedio 50-6	4-(3-(5-metoxi-1-oxoisoindolin-2-il)-2-metilfenil)-7-(metilsulfonilmetil)-9H-carbazol-1-carboxamida	554.1 $(M+H)^+$

REIVINDICACIONES

1. Un compuesto caracterizado porque tiene la formula (I):



(I)

o una de sus sales, en la que

las líneas discontinuas son ya sea enlaces simples o bien enlaces dobles;

A es halo, carbociclo C_{3-10} sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B;

B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-N(C(=O)O-R^1)_2$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$ o $-NR^{11}-R^1$;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^{1a}, alquinilo C_{2-6} sustituido con 0-3 R^{1a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{1a}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un

heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a};

R^{1a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ sustituido con 0-1 R^a;

uno de D^1 y D^2 es D y el otro es H o halo;

D es $-R^2$, halógeno, $-(C(R^{11})_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$, $-NR^{11}-R^2$, $-C(=O)NR^{11}-O-R^2$, $-OC(=O)O-R^2$, $-O^1C(=O)-R^2$ o CH=N-OH;

con la condición de que A no es halo cuando D es $-C(=O)O-R^2$,

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, alquinilo C_{2-6} sustituido con 0-3 R^{2a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S,

sustituido con 0-3 R^{2a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a};

R^{2a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, y $S(O)_p$ sustituido con 0-2 R^a;

R^{11} es independientemente hidrógeno o alquilo C_{1-4} sustituido con 0-1 R^f, CH_2-fenilo o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$;

de forma alternativa, R^{11} y junto con otro R^{11}, R^1, o R^2 en el mismo átomo de nitrógeno pueden unirse formando un azetidinilo, pirrolidinilo, piperidinilo, morfolinilo o 4-(alquil C_{1-6})piperazinilo;

R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-1 R^f, haloalquilo

C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, de forma alternativa, dos R^a en átomos de carbono adyacentes o en el mismo átomo forman un acetal cíclico de la fórmula $-O-(CH_2)_n-O-$ o $-O-CF_2-O-$, en el que n se selecciona de 1 ó 2;

R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6} sustituido con 0-1 R^f, cicloalquilo C_{3-6} o $(CH_2)_r$-fenilo sustituido con 0-1 R^f;

R^d es hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CH_2)_rC(O)R^c$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6} o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6} o $(CH_2)_r$-fenilo;

R^f es hidrógeno, halo, NH_2, OH u OCH_3;

r es 0, 1, 2, 3 ó 4; y

p es 0, 1 ó 2.

2. Un compuesto de conformidad con la reivindicación 1, caracterizado porque:

las líneas discontinuas son ya sea enlaces simples o bien enlaces dobles;

A es halo, cicloalquilo C_{3-10} sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos

seleccionados de N, O y S, sustituido con 0-3 B, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B;

B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, $-C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}C(=O)O-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$ o $-NR^{11}-R^1$;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^{1a}, alquinilo C_{2-6} sustituido con 0-3 R^{1a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{1a}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a};

R^{1a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$ sustituido con 0-1 R^a;

uno de D^1 y D^2 es D y el otro es H;

D es $-R^2$, halógeno, $-(C(R^{11})_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$ o $-NR^{11}-R^2$;

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, alquinilo C_{2-6} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a};

R^{2a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, $-(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR_{11}R^{11}$, $-NR^bS(O)^pR_c$, $-S(O)R^c$, $-S(O)^2R_c$, alquilo C_{1-6} sustituido con 0-2 R_a, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros sustituido con 0-1 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$ sustituido con 0-1 R^a;

R^{11} es independientemente hidrógeno o alquilo C_{1-4};

de forma alternativa, R^{11} y junto con otro R^{11}, R^1 o R^2 en el mismo átomo de nitrógeno pueden unirse formando un azetidinilo, pirrolidinilo, piperidinilo, morfolinilo o 4-(alquilo C_{1-6})piperazinilo; R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CH_2)_rOR^b$, $-(CH_2)_rSR^b$, $-(CH_2)_rC(O)R^b$, -

$(CH_2)_rC(O)OR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-(CH_2)_rC(O)NR^{11}R^{11}$, $-(CH_2)_rNR^bC(O)R^c$, $-(CH_2)_rNR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6}, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-14 miembros, o $-(CH_2)_r$-heterociclo de 5 a 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, de forma alternativa dos R^a en átomos de carbono adyacentes o en el mismo átomo de carbono forman un acetal cíclico de la fórmula $-O-(CH_2)_n-O-$ u $-O-CF_2-O-$, en el que n se selecciona de 1 ó 2;

R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo;

R^d es hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CH_2)_rC(O)R^b$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6} o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6}, o $(CH_2)_r$-fenilo;

r es 0, 1, 2, 3 ó 4; y

p es 0, 1 ó 2.

