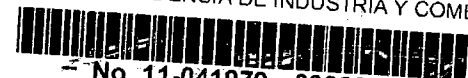


SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-041979-00000-0000

Fecha: 2011-04-05 17:31:29 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1361

Q.F. 21

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

**SOLICITUD
PATENTE DE INVENCION**

21. EXPEDIENTE No.

11-41979

54. TÍTULO

Compuesto para el tratamiento
de la HEPATITIS C.

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE

DOMICILIO

Bristol Myers Squibb Company
Route 206 AND Province Line Road,
Princeton, NJ. 08543-4000. Estados Unidos

74. APODERADO

Alvaro Correa Ochoa

22. BOGOTÁ, D.C.,

Abril 05, 2011

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-041979-00000-0000

Fecha: 2011-04-05 17:31:29 Dep. 2020 DIR.NUEVASCR
Tra. 31 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1361

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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 and Province Line Road Princeton, New Jersey 08543-4000 (US)

Nacionalidad o Domicilio: Estados Unidos
Lugar de Constitución: Estados Unidos

Teléfono: Fax:
E-Mail

IDENTIFICACION

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Número Cual

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 ☐

Número 79.143.366 Usaquén TP 20281

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de propiedad Industrial, sírvase indicar el número de radicación (del poder).

4

INVENTOR (ES)
(72)

Nombre: YEUNG, Kap-Sun; PARCELLA, Kyle E.; BENDER, John A.; BENO, Brett R.; GRANT-YOUNG, Katharine A.; HAN, Ying; HEWAWASAM, Piyasena; KADOW, John F.; NICKEL, Andrew

Dirección: Bristol Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US) y 572 S. Berkeley Avenue San Marino, California 91108 (US)

Nacionalidad o Domicilio: Estados Unidos

5

PCT (85)

Solicitud Internacional No. PCT/US2009/056166

Fecha 08/09/2009

Publicación Internacional No. WO2010/030592

Fecha 18/03/2010

6

Título (54)

Compuestos para el tratamiento de la Hepatitis C.

7

Clasificación Internacional (51)

C07D 307/84; C07D 405/04; C07D 405/10; C07D 405/12; C07D 407/12; C07D 409/12; C07D 413/10; C07D 413/12; C07D 417/10; C07D 417/12; C07D 453/00; C07D 491/10; A61K 31/14; A61P 31/14

8

Prioridad

SI ☒ X NO ☐

(33) País de Origen

US

(32) Fecha

11/09/2008

(31) Número de Solicitud

61/096,005

9

Comprobante de pago No.

11-009864, 11-003368, 11-003568

Fecha 02/02/2011, 13/01/2011, 13/01/2011

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso. Ver documento de Poder General radicado en el Expediente No. 08.129.339
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☒ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Extractos

11

FIGURA CARATERISTICA

12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.E. 79.143.366 de Usaquén

T.P. 20.281

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

-/-



RECIBO DE CAJA

No. 11 - 009864

Bogotá D.C., Febrero 02 de 2011 - 17:09:59

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	387471556	02/02/2011	121.118.700.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVICIOS ADMINISTRATIVOS	5.000.00	5.000.00
				\$5.000.00

SON: **CINCO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-041979- 00000-0000

Fecha: 2011-04-05 17:31:29 Dep. 2020 DIR.NUEVASCR
 Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
 Act. 411 PRESENTACION Folios: 1361

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Febrero 2 de 2011 - 17:10:37

4
2011/001

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 003368

Bogotá D.C., 13 de 2011 - 17:00:38

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	353200315	12/01/2011	148.414.500.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1 50005-01-09	OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVICIOS ADMINISTRATIVOS	22.000.00	22.000.00
				\$22.000.00

SON: **VEINTIDOS MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-041979- -00000-0000

Fecha: 2011-04-05 17:31:29 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1361

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Enero 13 de 2011 - 17:01:18

2011/001

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 003568

Bogotá D.C., 13 de 2011 - 17:00:38

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	353200315	12/01/2011	148.414.500.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNIDITARIO	Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	571.000.00	571.000.00
				\$571.000.00

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-041979- -00000-0000

Fecha: 2011-04-05 17:31:29 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1361



Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO PROPIETARIOS

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

(21) N° de solicitud:

(22) Fecha de solicitud:

(51) Clasificación Internacional :

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

(72) Inventor(es) YEUNG, Kap-Sun; PARCELLA, Kyle E.; BENDER, John A.; BENO, Brett R.; GRANT-YOUNG, Katharine A.; HAN, Ying; HEWAWASAM, Piyasena; KADOW, John F.; NICKEL, Andrew

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad

(31) **No. Prioridad**

(32)

Fecha

(33) **País**

61/096,005

11/09/2008

US

(85) Fecha inicio fase nacional: 11 de Abril de 2011

(87) Publicación internacional

(86) Datos relativos a la presentación de la solicitud PCT

Fecha: 18/03/2010

Fecha de presentación de la solicitud: 08/09/2009

N° publicación: WO2010/030592

No. de solicitud: PCT/US2009/056166

(54) Título: Compuestos para el tratamiento de la Hepatitis C



Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO TEMATICO

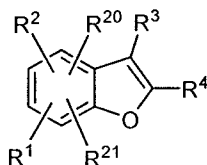
SUPERINTENDENCIA PATENTE DE INVENCION _____ PCT X MODELO DE UTILIDAD _____ DISEÑO INDUSTRIAL _____

(21) N° de solicitud:		(22) Fecha de solicitud:		
(51) Clasificación Internacional :				
(71) Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY				
(72) Inventor(es) YEUNG, Kap-Sun; PARCELLA, Kyle E.; BENDER, John A.; BENO, Brett R.; GRANT-YOUNG, Katharine A.; HAN, Ying; HEWAWASAM, Piyasena; KADOW, John F.; NICKEL, Andrew				
(74) Apoderado: ALVARO CORREA ORDOÑEZ				
(30) Prioridad	(31) No. Prioridad 61/096,005	(32) Fecha 11/09/2008	(33) País US	
(85) Fecha límite inicio fase nacional: 11 de Abril de 2011		(87) Publicación internacional:		
(86) Datos relativos a la presentación de la solíc. PCT		Fecha: 18/03/2010		
Fecha de presentación de la solicitud: 08/09/2009		No. Publicación : WO2010/030592		
No. de solicitud PCT/US2009/056166				
(54) Título: "Compuestos para el tratamiento de la Hepatitis C"				
(57) Resumen:				
La descripción proporciona compuestos de la fórmula I, incluyendo sus sales, así como composiciones y procedimientos para usar los compuestos. Los compuestos presentan actividad contra el virus de la hepatitis C (HCV) y pueden ser útiles en el tratamiento de los infectados por HCV.				
CONTINUA AL RESPALDO ...				

(21) N° de solicitud:		(51) Int Cl:	C07D 307/84; C07D 405/04; C07D 405/10; C07D 405/12; C07D 407/12; C07D409/12; C07D 413/10; C07D 413/12; C07D 417/10; C07D 417/12; C07D 453/00; C07D 491/10; A61K 31/14; A61P 31/14
22) Fecha de solicitud:	(30) Prioridad	(31) No. Prioridad	32) Fecha
		61/096,005	11/09/2008
			(33) País
			US
		(71) Solicitante(s)	BRISTOL-MYERS SQUIBB COMPANY
		(72) Inventor(es)	YEUNG, Kap-Sun; PARCELLA, Kyle E.; BENDER, John A.; BENO, Brett R.; GRANT-YOUNG, Katharine A.; HAN, Ying; HEWAWASAM, Piyasena; KADOW, John F.; NICKEL, Andrew
		(74) Apoderado:	ALVARO CORREA ORDOÑEZ
(54) Título: "Compuestos para el tratamiento de la Hepatitis C"			

Reivindicación(es):

1. Un compuesto de la fórmula I



I

R¹ es R⁵R⁶N; alcoxi; (alcoxicarbonilamino)alcoxi; (alquilfenil)alcoxi; (carboxi)alquenilo; (alcoxicarbonil)alquenilo; (benciloxycarbonil)alquenilo; ((N-dimetilbencil)aminocarbonil)alquenilo; o fenilo donde dicho fenilo está sustituido con 1-2 sustituyentes que se seleccionan a partir del grupo constituido por halo, ciano, alquilo, haloalquilo, hidroxialquilo, alcoxialquilo, (carboxi)alquilo, alcoxi, hidroxialquilo, alcoxialquilo, benciloxi, tetrahidropiraniloxi, carboxi, alcoxicarbonilo, alquilsulfonilo, (carboxi)alquenilo, (alcoxicarbonil)alquenilo, alquilcarboxamido, alcoxicarboxamido, alquilsulfamido, (alquilsulfamido)alquilo, Ar⁵, SO₂NR¹⁵R¹⁶, y CONR⁷R⁸; y donde dicho fenilo también está sustituido con 0-2 sustituyentes que se seleccionan a partir del grupo constituido por halo; nitro; alquilo; cicloalquilo; haloalquilo; aminoalquilo; hidroxialquilo; alcoxialquilo; hidroxi; alcoxi; OR¹⁷; cicloalcoxi; amino; alquilamino; dialquilamino; alquilcarboxamido; alcoxicarboxamido; alcoxialquilcarboxamido; furanilo, tienilo, o pirazolilo sustituido con 0-2 sustituyentes alquilo; piridinilo sustituido con 0-2 sustituyentes halo, ciano, alquilo, hidroxi, alcoxi, amino, o alquilaminocarbonilo; pirimidinilo; pirimidindionilo; aminopirimidinilo; indolilo; isoquinolinilo; y fenilo sustituido con 0-2 sustituyentes que se seleccionan a partir del grupo constituido por halo, alquilo, cianoalquilo, hidroxialquilo, alcoxialquilo, hidroxi, alcoxi, amino, carboxi, alcoxicarbonilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, alquilcarboxamido, carboxialquenilo, y fenilo;

R² es hidrógeno, halo, nitro, amino, fenilo, o R⁵R⁶N;

R³ es ciano, alcoxicarbonilo, (cicloalquil)oxycarbonilo, (alquilsulfonil)aminocarbonilo, CONR¹¹R¹², (R¹¹)(R¹²)NCONH, triazolilo, tiazolilo, o tetrazolilo;

R⁴ es fenilo sustituido con 0-2 sustituyentes halo; ...

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i v)		an assignment from YEUNG, Kap-Sun to BRISTOL-MYERS SQUIBB COMPANY, dated 01 October 2008 (01.10.2008)
VIII-2-1(i v)		an assignment from PARCELLA, Kyle E. to BRISTOL-MYERS SQUIBB COMPANY, dated 01 October 2008 (01.10.2008)
VIII-2-1(i v)		an assignment from BENDER, John A. to BRISTOL-MYERS SQUIBB COMPANY, dated 01 October 2008 (01.10.2008)
VIII-2-1(i v)		an assignment from BENO, Brett R. to BRISTOL-MYERS SQUIBB COMPANY, dated 01 October 2008 (01.10.2008)
VIII-2-1(i v)		an assignment from GRANT-YOUNG, Katharine A. to BRISTOL-MYERS SQUIBB COMPANY, dated 01 October 2008 (01.10.2008)
VIII-2-1(i v)		an assignment from HAN, Ying to BRISTOL-MYERS SQUIBB COMPANY, dated 01 October 2008 (01.10.2008)
VIII-2-1(i v)		an assignment from HEWAWASAM, Piyasena to BRISTOL-MYERS SQUIBB COMPANY, dated 01 October 2008 (01.10.2008)
VIII-2-1(i v)		an assignment from KADOW, John F. to BRISTOL-MYERS SQUIBB COMPANY, dated 24 September 2008 (24.09.2008)
VIII-2-1(i v)		an assignment from NICKEL, Andrew to BRISTOL-MYERS SQUIBB COMPANY, dated 15 September 2008 (15.09.2008)

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
18 March 2010 (18.03.2010)(10) International Publication Number
WO 2010/030592 A1

(51) International Patent Classification:

C07D 307/84 (2006.01) **C07D 413/12** (2006.01)
C07D 405/04 (2006.01) **C07D 417/10** (2006.01)
C07D 405/10 (2006.01) **C07D 417/12** (2006.01)
C07D 405/12 (2006.01) **C07D 453/00** (2006.01)
C07D 407/12 (2006.01) **C07D 491/10** (2006.01)
C07D 409/12 (2006.01) **A61K 31/14** (2006.01)
C07D 413/10 (2006.01) **A61P 31/14** (2006.01)

(21) International Application Number:

PCT/US2009/056166

(22) International Filing Date:

8 September 2009 (08.09.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/096,005 11 September 2008 (11.09.2008) 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): **YEUNG, Kap-Sun** [US/US]; c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **PARCELLA, Kyle E.** [US/US]; c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **BENDER, John A.** [US/US]; c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **BENO, Brett R.** [US/US]; c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **GRANT-YOUNG, Katharine A.** [US/US]; c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **HAN, Ying** [US/US]; c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **HEWAWASAM, Piyasena** [US/US]; c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US).

KADOW, John F. [US/US]; c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **NICKEL, Andrew** [US/US]; 572 S. Berkeley Avenue, San Marino, California 91108 (US).

(74) Agents: **EPPERSON, James 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.

(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))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

(57) Abstract: The disclosure provides compounds of formula I, including their salts, as well as compositions and methods of using the compounds. The compounds have activity against hepatitis C virus (HCV) and may be useful in treating those infected with HCV.

WO 2010/030592 A1

COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional application serial
5 number 61/096,005 filed September 11, 2008.

BACKGROUND OF THE INVENTION

[0002] The disclosure generally relates to the novel compounds of formula I,
including their salts, which have activity against hepatitis C virus (HCV) and are
10 useful in treating those infected with HCV. The disclosure also relates to
compositions and methods of using these compounds.

[0003] Hepatitis C virus (HCV) is a major human pathogen, infecting an
estimated 170 million persons worldwide - roughly five times the number infected by
human immunodeficiency virus type 1. A substantial fraction of these HCV infected
15 individuals develop serious progressive liver disease, including cirrhosis and
hepatocellular carcinoma (Lauer, G.M. et al., *N. Engl. J. Med.*, 345:41-52 (2001)).

[0004] HCV is a positive-stranded RNA virus. Based on a comparison of the
deduced amino acid sequence and the extensive similarity in the 5'-untranslated
region, HCV has been classified as a separate genus in the Flaviviridae family. All
20 members of the Flaviviridae family have enveloped virions that contain a positive
stranded RNA genome encoding all known virus-specific proteins via translation of a
single, uninterrupted, open reading frame.

[0005] Considerable heterogeneity is found within the nucleotide and encoded
amino acid sequence throughout the HCV genome. At least six major genotypes have
25 been characterized, and more than 50 subtypes have been described. The major
genotypes of HCV differ in their distribution worldwide, and the clinical significance
of the genetic heterogeneity of HCV remains elusive despite numerous studies of the
possible effect of genotypes on pathogenesis and therapy.

[0006] The single strand HCV RNA genome is approximately 9500 nucleotides
30 in length and has a single open reading frame (ORF) encoding a single large
polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved
at multiple sites by cellular and viral proteases to produce the structural and non-

structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV. The HCV NS5B protein is described in "Structural Analysis of the Hepatitis C Virus RNA Polymerase in Complex with Ribonucleotides (Bressanelli, S. et al., *J. Virol.*, 3482-3492 (2002); and Defrancesco et al., *Clinics in Liver Disease*, 7:211-242 (2003)).

[0007] Currently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients (Poynard, T. et al., *Lancet*, 352:1426-1432 (1998)). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy (Zeuzem, S. et al., *N. Engl. J. Med.*, 343:1666-1672 (2000)). However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and important need to develop effective therapeutics for treatment of HCV infection.

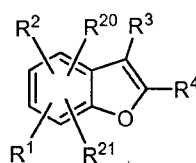
[0008] HCV-796, an HCV NS5B inhibitor, showed an ability to reduce HCV RNA levels in patients. The viral RNA levels decreased transiently and then rebounded during dosing when treatment was with the compound as a single agent but levels dropped more robustly when combined with the standard of care which is a form of interferon and ribavirin. The development of this compound was suspended due to hepatic toxicity observed during extended dosing of the combination regimens.

U.S. Patent No. 7,265,152 and the corresponding PCT patent application WO 2004/041201 A2 describe compounds of the HCV-796 class.

[0009] The invention provides technical advantages, for example, the compounds are novel and are effective against hepatitis C. Additionally, the compounds provide advantages for pharmaceutical uses, for example, with regard to one or more of their mechanism of action, binding, inhibition efficacy, target selectivity, solubility, safety profiles, or bioavailability.

DESCRIPTION OF THE INVENTION

10 [0010] One aspect of the invention is a compound of formula I



I

R^1 is R^5R^6N ; alkoxy; (alkoxycarbonylamino)alkoxy; (alkylphenyl)alkoxy; (carboxy)alkenyl; (alkoxycarbonyl)alkenyl; (benzyloxycarbonyl)alkenyl; ((N-dimethylbenzyl)aminocarbonyl)alkenyl; or phenyl where said phenyl is substituted with 1-2 substituents selected from the group consisting of halo, cyano, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (carboxy)alkyl, alkoxy, hydroxyalkyloxy, alkoxyalkyloxy, benzyloxy, tetrahydropyranyloxy, carboxy, alkoxycarbonyl, alkylsulfonyl, (carboxy)alkenyl, (alkoxycarbonyl)alkenyl, alkylcarboxamido, alkoxy-carboxamido, alkylsulfamido, (alkylsulfamido)alkyl, Ar^5 , $SO_2NR^{15}R^{16}$, and $CONR^7R^8$; and where said phenyl is also substituted with 0-2 substituents selected from the group consisting of halo; nitro; alkyl; cycloalkyl; haloalkyl; aminoalkyl; hydroxyalkyl; alkoxyalkyl; hydroxy; alkoxy; OR^{17} ; cycloalkoxy; amino; alkylamino; dialkylamino; alkylcarboxamido; alkoxycarboxamido; alkoxyalkylcarboxamido; furanyl, thienyl, or pyrazolyl substituted with 0-2 alkyl substituents; pyridinyl substituted with 0-2 halo, cyano, alkyl, hydroxy, alkoxy, amino, or alkylaminocarbonyl substituents; pyrimidinyl; pyrimidinedionyl; aminopyrimidinyl; indolyl; isoquinolinyl; or phenyl substituted with 0-2 substituents selected from halo, alkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, amino, carboxy,

alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarboxamido, carboxyalkenyl, and phenyl;

R^2 is hydrogen, halo, nitro, amino, phenyl, or R^5R^6N ;

R^3 is cyano, alkoxycarbonyl, (cycloalkyl)oxycarbonyl,

5 (alkylsulfonyl)aminocarbonyl, $CONR^{11}R^{12}$, $(R^{11})(R^{12})NCONH$, triazolyl, thiazolyl, or tetrazolyl;

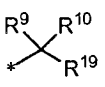
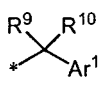
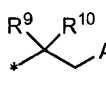
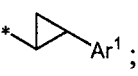
R^4 is phenyl substituted with 0-2 halo substituents;

R^5 is hydrogen, alkyl, or alkylsulfonyl;

R^6 is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or alkylsulfonyl;

10 R^7 is hydrogen, alkyl, alkenyl, alkynyl, cyanoalkyl, haloalkyl, hydroxyalkyl, dihydroxyalkyl, alkoxyalkyl, oxoalkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkyl)alkyl, cycloalkyl, (alkyl)cycloalkyl, (hydroxyalkyl)cycloalkyl, (tetrahydrofuranyl)alkyl, (tetrahydropyranyl)alkyl, (carboxy)alkyl, (alkoxycarbonyl)alkyl, (alkenyloxycarbonyl)alkyl,

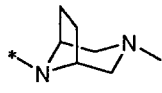
15 (alkoxycarbonyl)hydroxyalkyl, $(CONR^{13}R^{14})alkyl$, $(CONR^{13}R^{14})(hydroxyalkyl)alkyl$, $(CONR^{13}R^{14})cycloalkyl$, (alkylcarbonyl)aminoalkyl, (phenyl)alkyl, (pyridinyl)alkyl,

alkylsulfonyl, phenylsulfonyl, Ar^2 , Ar^3 , , , , or 

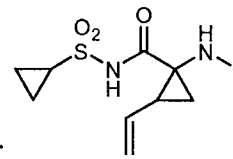
R^8 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

20 or R^7R^8N taken together is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, dihydroindolyl, or isoindolyl, and is substituted with 0-2 substituents selected from alkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, carboxy, alkoxycarbonyl, dialkylcarboxamido, alkylcarbonylamino, alkoxycarbonylamino, pyridinyl, and phenyl where said phenyl is substituted with 0-2 halo or alkyl

25 substituents;

or where R^7R^8N taken together is , (quinuclidinyl)amino, (quinuclidinyl)(alkyl)amino, (methylpyrrolidinyl)(alkyl)amino, ((imidazolyl)alkyl)(hydroxyalkyl)amino, (alkylthiazolyl)amino,

((carboxamido)cyclopentanyl)amino, ((halophenyl)cyclopentanyl)amino, 3H-



spiro(isobenzofuranyl)piperidinyl, (hydroxyindanyl)amino, or

R^9 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

R^{10} is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

5 or R^9 and R^{10} taken together is ethylene, propylene, butylene, pentylene, or hexylene;

R^{11} is hydrogen, alkyl, or cycloalkyl;

R^{12} is hydrogen, alkyl, or cycloalkyl;

or R^{11} and R^{12} taken together with the nitrogen to which they are attached is

10 azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

R^{13} is hydrogen, alkyl, cyanoalkyl, haloalkyl, alkenyl, alkynyl, or thiazolyl;

R^{14} is hydrogen or alkyl;

R^{15} is hydrogen, alkyl, hydroxyalkyl, cycloalkyl, or benzyl;

R^{16} is hydrogen or alkyl;

15 or R^{15} and R^{16} taken together with the nitrogen to which they are attached is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

R^{17} is haloalkyl, cyanoalkyl, (cycloalkyl)alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (R^{18})alkyl, (Ar^4)alkyl, alkynyl, or aminocycloalkyl;

R^{18} is $CONH_2$, H_2NCONH , dibenzylamino, phthalimido, amino, alkylamino,

20 dialkylamino, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl where azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl is substituted with 0-3 alkyl or alkoxy carbonyl substituents;

R^{19} is cyano, hydroxyalkyl, morpholinylalkyl, carboxy, alkoxy carbonyl, cycloalkylsulfoxamido, ((alkyl)pyrazolyl)amino, ((alkyl)isoxazolyl)amino,

25 (thiadiazolyl)amino, (triazinyl)amino, or alkynylaminocarbonyl;

R^{20} is hydrogen, halo, alkyl, or alkoxy;

R^{21} is hydrogen, halo, alkyl, or alkoxy;

Ar^1 is phenyl, naphthalenyl, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, oxadiathiazolyl,

30 triazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, or benzothiazolyl, and is substituted with

0-2 substituents selected from halo, alkyl, cycloalkyl, haloalkyl, alkoxyalkyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, aminocarbonyl, pyridinyl, phenyl, halophenyl, alkylphenyl, and alkoxyphenyl;

Ar² is phenyl, biphenyl, or pyridinyl and is substituted with 0-2 substituents
5 selected from halo, alkyl, cyano, hydroxy, alkoxy, and carboxy;

Ar³ is pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, oxathiadiazolyl, pyrimidinyl, or pyrizinyl and is substituted with 0-2 substituents selected from hydroxy, alkyl, hydroxyalkyl, and CONR¹³R¹⁴;

Ar⁴ is furanyl, thienyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl,
10 imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridinyl, indolyl, or phenyl and is substituted with 0-2 substituents selected from halo, alkyl, haloalkyl, hydroxyl, and alkoxy; and

Ar⁵ is pyrrolyl, imidazolyl, or oxadiazolyl and is substituted with 0-2 substituents selected from alkyl, carboxy, alkoxycarbonyl, benzyl, and phenyl;
15 or a pharmaceutically acceptable salt thereof.

[0011] Another aspect of the invention is a compound of formula I where R²⁰ and R²¹ are hydrogen.

[0012] Another aspect of the invention is a compound of formula I where
20 R¹ is R⁵R⁶N; (carboxy)alkenyl; (alkoxycarbonyl)alkenyl; (benzyloxycarbonyl)alkenyl; or phenyl where said phenyl is substituted with 1-2 substituents selected from the group consisting of cyano, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, hydroxyalkyloxy, alkoxyalkyloxy, haloalkyl, benzyloxy, carboxy, alkoxycarbonyl, alkylsulfonyl, (carboxy)alkenyl, (alkoxycarbonyl)alkenyl,
25 alkylcarboxamido, alkoxycarboxamido, alkylsulfamido, (alkylsulfamido)alkyl, tetrahydropyranyloxy, Ar⁵, SO₂NR¹⁵R¹⁶, and CONR⁷R⁸; and where said phenyl is also substituted with 0-1 substituents selected from the group consisting of halo; alkyl; hydroxyalkyl; alkoxyalkyl; hydroxyl; alkoxy; OR¹⁷; cycloalkoxy; amino; alkylamino; dialkylamino; alkylcarboxamido; alkoxyalkylcarboxamido; furanyl;
30 indolyl; isoquinolinyl; pyridinyl substituted with 0-2 halo, alkyl, hydroxy, or alkoxy substituents; pyrazolyl substituted with 0-2 alkyl substituents; and phenyl substituted with 0-2 halo, alkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy,

carboxy, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarboxamido, carboxyalkenyl, or phenyl substituents;

R^2 is hydrogen, nitro, or R^5R^6N ;

R^3 is cyano, alkoxy carbonyl, (cycloalkyl)oxy carbonyl,

5 (alkylsulfonyl)aminocarbonyl, $CONR^{11}R^{12}$, $(R^{11})(R^{12})NCONH$, triazolyl, thiazolyl, or tetrazolyl;

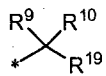
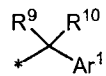
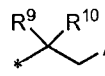
R^4 is phenyl substituted with 0-2 halo substituents;

R^5 is hydrogen, alkyl, or alkylsulfonyl;

R^6 is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or alkylsulfonyl;

10 R^7 is hydrogen, alkyl, alkenyl, alkynyl, cyanoalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, oxoalkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkyl)alkyl, cycloalkyl, (alkyl)cycloalkyl, (hydroxyalkyl)cycloalkyl, (tetrahydrofuranyl)alkyl, (tetrahydropyranyl)alkyl, (carboxy)alkyl, (alkoxy carbonyl)alkyl, (alkoxy carbonyl)hydroxyalkyl, $(CONR^{13}R^{14})$ alkyl,

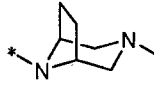
15 (alkylcarbonyl)aminoalkyl, (phenyl)alkyl, (pyridinyl)alkyl, alkylsulfonyl,

phenylsulfonyl, Ar^2 , Ar^3 , , , , or ;

R^8 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

or R^7R^8N taken together is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or dihydroindolyl, and is substituted with 0-2 substituents selected from

20 alkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, carboxy, alkoxy carbonyl, dimethylcarboxamido, alkylcarbonylamino, alkoxy carbonylamino, pyridinyl, and phenyl where phenyl is substituted with 0-2 substituents selected from halo and alkyl;

or where R^7R^8N taken together is , (quinuclidinyl)(alkyl)amino, (methylpyrrolidinyl)(alkyl)amino, (alkylthiazolyl)amino,

25 ((carboxamido)cyclopentanyl)amino, ((halophenyl)cyclopentanyl)amino, or (hydroxyindanyl)amino;

R^9 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

R^{10} is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

or R^9 and R^{10} taken together is ethylene, propylene, butylene, or pentylene;

30 R^{11} is hydrogen, alkyl, or cycloalkyl;

- R¹² is hydrogen, alkyl, or cycloalkyl;
 or R¹¹ and R¹² taken together with the nitrogen to which they are attached is
 azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;
 R¹³ is hydrogen, alkyl, cyanoalkyl, alkenyl, or alkynyl;
 5 R¹⁴ is hydrogen or alkyl;
 R¹⁵ is hydrogen or alkyl;
 R¹⁶ is hydrogen or alkyl;
 R¹⁷ is haloalkyl, hydroxyalkyl, alkoxyalkyl, alkynyl, (R¹⁸)alkyl or (Ar⁴)alkyl;
 R¹⁸ is CONH₂, dibenzylamino, amino, alkylamino, dialkylamino, azetidiny,
 10 pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl where azetidiny, pyrrolidinyl,
 piperidinyl, piperazinyl, or morpholinyl, and is substituted with 0-3 substituents
 selected from alkyl and alkoxycarbonyl;
 R¹⁹ is cyano, ((alkyl)pyrazolyl)amino, ((alkyl)isoxazolyl)amino
 (thiadiazolyl)amino, or (triazinyl)amino;
 15 R²⁰ and R²¹ are hydrogen;
 Ar¹ is phenyl, naphthalenyl, pyridinyl, thienyl, thiazolyl, or pyrazinyl and is
 substituted with 0-2 substituents selected from alkyl, halo, hydroxy, alkoxy, amino,
 alkylamino, and dialkylamino;
 Ar² is phenyl, biphenyl, or pyridinyl and is substituted with 0-2 substituents
 20 selected from halo, alkyl, cyano, hydroxy, and alkoxy;
 Ar³ is pyrazolyl isoxazolyl, thiazolyl, pyrimidinyl, or pyrizinyl and is
 substituted with 0-2 substituents selected from alkyl and hydroxyalkyl;
 Ar⁴ is pyrrolyl, imidazolyl, pyridinyl, indolyl, or phenyl and is substituted
 with 0-2 substituents selected from halo, alkyl, hydroxyl, and alkoxy; and
 25 Ar⁵ is pyrrolyl, imidazolyl, or oxadiazolyl and is substituted with 0-2
 substituents selected from alkyl, carboxy, alkoxycarbonyl, benzyl, and phenyl;
 or a pharmaceutically acceptable salt thereof.

- [0013] Another aspect of the invention is a compound of formula I where
 30 R¹ is alkoxy; (alkoxycarbonylamino)alkoxy; (alkylphenyl)alkoxy;
 (carboxy)alkenyl; ((N-dimethylbenzyl)aminocarbonyl)alkenyl; or phenyl where said
 phenyl is substituted with 1-2 substituents selected from the group consisting of halo,

cyano, alkyl, haloalkyl, hydroxyalkyl, (carboxy)alkyl, alkoxy, hydroxyalkyloxy, tetrahydropyranyloxy, carboxy, alkoxycarbonyl, (carboxy)alkenyl, alkylcarboxamido, alkoxycarboxamido, (alkylsulfamido)alkyl, Ar^5 , $SO_2NR^{15}R^{16}$, and $CONR^7R^8$; and where said phenyl is also substituted with 0-2 substituents selected from the group

5 consisting of halo; nitro; alkyl; cycloalkyl; haloalkyl; aminoalkyl; hydroxy; alkoxy; OR^{17} ; cycloalkoxy; amino; alkoxycarboxamido; furanyl, thienyl, or pyrazolyl substituted with 0-2 alkyl substituents; pyridinyl substituted with 0-2 halo, cyano, alkyl, hydroxy, alkoxy, amino, or alkylaminocarbonyl substituents; pyrimidinyl; pyrimidinedionyl; aminopyrimidinyl; indolyl; isoquinolinyl; and phenyl substituted

10 with 0-2 substituents selected from halo, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, amino, carboxy, aminocarbonyl, alkylaminocarbonyl, alkylcarboxamido, and carboxyalkenyl;

R^2 is hydrogen, halo, nitro, amino, phenyl, or R^5R^6N ;

R^3 is $CONR^{11}R^{12}$;

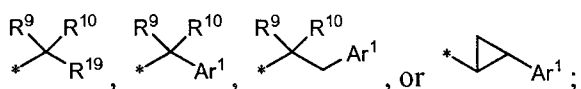
15 R^4 is phenyl substituted with 0-2 halo substituents;

R^5 is hydrogen or alkylsulfonyl;

R^6 is hydrogen, alkyl, hydroxyalkyl, or alkylsulfonyl;

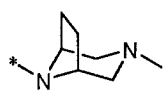
R^7 is hydrogen, alkyl, alkynyl, cyanoalkyl, haloalkyl, hydroxyalkyl, dihydroxyalkyl, alkoxyalkyl, oxoalkyl, (dialkylamino)alkyl, (cycloalkyl)alkyl,

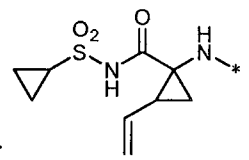
20 cycloalkyl, (alkyl)cycloalkyl, (hydroxyalkyl)cycloalkyl, (tetrahydrofuranyl)alkyl, (tetrahydropyranyl)alkyl, (carboxy)alkyl, (alkoxycarbonyl)alkyl, (alkenyloxycarbonyl)alkyl, (alkoxycarbonyl)hydroxyalkyl, $(CONR^{13}R^{14})$ alkyl, $(CONR^{13}R^{14})(hydroxyalkyl)$ alkyl, $(CONR^{13}R^{14})$ cycloalkyl, (alkylcarbonyl)aminoalkyl, (phenyl)alkyl, alkylsulfonyl, phenylsulfonyl, Ar^2 , Ar^3 ,

25 ; R^8 is hydrogen, alkyl, or alkoxyalkyl;

or R^7R^8N taken together is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, dihydroindolyl, or isoindolinyl, and is substituted with 0-2 substituents selected from alkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxycarbonyl,

30 dialkylcarboxamido, alkylcarbonylamino, pyridinyl, and phenyl where said phenyl is substituted with 0-2 halo or alkyl substituents;

or where R^7R^8N taken together is , (quinuclidinyl)amino, (quinuclidinyl)(alkyl)amino, (methylpyrrolidinyl)(alkyl)amino, ((imidazolyl)alkyl)(hydroxyalkyl)amino, (alkylthiazolyl)amino, ((carboxamido)cyclopentanyl)amino, ((halophenyl)cyclopentanyl)amino, 3H-



- 5 spiro(isobenzofuranyl)piperidinyl, (hydroxyindanyl)amino, or
 R^9 is hydrogen, alkyl, or hydroxyalkyl;
 R^{10} is hydrogen or alkyl;
or R^9 and R^{10} taken together is ethylene or propylene;
 R^{11} is alkyl;
10 R^{12} is hydrogen;
 R^{13} is hydrogen, alkyl, cyanoalkyl, haloalkyl, alkenyl, or thiazolyl;
 R^{14} is hydrogen or alkyl;
 R^{15} is alkyl, hydroxyalkyl, cycloalkyl, or benzyl;
 R^{16} is hydrogen;
15 or R^{15} and R^{16} taken together with the nitrogen to which they are attached is
azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;
 R^{17} is haloalkyl, cyanoalkyl, (cycloalkyl)alkyl, hydroxyalkyl, alkoxyalkyl,
aminoalkyl, (R^{18})alkyl, (Ar^4)alkyl, alkynyl, or aminocycloalkyl;
 R^{18} is $CONH_2$, H_2NCONH , dibenzylamino, phthalimido, amino,
20 dialkylamino, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl where azetidiny,
pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl is substituted with 0-3 alkyl or
alkoxycarbonyl substituents;
 R^{19} is cyano, hydroxyalkyl, morpholinylalkyl, carboxy, alkoxy, carbonyl,
cycloalkylsulfoxamido, ((alkyl)pyrazolyl)amino, ((alkyl)isoxazolyl)amino,
25 (thiadiazolyl)amino, (triazinyl)amino, or alkynylaminocarbonyl;
 R^{20} and R^{21} are hydrogen;
 Ar^1 is phenyl, naphthalenyl, pyridinyl, furanyl, pyrazolyl, isoxazolyl,
imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyrazinyl,

pyrimidinyl, or benzothiazolyl, and is substituted with 0-2 substituents selected from halo, alkyl, cycloalkyl, haloalkyl, alkoxyalkyl, hydroxy, alkoxy, amino, aminocarbonyl, pyridinyl, phenyl, halophenyl, alkylphenyl, and alkoxyphenyl;

Ar² is phenyl, biphenyl, or pyridinyl and is substituted with 0-2 substituents
5 selected from halo, alkyl, cyano, hydroxy, alkoxy, and carboxy;

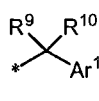
Ar³ is pyrazolyl, isoxazolyl, thiazolyl, triazolyl, pyrimidinyl, or pyridinyl and is substituted with 0-2 substituents selected from hydroxy, alkyl, and CONR¹³R¹⁴;

Ar⁴ is furanyl, pyrrolyl, pyrazolyl, isoxazolyl, imidazolyl, oxadiazolyl, triazolyl, pyridinyl, indolyl, or phenyl and is substituted with 0-2 substituents selected
10 from halo, alkyl, haloalkyl, and hydroxy; and

Ar⁵ is pyrrolyl, imidazolyl, or oxadiazolyl and is substituted with 0-2 substituents selected from alkyl, alkoxy, carbonyl, benzyl, and phenyl;

or a pharmaceutically acceptable salt thereof.

15 [0014] Another aspect of the invention is a compound of formula I where R¹ is phenyl substituted with 1 CONR⁷R⁸ substituent and also substituted with 0-2 halo, alkyl, or alkoxy substituents; R² is hydrogen, halo, or R⁵R⁶N; R³ CONR¹¹R¹²; R⁴ is

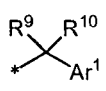
monofluorophenyl; R⁵ is alkylsulfonyl; R⁶ is hydroxyalkyl; R⁷ is ; R⁸ is hydrogen; R⁹ is alkyl; R¹⁰ is alkyl or R⁹ and R¹⁰ taken together is ethylene or
20 propylene; R¹¹ is alkyl; R¹² is hydrogen; R²⁰ and R²¹ are hydrogen; Ar¹ is phenyl, pyridinyl, pyrimidinyl, isoxazolyl, oxazolyl, or oxadiazolyl, and is substituted with 0-1 halo or alkyl substituents; or a pharmaceutically acceptable salt thereof.

[0015] Another aspect of the invention is a compound of formula I where R¹ is phenyl substituted with 1-2 substituents selected from the group consisting of halo, cyano, alkyl, haloalkyl, hydroxyalkyl, (carboxy)alkyl, alkoxy, hydroxyalkoxy, tetrahydropyranyloxy, carboxy, alkoxy, carbonyl, (carboxy)alkenyl, alkylcarboxamido, alkoxy, carboxamido, (alkylsulfamido)alkyl, Ar⁵, SO₂NR¹⁵R¹⁶, and CONR⁷R⁸; and
25 where said phenyl is also substituted with 0-2 substituents selected from the group consisting of halo; nitro; alkyl; cycloalkyl; haloalkyl; aminoalkyl; hydroxy; alkoxy; OR¹⁷; cycloalkoxy; amino; alkoxy, carboxamido; furanyl, thienyl, or pyrazolyl
30 substituted with 0-2 alkyl substituents; pyridinyl substituted with 0-2 halo, cyano,

alkyl, hydroxy, alkoxy, amino, or alkylaminocarbonyl substituents; pyrimidinyl; pyrimidinedionyl; aminopyrimidinyl; indolyl; isoquinolinyl; and phenyl substituted with 0-2 substituents selected from halo, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, amino, carboxy, aminocarbonyl, alkylaminocarbonyl, alkylcarboxamido, and carboxyalkenyl.

[0016] Another aspect of the invention is a compound of formula I where R^1 is phenyl substituted with 1 $CONR^7R^8$ substituent and also substituted with 0-2 halo, alkyl, or alkoxy substituents.

[0017] Another aspect of the invention is compound of formula I where R^7 is

10  and at least one of R^9 and R^{10} is not hydrogen.

[0018] Another aspect of the invention is compound of formula I where R^2 is R^5R^6N .

[0019] Another aspect of the invention is compound of formula I where R^3 is $CONR^{11}R^{12}$.

15 [0020] Another aspect of the invention is compound of formula I where R^4 is phenyl or monofluorophenyl.

[0021] Unless specified otherwise, these terms have the following meanings.

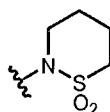
"Alkyl" means a straight or branched alkyl group composed of 1 to 6 carbons.

20 "Alkenyl" means a straight or branched alkyl group composed of 2 to 6 carbons with at least one double bond. "Cycloalkyl" means a monocyclic ring system composed of 3 to 7 carbons. "Hydroxyalkyl," "alkoxy" and other terms with a substituted alkyl moiety include straight and branched isomers composed of 1 to 6 carbon atoms for the alkyl moiety. "Haloalkyl" and "haloalkoxy" include all halogenated isomers from monohalo substituted alkyl to perhalo substituted alkyl. "Aryl" includes carbocyclic and heterocyclic aromatic substituents. Parenthetical and multiparenthetical terms are intended to clarify bonding relationships to those skilled in the art. For example, a term such as ((R)alkyl) means an alkyl substituent further substituted with the substituent R.

30 [0022] Substituents which are illustrated by chemical drawing to bond at variable positions on a multiple ring system (for example a bicyclic ring system) are intended

to bond to the ring where they are drawn to append. For example, substituents R¹ and R² of formula I are intended to bond to the benzene ring of formula I and not to the furan ring.

[0023] Ethylene means ethanediyl or -CH₂CH₂-; propylene means propanediyl or
5 -CH₂CH₂CH₂-; butylene means butanediyl or -CH₂CH₂CH₂CH₂-; pentylene means pentanediyl or -CH₂CH₂CH₂CH₂CH₂-.



[0024] Dioxothiazinyl means

[0025] Any scope of any variable, including R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, Ar¹, Ar², Ar³, Ar⁴, or Ar⁵ can
10 be used independently with the scope of any other instance of a variable.

[0026] The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made
15 according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucuronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine,
20 bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

[0027] Some of the compounds of the invention possess asymmetric carbon atoms. The invention includes all stereoisomeric forms, including enantiomers and
25 diastereomers as well as mixtures of stereoisomers such as racemates. Some stereoisomers can be made using methods known in the art. Stereoisomeric mixtures of the compounds and related intermediates can be separated into individual isomers according to methods known in the art.

[0028] The invention is intended to include all isotopes of atoms occurring in the
30 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

5 analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic

10 properties.

SYNTHETIC METHODS

[0029] The compounds may be made by methods known in the art including those described below and including variations within the skill of the art. Some reagents

15 and intermediates are known in the art. Other reagents and intermediates can be made by methods known in the art using readily available materials. The variables (*e.g.*, numbered "R" substituents) used to describe the synthesis of the compounds are intended only to illustrate how to make the compounds and are not to be confused with variables used in the claims or in other sections of the specification. The

20 following methods are for illustrative purposes and are not intended to limit the scope of the invention.

[0030] Abbreviations used in the schemes generally follow conventions used in the art. Chemical abbreviations used in the specification and examples are defined as follows: "NaHMDS" for sodium bis(trimethylsilyl)amide; "DMF" for N,N-

25 dimethylformamide; "MeOH" for methanol; "NBS" for N-bromosuccinimide; "Ar" for aryl; "TFA" for trifluoroacetic acid; "LAH" for lithium aluminum hydride; "BOC", "DMSO" for dimethylsulfoxide; "h" for hours; "rt" for room temperature or retention time (context will dictate); "min" for minutes; "EtOAc" for ethyl acetate; "THF" for tetrahydrofuran; "EDTA" for ethylenediaminetetraacetic acid; "Et₂O" for

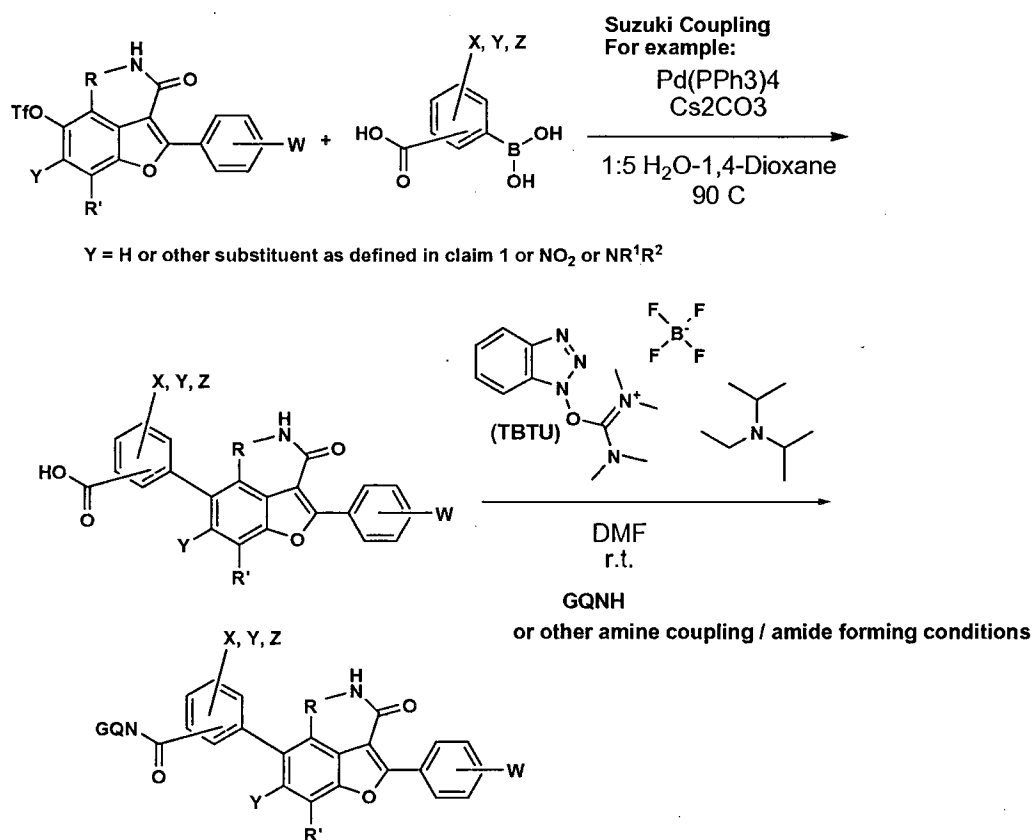
30 diethyl ether; "DMAP" for 4-dimethylaminopyridine; "DCE" for 1,2-dichloroethane; "ACN" for acetonitrile; "DME" for 1,2-dimethoxyethane; "HOBt" for 1-

hydroxybenzotriazole hydrate; "DIEA" for diisopropylethylamine, "Nf" for $\text{CF}_3(\text{CF}_2)_3\text{SO}_2^-$; and "TMOF" for trimethylorthoformate.

[0031] As shown in Scheme 1, some compounds of the invention may be prepared by coupling a benzofuran triflate or halide to a substituted phenyl boronic acid that in some examples contains a carboxylic acid or carboxylic acid ester. Other coupling techniques and conditions are also known in the art as are other carbon-carbon bond forming reactions. Acids and esters may be converted to amides by methods known in the art.

10

Scheme 1



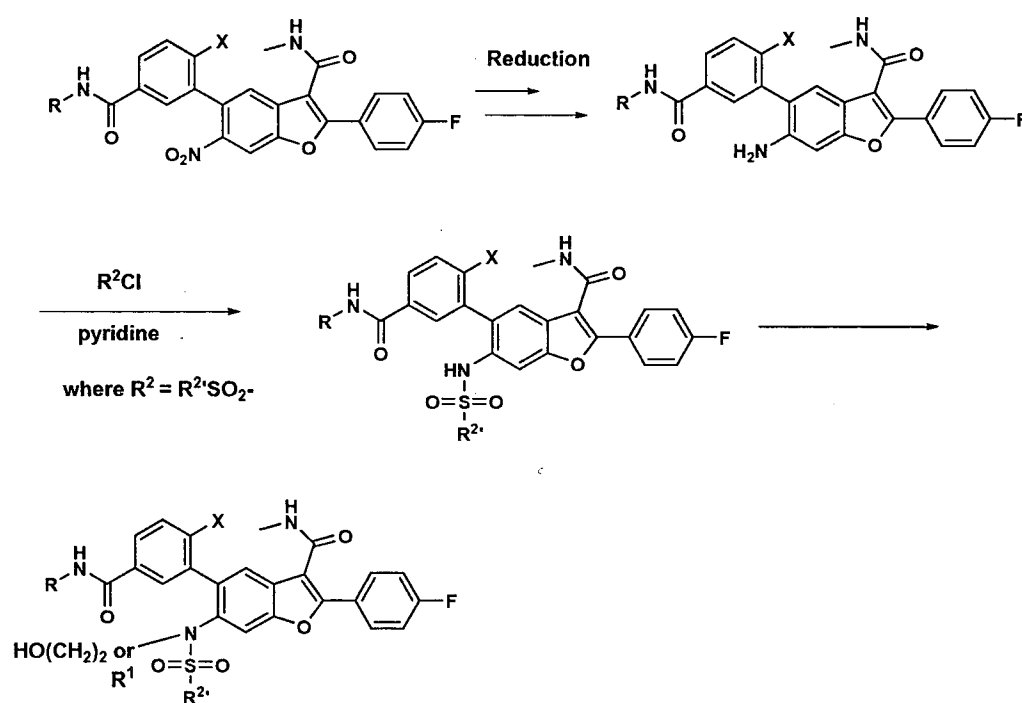
[0032] Scheme 2 depicts one specific example of Scheme 1.

15 [0033] As shown in Scheme 2, a nitro group on the benzofuran ring may be reduced and the resulting amino group may be functionalized using known chemistry. For example, the amine may be converted to a monosulfonamide via reaction with a

sulfonyl chloride or by preparation of a bis sulfonamide followed by selective hydrolysis. The monosulfonamide may be alkylated again with either a simple or functionalized alkyl. In Scheme 3, the hydroxyl ethyl group is unmasked via acidic removal of the silyl protecting group.

5

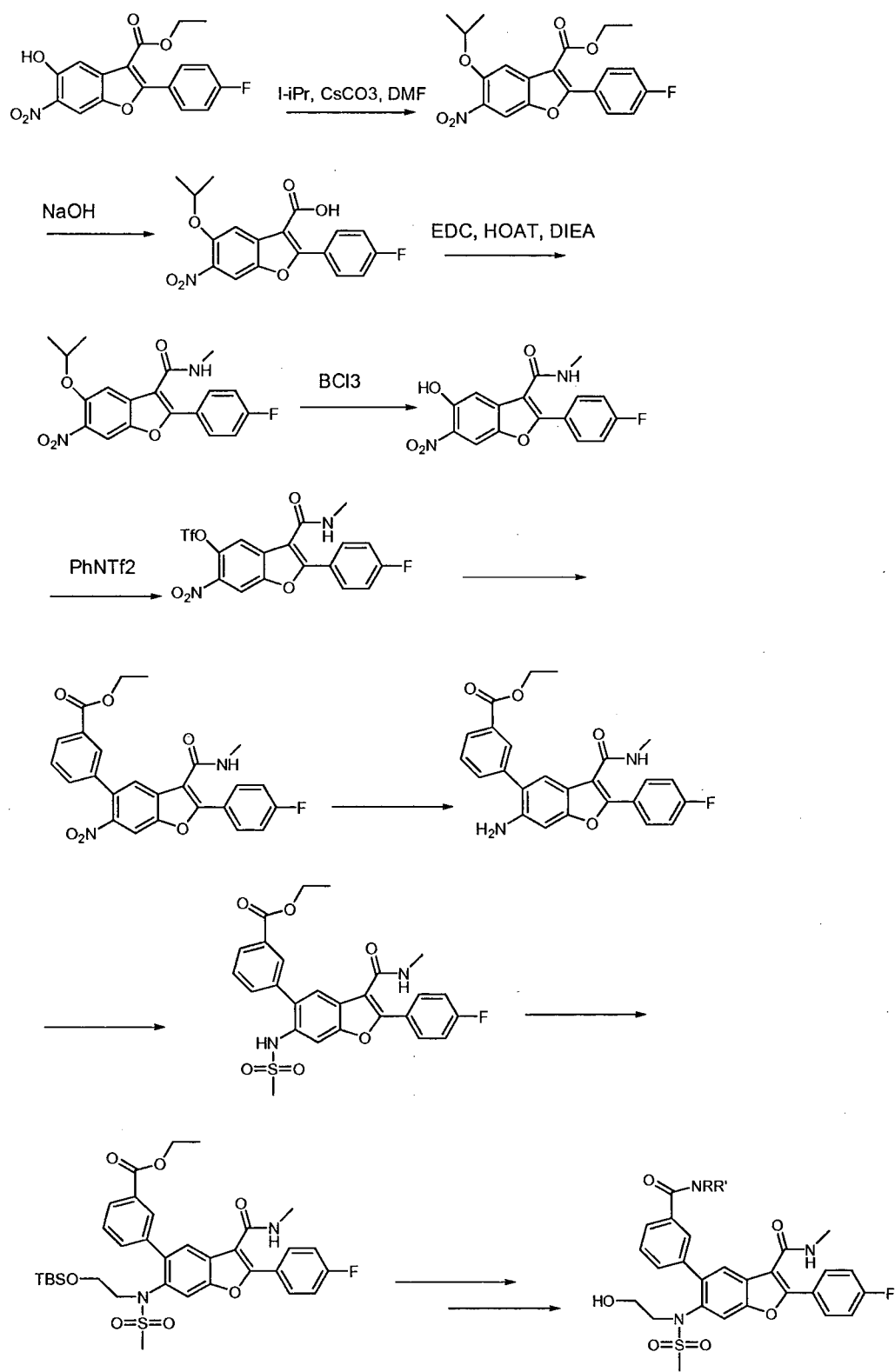
Scheme 2



[0034] Scheme 3 depicts the preparation of two intermediates labeled as common intermediate 1 and 2 which can be used to prepare some compounds of the invention. The isopropyl group is used to temporarily mask the C5 hydroxy group so the methyl amide can be constructed from the ethyl ester. The more advanced common intermediate 2 allows functionalization of the sulfonamide, acid deprotection and formation of some amide compounds after coupling of amines to the acid as described earlier.

15

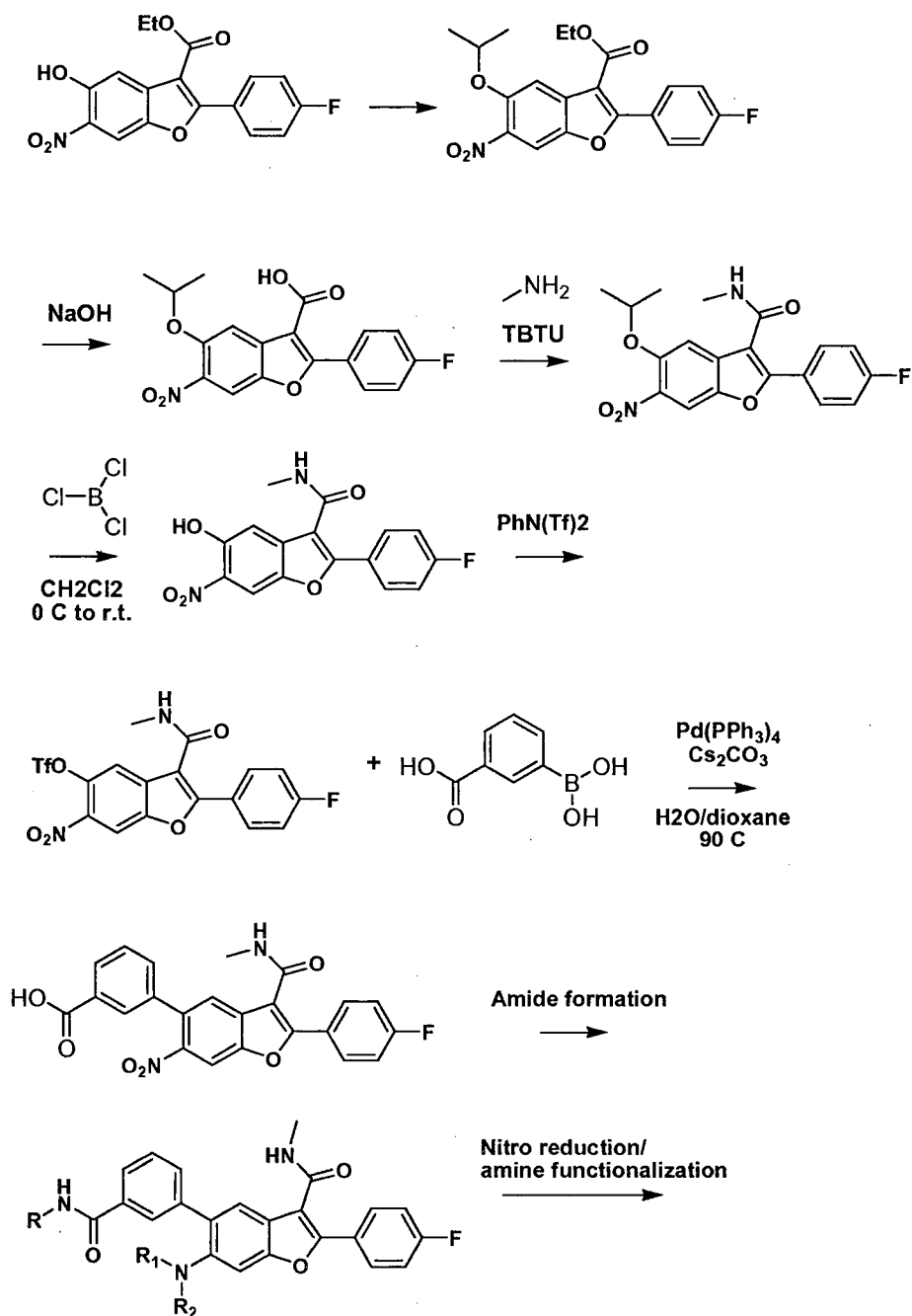
Scheme 3



[0035] Scheme 4 depicts some conditions for preparing some of the compounds described and for accessing an alternate common intermediate 3 which allows amide formation prior to nitro reduction and amine functionalization.

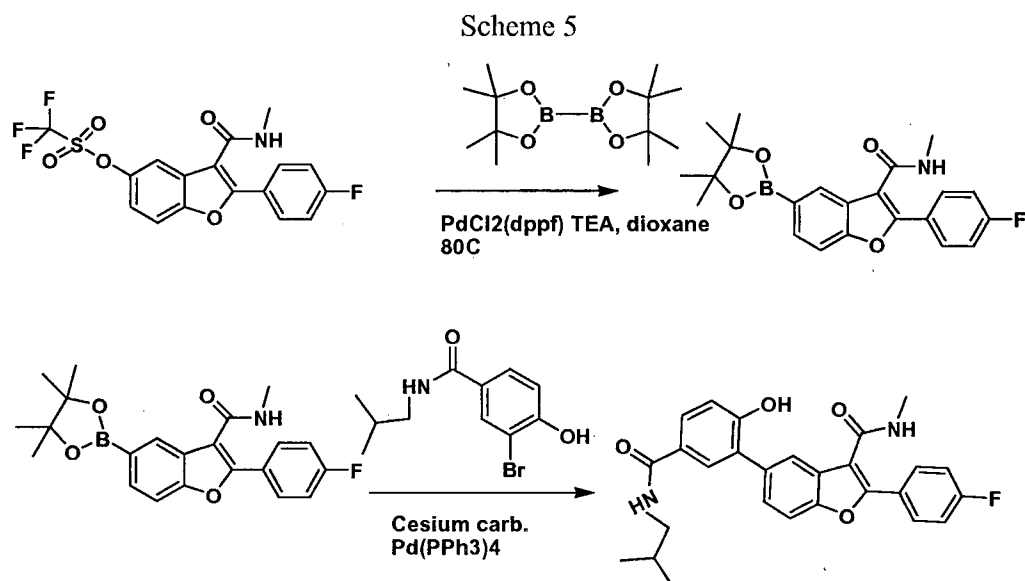
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Scheme 4



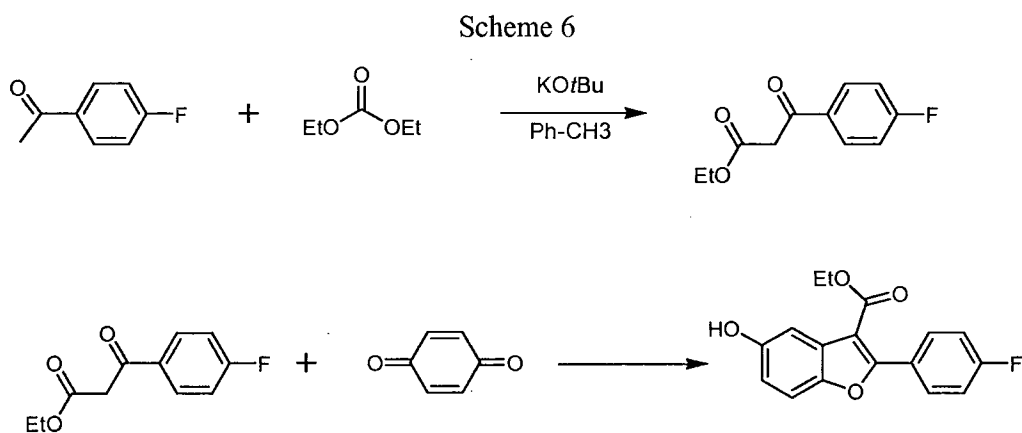
[0036] Scheme 5 illustrates a method for preparing some compounds by preparing 2-(4-fluorophenyl)-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide in which the boron is attached to the benzofuran and then coupling to triflates or halogen containing aryl moieties.

5



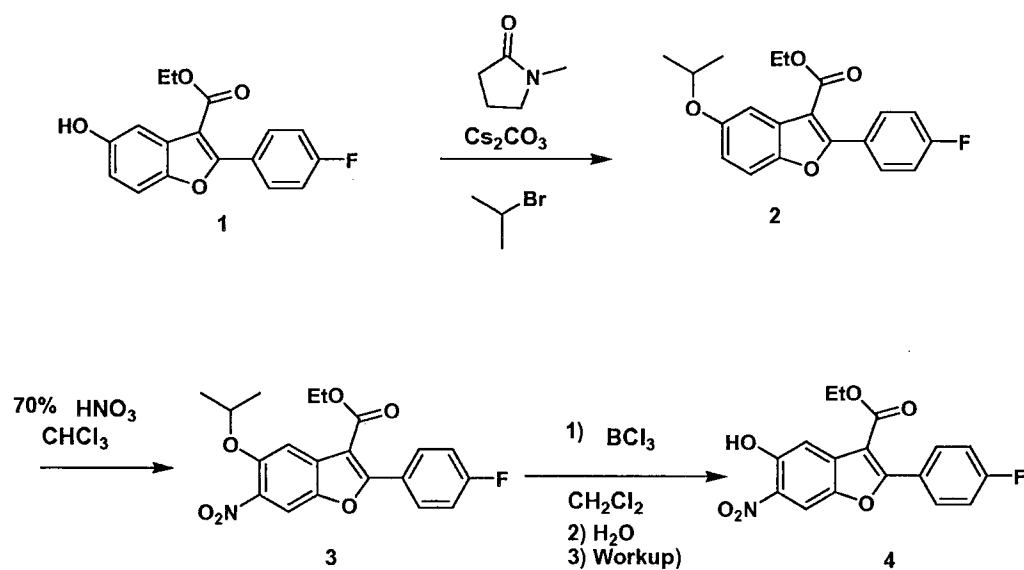
[0037] Scheme 6 shows a preparation of the functionalized benzofuran and

10 Scheme 7 shows one method for installation of nitrogen functionality which can then functionalized as described in the previous schemes.



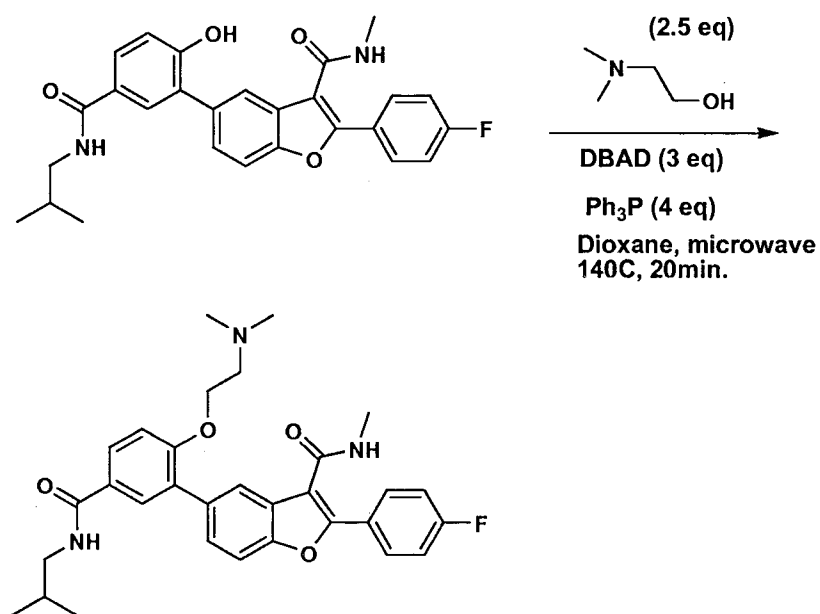
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Scheme 7

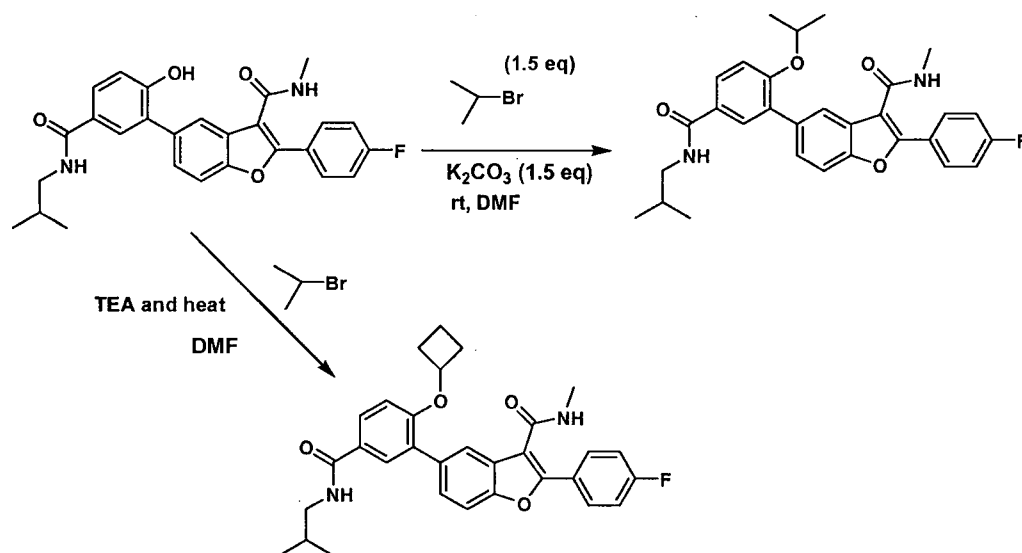


[0038] Scheme 8 illustrates that a free phenolic OH group can be used to form
5 some ether compounds. Scheme 9 provides an alkylation for forming ethers under
mild or more extreme conditions depending on the reactivity of the alkylating reagent.

Scheme 8

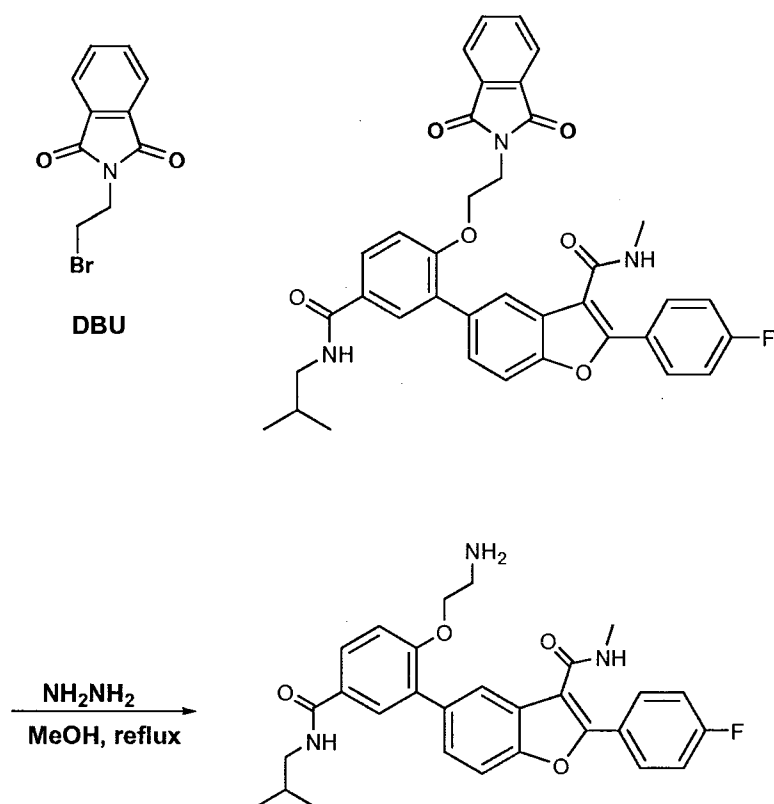


Scheme 9



[0039] Scheme 10 shows how an ether with a protected amine can be attached,
 5 and after subsequent deprotection of the phthalimide, a free amine is liberated which
 can be either incorporated into compounds of the invention or derivatized further via
 standard chemistry to provide secondary or tertiary amines or amides or
 sulfonamides.

Scheme 10



BIOLOGICAL METHODS

- 5 [0040] The compounds demonstrated activity against HCV NS5B as determined in the following HCV RdRp assays.

HCV NS5B RdRp Cloning, Expression, and Purification

- [0041] The cDNA encoding the NS5B protein of HCV, genotype 1b, was cloned into the pET21a expression vector. The protein was expressed with an 18 amino acid C-terminal truncation to enhance the solubility. The E. coli competent cell line BL21(DE3) was used for expression of the protein. Cultures were grown at 37 °C for ~ 4 hours until the cultures reached an optical density of 2.0 at 600 nm. The cultures were cooled to 20 °C and induced with 1 mM IPTG. Fresh ampicillin was added to a final concentration of 50 µg/ml and the cells were grown overnight at 20 °C.
- 10
- 15

[0042] Cell pellets (3L) were lysed for purification to yield 15-24 mgs of purified NS5B. The lysis buffer consisted of 20 mM Tris-HCl, pH 7.4, 500 mM NaCl, 0.5%

triton X-100, 1 mM DTT, 1mM EDTA, 20% glycerol, 0.5 mg/ml lysozyme, 10 mM MgCl₂, 15 ug/ml deoxyribonuclease I, and Complete TM protease inhibitor tablets (Roche). After addition of the lysis buffer, frozen cell pellets were resuspended using a tissue homogenizer. To reduce the viscosity of the sample, aliquots of the lysate
5 were sonicated on ice using a microtip attached to a Branson sonicator. The sonicated lysate was centrifuged at 100,000 x g for 1hr at 4 °C and filtered through a 0.2 µm filter unit (CORNING®).

[0043] The protein was purified using three sequential chromatography steps: Heparin sepharose CL-6B, polyU sepharose 4B, and HITRAP® SP sepharose
10 (Pharmacia). The chromatography buffers were identical to the lysis buffer but contained no lysozyme, deoxyribonuclease I, MgCl₂ or protease inhibitor and the NaCl concentration of the buffer was adjusted according to the requirements for charging the protein onto the column. Each column was eluted with a NaCl gradient which varied in length from 5-50 column volumes depending on the column type.
15 After the final chromatography step, the resulting purity of the enzyme is >90% based on SDS-PAGE analysis. The enzyme was aliquoted and stored at -80 °C.\

Standard HCV NS5B RdRp Enzyme Assay

[0044] HCV RdRp genotype 1b assays were run in a final volume of 60 µl in 96
20 well plates (COSTAR® 3912). The assay buffer is composed of 20 mM Hepes, pH 7.5, 2.5 mM KCl, 2.5 mM MgCl₂, 1 mM DTT, 1.6 U RNase inhibitor (Promega N2515), 0.1 mg/ml BSA (Promega R3961), and 2 % glycerol. All compounds were serially diluted (3-fold) in DMSO and diluted further in water such that the final concentration of DMSO in the assay was 2%. HCV RdRp genotype 1b enzyme was
25 used at a final concentration of 28 nM. A polyA template was used at 6 nM, and a biotinylated oligo-dT12 primer was used at 180 nM final concentration. Template was obtained commercially (Amersham 27-4110). Biotinylated primer was prepared by Sigma Genosys. 3H-UTP was used at 0.6 µCi (0.29 µM total UTP). Reactions
30 were initiated by the addition of enzyme, incubated at 30 °C for 60 min, and stopped by adding 25 µl of 50 mM EDTA containing SPA beads (4 µg/µl, Amersham RPNQ 0007). Plates were read on a Packard Top Count NXT after >1hr incubation at room temperature.

Modified HCV NS5B RdRp Enzyme Assay

[0045] A modified enzyme assay was performed essentially as described for the standard enzyme assay except for the following: The biotinylated oligo dT12 primer
5 was precaptured on streptavidin-coated SPA beads by mixing primer and beads in assay buffer and incubating at room temperature for one hour. Unbound primer was removed after centrifugation. The primer-bound beads were resuspended in 20 mM Hepes buffer, pH 7.5 and used in the assay at final concentrations of 20 nM primer and 0.67 $\mu\text{g}/\mu\text{l}$ beads. Order of addition in the assay: enzyme (14 nM) was added to
10 diluted compound followed by the addition of a mixture of template (0.2 nM), 3H-UTP (0.6 μCi , 0.29 μM), and primer-bound beads, to initiate the reaction; concentrations given are final. Reactions were allowed to proceed for 4 hours at 30 $^{\circ}\text{C}$.

[0046] IC_{50} values for compounds were determined using seven different [I]. IC_{50}
15 values were calculated from the inhibition using the formula $y = A + ((B - A) / (1 + ((C/x)^D)))$.

FRET Assay Preparation

[0047] To perform the HCV FRET screening assay, 96-well cell culture plates
20 were used. The FRET peptide (Anaspec, Inc.) (Taliani et al., *Anal. Biochem.*, 240:60-67 (1996)) contains a fluorescence donor, EDANS, near one end of the peptide and an acceptor, DABCYL, near the other end. The fluorescence of the peptide is quenched by intermolecular resonance energy transfer (RET) between the donor and the acceptor, but as the NS3 protease cleaves the peptide the products are released from
25 RET quenching and the fluorescence of the donor becomes apparent. The assay reagent was made as follows: 5X cell Luciferase cell culture lysis reagent from Promega (#E153A) diluted to 1X with dH_2O , NaCl added to 150 mM final, the FRET peptide diluted to 20 μM final from a 2 mM stock.

[0048] To prepare plates, HCV replicon cells, with or without a Renilla luciferase
30 reporter gene, were trypsinized and placed into each well of a 96-well plate with titrated test compounds added in columns 3 through 12; columns 1 and 2 contained a

control compound (HCV protease inhibitor), and the bottom row contained cells without compound. The plates were then placed in a CO₂ incubator at 37 °C.

Assays

5 [0049] Subsequent to addition of the test compounds described above (FRET Assay Preparation), at various times the plate was removed and Alamar blue solution (Trek Diagnostics, #00-100) was added per well as a measure of cellular toxicity. After reading in a CYTOFLUOR® 4000 instrument (PE Biosystems), plates were rinsed with PBS and then used for FRET assay by the addition of 30 ul of the FRET
10 peptide assay reagent described above (FRET Assay Preparation) per well. The plate was then placed into the CYTOFLUOR® 4000 instrument which had been set to 340 excite/490 emission, automatic mode for 20 cycles and the plate read in a kinetic mode. Typically, the signal to noise using an endpoint analysis after the reads was at least three-fold. Alternatively, after Alamar blue reading, plates were rinsed with
15 PBS, 50 ul of DMEM (high glucose) without phenol red was added and plates were then used for luciferase assay using the Promega DUAL-GLO® Luciferase Assay System.

[0050] Compound analysis was determined by quantification of the relative HCV replicon inhibition and the relative cytotoxicity values. To calculate cytotoxicity
20 values, the average Alamar Blue fluorescence signals from the control wells were set as 100% non-toxic. The individual signals in each of the compound test wells were then divided by the average control signal and multiplied by 100% to determine percent cytotoxicity. To calculate the HCV replicon inhibition values, an average background value was obtained from the two wells containing the highest amount of
25 HCV protease inhibitor at the end of the assay period. These numbers were similar to those obtained from naïve Huh-7 cells.

[0051] The background numbers were then subtracted from the average signal obtained from the control wells and this number was used as 100% activity. The individual signals in each of the compound test wells were then divided by the
30 averaged control values after background subtraction and multiplied by 100% to determine percent activity. EC₅₀ values for a protease inhibitor titration were calculated as the concentration which caused a 50% reduction in FRET or luciferase

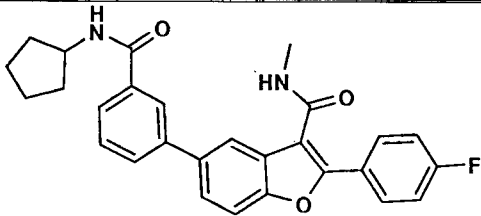
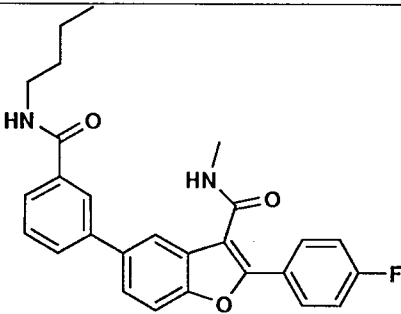
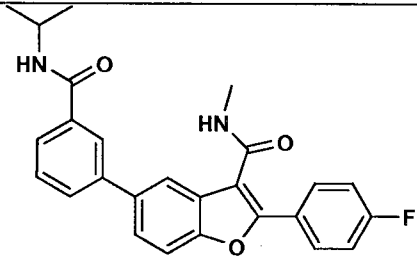
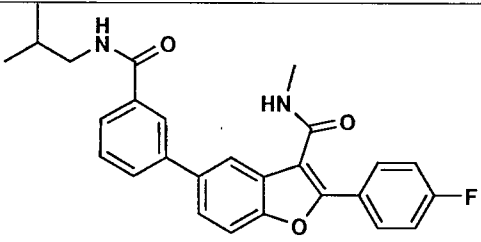
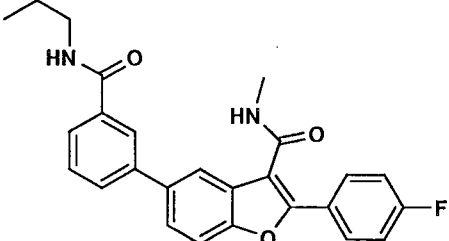
activity. The two numbers generated for the compound plate, percent cytotoxicity and percent activity were used to determine compounds of interest for further analysis.

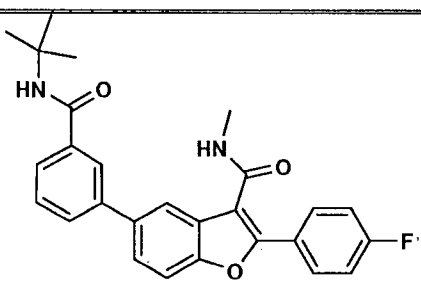
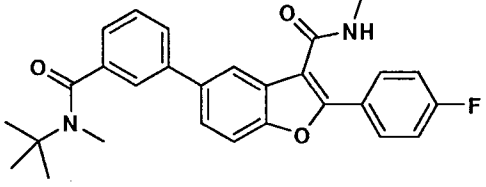
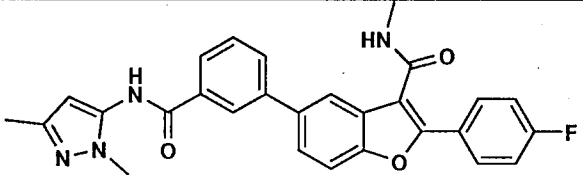
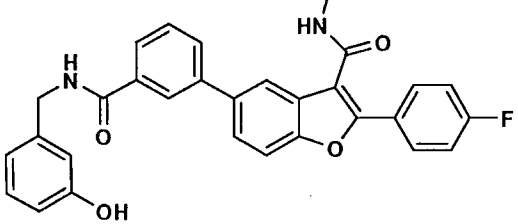
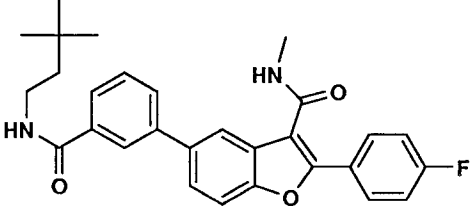
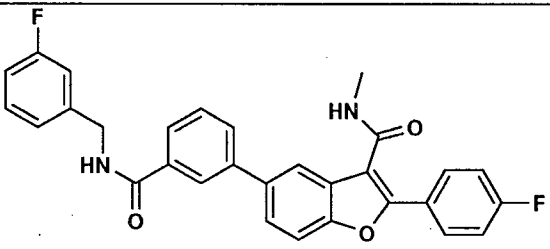
HCV Replicon Luciferase Reporter Assay

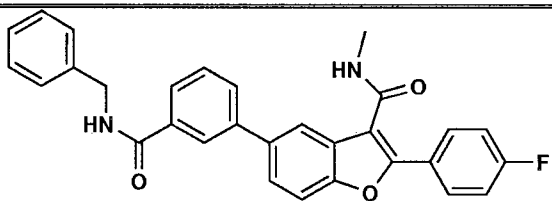
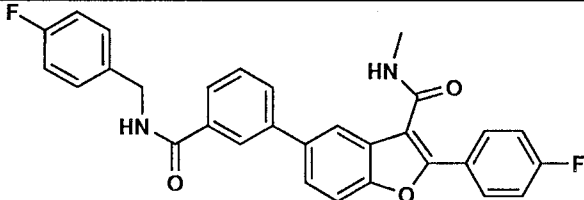
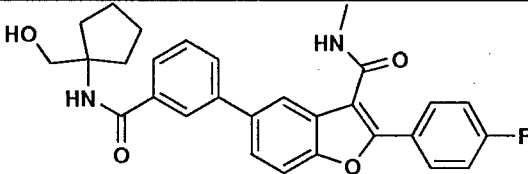
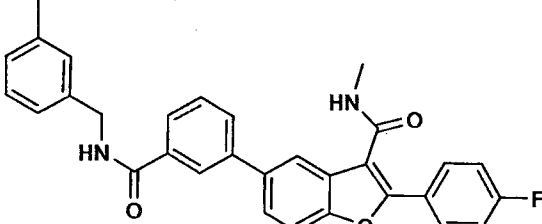
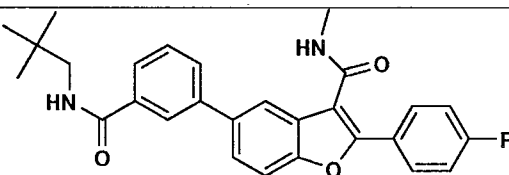
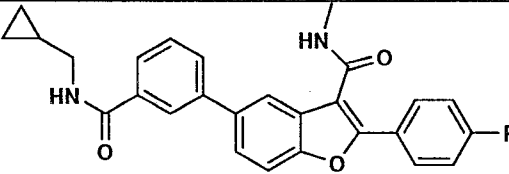
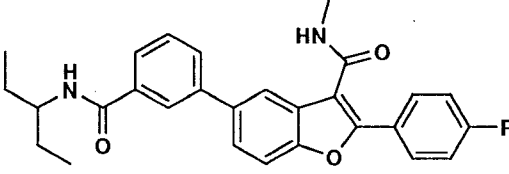
- 5 [0052] The HCV replicon luciferase assay was developed to monitor the inhibitory effects of compounds described in the disclosure on HCV viral replication. Utilization of a replicon luciferase reporter assay was first described by Krieger et al (Krieger, N. et al., *J. Virol.*, 75(10):4614-4624 (2001)). HUH-7 cells, constitutively expressing the HCV replicon, were grown in Dulbecco's Modified Eagle Media
- 10 (DMEM) (Gibco-BRL) containing 10% Fetal calf serum (FCS) (Sigma) and 1 mg/ml G418 (Gibco-BRL). Compounds were serially diluted 3 folds in DMSO for a twenty-point titration and subsequently transferred to sterile 384-well tissue-culture treated plates (CORNING® cat # 3571). The plates were then seeded with 50 µl of cells at a density of 3.0×10^3 cells/well in DMEM containing 4 % FCS (final DMSO
- 15 concentration at 0.5 %). After 3 days incubation at 37 °C, cells were analyzed for Renilla Luciferase activity using the EnduRen as substrate (Promega cat #E6485). The EnduRen substrate was diluted in DMEM and then added to the plates to a final concentration of 7.5 µM. The plates were incubated for 2 hrs at 37 °C and then read immediately for 30 seconds with VIEWLUX® Imager (PerkinElmer) using a
- 20 luminescence program. To assess cytotoxicity of compounds, CC₅₀ values were generated by multiplexing the EnduRen-containing plates with CELLTITER-BLUE® (Promega, cat # G8082). 3 µl of CellTiter Blue was added to each well and incubated for 8 hrs at 37 °C. The fluorescence signal from each well was read, with an excitation wavelength at 525/10 nm and an emission wavelength of 598/10 nm, using
- 25 the VIEWLUX® Imager.

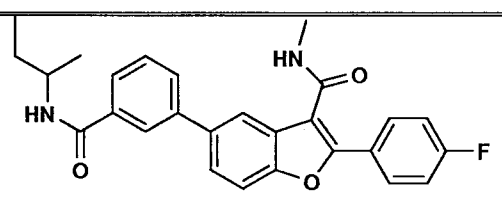
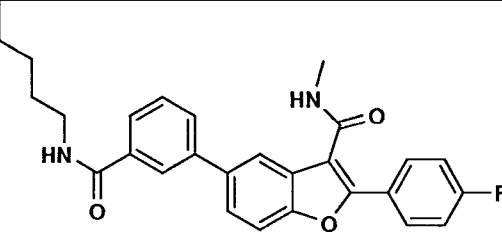
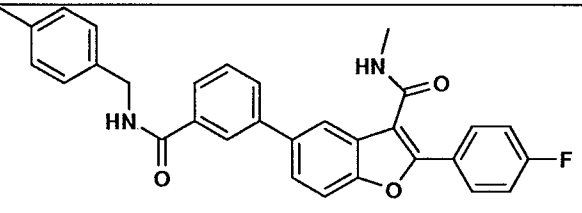
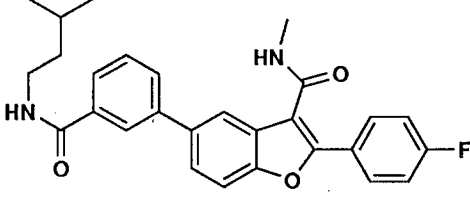
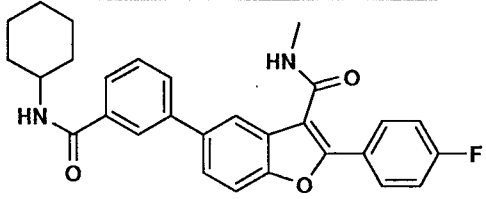
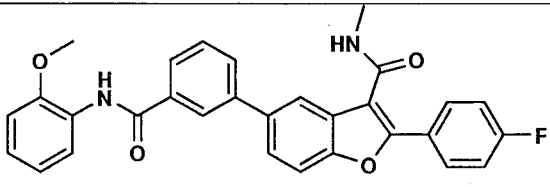
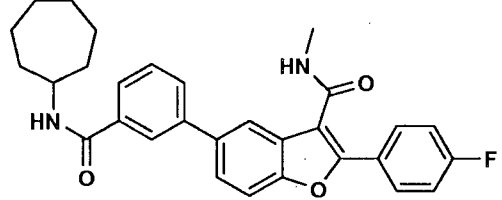
[0053] Representative data for compounds are reported in Tables 1a, 1b, and 1c.