3. El compuesto de conformidad con la reivindicación 1, caracterizado porque:

D es un $-R^2$, $-(CH_2)_r-R^2$, $-O-R^2$, $-C(=O)-R^2$, $-C(=O)O-R^2$, $-C(=O)NR^{11}-R^2$, $-S(=O)_2-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)O-R^2$, $-NR^{11}S(=O)_2-R^2$ o $-NR^{11}-R^2$;

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a},

alquenilo C_{3-10} sustituido con 0-3 R^{2a}, cicloalquilo C_{3-6} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a};

R^{2a} es hidrógeno, C=O, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, OR^b, SR^b, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, $-(CH_2)_r-$carbociclo de 3-14 miembros sustituido con 0-1 R^a, en el que el carbociclo es ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo; o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$ sustituido con 0-2 R^a;

r es 0, 1 ó 2.

4. El compuesto de conformidad con las reivindicaciones 1-2, caracterizado porque

A es halo, carbociclo C_{3-10} sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 B;

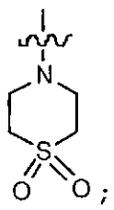
B es R^1, halógeno, ciano, nitro, $-O-R^1$, $-C(=O)-R^1$, -

$C(=O)O-R^1$, $-C(=O)NR^{11}-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $-N(S(=O)_2-R^1)_2$, o $-NR^{11}-R^1$;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}.

5. El compuesto de conformidad con las reivindicaciones 1-4, caracterizado porque

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, etenilo, cicloalquilo C_{3-10} sustituido con 0-3 R^{2a}, arilo C_{6-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, donde el heterociclilo es pirrolidinilo, piperidinilo, morfolinilo o piperazinilo, tetrahidropiranilo, oxazolidinilo (oxazolidin-ona), imidazolidinilo (imidazolidin-ona), dioxalanilo, o



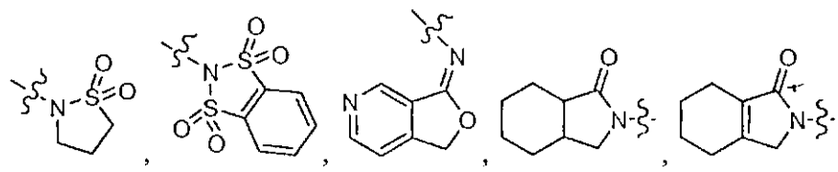
; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, donde el heteroarilo es pirimidinilo, imidazolilo, pirazinilo, tiadiazolilo, piridinilo, quinolinilo,

isoquinolinilo o tiazolilo.

6. El compuesto de conformidad con las reivindicaciones 1-5, caracterizado porque

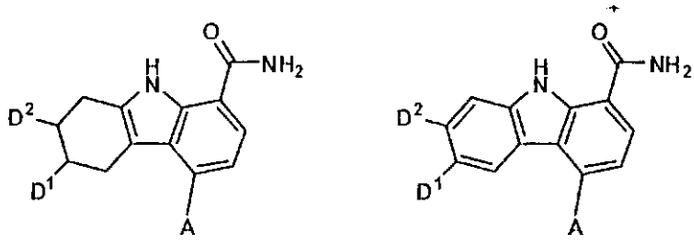
A es carbociclo C_6 sustituido con 0-3 B, arilo mono- o bicíclico C_{6-10} sustituido con 0-3 -B, un heterociclilo de 5-14 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 -B, donde el heterociclilo es cromanilo, 3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona, pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 -B, donde el heteroarilo es piridinilo, quinolinilo, isoquinolinilo, indolilo, indazolilo, benzimidazolilo, furanilo, benzofuranilo, dibenzofuranilo, imidazolilo, pirazolilo o tiazolilo;