TABLE 1a

Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	A	A
	A	A

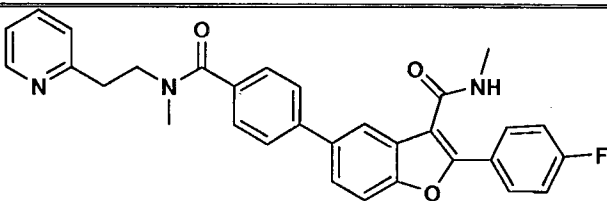
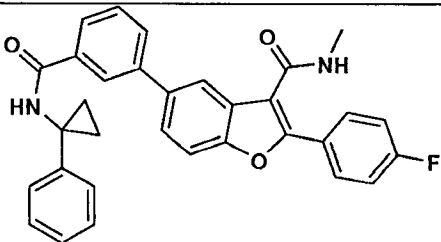
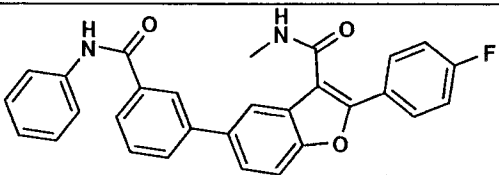
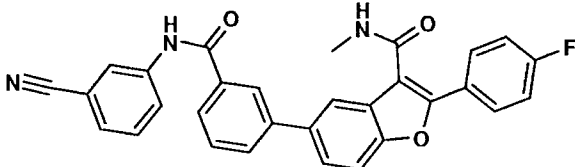
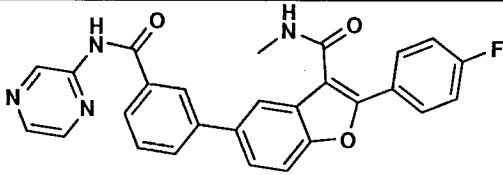
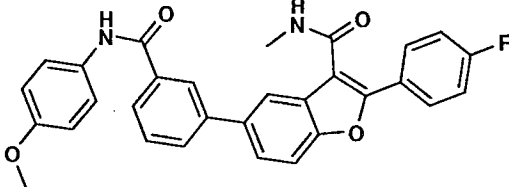
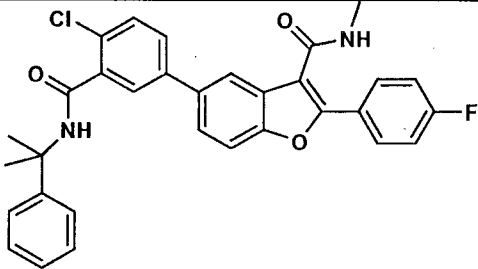
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	B	A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	A	A
	A	A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	B	A
	A	A
	B	A
	A	A

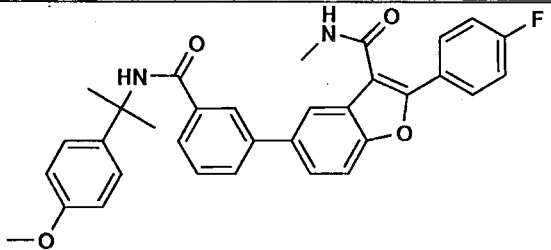
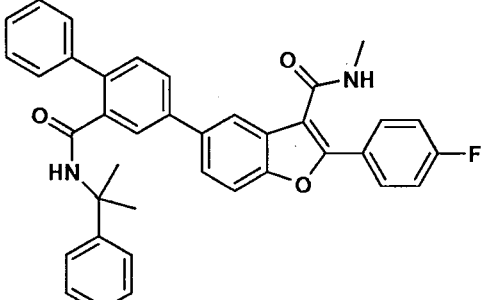
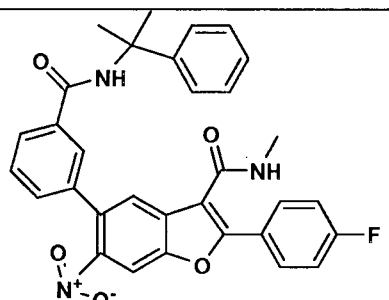
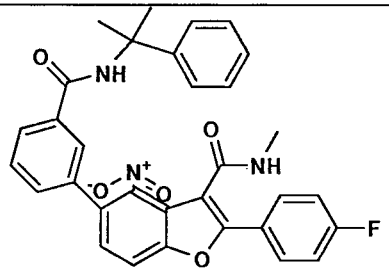
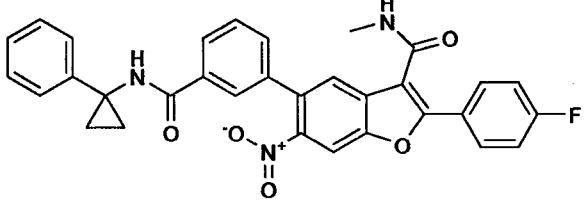
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	B	A
	A	A
	A	A
	A	A

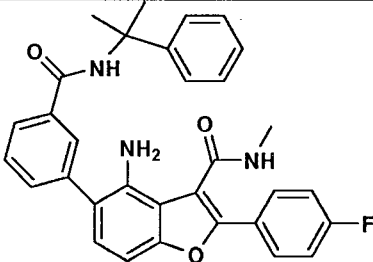
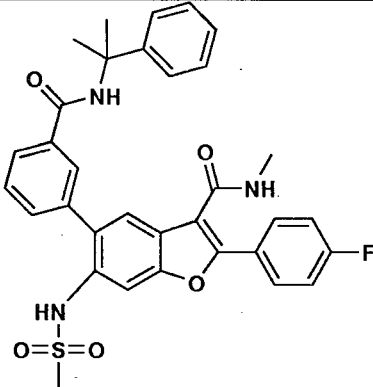
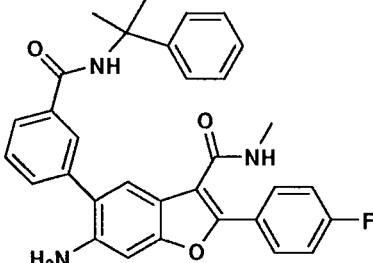
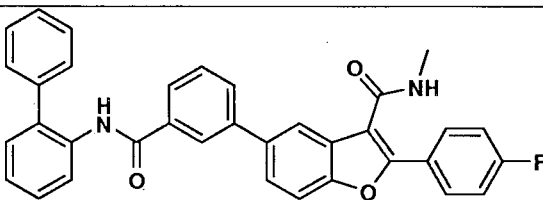
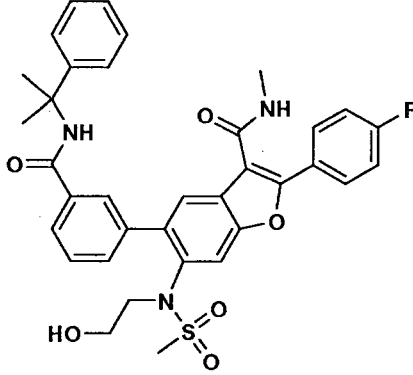
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
 Chiral	A	A
 Chiral	A	A
	A	A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	B	A
	A	A
	A	A
	A	A

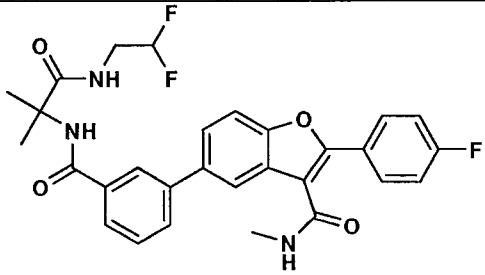
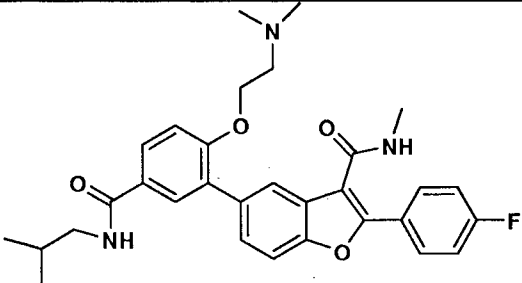
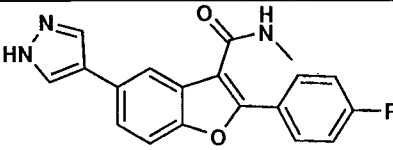
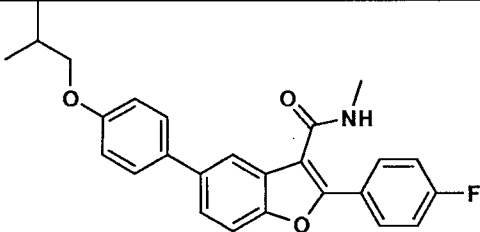
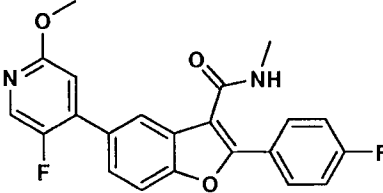
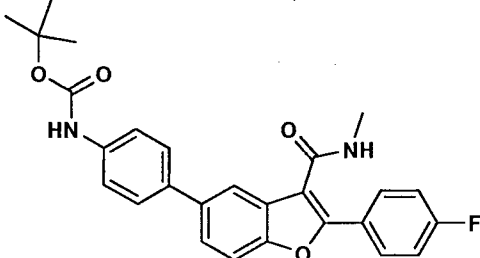
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
 Chiral	F	A
 Chiral	A	A
	A	A
	A	A

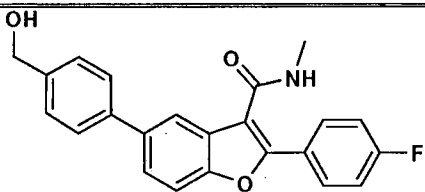
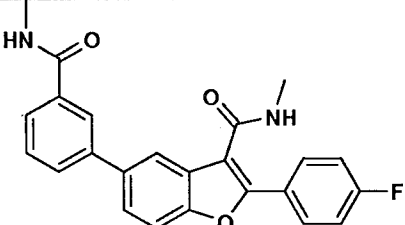
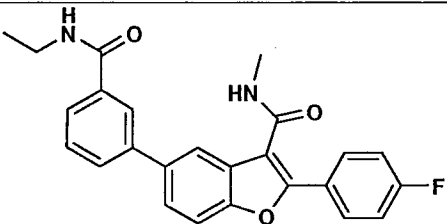
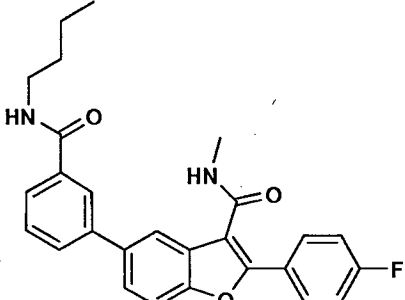
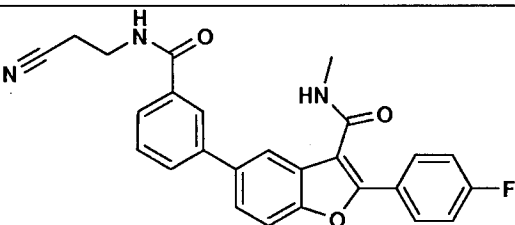
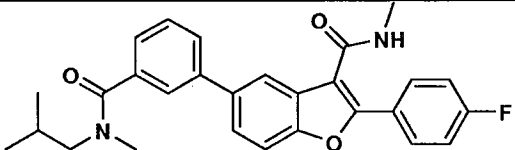
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	B	A
	A	A
	A	A
	A	A
	B	A

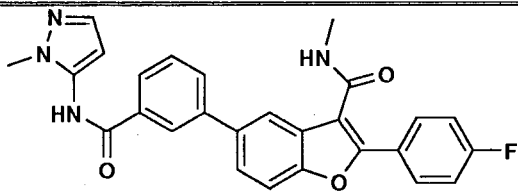
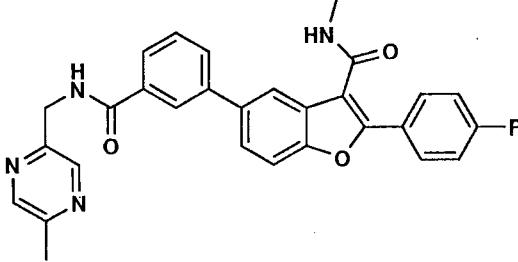
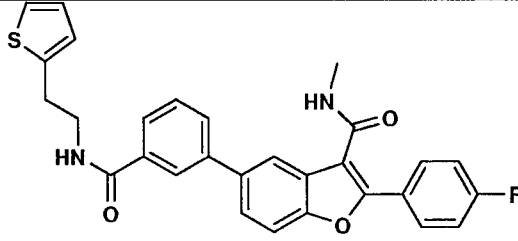
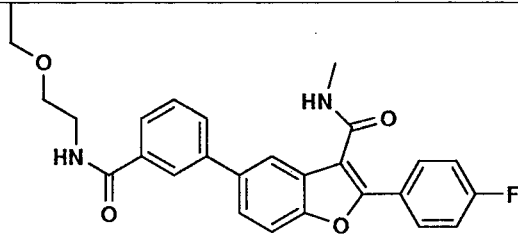
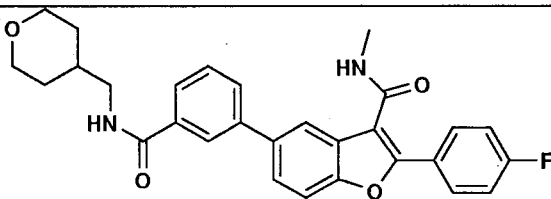
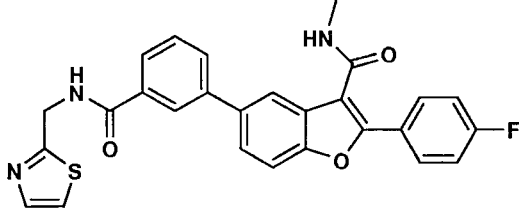
Structure	IC ₅₀	EC ₅₀
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	A	A
	A	A
	A	A
	A	A

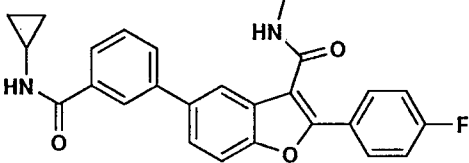
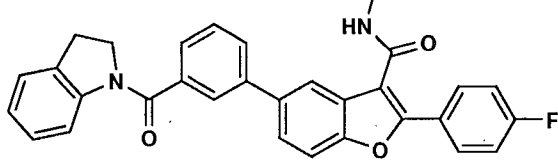
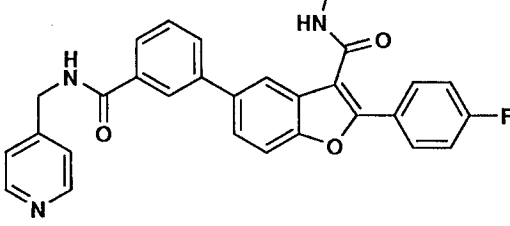
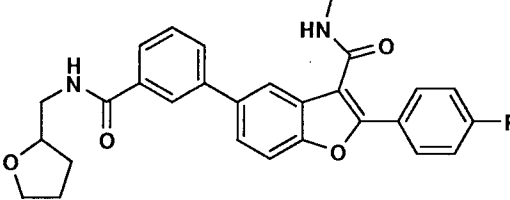
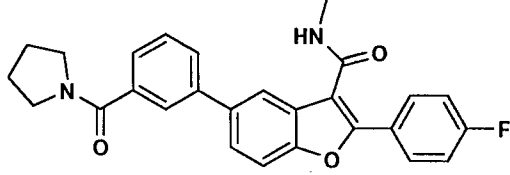
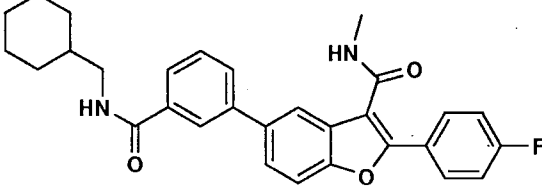
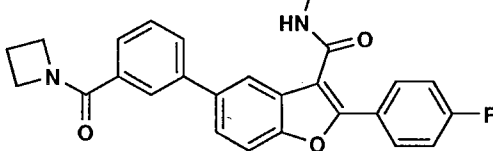
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	C	A
	A	A

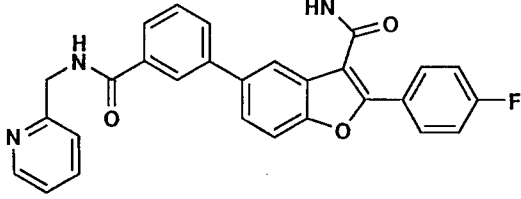
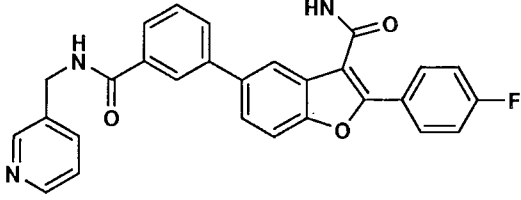
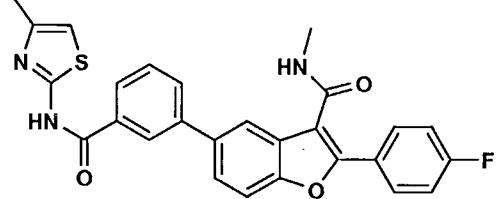
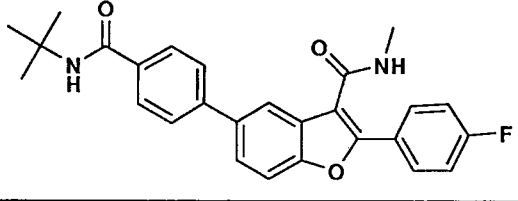
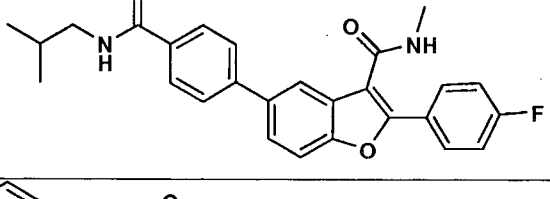
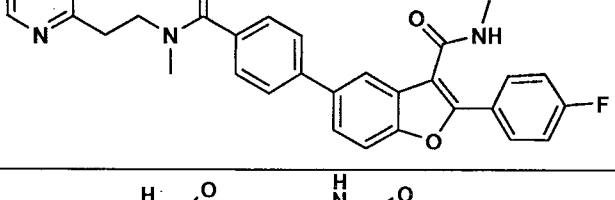
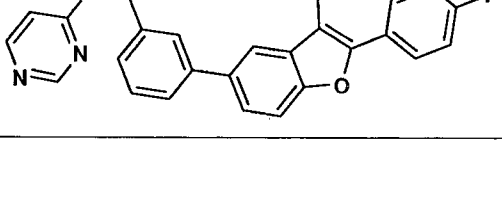
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	A	A
	A	A
	A	A
	A	A

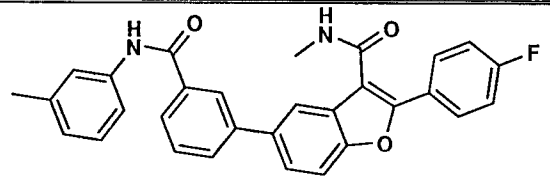
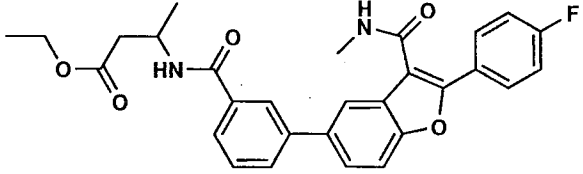
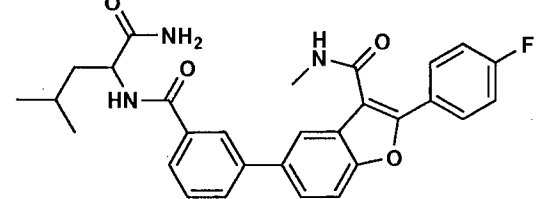
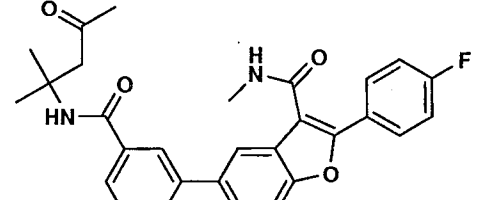
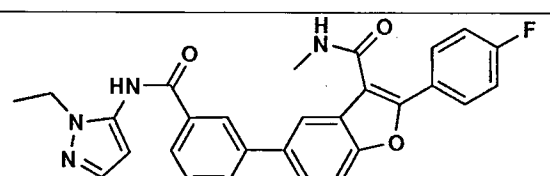
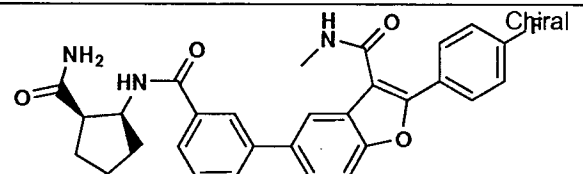
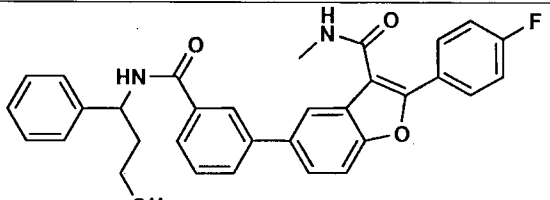
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	E	B
	E	F
	E	H
	E	F

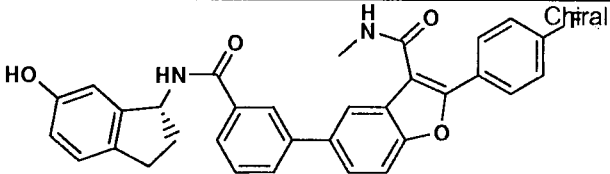
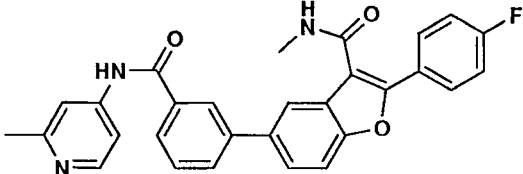
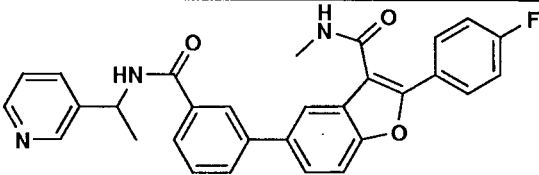
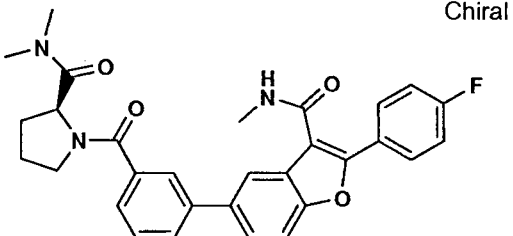
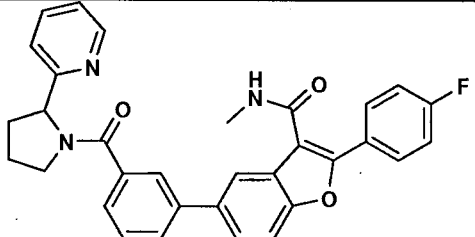
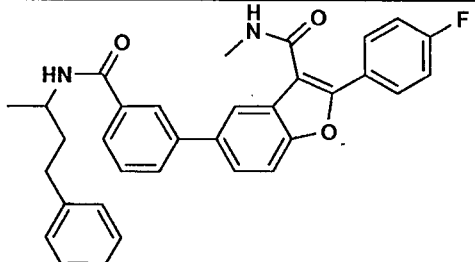
Structure	IC ₅₀	EC ₅₀
	E	B
	C	B
	B	B
	A	A
	B	B
	A	B

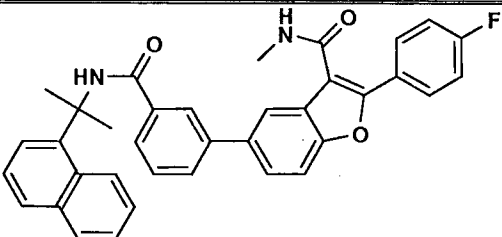
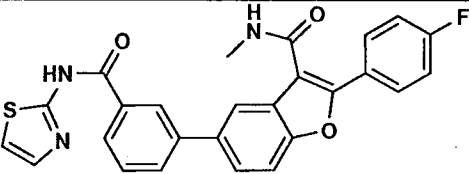
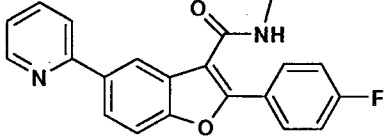
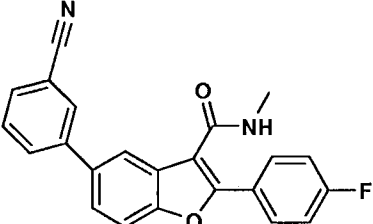
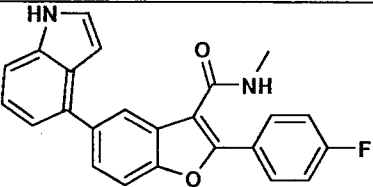
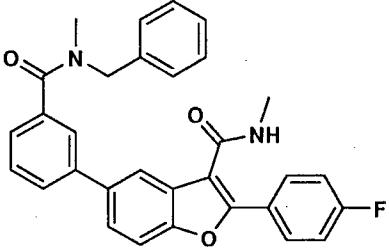
Structure	IC ₅₀	EC ₅₀
	B	B
	B	B
	B	B
	A	B
	A	B
	B	B

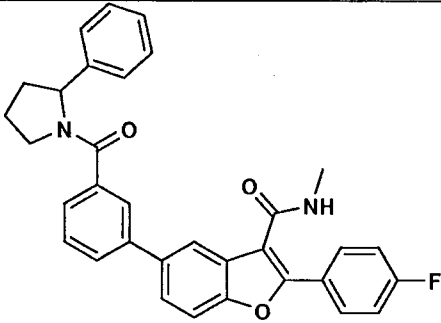
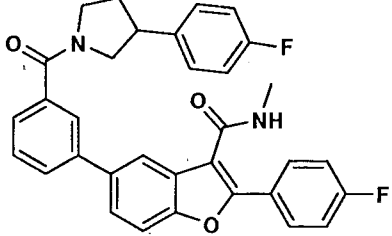
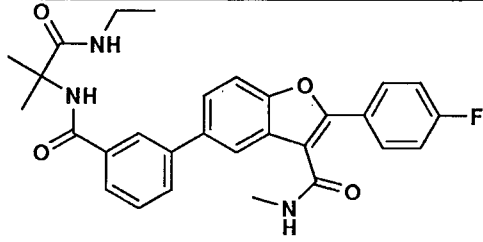
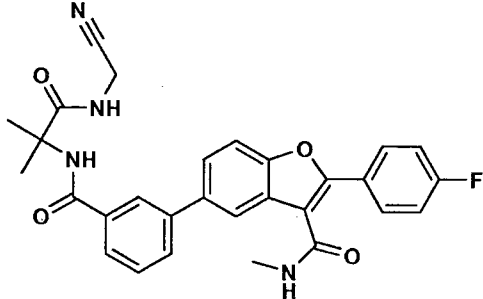
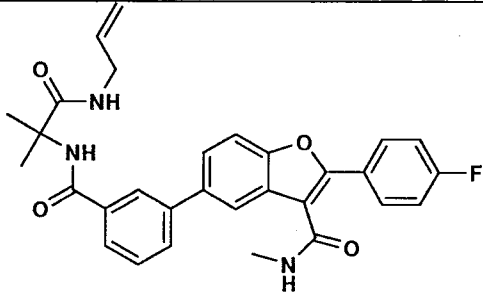
Structure	IC ₅₀	EC ₅₀
	B	B
	C	B
	A	B
	A	B
	B	B
	A	B
	B	B

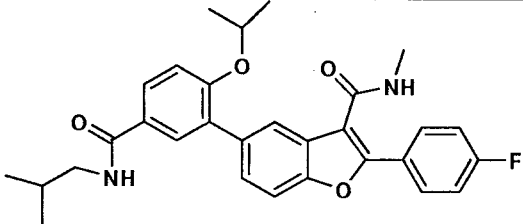
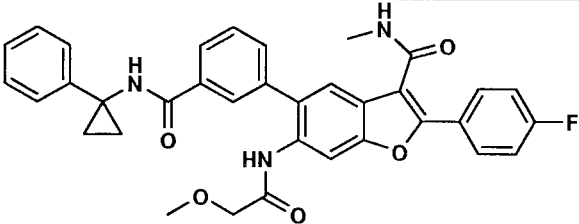
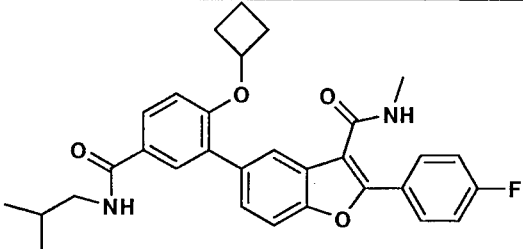
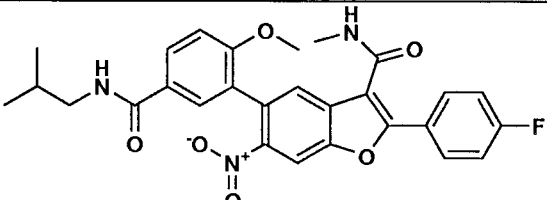
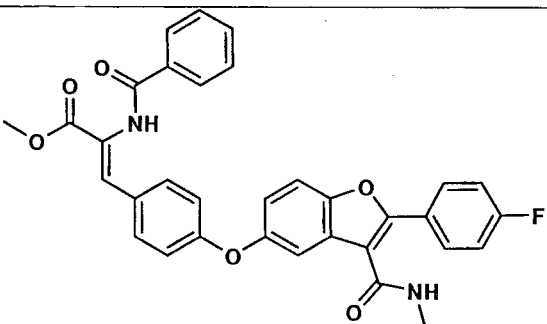
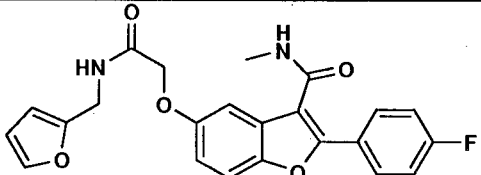
Structure	IC ₅₀	EC ₅₀
	A	B
	A	B
	A	B
	C	B
	E	B
	A	A
	B	B

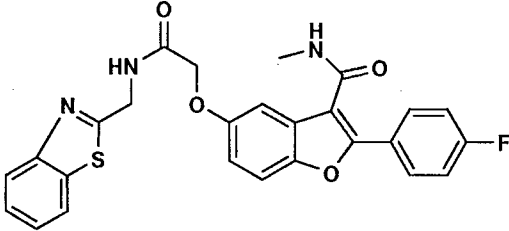
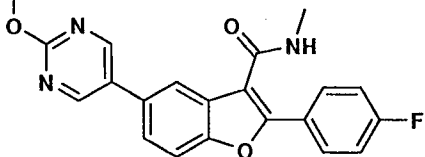
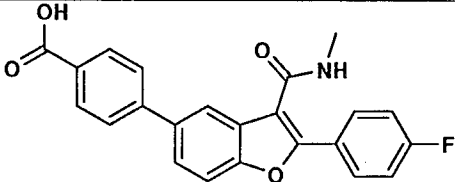
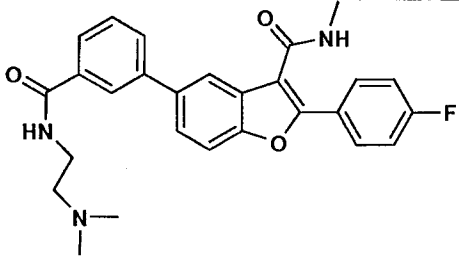
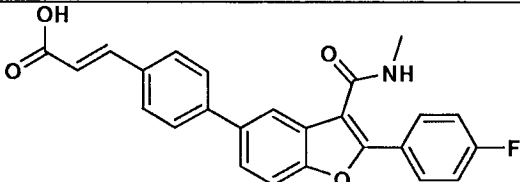
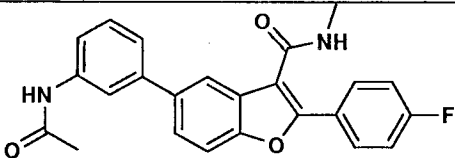
Structure	IC ₅₀	EC ₅₀
	B	B
	A	B
	B	B
	B	B
	B	B
	B	B
	A	B

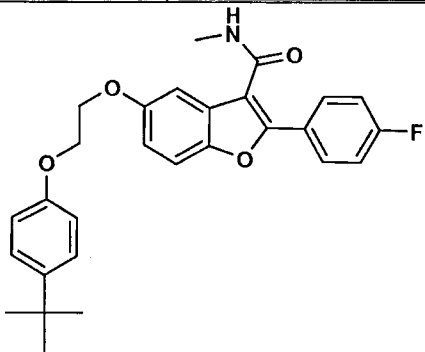
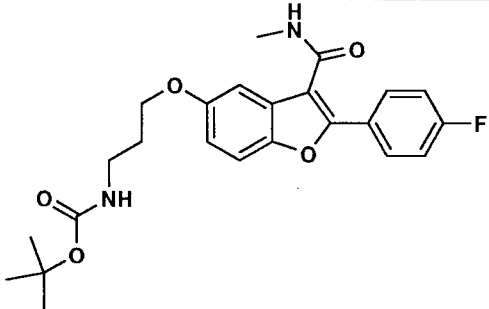
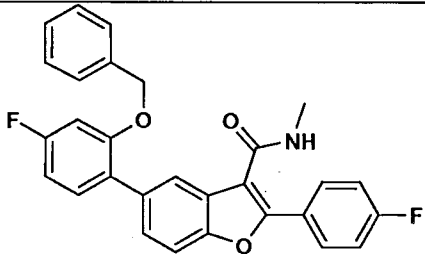
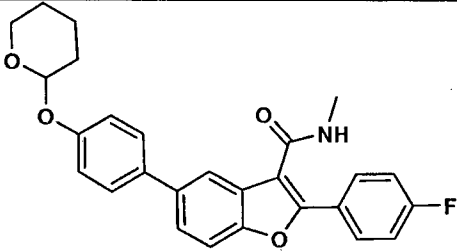
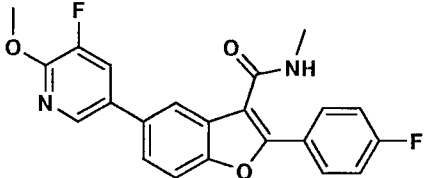
Structure	IC ₅₀	EC ₅₀
	G	B
	C	B
	A	B
	B	B
	B	B
	B	B

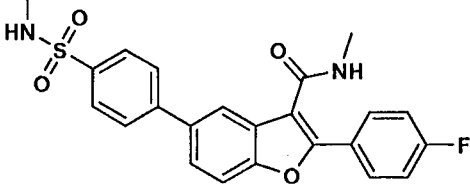
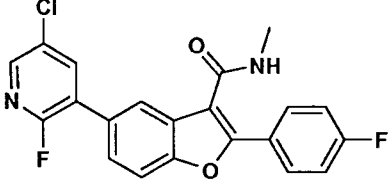
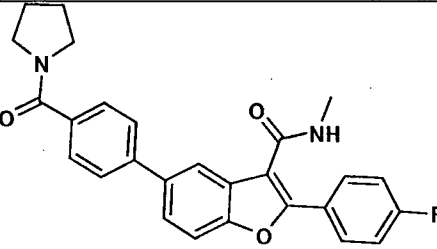
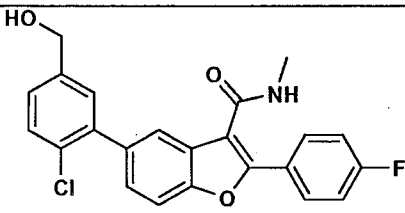
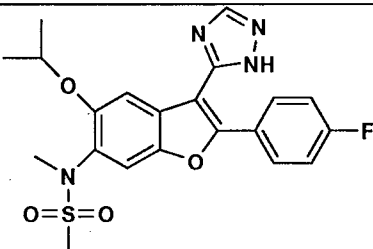
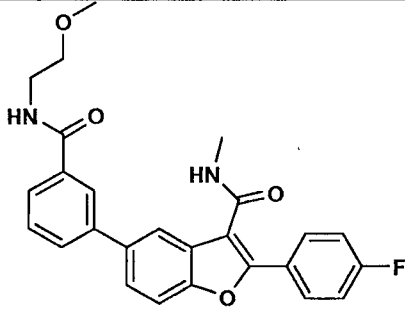
Structure	IC ₅₀	EC ₅₀
	B	B
	A	B
	C	B
	E	B
	E	B
	B	B

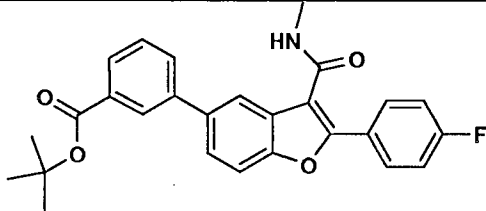
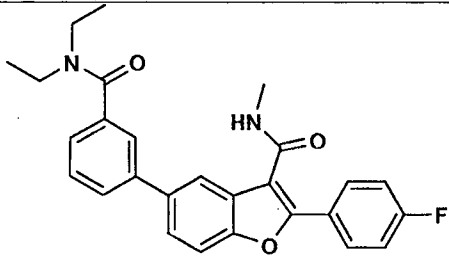
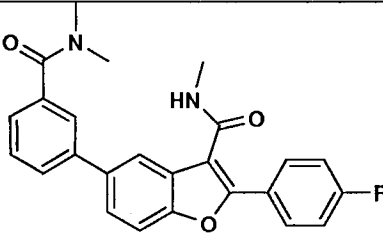
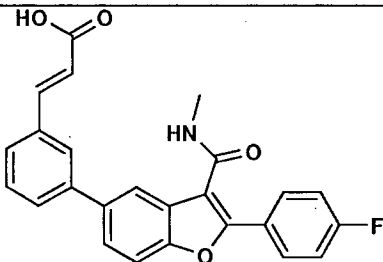
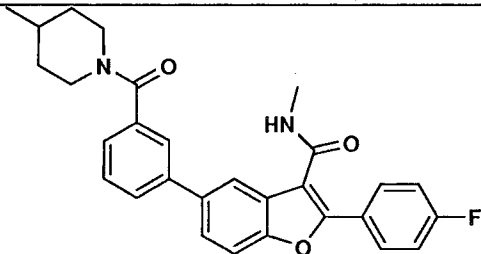
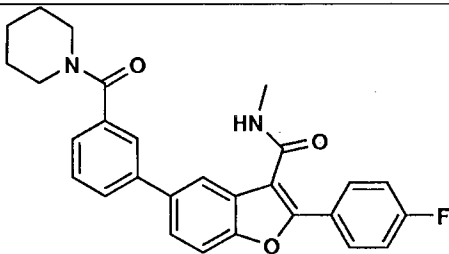
Structure	IC ₅₀	EC ₅₀
	B	B
	B	B
	B	B
	A	B
	B	B

Structure	IC ₅₀	EC ₅₀
	B	B
	B	B
	G	B
	B	B
	C	C
		C

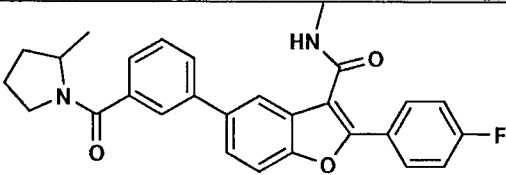
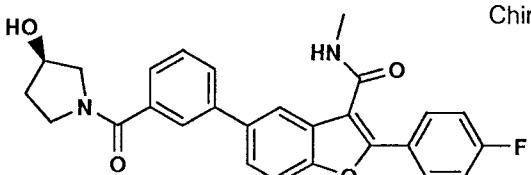
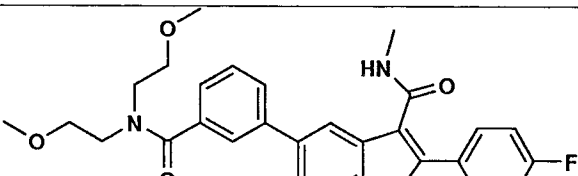
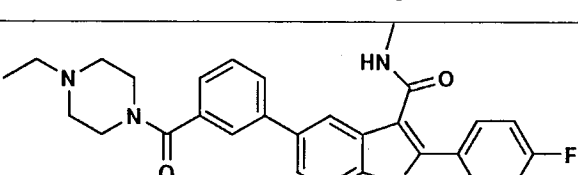
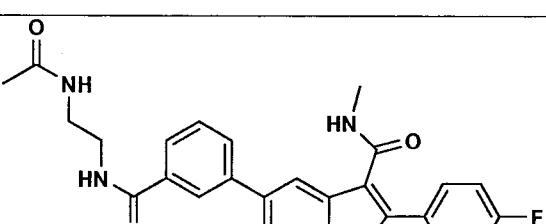
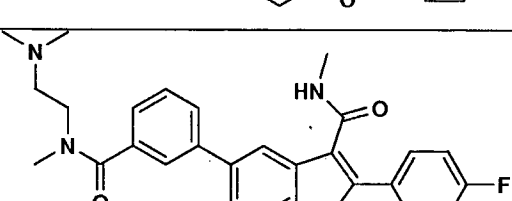
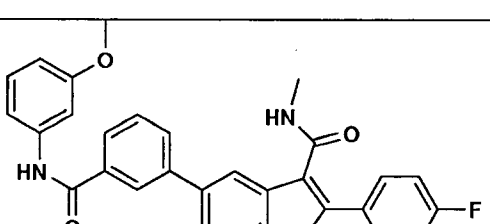
Structure	IC ₅₀	EC ₅₀
		C
	C	C
	B	C
	C	C
	C	C
	C	C

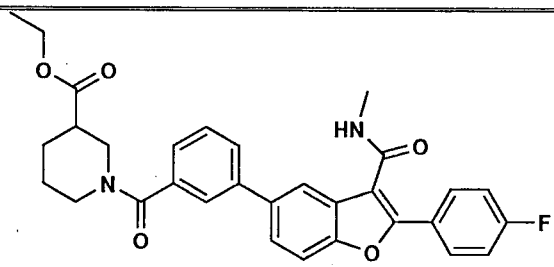
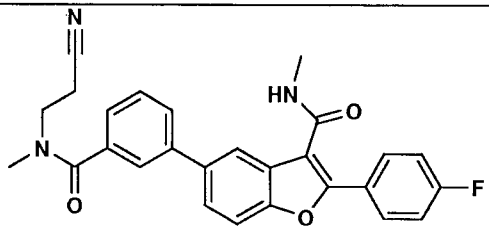
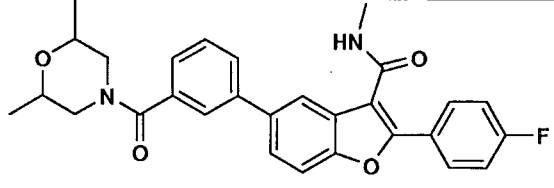
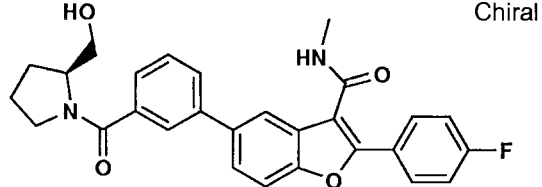
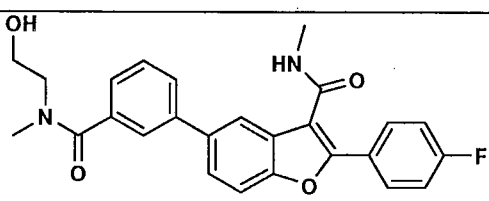
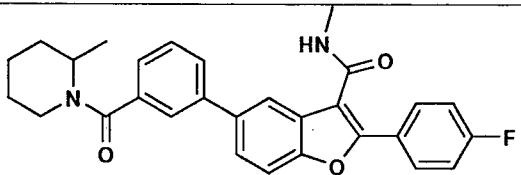
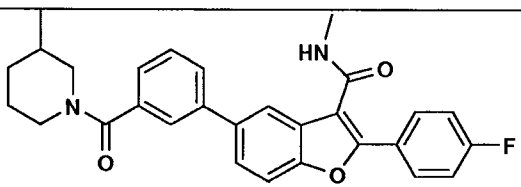
Structure	IC ₅₀	EC ₅₀
	E	C
	C	C
	E	C
	E	C
	E	C

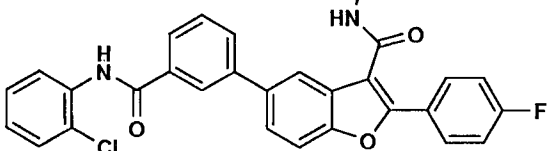
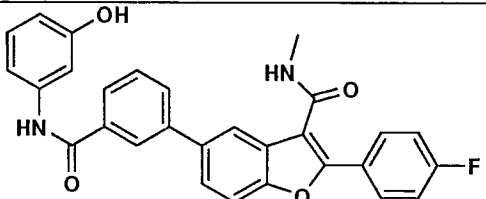
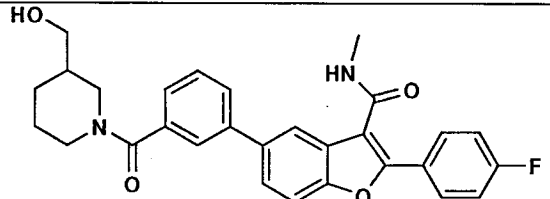
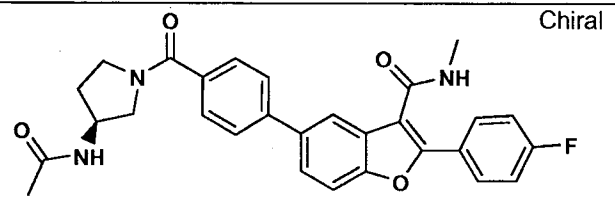
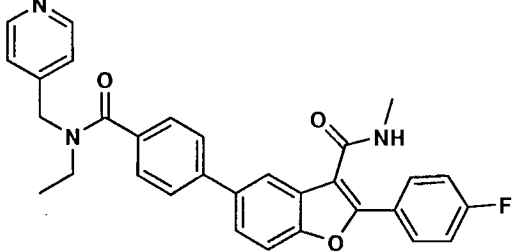
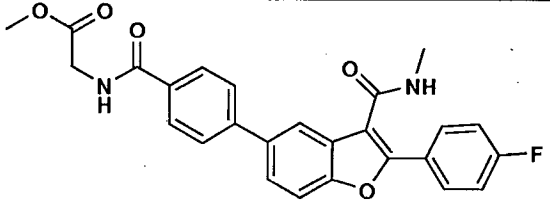
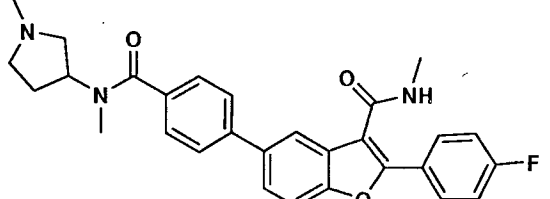
Structure	IC ₅₀	EC ₅₀
	E	C
	E	C
	C	C
	E	C
	B	C
	C	C

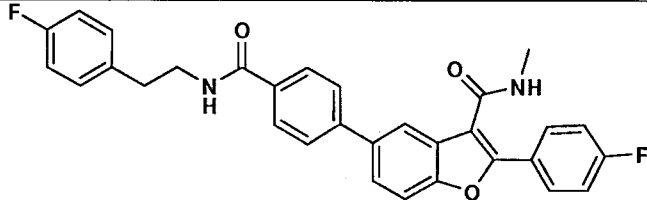
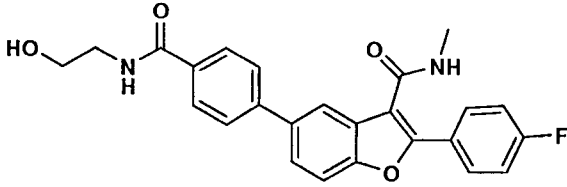
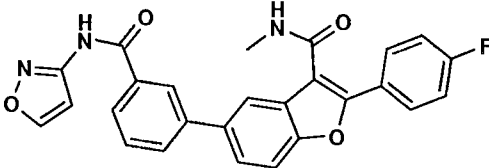
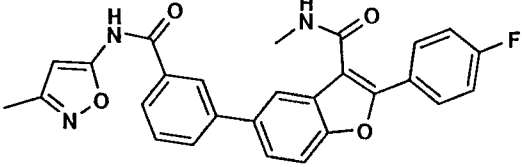
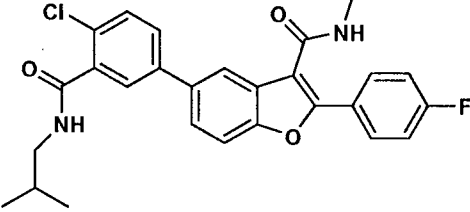
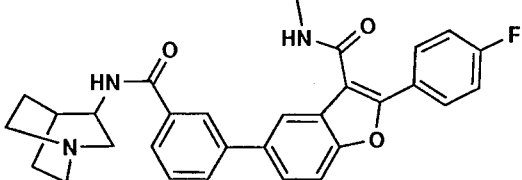
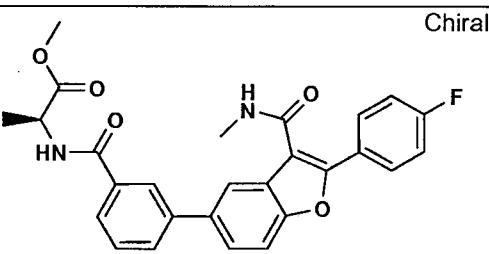
Structure	IC ₅₀	EC ₅₀
	C	C
	C	C
	C	C
	B	C
	C	C
	B	C

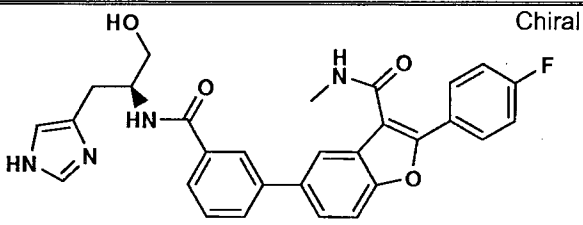
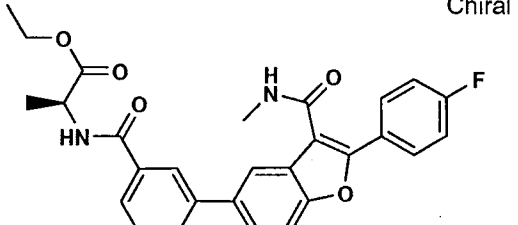
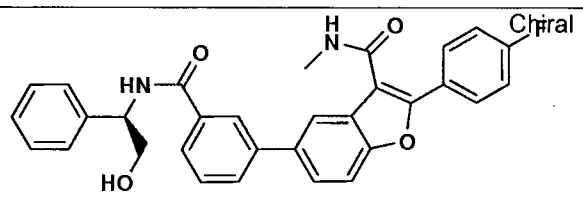
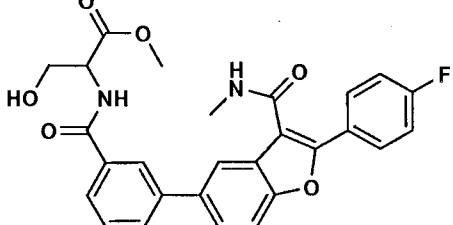
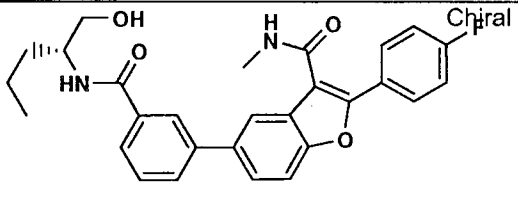
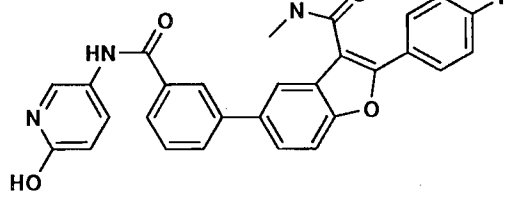
Structure	IC ₅₀	EC ₅₀
	C	C
	B	C
	C	C
	C	C
	C	C
	B	C
	B	C

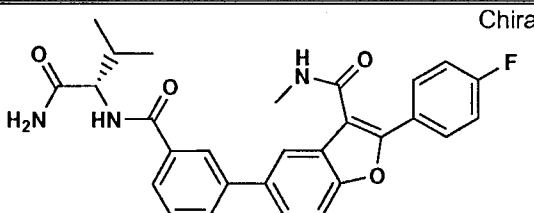
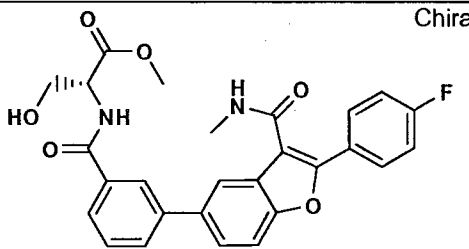
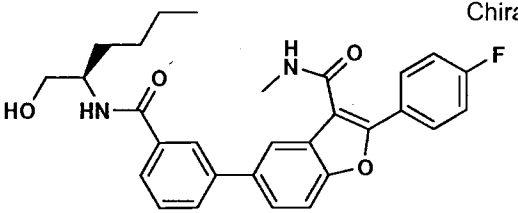
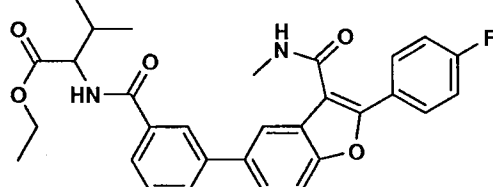
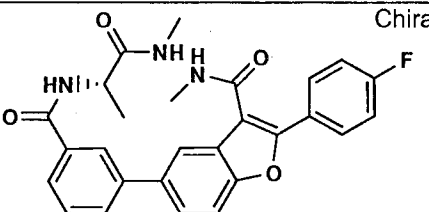
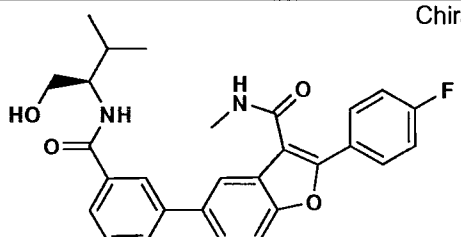
Structure	IC ₅₀	EC ₅₀
	B	C
 Chiral	C	C
	C	C
	C	C
	C	C
	E	C
	C	C

Structure	IC ₅₀	EC ₅₀
	C	C
	B	C
	C	C
 Chiral	B	C
	C	C
	B	C
	C	C

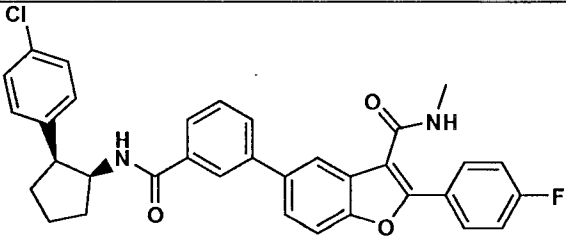
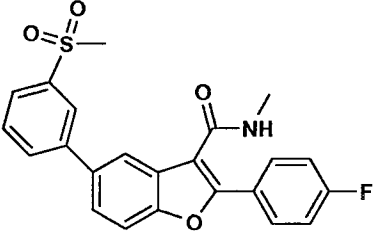
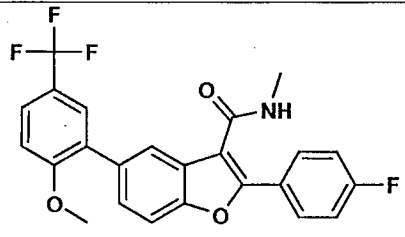
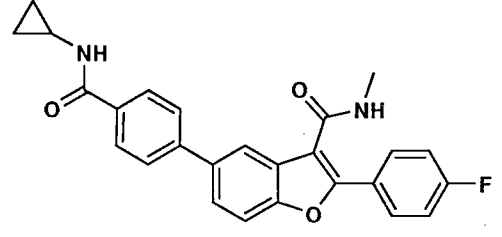
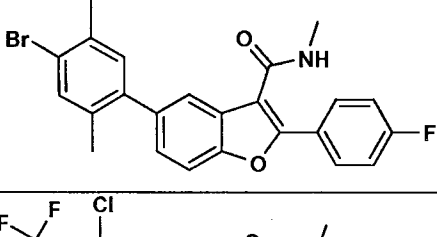
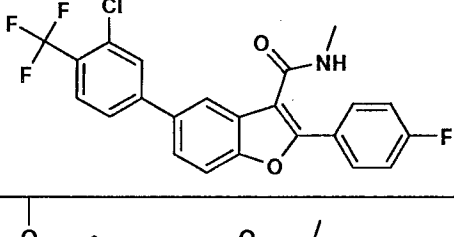
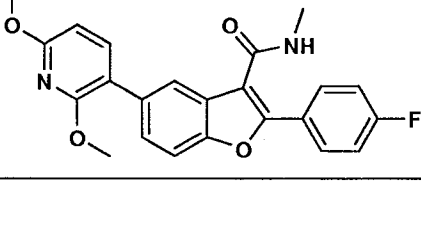
Structure	IC ₅₀	EC ₅₀
	C	C
	C	C
	C	C
	C	C
	E	C
	E	C
	E	C

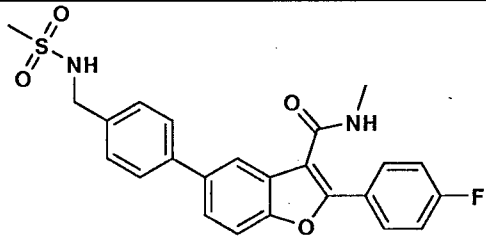
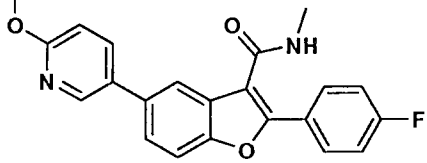
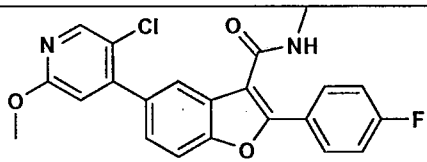
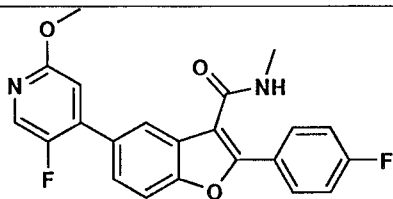
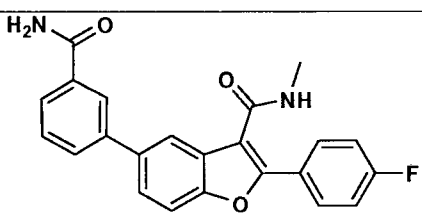
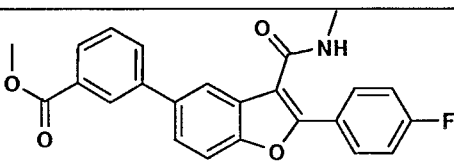
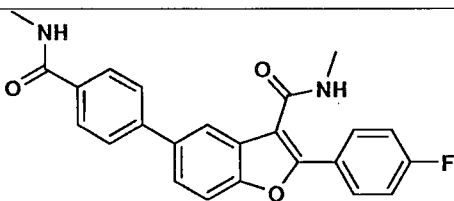
Structure	IC ₅₀	EC ₅₀
	E	C
	E	C
	B	C
	C	C
	C	C
	C	C
 Chiral	A	C

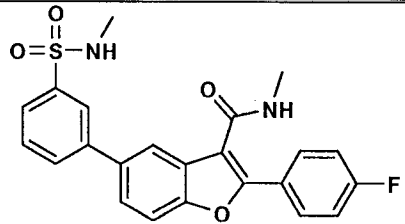
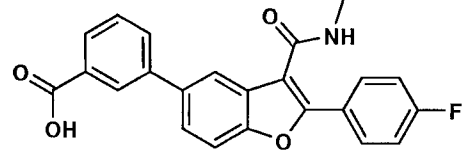
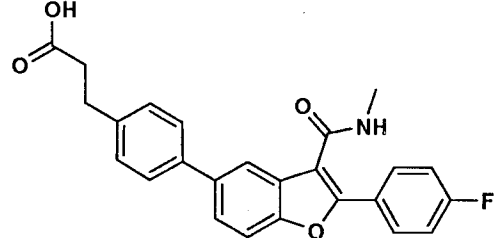
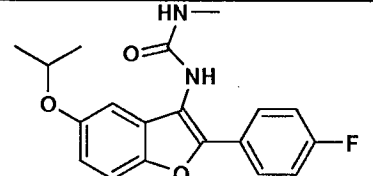
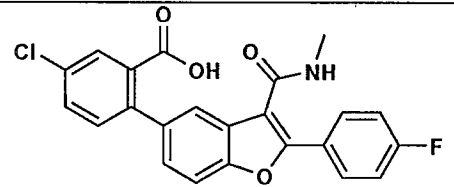
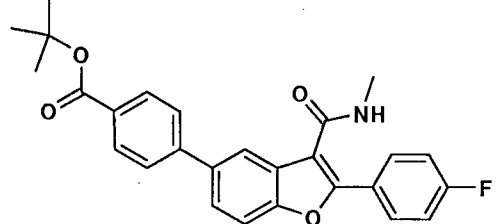
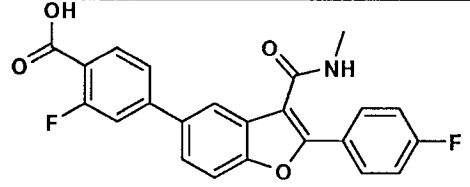
Structure	IC ₅₀	EC ₅₀
 Chiral	C	C
 Chiral	A	C
 Chiral	B	C
 Chiral	B	C
 Chiral	C	C
 Chiral	C	C

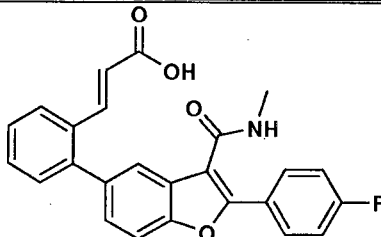
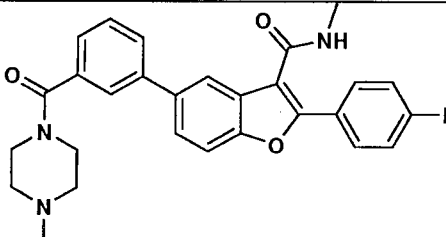
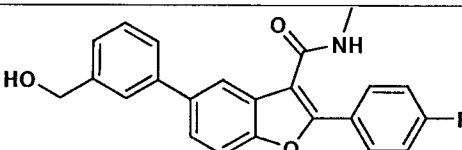
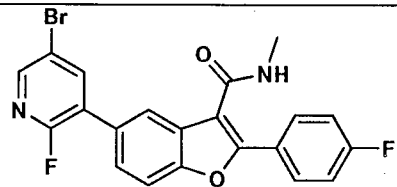
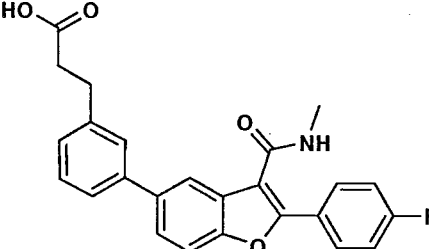
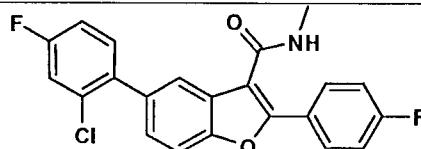
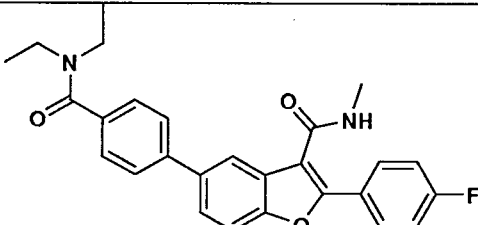
Structure	IC ₅₀	EC ₅₀
 Chiral	B	C
 Chiral	B	C
 Chiral	B	C
 Chiral	B	C
 Chiral	B	C
 Chiral	B	C

Structure	IC ₅₀	EC ₅₀
	C	C
	C	C
	F	C
	A	C
	A	C
	G	C
	C	C

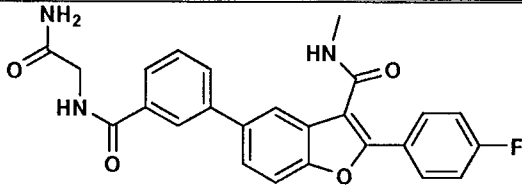
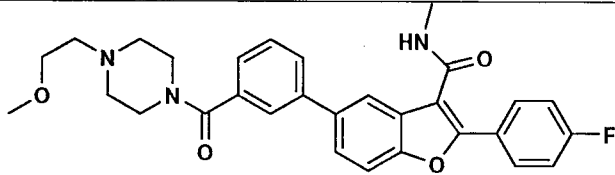
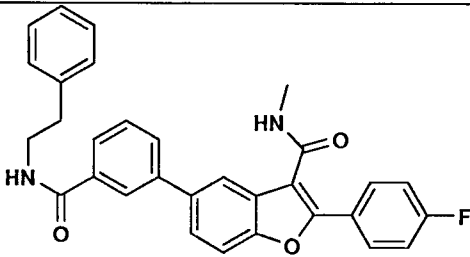
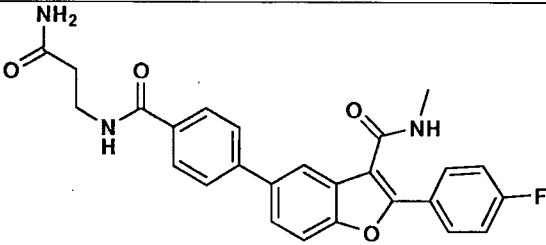
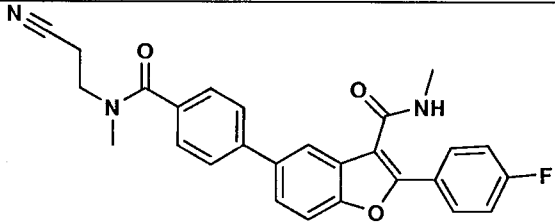
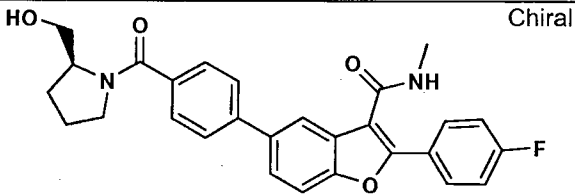
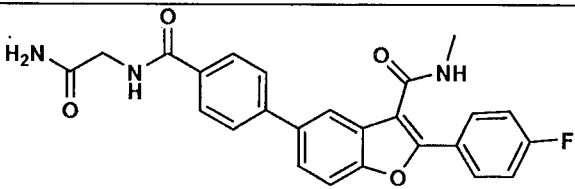
Structure	IC ₅₀	EC ₅₀
	E	C
	E	C
	E	J
	E	K
	E	J
	E	K
	E	K

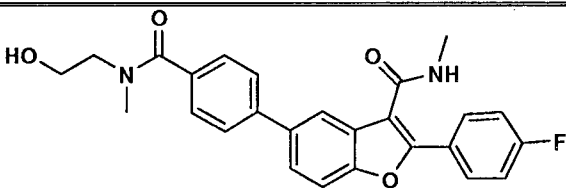
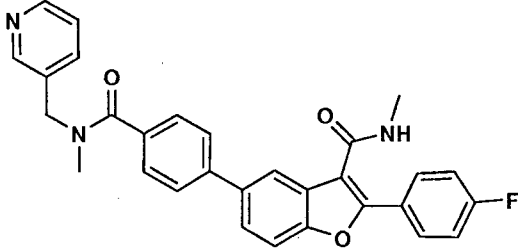
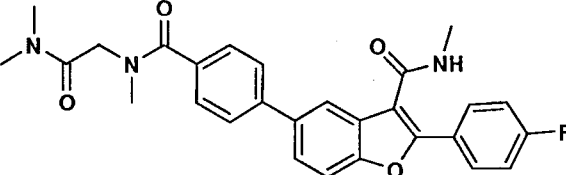
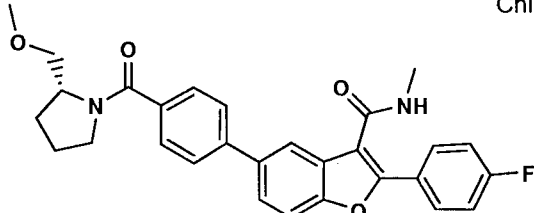
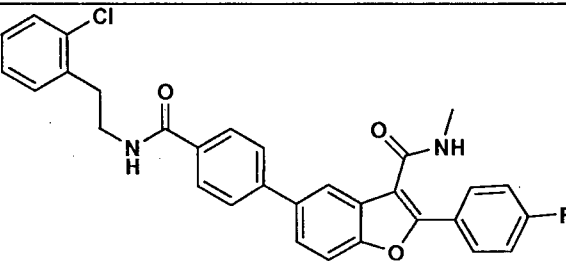
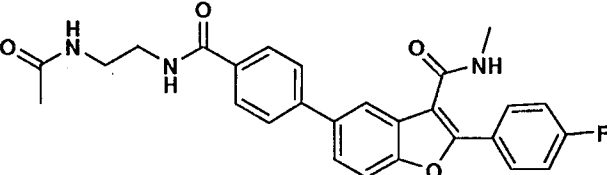
Structure	IC ₅₀	EC ₅₀
	E	K
	E	K
	E	K
	E	H
	C	J
	E	J
	E	J

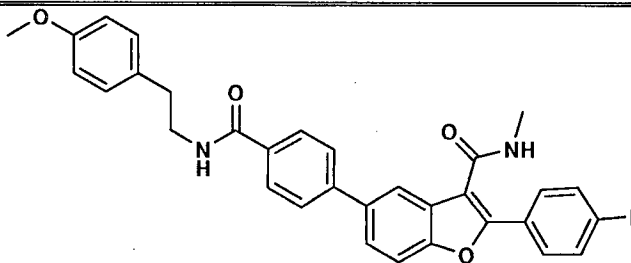
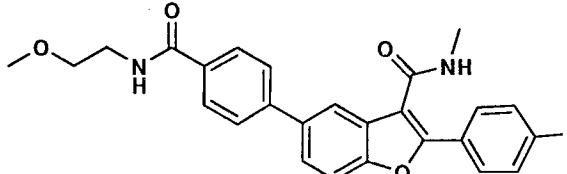
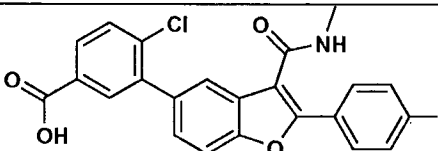
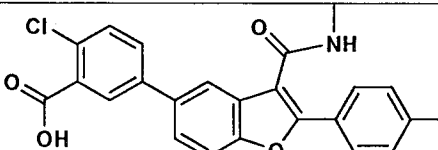
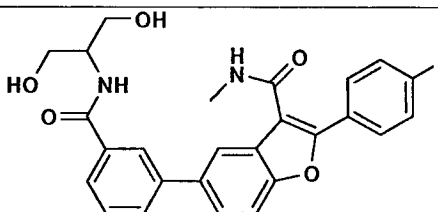
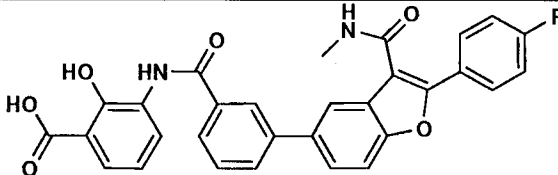
Structure	IC ₅₀	EC ₅₀
	E	J
	C	E
	C	E
	E	E
	C	E
	E	E
	C	E

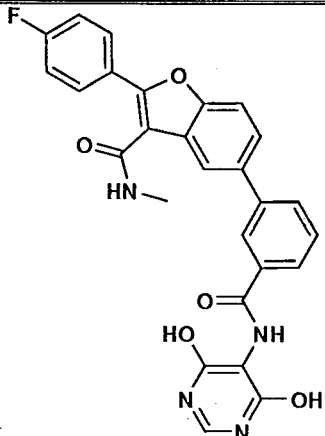
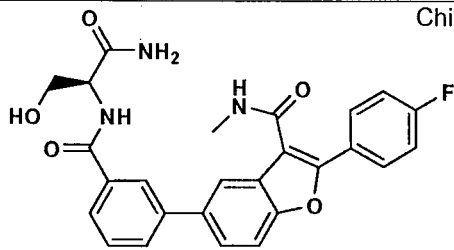
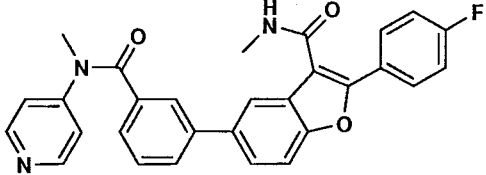
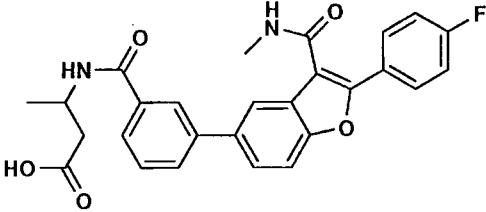
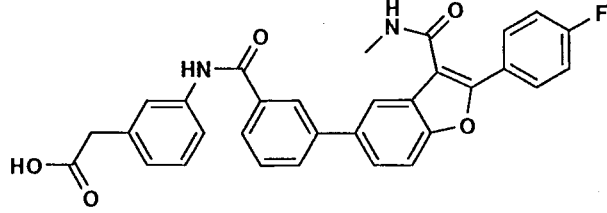
Structure	IC ₅₀	EC ₅₀
	C	E
	E	E
	E	E
	E	E
	C	E
	E	E
	C	E

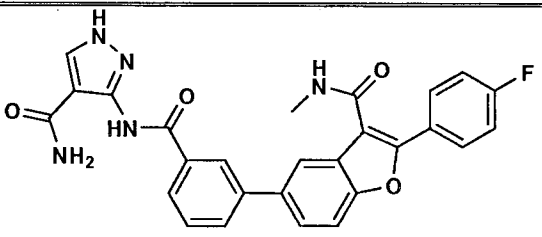
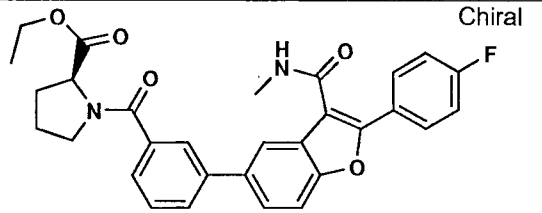
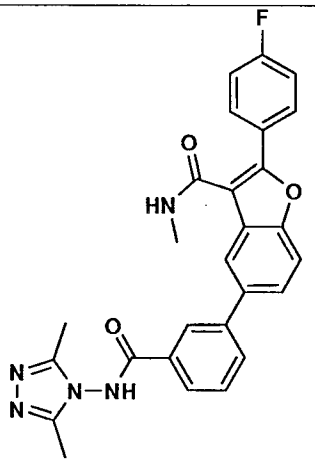
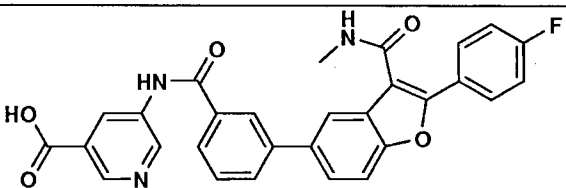
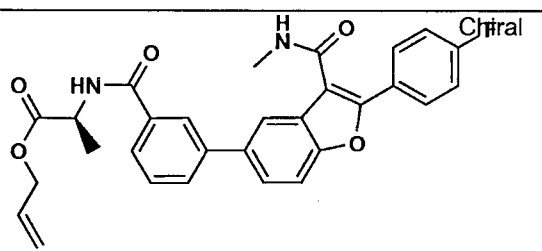
Structure	IC ₅₀	EC ₅₀
	C	E
	E	E
	E	E
	C	E
	B	E
	C	E
	C	E

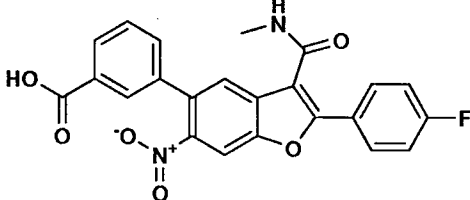
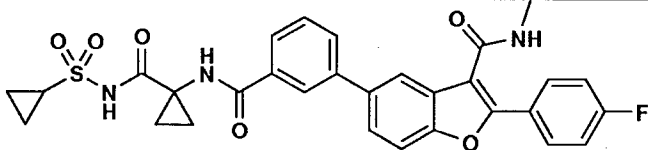
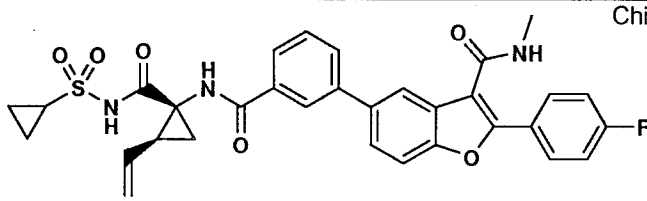
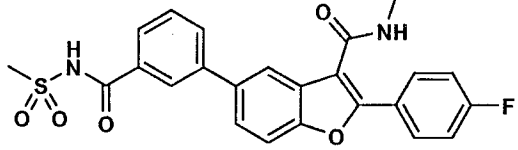
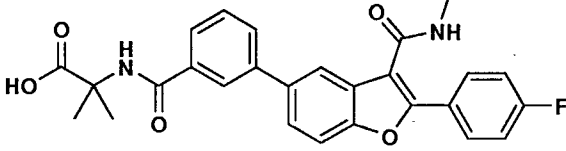
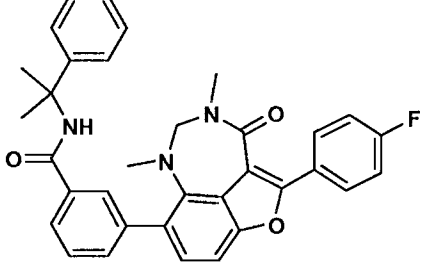
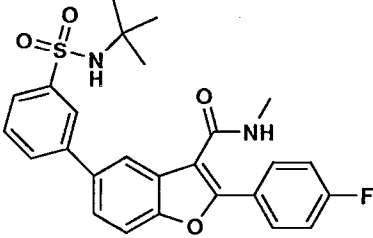
Structure	IC ₅₀	EC ₅₀
	E	E
	E	E
	E	E
	E	E
	C	E
 Chiral	E	E
	E	E

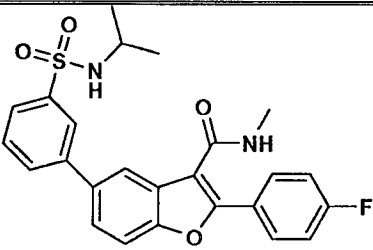
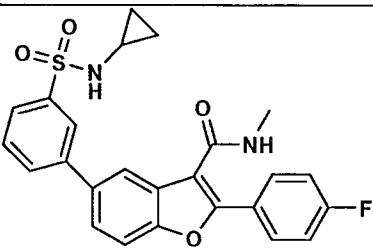
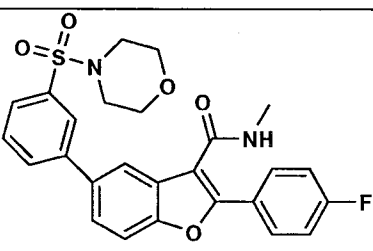
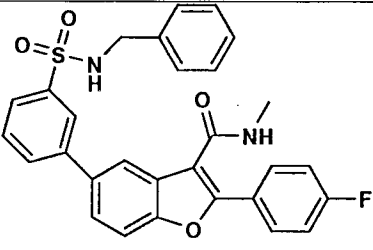
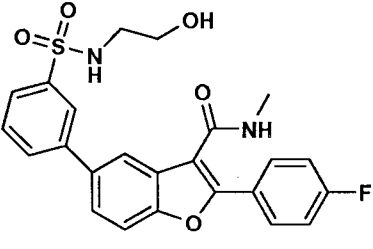
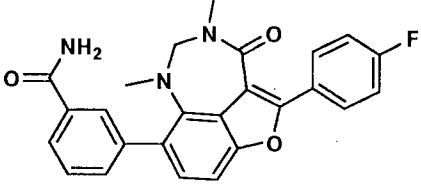
Structure	IC ₅₀	EC ₅₀
	C	E
	C	E
	E	E
Chiral 	E	E
	E	E
	E	E

Structure	IC ₅₀	EC ₅₀
	E	E
	E	E
	C	E
	C	E
	C	E
	B	E

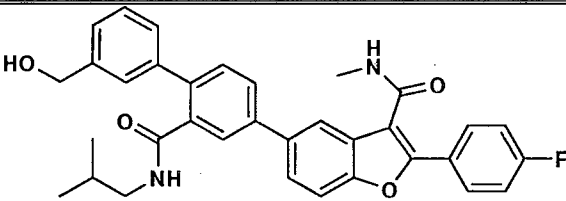
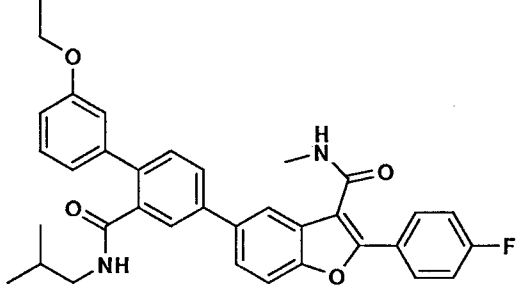
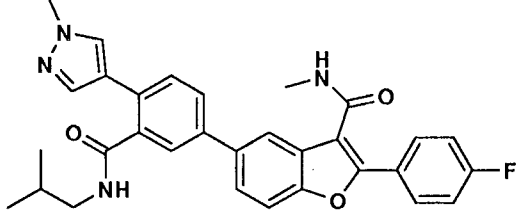
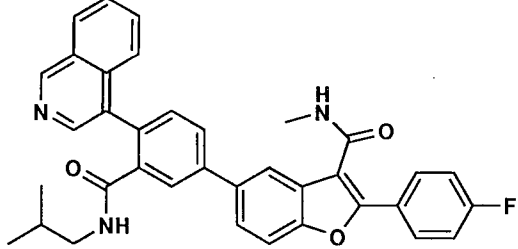
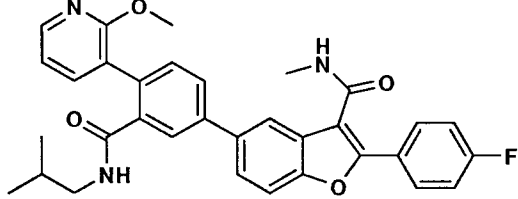
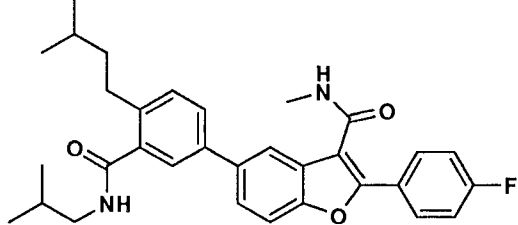
Structure	IC ₅₀	EC ₅₀
	B	E
Chiral 	C	E
	C	E
	B	E
	A	E

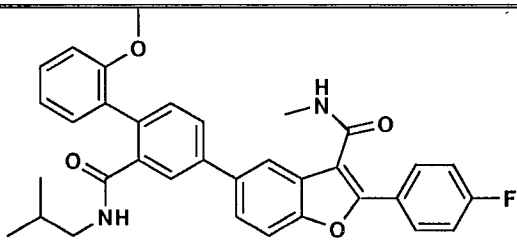
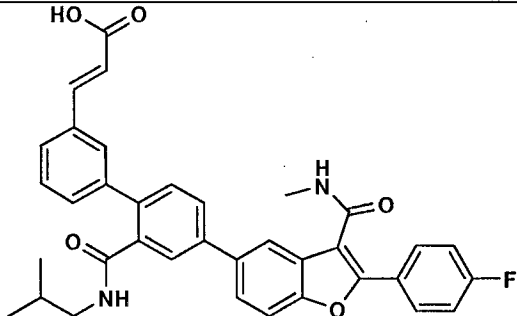
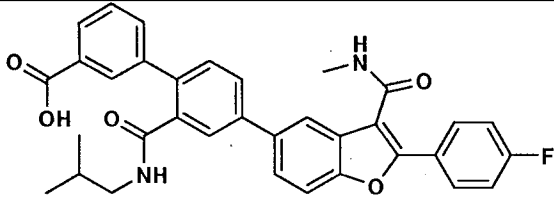
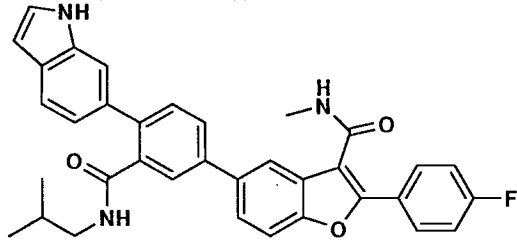
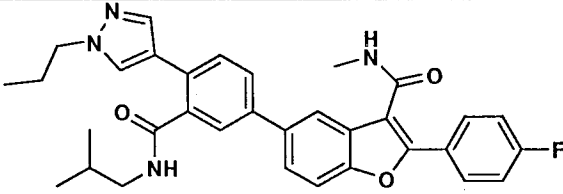
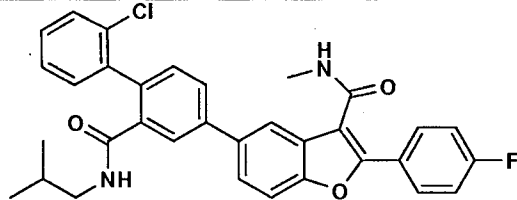
Structure	IC ₅₀	EC ₅₀
	C	E
	C	E
	B	E
	B	E
	A	E

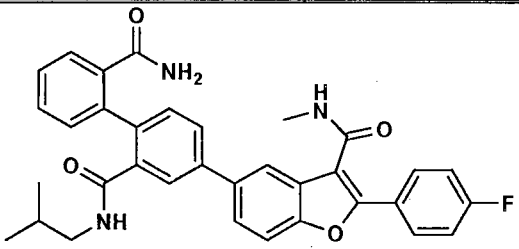
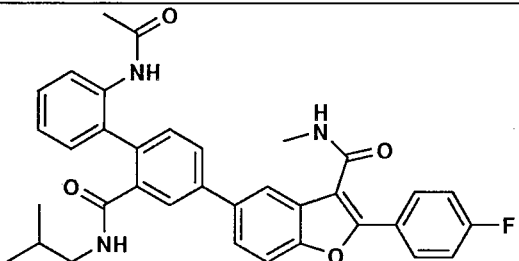
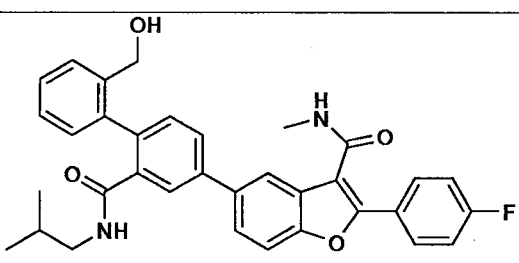
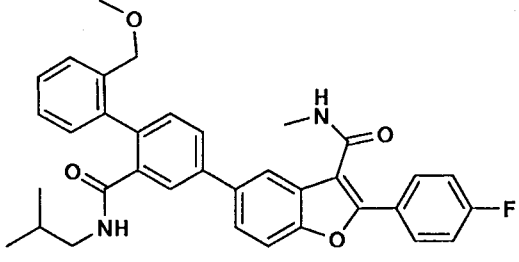
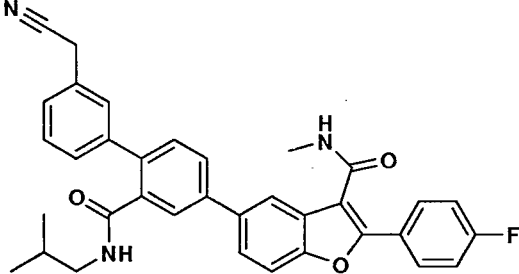
Structure	IC ₅₀	EC ₅₀
	C	E
	A	E
Chiral 	B	E
	B	E
	B	E
	E	E
	I	E

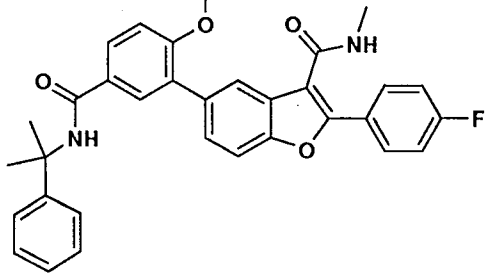
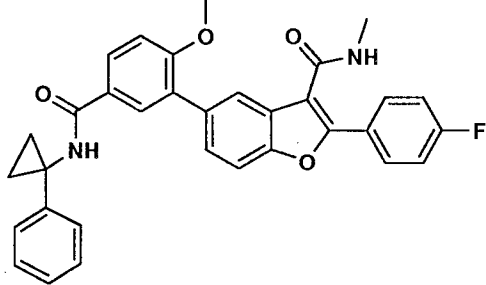
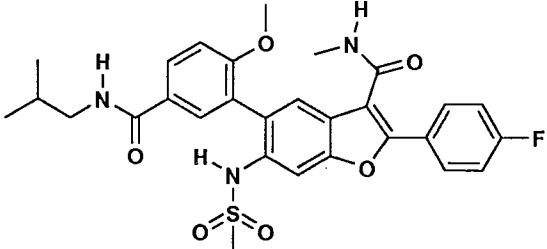
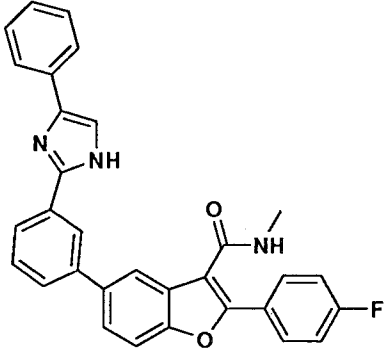
Structure	IC ₅₀	EC ₅₀
	E	E
	E	E
	E	E
	E	E
	C	E
	E	E

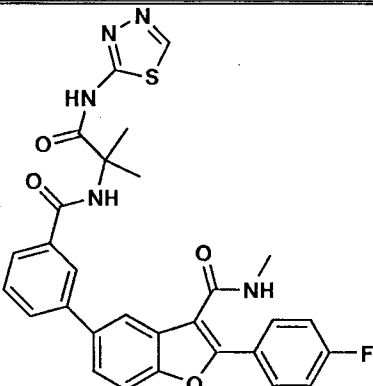
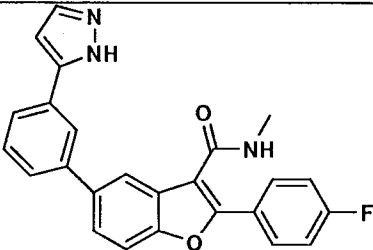
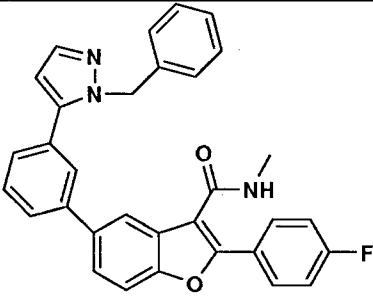
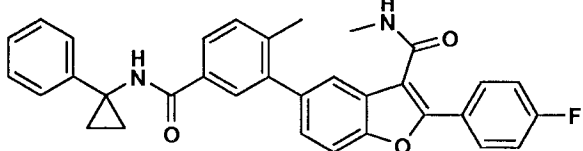
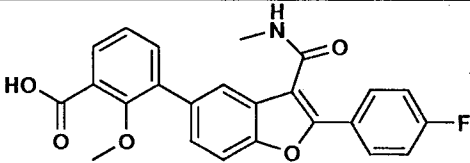
Structure	IC ₅₀	EC ₅₀
	E	C
		A
	A	A
	A	A
		A

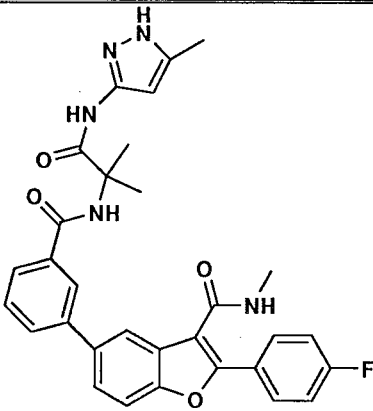
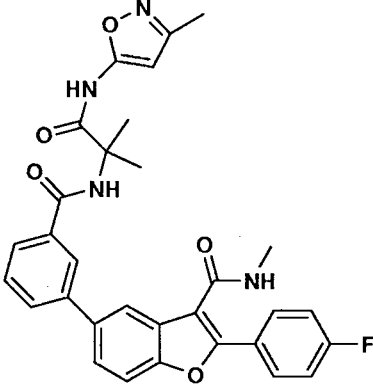
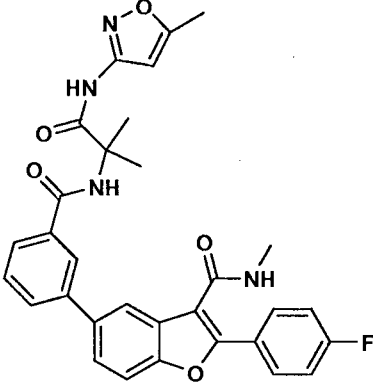
Structure	IC ₅₀	EC ₅₀
	A	A
		A
	A	A
	B	A
	A	A
		E