R^1 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{1a}, haloalquilo C_{1-6}, arilo C_{6-10} sustituido con 0-3 R^{1a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, donde el heterociclilo es 4,5,6,7-tetrahidrobenzo[d]tiazolilo, isoindolinilo, imidazo[1,2-a]pirazin-8(7H)-ona, 1H-pirrolo[3,4-c]piridin-3(2H)-ona, 1,3-dihidrofuro[3,4-c]piridina, ftalazina, isoquinolin-1(2H)-ona, isoindolinilo, isoindolin-1,3-diona, quinazolin-4(3H)-ona,



pirrolidinilo, piperidinilo, morfolinilo o piperazinilo; un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, donde heteroarilo es indazolilo, imidazolilo, pirimidinilo, benzimidazolilo, benzotiazolilo, quinolinilo, quinazolinilo, quinazolin-4(3H)-ona piridinilo o tiazolilo.

7. El compuesto de conformidad con las reivindicaciones 1-6, caracterizado porque el compuesto de fórmula I es un compuesto de fórmula (Ia) o (Ib)



(Ia) (Ib).

8. El compuesto de conformidad con las reivindicaciones 1-7, caracterizado porque

R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, $-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6} sustituido con 0-1 R^f, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo de 3-6 miembros, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos

seleccionados de N, O y $S(O)_p$, en el que el heterociclo es pirrolidinilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furilo, tienilo, piridilo, pirazinilo, pirimidinilo, morfolinilo, tiamorfolinilo, triazolilo, indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, benzimidazolilo, benzopiranilo, benzofurilo, benzoisotiazolilo, benzoisoxazolilo, benzodiazinilo o benzofurazanilo;

R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6} sustituido con 0-1 R^f, cicloalquilo C_{3-6} o $(CH_2)_r$-fenilo sustituido con 0-1 R^f;

R^d es hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-C(O)R^e$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6} o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6} o $(CH_2)_r$-fenilo;

R^f es hidrógeno, halo o NH_2;

r es 0 ó 1,

9. El compuesto de conformidad con las reivindicaciones 1-8, caracterizado porque

R^a es hidrógeno, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $-OR^b$, $-SR^b$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)R^b$, $-NR^{11}R^{11}$, $-C(O)NR^{11}R^{11}$, $-NR^bC(O)R^c$, $-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$,

$-S(O)R^c$, $-S(O)_2R^c$, alquilo C_{1-6}, haloalquilo C_{1-6}, $-(CH_2)_r$-carbociclo fenilo de 3-6 miembros, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, donde el heterociclo es tiazolilo, piridinilo, piperidinilo, morfolinilo, piperazinilo, pirrolidinilo, pirrolidinona,

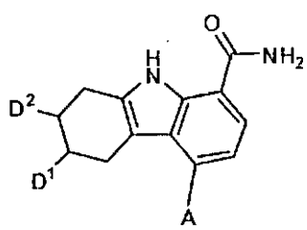
R^b es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-2 R^d, o $(CH_2)_r$-fenilo sustituido con 0-2 R^d;

R^c es alquilo C_{1-6}, cicloalquilo C_{3-6} o $(CH_2)_r$-fenilo;

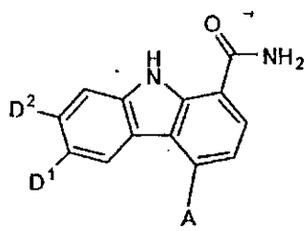
R^d es hidrógeno, F, Cl, Br, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-C(O)R^c$, $-NR^eR^e$, $-NR^eC(O)OR^c$, alquilo C_{1-6} o $(CH_2)_r$-fenilo;

R^e es hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-6} o $(CH_2)_r$-fenilo;

10. El compuesto de conformidad con las reivindicaciones 1-9, caracterizado porque que el compuesto de fórmula (I) es de la fórmula (Ia) ó (Ib)



(Ia)



(Ib)

A es carbociclo C_{3-10} sustituido con 0-3 B, donde el carbociclo es ciclohexilo o ciclohexenilo, arilo mono o bibíclico C_{6-10} sustituido con 0-3 -B, donde el grupo arilo es

fenilo o naftilo; un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 -B, donde el grupo heterociclilo es cromanilo, 3,4-dihidro-2H-benzo[e][1,3]oxazin-2-ona, pirrolidinilo o piperidinilo; o un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 -B, donde el grupo heteroarilo es piridinilo, quinolinilo, isoquinolinilo, indolilo, indazolilo, benzimidazolilo, furanilo, benzofuranilo, dibenzofuranilo, imidazolilo, pirazolilo o tiazolilo;

B es R^1, halógeno, $-C(=O)O-R^1$, $-S(=O)_2-R^1$, $-NR^{11}C(=O)-R^1$, $-NR^{11}C(=O)NR^{11}-R^1$, $-NR^{11}S(=O)_2-R^1$, $N(S(=O)_2-R^1)_2$ o $-NR^{11}-R^1$;

R^1 es hidrógeno, trifluorometilo, alquilo C_{1-4} sustituido con 0-1 R^{1a}, fenilo sustituido con 0-3 R^{1a}, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{1a}, en el que el heteroarilo es piridilo o tiazolilo;

Uno de D^1 y D^2 es D y el otro es hidrógeno;

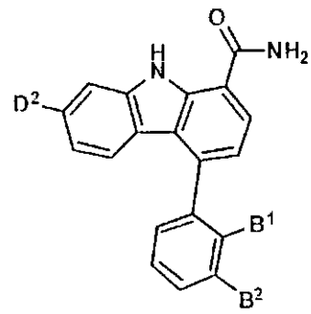
D es R^2, $-C(=O)-R^2$, $-OR^2$, $-C(=O)NR^{11}R^2$, $NR^{11}C(=O)R^2$, $NR^{11}C(=O)NR^{11}-R^2$, $NR^{11}S(=O)_2-R_2$ o $-NR^{11}-R^2$;

R^2 es hidrógeno, alquilo C_{2-6} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, donde el heterociclilo es tetrazolilo, pirrolidinilo,

piperidinilo, piperazinilo o morfolinilo;

R^{2a} es alquilo C_{1-4}, en el que el alquilo es metilo, etilo, propilo, i-propilo, butilo y t-butilo, sustituido con 0-1 R^a.

11. Un compuesto de conformidad con la reivindicación 1, caracterizado porque es de la fórmula (Ic):

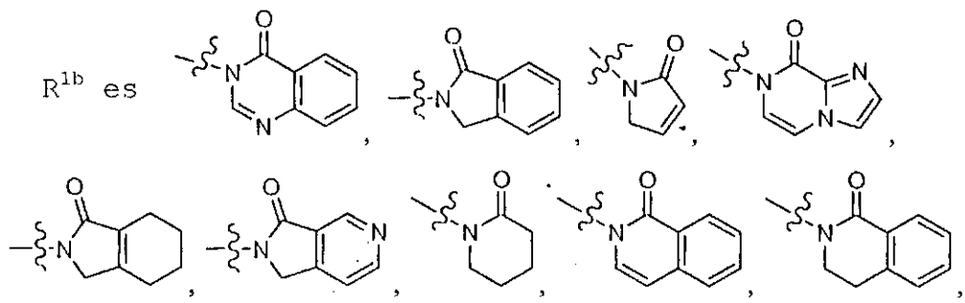


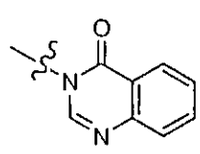
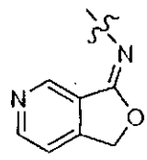
(Ic)

o una de sus sales, en la que

B^1 es metilo o flúor;

B^2 es R^{1b}, $-NR^{11}C(=O)-$ R^{1c}, $-NR^{11}C(=O)NR^{11}-$ R^{1d} o $-NR^{11}-$ R^{1e};

R^{1b} es 


, o

, cualquiera de los cuales está sustituido con 0-3 R^{1a};

R^{1c} es alquilo C_{1-6}, fenilo sustituido con 0-2 R^a, ciclopropilo, CH_2-tetrazolilo, o piridilo, tiazolilo, imidazolilo, benzimidazolilo, pirimidinilo, cualquiera de los cuales está sustituido con 0-2 R^a;

R^{1d} es tiazolilo sustituido con 0-1 R^{1a};