Structure	IC ₅₀	EC ₅₀
	A	A
	A	B
		C
	B	A
		A
	A	A

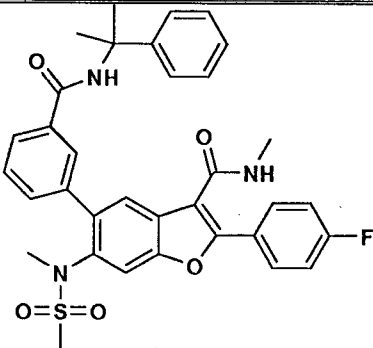
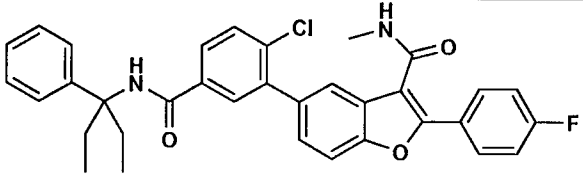
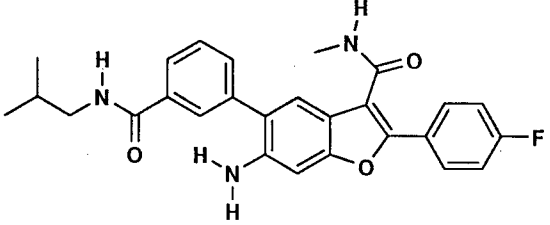
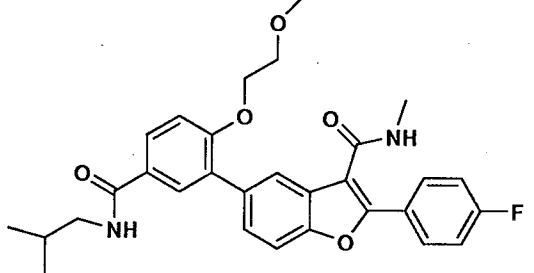
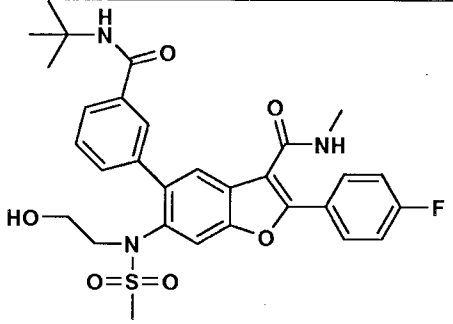
Structure	IC ₅₀	EC ₅₀
	A	A
	B	C
		A
	B	A
	A	A

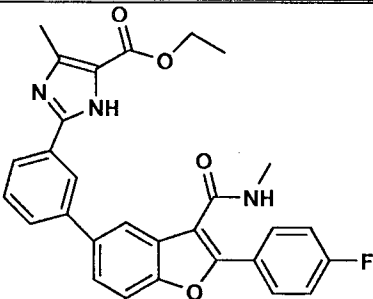
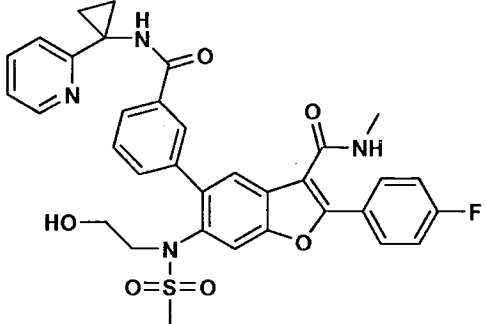
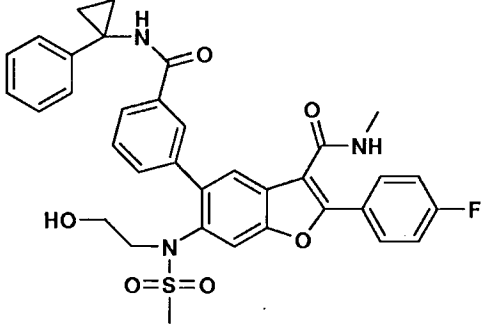
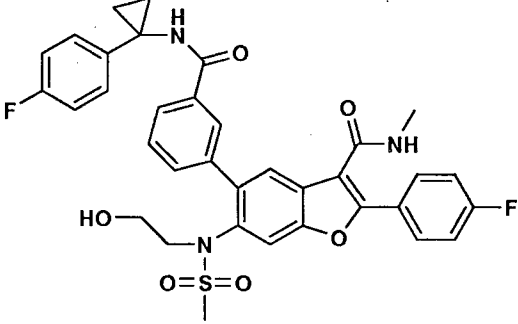
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	B	A

Structure	IC ₅₀	EC ₅₀
	A	A
	C	C
	A	A
	A	A
	C	E

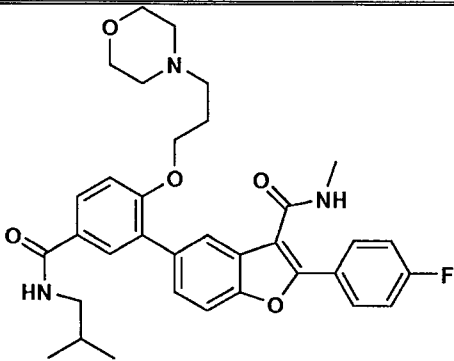
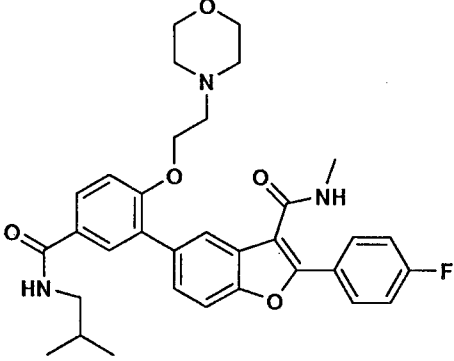
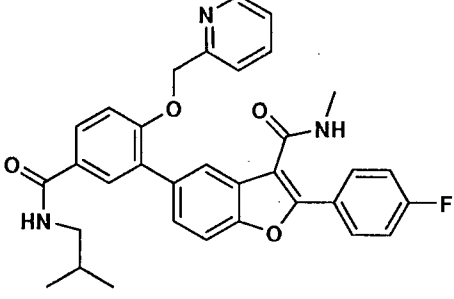
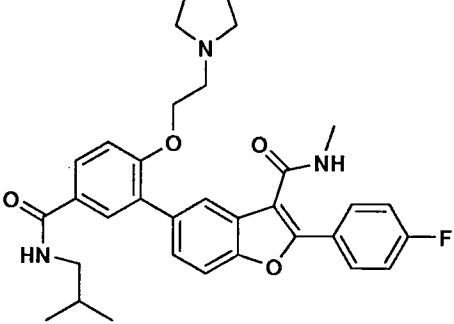
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A

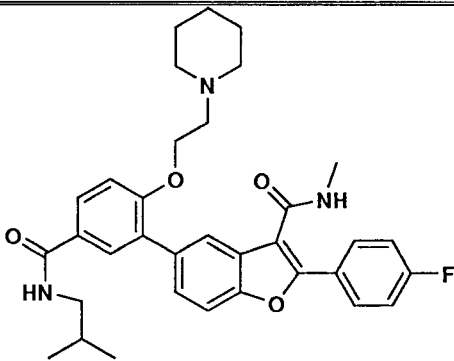
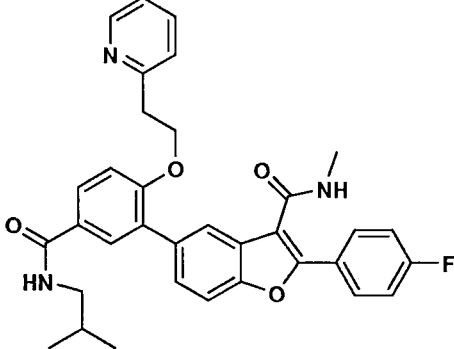
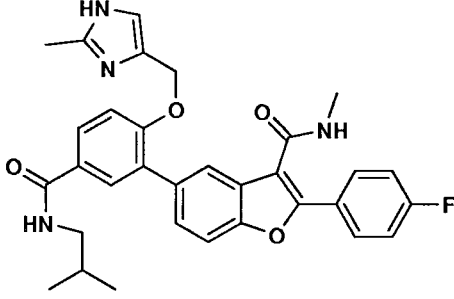
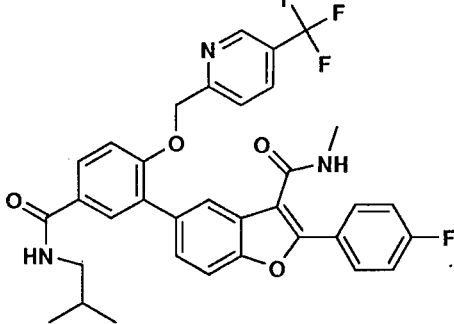
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	A	A
	E	E
	B	A

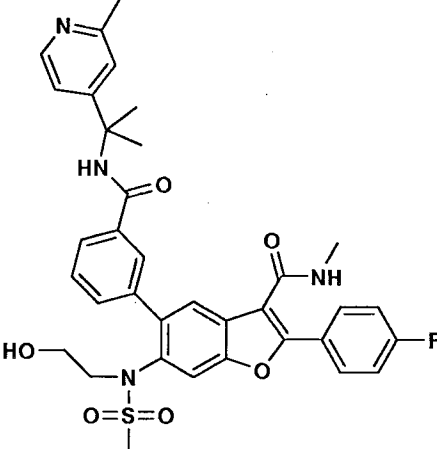
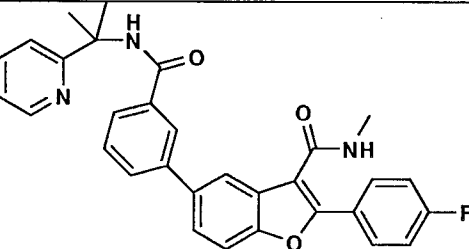
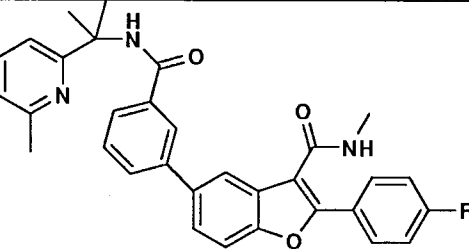
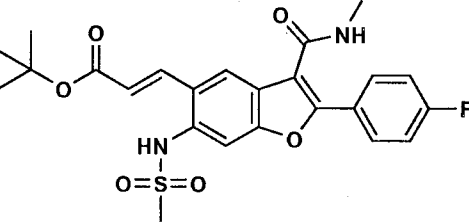
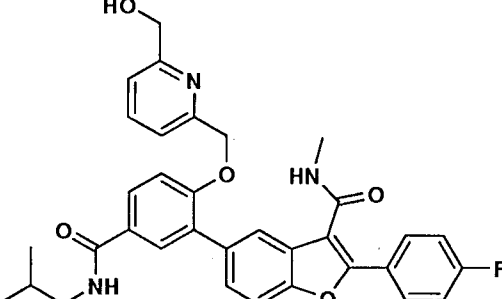
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	B	A
	A	A

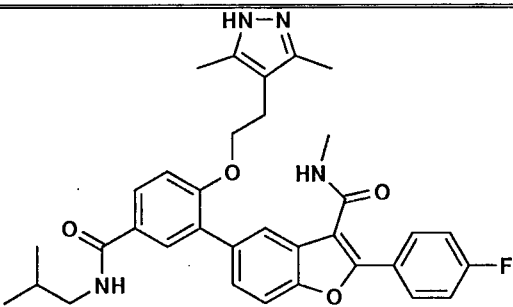
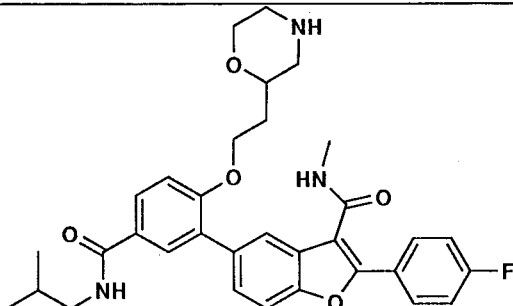
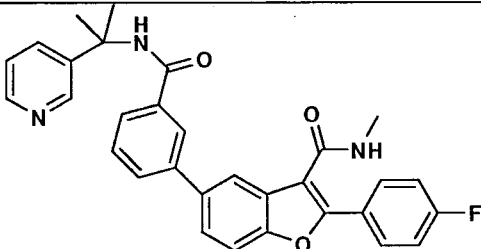
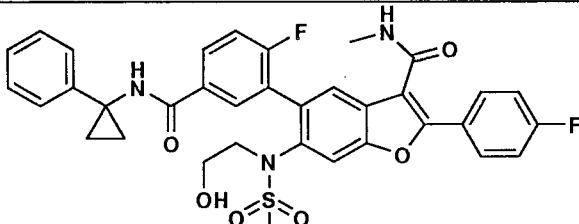
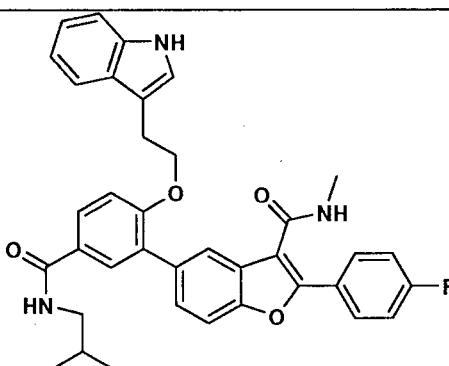
Structure	IC ₅₀	EC ₅₀
	A	
	A	A
	A	A
	A	A

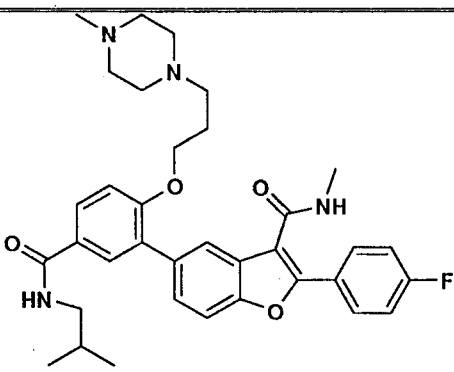
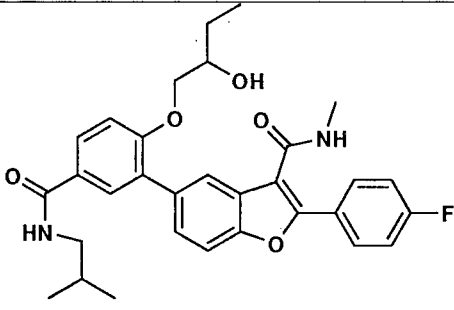
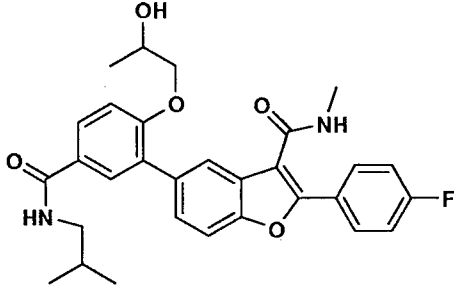
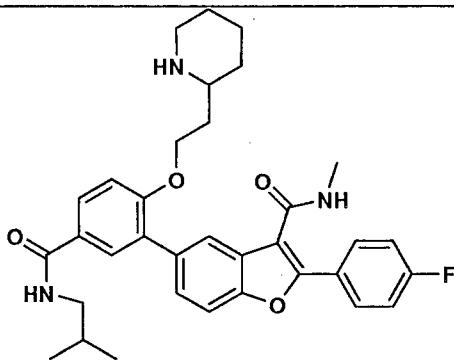
Structure	IC ₅₀	EC ₅₀
	B	B
	C	B
	E	E
	A	A

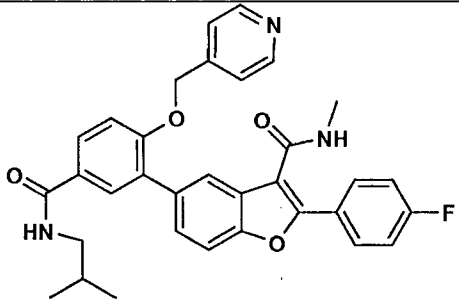
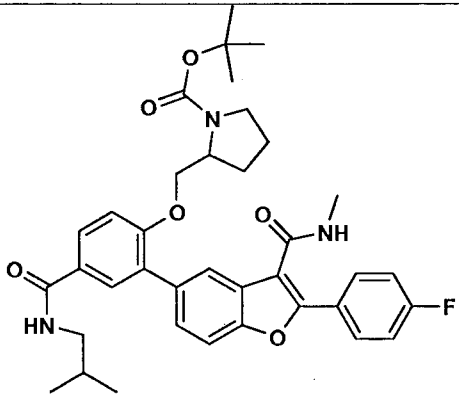
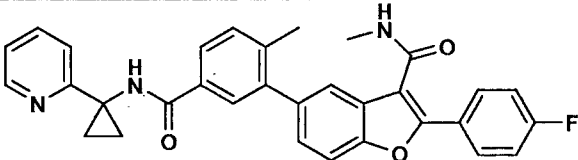
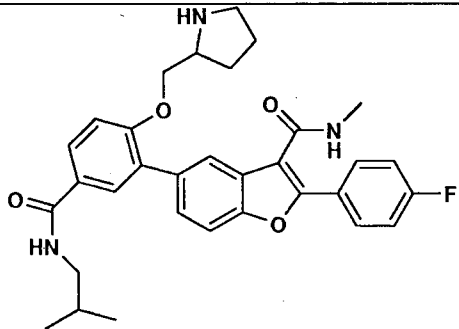
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	A	A

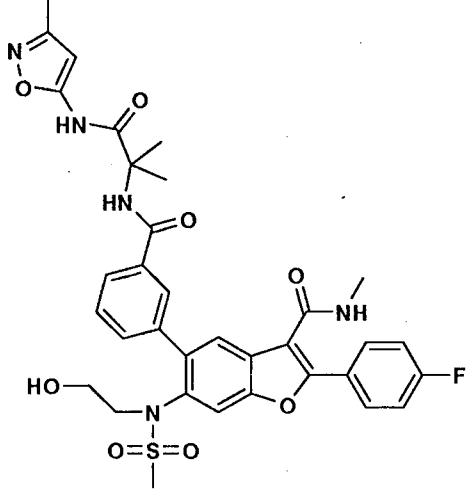
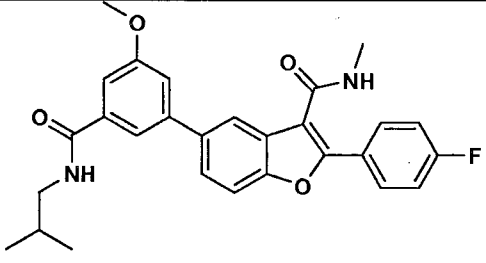
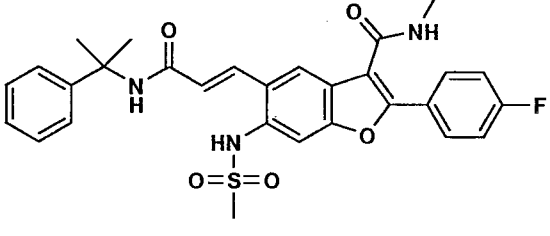
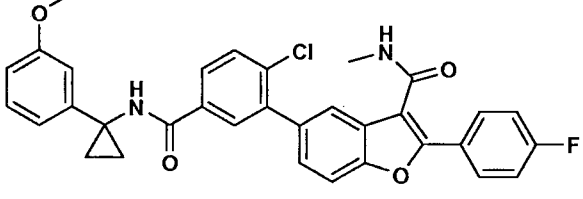
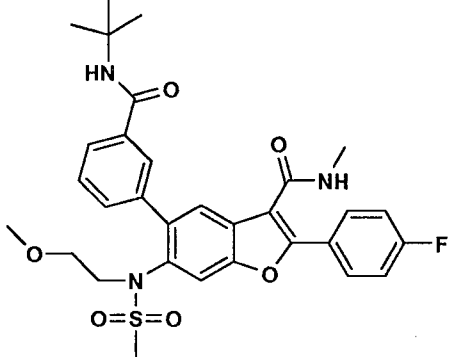
Structure	IC ₅₀	EC ₅₀
	B	A
	B	A
	A	A
	E	E

Structure	IC ₅₀	EC ₅₀
		A
		A
		B
		C
		

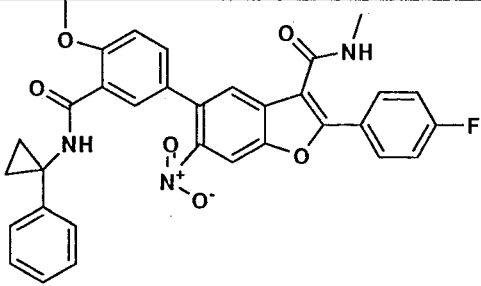
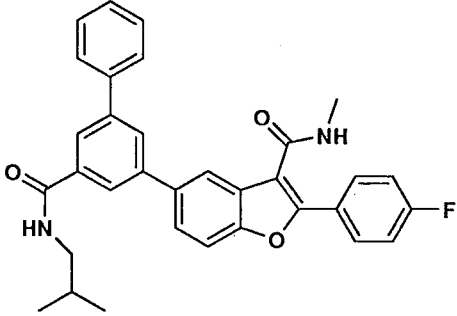
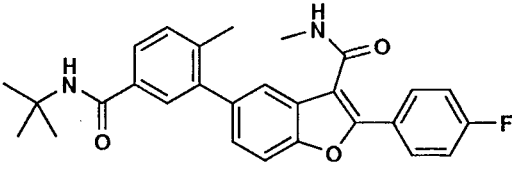
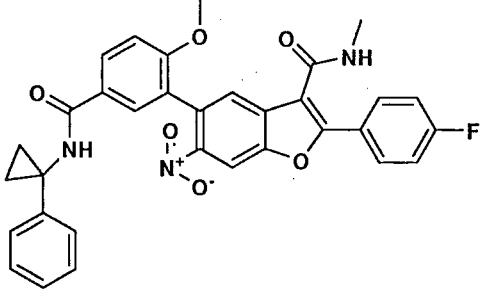
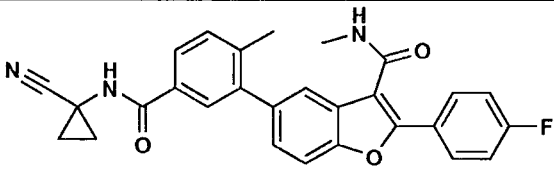
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	A	A
	C	C

Structure	IC ₅₀	EC ₅₀
	A	A
	B	B
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
	A	A
	E	C
	A	A
	A	B

Structure	IC ₅₀	EC ₅₀
	A	A
	B	B
	C	
		
		

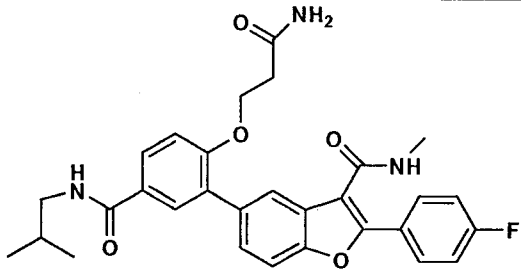
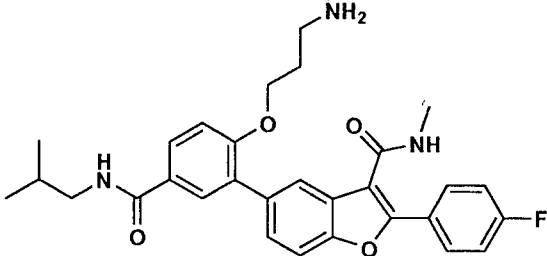
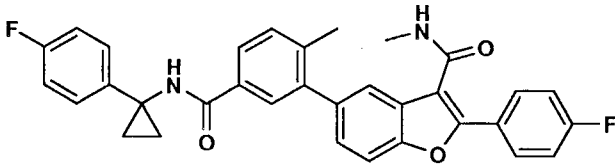
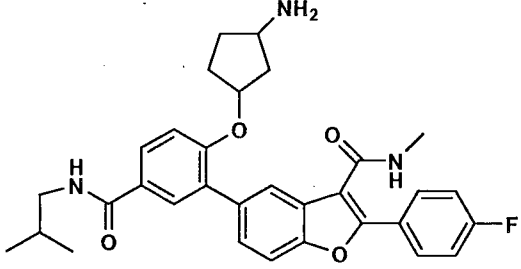
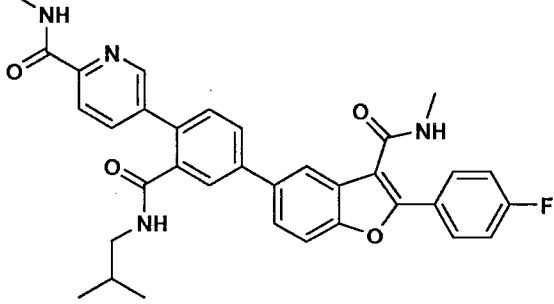
Structure	IC ₅₀	EC ₅₀
	A	A
	A	

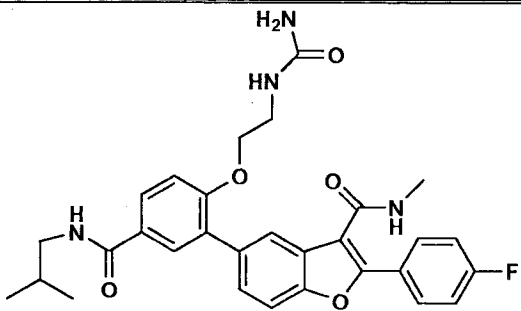
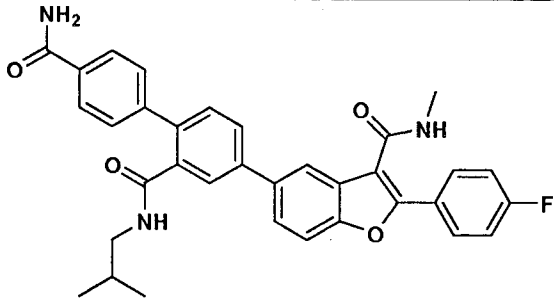
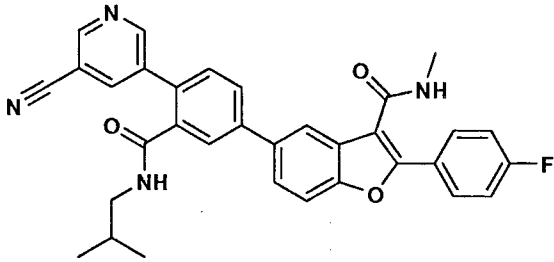
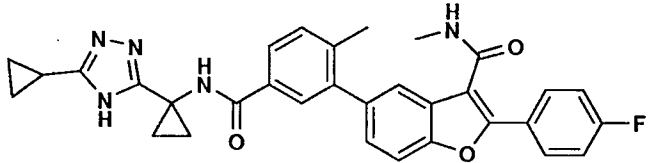
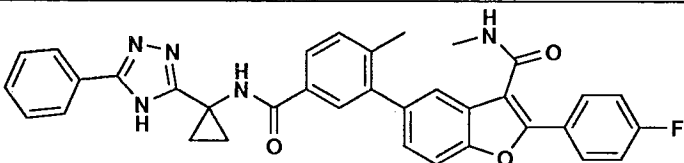
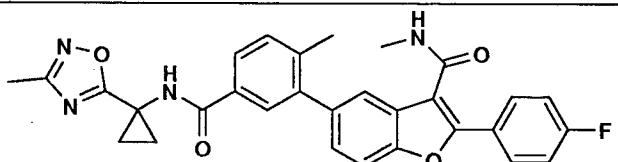
Structure	IC ₅₀	EC ₅₀
		
	E	E
	A	A
	A	B
	A	A

Structure	IC ₅₀	EC ₅₀
	A	A
	C	C
	A	A
	C	B
	A	A
	A	A
	A	A

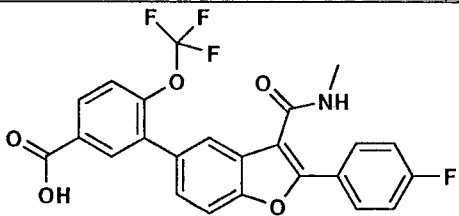
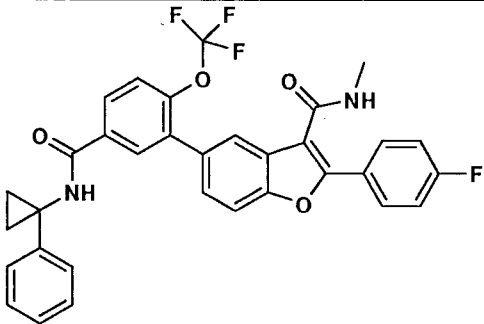
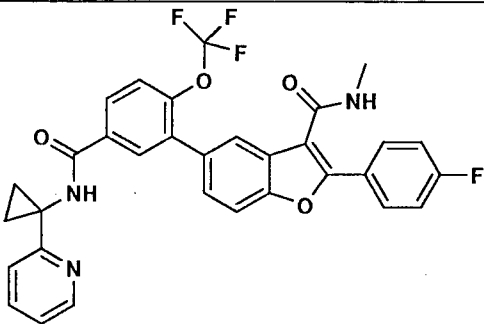
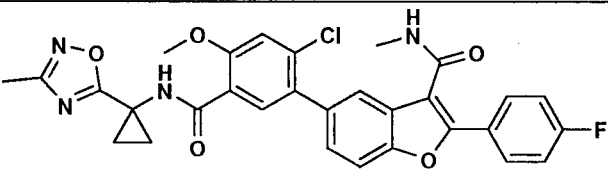
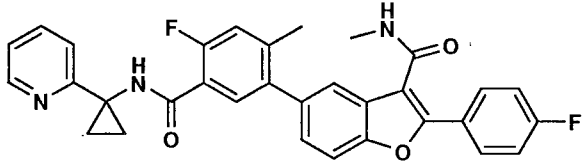
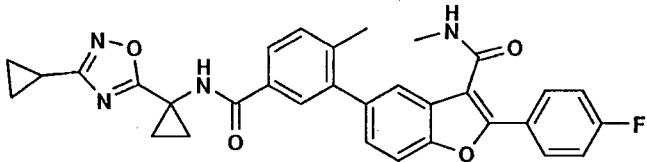
Structure	IC ₅₀	EC ₅₀
	A	A
	A	C
	C	C
	A	A
	A	A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
	A	C
	A	A
	C	E
	A	A
	A	A
	A	A

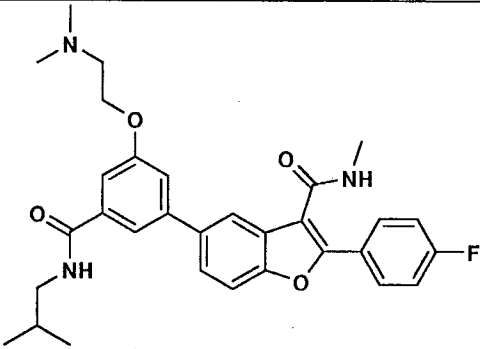
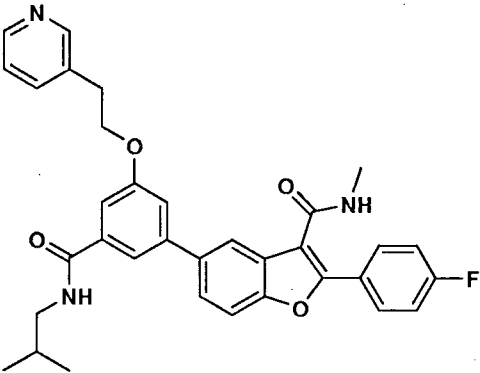
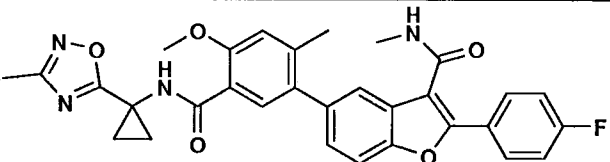
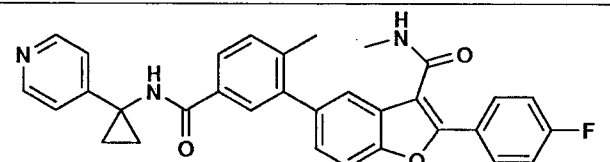
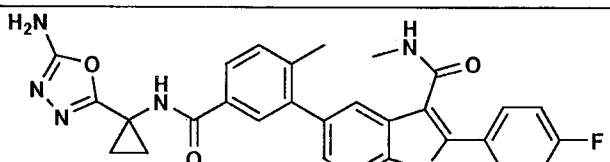
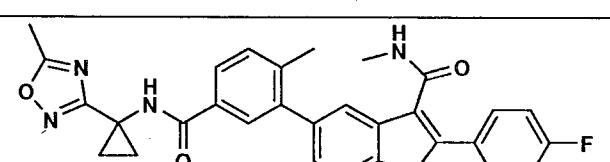
Structure	IC ₅₀	EC ₅₀
	E	E
	A	A
	A	A
	A	A
	E	E

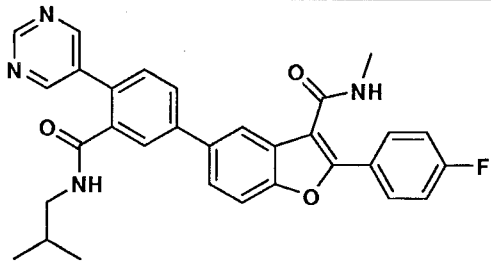
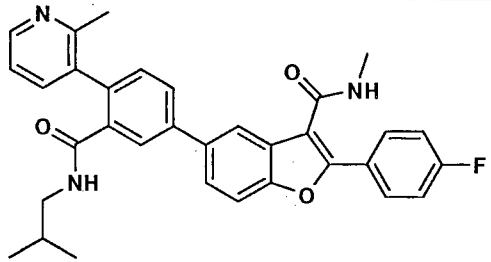
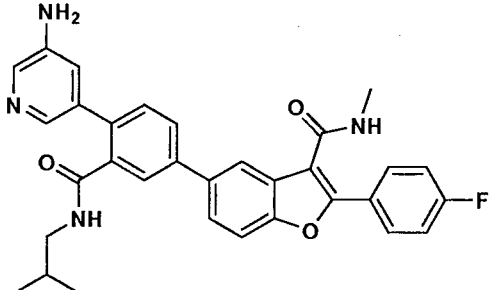
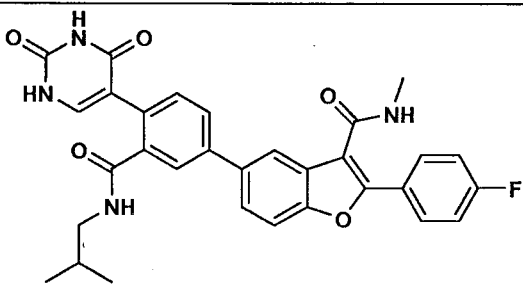
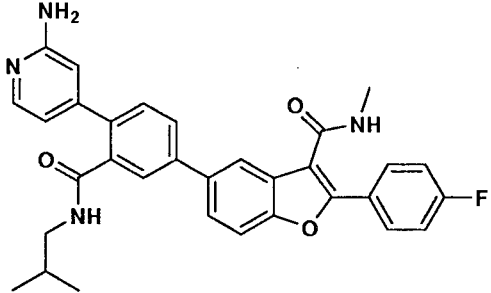
Structure	IC ₅₀	EC ₅₀
	A	A
	A	E
	A	B
	A	A
	A	A
		A

Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	C	E
	B	E
	A	B
	A	A

Structure	IC ₅₀	EC ₅₀
		E
	B	A
	B	A
	A	A
	A	A
	A	A

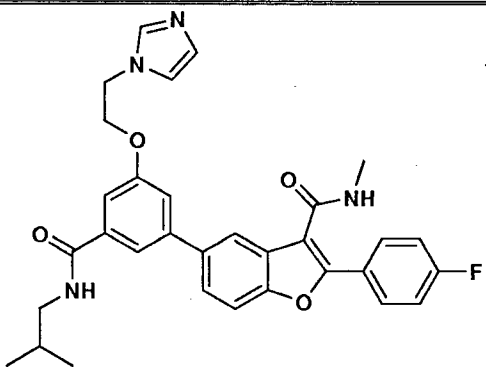
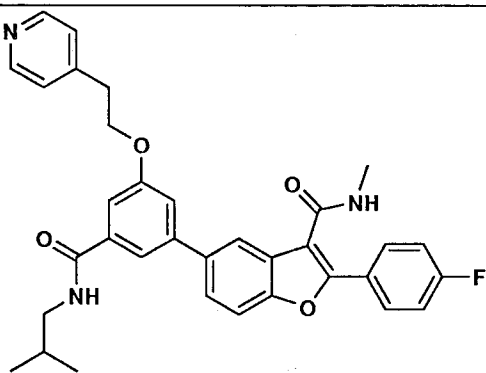
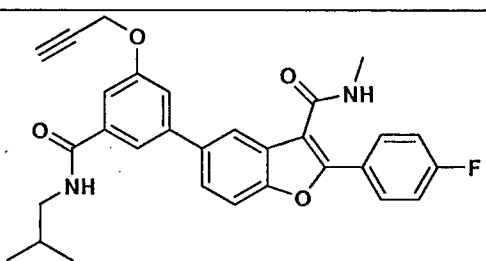
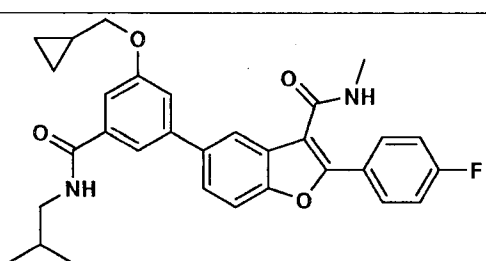
Structure	IC ₅₀	EC ₅₀
	E	B
	A	
	A	
	B	A
	A	A
	A	A

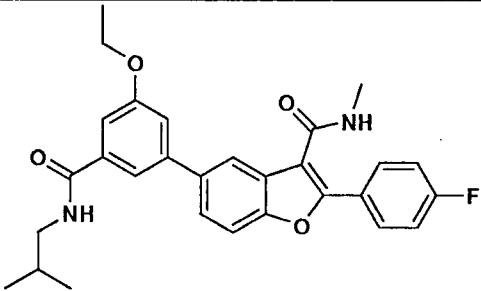
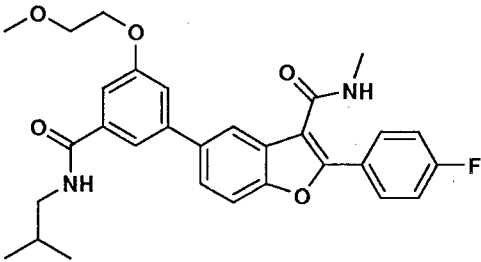
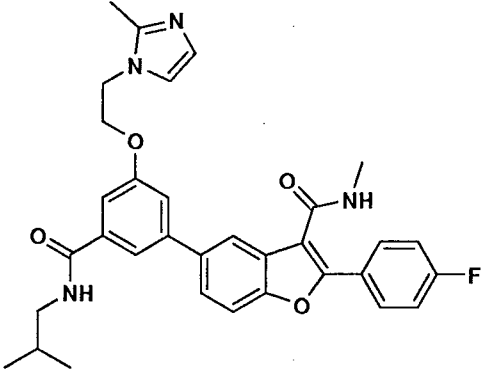
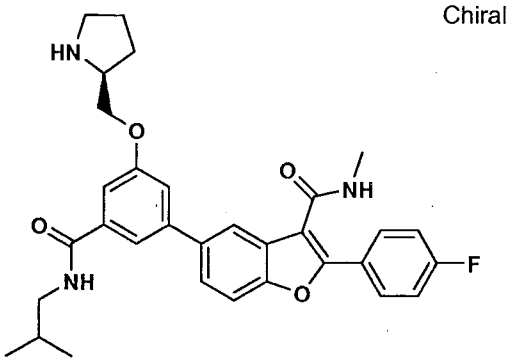
Structure	IC ₅₀	EC ₅₀
	B	B
	E	C
	A	A
	A	A
	A	A
	L	A

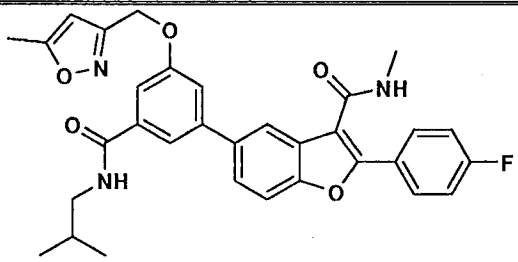
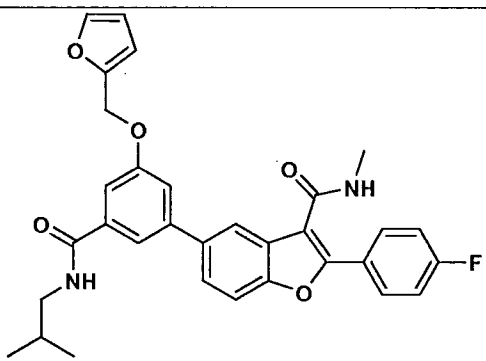
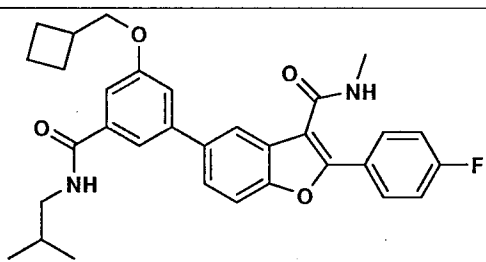
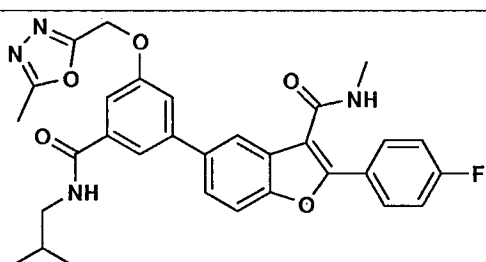
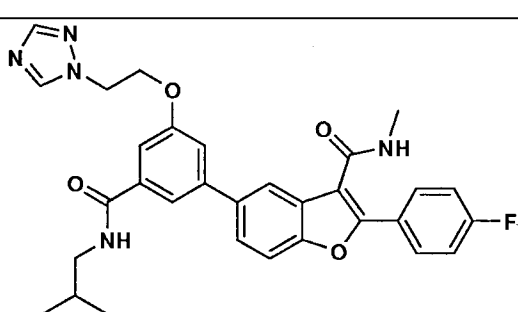
Structure	IC ₅₀	EC ₅₀
	A	
	A	A
	A	B
	A	
	L	A

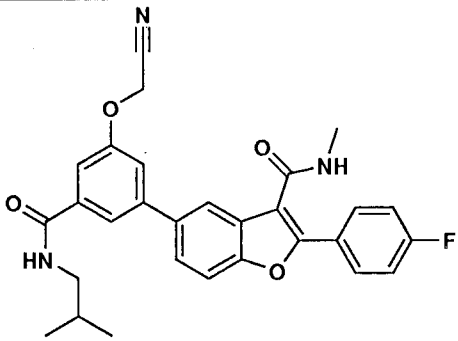
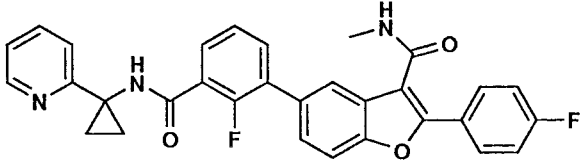
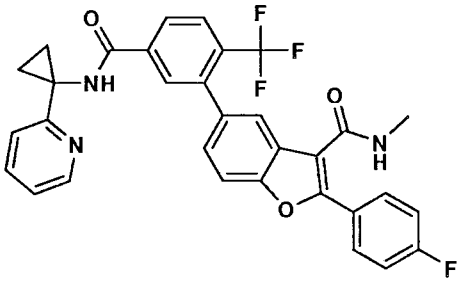
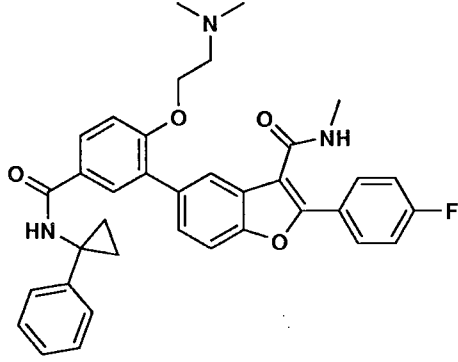
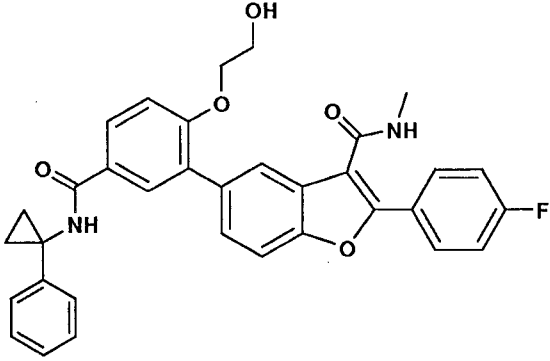
Structure	IC ₅₀	EC ₅₀
	B	
	A	
	B	
	A	
	A	B
	L	A

Structure	IC ₅₀	EC ₅₀
	B	
	B	
	A	B
	A	C
	A	A

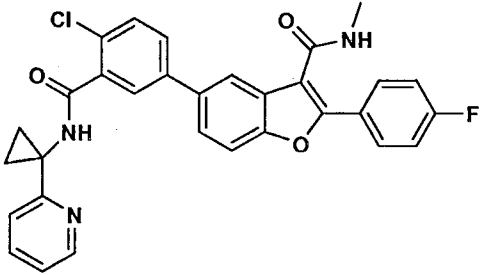
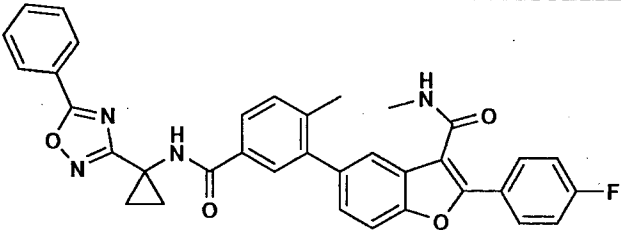
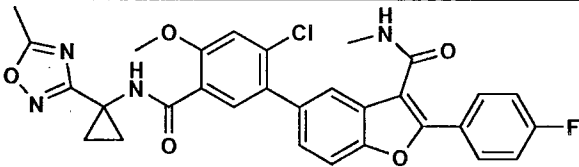
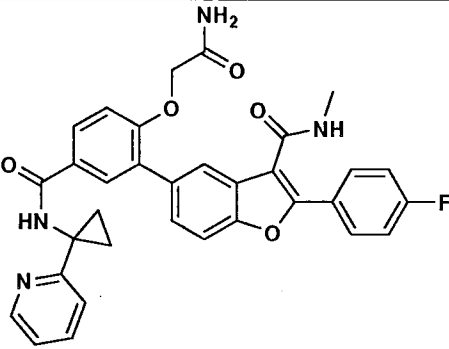
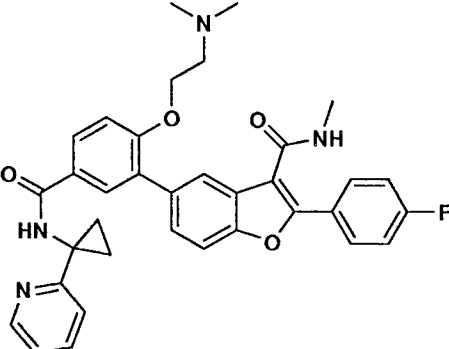
Structure	IC ₅₀	EC ₅₀
	C	C
	A	M
	C	C
	E	B

Structure	IC ₅₀	EC ₅₀
	M	C
	M	C
	C	C
 Chiral	C	C

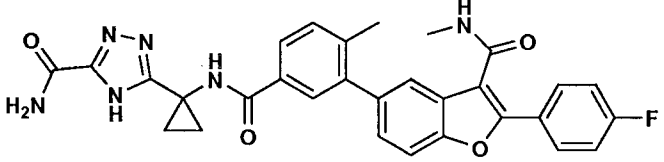
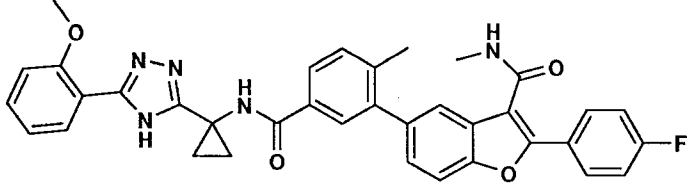
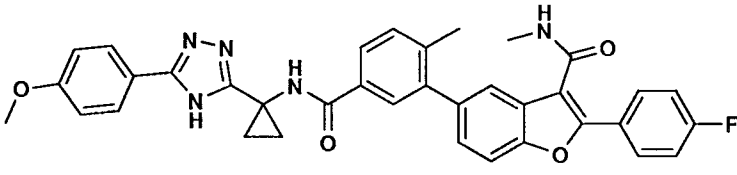
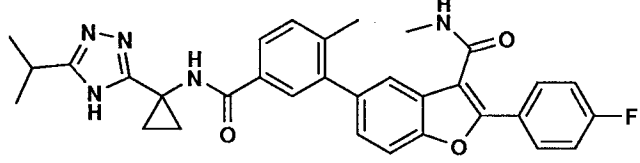
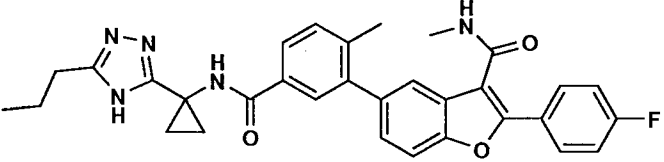
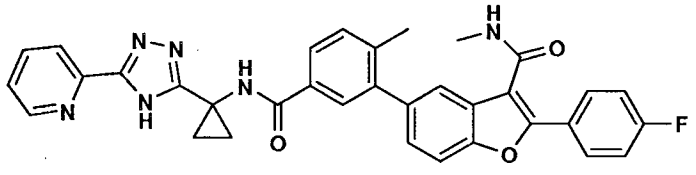
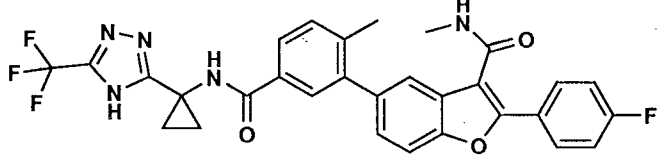
Structure	IC ₅₀	EC ₅₀
	G	C
	C	C
	E	C
	A	C
	B	C

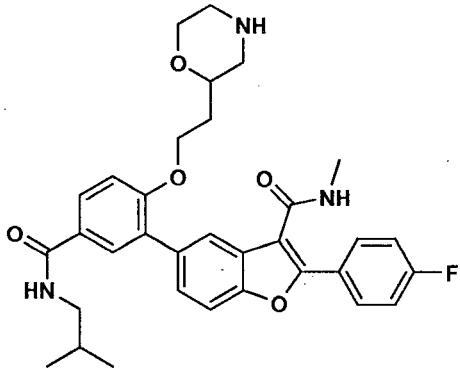
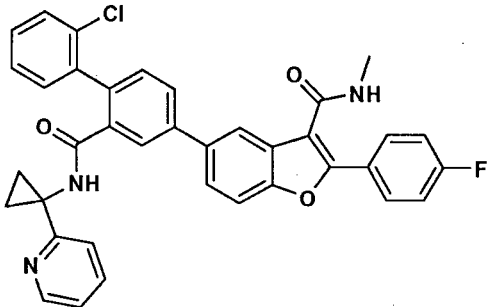
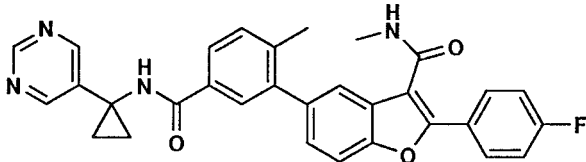
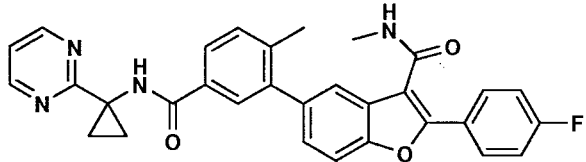
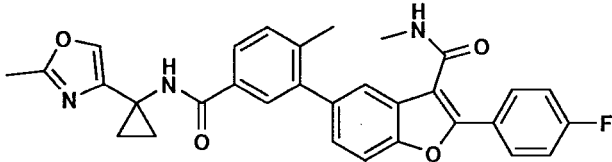
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	A	A
	A	A

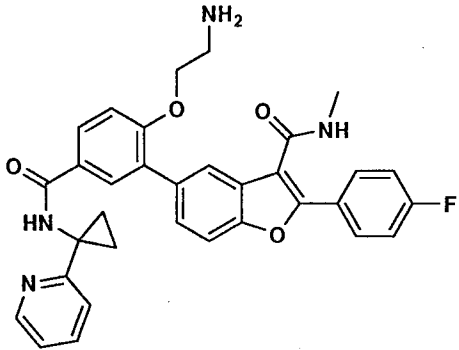
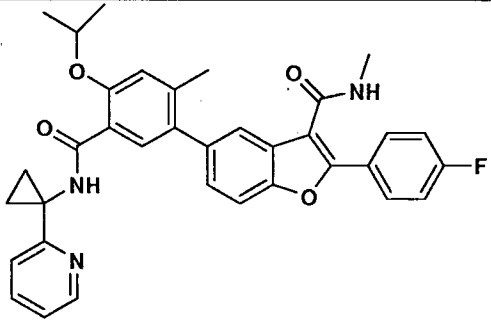
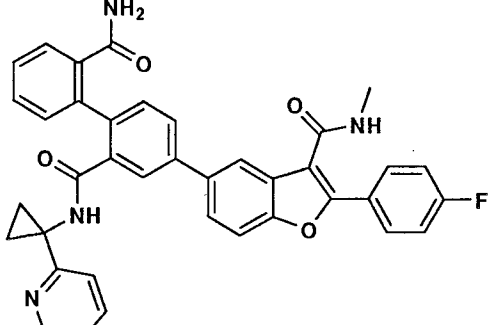
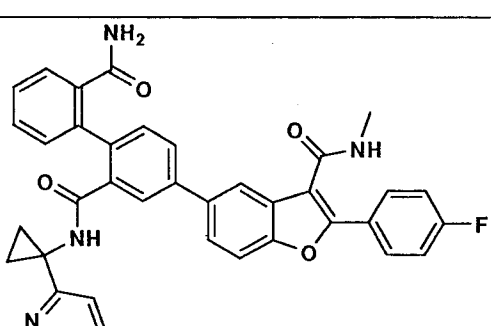
Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
	A	A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
	B	E
		A
		A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
		A
	A	A
	A	A
	A	A
	A	A
	A	A
	A	A
	B	A

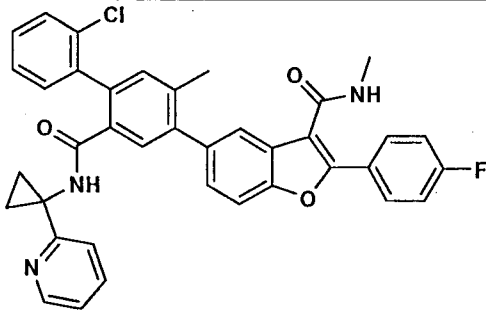
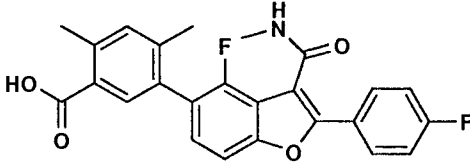
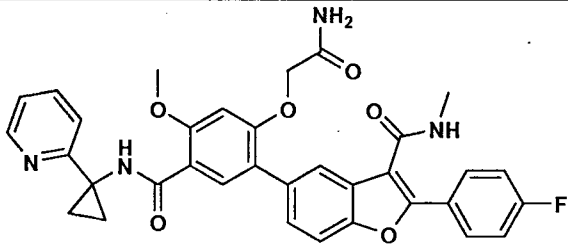
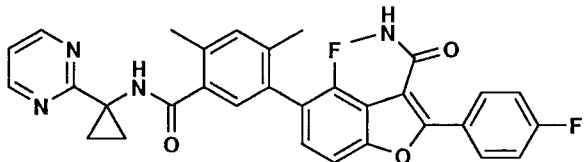
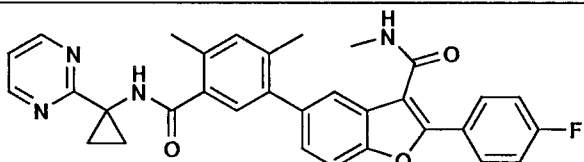
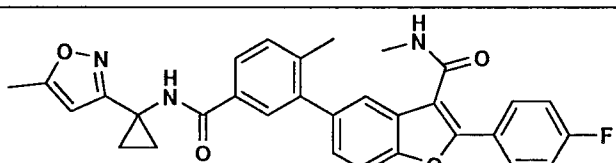
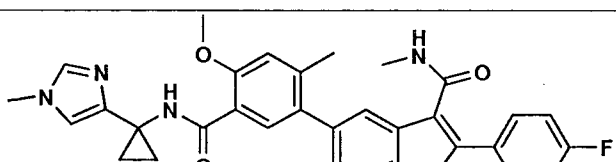
Structure	IC ₅₀	EC ₅₀
	A	B
		A
	A	A
	A	A
		A
	A	A
	A	A

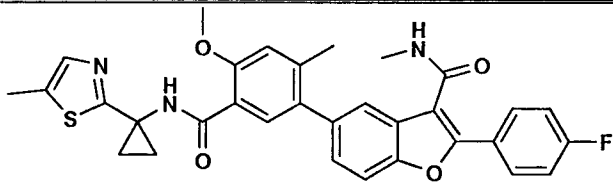
Structure	IC ₅₀	EC ₅₀
		A
		A
		A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
	N	A
	A	A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
	A	A
	A	A
		C
	N	A
	A	A
	A	A
	A	A

Structure	IC ₅₀	EC ₅₀
		A
	A	A
	N	A
	A	A
	A	A
	A	A
	A	A

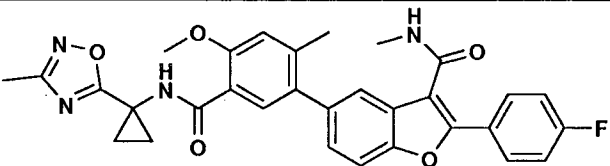
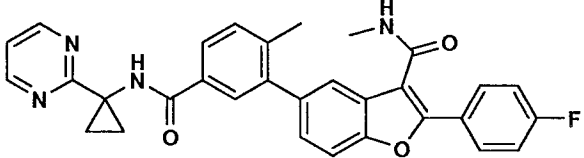
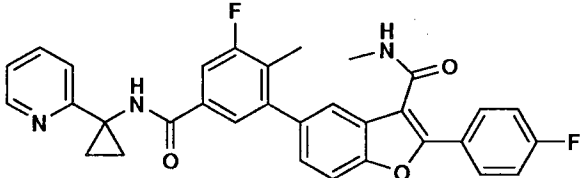
Structure	IC ₅₀	EC ₅₀
	A	A
	C	E
	N	A
	B	A
	A	A
		A
		A

Structure	IC ₅₀	EC ₅₀
		A

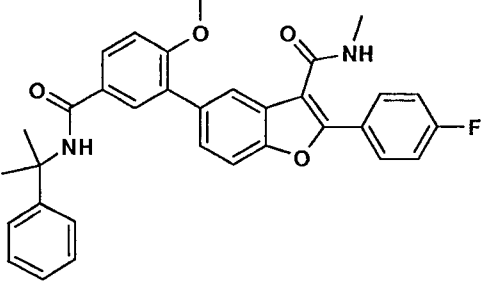
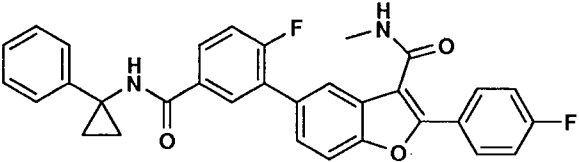
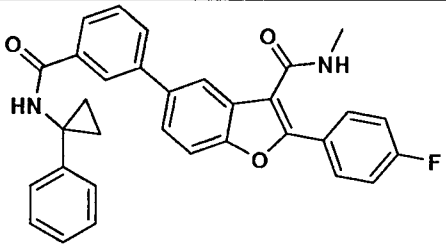
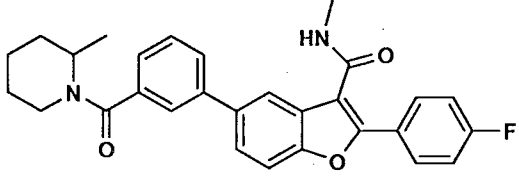
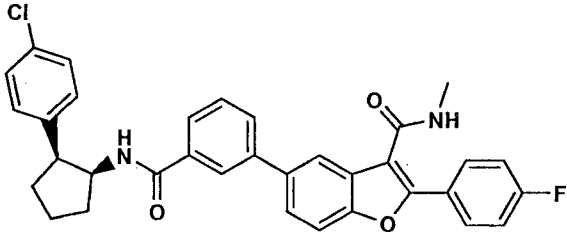
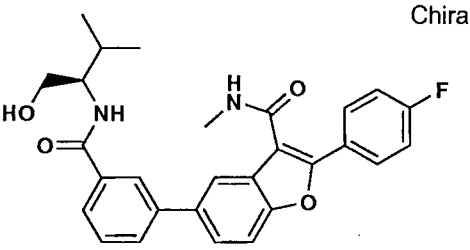
[0054] A 0.002 or less to 0.25 μM ; B $>0.25 \mu\text{M} - <1.0 \mu\text{M}$; C $1.0 \mu\text{M} - 10.0 \mu\text{M}$; D $>0.67 \mu\text{M}$ but an exact value was not determined; E $>10.0 \mu\text{M}$; F $>0.4 \mu\text{M}$; but an exact value was not determined; G $> 1.39 \mu\text{M}$ but an exact value was not determined; H $>0.62 \mu\text{M}$ but an exact value was not determined; I $>4 \mu\text{M}$ but an exact value was not determined; J $>3.7 \mu\text{M}$ but an exact value was not determined; K $>1.23 \mu\text{M}$ but an exact value was not determined; L $< 0.02 \mu\text{M}$ but an exact value was not determined; M >0.50 but an exact value was not determined. N <0.02 but an exact value was not determined.

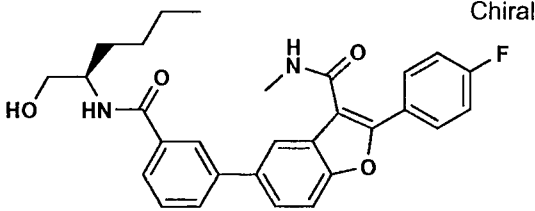
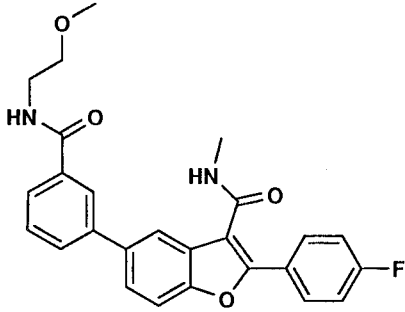
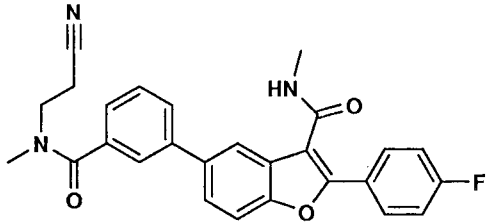
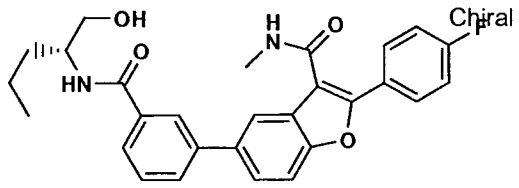
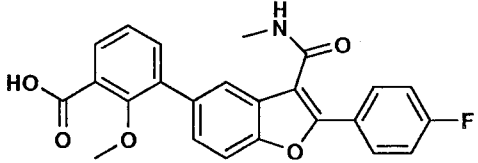
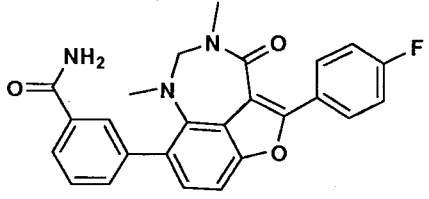
10

TABLE 1c

Structure	IC ₅₀ (μM)	EC ₅₀ (μM)
	0.02	1.60E-03*
	< 0.02	3.04E-04*
	0.01	4.25E-04*

Structure	IC ₅₀ (μM)	EC ₅₀ (μM)
	0.02	7.86E-04*
	7.20E-03	8.05E-04*
	3.95E-03	8.30E-04*
	9.95E-03	1.78E-03
	0.01	1.83E-03
	8.60E-03	1.95E-03
	5.45E-03	2.47E-03

Structure	IC ₅₀ (μM)	EC ₅₀ (μM)
	9.65E-03	3.04E-03
	0.02	3.57E-03
	5.90E-03	3.58E-03
	0.29	1.13
	> 12.50	1.13
 Chiral	0.80	1.25

Structure	IC ₅₀ (μM)	EC ₅₀ (μM)
 Chiral	0.60	1.26
	1.71	1.34
	0.80	1.38
 Chiral	1.15	1.39
	4.75	13.26
	> 12.50	13.66

[0058] Another aspect of the invention is a composition where the compound having anti-HCV activity is a cyclosporin. Another aspect of the invention is where the cyclosporin is cyclosporin A.

5 [0059] Another aspect of the invention is a composition where the compound having anti-HCV activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

10 [0060] Another aspect of the invention is a composition where the compound having anti-HCV activity is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, IMPDH, and a nucleoside analog for the treatment of an HCV infection.

15 [0061] Another aspect of the invention is a composition comprising a compound, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, an interferon and ribavirin.

[0062] Another aspect of the invention is a method of inhibiting the function of the HCV replicon comprising contacting the HCV replicon with a compound of formula I or a pharmaceutically acceptable salt thereof.

20 [0063] Another aspect of the invention is a method of inhibiting the function of the HCV NS5B protein comprising contacting the HCV NS5B protein with a compound of formula I or a pharmaceutically acceptable salt thereof.

[0064] Another aspect of the invention is a method of treating an HCV infection in a patient comprising administering to the patient a therapeutically effective amount
25 of a compound or a pharmaceutically acceptable salt thereof. Another aspect of the invention is a method of inhibiting the function of the HCV replicon. Another aspect of the invention is a method of inhibiting the function of the HCV NS5B protein.

[0065] Another aspect of the invention is a method of treating an HCV infection in a patient comprising administering to the patient a therapeutically effective amount
30 of a compound, or a pharmaceutically acceptable salt thereof, in conjunction with (prior to, after, or concurrently) another compound having anti-HCV activity.

[0066] Another aspect of the invention is the method where the other compound having anti-HCV activity is an interferon.

[0067] Another aspect of the invention is the method where the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, 5 interferon alpha 2A, and lymphoblastoid interferon tau.

[0068] Another aspect of the invention is the method where the other compound having anti-HCV activity is a cyclosporin.

[0069] Another aspect of the invention is the method where the cyclosporin is cyclosporin A.

10 [0070] Another aspect of the invention is the method where the other compound having anti-HCV activity is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

15 [0071] Another aspect of the invention is the method where the other compound having anti-HCV activity is effective to inhibit the function of a target selected from the group consisting of HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, IMPDH, and a nucleoside analog for the treatment of an 20 HCV infection.

[0072] Another aspect of the invention is the method where the other compound having anti-HCV activity is effective to inhibit the function of target in the HCV life cycle other than the HCV NS5B protein.

[0073] "Therapeutically effective" means the amount of agent required to provide 25 a meaningful patient benefit as understood by practitioners in the field of hepatitis and HCV infection.

[0074] "Patient" means a person infected with the HCV virus and suitable for therapy as understood by practitioners in the field of hepatitis and HCV infection.

[0075] "Treatment," "therapy," "regimen," "HCV infection," and related terms 30 are used as understood by practitioners in the field of hepatitis and HCV infection.

[0076] The compounds of this invention are generally given as pharmaceutical compositions comprised of a therapeutically effective amount of a compound or its

pharmaceutically acceptable salt and a pharmaceutically acceptable carrier and may contain conventional excipients. Pharmaceutically acceptable carriers are those conventionally known carriers having acceptable safety profiles. Compositions encompass all common solid and liquid forms including for example capsules, tablets, 5 lozenges, and powders as well as liquid suspensions, syrups, elixirs, and solutions. Compositions are made using common formulation techniques, and conventional excipients (such as binding and wetting agents) and vehicles (such as water and alcohols) are generally used for compositions. See, for example, *Remington's Pharmaceutical Sciences*, 17th edition, Mack Publishing Company, Easton, PA 10 (1985).

[0077] Solid compositions are normally formulated in dosage units and compositions providing from about 1 to 1000 mg of the active ingredient per dose are preferred. Some examples of dosages are 1 mg, 10 mg, 100 mg, 250 mg, 500 mg, and 1000 mg. Generally, other agents will be present in a unit range similar to agents of 15 that class used clinically. Typically, this is 0.25-1000 mg/unit.

[0078] Liquid compositions are usually in dosage unit ranges. Generally, the liquid composition will be in a unit dosage range of 1-100 mg/mL. Some examples of dosages are 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL, and 100 mg/mL. Generally, other agents will be present in a unit range similar to agents of that class used 20 clinically. Typically, this is 1-100 mg/mL.

[0079] The invention encompasses all conventional modes of administration; oral and parenteral methods are preferred. Generally, the dosing regimen will be similar to other agents used clinically. Typically, the daily dose will be 1-100 mg/kg body weight daily. Generally, more compound is required orally and less parenterally. 25 The specific dosing regime, however, will be determined by a physician using sound medical judgment.

[0080] The invention also encompasses methods where the compound is given in combination therapy. That is, the compound can be used in conjunction with, but separately from, other agents useful in treating hepatitis and HCV infection. In these 30 combination methods, the compound will generally be given in a daily dose of 1-100 mg/kg body weight daily in conjunction with other agents. The other agents

generally will be given in the amounts used therapeutically. The specific dosing regime, however, will be determined by a physician using sound medical judgment.

[0081] Some examples of compounds suitable for compositions and methods are listed in Table 2.

5

TABLE 2

Brand Name	Type of Inhibitor or Target	Source Company
Omega IFN	IFN- ω	Intarcia Therapeutics
BILN-2061	Serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
Summetrel	Antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
Roferon A	IFN- α 2a	F. Hoffmann-La Roche Ltd., Basel, Switzerland
Pegasys	PEGylated IFN- α 2a	F. Hoffmann-La Roche Ltd., Basel, Switzerland
Pegasys and Ribavirin	PEGylated IFN- α 2a/ribavirin	F. Hoffmann-La Roche Ltd., Basel, Switzerland
CELLCEPT®	HCV IgG immunosuppressant	F. Hoffmann-La Roche Ltd., Basel, Switzerland
Wellferon	Lymphoblastoid IFN- α n1	GlaxoSmithKline plc, Uxbridge, UK
Albuferon - α	Albumin IFN- α 2b	Human Genome Sciences Inc., Rockville, MD
Levovirin	Ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
IDN-6556	Caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA

Brand Name	Type of Inhibitor or Target	Source Company
IP-501	Antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
Actimmune	INF- γ	InterMune Inc., Brisbane, CA
Infergen A	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
ISIS 14803	Antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA / Elan Pharmaceuticals Inc., New York, NY
JTK-003	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Pegasys and Ceplene	PEGylated IFN- α 2a/immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Ceplene	Immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Civacir	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Intron A and Zadaxin	IFN- α 2b/ α 1-thymosin	RegeneRx Biopharmaceuticals Inc., Bethesda, MD / SciClone Pharmaceuticals Inc, San Mateo, CA
Levovirin	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Viramidine	Ribavirin prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO

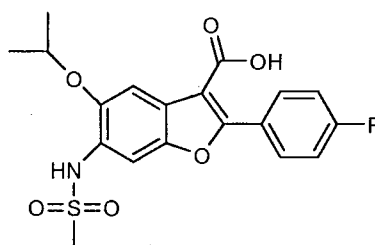
Brand Name	Type of Inhibitor or Target	Source Company
Intron A	IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron	PEGylated IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
Rebetron	IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Ribavirin	Ribavirin	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	PEGylated IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Zadazim	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Rebif	IFN- β 1a	Serono, Geneva, Switzerland
IFN- β and EMZ701	IFN- β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Batabulin (T67)	β -tubulin inhibitor	Tularik Inc., South San Francisco, CA
Merimepodib (VX-497)	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
Telaprevir (VX-950, LY-570310)	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA / Eli Lilly and Co. Inc., Indianapolis, IN

Brand Name	Type of Inhibitor or Target	Source Company
Omniferon	Natural IFN- α	Viragen Inc., Plantation, FL
XTL-6865 (XTL-002)	Monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Israel
HCV-796	NS5B replicase inhibitor	Wyeth / Viropharma
NM-283	NS5B replicase inhibitor	Idenix / Novartis
GL-59728	NS5B replicase inhibitor	Gene Labs / Novartis
GL-60667	NS5B replicase inhibitor	Gene Labs / Novartis
2'C MeA	NS5B replicase inhibitor	Gilead
PSI 6130	NS5B replicase inhibitor	Roche
R1626	NS5B replicase inhibitor	Roche
SCH 503034	Serine protease inhibitor	Schering-Plough
NIM811	Cyclophilin Inhibitor	Novartis
Suvus	Methylene blue	Bioenvision
Multiferon	Long lasting IFN	Viragen / Valentis
Actilon (CPG10101)	TLR9 agonist	Coley
Interferon- β	Interferon- β -1a	Serono
Zadaxin	Immunomodulator	SciClone
Pyrazolopyrimidine compounds and salts From WO 2005/047288	HCV Inhibitors	Arrow Therapeutics Ltd.
2'C Methyl adenosine	NS5B replicase inhibitor	Merck
GS-9132 (ACH-806)	HCV inhibitor	Achillion / Gilead

DESCRIPTION OF SPECIFIC EMBODIMENTS

[0082] Abbreviations as used herein, are defined as follows: “1 x” for once, “2 x” for twice, “3 x” for thrice, “°C” for degrees Celsius, “eq” for equivalent or 5 equivalents, “g” for gram or grams, “mg” for milligram or milligrams, “L” for liter or liters, “mL” for milliliter or milliliters, “ μ L” for microliter or microliters, “N” for normal, “M” for molar, “mmol” for millimole or millimoles, “min” for minute or

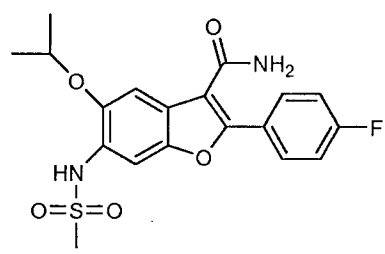
minutes, “h” for hour or hours, “rt” for room temperature, “RT” for retention time, “atm” for atmosphere, “psi” for pounds per square inch, “conc.” for concentrate, “sat” or “sat’d “ for saturated, “MW” for molecular weight, “mp” for melting point, “ee” for enantiomeric excess, “MS” or “Mass Spec” for mass spectrometry, “ESI” for electrospray ionization mass spectroscopy, “HR” for high resolution, “HRMS” for high resolution mass spectrometry, “LCMS” for liquid chromatography mass spectrometry, “HPLC” for high pressure liquid chromatography, “RP HPLC” for reverse phase HPLC, “TLC” or “tlc” for thin layer chromatography, “NMR” for nuclear magnetic resonance spectroscopy, “¹H” for proton, “δ” for delta, “s” for singlet, “d” for doublet, “t” for triplet, “q” for quartet, “m” for multiplet, “br” for broad, “Hz” for hertz, and “α”, “β”, “R”, “S”, “E”, and “Z” are stereochemical designations familiar to one skilled in the art.



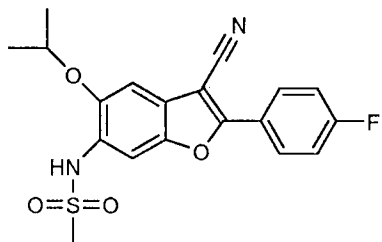
2-(4-Fluorophenyl)-5-isopropoxy-6-(methylsulfonamido)benzofuran-3-carboxylic acid

[0083] Excess NaOH (10 mL, 1N aq) was added to a stirring solution of methyl 2-(4-fluorophenyl)-5-isopropoxy-6-(methylsulfonamido)benzofuran-3-carboxylate (3.0 g, 6.89 mmol) in EtOH (34 mL) and THF (34 mL). It was allowed to stir at 60 °C overnight. The mixture was then heated to 67 °C and allowed to stir for 4 more hours. The mixture was concentrated then diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the titled compound (2.7 g, 96%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.31 - 1.38 (m, 6 H) 2.99 (s, 3 H) 4.63 - 4.73 (m, 1 H) 7.32 - 7.41 (m, 2 H) 8.00 - 8.08 (m, 2 H) 8.88 (s, 2 H) 13.05 (s, 1 H). LC-MS retention time: 1.03 min; m/z (MH⁻): 406. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5

ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was
5 determined using a MICROMASS® Platform for LC in electrospray mode.

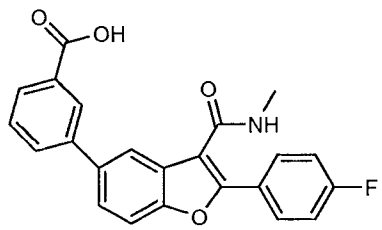


2-(4-Fluorophenyl)-5-isopropoxy-6-(methylsulfonamido)benzofuran-3-carboxamide
[0084] Ammonia (6.1 ml, 12.2 mmol, 2M in MeOH) was added to a stirring
10 solution of HATU (1.1 g, 2.95 mmol) and 2-(4-fluorophenyl)-5-isopropoxy-6-
(methylsulfonamido)benzofuran-3-carboxylic acid (1.0 g, 2.46 mmol) in DMF (20
ml) at 0 °C. It was allowed to warm to rt and stir for 1 hr. The mixture was diluted
with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was
dried over Na₂SO₄, filtered and concentrated to give the title compound (925 mg,
15 93%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.30 - 1.37 (m, 6 H) 2.98 (s, 3 H) 4.64 -
4.77 (m, 1 H) 7.19 (s, 1 H) 7.30 - 7.41 (m, 2 H) 7.54 (s, 1 H) 7.63 - 7.71 (m, 1 H) 7.89
(s, 1 H) 7.93 - 8.02 (m, 2 H) 8.85 (s, 1 H). LC-MS retention time: 1.26 min; m/z
(MH⁺) 407. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph
equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-
20 Vis detector at a detector wave length of 220nm. The elution conditions employed a
flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A /
100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time
of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate
and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data
25 was determined using a MICROMASS® Platform for LC in electrospray mode.



N-(3-Cyano-2-(4-fluorophenyl)-5-isopropoxybenzofuran-6-yl)methanesulfonamide.

[0085] Trifluoroacetic anhydride (375 μ L, 2.66 mmol) was added to a stirring solution of DIEA (928 μ L, 5.31 mmol), 2-(4-fluorophenyl)-5-isopropoxy-6
 5 (methylsulfonamido) benzofuran-3-carboxamide (300 mg, 0.738 mmol) in CH_2Cl_2 (4 mL) and THF (4 mL) at 0 $^\circ\text{C}$ for 1 hour. The mixture was diluted with EtOAc and washed with sat NaHCO_3 , and sat NaCl . The organic phase was dried over Na_2SO_4 , filtered and concentrated. The crude residue was purified by on silica gel (BIOTAGE®, gradient EtOAc/hexanes, fraction collection at $\lambda = 254 \text{ nm}$) to give the
 10 title compound (143 mg, 50%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 1.28 - 1.41 (m, 6 H) 3.01 (s, 3 H) 4.77 - 4.95 (m, 1 H) 7.35 (s, 1 H) 7.44 - 7.57 (m, 2 H) 7.68 (s, 1 H) 8.04 - 8.20 (m, 2 H) 9.01 (s, 1 H). LC-MS retention time: 1.65 min; m/z (MH $^-$): 387. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis
 15 detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data
 20 was determined using a MICROMASS® Platform for LC in electrospray mode.



3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

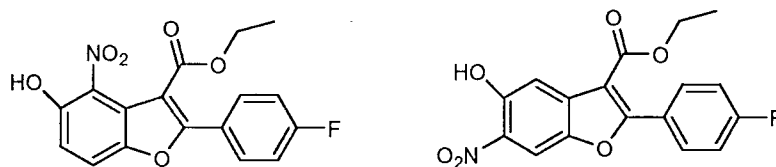
[0086] Cesium carbonate (3.5 g, 10.7 mmol) was added to Pd(Ph₃P)₄ (108 mg, 0.093 mmol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (3.0 g, 7.19 mmol), 3-boronobenzoic acid (1.97 g, 11.86 mmol). Dioxane (60 ml) and water (12 ml) was added at rt. The reaction was

5 degassed 3x and then heated to 95 °C and allowed to stir overnight. It was allowed to cool to rt. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The precipitate that formed was filtered and dried overnight at 55 °C under vacuum. The remaining organic phase was concentrated and triturated with DCM, followed by hot DCE and finally hot MeOH to afford the titled compound which was

10 combined with the previously collected precipitate (2.4 g, 87%). LC-MS retention time: 1.19 min; m/z (MH⁺): 390. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent

15 A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

20



Ethyl 2-(4-fluorophenyl)-5-hydroxy-4-nitrobenzofuran-3-carboxylate and

Ethyl 2-(4-fluorophenyl)-5-hydroxy-6-nitrobenzofuran-3-carboxylate

[0087] Nitric acid (21 µL, 0.33 mmol) was added to a stirring solution of ethyl 2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylate (100 mg, 0.33 mmol) in

25 chloroform (3.3 mL) at -20 °C. It was allowed to stir for 10 min. A 9:2 ratio of ethyl 2-(4-fluorophenyl)-5-hydroxy-4-nitrobenzofuran-3-carboxylate to ethyl 2-(4-fluorophenyl)-5-hydroxy-6-nitrobenzofuran-3-carboxylate was observed. The crude

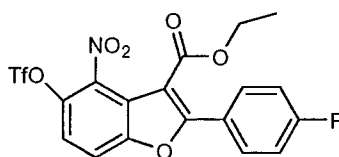
reaction was purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at $\lambda = 254$ nm) to give the titled compounds:

Ethyl 2-(4-fluorophenyl)-5-hydroxy-6-nitrobenzofuran-3-carboxylate

- 5 [0088] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 10.92 (1 H, s), 8.33 (1 H, s), 8.03 - 8.11 (2 H, m), 7.69 (1 H, s), 7.43 (2 H, t, $J=8.85$ Hz), 4.34 (2 H, q, $J=7.22$ Hz), 1.33 (3 H, t, $J=7.17$ Hz). LC-MS retention time: 1.79 min; m/z (MH $^-$): 344. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector
- 10 wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H $_2$ O / 10 mM ammonium acetate and solvent B was 5% H $_2$ O / 95% acetonitrile / 10 mM ammonium acetate. MS data was
- 15 determined using a MICROMASS® Platform for LC in electrospray mode.

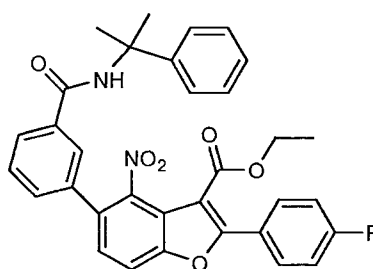
Ethyl 2-(4-fluorophenyl)-5-hydroxy-4-nitrobenzofuran-3-carboxylate

- [0089] ^1H NMR (500 MHz, DMSO- d_6) δ ppm 11.03 (1 H, s), 7.92 - 8.01 (2 H, m), 7.86 (1 H, d, $J=9.16$ Hz), 7.42 (2 H, t, $J=8.85$ Hz), 7.17 (1 H, d, $J=8.85$ Hz), 4.20
- 20 (2 H, q, $J=7.12$ Hz), 1.21 (3 H, t, $J=7.17$ Hz). LC-MS retention time: 1.56 min; m/z (MH $^-$): 344. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A /
- 25 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H $_2$ O / 10 mM ammonium acetate and solvent B was 5% H $_2$ O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Ethyl 2-(4-fluorophenyl)-4-nitro-5-(trifluoromethylsulfonyloxy)benzofuran-3-carboxylate

- [0090] Triethylamine (91 μ L, 0.652 mmol) was added to a stirring solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (116 mg, 0.326 mmol) and ethyl 2-(4-fluorophenyl)-5-hydroxy-4-nitrobenzofuran-3-carboxylate (75 mg, 0.217 mmol) in DCM (2.2 mL). The crude reaction was purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at $\lambda = 254$ nm) to give titled compound (78 mg, 75%). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 11.03 (1 H, s), 7.92 - 8.01 (2 H, m), 7.86 (1 H, d, $J=9.16$ Hz), 7.42 (2 H, t, $J=8.85$ Hz), 7.17 (1 H, d, $J=8.85$ Hz), 4.20 (2 H, q, $J=7.12$ Hz), 1.21 (3 H, t, $J=7.17$ Hz). LC-MS retention time: 1.91 min; m/z (MH $^+$): no ion detected. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H $_2$ O / 10 mM ammonium acetate and solvent B was 5% H $_2$ O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



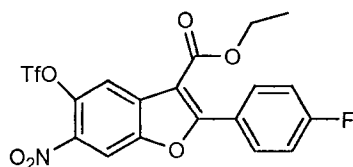
Ethyl 2-(4-fluorophenyl)-4-nitro-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxylate

[0091] Step 1: Cesium carbonate (333 mg, 1.021 mmol) was added to Pd(Ph₃P)₄ (39 mg, 0.034 mmol), ethyl 2-(4-fluorophenyl)-4-nitro-5-(trifluoromethylsulfonyloxy)benzofuran-3-carboxylate (325 mg, 0.681 mmol), 3-boronobenzoic acid (169 mg, 1.021 mmol). Dioxane (5.6 mL) and water (1.1 mL)

5 was added at rt. The reaction was degassed 3x and heated to 90 °C overnight. It was allowed to cool. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the *m*-acid.

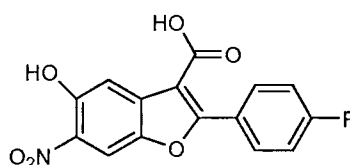
[0092] Step 2: The crude *m*-acid was diluted with DMF (5 mL) and treated with HATU (388 mg, 1.021 mmol), 2-phenylpropan-2-amine (138 mg, 1.021 mmol), and DIEA (357 μL, 2.043 mmol) and allowed to stir at rt for 1 hr. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the titled compound which was purified on silica gel (BIOTAGE® 25+M column, EtOAc/hexanes gradient; R_f

15 ~.2 for 20% EtOAc/hexanes; fraction collection at λ = 254 nm) to give a light yellow solid (294 mg, 76%). LC-MS retention time: 1.97 min; m/z (MH⁺): 567. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Ethyl 2-(4-fluorophenyl)-6-nitro-5-(trifluoromethylsulfonyloxy)benzofuran-3-carboxylate

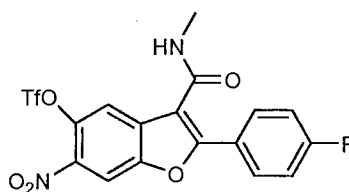
- [0093] Triethylamine (121 μ L, 0.869 mmol) was added to a stirring solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (155 mg, 0.434 mmol) and ethyl 2-(4-fluorophenyl)-5-hydroxy-6-nitrobenzofuran-3-carboxylate (100 mg, 0.290 mmol) in DCM (3 mL). It was allowed to stir overnight.
- 5 The mixture concentrated and was purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at $\lambda = 254$ nm) to give the titled compound (140 mg, 100%). ^1H NMR (300 MHz, DMSO- d_6) δ ppm 8.91 (1 H, s), 8.10 - 8.19 (3 H, m), 7.48 (2 H, t, $J=8.97$ Hz), 4.37 (2 H, q, $J=7.07$ Hz), 1.34 (3 H, t, $J=6.95$ Hz). LC-MS retention time: 1.91 min; m/z (MH $^+$): no ion detected. LC data
- 10 was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where
- 15 solvent A was 5% acetonitrile / 95% H $_2$ O / 10 mM ammonium acetate and solvent B was 5% H $_2$ O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



- 20 2-(4-Fluorophenyl)-5-hydroxy-6-nitrobenzofuran-3-carboxylic acid
- [0094] Excess NaOH (11 ml, 11.00 mmol, 1M aq) was added to a stirring solution of ethyl 2-(4-fluorophenyl)-5-hydroxy-6-nitrobenzofuran-3-carboxylate (1.9 g, 5.50 mmol) in EtOH (55 ml) and THF (55 ml) and was allowed to stir at 64 $^{\circ}$ C overnight. The mixture was concentrated and diluted with EtOAc and washed with 1M HCl, and
- 25 sat NaCl. The organic phase was dried over Na $_2$ SO $_4$, filtered and concentrated to give the titled compound (1.7 g, quant.). ^1H NMR (300 MHz, DMSO- d_6) δ ppm 7.31 - 7.48 (m, 2 H) 7.71 (s, 1 H) 8.00 - 8.14 (m, 2 H) 8.29 (s, 1 H) 10.80 (s, 1 H) 13.35 (s, 1 H). LC-MS retention time: 0.99 min; m/z (MH $^-$): 416. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18

4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5%

- 5 acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



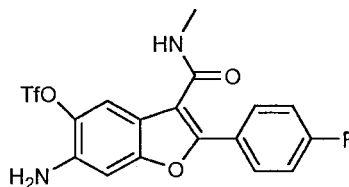
- 10 2-(4-Fluorophenyl)-3-(methylcarbamoyl)-6-nitrobenzofuran-5-yl trifluoromethanesulfonate.

[0095] Step 1: Methanamine (4.4 ml, 8.83 mmol) was added to a stirring solution of DIEA (3 ml, 17.65 mmol), BOP (2.9 g, 6.62 mmol), and 2-(4-fluorophenyl)-5-hydroxy-6-nitrobenzofuran-3-carboxylic acid (1.4 g, 4.41 mmol) in DMF (44 ml) at 0 °C. It was allowed to warm to rt and stir for 1 hr. The mixture was concentrated and diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give a crude product which was triturated with MeOH to give the methyl amide, nitro phenol-hmpa adduct (1.7 g, 78%).