R^{1e} es quinazolinilo sustituido con 0-1 R^{1a};

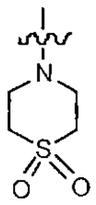
R^{1a} se selecciona de hidrógeno, halo, CN, metilo, etilo, CF_3, OH, O-metilo, CO_2CH_3, $N(CH_3)_2$, $NC(O)CH_3$,

D^2 es $-R^2$, $-(C(R^{11})_2)_r-R^2$, $-OR^2$, $-C(=O)-R^2$, $-C(=O)NR^{11}-R^2$, $-NR^{11}C(=O)-R^2$, $-NR^{11}C(=O)NR^{11}-R^2$, $-NR^{11}-R^2$ u $-OC(=O)-R^2$;

con la condición de que D^2 no es hidrógeno;

R^2 es hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^{2a}, ciclopropilo C_{3-10} sustituido con 0-3 R^{2a}, un heterociclilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, donde el heterociclilo se selecciona de piperazinilo, pirrolidinilo, tetrahidrofuranilo, morfolinilo, dioxolanilo, piperidinilo, oxazolidinilo

(oxazolidin-ona), imidazolidinilo (imidazolidin-ona),



, un heteroarilo de 5-10 miembros que contiene 1-4 heteroátomos seleccionados de N, O y S, sustituido con 0-3 R^{2a}, donde el heteroarilo se selecciona de piridinilo, imidazolilo, pirazinilo, pirimidinilo, tetrazolilo, tiadiazolilo;

R^{2a} es hidrógeno, $-(CH_2)_rOR^b$, $-(CH_2)_rOC(O)R^b$, $-(CH_2)_rNR^{11}R^{11}$, $-NR^bC(O)NR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-2 R^a, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$ sustituido con 0-2 R^a, donde el heterociclo se selecciona de piridinilo, pirrolidinilo, pirrolidinonilo, morfolinilo, imidazolilo, piperidinilo;

R^{11} es hidrógeno o alquilo C_{1-4} sustituido con 0-1 R^f;

R^a es hidrógeno, $-OR^b$, $-NR^{11}R^{11}$, o $-(CH_2)_r$-heterociclo de 5-7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, donde el heterociclo es imidazolilo o morfolinilo;

R^b es hidrógeno, o alquilo C_{1-6} sustituido con 0-2 R^d;

R^c es alquilo C_{1-6};

R^d es hidrógeno, $-OR^e$ o $-NR^eR^e$;

R^e es hidrógeno o alquilo C_{1-6};

R^f es hidrógeno, NH_2, OH u OCH_3.

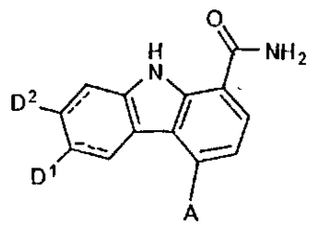
12. Un compuesto de conformidad con la reivindicación 1, caracterizado porque se revela en los Ejemplos, o una de sus sales farmacéuticamente aceptables.

13. Una composición farmacéutica caracterizada porque comprende uno o más compuestos de conformidad con las reivindicaciones 1-11 y un vehículo o diluyente farmacéuticamente aceptable.

14. Un procedimiento para tratar una enfermedad, caracterizado porque comprende administrar a un paciente que necesita el tratamiento, una cantidad terapéuticamente eficaz de un compuesto de acuerdo con las reivindicaciones 1-11, en el que la enfermedad es lupus eritematoso sistémico (LES), artritis reumatoide, esclerosis múltiple (EM) o rechazo de trasplante.

RESUMEN DE LA INVENCION

Los compuestos que tienen la fórmula (I), y sus enantiómeros y diastereómeros y sus sales farmacéuticamente aceptables,



(I)

son útiles como moduladores de cinasa, incluyendo la modulación de Btk.

POD-4002

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
   SALLY B. HANSEN
3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY
4. LLEVA EL SELLO DE:
   SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY
6. EL 28 DE JUNIO DE 2007
7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY
8. N° A295716
9. SELLO (APARECE ADHERIDO SELLO DORADO)
10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

AUTENTICACIÓN COPIA DE ORIGINAL
EL SUSCRITO NOTARIO TREINTA Y OCHO DEL CIRCULO DE BOGOTÁ D.C.
EL DOCUMENTO ORIGINAL QUE HE TENIDO A LA VISTA.
15 JUN 2011
(38)
RODOLFO BERMUDEZ
Notario 38 del Círculo de Bogotá D.C.