20 [0096] Step 2: The hmpa-adduct (100 mg, 0.203 mmol) was taken up in EtOH and treated with 1M NaOH (609 µL, 0.609 mmol) at 70 °C. It was allowed to stir overnight. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the nitro phenol (50 mg, 75%) as a brown solid. LC-MS retention time: 1.34 min; m/z (MH⁺): 331. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time

of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

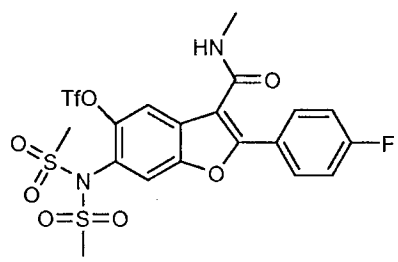
[0097] Step 3: Triethylamine (422 μ L, 3.03 mmol) was added to a stirring
 5 solution of N-Phenylbis(trifluoromethane)sulfonimide (649 mg, 1.817 mmol) and 2-(4-fluorophenyl)-5-hydroxy-N-methyl-6-nitrobenzofuran-3-carboxamide (400 mg, 1.211 mmol) in DCM (24 mL) at rt. The slurry was allowed to stir overnight. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give a crude
 10 residue which was purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, R_f ~.2 in 30% EtOAc/hexanes, fraction collection at λ = 254 nm) to give the titled compound (375 mg, 67%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.83 (1 H, s), 8.55 - 8.65 (1 H, m), 7.98 - 8.05 (2 H, m), 7.95 (1 H, s), 7.47 (2 H, t, *J*=8.85 Hz), 2.84 (3 H, d, *J*=4.58 Hz). LC-MS retention time: 1.96 min; *m/z* (MH⁻): 461. LC data was
 15 recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time
 20 of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



25 6-Amino-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate

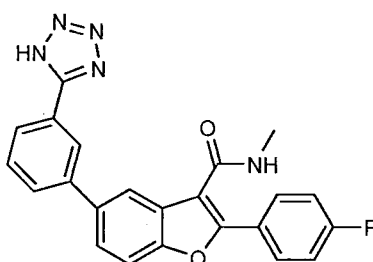
[0098] Iron (211 mg, 3.79 mmol) was added to a stirring solution of 2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-nitrobenzofuran-5-yl trifluoromethanesulfonate (350 mg, 0.757 mmol) in EtOH (8.4 mL) and AcOH (8.4 mL) at rt and then was

heated to 100 °C for 10 min. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl followed by 1M NaOH and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated to give a white solid which was 1:1 starting material:product. It was resubjected to the reaction conditions for 15 min and re-worked up to give the titled compound (275 mg, 84%). LC-MS retention time: 1.47 min; m/z (MH⁺): 433. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



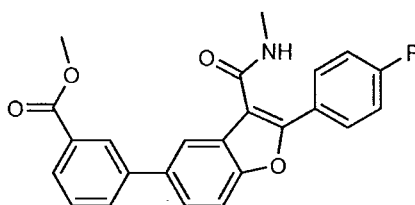
2-(4-Fluorophenyl)-3-(methylcarbamoyl)-6-(N-(methylsulfonyl)methylsulfonyl)benzofuran-5-yl trifluoromethanesulfonate [0099] Methanesulfonyl chloride (146 μL, 1.873 mmol) was added to a stirring solution of 6-amino-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (270 mg, 0.624 mmol) and DIEA (500 μL, 2.86 mmol) in DCM (6.3 mL) at 25 °C. It was allowed to stir for 1 hour and then diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated. It was purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at λ = 254 nm) to give the titled compound (300 mg, 82%). LC-MS retention time: 1.49 min; m/z (MH⁺): 589. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a

detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



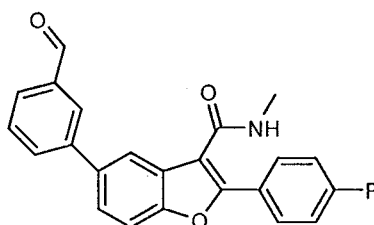
5-(3-(1H-Tetrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00100] Azidotrimethylsilane (161 μ L, 1.215 mmol) was added to a stirring solution of 5-(3-cyanophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (225 mg, 0.607 mmol) and dibutylstannanone (30 mg, 0.121 mmol) in toluene (6 mL) at rt. It was heated to 105 $^{\circ}$ C and allowed to stir overnight. The reaction, which remained a slurry, resulted in ~70% conversion. Additional equiv of reagents and solvents were added and the mixture was allowed to stir overnight at 105 $^{\circ}$ C. The reaction was allowed to cool and filtered to give the titled compound (205 mg, 82%). LC-MS retention time: 1.03 min; m/z (MH⁺): 414. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Methyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate

[00101] Trimethylsilyldiazomethane (500 μ L, 1.00 mmol, 2M in diethyl ether) was added to a stirring solution of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (100 mg, 0.257 mmol) in diethyl ether (2.5 mL) at 25 $^{\circ}$ C. It was allowed to stir for 2 hours. The mixture was concentrated to afford the titled compound (100 mg, 97%). LC-MS retention time: 2.46 min; m/z (MH⁺) : 404. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters SunFire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 10% acetonitrile / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

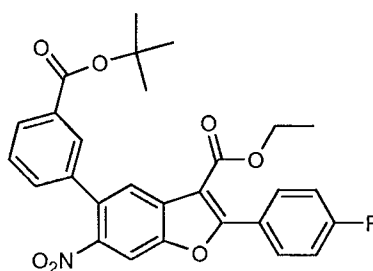


2-(4-Fluorophenyl)-5-(3-formylphenyl)-N-methylbenzofuran-3-carboxamide

[00102] Cesium carbonate (176 mg, 0.539 mmol) was added to Pd(Ph₃P)₄ (20 mg, 0.018 mmol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (150 mg, 0.359 mmol), 3-formylphenylboronic acid (59 mg, 0.395 mmol). Dioxane (3 mL) and water (600 μ L) was added at rt. The reaction was heated to 90 $^{\circ}$ C overnight. The mixture was diluted with ethyl acetate and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and triturated with DCM to give the titled compound (55

mg, 41%). LC-MS retention time: 1.49 min; m/z (MH^+): 374. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a
 5 gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

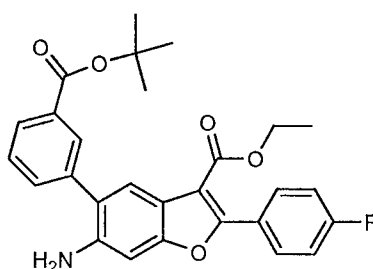
10



Ethyl 5-(3-(*tert*-butoxycarbonyl)phenyl)-2-(4-fluorophenyl)-6-nitrobenzofuran-3-carboxylate

[00103] Cesium carbonate (1.54 g, 4.71 mmol) was added to $Pd(Ph_3P)_4$ (182 mg, 0.157 mmol), ethyl 2-(4-fluorophenyl)-6-nitro-5-
 15 (trifluoromethylsulfonyloxy)benzofuran-3-carboxylate (1500 mg, 3.14 mmol), 3-(*tert*-butoxycarbonyl)phenylboronic acid (768 mg, 3.46 mmol). Dioxane (26 mL) and water (5 mL) was added at rt. The reaction was heated to 90 °C overnight. The reaction was allowed to cool was diluted with EtOAc and washed with sat $NaHCO_3$,
 20 and sat $NaCl$. The organic phase was dried over Na_2SO_4 , filtered and concentrated and purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at $\lambda = 254$ nm) to give to give the titled compound (1.10 g, 69%). 1H NMR (300 MHz, $DMSO-d_6$) δ ppm 8.60 (1 H, s), 8.08 - 8.18 (2 H, m), 8.02 (1 H, s), 7.95 - 8.01 (1 H, m), 7.88 (1 H, s), 7.58 - 7.70 (2 H, m), 7.46 (2 H, t, $J=8.78$ Hz), 4.34 (2 H, q, $J=7.20$ Hz), 1.56 (9 H, s), 1.27 (3 H, t, $J=7.14$ Hz). LC-MS retention time: 2.13 min;
 25 m/z (MH^+): parent does not ionize. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column

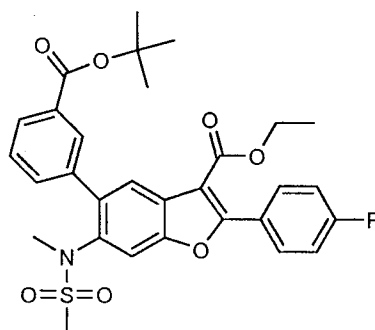
using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



10 Ethyl 6-amino-5-(3-(*tert*-butoxycarbonyl)phenyl)-2-(4-fluorophenyl)benzofuran-3-carboxylate

[00104] Iron (28 mg, 0.495 mmol) was added to a stirring solution of ethyl 5-(3-(*tert*-butoxycarbonyl)phenyl)-2-(4-fluorophenyl)-6-nitrobenzofuran-3-carboxylate (50 mg, 0.099 mmol) in EtOH (495 μ L) and AcOH (495 μ L) at 100 °C. It was allowed to stir for 1 hr. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the titled compound (45 mg, 96%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.99 - 8.06 (2 H, m), 7.89 - 7.96 (2 H, m), 7.65 - 7.72 (1 H, m), 7.61 (1 H, t, *J*=7.65 Hz), 7.55 (1 H, s), 7.31 - 7.40 (2 H, m), 7.00 (1 H, s), 5.10 (2 H, br. s.), 4.29 (2 H, q, *J*=7.03 Hz), 1.56 (9 H, s), 1.26 (3 H, t, *J*=7.15 Hz). LC-MS retention time: 2.03 min; *m/z* (MH⁺) : parent does not ionize. 420 (-tBu) was observed. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B

was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



5 Ethyl 5-(3-(*tert*-butoxycarbonyl)phenyl)-2-(4-fluorophenyl)-6-(N-methylmethanesulfonamido)benzofuran-3-carboxylate

[00105] Step 1: Methanesulfonyl chloride (16 μ L, 0.208 mmol) was added to a stirring solution of ethyl 6-amino-5-(3-(*tert*-butoxycarbonyl)phenyl)-2-(4-fluorophenyl)benzofuran-3-carboxylate (90 mg, 0.189 mmol) in pyridine (2 mL) at rt.

10 It was allowed to stir for 6 hrs, then 8 μ L of MsCl was added and the reaction was allowed to stir overnight. The reaction was concentrated and diluted with ethyl acetate and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the NH sulfonamide intermediate. LC-MS retention time: 1.93 min; m/z (MH⁻): 552. LC data was recorded on a Shimadzu

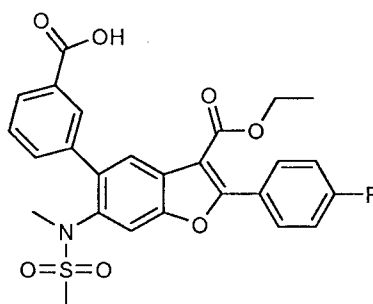
15 LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile /

20 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

[00106] Step 2: The crude residue was diluted with DMF (2mL) and treated with DIEA (99 μ L, 0.568 mmol) and Iodomethane (18 μ L, 0.284 mmol) followed by

25 Na₂CO₃ (20 mg). The reaction was allowed to stir for 3 days. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase

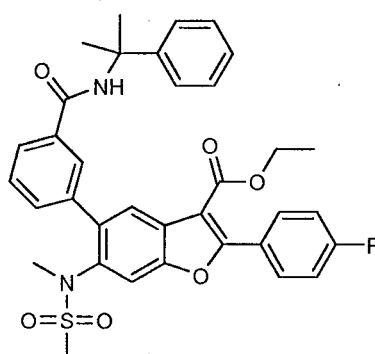
was dried over Na₂SO₄, filtered and concentrated to give the titled compound (100 mg, 93%). LC-MS retention time: 1.96 min; m/z (MH⁺): the parent does not ionize. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



3-(3-(Ethoxycarbonyl)-2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)benzoic acid

[00107] TFA (2 mL, 26.0 mmol) was added to a stirring solution of ethyl 5-(3-(*tert*-butoxycarbonyl)phenyl)-2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)benzofuran-3-carboxylate (100 mg, 0.176 mmol) in DCE (9 mL) at 25 °C. It was allowed to stir for several hours then concentrated to give the titled compound (92 mg, quant). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.05 - 8.12 (3 H, m), 7.92 - 8.03 (3 H, m), 7.65 - 7.75 (1 H, m), 7.53 - 7.64 (1 H, m), 7.44 (2 H, t, *J*=8.91 Hz), 4.33 (2 H, q, *J*=7.03 Hz), 3.12 (3 H, s), 2.93 (3 H, s), 1.26 (3 H, t, *J*=7.15 Hz). LC-MS retention time: 1.17 min; m/z (MH⁻): 510. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5%

acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

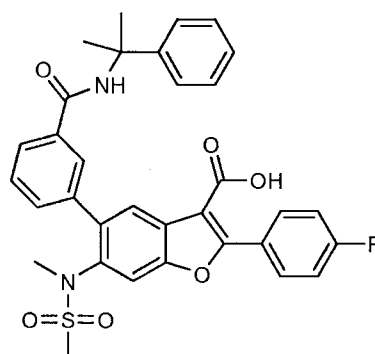


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Ethyl 2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxylate

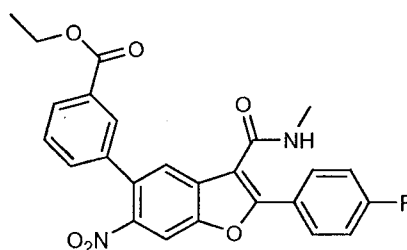
[00108] DIEA (51 μ L, 0.293 mmol) was added to a stirring solution of 3-(3-(ethoxycarbonyl)-2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)benzoic acid (50 mg, 0.098 mmol), 2-phenylpropan-2-amine (26 mg, 0.195 mmol), HATU (56 mg, 0.147 mmol) in DMF (1 mL) at 25 °C. It was allowed to stir for 1 hour. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the titled compound (50 mg, 81%). LC-MS retention time: 1.82 min; m/z (MH⁺) : 629. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

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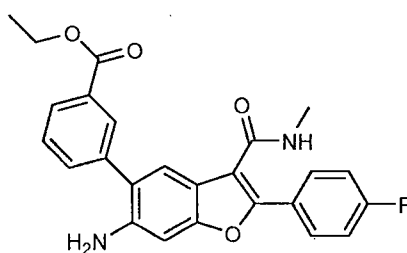


2-(4-Fluorophenyl)-6-(N-methylmethanysulfonamido)-5-(3-(2-phenylpropan-2-ylcarbamoyle)phenyl)benzofuran-3-carboxylic acid

[00109] NaOH (500 μ L, 0.500 mmol, 1M aq.) was added to a stirring solution of ethyl 2-(4-fluorophenyl)-6-(N-methylmethanysulfonamido)-5-(3-(2-phenylpropan-2-ylcarbamoyle)phenyl)benzofuran-3-carboxylate (50 mg, 0.080 mmol) in ethanol (795 μ L) at 60 $^{\circ}$ C. The slurry was allowed to stir overnight. DMF (2 mL) was added along with additional portion of NaOH and the mixture was warmed to 70 $^{\circ}$ C and allowed to stir overnight. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the titled compound (49 mg, quant). LC-MS retention time: 2.36 min; m/z (MH⁺): 601. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters SunFire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 10% acetonitrile / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

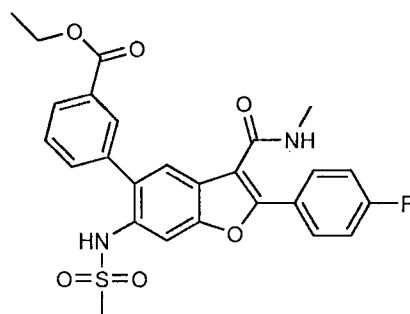


Ethyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-nitrobenzofuran-5-yl)benzoate
 [00110] Cesium carbonate (1.69 g, 5.19 mmol) was added to Pd(Ph₃P)₄ (250 mg,
 0.216 mmol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-nitrobenzofuran-5-yl
 trifluoromethanesulfonate (2.00 g, 4.33 mmol), 3-(ethoxycarbonyl)phenylboronic
 5 acid (1.01 g, 5.19 mmol). Dioxane (36 mL) and water (7 mL) was added at rt and the
 mixture was degassed 3x. The reaction was heated to 90 °C overnight. It was allowed
 to cool. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl.
 The organic phase was dried over Na₂SO₄, filter and concentrated. The crude solid
 was triturated with DCM to give the titled compound (1.70 g, 85%). ¹H NMR (400
 10 MHz, DMSO-d₆) δ ppm 8.55 - 8.61 (1 H, m), 8.54 (1 H, s), 8.00 - 8.09 (3 H, m),
 7.95 (1 H, s), 7.73 (1 H, s), 7.61 - 7.70 (2 H, m), 7.45 (2 H, t, *J*=8.91 Hz), 4.35 (2 H,
 q, *J*=7.19 Hz), 2.83 (3 H, d, *J*=4.52 Hz), 1.34 (3 H, t, *J*=7.03 Hz). LC-MS retention
 time: 1.62 min; *m/z* (MH⁺): 463. LC data was recorded on a Shimadzu LC-10AS
 liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column
 15 using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution
 conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0%
 solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of
 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O
 / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM
 20 ammonium acetate. MS data was determined using a MICROMASS® Platform for
 LC in electrospray mode.



Ethyl 3-(6-amino-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate
 25 [00111] Iron (1.03 g, 18.4 mmol) was added to a stirring solution of ethyl 3-(2-(4-
 fluorophenyl)-3-(methylcarbamoyl)-6-nitrobenzofuran-5-yl)benzoate (1.70 g, 3.68
 mmol) in EtOH (37 mL) and AcOH (37 mL) at 90 °C. The slurry was allowed to stir
 for 1 hour. The mixture was diluted with EtOAc and washed with 1M HCl, and sat

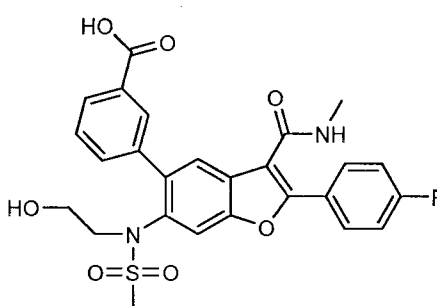
NaCl followed by 1M NaOH and sat. NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the titled compound (1.40 g 88%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.25 - 8.34 (1 H, m), 8.00 - 8.03 (1 H, m), 7.87 - 7.99 (3 H, m), 7.69 - 7.75 (1 H, m), 7.63 (1 H, t, *J*=7.65 Hz), 7.26 - 7.37 (2 H, m), 7.20 (1 H, s), 6.98 (1 H, s), 5.07 (2 H, s), 4.35 (2 H, q, *J*=7.03 Hz), 2.78 (3 H, d, *J*=4.52 Hz), 1.34 (3 H, t, *J*=7.03 Hz). LC-MS retention time: 1.46 min; *m/z* (MH⁺): 433. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Ethyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(methylsulfonamido)benzofuran-5-yl)benzoate

[00112] Methanesulfonyl chloride (303 μL, 3.88 mmol) was added to a stirring solution of ethyl 3-(6-amino-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate (1.40 g, 3.24 mmol) in pyridine (32 mL) at 25 °C. It was allowed to stir overnight at rt. The reaction was concentrated and was purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at λ = 254 nm) to give the titled compound (1.01 g, 61%). LC-MS retention time: 1.53 min; *m/z* (MH⁺): 511. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5

ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was
 5 determined using a MICROMASS® Platform for LC in electrospray mode.



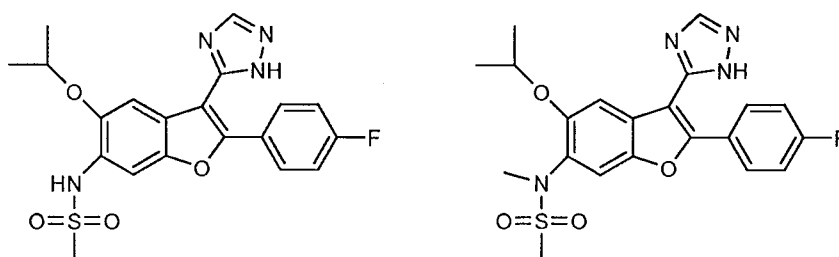
3-(2-(4-Fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

10 [00113] Step 1: (2-Bromoethoxy)(*tert*-butyl)dimethylsilane (189 μ L, 0.881 mmol) was added to a stirring suspension of Na₂CO₃ (311 mg, 2.94 mmol) and ethyl 3-(6-(N-(2-(*tert*-butyldimethylsilyloxy)ethyl)methylsulfonamido)-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate in DMF (6 mL) at 100 °C. It was allowed to stir for 5 hrs, and then allowed to cool to rt and stir overnight. The mixture
 15 was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated. LC-MS retention time: 2.12 min; m/z (MH⁺): 669. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution
 20 conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for
 25 LC in electrospray mode.

[00114] Step 2: The residue was diluted with EtOH (10 mL) and treated with NaOH (2938 μ L, 2.94 mmol) and allowed to stir at 60 °C for 4 hours. The mixture

was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated.

- [00115] Step 3: The crude residue was taken up in THF and treated with 1M HCl (making it 30% in THF). The reaction was allowed to stir for 1 hour. The mixture was
- 5 diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the titled compound (300 mg, 97%). LC-MS retention time: 1.09 min; m/z (MH⁺): 527. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of
- 10 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a
- 15 MICROMASS® Platform for LC in electrospray mode.



N-(2-(4-Fluorophenyl)-5-isopropoxy-3-(1H-1,2,4-triazol-5-yl)benzofuran-6-yl)methanesulfonamide, and

- 20 N-(2-(4-fluorophenyl)-5-isopropoxy-3-(1H-1,2,4-triazol-5-yl)benzofuran-6-yl)-N-methylmethanesulfonamide

- [00116] N,N-Dimethylformamide dimethyl acetal (500 μ L, 3.76 mmol) and 2-(4-fluorophenyl)-5-isopropoxy-6-(methylsulfonamido)benzofuran-3-carboxamide (100 mg, 0.246 mmol) were combined and heated to 85 $^{\circ}$ C. DMF (1 mL) was added. It was
- 25 allowed to stir for 1 hr. The mixture was concentrated and diluted with dioxane (200 μ l), acetic acid (1 ml) and treated with hydrazine (154 μ L, 4.92 mmol) and heated at 85 $^{\circ}$ C for several hours. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and

concentrated. The crude residue was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered gradient, and concentrated to give to give N-(2-(4-fluorophenyl)-5-isopropoxy-3-(1H-1,2,4-triazol-5-yl)benzofuran-6-yl)methanesulfonamide (25 mg, 0.058 mmol) and N-(2-(4-fluorophenyl)-5-isopropoxy-3-(1H-1,2,4-triazol-5-yl)benzofuran-6-yl)-N-methylmethanesulfonamide (11 mg, 0.025 mmol).

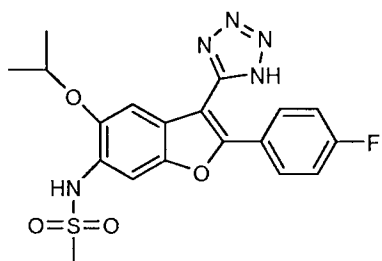
N-(2-(4-Fluorophenyl)-5-isopropoxy-3-(1H-1,2,4-triazol-5-yl)benzofuran-6-yl)methanesulfonamide

10 **[00117]** ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.30 - 1.42 (m, 6 H) 2.99 (s, 3 H) 4.57 - 4.73 (m, 1 H) 7.24 - 7.40 (m, 2 H) 7.57 (s, 1 H) 7.67 (s, 1 H) 8.06 - 8.22 (m, 2 H) 8.68 (s, 1 H). LC-MS retention time: 1.30 min; m/z (MH⁺): 431. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector
15 wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was
20 determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC were performed using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate =
25 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 10.71 min, purity = 94%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 9.74 min, purity = 97%.

30 N-(2-(4-Fluorophenyl)-5-isopropoxy-3-(1H-1,2,4-triazol-5-yl)benzofuran-6-yl)-N-methylmethanesulfonamide

[00118] ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.29 - 1.41 (m, 6 H) 3.04 (s, 3 H) 3.19 - 3.24 (m, 3 H) 4.61 - 4.80 (m, 1 H) 7.28 - 7.39 (m, 2 H) 7.61 (s, 1 H) 7.76 (s, 1

H) 8.08 - 8.27 (m, 2 H) 8.78 (s, 1 H) 14.34 (s, 1 H). LC-MS retention time: 1.36 min; m/z (MH⁺) 345. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 11.30 min, purity = >95%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 10.21 min, purity = >95%.



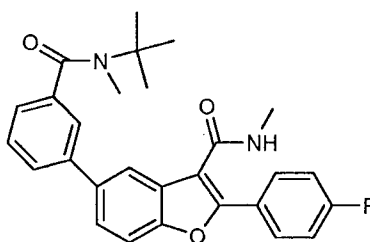
N-(2-(4-Fluorophenyl)-5-isopropoxy-3-(1H-1,2,4-triazol-5-yl)benzofuran-6-yl)methanesulfonamide

[00119] Azidotrimethylsilane (34.2 μL, 0.257 mmol) was added to a stirring solution of dibutyltin oxide (6.41 mg, 0.026 mmol) and N-(3-cyano-2-(4-fluorophenyl)-5-isopropoxybenzofuran-6-yl)methanesulfonamide (50 mg, 0.129 mmol) in dioxane (1.3 mL) at rt. It was subjected to microwave irradiation for 15 min at 150 °C. It was treated with additional equivalents of reagents and re-subjected for 30 min followed by 60 min. The mixture was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered gradient, and concentrated to give the titled compound (12 mg, 22%). ¹H NMR (300 MHz,

DMSO- d_6) δ ppm 1.29 - 1.39 (m, 6 H) 3.01 (s, 3 H) 4.62 - 4.81 (m, 1 H) 7.28 - 7.45 (m, 3 H) 7.65 (s, 1 H) 7.84 - 7.98 (m, 2 H) 8.92 (s, 1 H). LC-MS retention time: 1.04 min; m/z (MH⁺): 432. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μ m, R_t = 11.56 min, purity = 94%;
15 Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μ m, R_t = 10.55 min, purity = 96%.

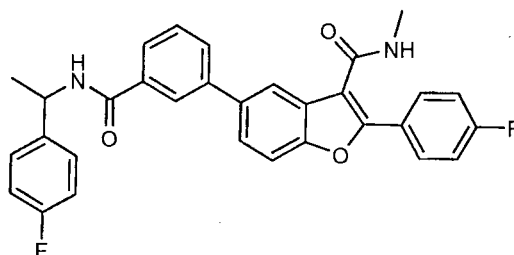
General Procedure: *m*-Amide Coupling

[00120] DIEA (36 μ L, 0.205 mmol) was added to a stirring solution of HATU (59 mg, 0.154 mmol), the appropriate amine (0.164 mmol), and 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (40 mg, 0.103 mmol) in DMF (1 mL) at room temperature. It was allowed to stir overnight. The reaction was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the expected
25 product. This general procedure was applied to Examples KP4 through KP14.



5-(3-(*tert*-Butyl(methyl)carbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00121] ¹H NMR (500 MHz, CD₃OD) δ ppm 1.54 - 1.57 (m, 9 H) 2.94 - 2.99 (m, 6 H) 7.25 (t, 2 H) 7.35 - 7.40 (m, 1 H) 7.53 (t, 1 H) 7.64 - 7.67 (m, 2 H) 7.67 - 7.68 (m, 1 H) 7.72 - 7.77 (m, 1 H) 7.88 - 7.90 (m, 1 H) 7.92 - 7.97 (m, 2 H). LC-MS retention time: 1.71 min; m/z (MH⁺): 459. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

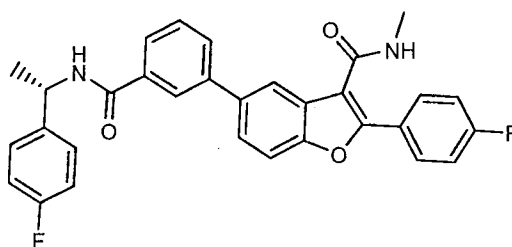


2-(4-Fluorophenyl)-5-(3-(1-(4-fluorophenyl)ethylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00122] ¹H NMR (500 MHz, CD₃OD) δ ppm 8.10 - 8.15 (1 H, m), 7.90 - 7.99 (3 H, m), 7.84 (2 H, t, *J*=9.61 Hz), 7.63 - 7.72 (2 H, m), 7.56 (1 H, t, *J*=7.78 Hz), 7.40 - 7.47 (2 H, m), 7.22 - 7.29 (2 H, m), 7.03 - 7.10 (2 H, m), 5.24 - 5.30 (1 H, m), 2.97 (3 H, s), 1.59 (3 H, d, *J*=7.02 Hz). LC-MS retention time: 1.67 min; m/z (MH⁺): 509. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B

was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Additional HPLC method: Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C1 C-18, 4.6 x 150 mm, 3 μm, R_t = 15.64 min, purity = 97%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 15.63 min, purity = 98%.



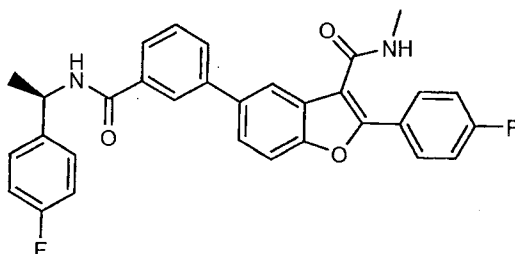
(S)-2-(4-Fluorophenyl)-5-(3-(1-(4-fluorophenyl)ethylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00123] ¹H NMR (500 MHz, CD₃OD) δ ppm 8.13 (1 H, s), 7.91 - 7.99 (3 H, m), 7.84 (2 H, t, J=9.31 Hz), 7.64 - 7.72 (2 H, m), 7.56 (1 H, t, J=7.78 Hz), 7.41 - 7.48 (2 H, m), 7.26 (2 H, t, J=8.85 Hz), 7.02 - 7.10 (2 H, m), 5.28 (1 H, q, J=7.22 Hz), 2.97 (3 H, s), 1.59 (3 H, d, J=7.02 Hz). LC-MS retention time: 1.67 min; m/z (MH⁺): 509.

LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Additional HPLC method: Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C1 C-18, 4.6 x 150 mm, 3 μm, R_t =

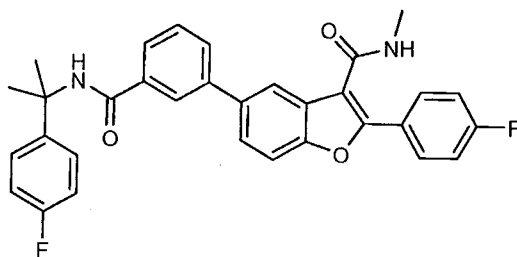
15.55 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μ m, R_t = 15.34 min, purity = 98%.



5 (R)-2-(4-Fluorophenyl)-5-(3-(1-(4-fluorophenyl)ethylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

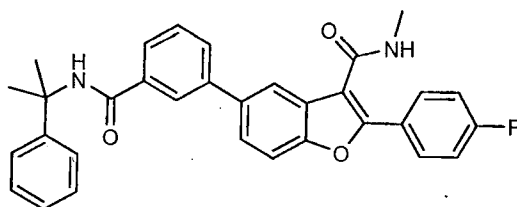
[00124] ^1H NMR (500 MHz, CD_3OD) δ ppm 8.14 (1 H, s), 7.92 - 7.99 (3 H, m), 7.81 - 7.87 (2 H, m), 7.65 - 7.72 (2 H, m), 7.57 (1 H, t, $J=7.63$ Hz), 7.42 - 7.47 (2 H, m), 7.23 - 7.29 (2 H, m), 7.04 - 7.10 (2 H, m), 5.28 (1 H, q, $J=7.02$ Hz), 2.97 (3 H, s), 1.59 (3 H, d, $J=7.02$ Hz). LC-MS retention time: 1.66 min; m/z (MH $^-$): 509. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% MeOH/95% H_2O /10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H_2O /10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C1 C-18, 4.6 x 150 mm, 3 μ m, R_t = 15.56 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μ m, R_t = 15.33 min, purity = 97%.

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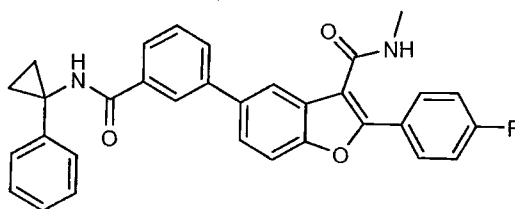
2-(4-Fluorophenyl)-5-(3-(2-(4-fluorophenyl)propan-2-ylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

- [00125] ¹H NMR (500 MHz, CD₃OD) δ ppm 8.04 - 8.10 (1 H, m), 7.89 - 7.99 (3 H, m), 7.76 - 7.86 (2 H, m), 7.63 - 7.73 (2 H, m), 7.56 (1 H, t, *J*=7.78 Hz), 7.42 - 7.51 (2 H, m), 7.26 (2 H, t, *J*=8.70 Hz), 6.98 - 7.06 (2 H, m), 2.98 (3 H, s), 1.78 (6 H, s).
- LC-MS retention time: 1.72 min; *m/z* (MH⁻): 523. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a
- MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C1 C-18, 4.6 x 150 mm, 3 μm, *R_t* = 15.73 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, *R_t* = 15.53 min, purity = 99%.



2-(4-Fluorophenyl)-N-methyl-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

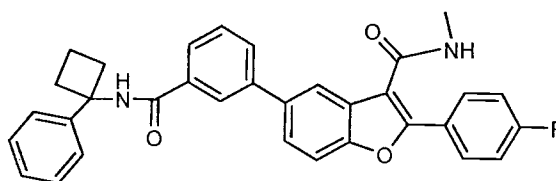
- [00126] ¹H NMR (500 MHz, CD₃OD) δ ppm 8.09 (1 H, s), 7.90 - 7.99 (3 H, m), 7.74 - 7.89 (1 H, m), 7.63 - 7.72 (2 H, m), 7.55 (1 H, t, *J*=7.63 Hz), 7.47 (2 H, d, *J*=7.32 Hz), 7.31 (2 H, t, *J*=7.78 Hz), 7.22 - 7.28 (2 H, m), 7.19 (1 H, t, *J*=7.32 Hz), 2.97 (3 H, s), 1.79 (6 H, s). LC-MS retention time: 1.71 min; *m/z* (MH⁺): 505. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.
- Additional HPLC method: Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C1 C-18, 4.6 x 150 mm, 3 μm, *R*_t = 15.79 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, *R*_t = 15.53 min, purity = 98%.



2-(4-Fluorophenyl)-N-methyl-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

- [00127] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.35 (1 H, s), 8.48 - 8.56 (1 H, m), 8.24 (1 H, s), 7.96 - 8.04 (2 H, m), 7.87 - 7.96 (3 H, m), 7.75 - 7.82 (2 H, m), 7.59 (1 H, t, *J*=7.63 Hz), 7.40 (2 H, t, *J*=8.70 Hz), 7.21 - 7.29 (4 H, m), 7.16 (1 H, t, *J*=7.17 Hz), 2.86 (3 H, d, *J*=4.58 Hz), 1.25 - 1.35 (4 H, m). LC-MS retention time: 1.63 min;

m/z (MH⁻): 503. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C1 C-18, 4.6 x 150 mm, 3 μm, R_t = 15.91 min, purity = 96%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 15.79 min, purity = 95%.

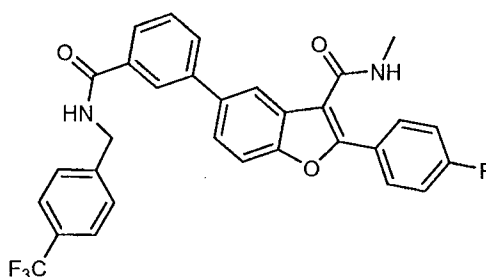


2-(4-Fluorophenyl)-N-methyl-5-(3-(1-phenylcyclobutylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00128] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.18 (1 H, s), 8.53 (1 H, q, J=4.48 Hz), 8.20 (1 H, s), 8.01 (2 H, dd, J=8.85, 5.49 Hz), 7.92 (1 H, d, J=1.22 Hz), 7.87 (2 H, dd, J=7.63, 1.53 Hz), 7.73 - 7.83 (2 H, m), 7.57 (1 H, t, J=7.78 Hz), 7.52 (2 H, d, J=7.32 Hz), 7.40 (2 H, t, J=9.00 Hz), 7.33 (2 H, t, J=7.78 Hz), 7.20 (1 H, t, J=7.32 Hz), 2.87 (3 H, d), 2.61 - 2.71 (2 H, m), 2.54 - 2.58 (2 H, m), 2.01 - 2.11 (1 H, m), 1.82 - 1.92 (1 H, m). LC-MS retention time 2.42 min; m/z (MH⁺): 519. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time

of 4 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 14.66 min, purity = 97%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 13.13 min, purity = 97%.

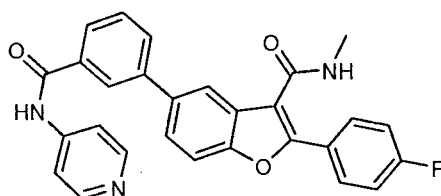


N-(2-(4-Fluorophenyl)-5-isopropoxy-3-(1H-1,2,4-triazol-5-yl)benzofuran-6-yl)methanesulfonamide

[00129] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 11.03 (1 H, s), 7.92 - 8.01 (2 H, m), 7.86 (1 H, d, J=9.16 Hz), 7.42 (2 H, t, J=8.85 Hz), 7.17 (1 H, d, J=8.85 Hz), 4.20 (2 H, q, J=7.12 Hz), 1.21 (3 H, t, J=7.17 Hz). LC-MS retention time: 1.70 min; m/z (MH⁺): 547. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 14.86 min, purity = 99%; Additional HPLC method 2:

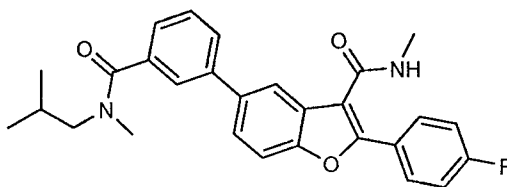
Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C-18, 4.6 x 150 mm, 3 μm, R_t = 17.53 min, purity = 99%.

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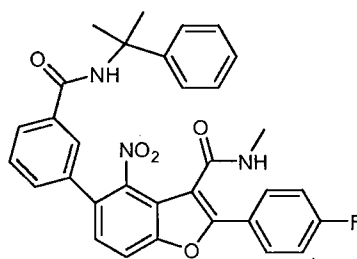
2-(4-Fluorophenyl)-N-methyl-5-(3-(pyridin-4-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00130] ¹H NMR (500 MHz, DMSO-d₆) δ ppm 11.15 (1 H, s), 8.64 (2 H, d, J=6.41 Hz), 8.48 - 8.55 (1 H, m), 8.30 (1 H, s), 8.05 - 8.08 (2 H, m), 7.97 - 8.03 (6 H, m), 7.76 - 7.85 (2 H, m), 7.71 (1 H, t, J=7.78 Hz), 7.41 (2 H, t, J=8.70 Hz), 2.83 - 2.92 (3 H, m). LC-MS retention time: 1.45 min; m/z (MH⁺): 466. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C-18, 4.6 x 150 mm, 3 μm, R_t = 15.11 min, purity = 97%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 14.81 min, purity = 96%.



2-(4-Fluorophenyl)-5-(3-(isobutyl(methyl)carbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00131] ¹H NMR (500 MHz, CD₃OD) δ ppm 7.93 - 7.98 (2 H, m), 7.88 - 7.91 (1 H, m), 7.74 - 7.81 (1 H, m), 7.63 - 7.70 (3 H, m), 7.51 - 7.60 (1 H, m), 7.32 - 7.41 (1 H, m), 7.25 (2 H, t), 3.43 (1 H, d), 3.21 (1 H, d), 3.10 (2 H, s), 3.03 (2 H, s), 2.96 (3 H, s), 2.10 - 2.21 (1 H, m), 1.92 - 2.07 (1 H, m), 1.01 (3 H, d), 0.78 (3 H, d). LC-MS retention time: 1.65 min; m/z (MH⁺): 459. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



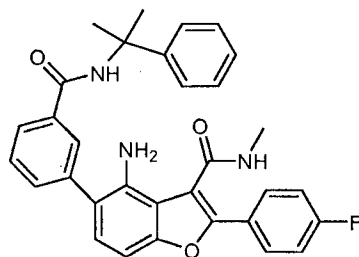
2-(4-Fluorophenyl)-N-methyl-4-nitro-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00132] Step1: Ethyl 2-(4-fluorophenyl)-4-nitro-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxylate (300 mg, 0.529 mmol) was diluted with EtOH (10 mL) and treated with NaOH (2.1 mL, 2.12 mmol, 1N aq.) and the mixture, which became a slurry, was allowed to stir overnight at 60 °C. The reaction

was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated.

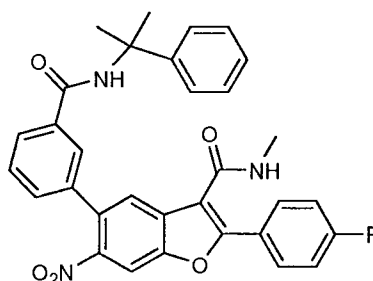
[00133] Step 2: EDC (128 mg, 0.668 mmol) was added to a stirring solution of the crude 2-(4-fluorophenyl)-4-nitro-5-(3-(2-phenylpropan-2-

- 5 ylcarbamoyl)phenyl)benzofuran-3-carboxylic acid (300 mg, 0.557 mmol), methanamine (306 μ L, 0.613 mmol), 1-hydroxy-7-azabenzotriazole (83 mg, 0.613 mmol), DIEA (204 μ L, 1.170 mmol) in DCM (5.5 mL) at rt. It was allowed to stir for 3 days. The slurry had gone into solution over that period of time. The mixture was concentrated and purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, 10 fraction collection at λ = 254 nm) to give the titled compound (220 mg, 95%). ¹H NMR (500 MHz, CD₃OD) δ ppm 7.90 - 7.99 (3 H, m), 7.85 - 7.90 (1 H, m), 7.82 - 7.84 (1 H, m), 7.49 - 7.56 (3 H, m), 7.45 (2 H, d, J =7.32 Hz), 7.27 - 7.34 (4 H, m), 7.19 (1 H, t, J =7.32 Hz), 2.87 (3 H, s), 1.76 (6 H, s). LC-MS retention time: 1.62 min; m/z (MH⁺): 552. LC data was recorded on a Shimadzu LC-10AS liquid 15 chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O 20 / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. 25 Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μ m, R_t = 13.60 min, purity = 94%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μ m, R_t = 12.66 min, purity = 96%.



4-Amino-2-(4-fluorophenyl)-N-methyl-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

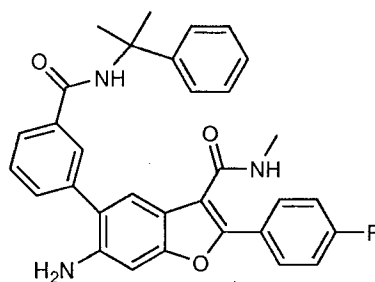
- [00134] Iron (25 mg, 0.453 mmol) was added to a stirring solution of 2-(4-fluorophenyl)-N-methyl-4-nitro-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide (50 mg, 0.091 mmol) in ethanol (1 mL) and AcOH (1 mL) at rt. It was placed in a reaction block set to 100 °C. It was allowed to stir for 1 hr. The mixture was allowed to cool and was diluted with EtOAc and washed with 1M HCl, followed by 1N NaOH and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and triturated with Et₂O to give the titled compound (28 mg, 56%). ¹H NMR (300 MHz, CD₃OD) δ ppm 7.83 - 7.89 (1 H, m), 7.73 - 7.81 (3 H, m), 7.52 - 7.64 (2 H, m), 7.42 - 7.49 (2 H, m), 7.10 - 7.35 (6 H, m), 6.98 (1 H, d, *J*=8.42 Hz), 2.87 (3 H, s), 1.76 (6 H, s). LC-MS retention time: 2.33 min; *m/z* (MH⁺): 522. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min.
- Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, *R*_t = 14.17 min, purity = 97%;
 Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, *R*_t = 12.84 min, purity = 98%.



2-(4-Fluorophenyl)-N-methyl-6-nitro-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

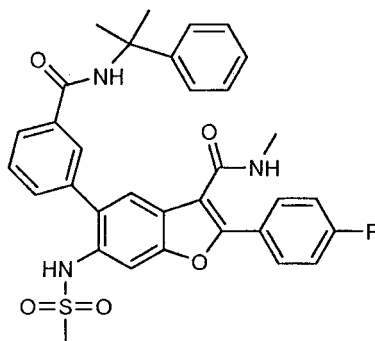
- [00136] Step 1: Cesium carbonate (143 mg, 0.440 mmol) was added to Pd(Ph₃P)₄ (17 mg, 0.015 mmol), ethyl 2-(4-fluorophenyl)-6-nitro-5-(trifluoromethylsulfonyloxy)benzofuran-3-carboxylate (140 mg, 0.293 mmol), 3-boronobenzoic acid (73 mg, 0.440 mmol). Dioxane (2.5 mL) and water (500 μ L) was added at rt. The reaction was degassed 3x and heated to 90 °C overnight. It was allowed to cool. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated.
- [00137] Step 2: The residue was diluted with DMF and treated with HATU (167 mg, 0.440 mmol), 2-phenylpropan-2-amine (60 mg, 0.440 mmol), and DIEA (154 μ L, 0.880 mmol) and allowed to stir at rt overnight. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at λ = 254 nm) to give ethyl 2-(4-fluorophenyl)-6-nitro-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxylate. (LC-MS retention time: 1.97 min; m/z (MH⁺): 567. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode).

- [00138] Step 3: This material was treated with NaOH (1 mL, 1.000 mmol) in ethanol (2.93 mL) at 60 °C for 2 hr then allowed to stir overnight while cooling to rt. The reaction was heated to 60 °C for 3 hrs. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄,
5 filtered and concentrated.
- [00139] Step 4: EDC (58 mg, 0.301 mmol), methanamine (1 mL, 2.000 mmol), 1-hydroxy-7-azabenzotriazole (38 mg, 0.276 mmol), DIEA (92 µL, 0.526 mmol) was added to the residue in DCE (2.5 mL) at rt. It was allowed to stir for 3 days. The slurry had gone into solution over that period of time. The crude reaction was purified
10 on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at λ = 254 nm) to give the titled compound (112 mg, 81%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.32 (1 H, s), 7.97 - 8.06 (2 H, m), 7.82 - 7.90 (2 H, m), 7.75 (1 H, s), 7.47 - 7.56 (2 H, m), 7.45 (2 H, d, *J*=7.32 Hz), 7.31 (4 H, t, *J*=8.09 Hz), 7.18 (1 H, t, *J*=7.32 Hz), 2.94 (3 H, s), 1.77 (6 H, s). LC-MS retention time: 3.10 min; *m/z* (MH⁺): 552. LC
15 data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time
20 of 4 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.
- Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time =
25 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 µm, *R*_t = 14.12 min, purity = 96%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 µm, *R*_t = 12.98 min, purity = 97%.



6-Amino-2-(4-fluorophenyl)-N-methyl-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

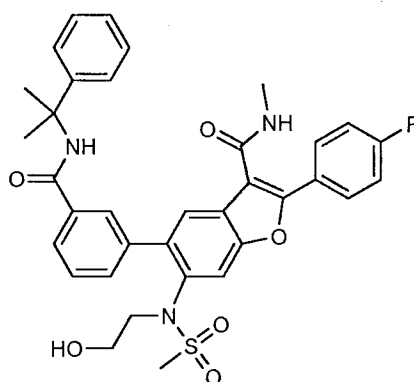
[00140] Iron (68 mg, 1.22 mmol) was added to a stirring solution of 2-(4-fluorophenyl)-N-methyl-6-nitro-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide (112 mg, 0.203 mmol) in ethanol (2.3 mL) and AcOH (2.3 mL) at rt. It was placed in a reaction block set to 100 °C and allowed to stir for 1 hr. The mixture was allowed to cool and was diluted with EtOAc and washed with 1M HCl, followed by 1N NaOH and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and triturated with Et₂O to give the titled compound (52 mg, 47%). ¹H NMR (500 MHz, CD₃OD) δ ppm 6.58 - 6.65 (3 H, m), 6.52 (1 H, d, *J*=7.63 Hz), 6.37 (1 H, d, *J*=7.93 Hz), 6.30 (1 H, t, *J*=7.63 Hz), 6.18 (2 H, d, *J*=7.32 Hz), 6.08 (1 H, s), 6.03 (2 H, t, *J*=7.78 Hz), 5.88 - 5.97 (3 H, m), 5.73 (1 H, s), 1.65 (3 H, s), 0.50 (6 H, s). LC-MS retention time 1.54 min; *m/z* (MH⁺): 520. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, *R*_t = 15.11 min, purity = 95%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, *R*_t = 11.11 min, purity = 94%.



2-(4-Fluorophenyl)-N-methyl-6-(methylsulfonamido)-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

- 5 [00141] Step 1: DIEA (134 μ L, 0.765 mmol) was added to $\text{Pd}(\text{Ph}_3\text{P})_4$ (30 mg, 0.025 mmol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-(methylsulfonyl)methylsulfonamido)benzofuran-5-yl trifluoromethanesulfonate (150 mg, 0.255 mmol), 3-(ethoxycarbonyl)phenylboronic acid (74 mg, 0.382 mmol). Dioxane (5 mL) and water (1 mL) was added at rt. The reaction was degassed 3x and
- 10 heated to 90 $^{\circ}\text{C}$ overnight. It was allowed to cool and left to stir for 3 days at rt.
- [00142] Step 2: The mixture was concentrated and diluted with EtOH (5 mL) and treated with excess 1N NaOH (~1 mL) and allowed to stir at rt overnight to give the meta-acid. The mixture was diluted with EtOAc and washed with 1M HCl, and 1M HCl. The organic phase was dried over Na_2SO_4 , filtered and concentrated.
- 15 [00143] Step 3: The crude residue was diluted with DMF (5 mL) and treated with HATU (145 mg, 0.382 mmol), 2-phenylpropan-2-amine (52 mg, 0.382 mmol) and DIEA (134 μ L, 0.765 mmol) and allowed to stir at rt overnight. The mixture was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered gradient, and concentrated. The isolated titled compound was re-
- 20 purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, $R_f \sim 0.2$ 50% EtOAc/hexanes, fraction collection at $\lambda = 254$ nm) to give the titled compound (7 mg, 4%). ^1H NMR (500 MHz, CD_3OD) δ ppm 7.94 - 8.01 (2 H, m), 7.92 (1 H, s), 7.83 (1 H, d, $J=7.63$ Hz), 7.77 (1 H, s), 7.63 - 7.68 (2 H, m), 7.59 (1 H, t, $J=7.63$ Hz), 7.46 (2 H, d, $J=7.32$ Hz), 7.24 - 7.32 (4 H, m), 7.18 (1 H, t, $J=7.32$ Hz), 2.94 (3 H, s), 2.88 (3
- 25 H, s), 1.77 (6 H, s). LC-MS retention time: 2.25 min; m/z (MH^+): 600. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters

SunFire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where
 5 solvent A was 5% acetonitrile / 95% H₂O / 0.1% TFA and solvent B was 5% H₂O / 95% acetonitrile / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate =
 10 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 12.87 min, purity = 96%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 11.97 min, purity = 98%.



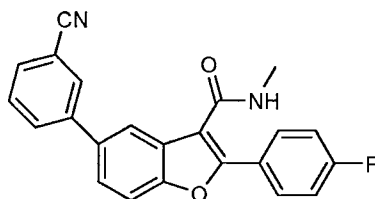
15 2-(4-Fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methyl-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00144] Step 1: Methanesulfonyl chloride (10 μL, 0.128 mmol) was added to a stirring solution of 6-amino-2-(4-fluorophenyl)-N-methyl-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide (50 mg, 0.096 mmol) in pyridine (1
 20 mL) at rt. It was allowed to stir for 2 hours and then concentrated and diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated.

[00145] Step 2: The crude residue was dissolved in DMF (1 mL) and treated with (2-bromoethoxy)(*tert*-butyl)dimethylsilane (102 μL, 0.479 mmol) and Na₂CO₃ (31
 25 mg, 0.288 mmol) at rt. It was heated to 100 °C for 4 hours and then diluted with

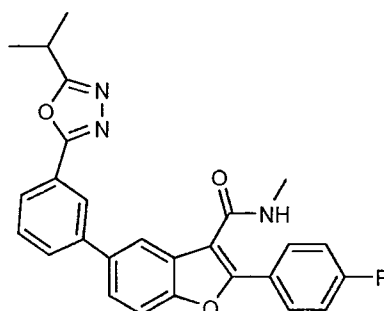
EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated.

- [00146] Step 3: The crude residue was taken up in THF (2 mL) and treated with 2 mL of 1N HCl, and allowed to stir at rt for 1 hr. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and triturated with Et₂O to give the titled compound (25 mg, 39%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.14 - 8.21 (1 H, m), 7.95 - 8.04 (2 H, m), 7.83 - 7.87 (1 H, m), 7.76 - 7.81 (1 H, m), 7.66 - 7.74 (2 H, m), 7.56 (1 H, t, *J*=7.63 Hz), 7.41 - 7.49 (2 H, m), 7.24 - 7.33 (4 H, m), 7.17 (1 H, t, *J*=7.32 Hz), 2.94 (3 H, s), 1.76 (6 H, s). LC-MS retention time 1.42 min; *m/z* (MH⁺): 644. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, *R*_t = 12.26 min, purity = 96%; Additional HPLC method: Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C-18, 4.6 x 150 mm, 3 μm, *R*_t = 13.61 min, purity = 94%.



5-(3-Cyanophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

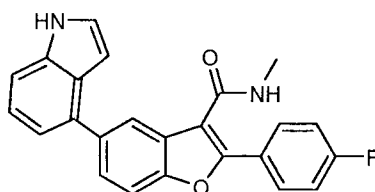
- [00147] Cesium carbonate (187 mg, 0.575 mmol) was added to Pd(Ph₃P)₄ (22 mg, 0.019 mmol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (160 mg, 0.383 mmol), 3-cyanophenylboronic acid (85 mg, 0.575 mmol). Dioxane (3 mL) and water (600 µL) was added at rt. The reaction was
- 5 degassed 3x and heated to 90 °C overnight. It was allowed to cool. The mixture was diluted with EtOAc and washed with 1M HCl, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated. The crude residue was taken up in DCM. A white precipitate formed which was filtered to give the titled compound. The filtrate was purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, R_f ~.4: 50%
- 10 EtOAc/Hex, fraction collection at λ = 254 nm) to give the titled compound which was combined with the previously collected precipitate (85 mg, 60%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.46 - 8.53 (1 H, m), 8.24 (1 H, s), 8.09 (1 H, d, J=7.93 Hz), 7.99 - 8.05 (2 H, m), 7.96 (1 H, d, J=1.53 Hz), 7.85 (1 H, d, J=7.63 Hz), 7.74 - 7.82 (2 H, m), 7.70 (1 H, t, J=7.78 Hz), 7.40 (2 H, t, J=8.85 Hz), 2.87 (3 H, d, J=4.58 Hz).
- 15 LC-MS retention time: 2.17 min; m/z (MH⁺): 371. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a
- 20 gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5%
- 25 H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 µm, R_t = 13.59 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 µm, R_t = 12.29 min, purity = 99%.



2-(4-Fluorophenyl)-5-(3-(5-isopropyl-1,3,4-oxadiazol-2-yl)phenyl)-N-methylbenzofuran-3-carboxamide

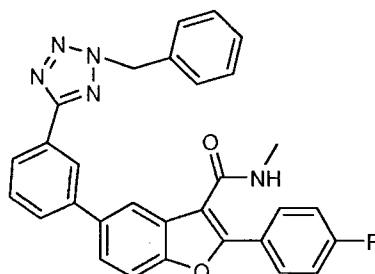
[00148] Isobutyryl chloride (90 mg, 0.847 mmol) was added to a stirring solution of 5-(3-(1H-tetrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (50 mg, 0.085 mmol) in pyridine (1 mL) at 100 °C. It was allowed to stir overnight. The reaction was concentrated and diluted with EtOH (3 mL) and treated with excess 1N NaOH (500 µL) and stirred at 60 °C for 2 hours to hydrolyze the acylated amide. The mixture was filtered and the filtrate was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at λ = 254 nm) to give the titled compound (8 mg, 20%).
¹H NMR (500 MHz, CD₃OD) δ ppm 8.31 - 8.35 (1 H, m), 8.03 (1 H, d, J=7.94 Hz), 7.95 - 8.00 (3 H, m), 7.93 (1 H, d, J=7.93 Hz), 7.67 - 7.74 (3 H, m), 7.25 - 7.30 (2 H, m), 3.37 - 3.40 (1 H, m), 2.99 (3 H, s), 1.49 (6 H, d, J=7.02 Hz). LC-MS retention time: 2.28 min; m/z (MH⁺): 456. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 µm, R_t = 14.30 min, purity = 94%;

Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μ m, R_t = 12.50 min, purity = 93%.



- 5 2-(4-Fluorophenyl)-5-(1H-indol-4-yl)-N-methylbenzofuran-3-carboxamide
 [00149] Cesium carbonate (176 mg, 0.539 mmol) was added to Pd(Ph₃P)₄ (20.77
 mg, 0.018 mmol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl
 trifluoromethanesulfonate (150 mg, 0.359 mmol), 1H-indol-4-ylboronic acid (87 mg,
 0.539 mmol). Dioxane (3 mL) and water (600 μ L) was added at rt. The reaction was
 10 degassed 3x and then heated to 90 °C overnight. It was allowed to cool. The mixture
 was diluted with ethyl acetate and washed with sat NaHCO₃, and sat NaCl. The
 organic phase was dried over Na₂SO₄, filtered and concentrated and purified on silica
 gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at λ = 254 nm) to give
 the titled compound (66 mg, 46%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 11.28 (1
 15 H, br. s.), 8.48 - 8.57 (1 H, m), 7.98 - 8.07 (2 H, m), 7.86 (1 H, br. s.), 7.79 (1 H, d,
 J =8.24 Hz), 7.69 (1 H, d, J =7.93 Hz), 7.37 - 7.47 (4 H, m), 7.21 (1 H, t, J =7.63 Hz),
 7.14 (1 H, d, J =7.02 Hz), 6.60 (1 H, br. s.), 2.84 (3 H, d, J =4.27 Hz). LC-MS
 retention time: 1.53 min; m/z (MH⁺): 385. LC data was recorded on a Shimadzu LC-
 10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm
 20 column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm.
 The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent
 A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold
 time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile /
 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile /
 25 10 mM ammonium acetate. MS data was determined using a MICROMASS®
 Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5%
 CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start
 %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate =
 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μ m, R_t = 13.46 min,

purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μ m, R_t = 12.27 min, purity = 97%.

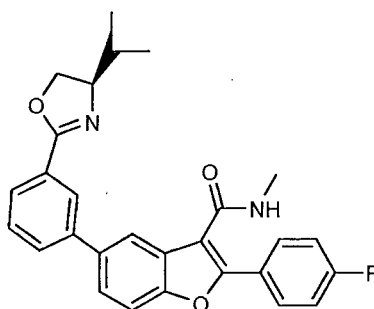


5 5-(3-(2-Benzyl-2H-tetrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00150] Benzyl bromide (29 μ L, 0.242 mmol) was added to a stirring solution of 5-(3-(1H-tetrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (50 mg, 0.121 mmol) and Na_2CO_3 (26 mg, 0.242 mmol) in DMF (1.2 mL) at 100 $^\circ\text{C}$.

- 10 It was allowed to stir overnight. The mixture was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gradient, and concentrated to give the titled compound (12 mg, 19%).
- ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.48 - 8.56 (1 H, m), 8.30 - 8.35 (1 H, m), 8.06 (1 H, d, $J=7.63$ Hz), 7.98 - 8.03 (2 H, m), 7.90 - 7.93 (2 H, m), 7.78 - 7.83 (1 H, m), 7.72 - 7.77 (1 H, m), 7.69 (1 H, t, $J=7.78$ Hz), 7.36 - 7.46 (7 H, m), 6.04 (2 H, s), 2.86 (3 H, d, $J=4.58$ Hz). LC-MS retention time: 1.78 min; m/z (MH^+): 504. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a
- 20 gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.
- 25 Additional HPLC method: Solvent A = 5% $\text{CH}_3\text{CN}/95\%$ $\text{H}_2\text{O}/0.1\%$ TFA, Solvent B = 95% $\text{CH}_3\text{CN}/5\%$ $\text{H}_2\text{O}/0.1\%$ TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18,

4.6 x 150 mm, 3.5 μ m, R_t = 15.69 min, purity = 97%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μ m, R_t = 13.95 min, purity = 98%.

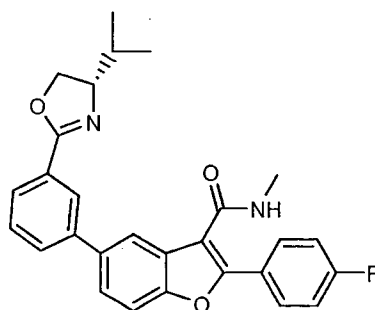


5 (R)-2-(4-Fluorophenyl)-5-(3-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-N-methylbenzofuran-3-carboxamide

[00151] Zinc chloride (8 mg, 0.054 mmol) was added to a stirring solution of 5-(3-cyanophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (40 mg, 0.108 mmol) and (R)-2-amino-3-methylbutan-1-ol (111 mg, 1.08 mmol) in PhCl (3 mL) at
 10 rt. It was subjected for two interactions to microwave irradiation for 1 hr at 200 °C. The mixture was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (13 mg, 25%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.24 (1 H, s), 7.93 - 7.99 (2 H, m), 7.89 - 7.93 (2 H, m), 7.86 (1 H, d, J =7.63 Hz), 7.63 - 7.69 (2 H,
 15 m), 7.56 (1 H, t, J =7.78 Hz), 7.26 (2 H, t, J =8.55 Hz), 4.52 (1 H, t, J =9.31 Hz), 4.30 (1 H, t, J =8.09 Hz), 4.14 - 4.22 (1 H, m), 2.98 (3 H, s), 1.87 - 1.97 (1 H, m), 1.04 (3 H, d, J =7.02 Hz), 0.97 (3 H, d, J =6.71 Hz). LC-MS retention time 1.64 min; m/z (MH⁺): 457. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-
 20 10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic
 25 acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final

%B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min.
 Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μ m, R_t = 10.13 min, purity = 95%;
 Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μ m, R_t = 10.58 min,
 purity = 94%.

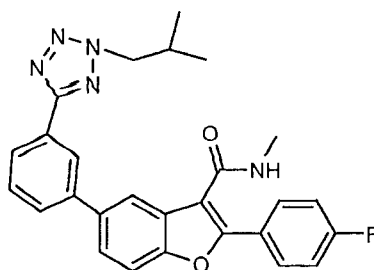
5



(S)-2-(4-Fluorophenyl)-5-(3-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-N-methylbenzofuran-3-carboxamide

[00152] Zinc chloride (8 mg, 0.054 mmol) was added to a stirring solution of 5-(3-cyanophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (40 mg, 0.108 mmol) and (S)-2-amino-3-methylbutan-1-ol (111 mg, 1.080 mmol) in PhCl (3 mL) at rt. It was subjected for two 1 hr iterations to microwave irradiation at 200 °C. The reaction was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (9 mg, 17%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.24 (1 H, s), 7.93 - 7.99 (2 H, m), 7.89 - 7.93 (2 H, m), 7.86 (1 H, d, J =7.63 Hz), 7.63 - 7.69 (2 H, m), 7.56 (1 H, t, J =7.78 Hz), 7.26 (2 H, t, J =8.70 Hz), 4.52 (1 H, t, J =9.31 Hz), 4.30 (1 H, t, J =8.09 Hz), 4.15 - 4.22 (1 H, m), 2.98 (3 H, s), 1.86 - 1.96 (1 H, m), 1.04 (3 H, d, J =6.71 Hz), 0.97 (3 H, d, J =6.71 Hz). LC-MS retention time: 1.63 min; m/z (MH⁺): 457. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

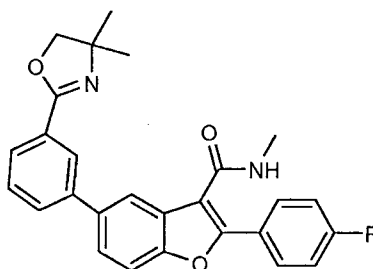
Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 10.06 min, purity = 95%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 10.53 min, purity = 95%.



2-(4-Fluorophenyl)-5-(3-(2-isobutyl-2H-tetrazol-5-yl)phenyl)-N-methylbenzofuran-3-carboxamide

- 10 [00153] 1-Bromo-2-methylpropane (23 mg, 0.169 mmol) was added to a stirring solution of 5-(3-(1H-tetrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (35 mg, 0.085 mmol) and Na₂CO₃ (18 mg, 0.169 mmol) in DMF (1 mL) at 100 °C. It was allowed to stir overnight. The mixture was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered
- 15 H₂O/CH₃CN gradient, and concentrated to give the titled compound (15 mg, 38%).
¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.49 - 8.56 (1 H, m), 8.34 (1 H, s), 8.08 (1 H, d, J=7.63 Hz), 7.99 - 8.04 (2 H, m), 7.87 - 7.94 (2 H, m), 7.79 - 7.84 (1 H, m), 7.73 - 7.78 (1 H, m), 7.70 (1 H, t, J=7.63 Hz), 7.41 (2 H, t, J=8.70 Hz), 4.62 (2 H, d, J=7.32 Hz), 2.87 (3 H, d, J=4.27 Hz), 2.31 - 2.39 (1 H, m), 0.95 (6 H, d, J=6.71 Hz). LC-MS
- 20 retention time: 2.09 min; m/z (MH⁺): 470. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min,
- 25 a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform

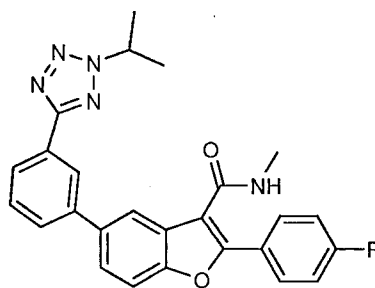
for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 16.08 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 13.89 min, purity = 99%.



5-(3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00154] Zinc chloride (1 mg) was added to a stirring solution of 5-(3-cyanophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (40 mg, 0.108 mmol) and 2-amino-2-methylpropan-1-ol (10 mg, 0.108 mmol) in PhCl (3 mL) at 130 °C. It was allowed to stir for 7 days. ~20% conversion was observed. Additional amounts of ZnCl (8 mg) and 2-amino-2-methylpropan-1-ol (50 mg) were added and the reaction was heated in the microwave for 1 hr at 200 °C. The reaction had progressed ~ 50%. The mixture was concentrated and purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, R_f ~.2 in 50% EtOAc/hexanes; fraction collection at λ = 254 nm) followed by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (7 mg, 14%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.24 (1 H, s), 7.97 (2 H, dd, J=8.09, 5.65 Hz), 7.93 (1 H, s), 7.88 (2 H, dd, J=11.44, 8.39 Hz), 7.68 (2 H, s), 7.57 (1 H, t, J=7.78 Hz), 7.27 (2 H, t, J=8.55 Hz), 4.25 (2 H, s), 2.99 (3 H, s), 1.42 (6 H, s). LC-MS retention time 1.60 min; m/z (MH⁺): 443. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100%

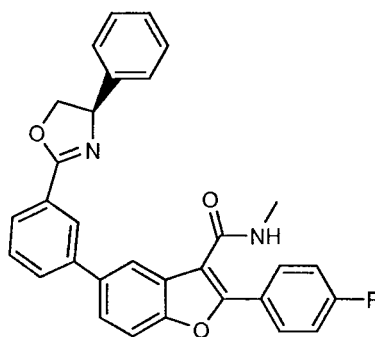
- solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a
- 5 MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 12.24 min, purity = 95%; Column: Waters XBridge phenyl column 4.6 x 150
- 10 mm, 3.5 μm, R_t = 10.02 min, purity = 95%.



2-(4-Fluorophenyl)-5-(3-(2-isopropyl-2H-tetrazol-5-yl)phenyl)-N-methylbenzofuran-3-carboxamide

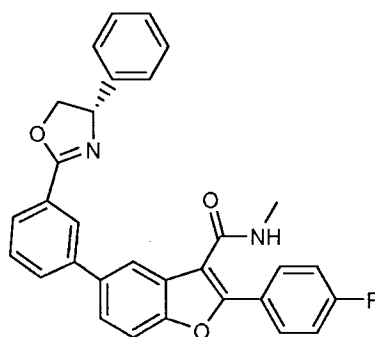
- 15 **[00155]** 2-Iodopropane (29 mg, 0.169 mmol) was added to a stirring solution of 5-(3-(1H-tetrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (35 mg, 0.085 mmol) and Na₂CO₃ (18 mg, 0.169 mmol) in DMF (1 mL) at 100 °C. It was allowed to stir overnight. The mixture was concentrated and purified by
- 20 preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (12 mg, 30%).
- ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.49 - 8.57 (1 H, m), 8.34 (1 H, s), 8.08 (1 H, d, J=7.32 Hz), 7.99 - 8.05 (2 H, m), 7.87 - 7.94 (2 H, m), 7.79 - 7.83 (1 H, m), 7.72 - 7.78 (1 H, m), 7.70 (1 H, t, J=7.78 Hz), 7.41 (2 H, t, J=8.70 Hz), 5.17 - 5.27 (1 H, m), 2.87 (3 H, d, J=4.58 Hz), 1.66 (6 H, d, J=6.71 Hz). LC-MS retention time: 2.02 min;
- 25 m/z (MH⁺): 456. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution

- conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μm, R_t = 15.35 min, purity = 96%;
- 10 Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 μm, R_t = 13.39 min, purity = 97%.



- (R)-2-(4-Fluorophenyl)-N-methyl-5-(3-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)benzofuran-3-carboxamide
- 15 [00156] Zinc chloride (8 mg, 0.054 mmol) was added to a stirring solution of 5-(3-cyanophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (40 mg, 0.108 mmol) and (R)-2-amino-2-phenylethanol (148 mg, 1.080 mmol) in PhCl (3 mL) at rt. It was subjected to two interactions of microwave irradiation at 200 °C for 1 hr. The
- 20 material was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (7 mg, 13%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.33 (1 H, s), 7.94 - 8.00 (4 H, m), 7.91 (1 H, d, J=7.94 Hz), 7.64 - 7.73 (2 H, m), 7.61 (1 H, t, J=7.78 Hz), 7.32 - 7.42 (6 H, m), 7.26 (2 H, t, J=8.55 Hz), 5.45 (1 H, t, J=9.16 Hz), 4.94 (1
- 25 H, t, J=9.31 Hz), 4.36 (1 H, t, J=8.24 Hz), 2.97 (3 H, s). LC-MS retention time 1.75 min; m/z (MH⁺): 491. LC data was recorded on a Shimadzu LC-10AS liquid

chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% MeOH/95% H₂O/10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H₂O/10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C-18, 4.6 x 150 mm, 3 µm, R_t = 18.32 min, purity = 97%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 µm, R_t = 18.11 min, purity = 97%.



(S)-2-(4-Fluorophenyl)-N-methyl-5-(3-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)benzofuran-3-carboxamide

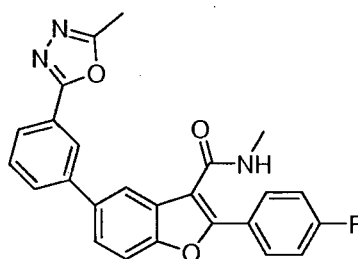
[00157] Zinc chloride (9 mg, 0.067 mmol) was added to a stirring solution of 5-(3-cyanophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (50 mg, 0.135 mmol) and (S)-2-amino-2-phenylethanol (93 mg, 0.675 mmol) in PhCl (3 mL) rt. It was subjected to two interactions of microwave irradiation at 200 °C for 1 hr. The material was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (16 mg, 23%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.33 (1 H, s), 7.94 - 8.00 (4 H, m), 7.91 (1 H, d, J=7.94 Hz), 7.64 - 7.73 (2 H, m), 7.61 (1 H, t, J=7.78 Hz), 7.32 - 7.42 (6 H, m), 7.26 (2 H, t, J=8.55 Hz), 5.45 (1 H, t, J=9.16 Hz),

4.94 (1 H, t, $J=9.31$ Hz), 4.36 (1 H, t, $J=8.24$ Hz), 2.97 (3 H, s). LC-MS retention time 1.76 min; m/z (MH^+): 491. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution

5 conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for

10 LC in electrospray mode. Additional HPLC method: Solvent A = 5% MeOH/95% H_2O /10 mM ammonium bicarbonate, Solvent B = 95% MeOH/5% H_2O /10 mM ammonium bicarbonate, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: PHENOMENEX® Gemini C-18, 4.6 x 150 mm, 3 μm , R_t = 18.32 min, purity = 99%; Column: Waters XBridge

15 phenyl column 4.6 x 150 mm, 3.5 μm , R_t = 18.10 min, purity = 99%.



2-(4-Fluorophenyl)-N-methyl-5-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)benzofuran-3-carboxamide

20 **[00158]** DIEA (50 μL , 0.288 mmol) was added to $Pd(Ph_3P)_4$ (6 mg, 4.79 μmol), - (4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (40 mg, 0.096 mmol), 3-(5-methyl-1,3,4-oxadiazol-2-yl)phenylboronic acid (29 mg, 0.144 mmol). Dioxane (1 mL) and water (200 μL) was added at rt. The reaction was

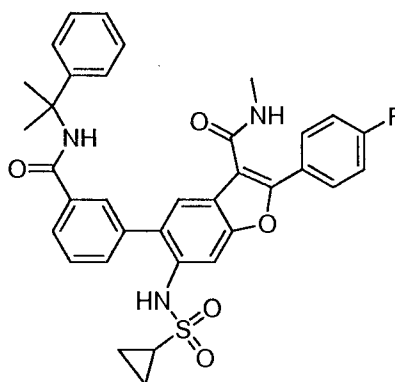
25 reverse phase HPLC on a C18 column using a suitably buffered H_2O/CH_3CN gradient, and concentrated to give the titled compound (16 mg, 37%). 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 8.49 - 8.56 (1 H, m), 8.24 (1 H, s), 7.98 - 8.05 (4 H, m), 7.93 (1 H, s), 7.79 - 7.83 (1 H, m), 7.68 - 7.76 (2 H, m), 7.41 (2 H, t, $J=8.70$ Hz), 2.87 (3

H, d, J=4.58 Hz), 2.62 (3 H, s). LC-MS retention time: 1.41 min; m/z (MH⁺): 426.

LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

- 10 Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, Rt = 12.96 min, purity = 95% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, Rt = 11.53 min, purity = 94%.

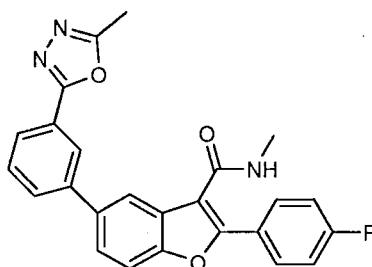
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6-(Cyclopropanesulfonamido)-2-(4-fluorophenyl)-N-methyl-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

- [00159] Cyclopropanesulfonyl chloride (8 μ L, 0.058 mmol) was added to a stirring solution of 6-amino-2-(4-fluorophenyl)-N-methyl-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide (20 mg, 0.038 mmol) in Pyridine (.5 mL) at rt. It was allowed to stir for 2 hours. The mixture was concentrated purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (17 mg, 70%).
- 25 ¹H NMR (500 MHz, CD₃OD) δ ppm 8.41 (1 H, br. s.), 7.91 - 8.01 (3 H, m), 7.78 -

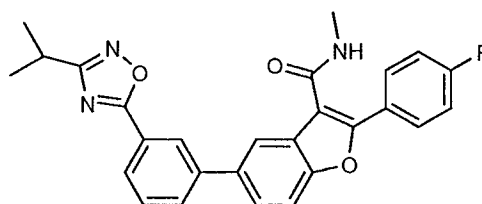
7.86 (2 H, m), 7.61 - 7.71 (2 H, m), 7.58 (1 H, t, J=7.63 Hz), 7.41 - 7.49 (2 H, m), 7.24 - 7.33 (4 H, m), 7.18 (1 H, t, J=6.87 Hz), 2.94 (3 H, s), 2.34 - 2.43 (1 H, m), 1.77 (6 H, s), 0.80 - 1.03 (4 H, m). LC-MS retention time: 1.53 min; m/z (MH⁺): 626. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, Rt = 15.40 min, purity = 99% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, Rt = 12.65 min, purity = 99%.



20 2-(4-Fluorophenyl)-N-methyl-5-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)benzofuran-3-carboxamide

[00160] DIEA (50 μ L, 0.288 mmol) was added to Pd(Ph₃P)₄ (6 mg, 4.79 μ mol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (40 mg, 0.096 mmol), 3-(5-methyl-1,3,4-oxadiazol-2-yl)phenylboronic acid (29 mg, 0.144 mmol). Dioxane (799 μ L) and water (160 μ L) was added at rt. The reaction was heated to 90 $^{\circ}$ C overnight. The mixture was cooled and purified by prep HPLC to give the titled compound (16 mg, 37%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.49 - 8.56 (1 H, m), 8.24 (1 H, s), 7.98 - 8.05 (4 H, m), 7.93 (1 H, s), 7.79 - 7.83 (1 H, m),

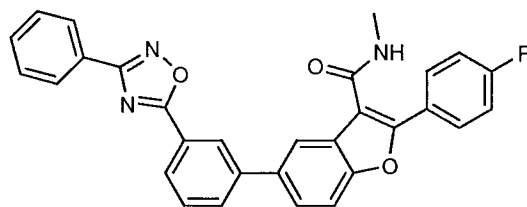
7.68 - 7.76 (2 H, m), 7.41 (2 H, t, $J=8.70$ Hz), 2.87 (3 H, d, $J=4.58$ Hz), 2.62 (3 H, s).
 LC-MS retention time: 1.41 min; m/z (MH⁻): 426. LC data was recorded on a
 Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18
 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of
 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100%
 5 solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min,
 a hold time of 1 min, and an analysis time of 3 min where solvent A was 5%
 acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95%
 acetonitrile / 10 mM ammonium acetate. MS data was determined using a
 10 MICROMASS® Platform for LC in electrospray mode. Analytical HPLC method:
 Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5%
 H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time =
 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μ m,
 R_t = 12.96 min, purity = 95% ; Column: Waters XBridge phenyl column 4.6 x 150
 15 mm, 3.5 μ m, R_t = 11.53 min, purity = 94%.



2-(4-Fluorophenyl)-5-(3-(3-isopropyl-1,2,4-oxadiazol-5-yl)phenyl)-N-
 methylbenzofuran-3-carboxamide

20 **[00161]** Sodium methoxide (33 mg, 0.620 mmol) was added to a stirring slurry of
 methyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate (50 mg,
 0.124 mmol) and (Z)-N'-hydroxyisobutyrimidamide (38 mg, 0.372 mmol) in EtOH
 (2.5 mL) at rt. The mixture was subjected to microwave irradiation for 5 min at 160
 °C. The mixture was concentrated and purified by preparative reverse phase HPLC on
 25 a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to
 give the titled compound (11 mg, 20%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.46 -
 8.54 (1 H, m), 8.35 (1 H, s), 8.11 (1 H, d, $J=7.78$ Hz), 7.97 - 8.08 (3 H, m), 7.92 -
 7.97 (1 H, m), 7.73 - 7.84 (3 H, m), 7.40 (2 H, t, $J=8.91$ Hz), 3.12 - 3.23 (1 H, m),
 2.87 (3 H, d, $J=4.52$ Hz), 1.36 (6 H, d, $J=7.03$ Hz). LC-MS retention time: 1.80 min;

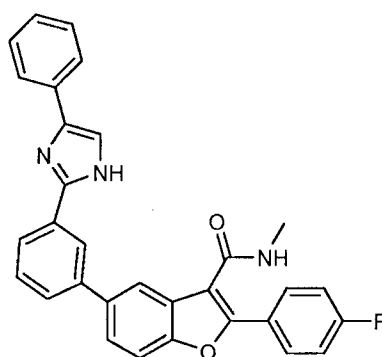
m/z (MH⁺) : 456. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 16.33 min, purity = 99% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 13.72 min, purity = 99%.



2-(4-Fluorophenyl)-N-methyl-5-(3-(3-phenyl-1,2,4-oxadiazol-5-yl)phenyl)benzofuran-3-carboxamide

[00162] Sodium methoxide (33 mg, 0.620 mmol) was added to a stirring slurry of methyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate (50 mg, 0.124 mmol) and (Z)-N'-hydroxybenzimidamide (51 mg, 0.372 mmol) in EtOH (2.5 mL) at rt. The mixture was subjected to microwave irradiation for 5 min at 160 °C. The mixture was concentrated and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (8.7 mg, 14%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.49 - 8.56 (1 H, m), 8.44 - 8.49 (1 H, m), 8.19 - 8.25 (1 H, m), 8.13 - 8.18 (2 H, m), 8.07 - 8.12 (1 H, m), 8.00 - 8.07 (2 H, m), 7.98 (1 H, s), 7.76 - 7.86 (3 H, m), 7.59 - 7.68 (3 H, m), 7.41 (2 H, t, J=8.91 Hz), 2.88 (3 H, d, J=4.77 Hz). LC-MS retention time: 1.94 min; m/z (MH⁺) : 490. LC data was recorded on a Shimadzu LC-10AS liquid

chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 17.39 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 14.58 min, purity = 98%.

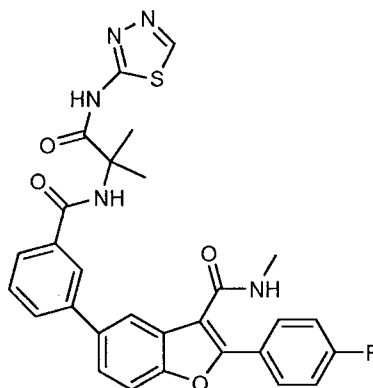


2-(4-Fluorophenyl)-N-methyl-5-(3-(4-phenyl-1H-imidazol-2-yl)phenyl)benzofuran-3-carboxamide

[00163] 2-Oxo-2-phenylacetaldehyde hydrate (10 mg, 0.066 mmol) in MeOH (1 mL) was added to a stirring solution of 2-(4-fluorophenyl)-5-(3-formylphenyl)-N-methylbenzofuran-3-carboxamide (20 mg, 0.054 mmol) and ammonium acetate (25 mg, 0.324 mmol) in MeOH (1 mL) at rt. It was allowed to stir overnight. The reaction was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (6.5 mg, 24%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 12.82 (1 H, br. s.), 8.51 - 8.58 (1 H, m), 8.35 (1 H, br. s.), 7.98 - 8.07 (3 H, m), 7.93 - 7.97 (1 H, m), 7.76 - 7.90 (4 H, m), 7.72 (1 H, d, J=7.63 Hz), 7.60 (1 H, t, J=7.78 Hz), 7.36 - 7.45 (4 H, m), 7.19 - 7.29 (1 H,

- m), 2.88 (3 H, d, $J=4.58$ Hz). LC-MS retention time: 1.57 min; m/z (MH^+) : 488.
- LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.
- 10 Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 9.54 min, purity = 96% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 10.41 min, purity = 97%.

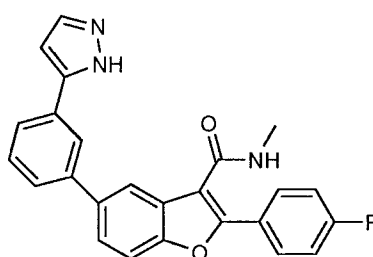
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5-(3-(1-(1,3,4-Thiadiazol-2-ylamino)-2-methyl-1-oxopropan-2-ylcarbamoyl)phenyl)-
2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00164] DIEA (44 μ L, 0.253 mmol) was added to a stirring solution of 2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzamido)-2-methylpropanoic acid (40 mg, 0.084 mmol), 1,3,4-thiadiazol-2-amine (17.05 mg, 0.169 mmol) in DMF (843 μ L) at rt. NaH (17 mg, 0.422 mmol) was added, and the slurry became a clear solution after 10 min. It was allowed to stir overnight. The reaction was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered
- 25 H₂O/CH₃CN gradient, and concentrated to give the titled compound (22 mg, 45%).

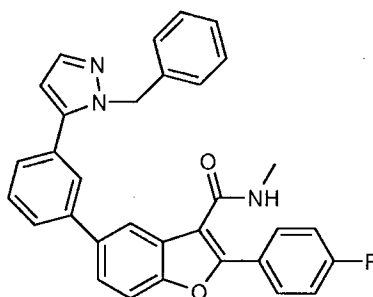
¹H NMR (500 MHz, DMSO-d₆) δ ppm 12.44 (1 H, br. s.), 9.14 (1 H, br. s.), 8.78 (1 H, br. s.), 8.47 - 8.57 (1 H, m), 8.30 (1 H, s), 7.97 - 8.04 (2 H, m), 7.88 - 7.95 (3 H, m), 7.75 - 7.84 (2 H, m), 7.61 (1 H, t, *J*=7.78 Hz), 7.41 (2 H, t), 2.86 (3 H, d, *J*=4.88 Hz), 1.57 (6 H, s). LC-MS retention time: 1.57 min; *m/z* (MH⁺): 488. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, *R*_t = 11.23 min, purity = 97% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, *R*_t = 10.56 min, purity = 96%.



5-(3-(1H-Pyrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00165] Cesium carbonate (234 mg, 0.719 mmol) was added to Pd(Ph₃P)₄ (20.77 mg, 0.018 mmol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (150 mg, 0.359 mmol), 5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (146 mg, 0.539 mmol). Dioxane (3 mL) and water (599 μL) was added at rt. The reaction was heated to 90 °C overnight. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and purified by

trituration with Et₂O to give the titled compound (140 mg, 92%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.40 (1 H, br. s.), 12.91 (1 H, br. s.), 8.45 - 8.55 (1 H, m), 8.13 (1 H, s), 7.97 - 8.08 (2 H, m), 7.85 - 7.95 (1 H, m), 7.73 - 7.85 (4 H, m), 7.59 - 7.67 (1 H, m), 7.49 - 7.58 (1 H, m), 7.35 - 7.45 (2 H, m), 6.84 (1 H, br. s.), 2.87 (3 H, d, *J*=4.52 Hz). LC-MS retention time: 1.41 min; *m/z* (MH⁺) : 412. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, *R*_t = 11.86 min, purity = 97% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, *R*_t = 10.97 min, purity = 99%.

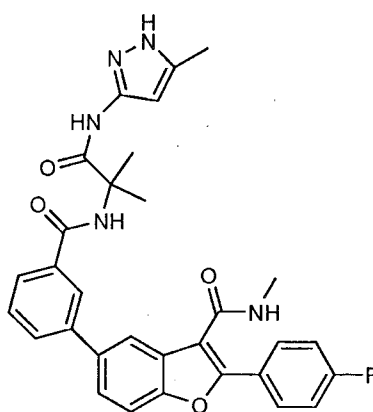


5-(3-(1-Benzyl-1H-pyrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00166] (Bromomethyl)benzene (17 mg, 0.097 mmol) was added to a stirring solution of Na₂CO₃ (11 mg, 0.097 mmol) and 5-(3-(1H-pyrazol-5-yl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (20 mg, 0.049 mmol) in DMF (486 μL) at 100 °C. It was allowed to stir overnight, filtered and purified by preparative reverse phase HPLC on a C18 column using a suitably buffered

H₂O/CH₃CN gradient, and concentrated to give the titled compound (8.6 mg, 35%).
¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.49 - 8.57 (1 H, m), 8.06 - 8.11 (1 H, m),
 7.98 - 8.04 (2 H, m), 7.92 (1 H, d, *J*=2.44 Hz), 7.86 - 7.89 (1 H, m), 7.75 - 7.83 (2 H,
 m), 7.69 - 7.75 (1 H, m), 7.63 (1 H, d, *J*=8.24 Hz), 7.51 (1 H, t, *J*=7.63 Hz), 7.34 -
 5 7.43 (4 H, m), 7.27 - 7.32 (3 H, m), 6.89 (1 H, d, *J*=2.44 Hz), 5.41 (2 H, s), 2.86 (3 H,
 d, *J*=4.58 Hz). LC-MS retention time: 2.00 min; *m/z* (MH⁺) : 502. LC data was
 recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a
 PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis
 detector at a detector wave length of 220nm. The elution conditions employed a flow
 10 rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A /
 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time
 of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and
 solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was
 determined using a MICROMASS® Platform for LC in electrospray mode.
 15 Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B
 = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time =
 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18,
 4.6 x 150 mm, 3.5 mm, *R*_t = 15.47 min, purity = 99% ; Column: Waters XBridge
 phenyl column 4.6 x 150 mm, 3.5 mm, *R*_t = 13.77 min, purity = 100%.

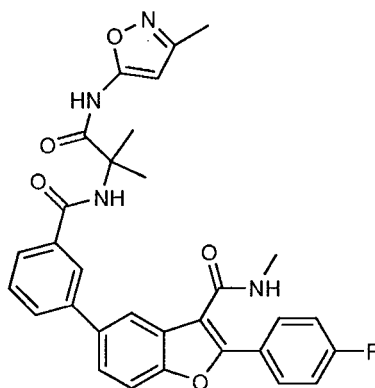
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2-(4-Fluorophenyl)-N-methyl-5-(3-(2-methyl-1-(5-methyl-1H-pyrazol-3-ylamino)-1-oxopropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

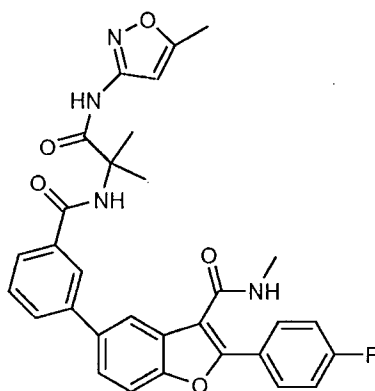
[00167] DIEA (28 μL, 0.158 mmol) was added to a stirring solution of 2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzamido)-2-methylpropanoic
 25

acid (25 mg, 0.053 mmol), 5-methyl-1H-pyrazol-3-amine (11 mg, 0.105 mmol) in DMF (527 μ L) at rt. It was allowed to stir for 30 min. NaH (11 mg, 0.263 mmol) was added and the reaction was allowed to stir overnight. The mixture was treated with a drop of MeOH and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (6.4 mg, 21%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 11.90 (1 H, br. s.), 9.84 (1 H, br. s.), 8.51 - 8.56 (1 H, m), 8.41 (1 H, br. s.), 8.23 - 8.28 (1 H, m), 7.98 - 8.03 (2 H, m), 7.86 - 7.93 (3 H, m), 7.76 - 7.83 (2 H, m), 7.59 (1 H, t, *J*=7.63 Hz), 7.37 - 7.43 (2 H, m), 6.28 (1 H, br. s.), 2.87 (3 H, d, *J*=4.88 Hz), 2.17 (3 H, s), 1.54 (6 H, s). LC-MS retention time: 1.56 min; *m/z* (MH⁺): 554. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, *R*_t = 10.47 min, purity = 97% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, *R*_t = 9.58 min, purity = 96%.



2-(4-Fluorophenyl)-N-methyl-5-(3-(2-methyl-1-(3-methylisoxazol-5-ylamino)-1-oxopropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

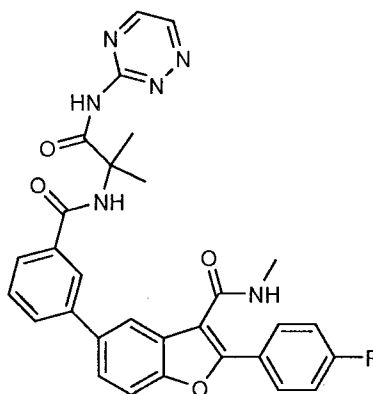
- [00168] DIEA (28 μ L, 0.158 mmol) was added to a stirring solution of 2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzamido)-2-methylpropanoic acid (25 mg, 0.053 mmol), 3-methylisoxazol-5-amine (11 mg, 0.105 mmol) in DMF (527 μ L) at rt. It was allowed to stir for 30 min. NaH (11 mg, 0.263 mmol) was added and the reaction was allowed to stir overnight. The mixture was treated with a drop of MeOH and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (3.3 mg, 11%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.18 - 8.24 (1 H, m), 7.93 - 8.00 (3 H, m), 7.84 - 7.91 (2 H, m), 7.65 - 7.74 (2 H, m), 7.58 (1 H, t, *J*=7.78 Hz), 7.23 - 7.31 (2 H, m), 2.98 (3 H, s), 2.24 (3 H, s), 1.65 (6 H, s). LC-MS retention time: 1.69 min; *m/z* (MH⁺) : 555. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, *R*_t = 12.09 min, purity = 100%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, *R*_t = 11.18 min, purity = 99%.



2-(4-Fluorophenyl)-N-methyl-5-(3-(2-methyl-1-(5-methylisoxazol-3-ylamino)-1-oxopropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00169] DIEA (28 μ L, 0.158 mmol) was added to a stirring solution of 2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzamido)-2-methylpropanoic acid (25 mg, 0.053 mmol), 5-methylisoxazol-3-amine (11 mg, 0.105 mmol) in DMF (527 μ L) at rt. It was allowed to stir for 30 min. NaH (11 mg, 0.263 mmol) was added and the reaction was allowed to stir overnight. The mixture was treated with a drop of MeOH and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (2.8 mg, 9%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.17 - 8.25 (1 H, m), 7.92 - 8.00 (3 H, m), 7.83 - 7.91 (2 H, m), 7.66 - 7.76 (2 H, m), 7.58 (1 H, t, *J*=7.78 Hz), 7.27 (2 H, t, *J*=8.85 Hz), 6.63 (1 H, s), 2.98 (3 H, s), 2.39 (3 H, s), 1.65 (6 H, s). LC-MS retention time: 1.69 min; *m/z* (MH⁺) : 555. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wavelength of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5

mm, R_t = 12.20 min, purity = 95% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 11.30 min, purity = 90%.



5 5-(3-(1-(1,2,4-Triazin-3-ylamino)-2-methyl-1-oxopropan-2-ylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00170] DIEA (28 μ L, 0.158 mmol) was added to a stirring solution of 2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzamido)-2-methylpropanoic acid (25 mg, 0.053 mmol), 1,2,4-triazin-3-amine (11 mg, 0.105 mmol) in DMF (527 μ L) at rt. It was allowed to stir for 30 min. NaH (11 mg, 0.263 mmol) was added and the reaction was allowed to stir overnight. The mixture was treated with a drop of MeOH and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H_2O/CH_3CN gradient, and concentrated to give the titled compound (7.4 mg, 25%). 1H NMR (500 MHz, CD_3OD) δ ppm 8.58 - 8.63 (1 H, m), 8.22 - 8.26 (1 H, m), 7.93 - 8.00 (3 H, m), 7.85 - 7.93 (2 H, m), 7.66 - 7.75 (2 H, m), 7.59 (1 H, t, $J=7.63$ Hz), 7.27 (2 H, t, $J=8.85$ Hz), 2.98 (3 H, s), 1.72 (6 H, s). LC-MS retention time: 1.56 min; m/z (MH^+): 553. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm.

20 The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for

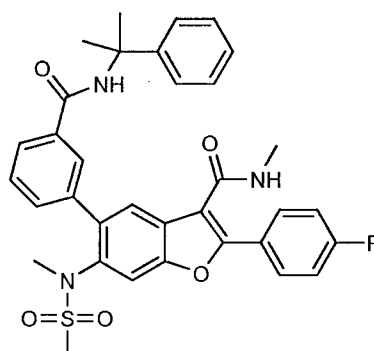
25 LC in electrospray mode. Additional HPLC method: Solvent A = 5% $CH_3CN/95\%$

H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min.

Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 9.65 min, purity = 97% ;

Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 9.58 min,

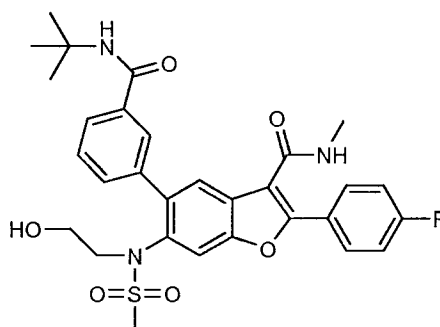
5 purity = 97%.



2-(4-Fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

- 10 [00171] Oxalyl chloride (22 μ L, 0.250 mmol) was added to a stirring solution of 2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxylic acid (50 mg, 0.083 mmol) in DCE (832 μ L) at rt. DMF (3 μ L, 0.042 mmol) was added. The mixture was allowed to stir for 30 min, concentrated and diluted with THF. DIEA (59 μ L, 0.333 mmol) and
- 15 methanamine (208 μ L, 0.416 mmol, 2M in THF) was added. It was allowed to stir overnight. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (11 mg,
- 20 20%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.46 - 8.56 (1 H, m), 8.36 (1 H, s), 7.97 - 8.05 (3 H, m), 7.94 (1 H, s), 7.86 (1 H, d, *J*=7.78 Hz), 7.59 - 7.67 (2 H, m), 7.53 (1 H, t, *J*=7.65 Hz), 7.35 - 7.42 (4 H, m), 7.29 (2 H, t, *J*=7.78 Hz), 7.17 (1 H, t, *J*=7.28 Hz), 3.06 (3 H, s), 3.01 (3 H, s), 2.82 (3 H, d, *J*=4.52 Hz), 1.69 (6 H, s). LC-MS retention time: 1.51 min; *m/z* (MH⁺) : 614. LC data was recorded on a Shimadzu
- 25 LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm.

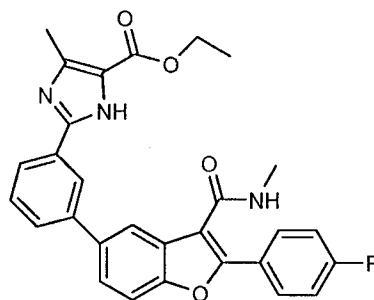
The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 12.89 min, purity = 92% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 12.11 min, purity = 91%.



5-(3-(*tert*-Butylcarbamoyl)phenyl)-2-(4-fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide
[00172] *tert*-Butylamine (21 μ L, 0.195 mmol) was added to a stirring solution of HATU (45 mg, 0.117 mmol), DIEA (41 μ L, 0.234 mmol), and 3-(6-(N-(2-(*tert*-butyldimethylsilyloxy)ethyl)methylsulfonamido)-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (50 mg, 0.078 mmol) in DMF (780 μ L) at rt. It was allowed to stir for 1 hour. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (11 mg, 23%). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.04 (1 H, br. s.), 7.94 - 8.02 (2 H, m), 7.77 - 7.86 (2 H, m), 7.66 - 7.73 (2 H, m), 7.49 - 7.59 (2 H, m), 7.24 - 7.34 (2 H, m), 3.56 - 3.66 (1 H, m), 3.35 - 3.43 (2 H, m), 3.27 (3 H, s),

2.94 (3 H, s), 2.78 - 2.87 (1 H, m), 1.47 (9 H, s). LC-MS retention time: 1.57 min; m/z (MH⁺): 582. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 10.88 min, purity = 97% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 10.27 min, purity = 96 %.

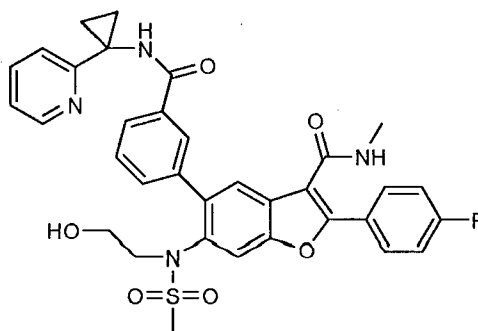


Ethyl 2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)phenyl)-4-methyl-1H-imidazole-5-carboxylate

[00173] Cesium carbonate (234 mg, 0.719 mmol) was added to Pd(Ph₃P)₄ (27.7 mg, 0.024 mmol), 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (200 mg, 0.479 mmol), ethyl 4-methyl-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazole-5-carboxylate (171 mg, 0.479 mmol). Dioxane (4 mL) and water (800 µL) was added at rt. The reaction was heated to 90 °C overnight. The mixture was diluted with ethyl acetate and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and was purified on silica gel (BIOTAGE®, EtOAc/hexanes gradient, fraction collection at λ = 254 nm) to give the titled compound (6.8 mg, 3%).

¹H NMR (500 MHz, DMSO-d₆) δ ppm 13.16 (0.34 H, s), 12.96 (0.66 H, s), 8.54 (1 H, q, *J*=4.48 Hz), 8.50 (0.32 H, s), 8.24 (0.68 H, s), 8.10 (0.31 H, d, *J*=7.93 Hz), 7.97 - 8.04 (2 H, m), 7.89 - 7.97 (2 H, m), 7.79 - 7.84 (1.35 H, m), 7.70 - 7.79 (2 H, m), 7.54 - 7.63 (1 H, m), 7.37 - 7.44 (2 H, m), 4.33 (0.65 H, q, *J*=7.22 Hz), 4.25 (1.42 H, q, *J*=7.22 Hz), 2.87 (3 H, d, *J*=4.88 Hz), 2.55 (2 H, s), 2.45 (1 H, s), 1.34 (1 H, t, *J*=7.02 Hz), 1.31 (2 H, t, *J*=7.17 Hz). LC-MS retention time: 1.46 min; *m/z* (MH⁺): 498. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, *R*_t = 9.90 min, purity = 99%.

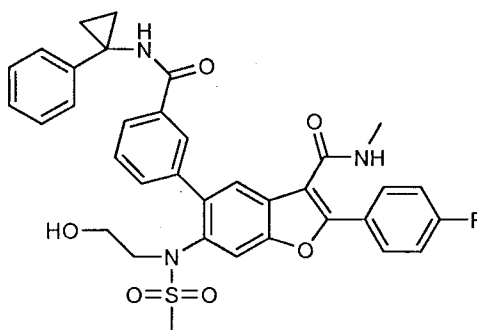


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2-(4-Fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methyl-5-(3-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

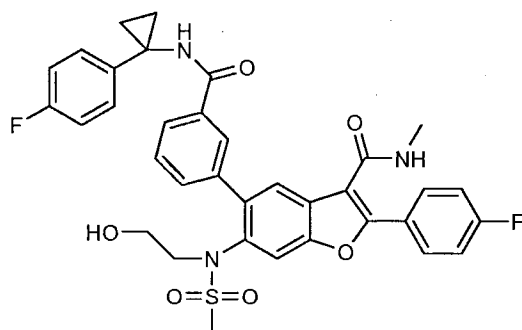
[00174] 1-(Pyridin-2-yl)cyclopropanamine dihydrochloride (24 mg, 0.114 mmol) was added to a stirring solution of HATU (54 mg, 0.142 mmol), DIEA (50 μL, 0.285 mmol), and 3-(2-(4-fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (50 mg, 0.095 mmol) in DMF (950

μL) at rt. It was allowed to stir for 1 hour. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (20 mg, 32%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.20 (1 H, s), 8.49 - 8.57 (1 H, m), 8.45 (1 H, d, *J*=3.97 Hz), 7.97 - 8.05 (3 H, m), 7.96 (1 H, s), 7.94 (1 H, d, *J*=7.93 Hz), 7.80 (1 H, d, *J*=7.93 Hz), 7.64 - 7.69 (1 H, m), 7.63 (1 H, s), 7.56 (1 H, t, *J*=7.63 Hz), 7.37 - 7.47 (3 H, m), 7.15 (1 H, dd, *J*=6.41, 4.88 Hz), 4.91 (1 H, br. s.), 3.51 - 3.60 (1 H, m), 3.22 (3 H, s), 2.89 - 2.98 (3 H, m), 2.81 (3 H, d), 1.50 - 1.60 (2 H, m), 1.23 - 1.33 (2 H, m). LC-MS retention time: 1.37 min; *m/z* (MH⁺): 643. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, *R*_t = 7.17 min, purity = 98%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, *R*_t = 7.89 min, purity = 99%.



2-(4-Fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methyl-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

- [00175] 1-Phenylcyclopropanamine hydrochloride (16 mg, 0.091 mmol) was added to a stirring solution of HATU (43 mg, 0.114 mmol), DIEA (40 μ L, 0.228 mmol), and 3-(2-(4-fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (40 mg, 0.076 mmol) in DMF (760 μ L) at rt. It was allowed to stir for 1 hour. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (22 mg, 44%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.12 (1 H, s), 8.49 - 8.56 (1 H, m), 7.97 - 8.05 (3 H, m), 7.95 (1 H, s), 7.90 (1 H, d, *J*=7.93 Hz), 7.78 (1 H, d, *J*=7.93 Hz), 7.62 (1 H, s), 7.54 (1 H, t, *J*=7.78 Hz), 7.37 - 7.46 (2 H, m), 7.28 (2 H, t, *J*=7.63 Hz), 7.19 - 7.24 (2 H, m), 7.15 (1 H, t, *J*=7.32 Hz), 4.90 (1 H, t, *J*=5.19 Hz), 3.50 - 3.58 (1 H, m), 3.25 - 3.28 (1 H, m), 3.21 (3 H, s), 2.88 - 2.96 (2 H, m), 2.82 (3 H, d, *J*=4.58 Hz), 1.22 - 1.32 (4 H, m). LC-MS retention time: 1.57 min; *m/z* (MH⁺): 642. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, *R*_t = 11.28 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, *R*_t = 10.86 min, purity = 98%.



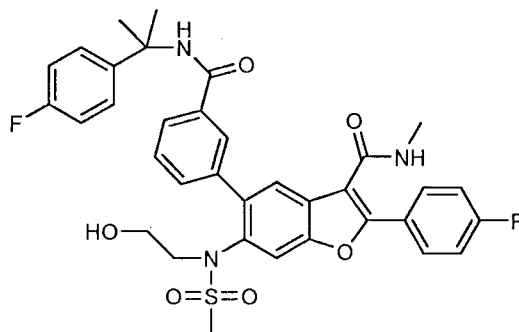
2-(4-Fluorophenyl)-5-(3-(1-(4-fluorophenyl)cyclopropylcarbamoyl)phenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide

[00176] 1-(4-Fluorophenyl)cyclopropanamine hydrochloride (22 mg, 0.114 mmol)

- 5 was added to a stirring solution of HATU (54 mg, 0.142 mmol), DIEA (50 μ L, 0.285 mmol), and 3-(2-(4-fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (50 mg, 0.095 mmol) in DMF (950 μ L) at rt. It was allowed to stir for 1 hour. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄,
- 10 filtered and concentrated and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (30 mg, 47%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.14 (1 H, s), 8.49 - 8.55 (1 H, m), 7.99 - 8.04 (2 H, m), 7.97 - 7.98 (1 H, m), 7.95 (1 H, s), 7.88 (1 H, d, *J*=8.24 Hz), 7.78 (1 H, d, *J*=7.93 Hz), 7.61 (1 H, s), 7.53 (1 H, t, *J*=7.78 Hz),
- 15 7.39 - 7.45 (2 H, m), 7.22 - 7.32 (2 H, m), 7.05 - 7.13 (2 H, m), 4.90 (1 H, t, *J*=5.04 Hz), 3.50 - 3.58 (1 H, m), 3.24 - 3.28 (1 H, m), 3.20 (3 H, s), 2.93 (2 H, br. s.), 2.81 (3 H, d, *J*=4.58 Hz), 1.25 (4 H, d, *J*=9.77 Hz). LC-MS retention time: 1.60 min; *m/z* (MH⁺): 660. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-
- 20 Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data
- 25 was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B

= 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 11.49 min, purity = 99% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 11.04 min, purity = 99%.

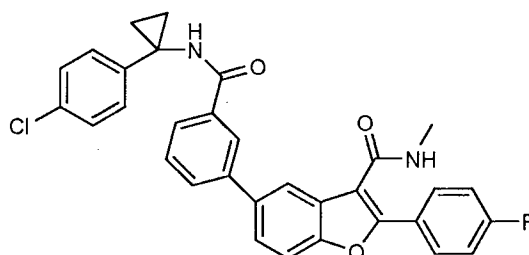
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2-(4-Fluorophenyl)-5-(3-(2-(4-fluorophenyl)propan-2-ylcarbamoyl)phenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide

[00177] 2-(4-Fluorophenyl)propan-2-amine (18 mg, 0.114 mmol) was added to a stirring solution of HATU (54 mg, 0.142 mmol), DIEA (50 μ L, 0.285 mmol), and 2-(4-fluorophenyl)propan-2-amine (18 mg, 0.114 mmol) in DMF (950 μ L) at rt. It was allowed to stir for 1 hour. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (18 mg, 28%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.50 - 8.56 (1 H, m), 8.31 (1 H, s), 7.98 - 8.05 (3 H, m), 7.96 (1 H, s), 7.83 (1 H, d, *J*=7.63 Hz), 7.73 (1 H, d, *J*=7.63 Hz), 7.62 (1 H, s), 7.53 (1 H, t, *J*=7.78 Hz), 7.38 - 7.47 (4 H, m), 7.09 (2 H, t, *J*=8.85 Hz), 4.90 (1 H, t, *J*=5.19 Hz), 3.50 - 3.58 (1 H, m), 3.26 - 3.29 (1 H, m), 3.23 (3 H, s), 2.87 - 2.93 (2 H, m), 2.82 (3 H, d, *J*=4.58 Hz), 1.67 (6 H, s). LC-MS retention time: 1.66 min; *m/z* (MH⁺): 662. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile /

95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 12.11 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 11.48 min, purity = 100%.



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5-(3-(1-(4-Chlorophenyl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00178] 1-(4-Chlorophenyl)cyclopropanamine hydrochloride (25 mg, 0.123 mmol) was added to a stirring solution of HATU (59 mg, 0.154 mmol), DIEA (54 μ L, 0.308 mmol), and 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (40 mg, 0.103 mmol) in DMF (1 mL) at rt. It was allowed to stir for 1 hour. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (8 mg, 14%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.37 (1 H, s), 8.46 - 8.55 (1 H, m), 8.22 (1 H, s), 7.95 - 8.05 (2 H, m), 7.86 - 7.95 (3 H, m), 7.74 - 7.83 (2 H, m), 7.59 (1 H, t, *J*=7.63 Hz), 7.38 - 7.44 (2 H, m), 7.30 - 7.36 (2 H, m), 7.20 - 7.28 (2 H, m), 2.86 (3 H, d, *J*=4.58 Hz), 1.26 - 1.36 (4 H, m). LC-MS retention time: 1.92 min; *m/z* (MH⁺): 539. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A /

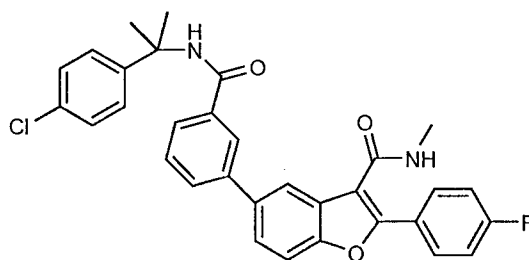
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100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

- 5 Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 14.56 min, purity = 99%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 13.20 min, purity = 97%.

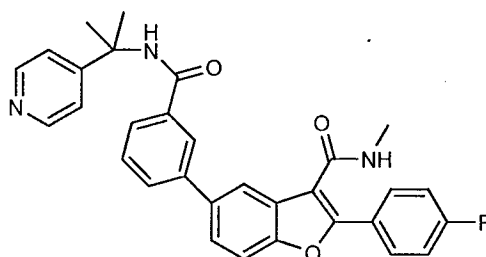
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5-(3-(2-(4-Chlorophenyl)propan-2-ylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00179] 2-(4-Chlorophenyl)propan-2-amine (21 mg, 0.123 mmol) was added to a stirring solution of HATU (59 mg, 0.154 mmol), DIEA (54 μ L, 0.308 mmol), and 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (40 mg, 0.103 mmol) in DMF (1 mL) at rt. It was allowed to stir for 1 hour. The mixture was diluted with EtOAc and washed with sat NaHCO₃, and sat NaCl. The organic phase was dried over Na₂SO₄, filtered and concentrated and was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (32 mg, 57%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.64 (1 H, s), 8.47 - 8.55 (1 H, m), 8.14 (1 H, s), 7.99 - 8.04 (2 H, m), 7.92 (1 H, s), 7.74 - 7.89 (4 H, m), 7.57 (1 H, t, *J*=7.78 Hz), 7.37 - 7.45 (4 H, m), 7.34 (2 H, d, *J*=8.85 Hz), 2.87 (3 H, d, *J*=4.58 Hz), 1.69 (6 H, s). LC-MS retention time: 1.95 min; *m/z* (MH⁺): 541. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent A / 0%

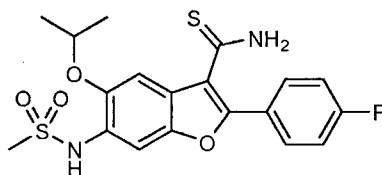
solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 15.18 min, purity = 99% ; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t = 13.66 min, purity = 99%.



2-(4-Fluorophenyl)-N-methyl-5-(3-(2-(pyridin-4-yl)propan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00180] 2-(Pyridin-4-yl)propan-2-amine dihydrochloride (26 mg, 0.123 mmol) was added to a stirring solution of HATU (59 mg, 0.154 mmol), DIEA (54 μ L, 0.308 mmol), and 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (40 mg, 0.103 mmol) in DMF (1 mL) at rt. It was allowed to stir for 1 hour. The reaction was purified by preparative reverse phase HPLC on a C18 column using a suitably buffered H₂O/CH₃CN gradient, and concentrated to give the titled compound (15 mg, 27%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.73 (1 H, s), 8.50 - 8.55 (1 H, m), 8.48 (2 H, dd, *J*=4.58, 1.53 Hz), 8.16 (1 H, s), 7.97 - 8.04 (2 H, m), 7.91 - 7.94 (1 H, m), 7.88 (1 H, d, *J*=7.63 Hz), 7.85 (1 H, d, *J*=7.93 Hz), 7.75 - 7.82 (2 H, m), 7.58 (1 H, t, *J*=7.63 Hz), 7.36 - 7.43 (4 H, m), 2.86 (3 H, d, *J*=4.58 Hz), 1.68 (6 H, s). LC-MS retention time: 1.59 min; *m/z* (MH⁺): 508. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters XBridge 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nm. The elution conditions employed a flow rate of 5 ml/min, a gradient of 100% solvent

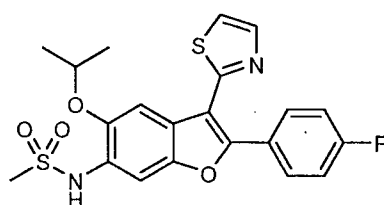
- A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% acetonitrile / 95% H₂O / 10 mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS®
- 5 Platform for LC in electrospray mode. Additional HPLC method: Solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, Solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 mm, R_t = 8.60 min, purity = 95%; Column: Waters XBridge phenyl column 4.6 x 150 mm, 3.5 mm, R_t =
- 10 9.26 min, purity = 96%.



2-(4-Fluorophenyl)-5-isopropoxy-6-(methylsulfonamido)benzofuran-3-carbothioamide

- 15 **[00181]** The reaction was run in two batches and combined for workup. In the first batch, Lawesson's reagent (27 mg, 0.067 mmol) was added to a solution of 2-(4-fluorophenyl)-5-isopropoxy-6-(methylsulfonamido)benzofuran-3-carboxamide (35 mg, 0.086 mmol) in THF (1.2 mL). The reaction was stirred at r.t. for 2 h, at which point additional Lawesson's reagent (8 mg, 0.020 mmol) was added. In the second
- 20 batch, Lawesson's reagent (129 mg, 0.32 mmol) was added to a solution of 2-(4-fluorophenyl)-5-isopropoxy-6-(methylsulfonamido)benzofuran-3-carboxamide (125 mg, 0.31 mmol) in THF (3 mL) was stirred at r.t. for 1.5 h. The two batches were then combined and partitioned between EtOAc (50 mL) and water (10 mL). The organic phase was washed with sat'd NaHCO₃ and brine, dried over Na₂SO₄, filtered, and
- 25 concentrated to give a yellow oil. The residue was purified by silica gel chromatography (BIOTAGE® 25+S silica gel cartridge, gradient elution: 20% to 80% EtOAc/hexanes over 20 column volumes, fraction collection at λ = 320 nm) to give 48 mg (29% yield) of the title compound. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.76 - 7.87 (m, 2 H) 7.71 (d, *J* = 5.86 Hz, 2 H) 7.53 (br. s., 1 H) 7.13 - 7.23 (m, 2 H)

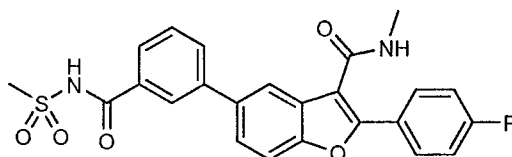
6.97 (s, 1 H) 6.90 (br. s., 1 H) 4.74 (dt, $J = 12.08, 6.04$ Hz, 1 H) 2.93 (s, 3 H) 1.40 (d, $J = 6.22$ Hz, 6 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 5% CH₃CN/95% H₂O/0.1% NH₄OAc, solvent B = 95% CH₃CN/5%H₂O/0.1% NH₄OAc, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 5 ml/min, column: XBridge C18 5 μ m 4.6 x 50 mm; HPLC $R_t = 1.39$ min, (ES+) m/z (MH⁺) = 423.



10 N-(2-(4-Fluorophenyl)-5-isopropoxy-3-(thiazol-2-yl)benzofuran-6-yl)methanesulfonamide

[00182] Chloroacetaldehyde (50% solution in water, 100 μ L, 0.79 mmol) was added to a stirred suspension of the intermediate 2-(4-fluorophenyl)-5-isopropoxy-6-(methanesulfonamido)benzofuran-3-carbothioamide (48 mg, 0.11 mmol) in ethanol (1.5 mL), and the reaction was brought to reflux (100 °C oil bath temp). After 4 h, additional chloroacetaldehyde solution (200 μ L, 1.6 mmol) was added and heating was continued overnight. The reaction was cooled to r.t., diluted with EtOAc (75 mL), washed with water (10 mL), sat'd NaHCO₃ (2 x 5 mL), and brine, dried over Na₂SO₄, filtered, and concentrated to give a brown oil. The residue was purified on silica gel (BIOTAGE® 12+M column, gradient elution 10% to 40% EtOAc/hexanes over 20 column volumes, fraction collection at $\lambda = 320$ nm) to give a colorless oil, 38 mg (75% yield). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.96 (d, $J = 3.29$ Hz, 1 H) 7.73 - 7.86 (m, 3 H) 7.56 (s, 1 H) 7.37 (d, $J = 3.29$ Hz, 1 H) 7.07 - 7.19 (m, 2 H) 6.98 (s, 1 H) 4.73 (spt, $J = 6.04$ Hz, 1 H) 2.96 (s, 3 H) 1.40 (d, $J = 5.86$ Hz, 7 H). An analytically pure sample was obtained by precipitation from Et₂O/hexanes to give a yellow ppt., which was triturated with Et₂O and air dried. LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 5% CH₃CN/95% H₂O/0.1% NH₄OAc, solvent B = 95% CH₃CN/5%H₂O/0.1% NH₄OAc, start %B = 0, final %B = 100,

gradient time = 2 min, stop time = 3 min, flow rate = 5 ml/min, column: XBridge C18 5 μ m 4.6 x 50 mm; HPLC R_t = 1.69 min, (ES+) m/z (MH^+) = 447. Analytical HPLC were performed using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: solvent A = 5% CH_3CN /95% H_2O /0.1% TFA, solvent B = 95% CH_3CN /5% H_2O /0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 μ m, R_t = 14.74 min, purity = 97%; column: Waters XBridge phenyl 4.6 x 150 mm, 3.5 μ m, R_t = 12.86 min, purity = 98%.



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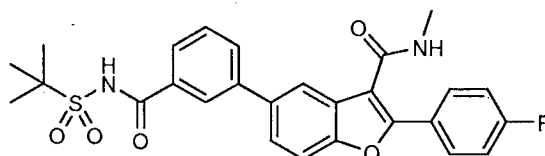
2-(4-Fluorophenyl)-N-methyl-5-(3-(methylsulfonylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00183] In a 1 dram vial with stir bar were combined 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (35 mg, 0.090 mmol), DMAP (33 mg, 0.27 mmol), EDC hydrochloride (26 mg, 0.14 mmol), and methanesulfonamide (25 mg, 0.26 mmol). DMF (0.5 mL) was added, the vial was capped, and the reaction was stirred at r.t. overnight. The reaction was filtered, purified by prep HPLC, and concentrated to give 30 mg (72% yield) of the title compound as a white powder. 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 12.36 (br. s., 1 H) 8.53 (d, J = 4.58 Hz, 1 H) 8.27 (s, 1 H) 7.97 - 8.05 (m, 2 H) 7.84 - 7.96 (m, 3 H) 7.77 - 7.82 (m, 1 H) 7.71 - 7.76 (m, 1 H) 7.56 (t, J = 7.78 Hz, 1 H) 7.40 (t, J = 8.85 Hz, 2 H) 3.17 (s, 3 H) 2.86 (d, J = 4.58 Hz, 3 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH_3CN /90% H_2O /0.1% TFA, solvent B = 90% CH_3CN /10% H_2O /0.1% TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μ m 4.6 x 50 mm; HPLC R_t = 1.56 min, (ES+) m/z (MH^+) = 467. Analytical HPLC were performed using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: solvent A = 5% CH_3OH /95% H_2O /10 mM NH_4HCO_3 , solvent B = 95% CH_3OH /5% H_2O /10 mM

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NH₄HCO₃, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: PHENOMENEX® Gemini C18, 4.6 mm, 3 μm, R_t = 11.93 min, purity = 100%; column: Waters XBridge phenyl 4.6 x 150 mm, 3.5 μm, R_t = 13.97 min, purity = 99%.

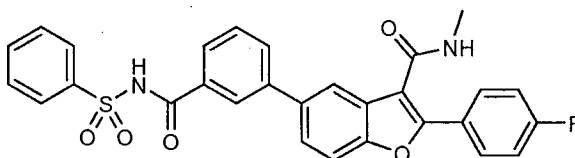
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5-(3-(*tert*-Butylsulfonylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

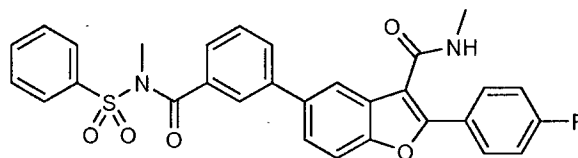
- [00184] In a 1 dram vial with stir bar were combined 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (35 mg, 0.090 mmol), DMAP (33 mg, 0.27 mmol), EDC hydrochloride (26 mg, 0.14 mmol), and *tert*-butylsulfonamide (37 mg, 0.27 mmol). 1,2-Dichloroethane (1 mL) and DMF (0.3 mL) were added, the vial was capped, and the reaction was stirred at r.t. overnight. The reaction was concentrated, filtered, purified by prep HPLC, and concentrated on a SPEEDVAC® to give 14 mg (31% yield) of the title compound as a white powder. ¹H NMR (500 MHz, CDCl₃) δ ppm 8.12 (s, 1 H) 7.97 (s, 1 H) 7.91 (dd, *J* = 8.55, 5.19 Hz, 2 H) 7.84 (d, *J* = 7.63 Hz, 1 H) 7.79 (d, *J* = 7.32 Hz, 1 H) 7.46 - 7.59 (m, 3 H) 7.19 (t, *J* = 8.55 Hz, 2 H) 6.04 (br. s., 1 H) 2.99 (d, *J* = 4.58 Hz, 3 H) 1.54 (s, 9 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH₃CN/90% H₂O/0.1% TFA, solvent B = 90% CH₃CN/10% H₂O/0.1% TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μm 4.6 x 50 mm; HPLC R_t = 1.71 min, (ES+) *m/z* (MH⁺) = 509. Analytical HPLC were performed using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: solvent A = 5% CH₃OH/95% H₂O/10 mM NH₄HCO₃, solvent B = 95% CH₃OH/5% H₂O/10 mM NH₄HCO₃, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: PHENOMENEX® Gemini C18, 4.6 mm, 3 μm, R_t = 16.49 min, purity =

100%; column: Waters XBridge phenyl 4.6 x 150 mm, 3.5 μ m, R_t = 15.35 min, purity = 100%.



5 2-(4-Fluorophenyl)-N-methyl-5-(3-(phenylsulfonylcarbamoyl)phenyl)benzofuran-3-carboxamide

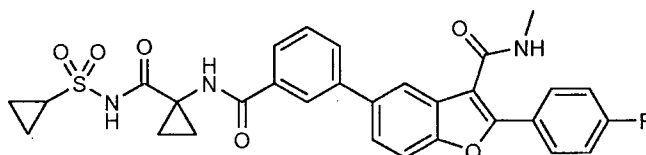
[00185] In a 1 dram vial with stir bar were combined 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (35 mg, 0.090 mmol), DMAP (33 mg, 0.27 mmol), EDC hydrochloride (26 mg, 0.14 mmol), and benzenesulfonamide (43 mg, 0.27 mmol). 1,2-Dichloroethane (1 mL) and DMF (0.3 mL) were added, the vial was capped, and the suspension was stirred at r.t. overnight, over which time the solids dissolved. The reaction was concentrated, filtered, purified by prep HPLC, and concentrated to give 32 mg (67% yield) of the title compound as a white powder. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 12.78 (br. s., 1 H) 8.52 (q, J = 4.48 Hz, 1 H) 8.24 (s, 1 H) 7.97 - 8.06 (m, 4 H) 7.90 - 7.97 (m, 2 H) 7.85 (d, J = 7.94 Hz, 1 H) 7.74 - 7.81 (m, 2 H) 7.66 - 7.73 (m, 1 H) 7.63 (t, J = 7.63 Hz, 2 H) 7.58 (t, J = 7.63 Hz, 1 H) 7.40 (t, J = 8.85 Hz, 2 H) 2.87 (d, J = 4.58 Hz, 3 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH₃CN/90% H₂O/0.1% TFA, solvent B = 90% CH₃CN/10%H₂O/0.1% TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μ m 4.6 x 50 mm; HPLC R_t = 1.77 min, (ES+) m/z (MH^+) = 529. Analytical HPLC were performed using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: solvent A = 5% CH₃OH/95% H₂O/10 mM NH₄HCO₃, solvent B = 95% CH₃OH/5% H₂O/10 mM NH₄HCO₃, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: PHENOMENEX® Gemini C18, 4.6 mm, 3 μ m, R_t = 15.70 min, purity = 100%; column: Waters XBridge phenyl 4.6 x 150 mm, 3.5 μ m, R_t = 14.90 min, purity = 99%.



2-(4-Fluorophenyl)-N-methyl-5-(3-

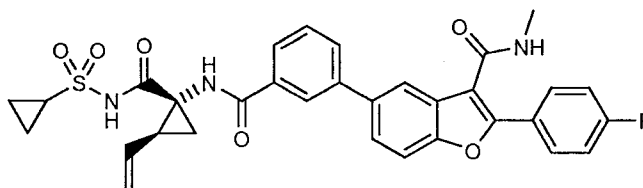
(methyl(phenylsulfonyl)carbamoyl)phenyl)benzofuran-3-carboxamide

- 5 [00186] In a 1 dram vial with stir bar were combined 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (35 mg, 0.090 mmol), DMAP (33 mg, 0.27 mmol), EDC hydrochloride (26 mg, 0.14 mmol), and *N*-methylbenzenesulfonamide (50 μ L, 0.26 mmol). 1,2-Dichloroethane (0.5 mL) and DMF (0.5 mL) were added, the vial was capped, and the reaction was stirred at r.t.
- 10 overnight. The reaction was filtered, purified by prep HPLC, and concentrated on a SPEEDVAC® to give 27 mg (55% yield) of the title compound as a white powder.
- ^1H NMR (500 MHz, CDCl_3) δ ppm 7.91 - 8.02 (m, 5 H) 7.75 - 7.82 (m, 2 H) 7.65 (t, J = 7.48 Hz, 1 H) 7.47 - 7.60 (m, 6 H) 7.15 - 7.24 (m, 2 H) 5.91 (d, J = 4.27 Hz, 1 H) 3.36 (s, 3 H) 3.04 (d, J = 4.88 Hz, 3 H). LC/MS was performed by using Shimadzu-
- 15 VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% $\text{CH}_3\text{CN}/90\%$ $\text{H}_2\text{O}/0.1\%$ TFA, Solvent B = 90% $\text{CH}_3\text{CN}/10\%$ $\text{H}_2\text{O}/0.1\%$ TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μm 4.6 x 50 mm; HPLC R_t = 1.89 min, (ES+) m/z (MH^+) = 543. Analytical HPLC were performed
- 20 using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: solvent A = 5% $\text{CH}_3\text{OH}/95\%$ $\text{H}_2\text{O}/10$ mM NH_4HCO_3 , solvent B = 95% $\text{CH}_3\text{OH}/5\%$ $\text{H}_2\text{O}/10$ mM NH_4HCO_3 , start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: PHENOMENEX® Gemini C18, 4.6 mm, 3 μm , R_t = 17.42 min, purity = 92%;
- 25 column: Waters XBridge phenyl 4.6 x 150 mm, 3.5 μm , R_t = 17.86 min, purity >90%.



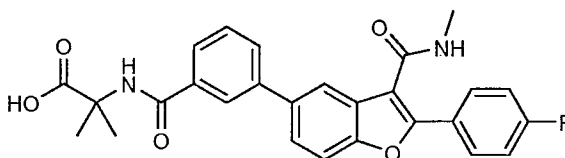
5-(3-(1-(Cyclopropylsulfonylcarbamoyl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00187] In a 7 mL scintillation vial were combined 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (30 mg, 0.077 mmol), 1-amino-*N*-(cyclopropylsulfonyl)cyclopropanecarboxamide hydrochloride (20 mg, 0.083 mmol), and HATU (40 mg, 0.10 mmol). DMF (0.4 mL) and DIPEA (0.1 mL, 0.57 mmol) were added, the vial was capped, and the solution was stirred at r.t. for 45 min. The reaction was diluted with MeOH, filtered, purified by prep HPLC, and the collected fractions were concentrated on a SPEEDVAC® to afford the title compound (23 mg, 52% yield) as a white powder. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.99 (br. s., 1 H) 8.53 (q, *J* = 4.78 Hz, 1 H) 8.25 (br. s., 1 H) 8.00 (dd, *J* = 8.85, 5.49 Hz, 2 H) 7.93 (s, 1 H) 7.89 (t, *J* = 7.78 Hz, 2 H) 7.72 - 7.83 (m, 2 H) 7.58 (t, *J* = 7.48 Hz, 1 H) 7.40 (t, *J* = 8.85 Hz, 2 H) 7.07 (br. s., 1 H) 2.89 - 2.98 (m, 1 H) 2.87 (d, *J* = 4.58 Hz, 3 H) 1.35 - 1.56 (m, 2 H) 0.77 - 1.28 (m, 6 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH₃CN/90% H₂O/0.1% TFA, solvent B = 90% CH₃CN/10%H₂O/0.1% TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μm 4.6 x 50 mm; HPLC *R*_t = 1.59 min, (ES+) *m/z* (MH⁺) = 576. Analytical HPLC were performed using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: solvent A = 5% CH₃OH/95% H₂O/10 mM NH₄HCO₃, solvent B = 95% CH₃OH/5% H₂O/10 mM NH₄HCO₃, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: PHENOMENEX® Gemini C18, 4.6 mm, 3 μm, *R*_t = 15.39 min, purity = 100%; column: Waters XBridge phenyl 4.6 x 150 mm, 3.5 μm, *R*_t = 14.50 min, purity = 100%.



5-(3-((1R,2S)-1-(Cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

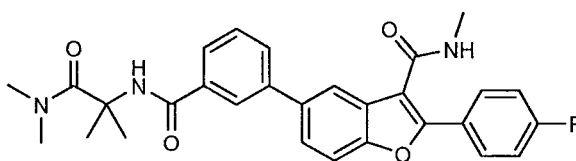
- [00188] In a 7 mL scintillation vial were combined 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (30 mg, 0.077 mmol), (1R,2S)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide 4-methylbenzenesulfonate (30 mg, 0.075 mmol), and HATU (40 mg, 0.10 mmol). DMF (0.4 mL) and DIPEA (0.1 mL, 0.57 mmol) were added, the vial was capped, and the solution was stirred at r.t. for 45 min. The reaction was diluted with MeOH, filtered, purified by prep HPLC, and the collected fractions were concentrated on a SPEEDVAC® to afford the title compound (25 mg, 54% yield) as a white powder. ¹H NMR (500 MHz, CDCl₃) δ ppm 8.01 (s, 1 H) 7.97 (s, 1 H) 7.88 (dd, *J* = 8.85, 5.19 Hz, 2 H) 7.80 (d, *J* = 7.63 Hz, 1 H) 7.74 (d, *J* = 7.63 Hz, 1 H) 7.59 (br. s., 1 H) 7.52 (s, 2 H) 7.48 (t, *J* = 7.63 Hz, 1 H) 7.18 (t, *J* = 8.55 Hz, 2 H) 6.00 (d, *J* = 3.97 Hz, 1 H) 5.61 - 5.73 (m, 1 H) 5.39 (d, *J* = 17.09 Hz, 1 H) 5.20 (d, *J* = 10.99 Hz, 1 H) 3.02 (d, *J* = 4.88 Hz, 3 H) 2.91 - 2.99 (m, 1 H) 2.34 (q, *J* = 8.44 Hz, 1 H) 2.05 - 2.09 (m, 1 H) 1.49 (dd, *J* = 9.31, 5.95 Hz, 1 H) 1.41 (dd, *J* = 5.80, 4.58 Hz, 1 H) 1.30 - 1.35 (m, 1 H) 1.22 - 1.30 (m, 1 H) 1.04 - 1.12 (m, 1 H) 0.96 - 1.04 (m, 1 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH₃CN/90% H₂O/0.1% TFA, solvent B = 90% CH₃CN/10%H₂O/0.1% TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μm 4.6 x 50 mm; HPLC *R*_t = 1.73 min, (ES⁺) *m/z* (MH⁺) = 602. Analytical HPLC were performed using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: solvent A = 5% CH₃OH/95% H₂O/10 mM NH₄HCO₃, solvent B = 95% CH₃OH/5% H₂O/10 mM NH₄HCO₃, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: PHENOMENEX® Gemini C18, 4.6 mm, 3 μm, *R*_t = 16.26 min, purity = 100%; column: Waters XBridge phenyl 4.6 x 150 mm, 3.5 μm, *R*_t = 15.28 min, purity = 100%.



2-(3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzamido)-2-methylpropanoic acid

- [00189] HATU (450 mg, 1.18 mmol) was added to a suspension of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (400 mg, 1.03 mmol), methyl 2-amino-2-methylpropanoate hydrochloride (180 mg, 1.17 mmol), and DIPEA (0.6 mL, 3.4 mmol) in DCE (10 mL). After 5 min, the solids had not dissolved. Add DMF (0.5 mL) and continue stirring the suspension at r.t. overnight. The reaction was then concentrated to give a thick suspension (DMF remained after concentration). Water and Et₂O were added and the flask swirled until a fine grey suspension was formed. The ppt. was collected by filtration, rinsed with 1 N HCl, water, and ether, and air dried to afford 550 mg (110% yield) of the title compound as a grey solid. LC/MS was performed on a Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 5% CH₃CN/95% H₂O/10 mM NH₄OAc, solvent B = 95% CH₃CN/5% H₂O/10 mM NH₄OAc, start %B = 0, sinl %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 5 ml/min, column: XBridge C18 5 μm 4.6 x 50 mm; HPLC R_t = 1.49 min, (ES⁺) m/z (MH⁺) = 489. To a suspension of the crude ester from above (~0.1 mmol) in MeOH (7 mL)/H₂O (2.1 mL) in a 20 mL scintillation vial with stir bar was added 10 N NaOH soln. (0.4 mL, 4.00 mmol). The vial was capped, stirred at r.t. overnight, then quenched by pouring into 8 mL of 1 N HCl. A white ppt. formed. The suspension was extracted with EtOAc, and the insoluble grey solid was collected by filtration and air dried (61 mg). The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to give a white powder. This was triturated with Et₂O and collected by filtration to give 360 mg of the white powder. Both crops of ppt. were identical by LC/MS and were combined to give 421 mg (86% over two steps) of the title compound as an off-white powder. ¹H NMR (300 MHz, CD₃OD) δ ppm 8.59 (s, 1 H) 8.50 (d, *J* = 3.29 Hz, 1 H) 8.10 - 8.16 (m, 1 H) 7.91 - 8.01 (m, 3 H) 7.83 (dd, *J* = 12.99, 7.87 Hz, 2 H) 7.64 - 7.74 (m, 2 H) 7.56 (t, *J* = 7.68 Hz, 1 H) 7.27

(t, $J = 8.78$ Hz, 2 H) 2.95 - 3.02 (m, 3 H) 1.62 (s, 6 H). LC/MS was performed on a Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 5% CH₃CN/95% H₂O/10 mM NH₄OAc, solvent B = 95% CH₃CN/5% H₂O/10 mM NH₄OAc, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 5 ml/min, column: XBridge C18 5 μ m 4.6 x 50 mm; HPLC R_t = 1.06 min, (ES+) m/z (MH⁺) = 475. Analytical HPLC were performed using a Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters Sunfire C-18, 3.5 μ m 4.6 x 150 mm, R_t = 10.91 min, purity = 98%; column: Waters XBridge phenyl 3.5 μ m 4.6 x 150 mm, R_t = 10.21 min, purity = 98%.

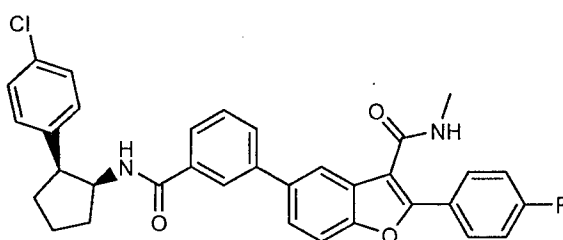


5-(3-(1-(Dimethylamino)-2-methyl-1-oxopropan-2-ylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00190] A solution of dimethylamine in THF (2 molar, 0.10 mL, 0.20 mmol) was added to 2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzamido)-2-methylpropanoic acid (17 mg, 0.036 mmol) and HATU (15 mg, 0.039 mmol) in a 1 dram vial. DMF (0.3 mL) was added, the vial was capped, and the homogeneous solution was stirred at r.t. for 1 h, at which point DIPEA (50 μ L, 0.29 mmol) was added. Stirring was continued for 3 h, at which point the reaction was filtered and purified directly by prep HPLC. Concentration of the collected fractions afforded the title compound as a white solid (13 mg, 71% yield). ¹H NMR (500 MHz, CD₃OD) δ ppm 8.09 - 8.17 (m, 1 H) 7.90 - 7.98 (m, 3 H) 7.86 (d, $J = 7.94$ Hz, 1 H) 7.79 - 7.84 (m, 1 H) 7.63 - 7.72 (m, 2 H) 7.57 (t, $J = 7.63$ Hz, 1 H) 7.20 - 7.32 (m, 2 H) 3.14 (br. s., 3 H) 2.98 (s, 6 H) 1.61 (s, 6 H). LC/MS was performed on a Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 5% CH₃CN/95% H₂O/10 mM NH₄OAc, solvent B = 95%

CH₃CN/5% H₂O/10 mM NH₄OAc, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 5 ml/min, column: XBridge C18 5 μ m 4.6 x 50 mm; HPLC R_t = 1.29 min, (ES+) m/z (MH⁺) = 502. Analytical HPLC method: solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, solvent B = 95% CH₃CN/5%

- 5 H₂O/0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters Sunfire C-18, 3.5 μ m 4.6 x 150 mm, R_t = 14.80 min, purity = 100%; column: Waters XBridge phenyl 3.5 μ m 4.6 x 150 mm, R_t = 10.37 min, purity = 100%.

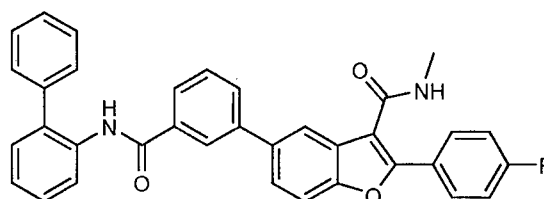


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5-(3-(((Cis)-2-(4-chlorophenyl)cyclopentylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00191] In a 1 dram vial were combined 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (20 mg, 0.051 mmol), *cis*-2-(4-chlorophenyl)cyclopentanamine (14 mg, 0.072 mmol), and HATU (31 mg, 0.082 mmol). DMF (0.4 mL) and DIPEA (50 μ L, 0.29 mmol) were added, and the vial was capped and stirred at r.t. for 2 h, then diluted with MeOH, filtered, and purify directly by prep HPLC. Concentration afforded the title compound (15 mg, 52% yield) as a fluffy white solid. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.47 - 8.59 (m, 1 H) 8.06 (d, *J* = 8.85 Hz, 1 H) 7.97 - 8.03 (m, 2 H) 7.86 (d, *J* = 1.83 Hz, 1 H) 7.75 - 7.82 (m, 2 H) 7.68 (s, 1 H) 7.65 (dd, *J* = 8.55, 1.83 Hz, 1 H) 7.45 - 7.53 (m, 2 H) 7.40 (t, *J* = 8.85 Hz, 2 H) 7.27 (s, 4 H) 4.60 - 4.71 (m, *J* = 7.67, 7.67, 7.55, 7.32 Hz, 1 H) 3.33 - 3.41 (m, 1 H) 2.87 (d, *J* = 4.58 Hz, 3 H) 1.99 - 2.15 (m, 3 H) 1.89 - 1.98 (m, 1 H) 1.72 - 1.82 (m, 1 H) 1.57 - 1.71 (m, 1 H). LC/MS was performed on a Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH₃CN/90% H₂O/0.1% TFA, solvent B = 90% CH₃CN/10% H₂O/0.1% TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μ m 4.6 x 50 mm;

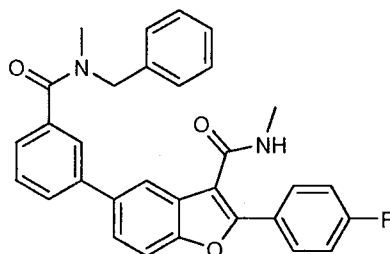
HPLC R_t = 2.02 min, (ES+) m/z (MH^+) = 567. Analytical HPLC method: solvent A = 5% CH_3CN /95% H_2O /0.1% TFA, solvent B = 95% CH_3CN /5% H_2O /0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters Sunfire C-18, 3.5 μm 4.6 x 150 mm, R_t = 15.42 min, purity = 98%; column: Waters XBridge phenyl 3.5 μm 4.6 x 150 mm, R_t = 13.74 min, purity = 97%.



5-(3-(Biphenyl-2-ylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

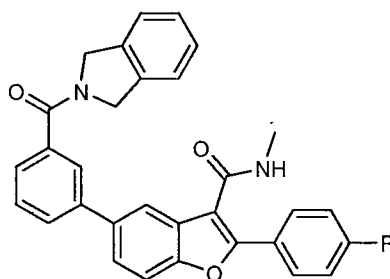
[00192] In a 1 dram vial were combined 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (30 mg, 0.077 mmol), biphenyl-2-amine (17 mg, 0.10 mmol), and HATU (40 mg, 0.105 mmol). DMF (0.4 mL) and DIPEA (50 μL , 0.29 mmol) were added, and the vial was capped and stirred at r.t. for overnight, then diluted with MeOH, filtered, and purified directly by prep HPLC. Concentration afforded the title compound (17 mg, 41% yield) as a fluffy white solid. 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 9.96 (s, 1 H) 8.53 (q, J = 4.58 Hz, 1 H) 7.96 - 8.06 (m, 3 H) 7.85 - 7.91 (m, 2 H) 7.80 (d, J = 8.55 Hz, 1 H) 7.77 (d, J = 7.32 Hz, 1 H) 7.70 (dd, J = 8.55, 1.83 Hz, 1 H) 7.57 - 7.61 (m, 1 H) 7.56 (d, J = 6.10 Hz, 1 H) 7.48 (d, J = 7.32 Hz, 2 H) 7.36 - 7.46 (m, 7 H) 7.31 (t, J = 7.48 Hz, 1 H) 2.87 (d, J = 4.88 Hz, 3 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH_3CN /90% H_2O /0.1% TFA, solvent B = 90% CH_3CN /10% H_2O /0.1% TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μm 4.6 x 50 mm; HPLC R_t = 2.02 min, (ES+) m/z (MH^+) = 541. Analytical HPLC method: solvent A = 5% CH_3CN /95% H_2O /0.1% TFA, solvent B = 95% CH_3CN /5% H_2O /0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters

Sunfire C-18, 3.5 μ m 4.6 x 150 mm, R_t = 15.37 min, purity = 100%; column: Waters XBridge phenyl 3.5 μ m 4.6 x 150 mm, R_t = 13.75 min, purity = 100%.



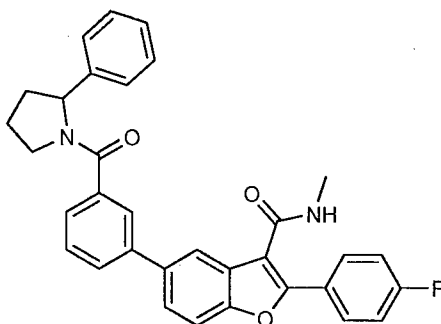
5 5-(3-(Benzyl(methyl)carbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00193] DIPEA (50 μ L, 0.29 mmol) and *N*-methylbenzylamine (20 μ L, 0.16 mmol) were added to a stirred suspension of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (20 mg, 0.051 mmol) and HATU (25 mg, 0.066 mmol) in DMF (0.5 mL) and the reaction was stirred at r.t. overnight. The reaction was then diluted with MeOH, filtered, purified by prep HPLC, and concentrated to give the title compound as a tan powder (12 mg, 47% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.50 (br. s., 1 H) 8.01 (dd, J = 8.39, 5.65 Hz, 2 H) 7.66 - 7.93 (m, 5 H) 7.58 (br. s., 1 H) 7.42 - 7.50 (m, 1 H) 7.35 - 7.42 (m, 4 H) 7.31 (d, J = 5.80 Hz, 1 H) 7.23 (d, J = 4.58 Hz, 1 H) 4.72 (br. s., 1 H) 4.54 (br. s., 1 H) 2.83 - 3.00 (m, 6 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH₃CN/90% H₂O/0.1% TFA, solvent B = 90% CH₃CN/10% H₂O/0.1% TFA, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 4 ml/min, column: Sunfire C18 5 μ m 4.6 x 50 mm; HPLC R_t = 1.85 min, (ES+) m/z (MH⁺) = 493. Analytical HPLC method: solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters Sunfire C-18, 3.5 μ m 4.6 x 150 mm, R_t = 16.26 min, purity = 99%; column: Waters XBridge phenyl 3.5 μ m 4.6 x 150 mm, R_t = 12.81 min, purity = 98%.



2-(4-Fluorophenyl)-5-(3-(isoindoline-2-carbonyl)phenyl)-N-methylbenzofuran-3-carboxamide

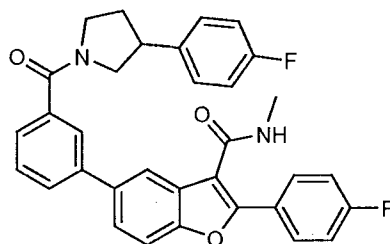
[00194] Isoindoline (20 μ L, 0.18 mmol) was added to a stirred suspension of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (20 mg, 0.051 mmol), HATU (25 mg, 0.066 mmol), and DIPEA (50 μ L, 0.29 mmol) in DMF (0.5 mL). The reaction was stirred at r.t. overnight. The reaction was then diluted with MeOH and an off-white ppt. formed. The ppt. was collected by filtration, triturated with MeOH, and air dried to afford the title compound (17 mg, 68% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.50 (q, J = 4.58 Hz, 1 H) 7.99 - 8.05 (m, 2 H) 7.90 - 7.95 (m, 2 H) 7.85 (dt, J = 6.10, 2.44 Hz, 1 H) 7.77 - 7.81 (m, 1 H) 7.73 - 7.77 (m, 1 H) 7.58 - 7.64 (m, 2 H) 7.36 - 7.45 (m, 3 H) 7.30 - 7.34 (m, 1 H) 7.29 (s, 2 H) 4.91 (s, 2 H) 4.84 (s, 2 H) 2.86 (d, J = 4.88 Hz, 3 H). LC/MS was performed on a Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH₃CN/90% H₂O/0.1% TFA, solvent B = 90% CH₃CN/10% H₂O/0.1% TFA, start %B = 0, final %B = 100, gradient time = 3 min, stop time = 4 min, flow rate = 4 ml/min, column: Sunfire C18 5 μ m 4.6 x 50 mm; HPLC R_t = 2.48 min, (ES+) m/z (MH^+) = 491. Analytical HPLC method: solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters Sunfire C-18, 3.5 μ m 4.6 x 150 mm, R_t = 13.81 min, purity = 100%; column: Waters XBridge phenyl 3.5 μ m 4.6 x 150 mm, R_t = 13.81 min, purity = 100%.



2-(4-Fluorophenyl)-N-methyl-5-(3-(2-phenylpyrrolidine-1-carbonyl)phenyl)benzofuran-3-carboxamide

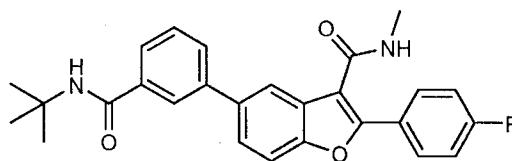
[00195] 2-Phenylpyrrolidine (20 mg, 0.14 mmol) was added to a stirred suspension of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (20 mg, 0.051 mmol), HATU (25 mg, 0.066 mmol), and DIPEA (50 μ L, 0.29 mmol) in DMF (0.5 mL). The reaction was stirred at r.t. overnight. The reaction was then diluted with MeOH, filtered, and purified by prep HPLC. Concentration afforded the title compound (21 mg, 78% yield) as a light pink solid. ^1H NMR (~3:2 ratio of amide rotamers, 500 MHz, DMSO- d_6) δ ppm 8.44 - 8.56 (m, 1 H) 7.96 - 8.07 (m, 2 H) 7.74 - 7.89 (m, 3 H) 7.56 - 7.67 (m, 2 H) 7.30 - 7.45 (m, 5.4 H) 7.16 - 7.29 (m, 2.6 H) 7.09 (d, J = 7.02 Hz, 1 H) 5.19 (t, J = 6.71 Hz, 0.6 H) 4.98 (d, J = 6.41 Hz, 0.4 H) 3.75 - 3.92 (m, 1.4 H) 3.53 - 3.64 (m, 0.6 H) 2.87 (m, 3 H) 2.40 (dd, J = 12.36, 6.56 Hz, 0.6 H) 2.30 - 2.38 (m, 0.4 H) 1.73 - 1.92 (m, 3 H). LC/MS was performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% $\text{CH}_3\text{CN}/90\%$ $\text{H}_2\text{O}/0.1\%$ TFA, solvent B = 90% $\text{CH}_3\text{CN}/10\%$ $\text{H}_2\text{O}/0.1\%$ TFA, start %B = 0, final %B = 100, gradient time = 3 min, stop time = 4 min, flow rate = 4 ml/min, column: Sunfire C18 5 μm 4.6 x 50 mm; HPLC R_t = 1.86 min, (ES+) m/z (MH^+) = 519. Analytical HPLC method: solvent A = 5% $\text{CH}_3\text{CN}/95\%$ $\text{H}_2\text{O}/0.1\%$ TFA, solvent B = 95% $\text{CH}_3\text{CN}/5\%$ $\text{H}_2\text{O}/0.1\%$ TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters Sunfire C-18, 3.5 μm 4.6 x 150 mm, R_t = 14.38 min, purity = 99%; column: Waters XBridge phenyl column 3.5 μm 4.6 x 150 mm, R_t = 13.01 min, purity = 99%.

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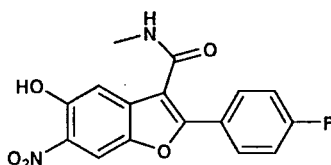
2-(4-Fluorophenyl)-5-(3-(3-(4-fluorophenyl)pyrrolidine-1-carbonyl)phenyl)-N-methylbenzofuran-3-carboxamide

- [00196] 3-(4-Fluorophenyl)pyrrolidine hydrochloride (25 mg, 0.12 mmol) was added to a stirred suspension of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (20 mg, 0.051 mmol), HATU (25 mg, 0.066 mmol), and DIPEA (50 μ L, 0.29 mmol) in DMF (0.5 mL). The reaction was stirred at r.t. overnight, then diluted with MeOH, filtered, and purified by prep HPLC. Concentration afforded the title compound (22 mg, 79% yield) as a pink solid.
- ¹H NMR (~1:1 ratio of amide rotamers, 500 MHz, DMSO-d₆) δ ppm 8.44 - 8.54 (m, 1 H) 7.98 - 8.06 (m, 2 H) 7.66 - 7.91 (m, 5 H) 7.52 - 7.61 (m, 2 H) 7.36 - 7.44 (m, 3 H) 7.33 (dd, J = 8.55, 5.49 Hz, 1 H) 7.18 (t, J = 8.85 Hz, 1 H) 7.12 (t, J = 8.85 Hz, 1 H) 4.01 (dd, J = 11.14, 7.17 Hz, 0.5 H) 3.72 - 3.82 (m, 1.5 H) 3.56 - 3.69 (m, 1.5 H) 3.36 - 3.55 (m, 1.5 H) 2.87 (d, J = 4.58 Hz, 1.5 H) 2.84 (d, J = 4.58 Hz, 1.5 H) 2.27 - 2.34 (m, 0.5 H) 2.24 (dd, J = 6.56, 3.51 Hz, 0.5 H) 2.04 - 2.12 (m, 0.5 H) 2.00 (dd, J = 19.84, 10.38 Hz, 0.5 H). LC/MS was performed on a Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. LC/MS method: solvent A = 10% CH₃CN/90% H₂O/0.1% TFA, solvent B = 90% CH₃CN/10% H₂O/0.1% TFA, start %B = 0, final %B = 100, gradient time = 3 min, stop time = 4 min, flow rate = 4 ml/min, column: Sunfire C18 5 μ m 4.6 x 50 mm; HPLC R_t = 1.89 min, (ES⁺) m/z (MH⁺) = 537. Analytical HPLC method: solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. Column: Waters Sunfire C-18, 3.5 μ m 4.6 x 150 mm, R_t = 14.43 min, purity = 99%; column: Waters XBridge phenyl 3.5 μ m 4.6 x 150 mm, R_t = 13.18 min, purity = 99%.



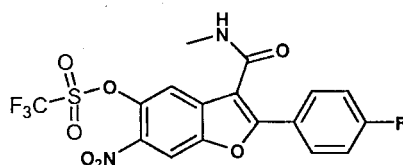
5-(3-(*tert*-Butylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00197] DIEA (50 μ L, 0.29 mmol) was added to a suspension of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (50 mg, 0.13 mmol) and HATU (60 mg, 0.16 mmol) in DMF (0.5 mL). The solids dissolved over 5 min, at which point *tert*-butylamine (20 μ L, 0.19 mmol) was added. The solution was stirred at r.t. for 1 h, then diluted with CH₃CN (1 mL), filtered, purified by prep HPLC, concentrated, and dried in a vacuum oven over the weekend at 40 °C to give the title compound (39 mg, 69% yield) as a white powder. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.53 (q, J = 4.37 Hz, 1 H) 8.08 (s, 1 H) 8.01 (dd, J = 8.24, 5.80 Hz, 2 H) 7.92 (d, J = 7.93 Hz, 2 H) 7.84 (d, J = 7.63 Hz, 1 H) 7.77 - 7.82 (m, 2 H) 7.73 - 7.77 (m, 1 H) 7.55 (t, J = 7.63 Hz, 1 H) 7.40 (t, J = 8.85 Hz, 2 H) 2.87 (d, J = 4.58 Hz, 3 H) 1.42 (s, 9 H). ¹³C NMR (125 MHz, DMSO-d₆) δ ppm 166.20 (s) 163.22 (s) 162.66 (d, J = 246 Hz) 152.56 (s) 152.52 (s) 140.06 (s) 136.53 (s) 135.76 (s) 129.38 (d, J = 12 Hz) 129.36 (s) 128.70 (s) 127.86 (s) 126.27 (s) 125.86 (s) 125.70 (d, J = 2.5 Hz) 124.83 (s) 118.90 (s) 115.93 (d, J = 20 Hz) 113.88 (s) 111.60 (s) 50.85 (s) 28.60 (s) 26.19 (s). LC/MS method: solvent A = 5% CH₃CN/95% H₂O/10 mM NH₄OAc, solvent B = 95% CH₃CN/5%H₂O/10 mM NH₄OAc, start %B = 0, final %B = 100, gradient time = 2 min, stop time = 3 min, flow rate = 5 ml/min, column: XBridge C18 5 μ m 4.6 x 50 mm; HPLC R_t = 1.57, (ES-) m/z (M^+) = 443. Analytical HPLC method: solvent A = 5% CH₃CN/95% H₂O/0.1% TFA, solvent B = 95% CH₃CN/5% H₂O/0.1% TFA, start %B = 10, final %B = 100, gradient time = 15 min, stop time = 18 min, flow rate = 1 ml/min. column: Waters Sunfire C-18, 3.5 μ m 4.6 x 150 mm, R_t = 11.71 min, purity = 100%; column: Waters XBridge phenyl column 3.5 μ m 4.6 x 150 mm, R_t = 9.53 min, purity = 100%.



2-(4-Fluorophenyl)-5-hydroxy-N-methyl-6-nitrobenzofuran-3-carboxamide

[00198] To a mixture of 2-(4-fluorophenyl)-5-isopropoxy-N-methyl-6-nitrobenzofuran-3-carboxamide (210.5 mg, 0.565 mmol) in CH₂Cl₂ (14 mL) at 0 °C under N₂ was added trichloroborane (1.70 mL, 1.7 mmol) (1M solution in CH₂Cl₂). The mixture was then stirred at r.t. for 17 hr. The mixture was evaporated. The reddish orange residue was added 7 ml H₂O, and then 3.5 ml 1N HCl, and left standing until the solid turned yellow. The yellow solid product was then filtered and washed with 3 x 3 ml H₂O and dried (182 mg, 93%). ¹H NMR (500 MHz, DMSO-d₆) δ 10.18 (broad s, 1H), 8.53 (m, 1H), 8.31 (s, 1H), 7.98 (apparent dd, *J* = 8.85, 5.49, 2H), 7.43 (apparent t, *J* = 8.85, 2H), 7.28 (s, 1H), 2.84 (appeared as d, *J* = 4.58, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 331.21, HPLC *R*_t = 1.442 min.



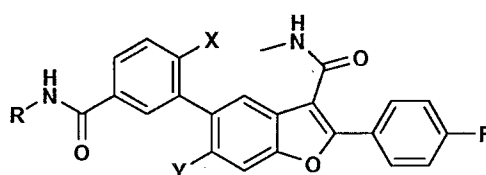
20 2-(4-Fluorophenyl)-3-(methoxycarbonyl)-6-nitrobenzofuran-5-yl trifluoromethanesulfonate

[00199] To a mixture of 2-(4-fluorophenyl)-5-hydroxy-N-methyl-6-nitrobenzofuran-3-carboxamide (100 mg, 0.303 mmol) in CH₂Cl₂ (4 mL) at r.t. under N₂ was added triethylamine (0.084 mL, 0.606 mmol). The mixture was then cooled to 0 °C, and then added 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (162 mg, 0.454 mmol). The orange suspension was then stirred at r.t. for 23 hr. The mixture was evaporated. The

grayish-green residue was added 3 ml H₂O, the solid product filtered and washed with 3 x 3 ml H₂O and dried (130.8 mg, 89%). ¹H NMR (500 MHz, DMSO-d₆) δ 8.84 (s, 1H), 8.62 (broad s, 1H), 8.02 (td, *J* = 5.65, 2.44, 2H), 7.96 (s, 1H), 7.48 (td, *J* = 8.77, 2.59, 2H), 2.85 (appeared as d, *J* = 3.97, 3H). LC/MS were performed by using

5 Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm, C18, 3.0 x 50 mm; (ES⁺) *m/z* (M+H)⁺ = 463.25, HPLC *R*_t = 1.700 min.

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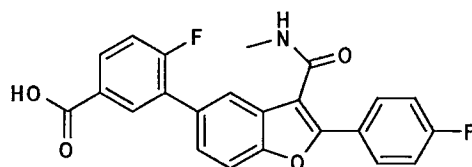


[00200] General procedure: A mixture of 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (or the 6-nitro analog) (0.3 mmol, 1 equiv.), 3-boronobenzoic acid (1.5 equiv.), cesium carbonate (1.7

15 equiv.) and Pd(PPh₃)₄ (0.1 equiv.) in a mixture of H₂O (0.6 mL)/1,4-dioxane (3.00 mL) under N₂ was stirred at 90 °C for about 1.5 to 5 hr. The mixture was cooled to r.t. and diluted with 3 ml 1,4-dioxane. The mixture was filtered through a Whatman PTFE 4.5 μm disk, and concentrated. The mixture was added 4 ml 1N HCl, diluted with 5 ml H₂O. The precipitates were filtered and washed with 3 x 4 ml H₂O, and

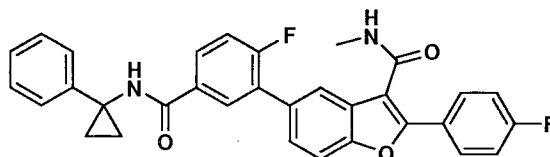
20 dried. The crude material was purified as indicated or used for the amide coupling step without further purification. To a mixture of 3-(benzofuran-5-yl)benzoic acid derivative obtained from above (0.074 mmol, 1 equiv.), amine (1.5 equiv.) and 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate (2

25 equiv.) in DMF (1 mL) at r.t. under N₂ was added N,N-diisopropylethylamine (3 equiv.). The mixture was stirred at r.t. for about 23 hr. The mixture was diluted with MeOH and purified as indicated, *e.g.*, by Shimadzu-VP preparative reverse phase HPLC.



4-Fluoro-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid.

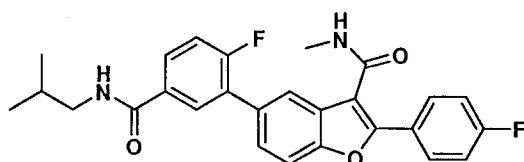
[00201] ^1H NMR (500 MHz, DMSO-d_6) δ 13.17 (s, 1H), 8.51 (q, $J = 4.27$, 1H), 8.13 (dd, $J = 7.78$, 1.98, 1H), 8.01 (apparent dd, $J = 8.70$, 5.34, 3H), 7.81 (d, $J = 8.54$, 1H), 7.80 (s, 1H), 7.61 (d, $J = 8.54$, 1H), 7.49 (dd, $J = 10.07$, 8.85, 1H), 7.41 (apparent t, $J = 8.85$, 2H), 2.85 (appeared as d, $J = 4.58$, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm , C18, 3.0 x 50 mm; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 408.29, HPLC R_t = 1.693 min.



15 5-(2-Fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

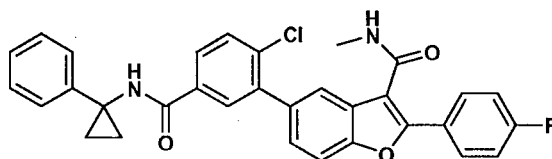
[00202] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.79 - 9.35 min. (UV detection at 220 nm). ^1H NMR (500 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.51 (q, $J = 4.58$, 1H), 8.15 (dd, $J = 7.48$, 2.29, 1H), 8.00 (dd, $J = 9.00$, 5.34, 2H), 7.97 (m, 1H), 7.83 (s, 1H), 7.82 (d, $J = 8.60$, 1H), 7.64 (d, $J = 8.55$, 1H), 7.46 (dd, $J = 10.22$, 8.70, 1H), 7.41 (t, $J = 9.00$, 2H), 7.29 (t, $J = 7.63$, 1H), 7.28 (d, $J = 7.32$, 1H), 7.23 (apparent d, $J = 7.10$, 2H), 7.17 (t, $J = 7.17$, 1H), 2.85 (appeared as d, $J = 4.58$, 3H), 1.30 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and

Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 523.44, HPLC R_t = 1.803 min.



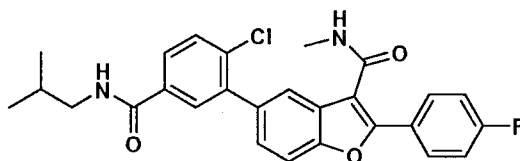
5-(2-Fluoro-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- 10 [00203] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.47 - 9.09 min. (UV detection at 220 nm). ¹H NMR
- 15 (500 MHz, CD₃OD, appeared as a mixture of two isomers) δ 8.06-8.04 (m, 1H), 8.00-7.97 (m, 2H), 7.90-7.87 (m, 2H), 7.70 (d, J = 8.50, major) and 7.69 (d, J = 8.50, minor) (1H), 7.63-7.62 (m, 1H), 7.36-7.27 (overlapping m, 3H), 3.23 (d, J = 7.02, major) and 3.23-3.22 (d, minor) (2H), 2.98 (s, major) and 2.97 (s, minor) (3H), 1.97 (m, 1H), 1.00 (d, J = 6.71, major) and 0.99 (d, J = 6.71, minor) (6H). LC/MS were
- 20 performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 463.38, HPLC R_t =
- 25 1.772 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, R_t = 8.85 min; Column:
- 30 XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 6.44 min.



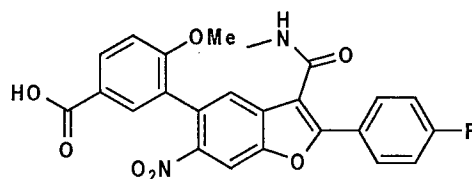
5-(2-Chloro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- 5 [00204] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 9.28 - 9.85 min. (UV detection at 220 nm). ¹H NMR
- 10 (500 MHz, CD₃OD, appeared as a mixture of two isomers) δ 9.36 (broad s, 1H), 7.98-7.94 (overlapping m, 3H), 7.85 (dd, *J* = 8.39, 2.29, major) and 7.86-7.83 (dd, minor) (1H), 7.75 (d, *J* = 1.83, major) and 7.75-7.74 (d, minor) (1H), 7.66 (d, *J* = 8.55, major) and 7.66-7.64 (d, minor) (1H), 7.633 (d, *J* = 8.00, major) and 7.626 (d, *J* = 8.50, minor) (1H), 7.48 (dd, *J* = 8.55, 1.83, major) and 7.49-7.47 (dd, minor) (1H),
- 15 7.29-7.25 (overlapping m, 6H), 7.17 (m, 1H), 2.95 (s, major) and 2.94 (s, minor) (3H), 1.36-1.34 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time
- 20 = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 539.37, 541.38, HPLC *R*_t = 1.868 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time =
- 25 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 10.84 min; Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 8.37 min.



5-(2-Chloro-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

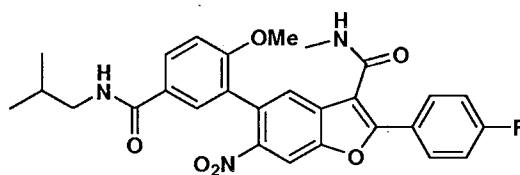
[00205] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 9.01 - 9.47 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD, appeared as a mixture of two isomers) δ 7.98 (major) and 7.97 (minor) (dd, 2H), 7.91 (d, *J* = 2.14, major) and 7.91-7.90 (d, minor) (1H), 7.82 (dd, *J* = 8.24, 2.14, major) and 7.82 -7.80 (dd, minor) (1H), 7.75 (m, 1H), 7.65 (dd, *J* = 16, 8.39, major) and 7.64 (dd, *J* = 16.5, 8.55, minor) (2H), 7.49 (dd, *J* = 8.24, 1.83, major) and 7.49-7.47 (dd, minor) (1H), 7.27 (t, *J* = 8.85, major) and 7.29-7.25 (apparent m, minor) (2H), 3.22 (d, *J* = 7.02, major) and 3.21 (d, *J* = 7.02, major) (2H), 2.96 (s, major) and 2.95 (s, minor) (3H), 1.95 (m, 1H), 0.98 (d, *J* = 6.71, major) and 0.97 (d, *J* = 6.71, minor) (6H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 479.33, 481.36, HPLC *R*_t = 1.830 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, *R*_t = 9.66 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, *R*_t = 7.19 min.



3-(2-(4-Fluorophenyl)-3-(methoxycarbonyl)-6-nitrobenzofuran-5-yl)-4-methoxybenzoic acid

[00206] LC/MS were performed by using Shimadzu-VP instrument with UV
 5 detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 465.31, HPLC R_t = 1.568 min.

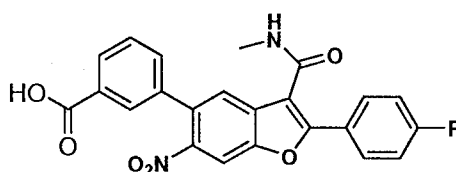
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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-methoxyphenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide

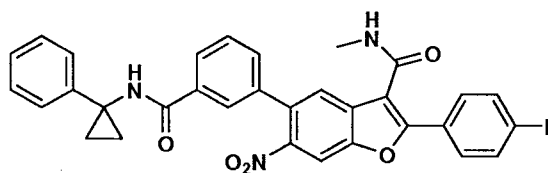
[00207] Purification by Shimadzu-VP preparative reverse phase HPLC using the
 15 separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.79 - 8.36 min. (UV detection at 220 nm). ¹H NMR (500 MHz, DMSO-d₆) δ 8.62 (q, J = 4.48, 1H), 8.48 (s, 1H), 8.46 (t, J = 5.80, 1H),
 20 8.05 (dd, J = 9.00, 5.34, 2H), 7.96 (dd, 1H), 7.95 (apparent s, 1H), 7.68 (s, 1H), 7.46 (t, J = 8.85, 2H), 7.14 (d, J = 8.55, 1H), 3.69 (s, 3H), 3.11 (broad d, 2H), 2.83 (appeared as d, J = 4.58, 3H), 1.87 (m, 1H), 0.91 (d, J = 6.71, 6H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1%
 25 TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column:

XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 520.40, HPLC R_t = 1.688 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 7.93 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 6.30 min.



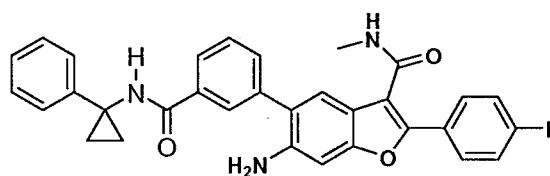
10 3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)-6-nitrobenzofuran-5-yl)benzoic acid.
 [00208] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100
 15 mm S5, Fraction Collection: 6.98 - 7.51 min. (UV detection at 220 nm). ¹H NMR (500 MHz, DMSO-d₆) δ 13.17 (s, 1H), 8.60 (m, 1H), 8.54 (s, 1H), 8.08-8.05 (overlapping m, 2H), 8.02 (d, J = 7.63, 1H), 7.95 (s, 1H), 7.74 (s, 1H), 7.67-7.61 (overlapping m, 2H), 7.46 (apprent t, J = 8.85, 2H), 2.84 (appeared as d, J = 4.58, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection
 20 at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 435.27, HPLC R_t = 1.588 min.

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2-(4-Fluorophenyl)-N-methyl-6-nitro-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

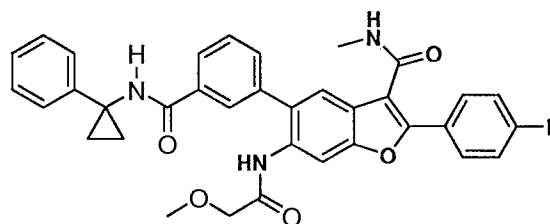
[00209] 2-(4-Fluorophenyl)-N-methyl-6-nitro-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide was prepared as described in the general procedure. The reaction mixture was concentrated, and then added excess water. The off white precipitates of the product were filtered, washed with 3 times of water and dried. ¹H NMR (500 MHz, DMSO-d₆) δ 9.31 (s, 1H), 8.60 (m, 1H), 8.55 (s, 1H), 8.05 (m, 2H), 7.99-7.97 (overlapping m, 2H), 7.75 (s, 1H), 7.59-7.53 (overlapping m, 2H), 7.46 (t, *J* = 8.70, 2H), 7.29 (t, *J* = 7.02, 2H), 7.24 (s, 1H), 7.23 (d, *J* = 7.02, 1H), 7.17 (t, *J* = 6.71, 1H), 2.83 (s, 3H), 1.29 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 550.45, HPLC *R*_t = 1.738 min.



6-Amino-2-(4-fluorophenyl)-N-methyl-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00210] 2-(4-Fluorophenyl)-N-methyl-6-nitro-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide (83.3 mg, 0.152 mmol) under N₂ at r.t. was dissolved in DMF (2 ml) and then added ethyl acetate (10 mL). The mixture remained as a clear light brown solution. The mixture was added palladium (97 mg, 0.045 mmol, 5%/C), flushed with H₂ using a balloon, and the mixture stirred under H₂ for about 8 hr. The mixture was diluted with EtOAc, and filtered through a Whatman PTFE 45 uM disk. The filtrate was evaporated. The residue was titrated with 3 x 1 ml Et₂O (the Et₂O solution was removed by using a pipette), and the light orange solid product dried (64.4 mg, 82%). ¹H NMR (500

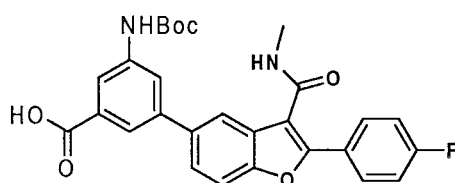
MHz, DMSO- d_6) δ 9.26 (s, 1H), 8.32 (q, J = 4.17, 1H), 7.94-7.89 (overlapping m, 3H), 7.97 (s, 1H), 7.62 (d, J = 6.8, 1H), 7.58 (q, 1H), 7.34 (t, J = 8.70, 2H), 7.29 (t, 1H), 7.28 (d, J = 7.50, 1H), 7.23 (s, 2H), 7.227 (d, J = 8.00, 1H), 7.17 (t, J = 7.17, 1H), 6.99 (s, 1H), 5.09 (s, 2H), 2.79 (appeared as d, J = 3.97, 3H), 1.29 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV
 5 detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ =
 10 520.39, HPLC R_t = 1.497 min.



2-(4-Fluorophenyl)-6-(2-methoxyacetamido)-N-methyl-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

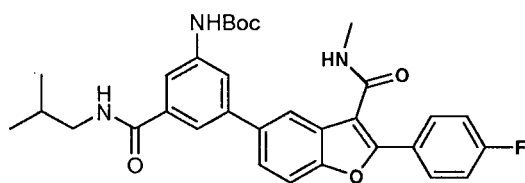
15 [00211] To a mixture of 2-methoxyacetic acid (10.40 mg, 0.115 mmol) in THF (3 mL) at r.t. under N₂ was added 1,1'-carbonyldiimidazole (CDI) (28.1 mg, 0.173 mmol). The mixture was stirred at 55 °C for 1 hr. The mixture was then transferred to a flask containing 6-amino-2-(4-fluorophenyl)-N-methyl-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide (30 mg, 0.058
 20 mmol) at r.t. under N₂. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.035 mL, 0.231 mmol) was then added and the mixture was stirred at 55 °C for 2 hr 35 min. The mixture was then left standing at r.t. overnight. The mixture was re-stirred at 55 °C for 3 hr. The mixture was cooled to r.t., diluted with MeOH and purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent
 25 A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.28 - 7.84 min. (UV detection at 220 nm). ¹H NMR (500 MHz, DMSO-

- d₆) δ 9.29 (s, 1H), 9.04 (s, 1H), 8.49 (q, $J = 4.58$, 1H), 8.31 (s, 1H), 8.03-8.00 (overlapping m, 3H), 7.98 (m, 1H), 7.59 (s, 1H), 7.63 (s, 1H), 7.625 (d, $J = 2.44$, 1H), 7.40 (t, $J = 9.00$, 2H), 7.28 (apparent t, $J = 7.63$, 2H), 7.23 (apparent d, 2H), 7.17 (t, $J = 7.17$, 1H), 3.90 (s, 2H), 3.18 (s, 3H), 2.83 (appeared as d, $J = 4.58$, 3H), 1.28 (s, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 592.49, HPLC R_t = 1.652 min.



3-(*tert*-Butoxycarbonylamino)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

- [00212] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M - Me₂CCH₂ + H)⁺ = 449.35, HPLC R_t = 1.808 min.

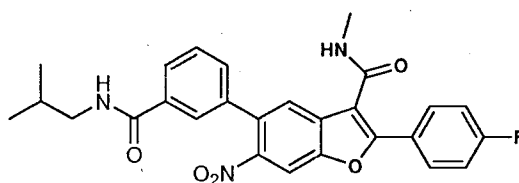


tert-Butyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-(isobutylcarbamoyl)phenylcarbamate

- [00213] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90%

MeOH-10% H₂O-0.1% TFA, Start %B = 70, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.13 - 7.93 min. (UV detection at 220 nm). ¹H NMR (500 MHz, DMSO-d₆) δ 9.57 (s, 1H), 8.55 (dt, *J* = 10.38, 5.19, 1H), 8.50 (broad s, 1H), 8.01-7.98 (m, 3H), 7.89 (s, 1H), 7.86-7.85 (m, 1H), 7.81 (apparent d, 1H), 7.75 (s, 1H), 7.70 (dd, *J* = 8.55, 1.83, 1H), 7.41 (apparent t, *J* = 8.85, 2H), 3.11 (t, *J* = 6.41, 2H), 2.87 (appeared as d, *J* = 4.58, 3H), 1.88 (ddd, *J* = 13.50, 6.64, 6.41, 1H), 1.55 (s) and 1.51 (s) (9H), 0.92 (d, *J* = 6.50, major) and 0.91 (d, *J* = 6.50, minor) (6H).

LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 560.40, HPLC *R*_t = 1.898 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 70, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, *R*_t = 5.77 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, *R*_t = 3.70 min.



2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)phenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide

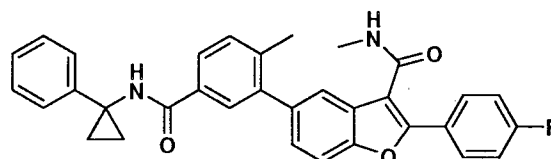
[00214] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.89 - 8.57 min. (UV detection at 220 nm). ¹H NMR (500 MHz, DMSO-d₆) δ 8.59 (m, 2H), 8.54 (s, 1H), 8.05 (m, 2H), 7.93 (d, *J* = 7.63,

1H), 7.90 (s, 1H), 7.75 (s, 1H), 7.57 (apparent t, $J = 7.63$, 1H), 7.54 (apparent t, 1H), 7.46 (apparent t, $J = 8.85$, 2H), 3.11 (t, $J = 6.41$, 2H), 2.84 (appeared as d, $J = 4.58$, 3H), 1.87 (m, 1H), 0.91 (d, $J = 6.71$, 6H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®.

5 HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 490.41, HPLC R_t = 1.693 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254

10 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 70, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 8.09 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 6.38 min.

15



2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00215] Purification by Shimadzu-VP preparative reverse phase HPLC using the

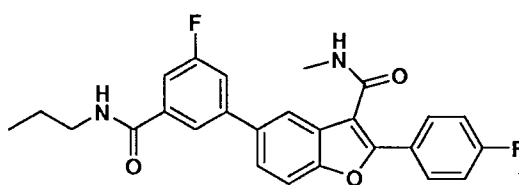
20 separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.92 - 9.62 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.97 (dd, $J = 8.85$, 5.49, 2H), 7.79 (m, 2H), 7.65-7.64 (d overlapping s, 1H), 7.64 (s, 1H), 7.42 (m, 1H), 7.37 (dd, $J = 8.24$, 1.83, 1H), 7.29-7.26 (overlapping m, 6H), 7.16 (m, 1H), 2.95 (s, 3H), 2.34 (s, 3H), 1.36-1.33 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA,

25

30 Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate

= 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 519.40, HPLC R_t = 1.832 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95%

- 5 MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 9.93 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 7.64 min.



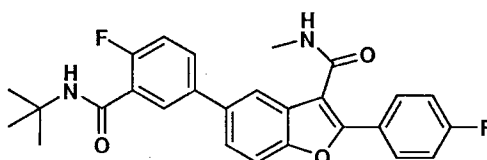
- 10 5-(3-Fluoro-5-(propylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00216] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10

- 15 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.32 - 8.96 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.00-7.97 (overlapping m, 4H), 7.74-7.69 (overlapping m, 2H), 7.65-7.62 (m, 1H), 7.58-7.55 (m, 1H), 7.29 (t, J = 8.70, 2H), 3.39 (t, J = 7.00, 2H), 3.00 (s, 3H), 1.69 (m, 2H), 1.02 (t, J = 7.48, 3H). LC/MS were performed by using

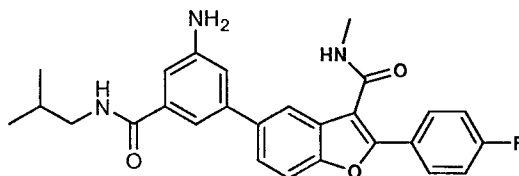
- 20 Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 449.40, HPLC R_t = 1.752 min. Analytical HPLC were
- 25 performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6

x 150 mm, R_t = 8.08 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 5.87 min.



5 5-(3-(*tert*-Butylcarbamoyl)-4-fluorophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

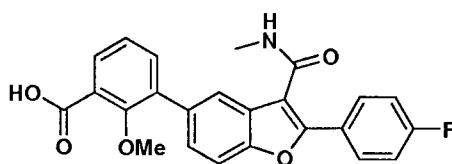
[00217] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.48 - 9.02 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.97-7.94 (overlapping m, 2H), 7.90 (dd, J = 6.87, 2.59, 1H), 7.88 (s, 1H), 7.78 (ddd, J = 8.47, 4.65, 2.44, 1H), 7.64 (m, 2H), 7.30-7.25 (overlapping m, 3H), 2.99 (s, 3H), 1.50 (2, 9H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 463.36, HPLC R_t = 1.788 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 9.97 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 6.81 min.



5-(3-Amino-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00218] Obtained as a hydrochloride salt from the deprotection of *tert*-Butyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-

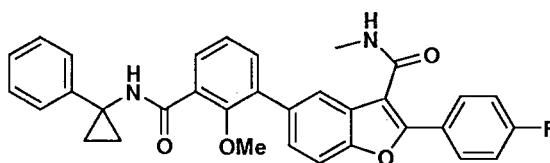
- 5 (isobutylcarbamoyl)phenylcarbamate using 4 M HCl in 1,4-dioxane (r.t.). ¹H NMR (500 MHz, CD₃OD) δ 8.26 (s, 1H), 8.02 (s, 1H), 7.97 (dd, *J* = 7.63, 5.49, 2H), 7.87 (s, 2H), 7.75 (s, 2H), 7.30 (t, *J* = 8.39, 2H), 3.28 (d, *J* = 7.02, 2H), 2.99 (s, 3H), 2.00 (m, 1H), 1.02 (d, *J* = 6.71, 6H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm, C18, 3.0 x 50 mm; (ES⁺) *m/z* (M+H)⁺ = 460.42, HPLC *R*_t = 1.510 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 8.96 min; Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 9.23 min.