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

AUTENTICACION DE COPIA DE ORIGINAL
EL SUSCRITO NOTARIO TREINTA Y SESENTA (38) CERTIFICA
QUE LA PRESENTE COPIA COINCIDE EXACTAMENTE CON
EL DOCUMENTO ORIGINAL QUE HE TENIDO A LA VISTA
15 JUN 2011
(38)
RODOLFO REY DERMUDEZ
Notario 38 (E) DEL CIRCULO DE BOGOTA D.C.

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

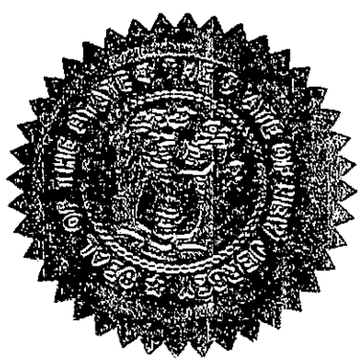
7. BY: Bradley Abelow, NEW JERSEY TREASURER

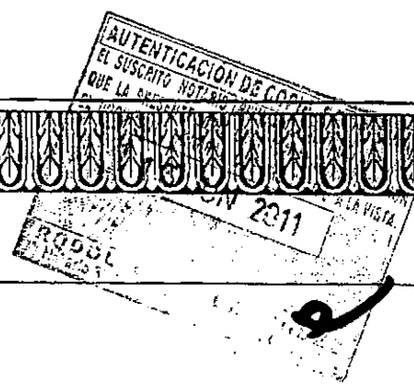
8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow





3

BAKER & MCKENZIE

Raisbeck, Lara, Rodriguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogota, Colombia

NIT: 860.068.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

AUTENTICACION DE COPIA DE ORIGINAL
EL SUSCRITO NOTARIO TREINTA Y OCHO(38) DEL CIRCULO DE BOGOTA D.C.
CERTIFICA:
QUE LA PRESENTE COPIA COINCIDE EXACTAMENTE CON EL DOCUMENTO ORIGINAL QUE HE TENIDO A LA VISTA.
15 JUN 2011
38
RODOLFO REY BERMUDEZ
NOTARIO TREINTA Y OCHO (38) DEL CIRCULO DE BOGOTA D.C.

4

NOTARIAL CERTIFICATION

On this 30 day of May

2007 , the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public

SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

AUTENTICACIÓN DE COPIA DE ORIGINAL
EL SUSCRITO NOTARIO TREINTA Y OCHO(38) DEL CIRCULO DE BOGOTÁ D.C. CERTIFICA QUE LA PRESENTE COPIA CONCUERDA EXACTAMENTE CON EL ORIGINAL QUE SE TUVO A LA VISTA.
JUN 2011
(38)
RODOLFO PEÑA JIMENEZ
Notario 38 (E) del Circulo de Bogotá D.C.

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo

de 2007 , el suscrito Notario

DA FE

1 Que Anastasia P. Winslow
mayor y domiciliado en Princeton, NJ
Estados Unidos de América
suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América
está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

5

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-074857- -00000-0000

Fecha: 2011-06-15 17:29:08 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 892

PATENTE DE INVENCIÓN ☐ MODELO D. ☐

- ☐ 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 ☐

Industria y Comercio
SUPERINTENDENCIA

Prosperidad para todos

Bogotá D.C.,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL - MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	11 074857
	Solicitud internacional	PCT/US2009/068415
	Fecha inicio fase nacional	19/07/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

13648

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Con respecto al resumen y de conformidad con lo dispuesto en el artículo 31 D. 486 en el cual se establece que el resumen consiste en una síntesis de la divulgación técnica contenida en la solicitud de patente, debe adecuar el resumen a los dispuesto en dicha norma, teniendo en cuenta que el extracto permitirá precisar el objeto de la invención, sus elementos característicos y el campo de aplicación.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se consideraró abandonada y perderá su prelación.

Continua en la página siguiente...

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista de fecha 02 SET. 2011
adpa11