3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoic acid

- [00219] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.02 - 7.76 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.00-7.97 (overlapping m, 2H), 7.84 (d, *J* = 1.53, 1H), 7.81 (dd, *J* = 7.63, 1.83, 1H), 7.67 (d, *J* = 8.50, 1H), 7.63-7.60 (overlapping m, 2H), 7.32-

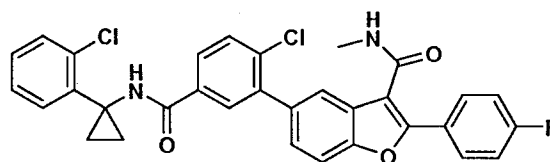
- 7.26 (overlapping m, 3H), 3.50 (s, 3H), 2.97 (s, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 420.27, HPLC R_t = 1.623 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 6.08 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 4.83 min.



- 2-(4-Fluorophenyl)-5-(2-methoxy-3-(1-phenylcyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

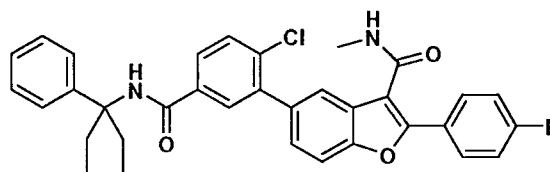
- [00220]** Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.65 - 9.45 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.99-7.96 (overlapping m, 2H), 7.87 (d, *J* = 1.83, 1H), 7.69-7.63 (overlapping m, 3H), 7.57 (dd, *J* = 7.48, 1.68, 1H), 7.40 (d, *J* = 7.63, 1H), 7.39 (s, 1H), 7.34-7.27 (overlapping m, 5H), 7.20 (t, *J* = 7.17, 1H), 3.41 (s, 3H), 2.97 (s, 3H), 1.40-1.37 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 535.45, HPLC R_t = 1.833 min. Analytical HPLC were

performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 9.93 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 7.75 min.



5-(2-Chloro-5-(1-(2-chlorophenyl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-
N-methylbenzofuran-3-carboxamide

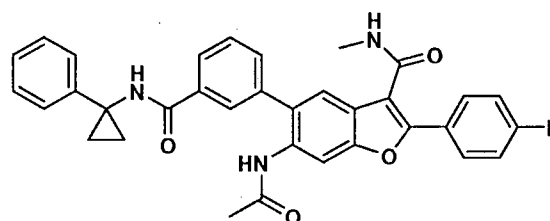
[00221] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 80, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 5.53 - 6.33 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.99-7.96 (overlapping m, 2H), 7.84 (d, *J* = 2.14, 1H), 7.79 (dd, *J* = 7.17, 1.98, 1H), 7.74 (dd, *J* = 8.39, 2.29, 1H), 7.72 (d, *J* = 1.53, 1H), 7.65 (d, *J* = 8.55, 1H), 7.58 (d, *J* = 8.54, 1H), 7.45 (dd, *J* = 8.55, 1.83, 1H), 7.37 (dd, *J* = 7.25, 1.75, 1H), 7.30-7.23 (overlapping m, 4H), 2.95 (s, 3H), 1.34-1.24 (appeared as d, 4H).
LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 573.38, HPLC R_t = 1.945 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 12.00 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 8.98 min.



5-(2-Chloro-5-(3-phenylpentan-3-ylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- 5 [00222] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 80, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.08 - 6.89 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.00-7.97 (overlapping m, 2H), 7.87 (d, *J* = 2.14, 1H), 7.80 (dd, *J* = 8.24, 2.14, 1H), 7.76 (d, *J* = 1.53, 1H), 7.68 (d, *J* = 8.54, 1H), 7.64 (d, *J* = 8.00, 1H), 7.50 (dd, *J* = 8.55, 1.53, 1H), 7.42 (d, *J* = 7.32, 2H), 7.34-7.27 (overlapping m, 4H), 7.20 (d, *J* = 7.32, 1H), 2.96 (s, 3H), 2.35 (m, 2H), 2.08 (m, 2H), 0.80 (t, *J* = 7.32, 6H). LC/MS were performed by using Shimadzu-VP instrument with UV
- 15 detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 569.47, HPLC *R*_t = 1.972 min. Analytical HPLC were performed by using
- 20 Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 13.37 min; Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 10.24 min.

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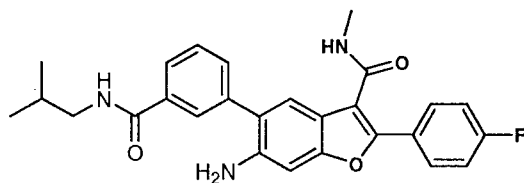


6-Acetamido-2-(4-fluorophenyl)-N-methyl-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00223] Prepared from 6-amino-2-(4-fluorophenyl)-N-methyl-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide in a similar manner

5 as described. ¹H NMR (500 MHz, DMSO-d₆) δ 9.34 (s, 1H), 9.28 (s, 1H), 8.48 (m, 1H), 8.03-8.00 (overlapping m, 3H), 7.93 (m, 1H), 7.89 (s, 1H), 7.58-7.56 (overlapping m, 3H), 7.40 (t, *J* = 8.85, 2H), 7.30-7.27 (overlapping m, 2H), 7.23-7.21 (overlapping m, 2H), 7.17 (t, *J* = 7.32, 1H), 2.83 (appeared as d, *J* = 4.58, 3H), 1.92 (s, 3H), 1.29 (appeared as s, 4H). LC/MS were performed by using Shimadzu-VP
10 instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 562.42, HPLC *R*_t = 1.547 min.

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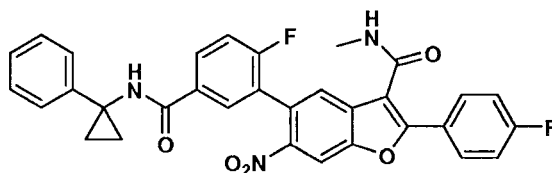


6-Amino-2-(4-fluorophenyl)-5-(3-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00224] Obtained from the reduction of 2-(4-fluorophenyl)-5-(3-

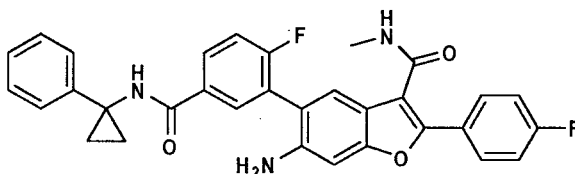
20 (isobutylcarbamoyl)phenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide using H₂ with 5% Pd/C as catalyst (1:6 DMF/EtOAc, r.t.) in a similar manner as described. ¹H NMR (500 MHz, DMSO-d₆) δ 8.54 (t, *J* = 5.95, 1H), 8.33 (q, *J* = 4.58, 1H), 7.94-7.91 (overlapping m, 3H), 7.85 (d, *J* = 7.32, 1H), 7.61-7.55 (overlapping m, 2H), 7.34 (t, *J* = 8.70, 2H), 7.23 (s, 1H), 6.99 (s, 1H), 5.05 (s, 2H), 3.11 (d, *J* = 7.02, 2H), 2.80-2.79 (appeared as d, 3H), 1.87 (m, 1H), 0.91 (d, *J* = 6.71, 6H). LC/MS were performed by
25 using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column:

XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 460.38, HPLC R_t = 1.407 min.



5 5-(2-Fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide

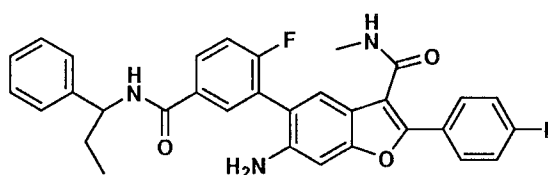
[00225] ¹H NMR (500 MHz, DMSO-d₆) δ 9.33 (s, 1H), 8.64 (s, 2H), 8.12 (dd, J = 7.32, 2.14, 1H), 8.08-8.05 (overlapping m, 3H), 7.83 (s, 1H), 7.47 (t, J = 8.85, 2H), 7.42 (t, J = 9.30, 1H), 7.31-7.28 (overlapping m, 2H), 7.25-7.23 (overlapping m, 2H), 7.17 (t, J = 7.17, 1H), 2.84 (appeared as d, J = 4.58, 3H), 1.31-1.28 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, 10
15 Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 568.39, HPLC R_t = 1.768 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, 20
Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 9.28 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 7.82 min.



25 6-Amino-5-(2-fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00226] Obtained from the reduction of 5-(2-fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide using H₂ with 5% Pd/C as catalyst (1:5 DMF/EtOAc, r.t.) in a similar manner as described. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 538.41, HPLC R_t = 1.510 min.

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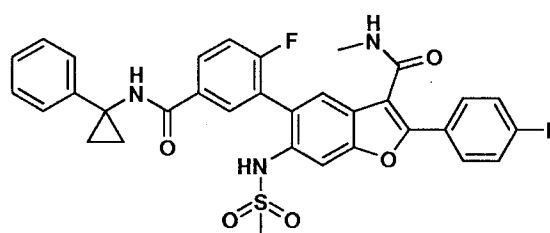
6-Amino-5-(2-fluoro-5-(1-phenylpropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00227] Obtained as a side product from the over-reduction of 5-(2-fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-

15 nitrobenzofuran-3-carboxamide under the conditions using H₂ with 5% Pd/C as catalyst (1:5 DMF/EtOAc, r.t.). The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.52 - 7.08 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, 1H), 7.93-7.91 (overlapping m, 3H), 7.51 (s, 1H), 7.40-7.38 (overlapping m, 2H), 7.34 (d, J = 7.60, 1H), 7.33 (t, J = 7.78, 2H), 7.27-7.23 (overlapping m, 4H), 4.99 (t, J = 7.48, 1H), 2.92 (s, 3H), 1.94 (m, 2H), 0.99 (t, J = 7.32, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4

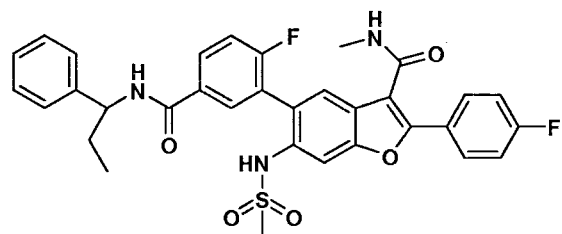
25

- ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 540.45, HPLC R_t = 1.587 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 6.56 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 5.42 min.



- 10 5-(2-Fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide
- [00228] Prepared from the coupling between 6-amino-5-(2-fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide and methanesulfonyl chloride (*N,N*-diisopropylethylamine, ClCH₂CH₂Cl, r.t.), followed by hydrolysis of the intermediate N-(methylsulfonyl)methanesulfonamide (Cs₂CO₃, 1:5 H₂O/1,4-dioxane, 90 °C). Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.70 - 7.25 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.00-7.95 (overlapping m, 4H), 7.83 (s, 1H), 7.66 (s, 1H), 7.35 (t, *J* = 9.00, 1H), 7.30-7.27 (overlapping m, 6H), 7.18 (m, 1H), 2.94 (s, 3H), 2.88 (s, 3H), 1.37-1.35 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ =

616.48, HPLC R_t = 1.563 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, 5 Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 6.57 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 5.80 min.

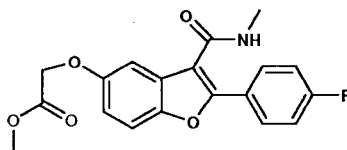


5-(2-Fluoro-5-(1-phenylpropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide

[00229] Prepared in a similar manner as 5-(2-fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.35 - 7.81 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.00-7.93 (overlapping m, 4H), 7.83 (s, 1H), 7.66 (s, 1H), 7.41 (d overlapping with s, J = 8.00, 1H), 7.40 (s, 1H), 7.35-7.32 (overlapping m, 3H), 7.29 (t, J = 8.10, 2H), 7.25 (t, J = 7.93, 1H), 4.99 (t, J = 7.48, 1H), 2.94 (s, 3H), 2.89 (s, 3H), 1.94 (m, 2H), 1.00 (t, J = 7.17, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 618.48, HPLC R_t = 1.637 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical

HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 7.76 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 6.37 min.

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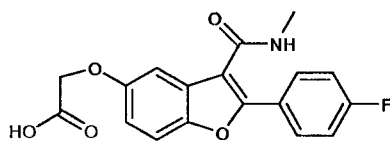


Methyl 2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yloxy)acetate

[00230] To a 50 mL round-bottomed flask was added 2-(4-fluorophenyl)-5-hydroxy-N-methylbenzofuran-3-carboxamide (285 mg, 1 mmol), potassium carbonate (207 mg, 1.500 mmol), and methyl bromoacetate (0.101 ml, 1.1 mmol) in DMF (3 mL) to give a yellow suspension. The mixture was stirred at room temperature under nitrogen overnight. The crude product was diluted with 100 mL of dichloromethane, washed with water, then brine and dried over magnesium sulfate. The residue was purified using a BIOTAGE® Horizon employing a gradient of 0 to 30% methanol in dichloromethane and a 40+M silica gel column. The product was then triturated with cold ethyl acetate to give a 73% yield (259 mgs) of product, a white amorphous solid after drying under vacuum.

[00231] The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® 10 μ m C18, 4.6 x 30mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 2 minutes with a 1 minute hold at a rate of 5 mL/minute. The NMR spectra was recorded at room temperature using a Bruker DRX300 spectrometer. Chemical shifts were reported in ppm relative to the deuterated solvent used. Coupling constants were reported in hertz. Peak multiplicity was reported using the following abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), br (broad). ¹H NMR (300 MHz, CD₃OD) δ ppm 2.93 (s, 3 H), 3.79 (s, 3 H), 4.75 (s, 2 H), 7.01 (dd, *J* = 8.97, 2.38 Hz, 1 H), 7.15 (d, *J* = 2.38 Hz, 1 H), 7.22 (t,

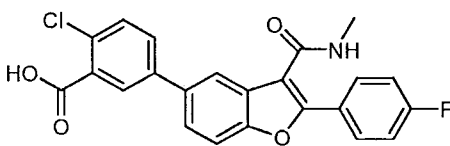
$J = 8.78$ Hz, 2 H), 7.46 (d, $J = 8.97$ Hz, 1 H), 7.88 (m, 2 H). LCMS m/z 358.27 (M+H), R_t 1.553 min., 97.4 % purity.



5 2-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yloxy)acetic acid

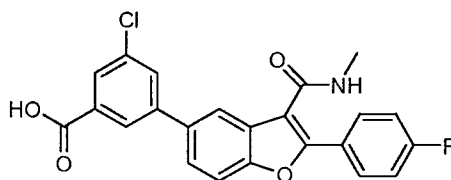
[00232] To a 50mL round-bottomed flask was added methyl 2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yloxy)acetate (132.3 mg, 0.370 mmol) and 2 equivalents of potassium trimethylsilanolate (95 mg, 0.740 mmol) along with a 1:1 solution of tetrahydrofuran/dichloromethane (10 ml) to give a yellow heterogeneous mixture. The mixture was stirred at room temperature overnight. The crude product was then cooled to 0°C, diluted further with dichloromethane, and acidified with 1 N HCl. The product was extracted, washed with water then brine, and dried over magnesium sulfate. After solvent evaporation, the product was triturated with hexane to give a 91% yield (115 mgs), a white amorphous solid after drying under vacuum.

15 The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® 10µm C18, 4.6 x 30mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 20 minutes with a 1 minute hold at a rate of 5 mL/minute. The NMR spectra was recorded at room temperature using a Bruker DRX300 spectrometer. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.82 (d, $J = 4.39$ Hz, 3 H), 4.72 (s, 2 H), 7.00 (dd, $J = 8.78$, 2.56 Hz, 1 H), 7.08 (d, $J = 2.56$ Hz, 1 H), 7.35 (t, $J = 8.97$ Hz, 2 H), 7.57 (d, $J = 8.78$ Hz, 1 H), 7.92 (dd, $J = 8.78$, 5.49 Hz, 2 H), 8.34 (m, 1 H). LCMS m/z 344.27 (M+H), 25 R_t 1.450 min., 96.0 % purity.



2-Chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

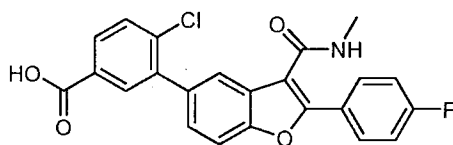
[00233] To a 250mL sealed tube was added 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (3.55 g, 8.5 mmol), dioxane (50 mL), water (10 mL), Tetrakis(triphenylphosphine)palladium(0) (0.196 g, 0.170 mmol), 5-borono-2-chlorobenzoic acid (2.55 g, 12.75 mmol), and cesium carbonate (4.15 g, 12.75 mmol). The tube was sealed and heated in an oil bath overnight at 85 °C. The reaction mixture was then cooled, diluted with 300mL of cold 0.5M HCl and stirred for 30minutes. The resulting solid was washed with 0.5 N HCl then with water and allowed to dry under vacuum giving a quantitative yield of 2-Chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid which was used without further purification. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. LCMS m/z 424.77 (M+H), R_t 2.150 min., 90 % purity.



3-Chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

[00234] To a 250mL sealed tube was added 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (3.55 g, 8.5 mmol), dioxane (50 mL), water (10 mL), Tetrakis(triphenylphosphine)palladium(0) (0.196 g, 0.170 mmol), 5-borono-3-chlorobenzoic acid (2.55 g, 12.75 mmol), and cesium carbonate (4.15 g, 12.75 mmol). The tube was sealed and heated in an oil bath overnight at 85 °C. The reaction mixture was then cooled, diluted with 300mL of cold 0.5M HCl and stirred for 30minutes. The resulting solid was washed with 0.5 N HCl then with water and allowed to dry under vacuum giving a quantitative yield of 3-Chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid which was used without further purification. The LC/MS data was obtained on a

Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. LCMS *m/z* 424.09 (M+H), *R_f* 2.658 min., 88 % purity.



4-Chloro-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

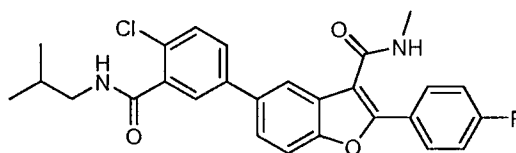
10 [00235] To a 250mL sealed tube was added 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (3.55 g, 8.5 mmol), dioxane (50 mL), water (10 mL), Tetrakis(triphenylphosphine)palladium(0) (0.196 g, 0.170 mmol), 3-borono-4-chlorobenzoic acid (2.55 g, 12.75 mmol), and cesium carbonate (4.15 g, 12.75 mmol). The tube was sealed and heated in an oil bath overnight at 85 °C. The reaction mixture was then cooled, diluted with 300mL of cold 0.5M HCl and stirred for 30minutes. The resulting solid was washed with 0.5 N HCl then with water and allowed to dry under vacuum giving a quantitative yield of 4-Chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid which was used without further purification. The LC/MS data was obtained on a

20 Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes

25 with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then

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confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10 mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water),
 5 (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, DMF-d₇) δ ppm 2.95 (d, J = 4.58 Hz, 3 H), 7.39 - 7.47 (m, 2 H), 7.57 (dd, J = 8.55, 1.83 Hz, 1 H), 7.81 (dd, J = 15.72, 8.39 Hz, 2 H), 7.87 (d, J = 1.83 Hz, 1 H), 8.04 - 8.14 (m, 4 H), 8.40 (d, J = 4.58 Hz, 1 H). LCMS m/z 424.90 (M+H), R_t 2.287
 10 min. HPLC R_t 9.749min. (Sunfire C18) and 10.518min. (XBridge phenyl C18), 94 % purity.



5-(4-Chloro-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-
 15 3-carboxamide

[00236] To a 250mL RBF was added 2-chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (3.62 g, 8.55 mmol), 2-methylpropan-1-amine (1.274 mL, 12.83 mmol), *N*-ethyl-*N,N*-diisopropylamine (2.98 mL, 17.10 mmol), and 3 eq. of HATU, (2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (9.75 g, 25.7 mmol)) along
 20 with 114mL of DMF. The mixture was stirred overnight at room temperature. The crude reaction mixture was transferred to a separatory funnel, diluted with 300mL of dichloromethane and washed with 100mL of 1 N HCl, water, and brine. After drying over magnesium sulfate the crude residue was pushed through a plug of silica gel and
 25 evaporated to a tan solid. The solid was triturated with diethyl ether then cold acetonitrile to give a 48% yield of 5-(4-chloro-3-(isobutylcarbamoyl) phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide, as a light yellow powder. The NMR spectrum was recorded at room temperature using a Bruker DRX500 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC /
 30 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:

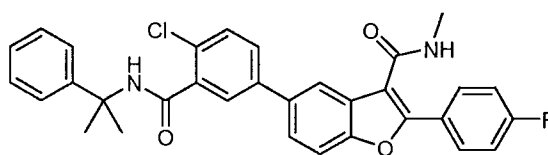
Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was

5 determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1

10 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 0.1% ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water /

15 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, acetone-d₆) δ ppm 1.02 (d, *J*=6.71 Hz, 6 H), 1.92 - 2.01 (m, 1 H), 2.99 (d, *J* = 4.88 Hz, 3 H), 3.28 (t, *J* = 6.41 Hz, 2 H), 7.33 (t, *J* = 8.70 Hz, 2 H), 7.56 (d, *J* = 8.24 Hz, 1 H), 7.61 (br. s., 1 H), 7.66 (br. s., 1 H), 7.68 - 7.74 (m, 2 H), 7.74 - 7.82 (m, 2 H), 8.01 - 8.06 (m, 1 H), 8.13 (dd, *J*=8.70, 5.34 Hz, 2 H). LCMS *m/z* 479.06 (M+H), *R_t* 2.367 min. HPLC *R_t* 10.263min. (Sunfire C18) and 11.753min. (XBridge phenyl C18), 93 % purity.

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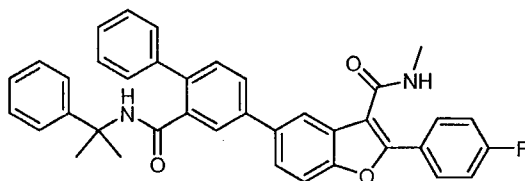


25 5-(4-Chloro-3-(2-phenylpropan-2-ylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00237] To a 2 dram vial was added 2-chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (42.4 mg, 0.1 mmol) in DMF (2 mL) along with cumylamine (0.029 mL, 0.200 mmol), *N,N*-Diisopropylethylamine (0.035 mL, 0.200 mmol) and HATU (114 mg, 0.300 mmol) to give a yellow solution. The

30 vial was shaken at room temperature overnight. The crude reaction mixture was then

evacuated to near dryness, taken up in 2 mL of methanol and purified using a Shimadzu preparative HPLC employing methanol/water/0.1%TFA where solvent A was 10% MeOH / 90% H₂O / 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% MeOH / 0.1% trifluoroacetic acid with a PHENOMENEX® Luna 10µm C18 30x100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 10 minutes with a 10 minute hold. The tubes containing purified product were evaporated overnight in a Savant/Thermo SPEEDVAC® to give a 45% yield of 5-(4-chloro-3-(2-phenylpropan-2-ylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide as a white powder. The NMR spectrum was recorded at room temperature using a Bruker DRX300 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (300 MHz, chloroform-d) δ ppm 1.87 (s, 6 H), 3.02 (d, *J* = 4.76 Hz, 3 H), 6.03 (d, *J* = 4.76 Hz, 1 H), 6.62 (s, 1 H), 7.13 - 7.23 (m, 2 H), 7.24 - 7.31 (m, 1 H), 7.33 - 7.42 (m, 2 H), 7.45 (d, *J* = 8.42 Hz, 1 H), 7.48 - 7.63 (m, 5 H), 7.83 - 8.00 (m, 4 H). LCMS *m/z* 542.90 (M+H), *R_t* 2.608 min. HPLC *R_t* 11.069min, (Sunfire C18) and 12.111min. (XBridge phenyl C18), 97.8 % purity.



2-(4-Fluorophenyl)-N-methyl-5-(2-(2-phenylpropan-2-ylcarbamoyl)biphenyl-4-yl)benzofuran-3-carboxamide

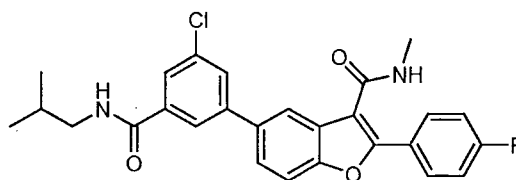
- 5 [00238] To a 2mL microwave vial was added dioxane (2 mL), water (0.200 mL), (S-Phos) dicyclohexyl (2',6'-dimethoxybiphenyl-2-yl)phosphine, (1.912 mg, 4.66 μ mol), 5-(4-chloro-3-(2-phenylpropan-2-ylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.0126 g, 0.023 mmol), potassium phosphate tribasic (0.020 g, 0.093 mmol), palladium(II) acetate (1.046 mg, 4.66 μ mol), and
- 10 phenylboronic acid (8.52 mg, 0.070 mmol). The vial was capped, degassed, flushed with N₂ and heated in the microwave for 10 minutes at 150°C. The crude product was taken up in a 1:1 solution of DMF/acetonitrile and purified by a Shimadzu preparative HPLC employing acetonitrile/0.1% TFA/water where solvent A was 10% acetonitrile / 90% H₂O/ 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90%
- 15 acetonitrile/ 0.1% trifluoroacetic acid with a Waters-Atlantis OBD 19 x 100mm 5 μ m column at a gradient of 50-100% B and a flow rate of 25 mL/min. over 10 minutes with a 10 minute hold. The purified product was evaporated to dryness overnight in a Savant Thermo SPEEDVAC® to give a 73% yield of 2-(4-fluorophenyl)-N-methyl-5-(2-(2-phenylpropan-2-ylcarbamoyl)biphenyl-4-yl) benzofuran-3-carboxamide. The
- 20 NMR spectrum was recorded at room temperature using a Bruker DRX500 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A =
- 25 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic

acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18

5 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, CD₃OD) δ ppm 1.54 (s, 6

10 H), 3.01 (s, 3 H), 7.15 - 7.20 (m, 1 H), 7.21 - 7.33 (m, 6 H), 7.43 - 7.50 (m, 3 H), 7.51 - 7.55 (m, 3 H), 7.69 - 7.72 (m, 1 H), 7.72 - 7.76 (m, 1 H), 7.80 (d, *J* = 1.53 Hz, 1 H), 7.84 (dd, *J* = 7.93, 1.83 Hz, 1 H), 7.96 - 8.02 (m, 3 H), 8.10 (br. s., 1 H). LCMS *m/z* 583.03 (M+H), *R_t* 2.811 min. HPLC *R_t* 11.683min. (Sunfire C18) and 12.609min. (XBridge phenyl C18), 99 % purity.

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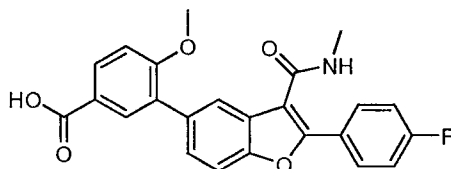
5-(3-Chloro-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00239] To a 250mL round-bottomed flask was added 3-chloro-5-(2-(4-

20 fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (3.62 g, 8.55 mmol), 2-methylpropan-1-amine (1.274 mL, 12.83 mmol), *N*-ethyl-*N,N*-diisopropylamine (2.98 mL, 17.10 mmol), and 3 eq. of HATU (2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (9.75 g, 25.7 mmol)) along with 114mL of DMF. The mixture was

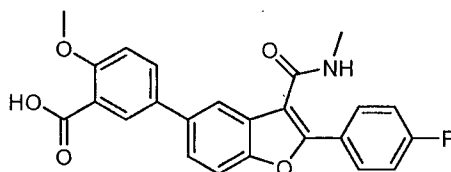
25 stirred overnight at room temperature. The crude reaction mixture was transferred to a separatory funnel, diluted with 300mL of dichloromethane and washed with 100mL of 1 N HCl, water, and brine. After drying over magnesium sulfate the crude residue was pushed through a plug of silica gel and evaporated to a tan solid. The solid was triturated with diethyl ether then cold acetonitrile to give a 52% yield of 5-(4-chloro-

3-(isobutylcarbamoyl) phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide, as a light yellow powder. The NMR spectrum was recorded at room temperature using a Bruker DRX500 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.94 (d, *J* = 6.41 Hz, 6 H), 1.72 - 1.97 (m, 1 H), 2.87 (d, *J* = 4.58 Hz, 3 H), 3.10 (t, *J* = 6.26 Hz, 2 H), 7.40 (t, *J* = 8.85 Hz, 2 H), 7.59 (d, *J* = 8.55 Hz, 1 H), 7.69 - 7.75 (m, 2 H), 7.76 - 7.82 (m, 2 H), 7.90 (br. s., 1 H), 7.97 - 8.07 (m, 2 H), 8.55 (br. s., 2 H). LCMS *m/z* 479.04 (M+H), *R_t* 2.658 min. HPLC *R_t* 10.810min. (Sunfire C18) and 12.154min. (XBridge phenyl C18), 92 % purity.

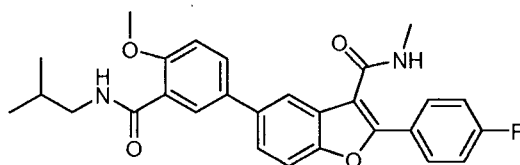


3-(2-(4-Fluorophenyl)-3-(methoxycarbonyl)benzofuran-5-yl)-4-methoxybenzoic acid

- [00240] To a 150mL sealed tube was added 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (1.252 g, 3 mmol), 3-borono-4-methoxybenzoic acid (0.882 g, 4.50 mmol), cesium carbonate (1.466 g, 4.50 mmol), tetrakis(triphenyl phosphine)palladium(0) (0.069 g, 0.060 mmol),
- 5 dioxane (18 mL) and water (3.60 mL). The vial was sealed and heated in an oil bath over night at 85°C. The reaction mixture was then filtered through CELITE® and concentrated *in vacuo*. Cold 0.5N HCl was then added and the heterogeneous mixture was stirred for 30 minutes. The resulting product, a white solid was filtered, washed with water and dried overnight to give a quantitative yield of 3-(2-(4-
- 10 fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methoxy benzoic acid which was carried on without further purification. LCMS *m/z* 420.88 (M+H), *Rt* 2.002 min., 88 % purity.



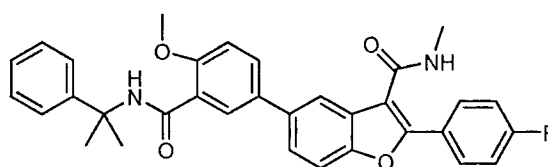
- 15 5-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoic acid
- [00241] To a 150mL sealed tube was added 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (1.252 g, 3 mmol), 5-borono-2-methoxybenzoic acid (0.882 g, 4.50 mmol), cesium carbonate (1.466 g, 4.50 mmol), tetrakis(triphenyl phosphine)palladium(0) (0.069 g, 0.060 mmol),
- 20 dioxane (18 mL) and water (3.60 mL). The vial was sealed and heated in an oil bath over night at 85°C. The reaction mixture was then filtered through CELITE® and concentrated *in vacuo*. Cold 0.5N HCl was then added and the heterogeneous mixture was stirred for 30 minutes. The resulting product, a white solid was filtered, washed with water and dried overnight to give a quantitative yield of 5-(2-(4-
- 25 fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy benzoic acid which was carried on without further purification. LCMS *m/z* 420.92 (M+H), *Rt* 2.003 min., 87 % purity.



2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-methoxyphenyl)-N-methylbenzofuran-3-carboxamide

- [00242] To a vial containing (5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoic acid (378.5 mg, 0.902 mmol)) was added DMF (5 mL), *N*,-ethyl-*N,N*-diisopropylamine (0.786 mL, 4.51 mmol), 2-methylpropan-1-amine (0.448 mL, 4.51 mmol), and HATU, (2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (1029 mg, 2.71 mmol)). The vial was capped and the solution shaken overnight at room temperature. The crude product was diluted with ethyl acetate, washed with 0.5M HCl, and extracted. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude reaction mixture was taken up in acetonitrile, filtered and purified using a Shimadzu preparative HPLC employing acetonitrile/water/TFA where solvent A was 10% acetonitrile / 90% H₂O/ 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile/ 0.1% trifluoroacetic acid with a PHENOMENEX® Luna 10µm C18 30x100mm at a gradient of 40-100% B and a flow rate of 25 mL/min. over 10 minutes with a 10 minute hold. The purified product was concentrated *in vacuo* to give a 38% yield of 2-(4-fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-methoxyphenyl)-N-methylbenzo- furan-3-carboxamide as a white solid. The NMR spectrum was recorded at room temperature using a Bruker DRX500 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B

(B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, acetone-d₆) δ ppm 1.00 (d, *J* = 6.41 Hz, 6 H), 1.92 - 1.96 (m, 1 H), 3.01 (d, *J* = 4.27 Hz, 3 H), 3.30 (t, *J* = 6.26 Hz, 2 H), 4.09 (s, 3 H), 7.23 - 7.39 (m, 3 H), 7.61 (br. s., 1 H), 7.69 (s, 2 H), 7.84 (dd, *J* = 8.39, 1.98 Hz, 1 H), 7.99 (s, 1 H), 8.13 (dd, *J* = 7.93, 5.49 Hz, 3 H), 8.39 (d, *J* = 2.14 Hz, 1 H). LCMS *m/z* 475.15 (M+H), *R_t* 2.452 min. HPLC *R_t* 10.648min. (Sunfire C18) and 12.301min. (XBridge phenyl C18), 100 % purity.

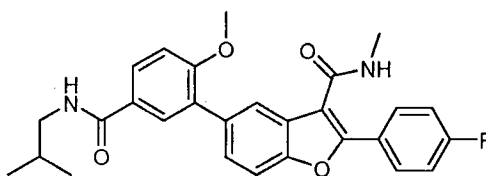


2-(4-Fluorophenyl)-5-(4-methoxy-3-(2-phenylpropan-2-ylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00243] To a vial containing (5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoic acid (61 mg, 0.145 mmol)) was added DMF (2 mL), *N*,*N*-ethyl-*N,N*-diisopropylamine (0.050 mL, 0.29 mmol), cumylamine (39.3mg, 0.291 mmol), and finally TBTU, *o*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (140 mg, 0.436 mmol)). The vial was capped and the solution shaken overnight at room temperature. The crude product was diluted with ethyl acetate, washed with 1M HCl, and extracted. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude reaction mixture was taken up in acetonitrile, filtered and purified using a Shimadzu preparative HPLC employing acetonitrile/water/TFA

where solvent A was 10% acetonitrile / 90% H₂O/ 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile/ 0.1% trifluoroacetic acid with a PHENOMENEX® Luna 10µm C18 30x100mm at a gradient of 40-100% B and a flow rate of 25 mL/min. over 10 minutes with a 10 minute hold. The purified product
5 was concentrated *in vacuo* to give a 42% yield of 2-(4-fluorophenyl)-5-(4-methoxy-3-(2-phenylpropan-2-ylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide as a white solid. The NMR spectrum was recorded at room temperature using a Bruker DRX500 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:
10 Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters
15 Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system
20 and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10
25 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, CD₃OD) δ ppm 1.69 - 1.88 (m, 6 H), 2.99 (s, 3 H), 4.09 (s, 3 H), 7.20 - 7.32 (m, 4 H), 7.36 (t, *J* = 7.63 Hz, 2 H), 7.52 (d, *J* = 8.24 Hz, 2 H), 7.57 - 7.64 (m, 2 H), 7.79 - 7.89 (m, 2 H), 7.96 (t, *J* = 6.10 Hz, 2 H), 8.12 (br. s., 1 H). LCMS *m/z* 537.13 (M+H), *R_t* 2.705 min. HPLC *R_t* 11.563min. (Sunfire C18) and 12.876min. (XBridge phenyl C18), 93 % purity.

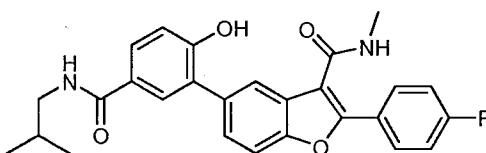
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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-methoxyphenyl)-N-methylbenzofuran-3-carboxamide

[00244] To a 100mL round-bottomed flask was added 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methoxybenzoic acid (1258 mg, 3 mmol), DMF (40mL), 2-methylpropan-1-amine (447 μ L, 4.50 mmol), *N*-ethyl-*N,N*-diisopropylamine (1.1 mL, 6.00 mmol), and finally HATU (2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (3422 mg, 9.00 mmol)). The mixture was stirred over night at room temperature. The crude product was diluted with ethyl acetate, washed with 1M HCl, and extracted. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was loaded onto 40M BIOTAGE® column and purified using a BIOTAGE® Horizon with 2200mL of 0-6% methanol in DCM). The product was concentrated *in vacuo* then triturated with cold acetonitrile to give a 60% yield of 2-(4-fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-methoxyphenyl)-N-methylbenzofuran-3-carboxamide as a light yellow solid. The NMR spectrum was recorded at room temperature using a Bruker DRX500 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column

using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, CD₃OD) δ ppm 0.89 - 1.07 (m, 6 H), 1.96 (dt, *J*=13.43, 6.71 Hz, 1 H), 2.97 (s, 3 H), 3.22 (d, *J*=6.10 Hz, 2 H), 3.80 - 3.98 (m, 3 H), 7.19 (d, *J*=9.46 Hz, 1 H), 7.24 - 7.33 (m, 2 H), 7.52 - 7.57 (m, 1 H), 7.57 - 7.65 (m, 1 H), 7.80 (s, 1 H), 7.84 - 7.92 (m, 2 H), 7.96 - 8.02 (m, 2 H), 8.46 (br. s., 1 H). LCMS *m/z* 475.02 (M+H), *R_t* 2.290 min. HPLC *R_t* 14.374min. (Sunfire C18) and 15.689min. (XBridge phenyl C18), 95 % purity.



2-(4-Fluorophenyl)-5-(2-hydroxy-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

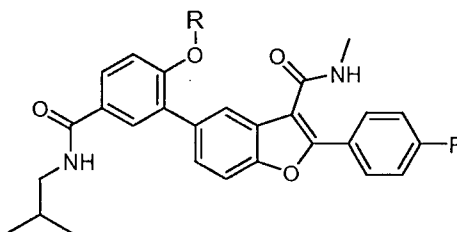
[00245] To a 250mL sealed tube was added toluene (150 mL) 2-(4-fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-methoxyphenyl)-N-methylbenzofuran-3-carboxamide (1.187 g, 2.50 mmol) and finally, under a steady stream of N₂ Boron tribromide-methyl sulfide complex (8.76 g, 28.0 mmol) was quickly added. The tube was sealed and heated to 100 °C in an oil bath for 30 hours. The crude reaction mixture was cooled to room temperature, filtered, washed with wet hexane, then diethyl ether and dried overnight under vacuum to give a 96% yield of a tan solid. The NMR spectrum was recorded at room temperature using a Bruker DRX500 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x

150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The

5 HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM

10 ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, DMF-d₇) δ ppm 0.92 (d, *J* = 6.71 Hz, 6 H), 1.86 - 1.97 (m, 1 H), 2.94 - 2.98 (m, 3 H), 3.17 - 3.23 (m, 2 H), 7.19 (d, *J* = 8.55 Hz, 1 H), 7.42 (t, *J* = 9.00 Hz, 2 H), 7.66 - 7.75 (m, 2 H), 7.88 (dd, *J* = 8.39, 2.29 Hz, 1 H), 8.06 - 8.14 (m, 3 H), 8.37 - 8.46 (m, 2 H). LCMS *m/z* 461.95 (M+H), *R_t*

15 2.033 min. HPLC *R_t* 8.929min. (Sunfire C18) and 11.454min. (XBridge phenyl C18), 96 % purity.

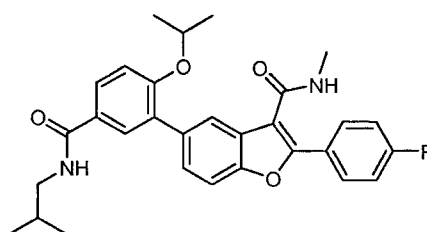


[00246] General procedure: To a 2 dram vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide (46.0

20 mg, 0.1 mmol), DMF (2 mL), and 1.5 equivalents (0.15mmol) of either triethyl amine or potassium carbonate and 1.5 equivalents (0.15mmol) of alkyl bromide. The vials were sealed and shaken at 22-70 °C in a dry bath. Upon reaction completion the crude products were concentrated, diluted with 2mL of acetonitrile and purified using

25 a Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% H₂O/ 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5 μ m C18 4.6 x 100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 8

minutes with a 10 minute hold. The desired products were evaporated to dryness in a Savant SPEEDVAC® overnight obtaining 25-60% yield of the desired ethers as white powders.

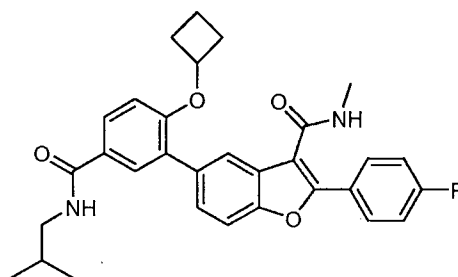


5

2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-isopropoxyphenyl)-N-methylbenzofuran-3-carboxamide

[00247] ^1H NMR (500 MHz, CD_3OD) δ ppm 1.00 (d, $J = 6.71$ Hz, 6 H), 1.32 (d, $J = 6.10$ Hz, 6 H), 1.87 - 2.05 (m, 1 H), 2.98 (s, 3 H), 3.22 (d, $J = 7.02$ Hz, 2 H), 4.64 - 4.79 (m, 1 H), 7.18 (d, $J = 8.55$ Hz, 1 H), 7.24 - 7.36 (m, 2 H), 7.57 - 7.67 (m, 2 H), 7.85 (dd, $J = 8.55, 2.44$ Hz, 1 H), 7.87 (s, 1 H), 7.90 (d, $J = 2.44$ Hz, 1 H), 7.95 - 8.01 (m, 2 H). LCMS m/z 503.12 (M+H), R_t 2.368 min. HPLC R_t 10.789min. (Sunfire C18) and 12.428min. (XBridge phenyl C18), 98.7 % purity.

10



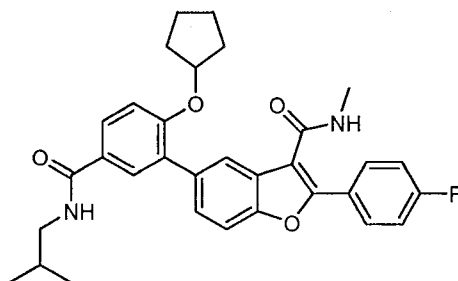
15

5-(2-(Cyclobutyloxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00248] ^1H NMR (500 MHz, CD_3OD) δ ppm 0.99 (d, $J = 6.41$ Hz, 6 H), 1.71 - 1.81 (m, 1 H), 1.83 - 1.91 (m, 1 H), 1.92 - 2.00 (m, 1 H), 2.08 - 2.20 (m, 2 H), 2.45 - 2.56 (m, 2 H), 2.99 (s, 3 H), 3.22 (d, $J = 6.71$ Hz, 2 H), 4.80 - 4.84 (m, 1 H), 7.01 (d, $J = 8.55$ Hz, 1 H), 7.28 (t, $J = 8.55$ Hz, 2 H), 7.58 - 7.66 (m, 2 H), 7.83 (d, $J = 8.24$ Hz, 1 H), 7.86 - 7.92 (m, 2 H), 7.96 - 8.03 (m, 2 H). LCMS m/z 515.21 (M+H), R_t 2.613

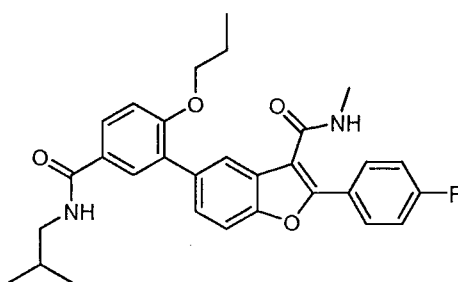
20

min. HPLC *R_t* 11.161min. (Sunfire C18) and 12.693min. (XBridge phenyl C18), 97 % purity.



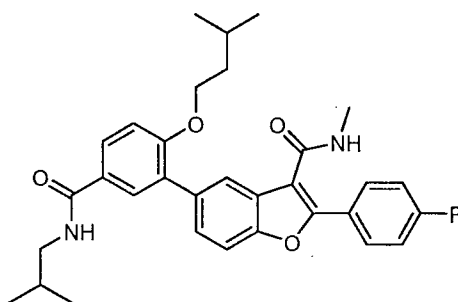
- 5 5-(2-(Cyclopentyloxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00249] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.04 (d, *J* = 6.78 Hz, 6 H), 1.63 - 1.82 (m, 4 H), 1.83 - 2.08 (m, 5 H), 3.02 (s, 3 H), 3.27 (d, *J* = 7.03 Hz, 2 H), 5.02 (ddd, *J* = 5.21, 2.89, 2.70 Hz, 1 H), 7.21 (d, *J* = 8.78 Hz, 1 H), 7.28 - 7.36 (m, 2 H),
10 7.58 - 7.69 (m, 2 H), 7.88 (dd, *J* = 8.53, 2.51 Hz, 1 H), 7.91 (d, *J* = 1.25 Hz, 1 H), 7.95 (d, *J* = 2.26 Hz, 1 H), 7.99 - 8.06 (m, 2 H). LCMS *m/z* 529.16 (M+H), *R_t* 2.685 min. HPLC *R_t* 12.879min. (XBridge phenyl C18), 100 % purity.



- 15 2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-propoxyphenyl)-N-methylbenzofuran-3-carboxamide

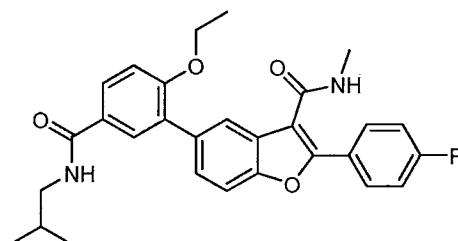
[00250] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.04 (m, 9 H), 1.75 - 1.90 (m, 2 H), 1.93 - 2.10 (m, 1 H), 3.02 (s, 3 H), 3.27 (d, *J* = 7.03 Hz, 2 H), 4.11 (t, *J* = 6.15 Hz, 2 H), 7.21 (d, *J* = 8.53 Hz, 1 H), 7.32 (t, *J* = 8.78 Hz, 2 H), 7.59 - 7.72 (m, 2 H), 7.88 -
20 7.98 (m, 3 H), 7.98 - 8.08 (m, 2 H). LCMS *m/z* 503.14 (M+H), *R_t* 2.548 min. HPLC *R_t* 12.554min. (XBridge phenyl C18), 100 % purity.



2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(isopentyloxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00251] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.93 - 1.01 (m, 6 H), 1.04 (d, $J = 6.78$ Hz, 6 H), 1.69 (q, $J = 6.53$ Hz, 2 H), 1.83 (ddd, $J = 13.61, 6.71, 6.53$ Hz, 1 H), 2.01 (dt, $J = 13.74, 6.81$ Hz, 1 H), 3.03 (s, 3 H), 3.27 (d, $J = 7.03$ Hz, 2 H), 4.18 (t, $J = 6.27$ Hz, 2 H), 7.22 (d, $J = 8.78$ Hz, 1 H), 7.28 - 7.39 (m, 2 H), 7.56 - 7.72 (m, 2 H), 7.86 - 7.98 (m, 3 H), 7.99 - 8.09 (m, 2 H). LCMS m/z 531.16 (M+H), R_t 2.791 min. HPLC R_t 13.122min. (XBridge phenyl C18), 100 % purity.

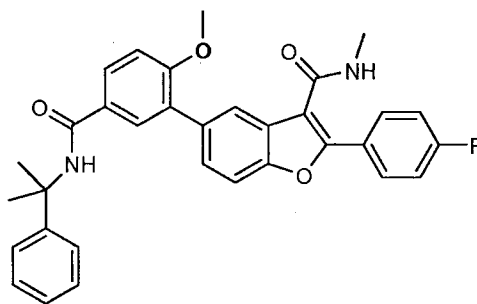
10



2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-ethoxyphenyl)-N-methylbenzofuran-3-carboxamide

[00252] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.04 (d, $J = 6.53$ Hz, 6 H), 1.42 (t, $J = 6.78$ Hz, 3 H), 1.90 - 2.11 (m, 1 H), 3.02 (s, 3 H), 3.27 (d, $J = 7.03$ Hz, 2 H), 4.22 (q, $J = 6.78$ Hz, 2 H), 7.18 - 7.24 (m, 1 H), 7.29 - 7.38 (m, 2 H), 7.64 - 7.67 (m, 2 H), 7.87 - 7.93 (m, 2 H), 7.93 - 7.96 (m, 1 H), 8.00 - 8.08 (m, 2 H). LCMS m/z 489.15 (M+H), R_t 2.432 min. HPLC R_t 10.571min. (Sunfire C18) and 12.193min. (XBridge phenyl C18), 93 % purity.

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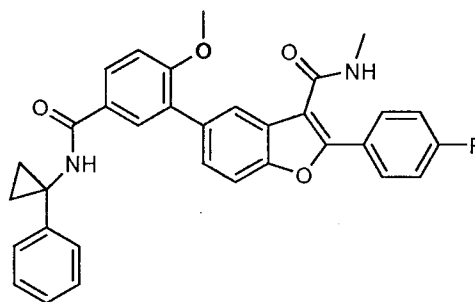


2-(4-Fluorophenyl)-5-(2-methoxy-5-(2-phenylpropan-2-ylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

- [00253] To a 50mL RBF was added 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methoxybenzoic acid (433.9 mg, 1.035 mmol), DMF (15 mL), 2-phenylpropan-2-amine (210 mg, 1.552 mmol), N-ethyl-N-isopropylpropan-2-amine (0.360 mL, 2.069 mmol), and finally HATU, 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (1180 mg, 3.10 mmol). The mixture was stirred over night at room temperature. The resulting mixture was diluted with dichloromethane, washed with 0.5M HCl, then brine and dried over MgSO₄. The solution was concentrated to give a tan oil. The crude product was taken up in 10mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% H₂O/ 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile/ 0.1% trifluoroacetic acid with a PHENOMENEX® Luna 10µm C18 30 x 100mm column at a gradient of 40-100% B and a flow rate of 40 mL/min. over 8 minutes with a 12 minute hold to give a 80% yield of product as a white powder. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A

= 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column
 5 employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. All NMR spectra were recorded at room temperature using a Bruker
 10 DRX400 spectrometer. LCMS *m/z* 537.18 (M+H), *R_t* 2.492 min. HPLC *R_t* 10.694 min. (Sunfire C18), 99.6% purity and 12.230 min. (XBridge phenyl C18), 99.6 % purity. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.82 (s, 6 H), 3.01 (s, 3 H), 3.94 (s, 3 H), 7.18 - 7.27 (m, 2 H), 7.28 - 7.40 (m, 4 H), 7.50 (d, *J* = 7.53 Hz, 2 H), 7.57 - 7.67 (m, 2 H), 7.85 (d, *J* = 1.00 Hz, 1 H), 7.89 - 7.95 (m, 2 H), 7.98 - 8.09 (m, 2 H).

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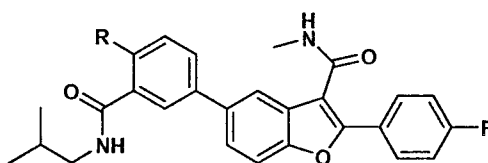


2-(4-Fluorophenyl)-5-(2-methoxy-5-(1-phenylcyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

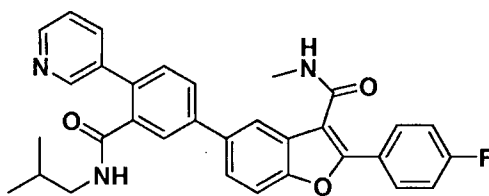
[00254] To a 50mL RBF was added 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methoxybenzoic acid (433.9 mg, 1.035 mmol),
 20 DMF (15 mL), 1-phenylcyclopropan- amine, HCl (214 mg, 1.259 mmol), N-ethyl-N-isopropylpropan-2-amine (0.438 mL, 2.52 mmol), and finally HATU, 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (1180 mg, 3.10 mmol). The mixture was stirred over night
 25 at room temperature. The reaction mixture was diluted with dichloromethane, washed with 0.5M HCl, then brine and dried over MgSO₄. The solution was concentrated to give a tan oil. The crude product was taken up in 10mL of

acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% H₂O/ 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile/ 0.1% trifluoroacetic acid with a PHENOMENEX® Luna 10µm C18 30 x 100mm column at a gradient of 40-100% B and a flow rate of 40 mL/min. over 8 minutes with a 12 minute hold to give a 77% yield of product as a white powder. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 220nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. All NMR spectra were recorded at room temperature using a Bruker DRX400 spectrometer. LCMS *m/z* 535.16 (M+H), *R_t* 2.373 min. HPLC *R_t* 10.314 min. (Sunfire C18), 95.78% purity and 12.230 min. (XBridge phenyl C18), 99.6 % purity. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.40 (dd, *J* = 7.03, 2.01 Hz, 4 H), 3.01 (s, 3 H), 3.94 (s, 3 H), 7.18 - 7.26 (m, 2 H), 7.28 - 7.38 (m, 6 H), 7.56 - 7.62 (m, 1 H), 7.62 - 7.67 (m, 1 H), 7.85 (d, *J* = 1.51 Hz, 1 H), 7.94 - 8.05 (m, 4 H).

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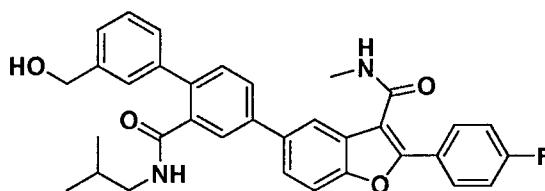
[00255] General procedure: To a BIOTAGE® microwave vial (2-5 mL) was added 5-(4-chloro-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.075 mmol, 1 eq.) in dry 1,4-Dioxane (1 mL) along with the desired boronic acid (0.150 mmol, 2 eq.), potassium phosphate, tribasic (0.300 mmol, 52.3 mg) in water (0.2 mL), dicyclohexyl(2',6'-dimethoxybiphenyl-3-yl)phosphine (S-Phos) (6.16 mg, 0.015 mmol), and finally palladium (II) acetate (3.37 mg, 0.015 mmol) in 1,4-dioxane (0.5 mL). The vial was flushed with nitrogen then capped and placed into a BIOTAGE® microwave for 10 minutes at 150 °C. The solvent was removed in a Thermo/Savant SPEEDVAC® and the crude products were dissolved in DMF (1.8 mL) and purified by preparative HPLC employing a DIONEX® Prep HPLC system equipped with an ELS (Evaporative Light Scattering) detector. A PHENOMENEX® Gemini 5µm C18 21.2 x 250mm column was used with acetonitrile/HPLC grade water/20mM ammonium acetate where solvent A was HPLC grade water with 20mM ammonium acetate and solvent B was 100% acetonitrile at a gradient of 30-95% B in 23.5 minutes with a 2.5 minute hold at 20mL/minute. HPLC purity was determined using a Waters ZQ with ESCi mass spectrometer with a SUPELCO® Ascentis 2.7 µm C18 4.6 x 50mm column employing acetonitrile/HPLC grade water/0.1% trifluoroacetic acid where solvent A was 5% acetonitrile, 95% HPLC grade water with 0.1% trifluoroacetic acid and solvent B was 95% acetonitrile, 5% HPLC grade water with 0.1% trifluoroacetic acid at a gradient of 10-95% B in 8 minutes with a 1 minute hold at 2mL/minute. The NMR spectra were recorded at room temperature using a Varian 400MHz flow spectrometer. Chemical shifts were reported in ppm relative to the DMSO-d₆/CDCl₃ solvent used.



2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(pyridin-3-yl)phenyl)-*N*-methylbenzofuran-3-carboxamide

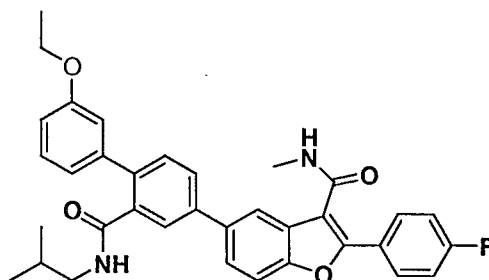
[00256] LCMS m/z 522.19 (M+H), R_t 3.21 min., 100 % purity.

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2-(4-Fluorophenyl)-5-(3'-(hydroxymethyl)-2-(isobutylcarbamoyl)biphenyl-4-yl)-*N*-methylbenzofuran-3-carboxamide

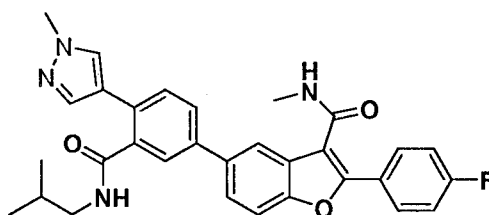
[00257] ^1H NMR δ ppm 0.76 (d, J = 6.74 Hz, 6 H), 1.68 (m, 1 H), 2.29 (s, 3 H),
 10 2.81 - 3.00 (m, 4 H), 7.07 - 7.18 (m, 1 H), 7.22 (t, J = 7.47 Hz, 1 H), 7.26 - 7.37 (m, 2 H), 7.39 (s, 1 H), 7.48 (d, J = 7.91 Hz, 1 H), 7.72 (br. s., 2 H), 7.80 (d, J = 8.20 Hz, 1 H), 7.92 (s, 1 H), 8.01 (dd, J = 7.47, 5.42 Hz, 2 H), 8.22 (s, 2 H), 8.46 (br. s., 1 H).
 LCMS m/z 551.23 (M+H), R_t 4.23 min., 100 % purity.



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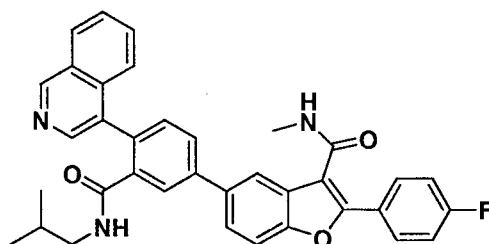
5-(3'-Ethoxy-2-(isobutylcarbamoyl)biphenyl-4-yl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00258] LCMS m/z 565.24 (M+H), R_t 5.28 min., 93.4 % purity.



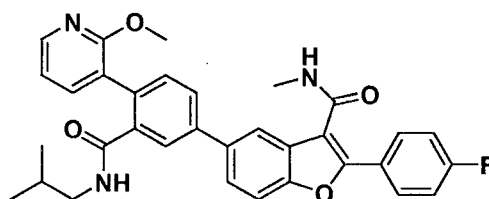
2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-
N-methylbenzofuran-3-carboxamide

[00259] ^1H NMR δ ppm 0.93 (d, J = 6.74 Hz, 6 H), 1.82 - 1.99 (m, 1 H), 2.37 (s, 3 H), 2.89 - 3.00 (m, 2 H), 3.94 (s, 3 H), 7.15 - 7.25 (m, 1 H), 7.25 - 7.33 (m, 1 H), 7.39 (t, J = 8.20 Hz, 1 H), 7.62 - 7.82 (m, 5 H), 7.93 (d, J = 12.89 Hz, 1 H), 8.02 - 8.12 (m, 1 H), 8.36 - 8.45 (m, 1 H), 8.53 (d, 1 H). LCMS m/z 525.21 (M+H), R_t 4.00 min., 100 % purity.



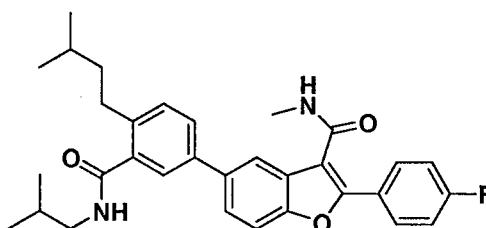
2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(isoquinolin-4-yl)phenyl)-N-
methylbenzofuran-3-carboxamide

[00260] ^1H NMR δ ppm 0.64 (d, J = 6.44 Hz, 6 H), 1.38 - 1.48 (m, 1 H), 2.37 (s, 3 H), 2.93 - 3.02 (m, 2 H), 7.14 - 7.24 (m, 2 H), 7.25 - 7.33 (m, 2 H), 7.40 (t, J = 8.79 Hz, 1 H), 7.57 (d, J = 7.32 Hz, 1 H), 7.75 (br. s., 2 H), 7.81 - 7.90 (m, 1 H), 7.95 - 8.03 (m, 2 H), 8.08 (br. s., 2 H), 8.18 - 8.25 (m, 1 H), 8.31 - 8.37 (m, 1 H), 8.48 (s, 1 H), 8.55 (br. s., 1 H). LCMS m/z 572.22 (M+H), R_t 3.49 min., 100 % purity.



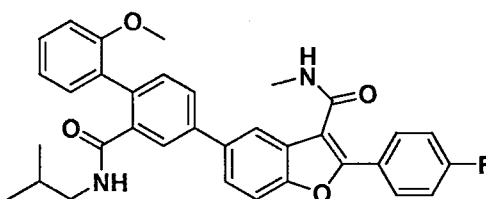
2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(2-methoxypyridin-3-yl)phenyl)-N-
methylbenzo-furan-3-carboxamide

[00261] ^1H NMR δ ppm 0.88 (d, $J = 6.74$ Hz, 6 H), 1.68 - 1.83 (m, 1 H), 2.37 (s, 3 H), 2.96 (d, $J = 4.69$ Hz, 2 H), 3.86 (s, 3 H), 7.04 - 7.13 (m, 1 H), 7.21 (d, $J = 7.32$ Hz, 1 H), 7.28 (d, $J = 7.03$ Hz, 1 H), 7.39 (t, $J = 8.05$ Hz, 1 H), 7.48 (d, $J = 8.49$ Hz, 1 H), 7.67 (d, $J = 7.03$ Hz, 1 H), 7.82 (s, 2 H), 7.88 (br. s., 2 H), 8.04 (s, 1 H), 8.06 - 8.12 (m, 1 H), 8.18 (d, $J = 4.98$ Hz, 1 H), 8.54 (br. s., 1 H). LCMS m/z 552.21 (M+H), R_t 4.56 min., 90.5 % purity.



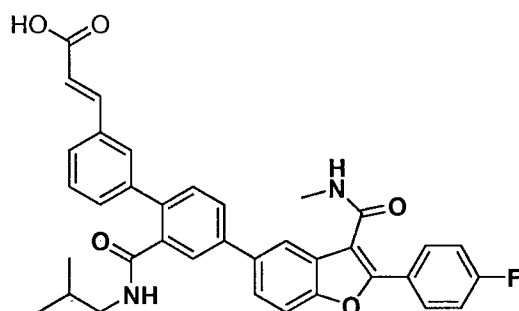
2-(4-Fluorophenyl)-5-(2-(isobutylcarbamoyl)-4'-isopentylbiphenyl-4-yl)-*N*-methylbenzofuran-3-carboxamide

[00262] ^1H NMR δ ppm 0.99 (dd, $J = 12.74, 6.59$ Hz, 9 H), 1.23 - 1.37 (m, 3 H), 1.59 - 1.70 (m, 1 H), 1.88 - 2.00 (m, 1 H), 2.37 (s, 3 H), 2.76 - 2.87 (m, 2 H), 2.91 - 2.99 (m, 2 H), 3.10 - 3.20 (m, 2 H), 7.14 - 7.25 (m, 1 H), 7.29 (t, $J = 7.32$ Hz, 1 H), 7.38 (t, $J = 8.05$ Hz, 2 H), 7.64 (s, 1 H), 7.72 (dd, $J = 16.26, 8.05$ Hz, 2 H), 7.93 (s, 1 H), 8.01 - 8.11 (m, 2 H), 8.44 (br. s., 1 H), 8.52 (br. s., 1 H). LCMS m/z 515.26 (M+H), R_t 5.63 min., 100 % purity.



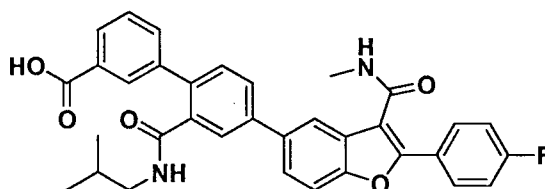
2-(4-Fluorophenyl)-5-(2-(isobutylcarbamoyl)-2'-methoxybiphenyl-4-yl)-*N*-methylbenzofuran-3-carboxamide

[00263] ^1H NMR δ ppm 0.85 (d, $J = 6.74$ Hz, 6 H), 1.63 - 1.77 (m, 1 H), 2.37 (s, 3 H), 2.96 (d, $J = 4.39$ Hz, 2 H), 3.77 (s, 3 H), 6.99 - 7.09 (m, 1 H), 7.21 (d, $J = 7.62$ Hz, 1 H), 7.29 (t, $J = 7.62$ Hz, 2 H), 7.34 - 7.46 (m, 3 H), 7.76 - 7.88 (m, 3 H), 7.92 - 7.98 (m, 1 H), 8.02 (s, 1 H), 8.09 (dd, $J = 7.76, 6.00$ Hz, 2 H), 8.54 (br. s., 1 H). LCMS m/z 551.22 (M+H), R_t 5.07 min., 93.7 % purity.



(*E*)-3-(4'-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2'-(isobutylcarbamoyl)biphenyl-3-yl)acrylic acid

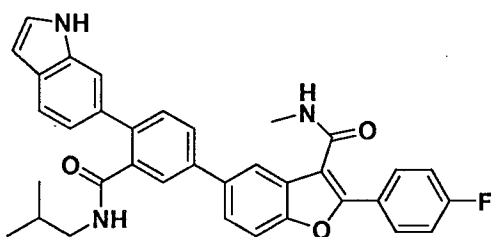
- 5 [00264] ^1H NMR δ ppm 0.81 (d, $J = 6.44$ Hz, 6 H), 1.65 - 1.77 (m, 1 H), 2.37 (s, 3 H), 2.96 (d, $J = 4.39$ Hz, 2 H), 6.55 (d, $J = 15.82$ Hz, 1 H), 7.14 - 7.25 (m, 2 H), 7.25 - 7.33 (m, 1 H), 7.40 (t, $J = 8.49$ Hz, 2 H), 7.47 - 7.56 (m, 1 H), 7.61 (d, $J = 8.20$ Hz, 1 H), 7.67 (br. s., 1 H), 7.73 (br. s., 1 H), 7.80 (br. s., 2 H), 7.90 (d, $J = 7.91$ Hz, 1 H), 8.01 (s, 1 H), 8.04 - 8.13 (m, 1 H), 8.36 (br. s., 1 H), 8.53 (br. s., 1 H). LCMS m/z
- 10 591.23 (M+H), R_t 4.37 min., 100 % purity.



4'-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2'-(isobutylcarbamoyl)biphenyl-3-carboxylic acid

- 15 [00265] ^1H NMR δ ppm 0.80 (d, $J = 6.74$ Hz, 6 H), 1.67 - 1.79 (m, 1 H), 2.37 (s, 3 H), 2.96 (d, $J = 4.69$ Hz, 2 H), 7.16 - 7.25 (m, 2 H), 7.26 - 7.32 (m, 1 H), 7.33 - 7.44 (m, 2 H), 7.50 - 7.62 (m, 2 H), 7.66 - 7.73 (m, 1 H), 7.76 - 7.84 (m, 2 H), 7.90 (d, $J = 7.91$ Hz, 1 H), 7.95 - 8.02 (m, 1 H), 8.04 - 8.14 (m, 2 H), 8.32 - 8.37 (m, 1 H), 8.55 (br. s., 1 H). LCMS m/z 565.22 (M+H), R_t 4.22 min., 100 % purity.

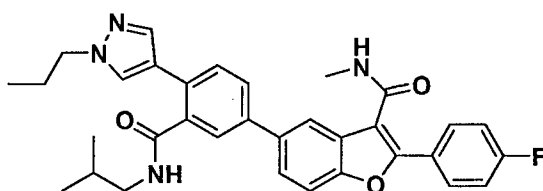
20



5-(4-(1*H*-Indol-6-yl)-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00266] LCMS m/z 560.23 (M+H), R_t 4.90 min., 97.2 % purity.

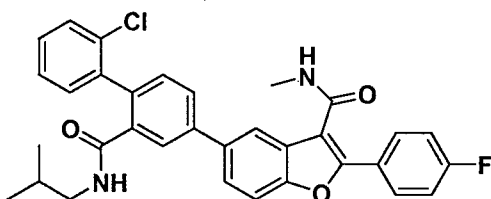
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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(1-propyl-1*H*-pyrazol-4-yl)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00267] LCMS m/z 553.25 (M+H), R_t 4.49 min., 96 % purity.

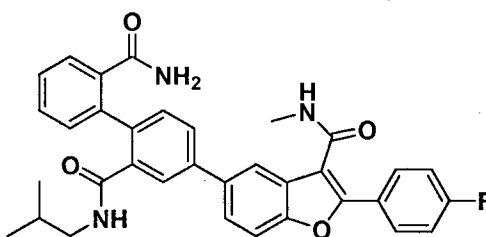
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5-(2'-Chloro-2-(isobutylcarbamoyl)biphenyl-4-yl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

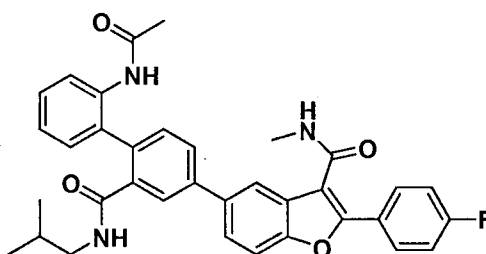
[00268] ^1H NMR δ ppm 0.85 (d, J = 6.44 Hz, 6 H), 1.65 - 1.80 (m, 1 H), 2.37 (s, 3 H), 2.93 - 2.97 (m, 2 H), 7.06 (br. s., 1 H), 7.15 - 7.24 (m, 2 H), 7.25 - 7.35 (m, 2 H), 7.35 - 7.47 (m, 4 H), 7.49 - 7.55 (m, 1 H), 7.79 - 7.86 (m, 1 H), 7.87 - 7.93 (m, 1 H), 7.98 - 8.13 (m, 2 H), 8.21 - 8.27 (m, 1 H), 8.53 (br. s., 1 H). LCMS m/z 556.19 (M+H), R_t 5.28 min., 100 % purity.

15



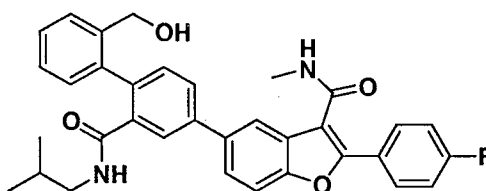
4-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-N2-isobutylbiphenyl-2,2'-dicarboxamide

[00269] ^1H NMR δ ppm 0.69 (d, $J = 6.44$ Hz, 6 H), 1.42 - 1.54 (m, 1 H), 2.37 (s, 3 H), 2.92 - 2.97 (m, 2 H), 7.13 - 7.23 (m, 2 H), 7.23 - 7.33 (m, 2 H), 7.39 (t, $J = 8.64$ Hz, 1 H), 7.43 - 7.51 (m, 2 H), 7.61 (d, $J = 4.69$ Hz, 1 H), 7.75 - 7.82 (m, 2 H), 7.86 (s, 1 H), 7.96 - 8.03 (m, 1 H), 8.08 (d, $J = 5.27$ Hz, 1 H), 8.13 - 8.18 (m, 1 H), 8.51 (br. s., 1 H), 8.65 (br. s., 1 H). LCMS m/z 564.24 (M+H), R_t 4.07 min., 98.9 % purity.



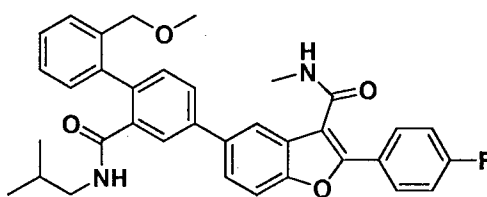
5-(2'-(Acetamido)-2-(isobutylcarbamoyl)biphenyl-4-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00270] ^1H NMR δ ppm 0.50 - 0.73 (m, 6 H), 1.33 - 1.50 (m, 1 H), 1.90 (s, 3 H), 2.37 (s, 3 H), 2.92 - 2.97 (m, 2 H), 7.20 (t, $J = 7.91$ Hz, 3 H), 7.25 - 7.44 (m, 6 H), 7.75 - 7.82 (m, 2 H), 7.91 (s, 1 H), 7.96 - 8.03 (m, 1 H), 8.04 - 8.11 (m, 1 H), 8.24 (br. s., 1 H), 8.52 (br. s., 1 H), 9.89 - 9.96 (m, 1 H). LCMS m/z 578.24 (M+H), R_t 4.26 min., 93.5 % purity.



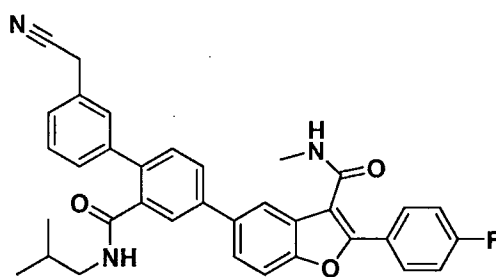
2-(4-Fluorophenyl)-5-(2'-(hydroxymethyl)-2-(isobutylcarbamoyl)biphenyl-4-yl)-*N*-methylbenzofuran-3-carboxamide

[00271] ^1H NMR δ ppm 0.71 (d, $J = 5.27$ Hz, 6 H), 1.45 - 1.57 (m, 1 H), 2.37 (s, 3 H), 2.90 (br. s., 2 H), 2.96 (d, $J = 4.69$ Hz, 2 H), 7.13 - 7.25 (m, 2 H), 7.25 - 7.35 (m, 1 H), 7.35 - 7.44 (m, 3 H), 7.56 (d, $J = 7.32$ Hz, 1 H), 7.81 (s, 2 H), 7.83 - 7.89 (m, 2 H), 8.01 (s, 1 H), 8.09 (dd, $J = 8.64, 5.42$ Hz, 2 H), 8.52 (br. s., 1 H). LCMS m/z 551.22 (M+H), R_t 4.58 min., 96 % purity.



10 2-(4-Fluorophenyl)-5-(2-(isobutylcarbamoyl)-2'-(methoxymethyl)biphenyl-4-yl)-*N*-methylbenzofuran-3-carboxamide

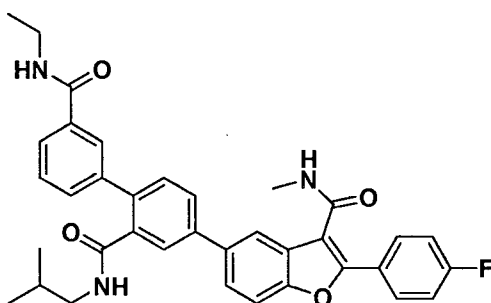
[00272] ^1H NMR δ ppm 0.64 - 0.79 (m, 6 H), 1.47 - 1.59 (m, 1 H), 2.37 (s, 3 H), 2.86 - 2.93 (m, 2 H), 2.93 - 2.99 (m, 2 H), 3.25 (s, 3 H), 7.15 - 7.25 (m, 2 H), 7.26 - 7.32 (m, 1 H), 7.33 - 7.44 (m, 4 H), 7.49 - 7.55 (m, 1 H), 7.81 (s, 2 H), 7.87 (br. s., 2 H), 8.02 (br. s., 1 H), 8.05 - 8.12 (m, 1 H), 8.53 (br. s., 1 H). LCMS m/z 565.22 (M+H), R_t 5.30 min., 100 % purity.



20 5-(3'-(Cyanomethyl)-2-(isobutylcarbamoyl)biphenyl-4-yl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

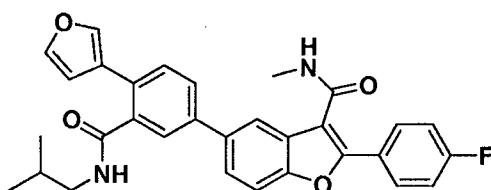
[00273] ^1H NMR δ ppm 0.83 (d, $J = 6.44$ Hz, 6 H), 1.67 - 1.81 (m, 1 H), 2.37 (s, 3 H), 2.96 (d, $J = 4.39$ Hz, 2 H), 4.08 (s, 2 H), 7.14 - 7.25 (m, 2 H), 7.26 - 7.32 (m, 1 H), 7.35 - 7.44 (m, 2 H), 7.48 (d, $J = 5.27$ Hz, 2 H), 7.56 (d, $J = 7.91$ Hz, 1 H), 7.80 (br. s., 2 H), 7.90 (d, $J = 7.62$ Hz, 1 H), 8.00 (s, 1 H), 8.04 - 8.13 (m, 2 H), 8.35 (br. s.,

1 H), 8.54 (d, $J = 3.81$ Hz, 1 H). LCMS m/z 560.23 (M+H), R_t 4.67 min., 91.5 % purity.



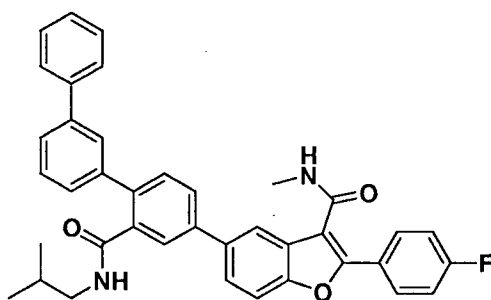
- 5 *N*3'-Ethyl-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-*N*2-isobutylbiphenyl-2,3'-dicarboxamide

[00274] LCMS m/z 592.26 (M+H), R_t 4.28 min., 94.1 % purity.



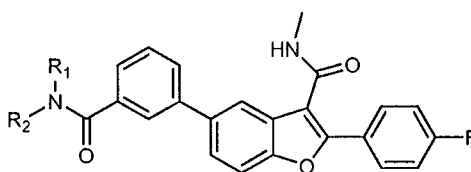
- 10 2-(4-Fluorophenyl)-5-(4-(furan-3-yl)-3-(isobutylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00275] ^1H NMR δ ppm 0.86 - 1.03 (m, 6 H), 1.80 - 1.94 (m, 1 H), 2.37 (s, 3 H), 2.92 - 3.00 (m, 2 H), 6.79 (s, 1 H), 7.15 - 7.24 (m, 2 H), 7.28 (d, $J = 7.03$ Hz, 2 H), 7.35 - 7.42 (m, 1 H), 7.69 (t, $J = 7.91$ Hz, 2 H), 7.73 - 7.85 (m, 3 H), 7.94 (d, $J =$
15 19.33 Hz, 1 H), 8.04 - 8.12 (m, 1 H), 8.41 - 8.48 (m, 1 H), 8.53 (d, 1 H). LCMS m/z 511.17 (M+H), R_t 4.69 min., 86.5 % purity.

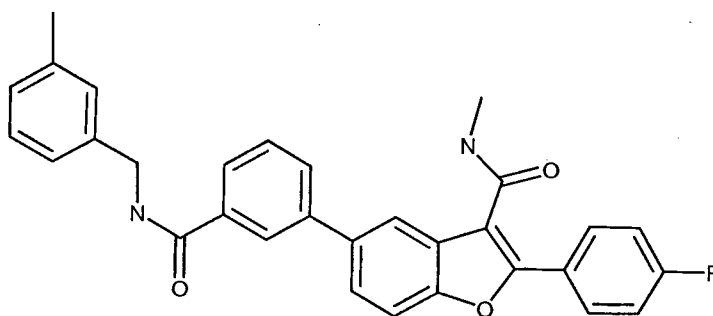


3'-Phenyl-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-N2-isobutylbiphenyl-2,3'-dicarboxamide

[00276] ^1H NMR δ ppm 0.75 (d, $J = 6.74$ Hz, 6 H), 1.59 - 1.72 (m, 1 H), 2.37 (s, 3 H), 2.94 - 2.98 (m, 2 H), 7.15 - 7.24 (m, 3 H), 7.25 - 7.33 (m, 2 H), 7.34 - 7.47 (m, 4 H), 7.49 - 7.58 (m, 2 H), 7.63 - 7.74 (m, 2 H), 7.75 - 7.83 (m, 3 H), 7.89 (br. s., 1 H), 8.00 (s, 1 H), 8.07 (br. s., 1 H), 8.54 (br. s., 1 H). LCMS m/z 597.27 (M+H), R_t 5.74 min., 80 % purity.

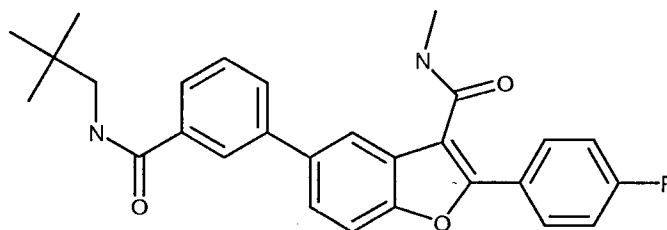


10 [00277] The general procedures (for amide formations) below pertain to the experimental procedures. Some of the compounds were made with different scales of the acids. The acid (0.075 mmol, 1 eq.) was dissolved in dried DMF and followed by adding HATU (0.090 mmol, 1.2 eq.) and DIPEA (0.225 mmol, 3.0 eq.). The solution was stirred for 2 minutes and added into amine (0.090 mmol, 1.2 eq.) at room
15 temperature. The mixture was stirred 14 h and purified by prep-HPLC.



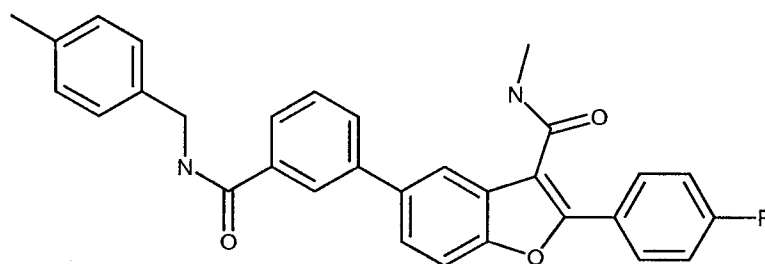
2-(4-Fluorophenyl)-N-methyl-5-(3-(3-methylbenzylcarbamoyl)phenyl)benzofuran-3-carboxamide

20 [00278] ^1H NMR (600 MHz, DMSO- d_6 - CDCl_3) δ ppm 9.15 (1 H, t, $J = 5.86$ Hz), 8.48 (1 H, d, $J = 4.69$ Hz), 8.27 (2 H, d, $J = 4.69$ Hz), 8.00 - 8.08 (1 H, m), 7.92 - 7.97 (2 H, m), 7.89 (1 H, d, $J = 7.62$ Hz), 7.77 (2 H, s), 7.61 (1 H, t, $J = 7.62$ Hz), 7.37 (2 H, t, $J = 8.50$ Hz), 7.24 (1 H, t, $J = 7.32$ Hz), 7.14 - 7.22 (2 H, m), 7.08 (1 H, d, $J = 7.03$ Hz), 4.54 (2 H, d, $J = 5.86$ Hz), 2.92 (3 H, d, $J = 4.10$ Hz), 2.34 (3 H, s).



2-(4-Fluorophenyl)-N-methyl-5-(3-(neopentylcarbamoyl)phenyl)benzofuran-3-carboxamide

- 5 [00279] ^1H NMR (600 MHz, DMSO- d_6 - CDCl_3) δ ppm 8.44 - 8.51 (m, 2 H), 8.27 (s, 1 H), 8.20 (s, 1 H), 8.02 - 8.07 (m, 1 H), 7.96 (s, 1 H), 7.88 (t, $J=7.32$ Hz, 2 H), 7.77 (s, 2 H), 7.59 (t, $J=7.62$ Hz, 1 H), 7.37 (t, $J=8.50$ Hz, 2 H), 3.20 (d, $J=6.44$ Hz, 2 H), 2.92 (d, $J=4.69$ Hz, 3 H), 0.98 (s, 9 H).



10

2-(4-Fluorophenyl)-N-methyl-5-(3-(4-methylbenzylcarbamoyl)phenyl)benzofuran-3-carboxamide

- [00280] ^1H NMR (600 MHz, DMSO- d_6 - CDCl_3) δ ppm 9.14 (t, $J=5.86$ Hz, 1 H), 8.48 (d, $J=4.69$ Hz, 1 H), 8.27 (s, 1 H), 8.25 (s, 1 H), 8.01 - 8.06 (m, 1 H), 7.95 (s, 1 H), 7.93 (d, $J=7.62$ Hz, 1 H), 7.89 (d, $J=7.62$ Hz, 1 H), 7.77 (s, 2 H), 7.61 (t, $J=7.62$ Hz, 1 H), 7.37 (t, $J=8.50$ Hz, 2 H), 7.27 (d, $J=7.62$ Hz, 2 H), 7.16 (d, $J=7.62$ Hz, 2 H), 4.52 (d, $J=5.86$ Hz, 2 H), 2.92 (d, $J=4.10$ Hz, 3 H), 2.30 - 2.35 (m, 3 H).
- 15

- [00281] HPLC purity was determined using a Waters LCT Mass Spectrometer with four way MUX source analytical LC at 220nm with employing acetonitrile and water or Waters ZQ with ESCi mass spectrometer. A = 5:95 CH_3CN :Water; B = 95:5 CH_3CN :Water; Modifier = 10 mM NH_4OAc . Retention time was recorded in minutes.
- 20

Analytical Method A:

Column Waters XTERRA® 2.1x50mm 5 um C18

Time	B%	Flow
0.00	0	1.0
4.00	100	1.0
5.00	100	1.0

Analytical Method B:

5 Column: Waters XBridge 2.1x50mm 5 um C18

Time	B%	Flow
0.00	0	1.0
4.00	100	1.0
5.00	100	1.0
5.05	100	1.0
6.00	0	1.0

Analytical Method C:

Column: Waters XBridge 4.6x50mm 5 um C18

Time	B%	Flow
0.00	0	2.0
8.00	100	2.0
9.00	100	2.0

10 Analytical Method D:

Column: Waters XBridge 4.6x50mm 5 um C18

Time	B%	Flow
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8.00	100	1.0
9.00	100	1.0
9.10	100	1.0

Time	B%	Flow
1.00	0	10

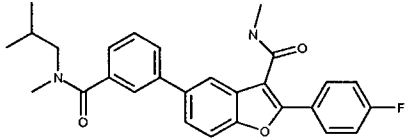
Analytical Method E:
Waters ZQ with ESCi mass spectrometer
Column: SUPELCO® Ascentis 4.6x50mm 2.7 um C18

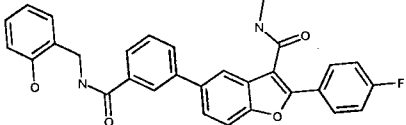
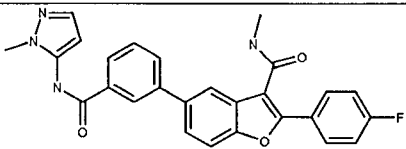
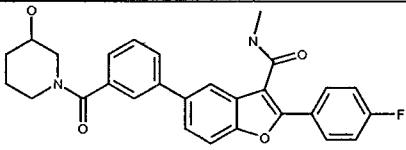
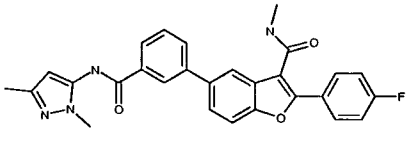
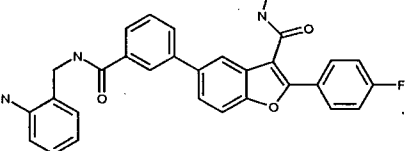
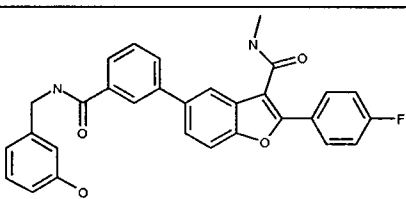
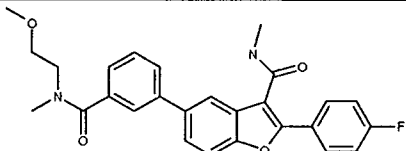
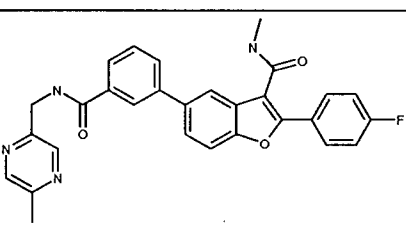
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5.30	95	3.00
6.00	95	3.00
6.20	10	3.00
7.00	10	3.00

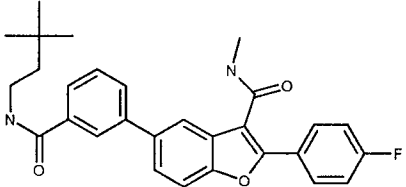
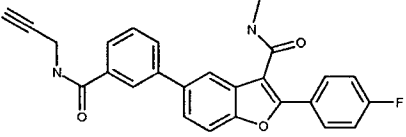
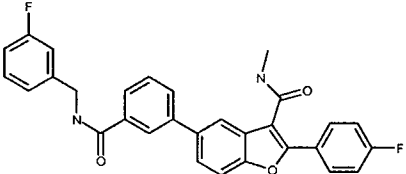
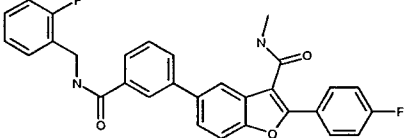
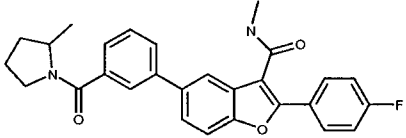
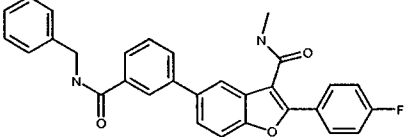
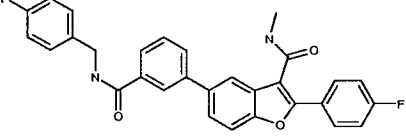
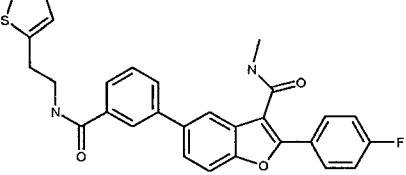
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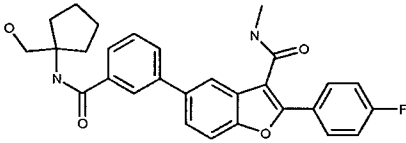
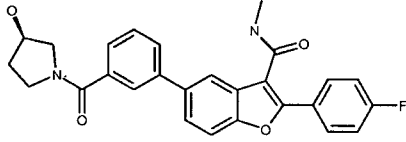
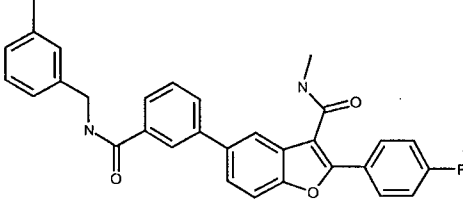
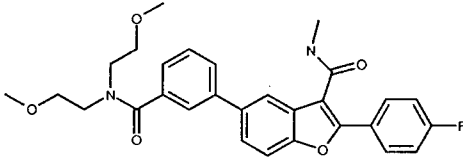
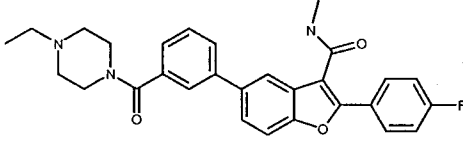
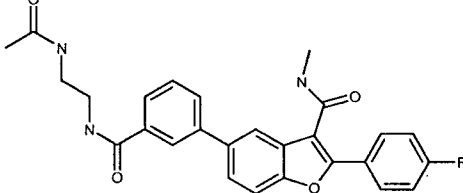
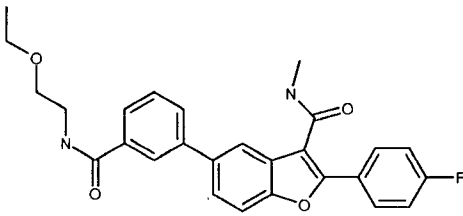
Analytical Method F:
Waters ZQ with ESCi mass spectrometer
Column: PHENOMENEX® Gemini 4.6x150mm 3 um C18

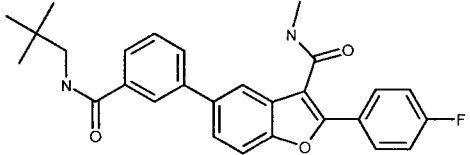
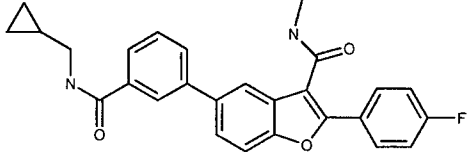
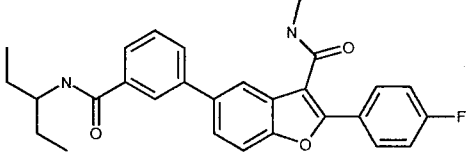
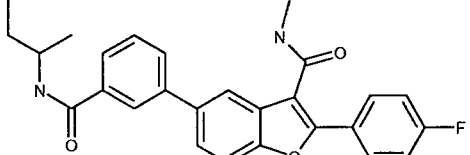
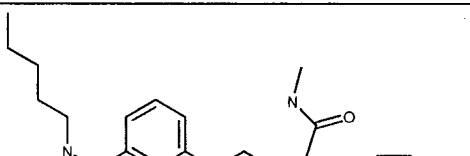
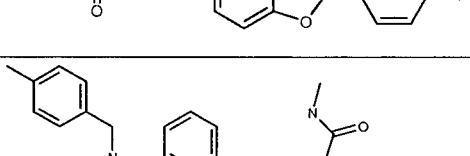
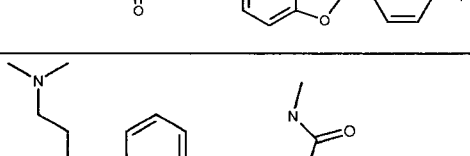
Time	B%	Flow
0.00	10	1.0
10.00	95	1.0
13.00	95	1.0
13.50	10	1.0
15.00	10	1.0

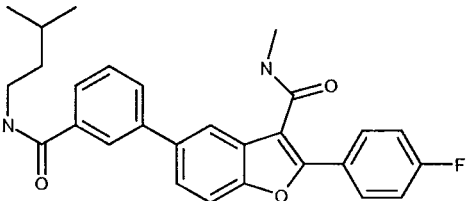
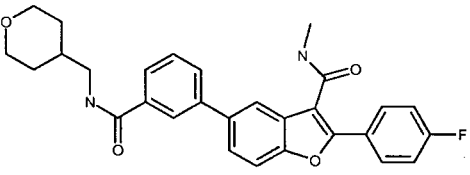
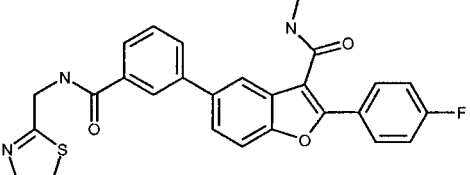
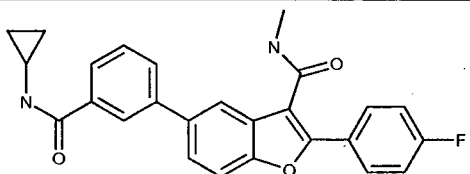
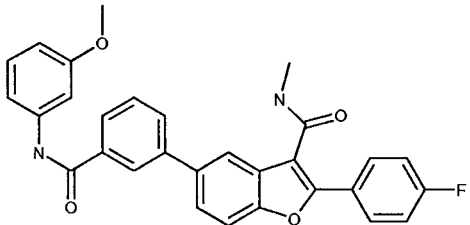
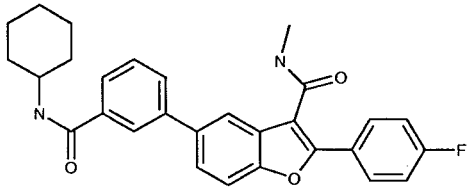
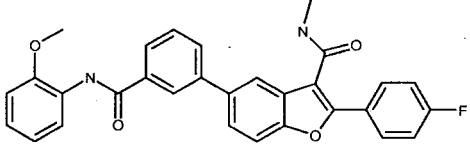
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.81	100	458.93	Method A

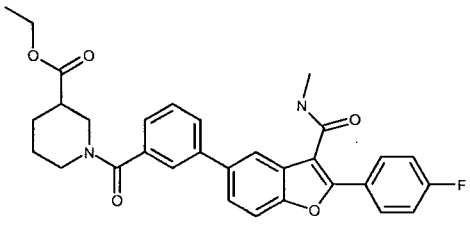
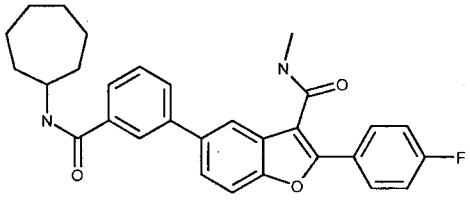
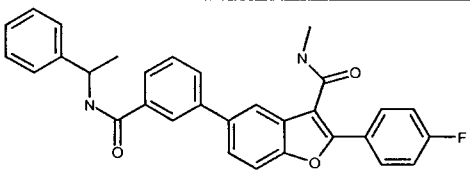
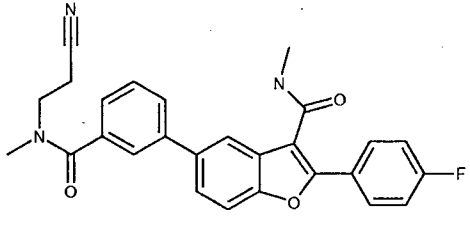
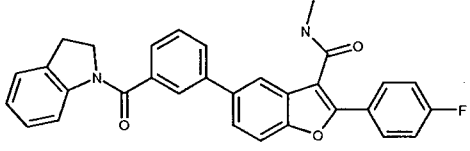
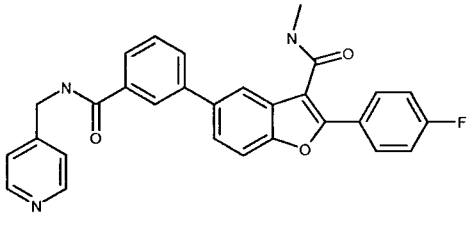
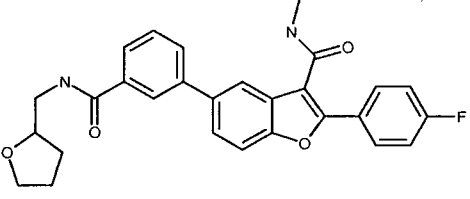
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.75	100	494.89	Method A
	2.38	100	468.9	Method A
	2.22	100	472.91	Method A
	2.46	100	482.9	Method A
	2.68	95.0177	493.92	Method A
	2.5	98.5972	494.9	Method A
	2.42	100	460.91	Method A
	2.34	100	494.9	Method A

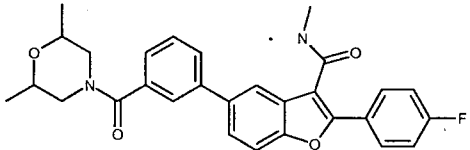
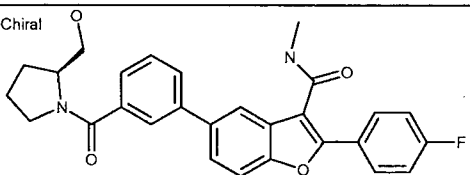
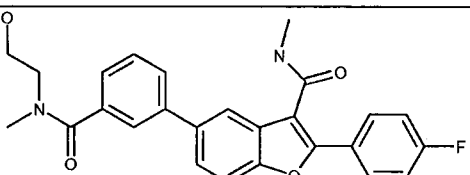
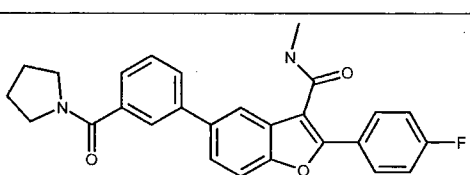
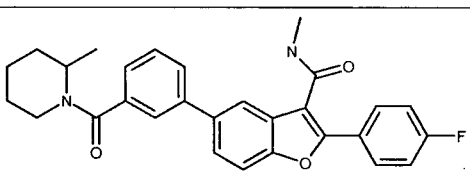
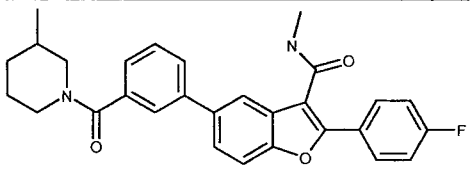
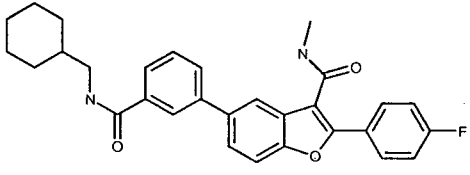
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	3.05	100	472.96	Method A
	2.48	100	426.91	Method A
	2.86	100	513.92	Method A
	2.89	100	513.91	Method A
	2.69	100	456.95	Method A
	2.8	100	495.94	Method A
	2.84	100	513.93	Method A
	2.85	100	498.9	Method A

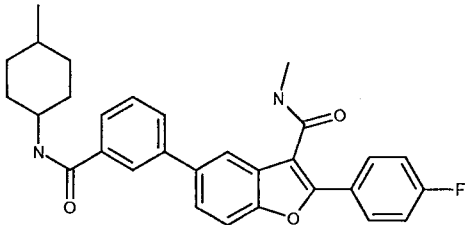
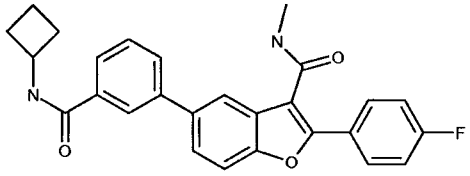
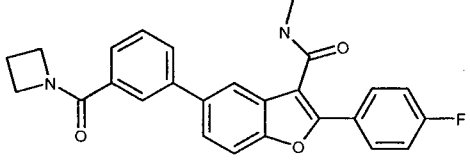
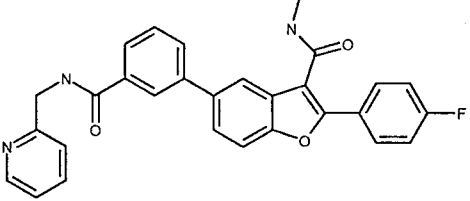
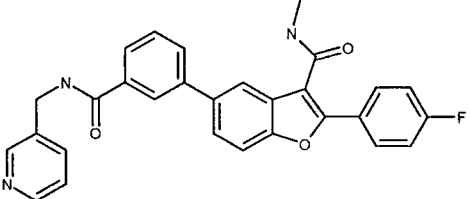
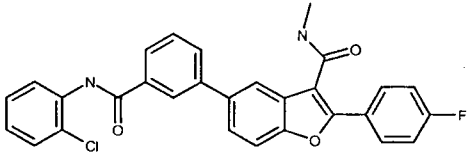
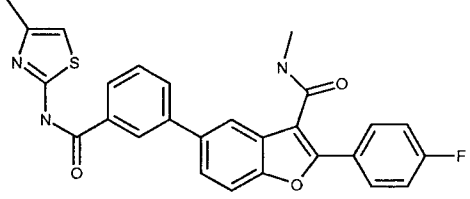
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.56	100	486.94	Method A
Chiral 	2.1	100	458.91	Method A
	2.93	100	509.94	Method A
	2.53	100	504.9	Method A
	2.23	100	485.92	Method A
	2.11	100	473.91	Method A
	2.51	100	460.92	Method A

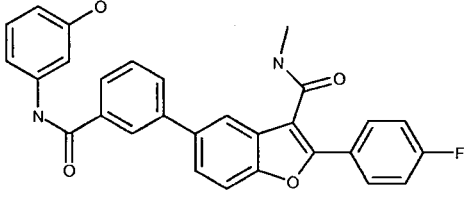
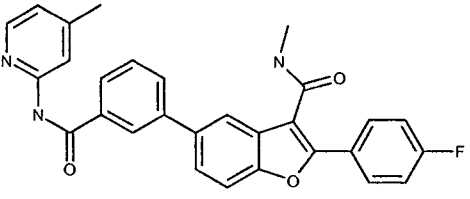
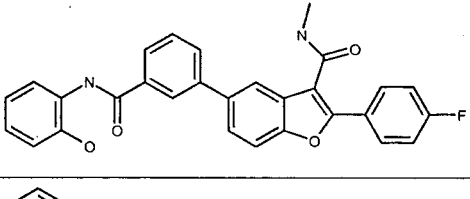
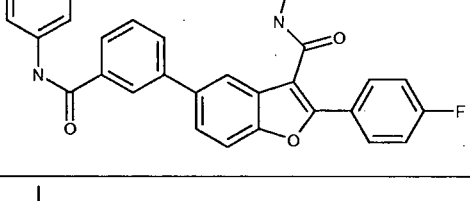
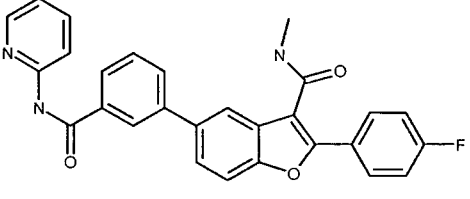
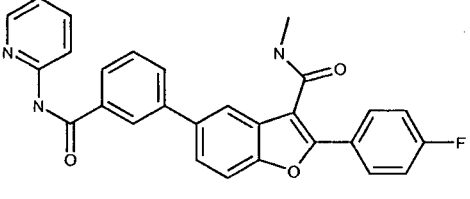
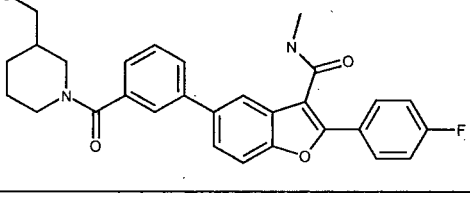
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.89	100	458.94	Method A
	2.62	100	459.94	Method A
	2.85	100	475.95	Method A
	2.72	100	444.94	Method A
	2.91	100	475.95	Method A
	2.97	100	509.93	Method A
	2	100	473.92	Method A

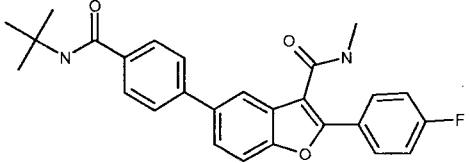
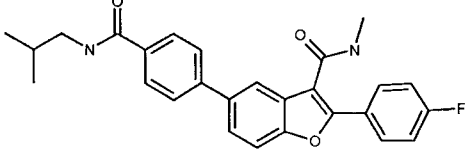
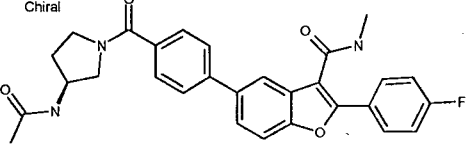
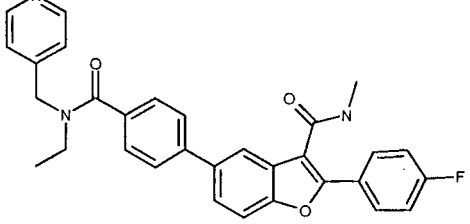
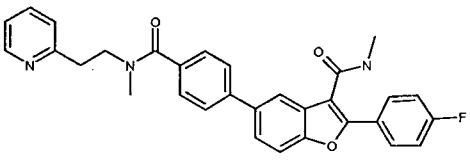
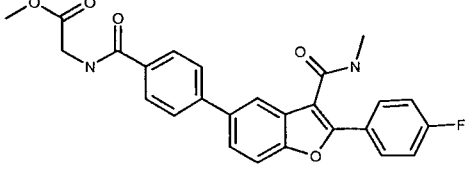
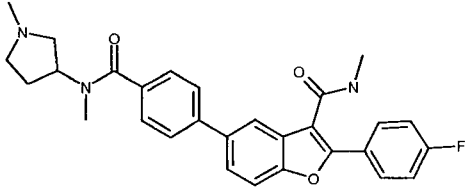
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.89	100	475.95	Method A
	2.43	100	486.93	Method A
	2.44	100	485.85	Method A
	2.39	100	856.65	Method B
	2.81	96.6226	494.8	Method B
	2.75	100	940.66	Method B
	2.89	99.0179	988.56	Method B

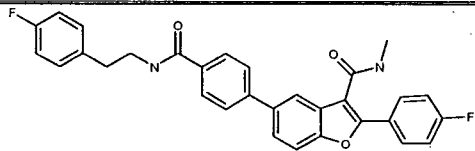
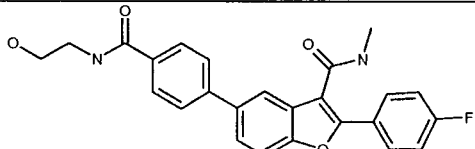
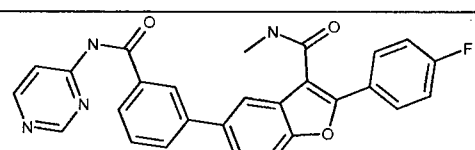
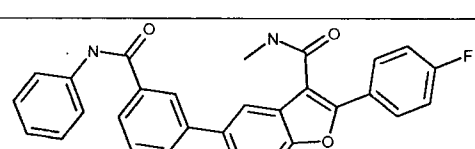
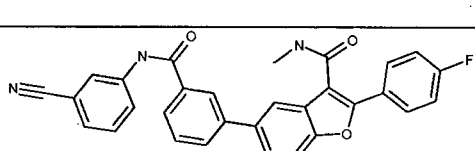
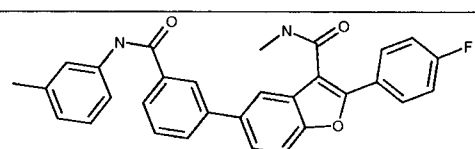
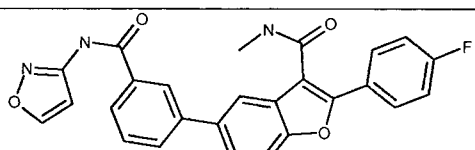
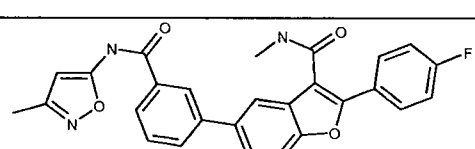
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.7	100	1056.6	Method B
	2.94	89.8624	968.67	Method B
	2.75	100	984.61	Method B
	2.29	100	455.82	Method B
	2.92	98.0936	980.59	Method B
	2.32	98.0376	479.8	Method B
	2.35	100	472.83	Method B

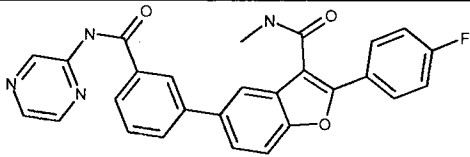
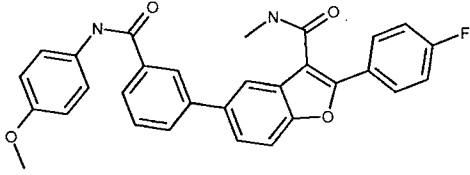
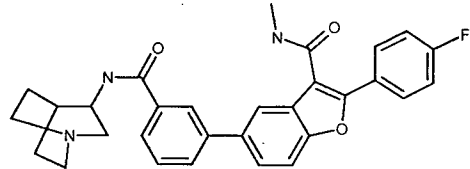
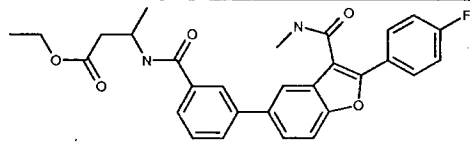
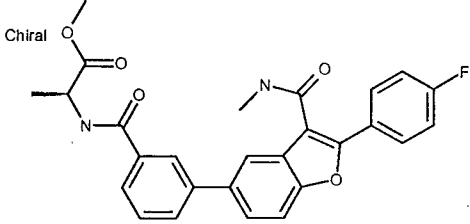
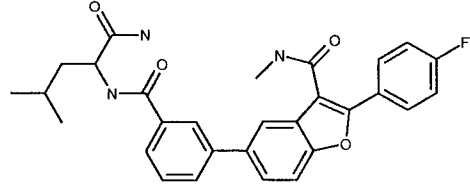
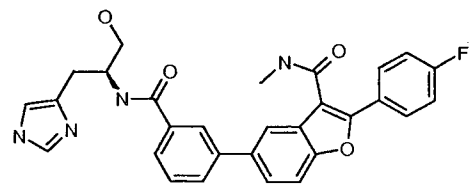
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.56	100	972.64	Method B
Chiral 	2.26	100	472.83	Method B
	2.06	98.6458	892.65	Method B
	2.43	100	884.66	Method B
	2.81	100	940.69	Method B
	2.82	100	940.7	Method B
	2.93	100	968.72	Method B

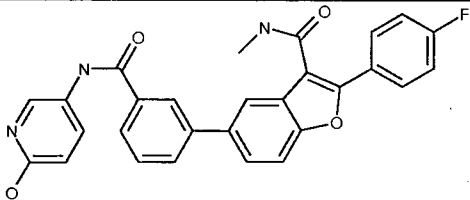
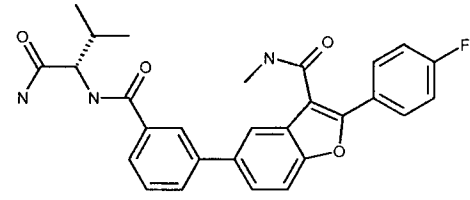
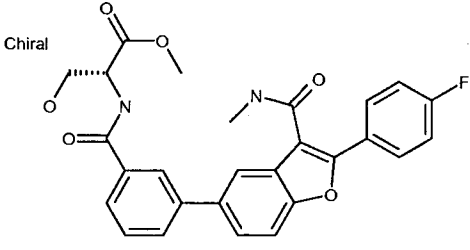
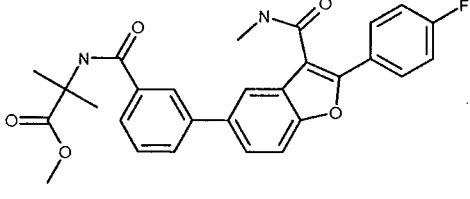
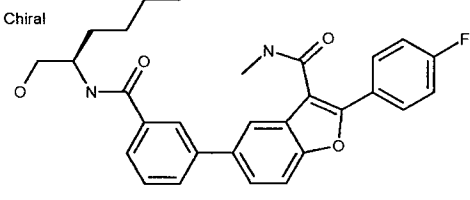
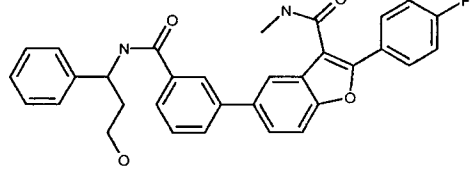
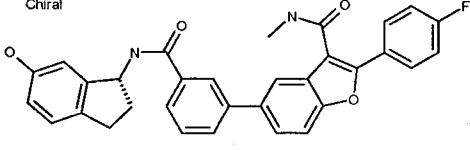
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.95	100	968.7	Method B
	2.6	100	884.67	Method B
	2.35	100	856.66	Method B
	2.34	96.8795	958.6	Method B
	2.26	100	479.81	Method B
	2.82	100	806.66	Method B
	2.75	100	970.55	Method B

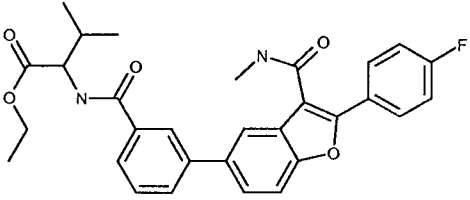
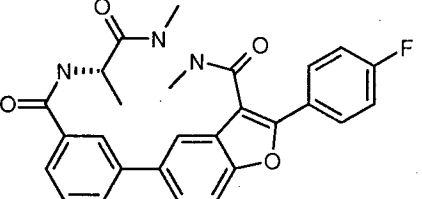
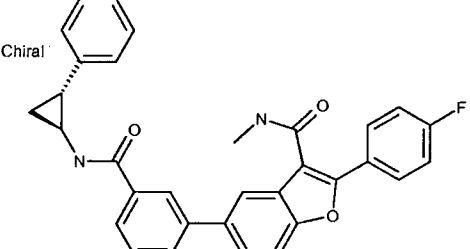
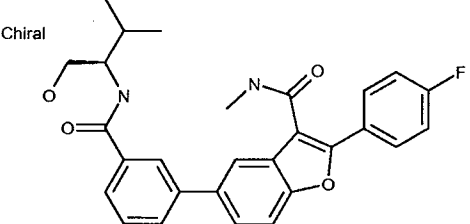
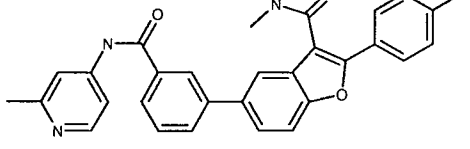
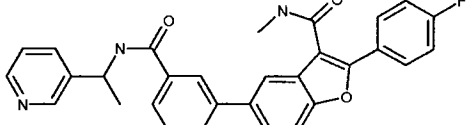
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.48	100	480.8	Method B
	2.77	100	479.81	Method B
	2.7	98.233	480.8	Method B
	2.57	100	465.64	Method B
	2.85	97.8741	958.25	Method B
	2.64	100	930.26	Method B
	2.24	100	972.33	Method B

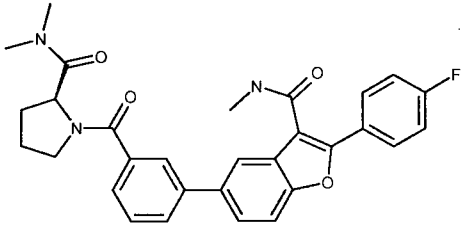
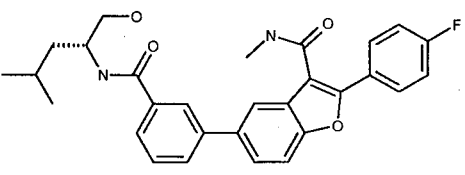
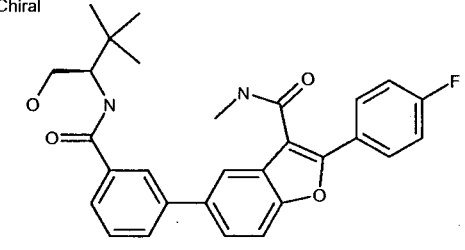
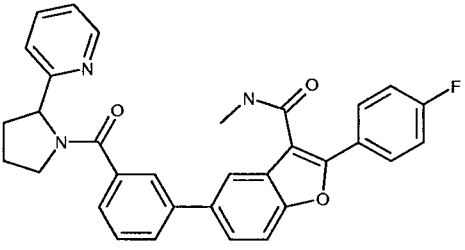
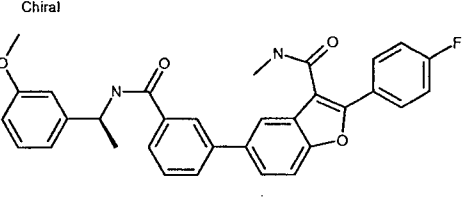
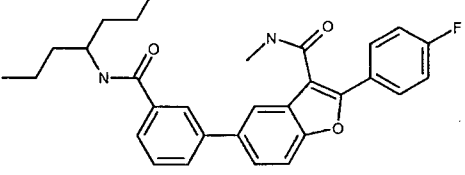
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	5.21	100	444.95	Method C
	4.95	100	444.96	Method C
Chiral 	3.74	100	499.93	Method C
	4.54	100	507.94	Method C
	4.37	100	507.93	Method C
	4.32	100	460.91	Method C
	3.68	100	485.94	Method C

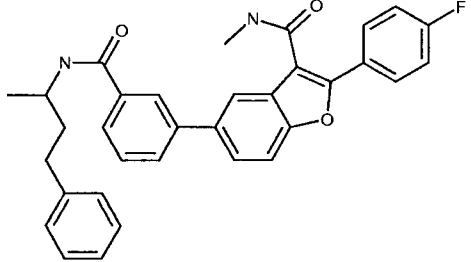
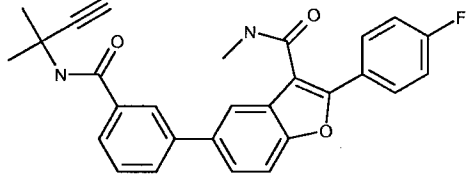
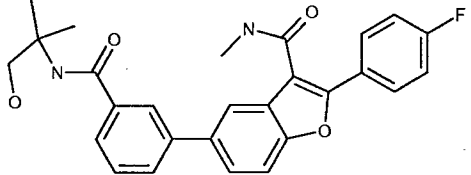
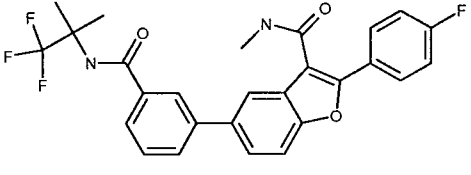
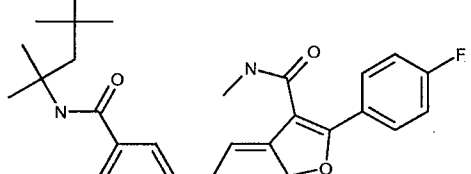
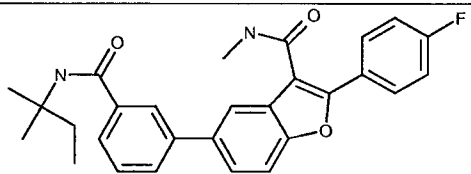
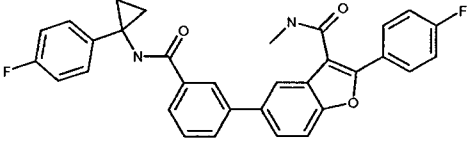
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	5.31	100	510.91	Method C
	3.78	100	432.93	Method C
	4.68	93.1925	466.91	Method D
	5.72	96.6697	464.93	Method D
	5.57	96.8314	489.9	Method D
	5.72	94.0943	478.93	Method D
	4.93	94.4826	455.9	Method D
	5.26	88.6355	469.92	Method D

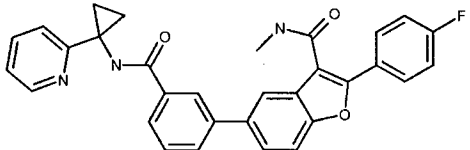
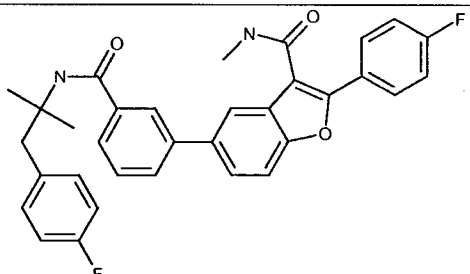
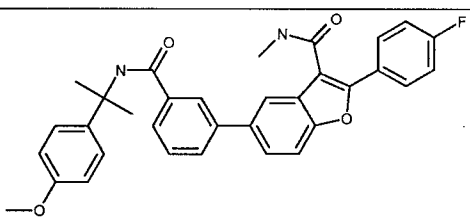
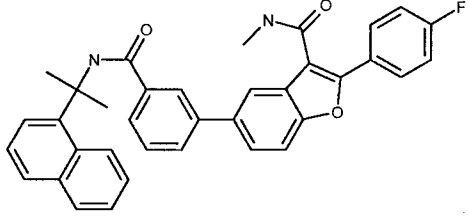
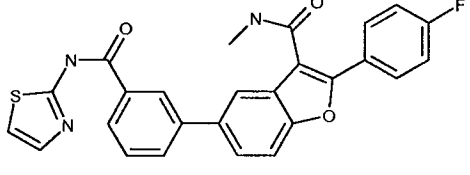
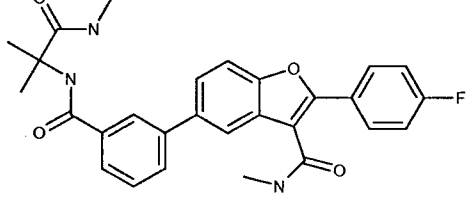
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	4.7	100	466.92	Method D
	5.59	97.7461	494.92	Method D
	4.06	100	497.98	Method D
	5.05	97.6492	502.96	Method D
Chiral 	4.7	100	474.95	Method D
	4.7	100	501.98	Method D
Chiral 	3.74	100	512.96	Method D

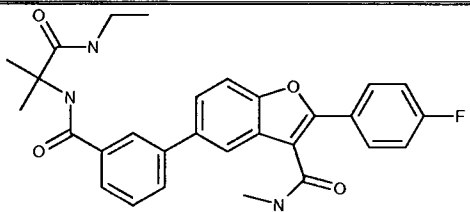
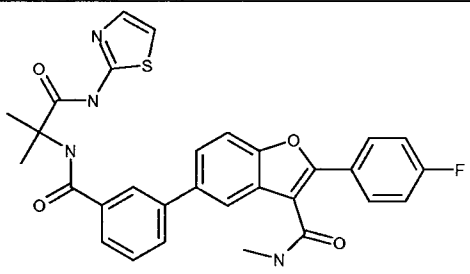
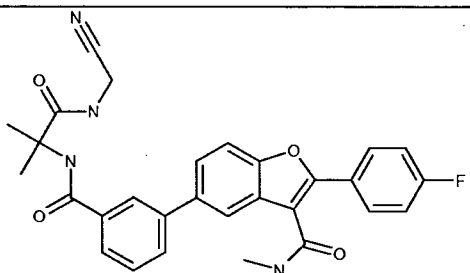
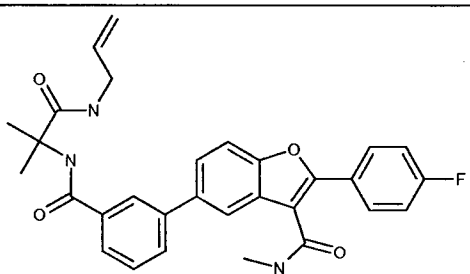
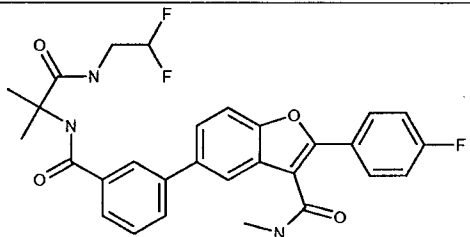
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	4.04	95.8428	481.93	Method D
Chiral 	4.5	93.8873	487.97	Method D
Chiral 	4.26	100	490.94	Method D
	4.88	100	488.93	Method D
Chiral 	5.11	100	488.97	Method D
	4.81	100	522.93	Method D
Chiral 	5.06	100	520.93	Method D

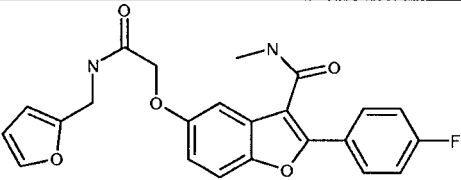
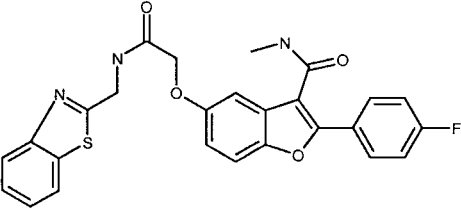
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	5.74	100	516.94	Method D
Chiral 	4.26	100	473.94	Method D
Chiral 	5.85	100	504.94	Method D
Chiral 	4.69	100	474.96	Method D
	4.74	100	479.92	Method D
	4.71	100	493.93	Method D

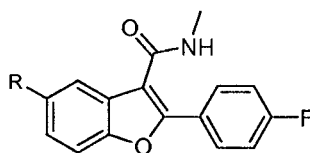
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
Chiral 	4.19	100	513.95	Method D
Chiral 	5.04	100	488.97	Method D
Chiral 	4.97	100	488.96	Method D
	4.7	98.2446	519.93	Method D
Chiral 	5.64	100	522.94	Method D
	5.97	100	487	Method D

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	6.1	100	520.96	Method D
	3.168	100	455.14	Method E
	2.754	100	461.15	Method E
	3.53	95.5615	499.12	Method E
	4.061	100	501.23	Method E
	3.539	98.8021	459.19	Method E
	3.496	100	523.18	Method E

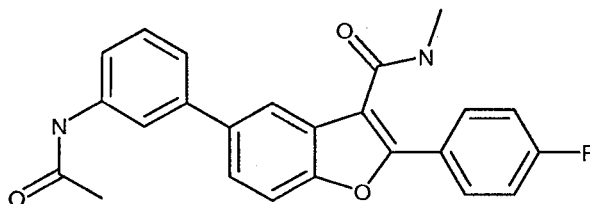
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	3.008	100	506.17	Method E
	3.896	98.8111	539.22	Method E
	3.608	100	537.21	Method E
	3.868	98.488	557.22	Method E
	3.179	100	472.1	Method E
	2.536	100	488.16	Method E

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.718	100	502.19	Method E
	3.025	100	557.15	Method E
	2.664	100	513.16	Method E
	2.835	100	514.17	Method E
	2.87	100	538.16	Method E

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	8.435	100	423.19	Method F
	8.778	100	490.13	Method F

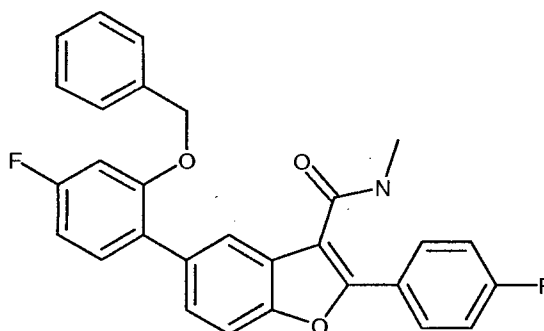


- [00282] The general procedures below pertain to the experimental procedures. Some of the compounds were made with different scales. 2-(4-fluorophenyl)-3-
- 5 (methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (0.100 mmol, 1 eq.) was dissolved in dried 1,4-Dioxane (1 mL) and added into BIOTAGE® microwave vial (0.5-2 mL) containing boronic acid (0.340 mmol, 3.4 eq.). Then Cs₂CO₃ (0.300 mmol, 3 eq.) was added as a solid and following by adding water (0.25 mL). The vial
- 10 was flushed with nitrogen and Pd(PPh₃)₄ was added. After the vial was re-flushed with nitrogen and capped, it was heated in a BIOTAGE® microwave reactor at 150 °C for 15 minutes. The mixture was filtered with a 0.45 um filter and dried with a SPEEDVAC®. The sample was dissolved in DMF (1.6 mL) and purified by prep-HPLC.



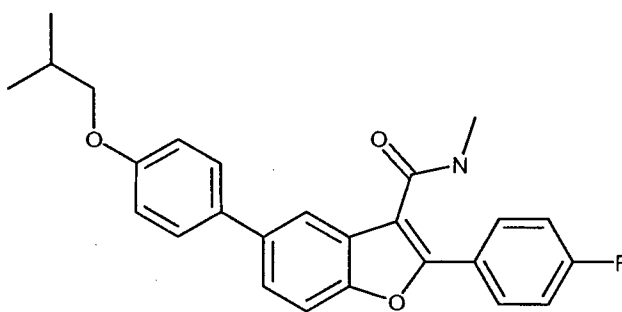
5-(3-Acetamidophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00283] ^1H NMR (600 MHz, DMSO- d_6 -CDCl $_3$) δ ppm 10.03 (br. s., 1 H), 8.49 (d, $J=4.69$ Hz, 1 H), 8.28 (s, 1 H), 8.03 (dd, $J=8.79$, 5.27 Hz, 2 H), 7.93 (br. s., 1 H), 7.84 (s, 1 H), 7.75 (d, $J=8.20$ Hz, 1 H), 7.64 (d, $J=6.44$ Hz, 2 H), 7.29 - 7.45 (m, 3 H), 2.92 (s, 3 H), 2.12 (s, 3 H).



5-(2-(Benzyloxy)-4-fluorophenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- 10 [00284] ^1H NMR (600 MHz, DMSO- d_6 -CDCl $_3$) δ ppm 8.41 (d, $J=4.69$ Hz, 1 H), 8.28 (s, 1 H), 8.03 (dd, $J=8.79$, 5.27 Hz, 2 H), 7.82 (s, 1 H), 7.67 (d, $J=8.20$ Hz, 1 H), 7.55 (d, $J=7.03$ Hz, 1 H), 7.34 - 7.47 (m, 7 H), 7.13 (d, $J=9.37$ Hz, 1 H), 6.83 - 6.94 (m, 1 H), 5.19 (s, 2 H), 2.88 (d, $J=4.10$ Hz, 3 H).



15

2-(4-Fluorophenyl)-5-(4-isobutoxyphenyl)-N-methylbenzofuran-3-carboxamide

- [00285] ^1H NMR (600 MHz, DMSO- d_6 -CDCl $_3$) δ ppm 8.46 (d, $J=4.69$ Hz, 1 H), 8.28 (s, 1 H), 8.04 (dd, $J=8.50$, 5.57 Hz, 1 H), 7.81 (s, 1 H), 7.67 - 7.73 (m, 1 H), 7.60 - 7.67 (m, 2 H), 7.36 (t, $J=8.79$ Hz, 1 H), 7.05 (d, $J=8.79$ Hz, 2 H), 3.83 (d, $J=6.44$ Hz, 2 H), 2.91 (d, $J=4.69$ Hz, 3 H), 2.09 (ddd, $J=13.33$, 6.59, 6.44 Hz, 1 H), 1.05 (d, $J=7.03$ Hz, 6 H).
- 20

[00286] HPLC purity was determined using a Waters LCT Mass Spectrometer with four way MUX source analytical LC at 220nm with employing acetonitrile and water or Waters ZQ with ESCi mass spectrometer. A = 5:95 CH₃CN :Water; B = 95:5

- 5 CH₃CN :Water; Modifier = 10 mM NH₄OAc. Retention time was recorded in minutes.

Analytical Method A:

Column Waters XTERRA® 2.1x50mm 5 um C18

Time	B%	Flow
0.00	0	1.0
4.00	100	1.0
5.00	100	1.0

10

Analytical Method B:

Column: Waters XBridge 2.1x50mm 5 um C18

Time	B%	Flow
0.00	0	1.0
4.00	100	1.0
5.00	100	1.0
5.05	100	1.0
6.00	0	1.0

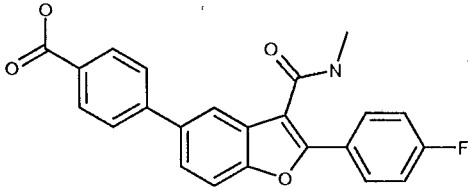
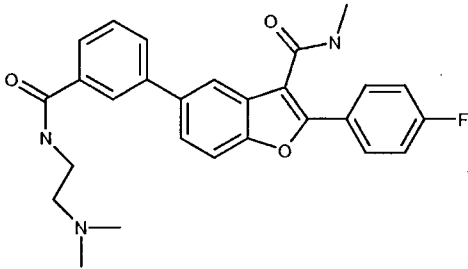
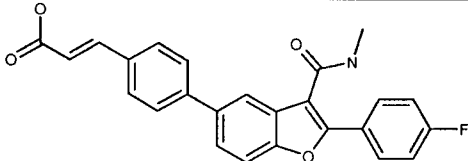
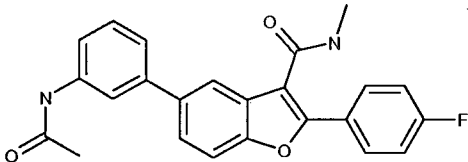
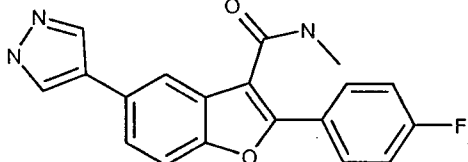
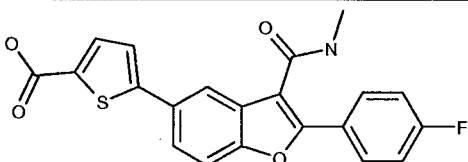
Analytical Method F:

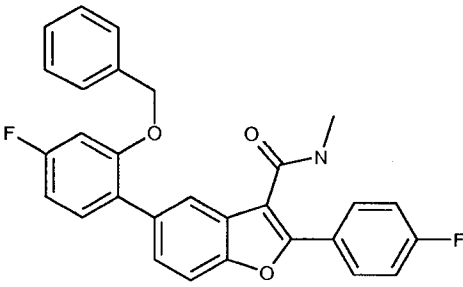
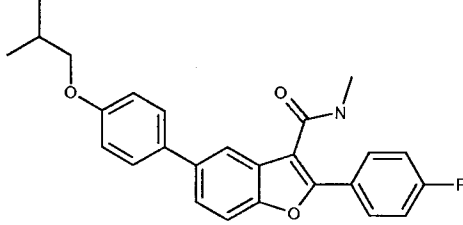
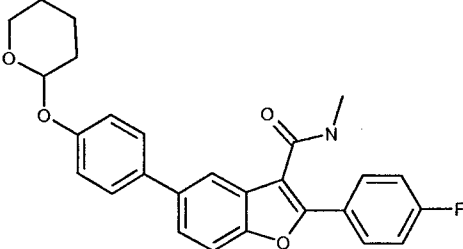
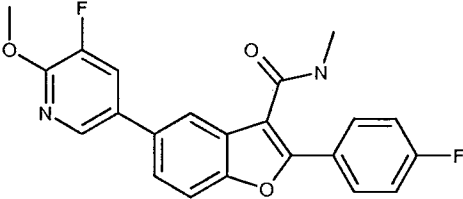
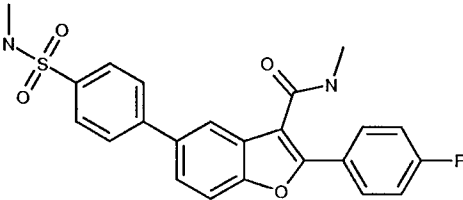
- 15 Waters ZQ with ESCi mass spectrometer

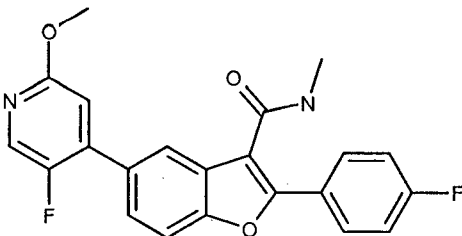
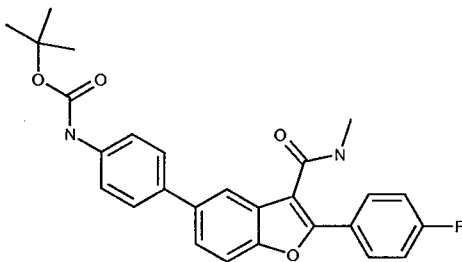
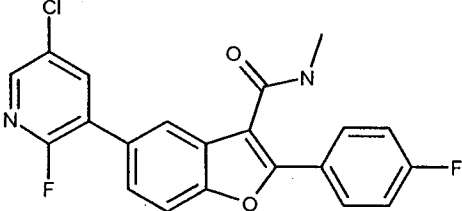
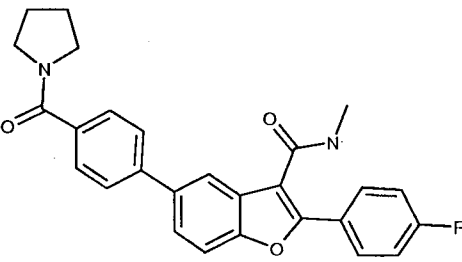
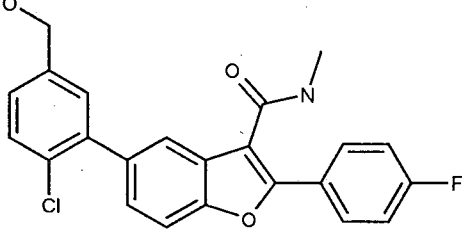
Column: PHENOMENEX® Gemini 4.6x150mm 3 um C18

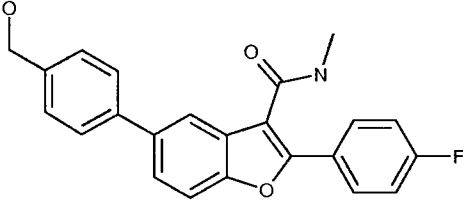
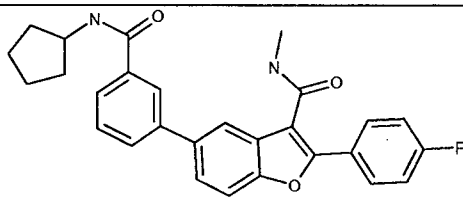
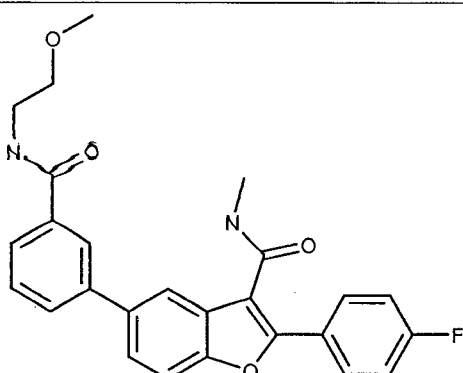
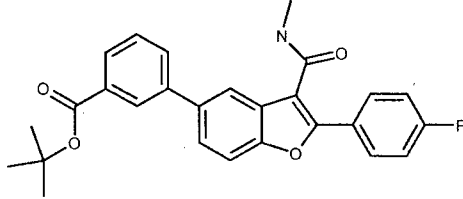
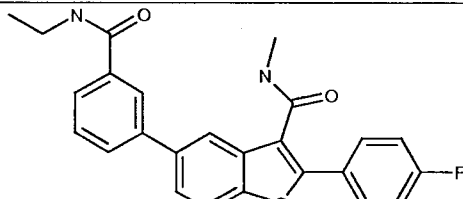
Time	B%	Flow
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10.00	95	1.0
13.00	95	1.0

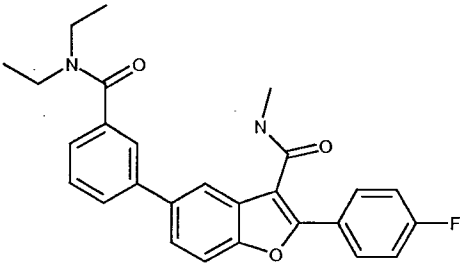
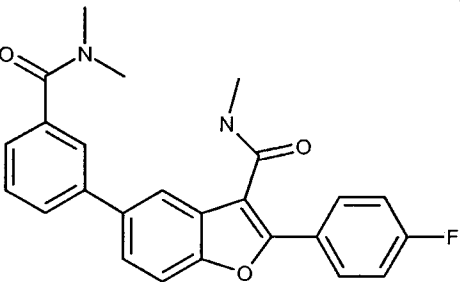
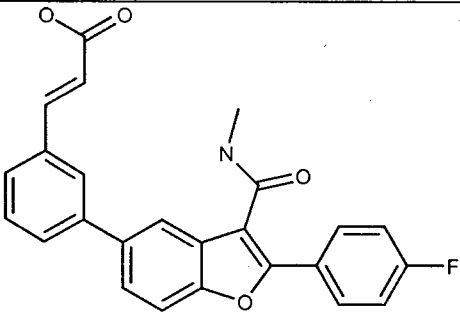
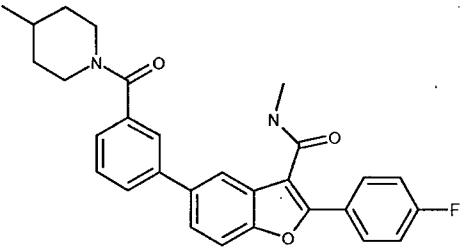
Time	B%	Flow
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15.00	10	1.0

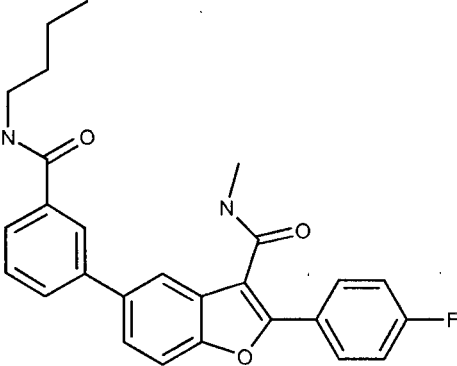
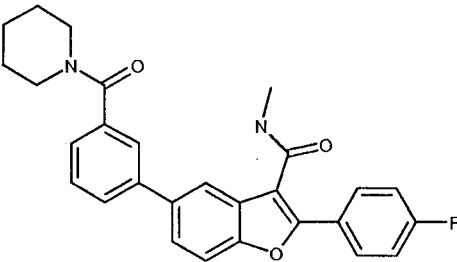
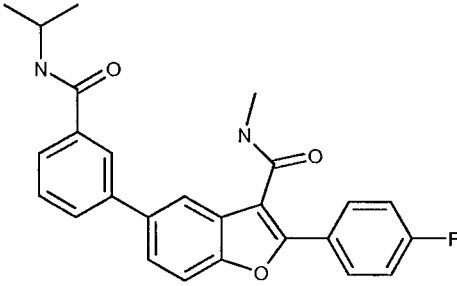
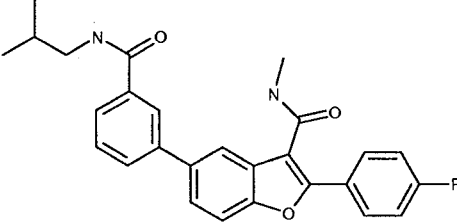
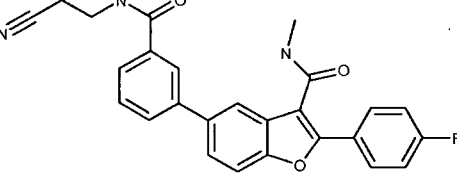
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	7.23	100	390.16	Method F
	3.842	100	460.23	Method F
	7.666	100	416.18	Method F
	7.018	100	403.2	Method F
	5.322	100	336.23	Method F
	7.091	100	396.13	Method F

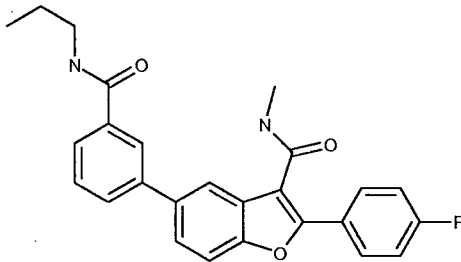
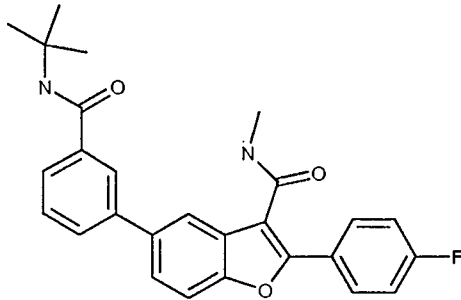
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	12.982	100	470.3	Method F
	13.755	100	418.33	Method F
	12.669	100	446.26	Method F
	10.775	100	395.28	Method F
	8.933	100	439.24	Method F

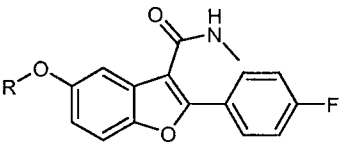
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	10.716	100	395.31	Method F
	11.858	100	461.33	Method F
	10.916	100	399.21	Method F
	2.49	100	443.06	Method B
	2.56	100	410	Method B

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.36	100	376.05	Method B
	2.75	90.0925	457.45	Method B
	2.36	95.5596	447.39	Method B
	3.34	100	446.41	Method B
	2.43	100	417.4	Method B

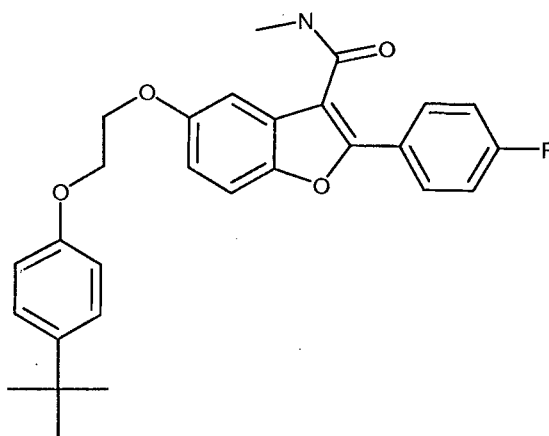
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.67	97.2446	445.4	Method B
	2.37	100	417.33	Method B
	2.02	100	416.3	Method B
	2.92	100	471.37	Method B

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.76	100	445.37	Method B
	2.71	100	457.35	Method B
	2.52	100	431.35	Method B
	2.725	94.4043	445.36	Method B
	2.38	95.3608	442.32	Method B

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	2.56	100	431.34	Method B
	2.76	97.5284	445.38	Method B



[00287] The general procedures below pertain to the experimental procedures. 2-(4-fluorophenyl)-5-hydroxy-N-methylbenzofuran-3-carboxamide (0.120 mmol, 1 eq.) in THF (2.3 mL) was added into BIOTAGE® microwave vial(5 mL) containing ROH (2.28 eq.) and PPh₃ (1.4 eq.). Then DEAD (1.4 eq.) was added as neat. The vial was flushed with nitrogen, capped and heated at 140 °C for 20 minutes in a BIOTAGE® microwave reactor. The mixture was dried with SPEEDVAC®, dissolved in DMF (1.6 mL) and purified by prep-HPLC.



5-(2-(4-*tert*-Butylphenoxy)ethoxy)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

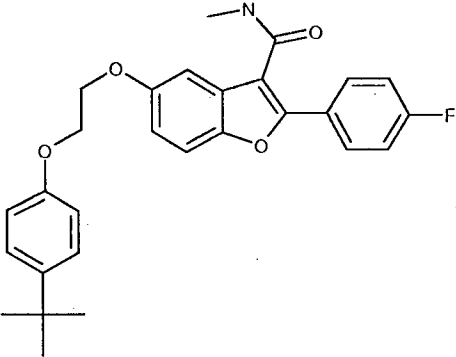
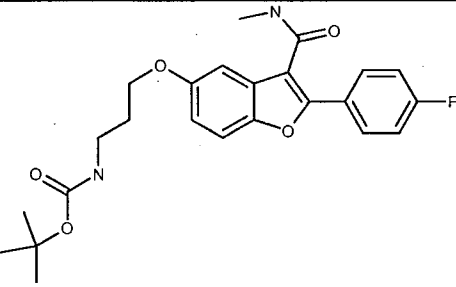
[00288] ¹H NMR (600 MHz, DMSO-d₆-CDCl₃) δ ppm 8.36 (d, J=4.69 Hz, 1 H), 8.27 (s, 1 H), 7.99 (dd, J=8.50, 5.57 Hz, 1 H), 7.56 (d, J=8.79 Hz, 1 H), 7.28 - 7.39 (m, 3 H), 7.21 (d, J=2.34 Hz, 1 H), 7.05 (dd, J=9.37, 2.34 Hz, 1 H), 6.94 (d, J=8.79 Hz, 3 H), 4.28 - 4.45 (m, 4 H), 2.89 (d, J=4.69 Hz, 3 H), 1.30 (s, 9 H).

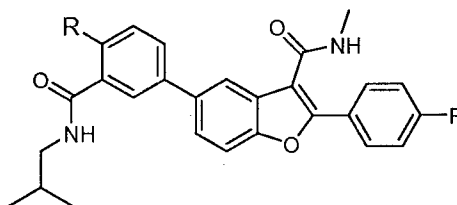
[00289] HPLC purity was determined using a Waters LCT Mass Spectrometer with four way MUX source analytical LC at 220nm with employing acetonitrile and water. A = 5:95 CH₃CN :Water; B = 95:5 CH₃CN :Water; Modifier = 10 mM NH₄OAc. Retention. Time was recorded in minutes.

Analytical Method B:

15 Column: Waters XBridge 2.1x50mm 5 um C18

Time	B%	Flow
0.00	0	1.0
4.00	100	1.0
5.00	100	1.0
5.05	100	1.0
6.00	0	1.0

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	3.63	100	461.8073	Method B
	2.81	100	442.825	Method B



- [00290] The general procedures below pertain to the experimental procedures. 4-[2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl]-2-
- 5 (isobutylcarbamoyl)phenyl trifluoromethanesulfonate (0.076 mmol, 45 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (6.24 mg, 0.02 mmol), boronic acid (0.175 mmol) and potassium phosphate (0.190 mmol, 40.2 mg) were added into BIOTAGE® microwave vial (5mL), and followed by adding dioxane (3 mL) and water (0.3 mL). The vial was flushed with nitrogen and Pd(OAc)₂ (0.076
- 10 mmol, 1.7 mg) was added. The vial was heated in a BIOTAGE® Initiator at 110 °C for 10 minutes and dried with a SPEEDVAC®-250 at 40 °C overnight. The samples were dissolved in DMF-MeOH, filtered via a plate with filters, and purified by prep-

HPLC. Prep-HPLC: DIONEX® APS-30000, UV 220nm, Column: Waters XBridge 19 x 200 mm, 5 um, C18. Solvents: A = Water, 20 mM NH₄OH, B = Acetonitrile).

Analytical Method A:

5 Waters LCT mass spectrometer with 4 way MUX source.

LC Conditions:

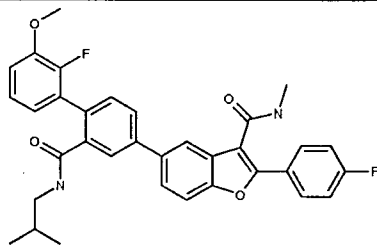
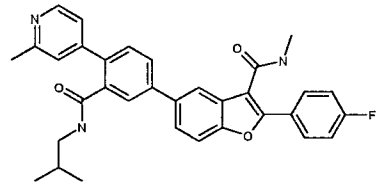
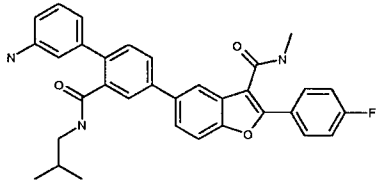
Column: Ascentis 4.6x50mm 5 um C18

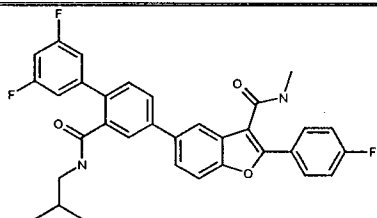
Mobile Phase: A = 5:95 MeCN:Water; B = 95:5 MeCN:Water; Modifier = 10 mM

10 NH₄OAc

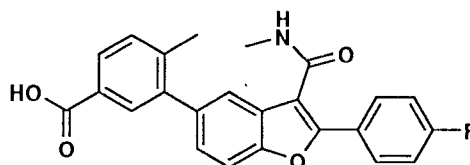
Retention Time Rt was recorded in minutes.

Time	B%	Flow
0.00'	0	2.0
8.00'	100	2.0
9.00'	100	2.0

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	5.77	96	569.286	Method A
	4.86	95	536.2426	Method A
	5.20	97	536.26428	Method A

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	5.93	100	557.2553	Method A

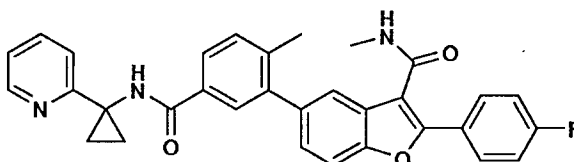
[00291] The following examples/intermediates were prepared by the Suzuki coupling of the corresponding benzofuran-5-yl trifluoromethanesulfonate with 3-boronic acid (or ester) of the corresponding benzoic acid, and the acid intermediate
5 obtained was coupled to cyclopropylamine as described before.



3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid

[00292] LC/MS were performed by using Shimadzu-VP instrument with UV
10 detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES⁺) m/z (M+H)⁺ = 404.04, HPLC R_t = 1.728 min.

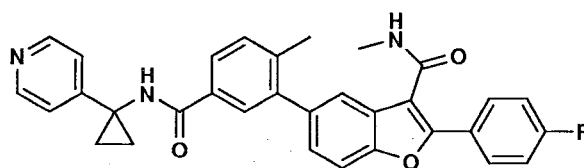
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2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

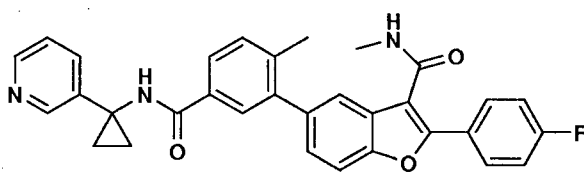
[00293] The product was obtained as a TFA salt after purification by Shimadzu-VP
20 preparative reverse phase HPLC first using the separation method: Solvent A = 10%

MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.80 - 9.26 min. (UV detection at 220 nm). The desired fractions collected were evaporated and the white solid obtained was purified again by the same method except with Start %B = 50, Final %B = 100, Fraction Collection: 5.34 - 6.15 min. ¹H NMR (500 MHz, CD₃OD) δ 8.61 (d, *J* = 5.80, 1H), 8.44 (t, *J* = 7.32, 1H), 7.97 (dd, *J* = 8.85, 5.19, 2H), 7.87 (s, 1H), 7.85 (d, *J* = 6.71, 1H), 7.83-7.81 (m, 2H), 7.67 (d, *J* = 8.24, 1H), 7.64 (d, *J* = 0.92, 1H), 7.47 (d, *J* = 8.55, 1H), 7.38 (dd, *J* = 8.39, 1.68, 1H), 7.29 (t, *J* = 8.85, 2H), 2.95 (s, 3H), 2.36 (s, 3H), 1.82 (m, 2H), 1.75 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 520.41, HPLC *R*_t = 1.513 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, *R*_t = 8.90 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, *R*_t = 9.43 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl, *R*_t = 13.20 min.



2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyridin-4-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

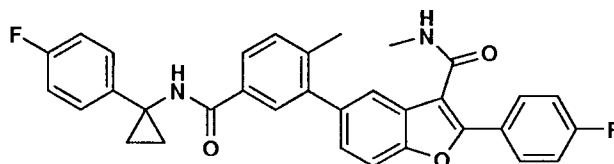
[00294] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 5.07 - 5.88 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.68 (d, *J* = 7.32, 1H), 7.97 (dd, *J* = 8.85, 5.19, 2H), 7.87 (d, *J* = 2.14, 1H), 7.86 (m overlapped with d, 1H), 7.81 (d, *J* = 7.02, 1H), 7.67 (d, *J* = 8.55, 1H), 7.65 (d, *J* = 1.22, 1H), 7.48 (d, *J* = 8.55, 1H), 7.39 (dd, *J* = 8.39, 1.68, 1H), 7.28 (t, *J* = 8.85, 2H), 2.95 (s, 3H), 2.37 (s, 3H), 1.83 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 520.15, HPLC *R*_t = 1.435 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 8.03 min; Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm (Start %B = 10, Final %B = 100), *R*_t = 14.09 min.



25 2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyridin-3-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00295] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC first using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate =

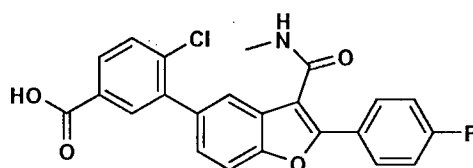
25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 5.05 - 5.76 min. (UV detection at 220 nm). The desired fractions collected were evaporated and the residue obtained was purified again by the same method except with Start %B = 10, Final %B = 100, Fraction Collection: 8.74 - 9.27 min. ¹H NMR (500 MHz, CD₃OD) δ 8.76 (d, *J* = 2.44, 1H), 8.71 (dd, *J* = 5.80, 0.92, 1H), 8.50 (ddd, *J* = 8.32, 2.21, 1.37, 1H), 8.04 (dd, *J* = 8.39, 5.65, 1H), 7.96 (dd, *J* = 9.00, 5.34, 2H), 7.83 (d, *J* = 1.53, 1H), 7.82 (m overlapped with d, 1H), 7.66 (d, *J* = 8.24, 1H), 7.64 (d, *J* = 1.83, 1H), 7.45 (d, *J* = 8.55, 1H), 7.28 (t, *J* = 8.70, 2H), 2.95 (s, 3H), 2.35 (s, 3H), 1.60 (appeared as td, *J* = 4.20, 2.59, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 520.08, HPLC *R*_t = 1.482 min.



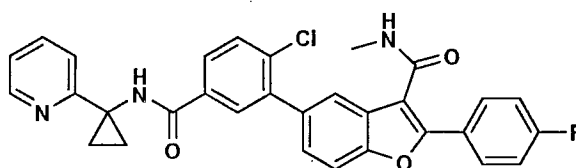
2-(4-Fluorophenyl)-5-(5-(1-(4-fluorophenyl)cyclopropylcarbamoyl)-2-methylphenyl)-N-methylbenzofuran-3-carboxamide

[00296] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 9.08 - 9.63 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.97 (dd, *J* = 8.85, 5.19, 2H), 7.78 - 7.77 (overlapping m, 2H), 7.65 (d, *J* = 8.55, 1H), 7.63 (d, *J* = 1.22, 1H), 7.41 (d, *J* = 8.55, 1H), 7.37 - 7.33 (overlapping m, 3H), 7.28 (t, *J* = 8.85, 2H), 7.01 (t, *J* = 8.85, 2H), 2.95 (s, 3H), 2.33 (s, 3H), 1.32 (m, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA,

- Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 537.08, HPLC R_t = 1.840 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm.
- 5 HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 10.20 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm (Start %B = 10, Final %B = 100), R_t = 8.16 min. Analytical HPLC method: Solvent A = 5% MeOH-
- 10 95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 14.20 min.



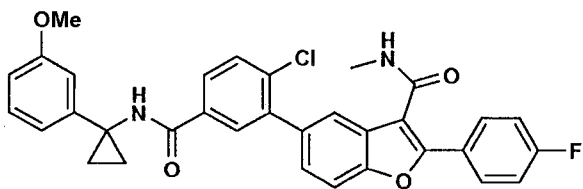
- 15 4-Chloro-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid
[00297] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4
- 20 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 424.26, 426.25, HPLC R_t = 1.763 min.



- 25 5-(2-Chloro-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide
[00298] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC first using the separation method: Solvent A = 10%

MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.02 - 6.54 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.62 (dd, *J* = 5.80, 0.61, 1H), 8.44 (td, *J* = 7.93, 1.53 1H), 8.04 (d, *J* = 2.44, 1H), 7.96 (dd, *J* = 8.85, 5.19, 2H), 7.93 (dd, *J* = 8.39, 2.29 1H), 7.84 - 7.81 (overlapping m, 2H), 7.76 (d, *J* = 1.83, 1H), 7.69 (d, *J* = 2.44, 1H), 7.67 (d, *J* = 2.75, 1H), 7.50 (dd, *J* = 8.55, 1.53, 1H), 7.28 (t, *J* = 8.70, 2H), 2.95 (s, 3H), 1.83 (m, 2H), 1.76 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 540.33, 542.33, HPLC *R*_t = 1.568 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, *R*_t = 9.19 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, *R*_t = 9.89 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl, *R*_t = 16.19 min.

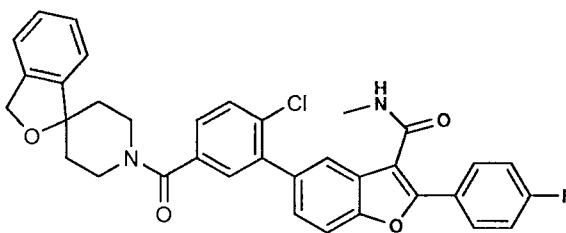
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5-(2-Chloro-5-(1-(3-methoxyphenyl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00299] Purification by Shimadzu-VP preparative reverse phase HPLC first using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B =

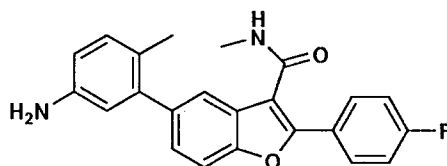
- 90% MeOH-10% H₂O-0.1% TFA, Start %B = 70, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.61 - 7.41 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.97 (dd, *J* = 8.70, 5.34, 2H), 7.94 (d, *J* = 2.14, 1H), 7.85 (dd, *J* = 8.39, 1.98, 1H), 7.76 (s, 1H), 7.65 (dd, *J* = 12.51, 8.55, 2H), 7.49 (dd, *J* = 8.55, 1.53, 1H), 7.28 (t, *J* = 8.70, 2H), 7.20 (t, *J* = 7.93, 1H), 6.87 (s, 1H), 6.85 (m overlapped with s, 1H), 6.75 (dd, *J* = 8.70, 1.68, 1H), 3.77 (s, 3H), 2.95 (s, 3H), 1.34 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A =
- 10 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 mL/min, Column: XTERRA® MS 7 μm, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 569.39, HPLC *R_t* = 1.858 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical
- 15 HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 mL/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R_t* = 10.33 min; Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R_t* = 7.96 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃,
- 20 Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 mL/min, Column: XBridge phenyl 3, *R_t* = 14.80 min.



- 25 5-(2-Chloro-5-(3H-spiro[isobenzofuran-1,4'-piperidine]-1'-ylcarbonyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00300] Purification by Shimadzu-VP preparative reverse phase HPLC first using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B =

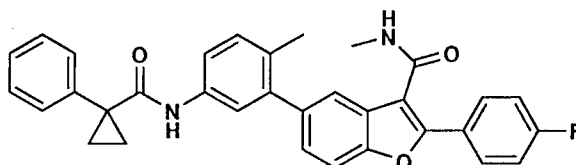
90% MeOH-10% H₂O-0.1% TFA, Start %B = 70, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.88 - 8.49 min. (UV detection at 220 nm). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 595.39, HPLC R_t = 1.952 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, R_t = 11.75 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 8.68 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3, R_t = 15.85 min.



5-(5-Amino-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00301] The Suzuki coupling with 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline was performed by using: dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos), Pd(OAc)₂, K₂CO₃, (1:2 H₂O/1,4-dioxane, 90 °C). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4

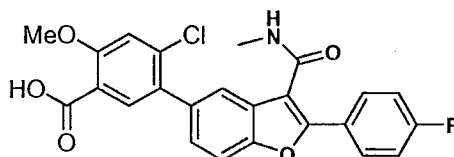
ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 375.22, HPLC R_t = 1.362 min.



5 2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-phenylcyclopropanecarboxamido)phenyl)benzofuran-3-carboxamide

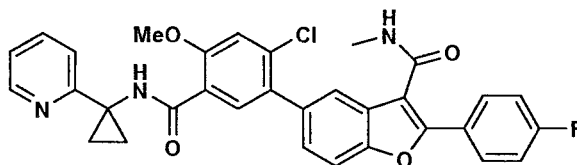
[00302] Purification by Shimadzu-VP preparative reverse phase HPLC first using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 10.05 - 10.51 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.97 (dd, J = 8.85, 5.49, 2H), 7.60 (d, J = 8.55, 1H), 7.55 (d, J = 1.53, 1H), 7.52 (dd overlapped with s, 1H), 7.51 (s, 1H), 7.44 (t, J = 7.48, 2H), 7.36 (m, 1H), 7.30 (dd overlapped with m, J = 1.53, 1H), 7.29 – 7.27 (overlapping m, 3H), 7.25 (d, J = 2.14, 1H), 7.21 (appeared as d, 1H), 2.95 (s, 3H), 2.21 (s, 3H), 1.60 (m, 2H), 1.19 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+Na)⁺ = 541.36, HPLC R_t = 1.952 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 12.49 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 9.11 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100,

Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3, R_t = 15.98 min.



5 4-Chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoic acid

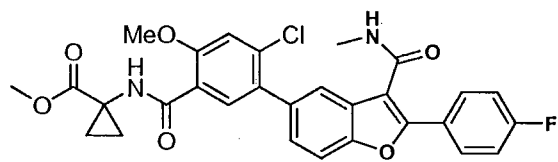
[00303] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start
10 %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 453.93, HPLC R_t = 1.757 min.



15 5-(2-Chloro-4-methoxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

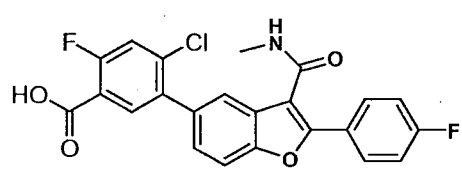
[00304] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start
20 %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.00 - 6.58 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.61 (d, J = 5.80, 1H), 8.42 (td, J = 8.01, 1.68, 1H), 7.99 (s, 1H), 7.96 (m, J = 8.85, 5.19, 2H), 7.87 (d, J = 8.24, 1H), 7.79 (ddd, J = 7.40, 6.03, 0.92, 1H), 7.69 (d, J = 1.83, 1H),
25 7.64 (d, J = 8.55, 1H), 7.44 (dd, J = 8.55, 1.83, 1H), 7.40 (s, 1H), 7.27 (t, J = 8.85, 2H), 4.10 (s, 3H), 2.95 (s, 3H), 1.84 (m, 2H), 1.75 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters

MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 569.90, 570.79, 571.82, HPLC R_t = 1.592 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, R_t = 9.56 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 9.97 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 16.35 min.



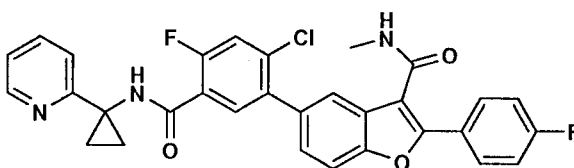
Methyl 1-(4-chloro-5-(2-(4-fluorophenyl)-3-(methoxycarbonyl)benzofuran-5-yl)-2-methoxybenzamido)cyclopropanecarboxylate

[00305] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 551.02, HPLC R_t = 1.753 min.



4-Chloro-2-fluoro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

[00306] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 441.91, HPLC R_t = 1.803 min.



5-(2-Chloro-4-fluoro-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

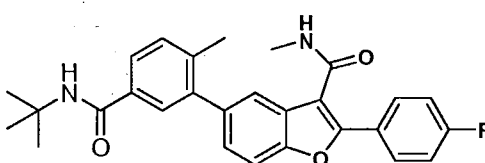
[00307] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10%

15 MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 5.63 - 6.40 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.60 (d, J = 5.49, 1H), 8.34 (td, J = 7.93, 1.83, 1H), 7.97 (m, J = 8.85, 5.19, 2H), 7.90 (d, J = 7.63, 1H), 7.83 (d, J = 8.24, 1H), 7.73 (overlapping, 2H), 7.68 (d, J = 8.54, 1H), 7.56 (d, J = 10.38, 1H), 7.47 (dd, J = 8.55, 1.83, 1H), 7.29 (t, J = 8.70, 2H), 2.95 (s, 3H), 1.82 (m, 2H), 1.70 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 558.04, HPLC R_t = 1.558 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95%

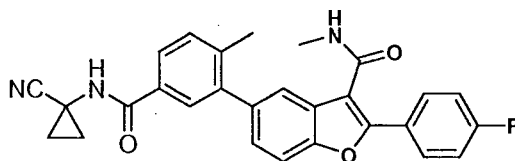
MeCN-5% H_2O -0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm , 4.6 x 150 mm, R_t = 3.10 min; Column: XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 3.60 min.

Analytical HPLC method: Solvent A = 5% MeOH-95% H_2O -10 mM NH_4HCO_3 ,

- 5 Solvent B = 95% MeOH-5% H_2O -10 mM NH_4HCO_3 , Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 13.24 min.

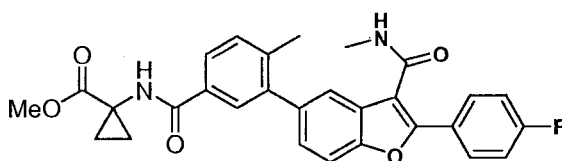


- 10 [00308] 5-(5-(*tert*-Butylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column:
- 15 Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.62 - 9.21 min. (UV detection at 220 nm). ^1H NMR (500 MHz, CD_3OD) δ 7.98 (m, J = 8.85, 5.49, 2H), 7.67 (d overlapping with s, 1H), 7.67 (s, 1H), 7.65 (d, J = 8.55, 1H), 7.63 (d, J = 1.22, 1H), 7.38 (d overlapping with dd, 1H), 7.37 (dd, J = 1.53, 1H), 7.28 (t, J = 8.70, 2H), 2.96 (s, 3H), 2.32 (s, 3H), 1.47 (s, 9H). LC/MS were performed by using Shimadzu-VP
- 20 instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm , C18, 3.0 x 50 mm; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 459.31, HPLC R_t = 1.763 min. Analytical HPLC were
- 25 performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H_2O -0.1% TFA, Solvent B = 95% MeCN-5% H_2O -0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm , 4.6 x 150 mm, R_t = 17.08 min; XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 14.81 min.



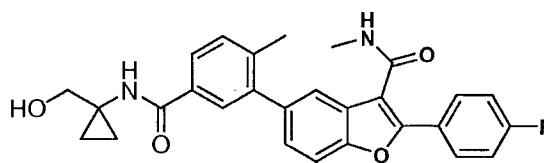
5-(5-(1-Cyanocyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- 5 [00309] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.13 - 7.85 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, *J* = 8.70, 5.34, 2H), 7.77 (d overlapping with s, 1H), 7.76 (s, 1H), 7.66 (d, *J* = 8.24, 1H), 7.63 (d, *J* = 1.53, 1H), 7.44 (d, *J* = 8.24, 1H), 7.37 (dd, *J* = 8.39, 1.68, 1H), 7.28 (t, *J* = 8.85, 2H), 2.95 (s, 3H), 2.34 (s, 3H), 1.59 (m, 2H), 1.36 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm, C18, 3.0 x 50 mm; (ES⁺) *m/z* (M+H)⁺ = 468.28, HPLC *R*_t = 1.633 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm.
- 10 HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 14.21 min; XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 12.79 min.



Methyl 1-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzamido)cyclopropanecarboxylate

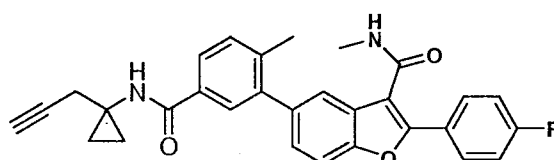
[00310] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.26 - 7.97 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, *J* = 8.85, 5.19, 2H), 7.77 (dd, *J* = 4.27, 2.14, 2H), 7.66 (d, *J* = 8.55, 1H), 7.63 (d, *J* = 1.22, 1H), 7.42 (d, *J* = 8.55, 1H), 7.37 (dd, *J* = 8.39, 1.68, 1H), 7.28 (t, *J* = 8.85, 2H), 3.71 (s, 3H), 2.96 (s, 3H), 2.34 (s, 3H), 1.59 (m, 2H), 1.26 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm, C18, 3.0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 501.23, HPLC *R*_t = 1.657 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 6.81 min; XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 5.58 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3, *R*_t = 12.48 min.



25 2-(4-Fluorophenyl)-5-(5-(1-(hydroxymethyl)cyclopropylcarbamoyl)-2-methylphenyl)-N-methylbenzofuran-3-carboxamide

[00311] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10

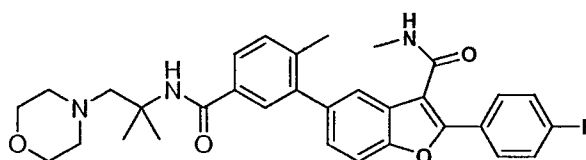
min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.78 - 9.06 min. (UV detection at 220 nm). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 473.33, HPLC R_t = 1.827 min.



2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(prop-2-ynylcarbamoyl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

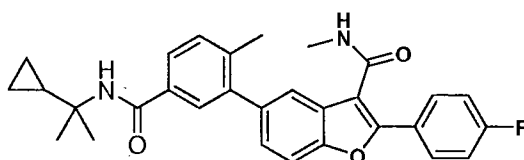
[00312] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90%

MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.43 - 7.91 min. (UV detection at 220 nm). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 524.21, HPLC R_t = 1.642 min.



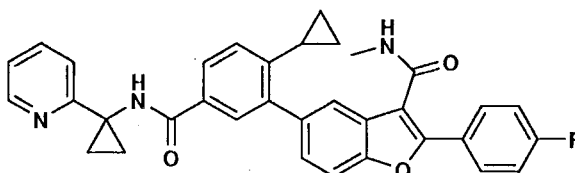
2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(2-methyl-1-morpholinopropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00313] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 20, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.64 - 8.27 min. (UV detection at 220 nm). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 544.38, HPLC R_t = 1.503 min.



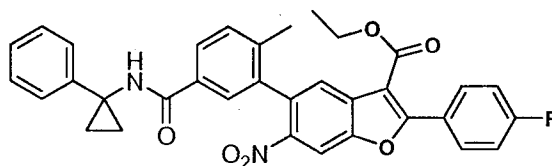
5-(5-(2-Cyclopropylpropan-2-ylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00314] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 9.21 - 9.86 min. (UV detection at 220 nm). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 485.34, HPLC R_t = 1.842 min.



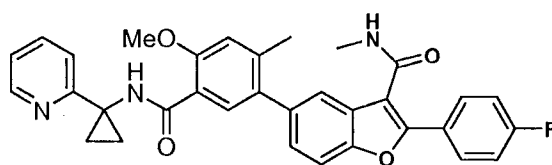
5-(2-Cyclopropyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00315] The product was obtained as a TFA salt after purification by Shimadzu-VP
- 5 preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.26 - 6.59 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.54 (d, *J* = 5.19, 1H), 8.17 (m, 1H), 7.98 (m, *J* = 8.85, 5.19, 2H), 7.87 - 7.86 (overlapped m, 2H), 7.77 (d, *J* = 1.53, 1H), 7.69 (d overlapped with d, 1H), 7.68 (d, *J* = 8.24, 1H), 7.58 (m, 1H), 7.50 (dd, *J* = 8.55, 1.83, 1H), 7.29 (t, *J* = 8.85, 2H), 7.11 (d, *J* = 8.55, 1H), 2.96 (s, 3H), 1.98 (m, 1H), 1.77 (m, 2H), 1.61 (m, 2H), 0.96 (m, 2H), 0.82 (m, 2H).
- 10 LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES⁺) *m/z* (M+H)⁺ = 546.04, HPLC *R*_t = 1.603 min. Analytical HPLC were performed by using Shimadzu-VP instrument with
- 15 UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, *R*_t = 9.71 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, *R*_t = 10.26 min. Analytical HPLC method:
- 20 Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, *R*_t = 13.95 min.
- 25



Ethyl 2-(4-fluorophenyl)-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)-6-nitrobenzofuran-3-carboxylate

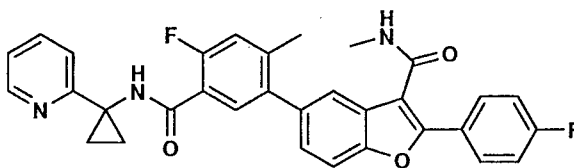
[00316] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES⁺) m/z (M+H)⁺ = 579.41, HPLC R_t = 2.032 min.



2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00317] A mixture of 5-(2-chloro-4-methoxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (62.7 mg, 0.11 mmol, crude), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (52.4 mg, 0.11 mmol), MeBF₃K (20.12 mg, 0.165 mmol), diacetoxypalladium (12.35 mg, 0.055 mmol) and potassium carbonate (76 mg, 0.550 mmol) in a mixture of H₂O (0.2 mL)/THF (2 mL) was stirred at 90 °C under N₂ for 6 hours 30 min. The mixture was left standing at r.t. overnight, and then diluted with MeOH and filtered through a Whatman 0.45 μ m PVDF with GMF disk. The filtrate was purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 70, Final %B = 90, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 2.26 - 2.77 min. (UV detection at 220 nm) to obtain the product as a TFA salt. ¹H NMR (500 MHz, CD₃OD) δ 8.60 (d, *J* = 5.80, 1H), 8.41 (m, 1H),

- 7.96 (m, $J = 9.00$, 5.34, 2H), 7.87 (s, 1H), 7.85 (d, $J = 9.00$, 1H), 7.79 (t, $J = 6.56$, 1H), 7.64 (d, $J = 8.24$, 1H), 7.58 (d, $J = 1.53$, 1H), 7.33 (dd, $J = 8.55$, 1.83, 1H), 7.17 (s, 1H), 7.28 (t, $J = 8.85$, 2H), 4.09 (s, 3H), 2.95 (s, 3H), 2.38 (s, 3H), 1.84 (m, 2H), 1.75 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV
- 5 detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 550.00, HPLC R_t = 1.588 min. Analytical HPLC were performed by using
- 10 Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 9.12 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 9.82 min.
- 15 Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 13.46 min.

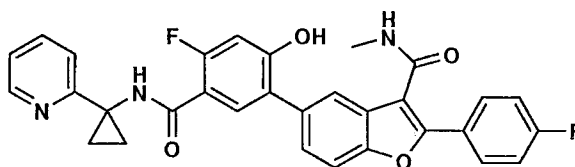


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5-(4-Fluoro-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

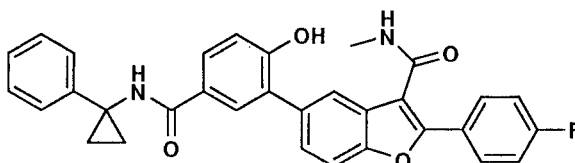
- [00318] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC twice using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start
- 25 %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 5.58 - 5.94 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.57 (d, $J = 5.49$, 1H), 8.26 (td, $J = 7.93$, 1.53, 1H), 7.97 (m, $J = 9.16$, 5.19, 2H), 7.79 (d, $J = 8.24$,

- 1H), 7.73 (d, $J = 7.63$, 1H), 7.67 (d, $J = 8.55$, 1H), 7.65 (m overlapping with d, 1H), 7.62 (d, $J = 1.83$, 1H), 7.35 (dd, $J = 8.39$, 1.68, 1H), 7.29 (t, $J = 8.85$, 2H), 7.25 (d, $J = 11.90$, 1H), 2.95 (s, 3H), 2.35 (s, 3H), 1.80 (m, 2H), 1.66 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and
- 5 Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 538.04, HPLC R_t = 1.497 min. Analytical HPLC were performed by using Shimadzu-VP instrument with
- 10 UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 9.46 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 9.66 min. Analytical HPLC method:
- 15 Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 12.95 min.



- 20 5-(4-Fluoro-2-hydroxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide
- [00319] 5-(4-Fluoro-2-hydroxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide was obtained as a side
- 25 product during the synthesis of 5-(4-fluoro-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide. The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC twice using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-

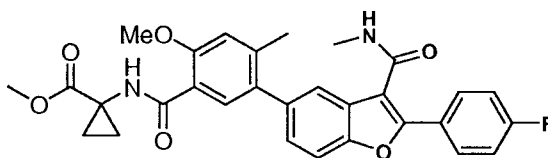
0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 4.16 - 4.55 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.55 (broad d, *J* = 3.66, 1H), 8.19 (t, *J* = 7.78, 1H), 7.97 (m, *J* = 8.85, 5.19, 2H), 7.86 (d, *J* = 8.54, 1H), 7.82 (s, 1H), 7.74 (d, *J* = 8.24, 1H), 7.61 (t overlapping with dd, 1H), 7.58 (dd, 2H), 7.28 (t, *J* = 8.70, 2H), 6.79 (d, *J* = 12.51, 1H), 2.97 (s, 3H), 1.78 (appeared as s, 2H), 1.63 (appeared as s, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 540.07, HPLC *R*_t = 1.342 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 8.06 min; Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 8.56 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 13.91 min.



25 2-(4-Fluorophenyl)-5-(2-hydroxy-5-(1-phenylcyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00320] 2-(4-Fluorophenyl)-5-(2-hydroxy-5-(1-phenylcyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide was obtained as a side product from a similar reaction. Purification by Shimadzu-VP

- preparative reverse phase HPLC twice using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.79 - 8.24 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, *J* = 9.00, 5.34, 2H), 7.91 (d, *J* = 2.14, 1H), 7.88 (d, *J* = 1.53, 1H), 7.76 (dd, *J* = 8.55, 2.14, 1H), 7.65 - 7.61 (overlapping m, 2H), 7.29 - 7.27 (overlapping m, 6H), 7.16 (m, 1H), 7.00 (d, *J* = 8.55, 1H), 2.97 (s, 3H), 1.35 (m, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®.
- 5 HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm, C18, 3.0 x 50 mm; (ES⁺) *m/z* (M+H)⁺ = 521.28, HPLC *R*_t = 1.695 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254
- 10 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 6.84 min; Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 5.71 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM
- 15 NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl, *R*_t = 12.68 min.

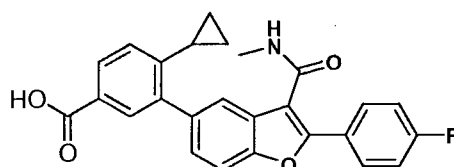


- 25 Methyl 1-(5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzamido)cyclopropanecarboxylate

[00321] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10

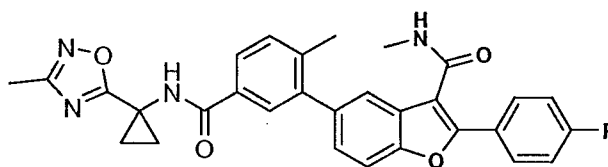
30 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100

mm S5, Fraction Collection: 8.07 - 8.45 min. (UV detection at 220 nm). ^1H NMR (500 MHz, CD_3OD) δ 7.98 (m, 2H), 7.85 (s, 1H), 7.63 (d, $J = 8.55$, 1H), 7.58 (d, $J = 1.22$, 1H), 7.33 (dd, $J = 8.55$, 1.83, 1H), 7.27 (t, $J = 8.85$, 2H), 7.11 (s, 1H), 4.03 (s, 3H), 3.71 (s, 3H), 2.96 (s, 3H), 2.35 (s, 3H), 1.61 (m, 2H), 1.28 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 531.23, HPLC R_t = 1.715 min.



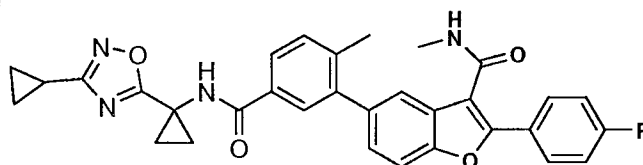
4-Cyclopropyl-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

[00322] 4-Cyclopropyl-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid was prepared in a similar manner as described by using potassium cyclopropyltrifluoroborate. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μm , C18, 3.0 x 50 mm; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 430.07, HPLC R_t = 1.802 min.



25 2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(3-methyl-1,2,4-oxadiazol-5-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

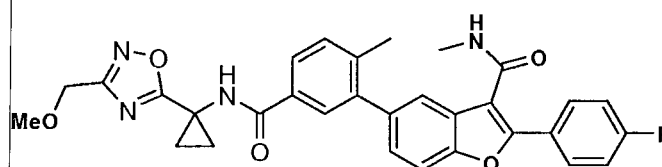
- [00323]** A mixture of methyl 1-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzamido)cyclopropanecarboxylate (25.3 mg, 0.051 mmol), N'-hydroxyacetimidamide (11.23 mg, 0.152 mmol) and K₂CO₃ (41.9 mg, 0.303 mmol) in toluene (1 mL) under N₂ in a re-usable sealed tube was stirred at 150 °C for two hours. The mixture was evaporated, diluted with MeOH and purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.54 - 8.08 min. (UV detection at 220 nm), to give the product as a white solid (19.9 mg, 75%). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, *J* = 9.00, 5.34, 2H), 7.82 (d, *J* = 2.14, 1H), 7.81 (overlapping m, 1H), 7.66 (d, *J* = 8.55, 1H), 7.65 (d, *J* = 1.50, 1H), 7.44 (d, *J* = 8.55, 1H), 7.38 (dd, *J* = 8.24, 1.83, 1H), 7.28 (m, *J* = 8.85, 2H), 2.95 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H), 1.75 (m, 2H), 1.58 (m, 2H).
- LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 525.12, HPLC R_t = 1.700 min.



5-(5-(1-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)cyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00324]** Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.32 - 8.92 min. (UV detection at 220 nm). ¹H NMR

(500 MHz, CD₃OD) δ 7.98 (m, J = 8.85, 5.49, 2H), 7.81 (d, J = 1.83, 1H), 7.80 (broad s overlapping with d, 1H), 7.66 (d overlapping with d, 1H), 7.64 (d, J = 1.53, 1H), 7.44 (d, J = 8.55, 1H), 7.38 (dd, J = 8.39, 1.68, 1H), 7.28 (m, J = 8.85, 2H), 2.95 (s, 3H), 2.35 (s, 3H), 2.02 (m, 1H), 1.72 (m, 2H), 1.54 (m, 2H), 1.04 (m, 2H), 0.95 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 551.09, HPLC R_t = 1.763 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 8.73 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 6.96 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 13.22 min.



2-(4-Fluorophenyl)-5-(5-(1-(3-(methoxymethyl)-1,2,4-oxadiazol-5-

yl)cyclopropylcarbamoyl)-2-methylphenyl)-N-methylbenzofuran-3-carboxamide

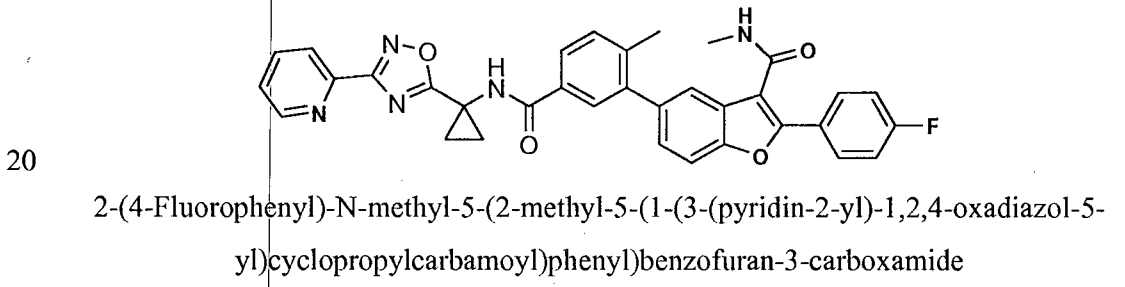
[00325] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.92 - 8.52 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, J = 9.00, 5.34, 2H), 7.82 (d, J = 2.14, 1H), 7.81 (t

overlapped with d, 1H), 7.66 (d overlapped with d, 1H), 7.65 (d, $J = 1.83$, 1H), 7.45 (d, $J = 8.55$, 1H), 7.38 (dd, $J = 8.55$, 1.83, 1H), 7.28 (t, $J = 8.70$, 2H), 4.51 (s, 2H), 3.42 (s, 3H), 2.95 (s, 3H), 2.36 (s, 3H), 1.79 (m, 2H), 1.60 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and

5 Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 555.23, HPLC R_t = 1.700 min. Analytical HPLC were performed by using Shimadzu-VP instrument with

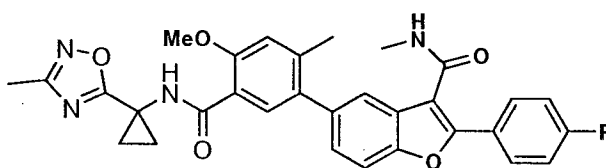
10 UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 7.11 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 5.57 min. Analytical HPLC method:

15 Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 12.51 min.



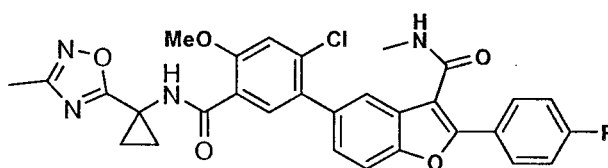
[00326] The product was obtained as a TFA salt after Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.83 - 8.56 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.71 (d, $J = 4.88$, 1H), 8.19 (d, $J = 7.93$, 1H), 8.08 (td, $J = 7.78$, 1.53, 1H), 7.97(m, $J = 9.00$, 5.34,

- 2H), 7.85 (s, 1H), 7.84 (m overlapping with s, 1H), 7.66 -7.63 (overlapping m, 3H), 7.45 (d, $J = 8.55$, 1H), 7.38 (dd, $J = 8.55$, 1.83, 1H), 7.28 (m, $J = 8.85$, 2H), 2.95 (s, 3H), 2.36 (s, 3H), 1.91 (m, 2H), 1.67 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®.
- 5 HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 588.07, HPLC R_t = 1.728 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and
- 10 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 6.96 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 5.83 min. Analytical HPLC method: Solvent A = 5% MeOH-95%
- 15 H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 13.15 min.



- 20 2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(3-methyl-1,2,4-oxadiazol-5-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide
- [00327] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10
- 25 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.80 - 8.36 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, $J = 9.00$, 5.34, 2H), 7.86 (s, 1H), 7.63 (d, $J = 8.55$, 1H), 7.59 (d, $J = 1.83$, 1H), 7.33 (dd, $J = 8.24$, 1.83, 1H), 7.27 (t, $J = 8.85$, 2H), 7.13 (s, 1H), 4.06 (s, 3H), 2.96 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H), 1.77 (m, 2H), 1.60 (m,

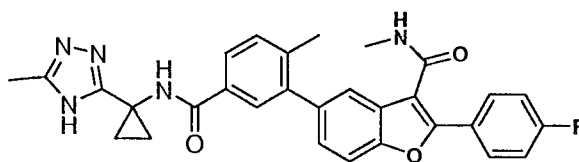
2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 555.10, HPLC R_t = 1.723 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, R_t = 5.98 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, R_t = 12.98 min.



5-(2-Chloro-4-methoxy-5-(1-(3-methyl-1,2,4-oxadiazol-5-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00328] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.06 - 8.56 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.99-7.96 (m overlapping with s, 2H), 7.97 (s, 1H), 7.71 (d, J = 1.53, 1H), 7.64 (d, J = 8.55, 1H), 7.45 (dd, J = 8.55, 1.83, 1H), 7.37 (s, 1H), 7.27 (t, J = 8.85, 2H), 4.06 (s, 3H), 2.96 (s, 3H), 2.32 (s, 3H), 1.78 (m, 2H), 1.61 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90%

H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 575.08, HPLC R_t = 1.752 min. Analytical HPLC were performed by using Shimadzu-VP instrument with
 5 UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 8.23 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 6.39 min. Analytical HPLC method:
 10 Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 13.49 min.

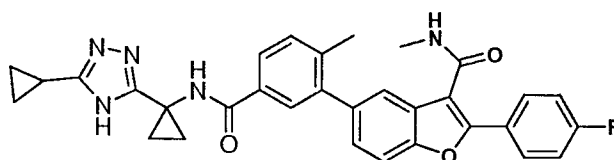


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2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(5-methyl-4H-1,2,4-triazol-3-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00329] A mixture of 5-(5-(1-cyanocyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (33.8 mg, 0.072 mmol),
 20 acetohydrazide (16.07 mg, 0.217 mmol) and K₂CO₃ (9.99 mg, 0.072 mmol) in n-BuOH (1 mL) under N₂ in a re-usable sealed tube was stirred at 150 °C for four hours. The mixture was diluted with MeOH and purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate =
 25 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 5.93 - 6.53 min. (UV detection at 220 nm) to obtain the product as a TFA solvate. ¹H NMR (500 MHz, CD₃OD) δ 7.97 (m, J = 8.85, 5.49, 2H), 7.85 (s, 1H), 7.85 (m overlapped with s, J = 1.83, 1H), 7.66 (d, J = 8.55, 1H), 7.64 (d, J = 1.22, 1H), 7.45 (d, J = 7.63, 1H), 7.38 (dd, J = 8.39, 1.68, 1H), 7.29 (t, J = 8.70, 2H), 2.95 (s, 3H), 2.56 (s, 3H),
 30 1H), 7.38 (dd, J = 8.39, 1.68, 1H), 7.29 (t, J = 8.70, 2H), 2.95 (s, 3H), 2.56 (s, 3H),

2.36 (s, 3H), 1.68 (m, 2H), 1.57 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 524.23, HPLC R_t = 1.545 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 11.80 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 12.13 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge-phenyl 3, R_t = 11.87 min.



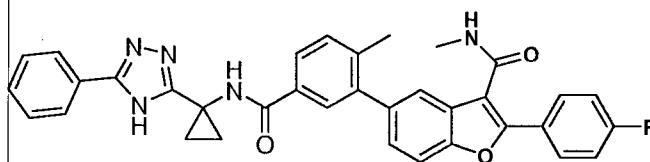
5-(5-(1-(5-Cyclopropyl-4H-1,2,4-triazol-3-yl)cyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00330] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.05 - 8.58 min. (UV detection at 220 nm) to obtain the product as a TFA solvate. ¹H NMR (500 MHz, CD₃OD) δ 7.97 (m, *J* = 8.85, 5.19, 2H), 7.85 (s, 1H), 7.84 (dd overlapping with s, *J* = 1.83, 1H), 7.67 (d, *J* = 8.24, 1H), 7.64 (d, *J* = 1.53, 1H), 7.45 (d, *J* = 7.63, 1H), 7.38 (dd, *J* = 8.39, 1.68, 1H), 7.29 (t, *J* = 8.85, 2H), 2.95 (s, 3H), 2.36 (s, 3H), 2.15 (m, 1H), 1.66 (m, 2H), 1.55 (m, 2H), 1.23 (m, 2H), 1.11 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A

= 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 500.00, HPLC R_t = 1.598 min. Analytical HPLC were performed by using

5 Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 9.45 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 9.81 min.

10 Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl, R_t = 15.29 min.



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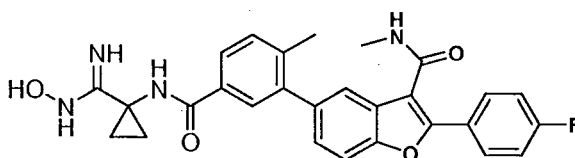
2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(5-phenyl-4H-1,2,4-triazol-3-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00331] Purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90%

20 MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.48 - 7.03 min. (UV detection at 220 nm) to obtain the product as a TFA solvate. ¹H NMR (500 MHz, CD₃OD) δ 7.99 - 7.95 (overlapping m, 4H), 7.88 - 7.85 (overlapping m, 2H), 7.67 - 7.65 (overlapping m, 2H), 7.49 - 7.45 (overlapping m, 3H), 7.44 (d, *J* = 7.93, 1H), 7.39 (dd, *J* = 8.55, 1.53, 1H), 7.28 (t, *J* = 8.70, 2H), 2.95 (s, 3H), 2.35 (s, 3H), 1.72 (m, 2H), 1.48 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column:

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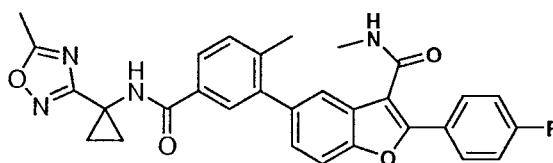
XTERRA® MS 7 μm , C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 585.89, HPLC R_t = 1.765 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm , 4.6 x 150 mm, R_t = 6.85 min; Column: XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 5.81 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl, R_t = 13.04 min.



2-(4-Fluorophenyl)-5-(5-(1-(N-hydroxycarbamimidoyl)cyclopropylcarbamoyl)-2-methylphenyl)-N-methylbenzofuran-3-carboxamide

[00332] To a mixture of 5-(5-(1-cyanocyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (43.5 mg, 0.093 mmol) in ethanol (1.5 mL) at r.t. under N₂ was added hydroxylamine hydrochloride (12.93 mg, 0.186 mmol), followed by Et₃N (0.039 mL, 0.279 mmol). The mixture was stirred at reflux (115 °C) for about 4 hours. The mixture was cooled to r.t. and evaporated.

The residue was used for the next step without further purification. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 501.13, HPLC R_t = 1.385 min.

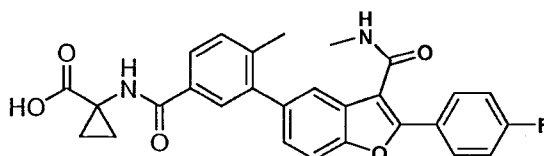


2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(5-methyl-1,2,4-oxadiazol-3-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

- [00333] To a mixture of 2-(4-fluorophenyl)-5-(5-(1-(N-hydroxycarbamimidoyl)cyclopropylcarbamoyl)-2-methylphenyl)-N-methylbenzofuran-3-carboxamide (46.5 mg, 0.093 mmol, crude) in pyridine (0.5 mL, 6.18 mmol) at r.t. under N₂ was added acetyl chloride (0.020 mL, 0.279 mmol). The mixture was stirred at 115 °C for 2 hours. The mixture was cooled to r.t., diluted with MeOH and purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.64 - 7.95 min. (UV detection at 220 nm). The residue obtained after evaporation of the combined fractions was further purified by preparative TLC, 10% MeOH/CH₂Cl₂, two 20 cm x 20 cm x 0.5 mm plates. R_f about 0.67 (10% MeOH/CH₂Cl₂). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, *J* = 9.00, 5.34, 2H), 7.81 (s, 1H), 7.80 ((m overlapped with s, *J* = 2.14, 1H), 7.66 (d, *J* = 8.55, 1H), 7.65 (d, *J* = 1.22, 1H), 7.43 (d, *J* = 8.55, 1H), 7.36 (dd, *J* = 8.55, 1.83, 1H), 7.28 (m, *J* = 8.70, 2H), 2.96 (s, 3H), 2.54 (s, 3H), 2.35 (s, 3H), 1.59 (m, 2H), 1.43 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 525.07, HPLC R_t = 1.682 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, R_t = 6.67 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 5.22 min. Analytical HPLC method:

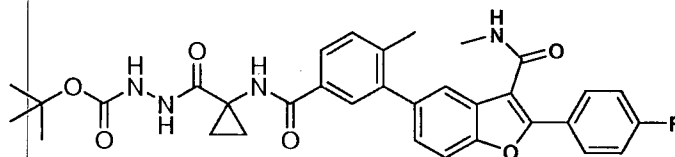
Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 12.36 min.

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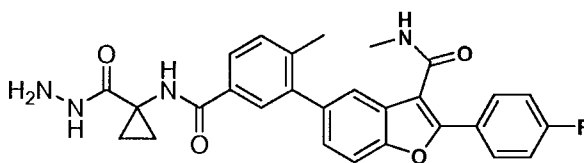
1-(3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzamido)cyclopropanecarboxylic acid

- [00334] ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, *J* = 9.00, 5.34, 2H), 7.78 (s, 1H), 7.77 (m overlapping with s, 1H), 7.66 (d, *J* = 8.55, 1H), 7.64 (d, *J* = 1.22, 1H), 7.42 (d, *J* = 8.55, 1H), 7.38 (dd, *J* = 8.55, 1.83, 1H), 7.28 (t, *J* = 8.70, 2H), 2.96 (s, 3H), 2.34 (s, 3H), 1.60 (m, 2H), 1.25 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES⁺) *m/z* (M+H)⁺ = 487.27, HPLC R_t = 1.625 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 5.38 min; XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 4.43 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3, R_t = 10.67 min.



tert-Butyl 2-(1-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzamido)cyclopropanecarbonyl)hydrazinecarboxylate

- [00335] To a mixture of 1-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzamido)cyclopropanecarboxylic acid (41.6 mg, 0.086 mmol), *tert*-butyl hydrazinecarboxylate (16.95 mg, 0.128 mmol) and 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate (54.9 mg, 0.171 mmol) in DMF (1 mL) at r.t. under N₂ was added N, N-diisopropylethylamine (0.060 mL, 0.342 mmol). The mixture was stirred at r.t. for 19 hours. The mixture was added 5 ml H₂O. The white precipitates were filtered, washed with 3 x 2 ml H₂O and dried (33.1 mg), and was used without further purification. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; HPLC R_t = 1.750 min.

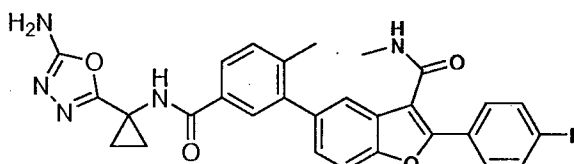


2-(4-Fluorophenyl)-5-(5-(1-(hydrazinecarbonyl)cyclopropylcarbamoyl)-2-methylphenyl)-N-methylbenzofuran-3-carboxamide

- [00336] To *tert*-butyl 2-(1-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzamido)cyclopropanecarbonyl)hydrazinecarboxylate (33.1 mg, 0.055 mmol) in a round-bottom flask at r.t. under N₂ was added HCl (1 ml, 4.00 mmol, 4 M in 1,4-dioxane). The mixture was stirred at r.t. for four hours. The mixture was evaporated, and the crude hydrochloride salt used without further purification. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90%

H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 501.06, HPLC R_t = 1.483 min.

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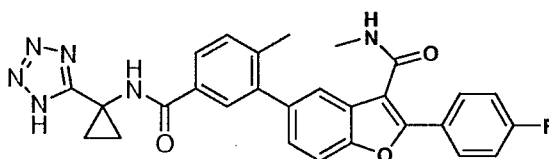


5-(5-(1-(5-Amino-1,3,4-oxadiazol-2-yl)cyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00337] To a mixture of 2-(4-fluorophenyl)-5-(5-(1-

- 10 (hydrazinecarbonyl)cyclopropylcarbamoyl)-2-methylphenyl)-N-methylbenzofuran-3-carboxamide, hydrochloride (29.5 mg, 0.055 mmol, crude) in 1,4-dioxane (1 ml) at r.t. was added a solution of cyanic bromide (58.3 mg, 0.550 mmol) in acetonitrile (0.5 mL), and then sat. aq. NaHCO₃ (0.1 ml). The mixture was stirred at r.t. for about 5 hours. The mixture was added 0.3 ml 1N HCl, diluted with MeOH and purified by
- 15 Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.53 - 7.18 min. (UV detection at 220 nm) to obtain the product as a TFA salt. ¹H NMR (500 MHz, CD₃OD) δ 7.97 (dd, J = 8.55, 5.19, 2H), 7.80 (s, 1H), 7.80 ((m overlapped with s, 1H), 7.66 (d, J = 8.55, 1H), 7.63 (s, 1H), 7.44 (d, J = 8.55, 1H), 7.37 (dd, J = 8.24, 1.22, 1H), 7.29 (t, J = 8.70, 2H), 2.95 (s, 3H), 2.35 (s, 3H), 1.64 (m, 2H), 1.49 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC
- 25 method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 526.05, HPLC R_t = 1.577 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254

nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 3.23 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 3.39 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 11.04 min.



5-(5-(1-(1*H*-Tetrazol-5-yl)cyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00338] To a mixture of 5-(5-(1-cyanocyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (25.1 mg, 0.054 mmol) in

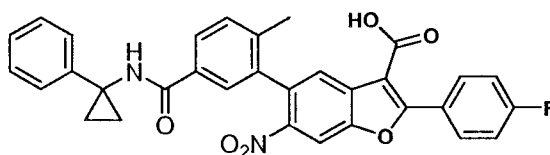
DMF (1 mL) at r.t. under N₂ was added ammonium chloride (8.62 mg, 0.161 mmol), and then sodium azide (6.98 mg, 0.107 mmol). The mixture was stirred at 120 °C for about 4 hours. The mixture was cooled to r.t., and added with another 18 mg of NH₄Cl and then 14 mg of NaN₃. The mixture was stirred at 120 °C for 14.5 hours.

The mixture was cooled to r.t., and added with another 26 mg of NH₄Cl, followed by 21 mg of NaN₃. The mixture was re-stirred at 120 °C for 24 hours. The mixture was cooled to r.t., and diluted with MeOH and purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min,

Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.82 - 7.27 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.97 (m, J = 9.00, 5.34, 2H), 7.85 (d, J = 1.22, 1H), 7.84 (dd overlapping with d, J = 1.83, 1H), 7.67 (d, J = 8.24, 1H), 7.65 (d, J = 1.22, 1H), 7.45 (d, J = 7.63, 1H), 7.39 (dd, J = 8.55, 1.83, 1H), 7.29 (t, J = 8.85, 2H), 2.95 (s, 3H), 2.36 (s, 3H), 1.70 (m, 2H), 1.58 (m, 2H). LC/MS were

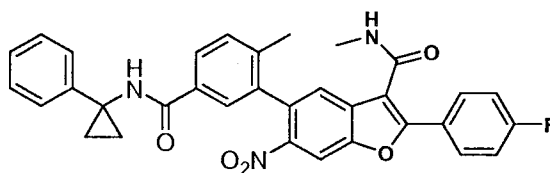
performed by using Shimadzu-VP instrument with UV detection at 220 nm and

Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 511.28, HPLC R_t = 1.595 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, R_t = 5.10 min; XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 4.23 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3, R_t = 10.58 min.



2-(4-Fluorophenyl)-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)-6-nitrobenzofuran-3-carboxylic acid

[00339] Prepared by the hydrolysis of ethyl 2-(4-fluorophenyl)-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)-6-nitrobenzofuran-3-carboxylate. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 551.34, HPLC R_t = 1.895 min.

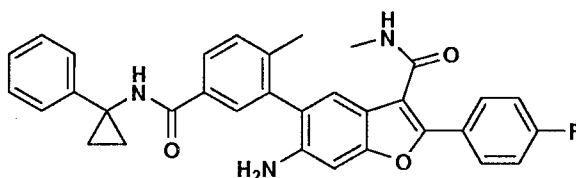


2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-

phenylcyclopropylcarbamoyl)phenyl)-6-nitrobenzofuran-3-carboxamide

[00340] Prepared by the coupling of 2-(4-fluorophenyl)-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)-6-nitrobenzofuran-3-carboxylic acid with

5 methylamine hydrochloride under the conditions as described. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 564.36, HPLC R_t = 1.768 min.



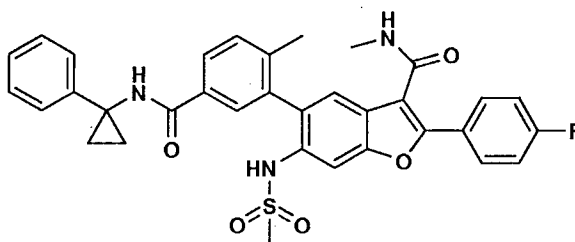
6-Amino-2-(4-fluorophenyl)-N-methyl-5-(2-methyl-5-(1-

15 phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00341] Obtained as a TFA salt from the reduction of 2-(4-fluorophenyl)-N-methyl-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)-6-nitrobenzofuran-3-carboxamide using H₂ with 5% Pd/C as catalyst (2:5 DMF/EtOAc, r.t.) after purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.17 - 6.79 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.94 (m, J = 8.85, 5.19, 2H), 7.87 (dd, J = 8.09, 1.98, 1H), 7.74 (d, J = 1.83, 1H), 7.50 (d, J = 7.93, 1H), 7.44 (s, 1H), 7.38 (s, 1H), 7.17 (m, 1H), 7.29 (s, 1H), 7.29 - 7.25 (overlapping m, 5H), 2.92 (s, 3H), 2.24 (s, 3H), 1.35 (m, 4H).

LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final

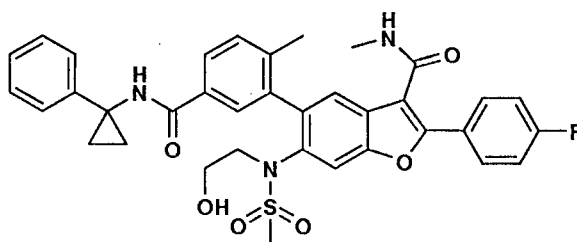
- %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 534.26, HPLC R_t = 1.563 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 11.58 min; XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 4.96 min (Start %B = 50). Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl, R_t = 15.09 min.



- 15 2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)-6-(methylsulfonamido)benzofuran-3-carboxamide

- [00342] To a mixture of 6-amino-2-(4-fluorophenyl)-N-methyl-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide (53.3 mg, 0.100 mmol) (crude) in ClCH₂CH₂Cl (1 ml) at r.t. under N₂ was added pyridine (0.024 mL, 0.300 mmol). The mixture was then added a solution of methanesulfonyl chloride (22.88 mg, 0.200 mmol) in ClCH₂CH₂Cl (0.3 ml), and stirred for about 22 hours. The mixture was diluted with MeOH and purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.75 - 7.37 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, J = 8.85, 5.19, 2H), 7.85 (dd, J

- = 8.09, 1.98, 1H), 7.79 (s, 1H), 7.75 (d, $J = 1.53$, 1H), 7.51 (s, 1H), 7.47 (d, $J = 7.93$, 1H), 7.17 (m, 1H), 7.30 - 7.26 (overlapping m, 5H), 7.29 (s, 1H), 2.93 (s, 3H), 2.88 (s, 3H), 2.23 (s, 3H), 1.35 (appeared as d, 4H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®.
- 5 HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 612.34, HPLC R_t = 1.583 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254
- 10 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 7.48 min; XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 6.24 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃,
- 15 Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl, R_t = 11.46 min.



- 20 2-(4-Fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methyl-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide
- [00343] 2-(4-Fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methyl-5-(2-methyl-5-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide was prepared from the alkylation of 2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-
- 25 phenylcyclopropylcarbamoyl)phenyl)-6-(methylsulfonamido)benzofuran-3-carboxamide using (2-bromoethoxy)(*tert*-butyl)dimethylsilane (K₂CO₃, DMF 55 °C) followed by deprotection using HCl in 1,4-dioxane at r.t. Purification was preformed by Shimadzu-VP preparative reverse phase HPLC using the separation method:

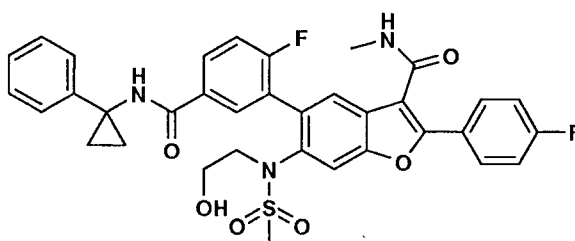
Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.32 - 6.81 min. (UV detection at 220 nm). LC/MS were performed by

5 using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 um, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 656.06, HPLC R_t =

10 1.563 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, R_t = 6.05 min; XBridge phenyl

15 3.5 um, 4.6 x 150 mm, R_t = 5.38 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 11.42 min.

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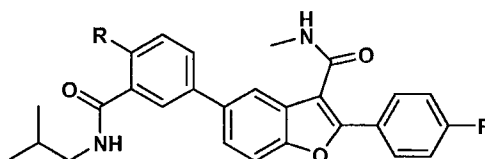


5-(2-Fluoro-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide

[00344] Purification was preformed by Shimadzu-VP preparative reverse phase

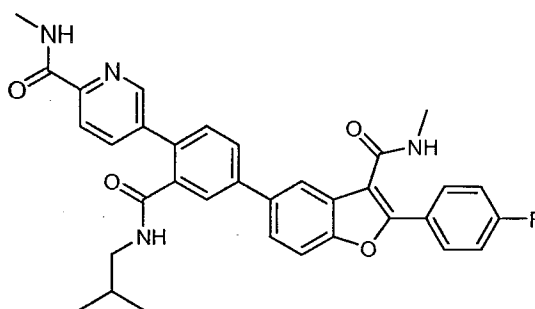
25 HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 30, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.06 - 8.30 min. (UV detection

at 220 nm). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: XTERRA® MS 7 μ m, C18, 3.0 x 50 mm; (ES+) m/z (M+H)⁺ = 660.50, HPLC R_t = 1.530 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 5.68 min; XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 5.18 min.



[00345] General procedure: To a BIOTAGE® microwave vial (2-5 mL) was added either 5-(4-chloro-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (0.075 mmol, 1 eq.) or 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-(isobutylcarbamoyl)phenyl trifluoromethane sulfonate (0.075 mmol, 1 eq.) in dry 1,4-Dioxane (1 mL) along with the desired boronic acid (0.150 mmol, 2 eq.), potassium phosphate, tribasic (0.300 mmol, 52.3 mg) in water (0.2 mL), dicyclohexyl(2',6'-dimethoxybiphenyl-3-yl)phosphine (S-Phos) (6.16 mg, 0.015 mmol), and finally palladium (II) acetate (3.37 mg, 0.015 mmol) in 1,4-dioxane (0.5 mL). The vial was flushed with nitrogen then capped and placed into the BIOTAGE® microwave for 10 minutes at 150 °C. The solvent was removed in a Thermo/Savant SPEEDVAC® and the crude products were dissolved in DMF (1.8 mL) and purified by preparative HPLC using a Shimadzu Prep HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% H₂O/ 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5 μ m C18 30x100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 8 minutes with a 10 minute hold. The tubes with desired product were evaporated overnight in a Thermo/Savant

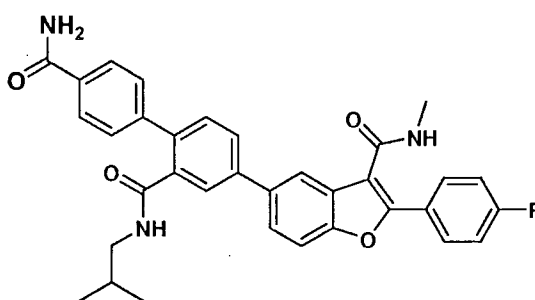
SPEEDVAC®. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% TFA/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% TFA/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/ 0.1%TFA with a gradient of 20-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a PHENOMENEX® Gemini C18 3µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 20-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. Rt represents the LC retention time in minutes. All NMR spectra were recorded at room temperature using deuterated NMR solvents.



5-(4-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-(isobutylcarbamoyl)phenyl)-N-methylpicolinamide

[00346] ¹H NMR (400 MHz, THF-d₈) δ ppm 0.75 (d, *J*=7 Hz, 6 H), 1.63 - 1.71 (m, 1 H), 2.93 (d, *J*=5 Hz, 6 H), 3.00 (t, *J*=6 Hz, 2 H), 7.23 (t, *J*=9 Hz, 2 H), 7.37 (t, *J*=6 Hz, 1 H), 7.44 - 7.51 (m, 1 H), 7.53 (d, *J*=8 Hz, 1 H), 7.60 - 7.66 (m, 1 H), 7.67 - 7.73 (m, 1 H), 7.80 - 7.88 (m, 2 H), 7.98 (dd, *J*=8, 2 Hz, 1 H), 8.05 (s, 1 H), 8.08 -

8.18 (m, 3 H), 8.30 (d, $J=5$ Hz, 1 H), 8.66 (d, $J=2$ Hz, 1 H). LCMS Rt 2.125 min., m/z 579.32 (M+H), HPLC Rt 8.594 min. (Sunfire C18), 98.7 % purity and 11.276 min. (Gemini C18), 100 % purity.

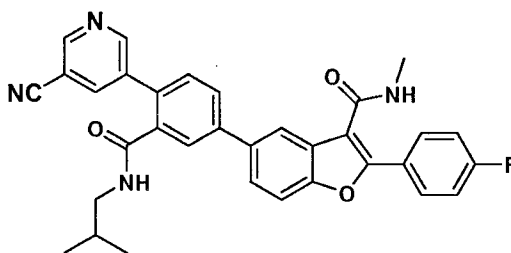


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4-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-N2-isobutylbiphenyl-2,4'-dicarboxamide

[00347] ^1H NMR (400 MHz, DMF- d_7) δ ppm 0.81 (d, $J=6.78$ Hz, 6 H), 1.71 - 1.82 (m, 1 H), 3.00 (d, $J=4.77$ Hz, 3 H), 3.06 (t, $J=6.40$ Hz, 2 H), 7.42 - 7.48 (m, 2 H), 7.57 (d, $J=8.28$ Hz, 1 H), 7.62 (m, 2 H), 7.78 (d, $J=8.28$ Hz, 1 H), 7.84 (m, 2 H), 7.94 (d, $J=8.03$ Hz, 1 H), 8.00 (d, $J=8.28$ Hz, 2 H), 8.06 - 8.08 (m, 1 H), 8.10 - 8.14 (m, 2 H), 8.20 (t, $J=5.77$ Hz, 1 H), 8.40 (d, $J=4.52$ Hz, 1 H). LCMS Rt 2.020 min, m/z 564.25 (M+H). HPLC Rt 8.224 min. (Sunfire C18), 98.2 % purity and 11.098 min. (Gemini C18), 98.3 % purity.

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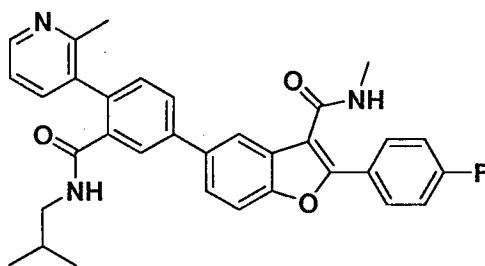


5-(4-(5-Cyanopyridin-3-yl)-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00348] ^1H NMR (400 MHz, THF- d_8) δ ppm 0.82 (d, $J=6.78$ Hz, 6 H), 1.74 - 1.80 (m, 1 H), 2.93 (d, $J=4.52$ Hz, 3 H), 3.01 - 3.11 (m, 2 H), 7.18 - 7.30 (m, 2 H), 7.42 - 7.51 (m, 1 H), 7.55 (d, $J=7.78$ Hz, 1 H), 7.56 - 7.61 (m, 1 H), 7.62 - 7.67 (m, 1 H), 7.68 - 7.75 (m, 1 H), 7.83 - 7.92 (m, 2 H), 8.04 - 8.15 (m, 3 H), 8.20 (t, $J=2.13$ Hz, 1

H), 8.85 (dd, $J=13.93, 2.13$ Hz, 2 H). LCMS Rt 2.278 min, m/z 547.23 (M+H). HPLC Rt 9.246 min. (Sunfire C18), 96.0 % purity and 11.343 min. (Gemini C18), 98.6 % purity.

[00349] An alternative approach to the coupling. To a small sized microwave vial
 5 was added 5-(4-chloro-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (47.9 mg, 0.1 mmol), BuOH (2 mL), boronic acid/ester (0.150 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (19.07 mg, 0.040 mmol), potassium phosphate, tribasic (85 mg, 0.400 mmol) and finally Tris(dibenzylideneacetone) dipalladium(0) (18.31 mg, 0.020 mmol). The vial
 10 was capped and subjected to microwave heating (130 °C) for 12 minutes. Butanol was removed under a stream of nitrogen and the crude products were dissolved in DMF (1.8 mL) and purified by preparative HPLC employing a DIONEX® Prep HPLC system equipped with an ELS (Evaporative Light Scattering) detector. A Waters XBridge 19x200mm 5 μ m C18 column was used with acetonitrile/HPLC
 15 grade water/10mM ammonium acetate where solvent A was HPLC grade water with 10mM ammonium acetate and solvent B was 100% acetonitrile at a gradient of 30-95% B in 30 minutes with a flow rate of 25mL/minute. LCMS was run using a Waters ZQ with ESCi mass spectrometer with a SUPELCO® Ascentis Express 3 μ m C18 4.5 x 50mm column employing acetonitrile/HPLC grade water/10mM
 20 ammonium acetate where solvent A was 5% acetonitrile, 95% HPLC grade water with 10mM ammonium acetate and solvent B was 95% acetonitrile, 5% HPLC grade water with 10mM ammonium acetate at a gradient of 0-100% B in 8 minutes with a 1 minute hold at 2mL/minute.



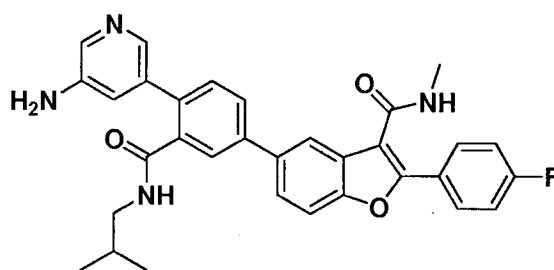
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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(2-methylpyridin-3-yl)phenyl)-N-methylbenzofuran-3-carboxamide

WO 2010/030592

PCT/US2009/056166

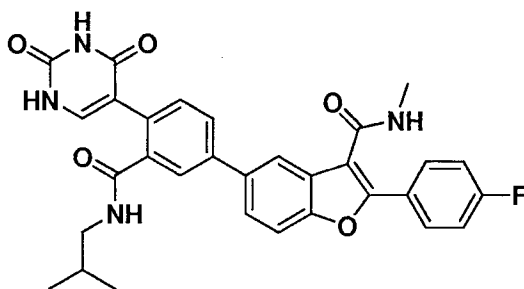
[00350] LCMS m/z 535.90 (M+H), Rt 4.89 min., 100 % purity.



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5-(4-(5-Aminopyridin-3-yl)-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

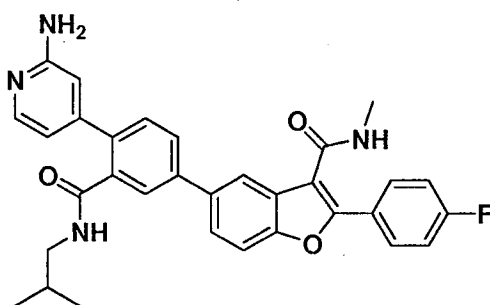
[00351] LCMS m/z 536.96 (M+H), Rt 4.37 min., 100 % purity.



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5-(4-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

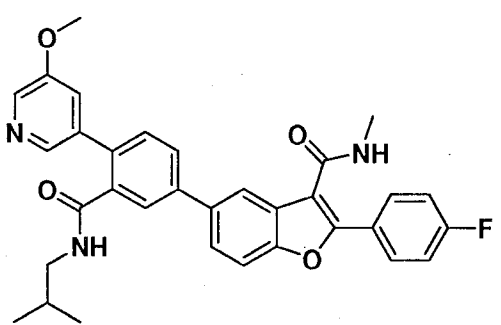
[00352] LCMS m/z 554.94 (M+H), Rt 3.88 min., 100 % purity.



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5-(4-(2-Aminopyridin-4-yl)-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

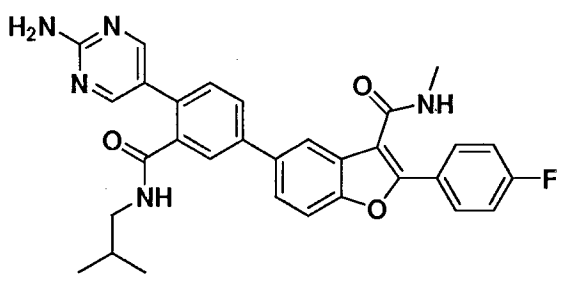
[00353] LCMS m/z 536.97 (M+H), Rt 4.55 min., 100 % purity.



2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(5-methoxypyridin-3-yl)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00354] LCMS m/z 551.96 (M+H), Rt 4.97 min., 89 % purity.

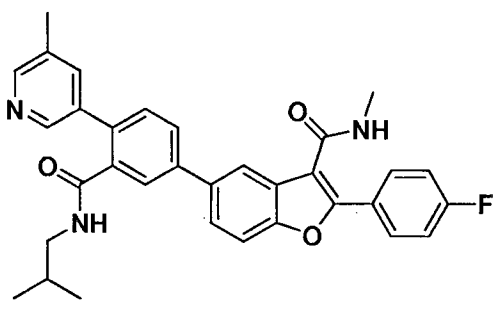
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5-(4-(2-Aminopyrimidin-5-yl)-3-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00355] LCMS m/z 537.97 (M+H), Rt 4.23 min., 96 % purity.

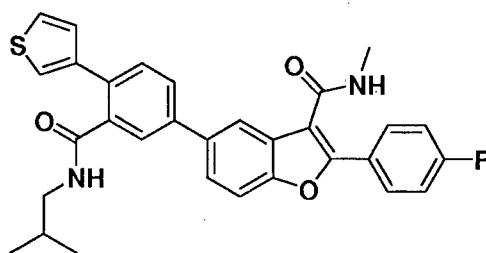
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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(5-methylpyridin-3-yl)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00356] LCMS m/z 535.95 (M+H), Rt 4.99 min., 100 % purity.

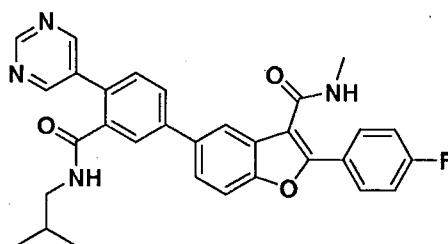
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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(thiophen-3-yl)phenyl)-N-methylbenzofuran-3-carboxamide

[00357] LCMS m/z 526.96 (M+H), Rt 5.83 min., 74 % purity.

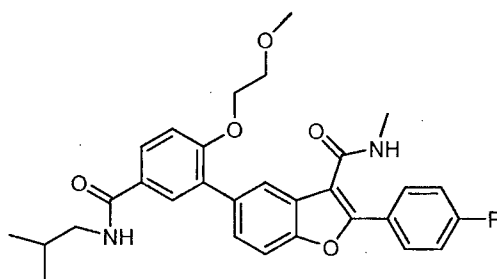
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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-(pyrimidin-5-yl)phenyl)-N-methylbenzofuran-3-carboxamide

- [00358] Purification by using a Shimadzu preparative HPLC employing
- 10 CH₃CN/water/TFA where solvent A was 10% acetonitrile / 90% H₂O/ 0.1% trifluoroacetic acid and solvent B was 10% H₂O / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5u C18 30x100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 10 minutes with a 10 minute hold. Post purification LC/MS data was obtained on a Shimadzu analytical LC /
- 15 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% TFA/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% TFA/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a
- 20 Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/ 0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade

acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a PHENOMENEX® Gemini C18 3 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a
 5 gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.76 (d, *J*=6.78 Hz, 6 H), 1.61 - 1.74 (m, 1 H), 2.87 (d, *J*=4.52 Hz, 3 H), 2.96 (t, *J*=6.27 Hz, 2 H),
 10 7.39 (t, *J*=8.91 Hz, 2 H), 7.64 (d, *J*=8.03 Hz, 1 H), 7.77 - 7.87 (m, 3 H), 7.91 - 8.07 (m, 4 H), 8.47 - 8.60 (m, 2 H), 8.81 (s, 2 H), 9.16 (s, 1 H). LCMS *m/z* 523.22 (M+H), Rt 2.052 min. HPLC Rt 8.908 min. (Sunfire C18), 96.0 % purity and 11.353 min. (Gemini C18), 98.6 % purity.



15

2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-methoxyethoxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00359] To a small microwave vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(isobutylcarbamoyl) phenyl)-N-methylbenzofuran-3-carboxamide (33 mg, 0.072
 20 mmol), tetrahydrofuran (2 mL), triphenylphosphine (37.6 mg, 0.143 mmol), 2-methoxyethanol (0.011 mL, 0.139 mmol), and di-*tert*-butyl azodicarboxylate (33.0 mg, 0.143 mmol). The vial was crimped and heated to 100 °C for 10 minutes. After returning to room temperature tetrahydrofuran was removed under a stream of nitrogen. The crude product was taken up in 2mL of acetonitrile and purified using a
 25 Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5 μ m

C18 30 x 100mm column at a gradient of 40-100% B and a flow rate of 40 mL/min. over 8 minutes with a 10 minute hold. The desired material was concentrated to dryness. The resulting white solid (41% yield) was placed under high vacuum prior to final analysis. The LC/MS data was obtained on a Shimadzu analytical LC /

5 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was

10 determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1

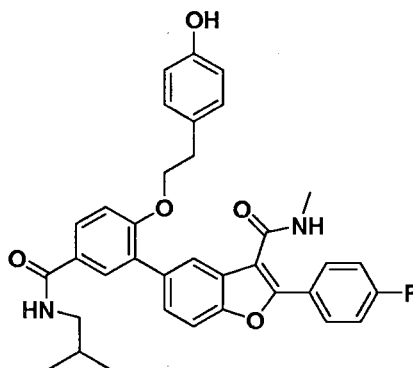
15 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water /

20 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The NMR spectrum was recorded at room temperature using a Bruker DRX400 spectrometer. Chemical shifts were reported in ppm relative to the deuterated solvent used. Coupling constants were reported in hertz. Peak multiplicity was reported using the following abbreviations: s (singlet), d

25 (doublet), dd (doublet of doublets), t (triplet), m (multiplet), br (broad). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.04 (d, J = 6.53 Hz, 6 H), 1.35 - 1.40 (m, 3 H), 1.96 - 2.08 (m, 1 H), 2.97 - 3.10 (m, 3 H), 3.24 - 3.32 (m, 2 H), 3.73 - 3.82 (m, 2 H), 4.25 - 4.34 (m, 2 H), 7.24 (d, J = 8.53 Hz, 1 H), 7.29 - 7.38 (m, 2 H), 7.63 - 7.72 (m, 2 H), 7.91 (dd, J = 8.53, 2.26 Hz, 1 H), 7.94 - 7.99 (m, 2 H), 8.00 - 8.09 (m, 2 H), 8.48 (br. s., 1 H).

30 LCMS m/z 519.25 (M+H), Rt 2.292 min. HPLC (Sunfire C18) Rt 10.054 min, 96% purity and (XBridge phenyl C18) Rt 11.846 min., 97 % purity.

[00360] Additional examples of ether linked compounds are shown below. The compounds were synthesized in the same manner as above. The solvent (tetrahydrofuran) was removed under a stream of nitrogen and the crude products were dissolved in DMF (1.8 mL) and purified by preparative HPLC employing a DIONEX® Prep HPLC system equipped with an ELS (Evaporative Light Scattering) detector. A SUPELCO® Ascentis 5µm C18 21.2 x 250mm column was used with acetonitrile/HPLC grade water/10mM ammonium acetate where solvent A was 99.9% HPLC grade water with 10mM ammonium acetate and solvent B was 100% acetonitrile at a gradient of 30-95% B in 20 minutes with a 2.5 minute hold at 20mL/minute. LCMS was run using a Waters ZQ with ESCi mass spectrometer with a SUPELCO® Ascentis Express 3 µm C18 4.5 x 50mm column employing acetonitrile/HPLC grade water/10mM ammonium acetate where solvent A was 5% acetonitrile, 95% HPLC grade water with 10mM ammonium acetate and solvent B was 95% acetonitrile, 5% HPLC grade water with 10mM ammonium acetate at a gradient of 0-100% B in 8 minutes with a 1 minute hold at 2mL/minute. The NMR spectra were recorded at room temperature using a Varian 600MHz flow spectrometer. Chemical shifts were reported in ppm relative to the 75% DMSO-d₆/25% CDCl₃ (v/v) solvent used.

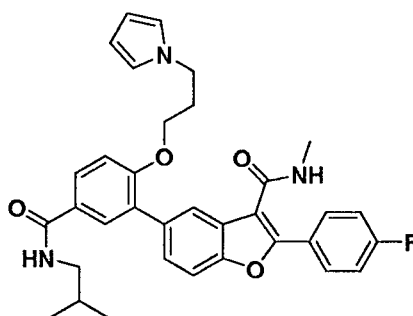


20 2-(4-Fluorophenyl)-5-(2-(4-hydroxyphenethoxy))-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00361] ¹H NMR (600 MHz, DMSO-d₆/CDCl₃) δ ppm 0.88 (d, J=7.03 Hz, 6 H), 1.85 (ddd, J=13.33, 6.59, 6.44 Hz, 1 H), 2.77 - 2.94 (m, 5 H), 3.08 (t, J=6.15 Hz, 2 H), 4.20 (t, J=6.44 Hz, 2 H), 6.59 - 6.68 (m, 2 H), 6.98 (d, J=8.20 Hz, 2 H), 7.13 (d,

$J=8.79$ Hz, 1 H), 7.32 (t, $J=8.79$ Hz, 1 H), 7.41 (d, $J=8.79$ Hz, 1 H), 7.59 (d, $J=8.20$ Hz, 1 H), 7.75 (s, 1 H), 7.81 - 7.91 (m, 2 H), 8.00 (dd, $J=8.20, 5.27$ Hz, 1 H), 8.33 (t, $J=5.57$ Hz, 1 H), 8.39 (d, $J=4.10$ Hz, 1 H). LCMS m/z 581.48 (M+H), Rt 5.30 min., 90 % purity.

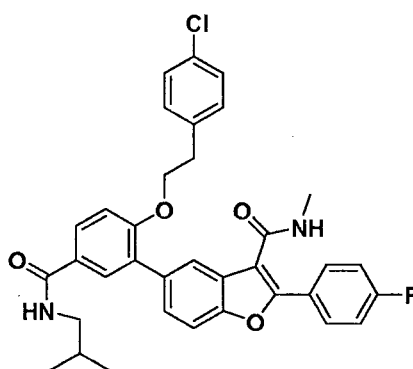
5



5-(2-(3-(1H-Pyrrol-1-yl)propoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-
N-methylbenzofuran-3-carboxamide

[00362] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=6.44$ Hz, 6 H), 1.80 - 1.91 (m, 1 H), 2.07 (m, 2 H), 2.79 (d, $J=4.10$ Hz, 3 H), 3.09 (t, $J=6.44$ Hz, 2 H), 3.90 - 4.01 (m, 4 H), 5.94 (s, 2 H), 6.61 (s, 2 H), 7.08 (d, $J=8.79$ Hz, 1 H), 7.32 (t, $J=8.50$ Hz, 2 H), 7.58 (d, $J=8.20$ Hz, 1 H), 7.70 (d, $J=8.79$ Hz, 1 H), 7.79 - 7.87 (m, 2 H), 7.92 (s, 1 H), 7.97 (dd, $J=8.50, 5.57$ Hz, 2 H), 8.32 - 8.42 (m, 2 H). LCMS m/z 568.47 (M+H), Rt 5.98 min., 100 % purity.

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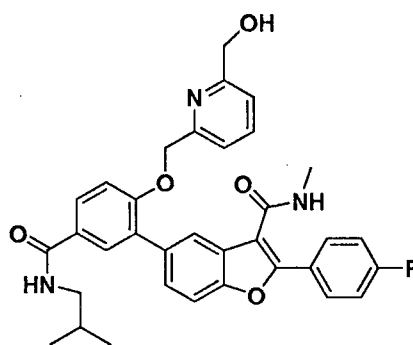
2-(4-Fluorophenyl)-5-(2-(4-chlorophenethoxy)-5-(isobutylcarbamoyl)phenyl)-N-
methylbenzofuran-3-carboxamide

[00363] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.88 (d, $J=7.03$ Hz, 6 H), 1.80 - 1.90 (m, 1 H), 2.84 (d, $J=4.69$ Hz, 3 H), 2.96 (t, $J=6.15$ Hz, 2 H), 3.08 (t,

20

$J=6.15$ Hz, 2 H), 4.26 (t, $J=6.44$ Hz, 2 H), 7.14 (d, $J=8.79$ Hz, 1 H), 7.19 (d, $J=8.20$ Hz, 2 H), 7.23 - 7.27 (m, 2 H), 7.29 - 7.39 (m, 3 H), 7.58 (d, $J=8.79$ Hz, 1 H), 7.73 (s, 1 H), 7.83 - 7.89 (m, 2 H), 8.00 (dd, $J=8.50, 5.57$ Hz, 2 H), 8.33 (t, $J=5.27$ Hz, 1 H), 8.38 (d, $J=4.10$ Hz, 1 H). LCMS m/z 599.47 (M+H), Rt 6.52 min., 92 % purity.

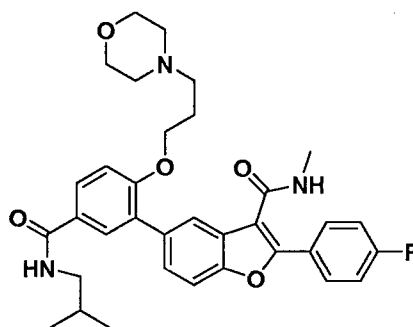
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2-(4-Fluorophenyl)-5-(2-((6-(hydroxymethyl)pyridin-2-yl)methoxy)-5-(isobutylcarbamoyl) phenyl)-N-methylbenzofuran-3-carboxamide

[00364] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=6.44$ Hz, 6 H), 1.79 - 1.91 (m, 1 H), 2.82 (d, $J=4.10$ Hz, 3 H), 3.09 (t, $J=6.44$ Hz, 2 H), 4.56 (s, 2 H), 5.23 (s, 2 H), 7.24 (t, $J=9.37$ Hz, 2 H), 7.32 (t, $J=8.79$ Hz, 2 H), 7.37 (d, $J=8.20$ Hz, 1 H), 7.60 - 7.65 (m, 1 H), 7.66 - 7.70 (m, 1 H), 7.75 (t, $J=7.62$ Hz, 1 H), 7.84 - 7.90 (m, 2 H), 7.93 (s, 1 H), 7.96 - 8.03 (m, 2 H), 8.36 (t, $J=5.57$ Hz, 1 H), 8.40 (d, 1 H). LCMS m/z 582.48 (M+H), Rt 4.57 min., 93 % purity.

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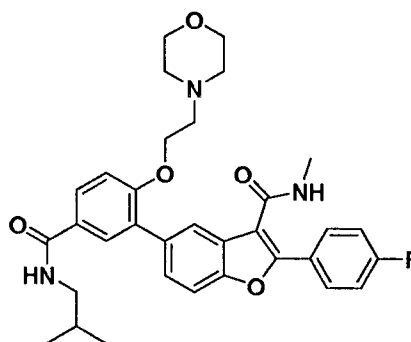


2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(3-morpholinopropoxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00365] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=7.03$ Hz, 6 H), 1.77 - 1.91 (m, 3 H), 2.23 - 2.43 (m, 6 H), 2.84 (d, $J=4.10$ Hz, 3 H), 3.08 (t, $J=6.44$

Hz, 2 H), 3.53 (br. s., 4 H), 4.09 (t, $J=5.86$ Hz, 2 H), 7.14 (d, $J=8.20$ Hz, 1 H), 7.32 (t, $J=8.79$ Hz, 2 H), 7.53 (d, $J=9.37$ Hz, 1 H), 7.65 (d, $J=8.79$ Hz, 1 H), 7.78 (s, 1 H), 7.84 - 7.92 (m, 2 H), 7.98 (dd, $J=7.91, 5.57$ Hz, 2 H), 8.31 - 8.43 (m, 2 H). LCMS m/z 588.40 (M+H), Rt 4.05 min., 98.7 % purity.

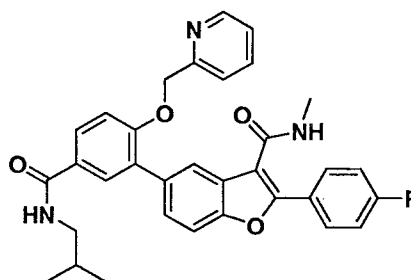
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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-morpholinoethoxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00366] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=6.44$ Hz, 6 H), 1.79 - 1.91 (m, 1 H), 2.38 (br. s., 4 H), 2.64 (t, $J=5.57$ Hz, 2 H), 2.84 (d, $J=4.10$ Hz, 3 H), 3.08 (t, $J=6.15$ Hz, 2 H), 3.52 (t, $J=4.39$ Hz, 4 H), 4.17 (t, $J=5.57$ Hz, 2 H), 7.16 (d, $J=8.79$ Hz, 1 H), 7.32 (t, $J=8.79$ Hz, 2 H), 7.56 - 7.61 (m, 1 H), 7.61 - 7.66 (m, 1 H), 7.75 (s, 1 H), 7.83 - 7.91 (m, 2 H), 7.98 (dd, $J=8.20, 5.86$ Hz, 2 H), 8.35 (t, $J=5.27$ Hz, 1 H), 8.38 (d, 1 H). LCMS m/z 574.35 (M+H), Rt 3.95 min., 100 % purity.

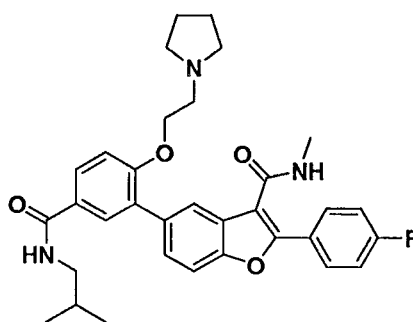
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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(pyridin-2-ylmethoxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00367] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=7.03$ Hz, 6 H), 1.82 - 1.91 (m, 1 H), 2.79 - 2.86 (m, 3 H), 3.09 (t, $J=6.44$ Hz, 2 H), 5.27 (s, 2 H), 7.22 - 7.30 (m, 2 H), 7.33 (t, $J=8.50$ Hz, 2 H), 7.40 (d, $J=7.62$ Hz, 1 H), 7.62 (d, $J=8.79$

Hz, 1 H), 7.66 - 7.71 (m, 1 H), 7.76 (t, $J=7.62$ Hz, 1 H), 7.84 - 7.91 (m, 2 H), 7.94 (s, 1 H), 7.99 (dd, $J=8.50, 5.57$ Hz, 2 H), 8.35 - 8.44 (m, 2 H), 8.53 (d, $J=4.69$ Hz, 1 H).
LCMS m/z 552.29 (M+H), Rt 4.29 min., 100 % purity.

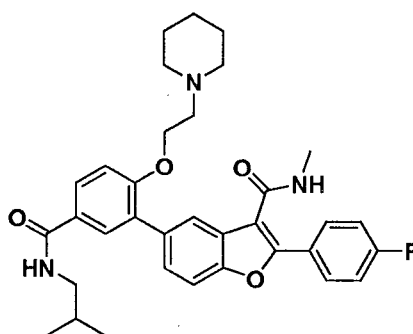


5

2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-
N-methylbenzofuran-3-carboxamide

[00368] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=6.44$ Hz, 6 H), 1.64 (br. s., 4 H), 1.80 - 1.91 (m, 1 H), 2.47 (br. s., 4 H), 2.75 - 2.82 (m, 2 H), 2.84 (d, $J=4.10$ Hz, 3 H), 3.08 (t, $J=6.44$ Hz, 2 H), 4.16 (t, $J=5.27$ Hz, 2 H), 7.16 (d, 1 H), 7.32 (t, $J=8.79$ Hz, 2 H), 7.56 - 7.61 (m, 1 H), 7.61 - 7.66 (m, 1 H), 7.78 (s, 1 H), 7.86 (d, $J=8.20$ Hz, 1 H), 7.89 (s, 1 H), 7.98 (dd, $J=8.20, 5.27$ Hz, 2 H), 8.31 - 8.43 (m, 2 H).
LCMS m/z 558.37 (M+H), Rt 3.52 min., 100 % purity.

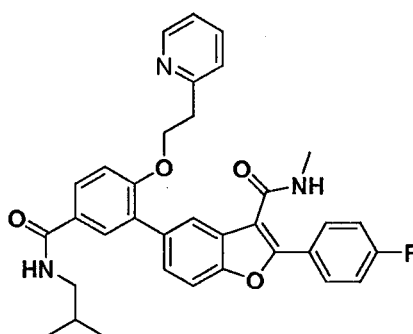
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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-(piperidin-1-yl)ethoxy)phenyl)-*N*-
methylbenzofuran-3-carboxamide

[00369] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=6.44$ Hz, 6 H), 1.32 - 1.38 (m, 2 H), 1.38 - 1.43 (m, 2 H), 1.44 - 1.52 (m, 2 H), 1.79 - 1.93 (m, 1 H), 2.32 - 2.45 (m, 4 H), 2.57 - 2.68 (m, 2 H), 2.84 (d, $J=4.10$ Hz, 3 H), 3.08 (t, $J=6.15$ Hz, 2 H), 4.10 - 4.20 (m, 2 H), 7.16 (d, $J=8.79$ Hz, 1 H), 7.32 (t, $J=8.79$ Hz, 2 H),

7.61 (q, $J=8.79$ Hz, 2 H), 7.76 (s, 1 H), 7.86 (d, $J=8.20$ Hz, 1 H), 7.89 (s, 1 H), 7.98 (dd, $J=8.20, 5.86$ Hz, 2 H), 8.31 - 8.44 (m, 2 H). LCMS m/z 572.37 (M+H), Rt 3.89 min., 95.4 % purity.

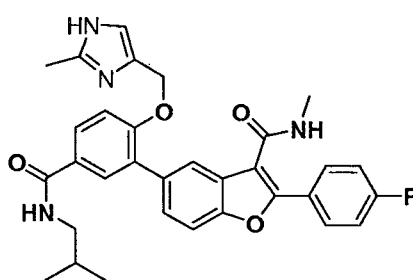


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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-(pyridin-2-yl)ethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00370] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.88 (d, $J=6.44$ Hz, 6 H), 1.79 - 1.91 (m, 1 H), 2.84 (d, $J=4.69$ Hz, 3 H), 3.08 (t, $J=6.15$ Hz, 2 H), 3.21 (t, $J=6.15$ Hz, 2 H), 4.47 (t, $J=6.15$ Hz, 2 H), 7.20 (dd, $J=19.92, 8.20$ Hz, 2 H), 7.29 - 7.41 (m, 4 H), 7.50 (d, $J=8.79$ Hz, 1 H), 7.67 (s, 1 H), 7.79 - 7.91 (m, 3 H), 8.00 (dd, $J=8.50, 5.57$ Hz, 2 H), 8.34 (t, $J=5.57$ Hz, 1 H), 8.45 (d, $J=4.10$ Hz, 1 H), 8.51 (d, $J=4.69$ Hz, 1 H). LCMS m/z 566.34 (M+H), Rt 4.32 min., 100 % purity.

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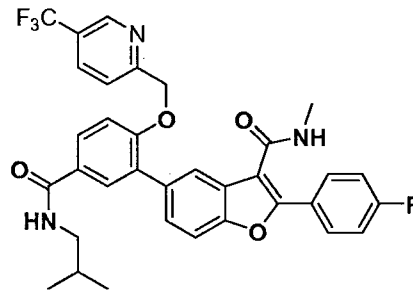
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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-((2-methyl-1*H*-imidazol-4-yl)methoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00371] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=6.44$ Hz, 6 H), 1.85 (dd, $J=12.01, 6.74$ Hz, 1 H), 2.14 - 2.38 (m, 3 H), 2.81 - 2.88 (m, 3 H), 3.04 - 3.12 (m, 2 H), 5.00 (s, 1 H), 6.91 - 7.03 (m, 1 H), 7.32 (t, $J=9.08$ Hz, 2 H), 7.50 - 7.68 (m, 2 H), 7.70 (d, $J=6.44$ Hz, 1 H), 7.79 (d, $J=4.10$ Hz, 2 H), 7.86 (d, $J=11.72$ Hz, 1

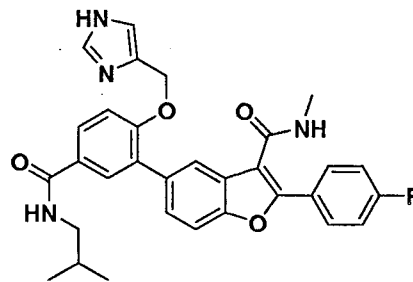
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H), 7.94 (s, 1 H), 7.96 - 8.04 (m, 1 H), 8.34 (t, $J=5.57$ Hz, 1 H), 8.40 (d, $J=4.69$ Hz, 1 H). LCMS m/z 555.34 (M+H), Rt 3.57 min., 93.3 % purity.



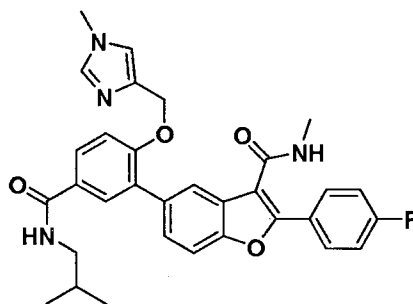
- 5 2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-((5-(trifluoromethyl)pyridin-2-yl)methoxy) phenyl)-*N*-methylbenzofuran-3-carboxamide

[00372] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.90 (d, $J=7.03$ Hz, 6 H), 1.82 - 1.92 (m, 1 H), 2.79 (d, $J=4.69$ Hz, 3 H), 3.09 (t, $J=6.15$ Hz, 2 H), 5.39 (s, 2 H), 7.27 (d, $J=8.79$ Hz, 1 H), 7.34 (t, $J=8.50$ Hz, 2 H), 7.62 (t, $J=8.50$ Hz, 2 H), 7.71 (d, $J=8.20$ Hz, 1 H), 7.89 (d, $J=8.20$ Hz, 1 H), 7.92 (s, 1 H), 7.95 - 8.02 (m, 3 H), 8.16 (d, $J=8.20$ Hz, 1 H), 8.39 (t, $J=5.57$ Hz, 1 H), 8.44 (d, $J=4.69$ Hz, 1 H), 8.90 (s, 1 H).
10 LCMS m/z 620.32 (M+H), Rt 5.09 min., 97.9 % purity.



- 15 5-(2-((1*H*-Imidazol-4-yl)methoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

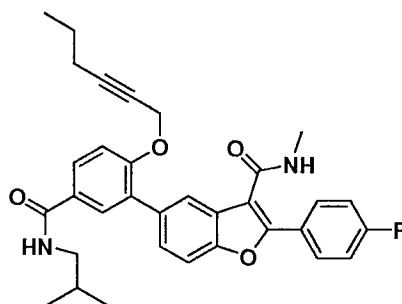
[00373] LCMS m/z 541.29 (M+H), Rt 3.51 min., 100 % purity.



2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-((1-methyl-1H-imidazol-4-yl)methoxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00374] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.88 (d, $J=6.44$ Hz, 6 H),
 5 1.83 (dt, $J=13.48, 6.74$ Hz, 1 H), 2.84 (d, $J=4.69$ Hz, 3 H), 3.06 (t, $J=6.44$ Hz, 2 H),
 3.63 (s, 3 H), 3.88 (s, 2 H), 7.00 (s, 1 H), 7.32 (t, $J=8.79$ Hz, 2 H), 7.55 (d, $J=8.20$ Hz,
 1 H), 7.63 - 7.70 (m, 3 H), 7.74 (d, $J=14.65$ Hz, 2 H), 7.94 (s, 1 H), 7.99 (dd, $J=8.20,$
 5.27 Hz, 2 H), 8.23 (s, 1 H), 8.39 (d, $J=4.10$ Hz, 1 H). LCMS m/z 555.35 (M+H), Rt
 4.11 min., 100 % purity.

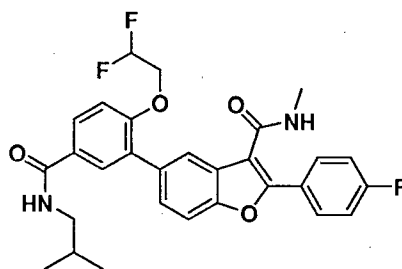
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2-(4-Fluorophenyl)-5-(2-(hex-2-ynyloxy)-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00375] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.83 - 0.97 (m, 9 H), 1.36 -
 15 1.48 (m, 2 H), 1.82 - 1.90 (m, 1 H), 2.16 (t, $J=6.74$ Hz, 2 H), 2.84 (d, $J=4.69$ Hz, 3
 H), 3.09 (t, $J=6.44$ Hz, 2 H), 4.82 (br. s., 2 H), 7.23 (d, $J=8.20$ Hz, 1 H), 7.29 - 7.33
 (m, 2 H), 7.51 (d, $J=8.79$ Hz, 1 H), 7.65 (d, $J=8.20$ Hz, 1 H), 7.72 (s, 1 H), 7.84 - 7.91
 (m, 2 H), 7.99 (dd, $J=8.20, 5.27$ Hz, 2 H), 8.36 (t, $J=5.57$ Hz, 1 H), 8.40 (d, $J=4.10$
 Hz, 1 H). LCMS m/z 541.35 (M+H), Rt 5.20 min., 95.3 % purity.

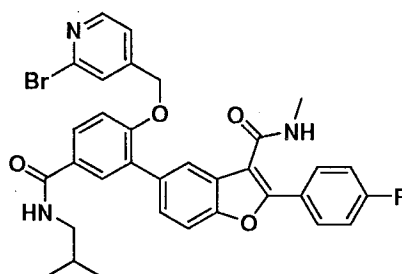
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5-(2-(2,2-Difluoroethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00376] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=6.44$ Hz, 6 H), 1.86 (dt, $J=13.48, 6.74$ Hz, 1 H), 2.84 (d, $J=4.10$ Hz, 3 H), 3.09 (t, $J=6.44$ Hz, 2 H), 4.39 (td, $J=14.35, 2.93$ Hz, 2 H), 6.15 - 6.40 (m, 1 H), 7.23 (d, $J=8.79$ Hz, 1 H), 7.32 (t, $J=8.79$ Hz, 2 H), 7.56 (d, $J=8.79$ Hz, 1 H), 7.66 (d, $J=8.20$ Hz, 1 H), 7.79 (s, 1 H), 7.89 (d, $J=8.79$ Hz, 1 H), 7.93 (s, 1 H), 7.99 (dd, $J=8.20, 5.27$ Hz, 2 H), 8.35 - 8.44 (m, 2 H). LCMS m/z 525.27 (M+H), Rt 4.44 min., 97.4 % purity.

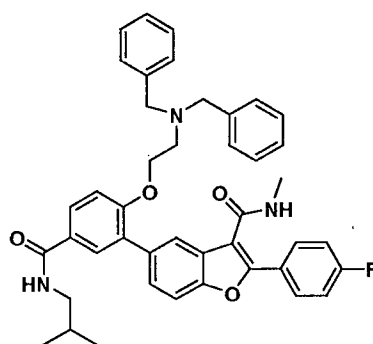
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5-(2-((2-Bromopyridin-4-yl)methoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

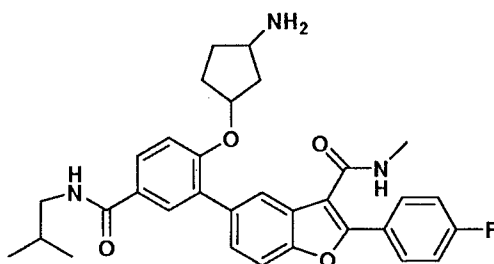
[00377] ^1H NMR (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0.89 (d, $J=6.44$ Hz, 6 H), 1.81 - 1.91 (m, 1 H), 2.82 (d, $J=4.69$ Hz, 3 H), 3.09 (t, $J=6.15$ Hz, 2 H), 5.27 (s, 2 H), 7.21 (d, $J=8.79$ Hz, 1 H), 7.33 (t, $J=8.50$ Hz, 2 H), 7.37 (d, $J=4.69$ Hz, 1 H), 7.54 (s, 1 H), 7.61 (d, $J=8.79$ Hz, 1 H), 7.70 (d, $J=8.79$ Hz, 1 H), 7.83 (s, 1 H), 7.89 (d, $J=8.79$ Hz, 1 H), 7.94 (s, 1 H), 7.99 (dd, $J=8.20, 5.27$ Hz, 2 H), 8.32 (d, $J=5.27$ Hz, 1 H), 8.38 (d, $J=4.69$ Hz, 2 H). LCMS m/z 630.26 (M+H), Rt 4.71 min., 98.4 % purity.

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5-(2-(2-(Dibenzylamino)ethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-
N-methylbenzofuran-3-carboxamide

- [00378] Post purification LC/MS data was obtained on a Shimadzu analytical LC /
- 5 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was
- 10 determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol / 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10
- 15 minutes with a 10 minute hold at a rate of 1 mL/minute. The NMR spectrum was recorded at room temperature using a Bruker DRX400 spectrometer. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.96 (d, *J* = 6.53 Hz, 6 H), 1.83 - 2.07 (m, 1 H), 2.81 (t, *J* = 5.40 Hz, 2 H), 2.90 (s, 3 H), 3.19 (d, *J* = 7.03 Hz, 2 H), 3.53 (s, 4 H), 4.10 (t, *J* = 5.40 Hz, 2 H), 6.99 (d, *J* = 8.53 Hz, 1 H), 7.14 (dd, *J* = 5.52, 3.01 Hz, 2 H), 7.17 - 7.23 (m, 8 H), 7.23 - 7.29 (m, 2 H), 7.41 - 7.47 (m, 1 H), 7.48 - 7.55 (m, 1 H), 7.75 - 7.82 (m, 2 H), 7.84 (d, *J* = 2.26 Hz, 1 H), 7.92 (dd, *J* = 8.66, 5.40 Hz, 2 H). LCMS *m/z* 684.40 (M+H), Rt = 1.897min. HPLC Rt 14.159 min. (XBridge phenyl C18), 100 % purity.
- 20

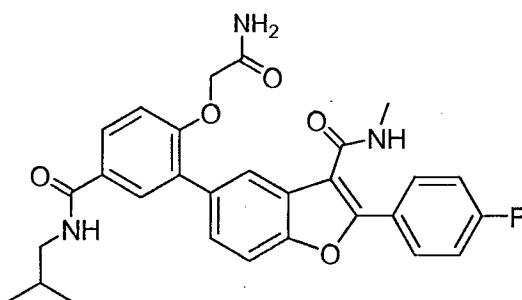


5-(2-(3-Aminocyclopentyloxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00379] Post purification LC/MS data was obtained on a Shimadzu analytical LC /
 5 MICROMASS® Platform LC (ESI+/-) at 220nm using the following set of
 conditions: Luna 10µm C18, 3.0 x 50mm column, with a gradient of 0-100%B (B =
 95% HPLC grade acetonitrile/ 10mM ammonium acetate/ 5% HPLC grade water), (A
 = 95% HPLC grade water / 10mM ammonium acetate/ 5% HPLC grade acetonitrile),
 in 4 minutes with a 1 minute hold at a rate of 5 mL/minute. HPLC purity was
 10 determined using a Shimadzu analytical LC at 254nm and 256nm with a Gemini C18
 3.0µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium
 bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM
 ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water /
 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10
 15 minute hold at a rate of 1 mL/minute. The NMR spectrum was recorded at room
 temperature using a Bruker DRX400 spectrometer. ¹H NMR (400 MHz, THF-d₈) δ
 ppm 0.93 (d, *J* = 6.78 Hz, 6 H), 1.77 - 1.97 (m, 3 H), 2.04 - 2.19 (m, 2 H), 2.19 - 2.32
 (m, 2 H), 2.90 (d, *J* = 4.52 Hz, 3 H), 3.17 (t, *J* = 6.40 Hz, 2 H), 3.69 - 3.82 (m, 2 H),
 7.04 (d, *J* = 8.53 Hz, 1 H), 7.21 (t, *J* = 8.78 Hz, 2 H), 7.41 - 7.50 (m, 1 H), 7.50 - 7.56
 20 (m, 1 H), 7.60 - 7.72 (m, 2 H), 7.81 (dd, *J* = 8.66, 2.13 Hz, 1 H), 7.85 (d, *J* = 1.25 Hz,
 1 H), 7.90 (d, *J* = 2.01 Hz, 1 H), 7.99 - 8.10 (m, 2 H), 8.42 (br. s., 2 H). LCMS Rt
 1.937min., *m/z* 542.34 (M-H) and *m/z* 544.29 (M+H). HPLC Rt 6.870 min. (Sunfire
 C18), 99.1 % purity and 11.133 min. (Gemini C18), 98.9 % purity.

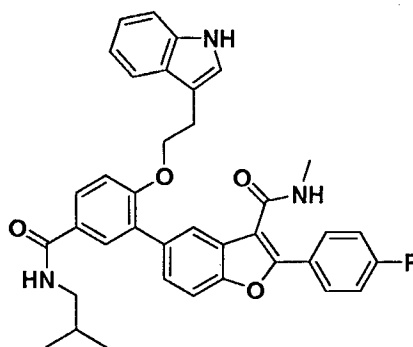
[00380] An alternative synthesis to these ether linked analogs was carried out
 25 using phenol template in DMF with alkyl bromides and DBU. To a 2 dram vial was
 added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(isobutylcarbamoyl)phenyl)-*N*-
 methylbenzofuran-3-carboxamide (46.0 mg, 0.1 mmol), DMF (2 mL), 4.0 equivalents
 of DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.4mmol) and 3.0 equivalents

(0.3mmol) of alkyl bromide. The vials were sealed and shaken at 75 °C in a dry bath. Upon reaction completion the crude products were concentrated, diluted with 2mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5µm C18 4.6 x 100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 8 minutes with a 10 minute hold. The desired products were evaporated to dryness in a Savant SPEEDVAC® overnight obtaining 25-60% yield of the desired ethers as powders. The NMR spectrum was recorded at room temperature using a Bruker DRX400 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute.



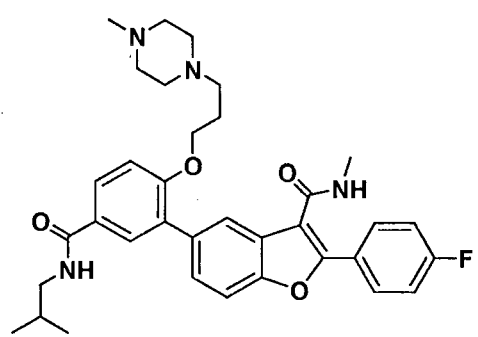
5-(2-(2-Amino-2-oxoethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00381] ^1H NMR (400 MHz, THF- d_8) δ ppm 0.86 - 1.02 (m, 6 H), 1.81 - 1.99 (m, 1 H), 2.91 (d, J = 4.77 Hz, 3 H), 3.06 - 3.29 (m, 2 H), 4.46 (s, 2 H), 6.43 (br. s., 1 H), 6.69 (br. s., 1 H), 7.08 (d, J = 8.78 Hz, 1 H), 7.16 - 7.27 (m, 2 H), 7.53 (br. s., 1 H), 7.56 - 7.62 (m, 2 H), 7.86 (dd, J = 8.53, 2.26 Hz, 1 H), 7.93 (d, J = 2.26 Hz, 1 H), 7.97 (s, 1 H), 8.09 - 8.19 (m, 2 H). LCMS m/z 518.36 (M+H), Rt 1.880 min. HPLC (Sunfire C18) Rt 8.209min, 100% purity and (XBridge phenyl C18) Rt 11.254 min., 99.8 % purity.



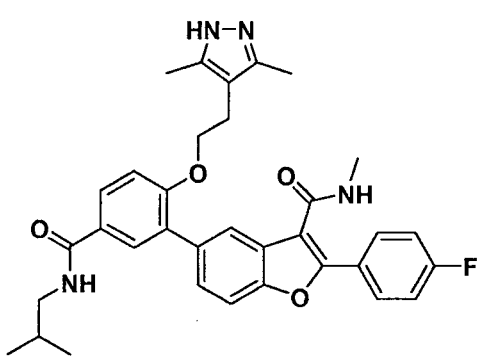
5-(2-(2-(1*H*-Indol-3-yl)ethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00382] ^1H NMR (500 MHz, CD_3OD) δ ppm 0.92 - 1.04 (m, 6 H), 1.87 - 2.03 (m, 1 H), 2.95 (s, 3 H), 3.15 - 3.24 (m, 4 H), 4.37 (t, J = 6.71 Hz, 2 H), 6.94 (t, J = 7.48 Hz, 1 H), 6.98 (s, 1 H), 7.07 (t, J = 7.63 Hz, 1 H), 7.18 (d, J = 8.55 Hz, 1 H), 7.24 - 7.36 (m, 3 H), 7.44 - 7.50 (m, 2 H), 7.51 - 7.56 (m, 1 H), 7.84 (td, J = 4.27, 2.44 Hz, 2 H), 7.88 (d, J = 2.14 Hz, 1 H), 7.94 - 8.03 (m, 2 H). LCMS m/z 604.31 (M+H), Rt 2.621 min. HPLC Rt 11.054 min. (Sunfire C18), 98.1 % purity and 12.561 min. (XBridge phenyl C18), 97.8 % purity.



5-(2-(2-(1H-Indol-3-yl)ethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

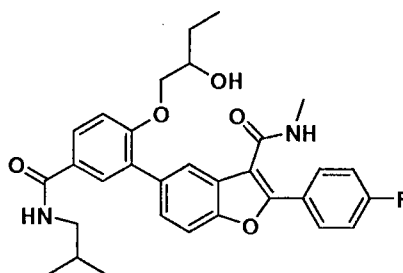
5 [00383] ¹H NMR (500 MHz, CD₃OD) δ ppm 0.87 - 1.03 (m, 6 H), 1.83 - 2.00 (m, 1 H), 2.17 (dd, *J* = 9.77, 5.49 Hz, 2 H), 2.81 - 2.90 (s, 3 H), 2.90 - 3.00 (s, 3 H), 3.12 - 3.25 (m, 4 H), 3.42 (br. s., 8 H), 4.21 (t, *J* = 5.65 Hz, 2 H), 7.17 (d, *J* = 8.85 Hz, 1 H), 7.22 - 7.33 (m, 2 H), 7.53 (dd, *J* = 8.55, 1.83 Hz, 1 H), 7.65 (d, *J* = 8.24 Hz, 1 H), 7.86 (td, *J* = 8.47, 2.29 Hz, 3 H), 7.89 - 7.96 (m, 2 H). LCMS *m/z* 601.36 (M+H), Rt 1.375 min. HPLC Rt 6.010 min. (Sunfire C18), 99.3% purity and 11.793 min. (XBridge phenyl C18), 98.4% purity.



5-(2-(2-(3,5-Dimethyl-1H-pyrazol-4-yl)ethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

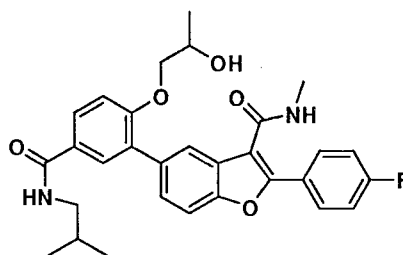
15 [00384] ¹H NMR (500 MHz, CD₃OD) δ ppm 0.89 - 1.01 (m, 6 H), 1.86 - 1.98 (m, 1 H), 2.02 (s, 6 H), 2.90 (t, *J* = 5.95 Hz, 2 H), 2.95 (s, 3 H), 3.14 - 3.22 (m, 2 H), 4.24 (t, *J* = 5.95 Hz, 2 H), 7.18 (d, *J* = 8.55 Hz, 1 H), 7.24 - 7.33 (m, 2 H), 7.37 (dd, *J* = 8.39, 1.68 Hz, 1 H), 7.59 (d, *J* = 8.55 Hz, 1 H), 7.68 (d, *J* = 1.83 Hz, 1 H), 7.80 (d, *J* = 2.44 Hz, 1 H), 7.85 (dd, *J* = 8.70, 2.29 Hz, 1 H), 7.93 - 8.02 (m, 2 H). LCMS *m/z* 583.32

(M+H), Rt 1.698 min. HPLC Rt 7.270 min. (Sunfire C18), 92.6 % purity and 11.994 min. (XBridge phenyl C18), 92.0 % purity.



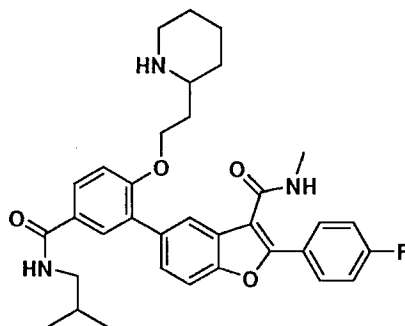
5 2-(4-Fluorophenyl)-5-(2-(2-hydroxybutoxy)-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00385] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.93 - 1.15 (m, 9 H), 1.45 - 1.61 (m, 1 H), 1.61 - 1.77 (m, 1 H), 2.01 (dt, $J=13.55, 6.78$ Hz, 1 H), 3.03 (s, 3 H), 3.27 (d, $J=7.03$ Hz, 2 H), 3.81 - 3.90 (m, 1 H), 4.10 (d, $J=5.02$ Hz, 2 H), 7.24 (d, $J=8.78$ Hz, 1 H), 7.28 - 7.38 (m, 2 H), 7.62 - 7.72 (m, 2 H), 7.91 (dd, $J=8.53, 2.26$ Hz, 1 H), 7.96 (d, $J=2.01$ Hz, 2 H), 8.00 - 8.08 (m, 2 H). LCMS m/z 533.30 (M+H), Rt 2.238 min. HPLC Rt 11.383 min. (Sunfire C18), 95.4 % purity and 11.896 min. (XBridge phenyl C18), 98.5% purity.



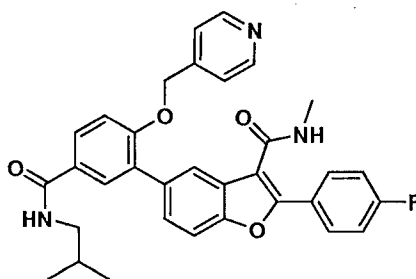
15 2-(4-Fluorophenyl)-5-(2-(2-hydroxypropoxy)-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00386] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.04 (d, $J=6.53$ Hz, 6 H), 1.27 (d, $J=6.27$ Hz, 3 H), 1.93 - 2.08 (m, 1 H), 3.03 (s, 3 H), 3.27 (d, $J=7.03$ Hz, 2 H), 3.97 - 4.15 (m, 3 H), 7.23 (d, $J=8.53$ Hz, 1 H), 7.32 (t, $J=8.91$ Hz, 2 H), 7.67 (d, $J=1.00$ Hz, 2 H), 7.86 - 7.93 (m, 1 H), 7.96 (d, $J=2.26$ Hz, 2 H), 8.03 (dd, $J=9.04, 5.27$ Hz, 2 H). LCMS m/z 519.28 (M+H), Rt 2.100 min. HPLC Rt 9.279 min. (Sunfire C18), 98.4 % purity and 11.674 min. (XBridge phenyl C18), 98.8% purity.



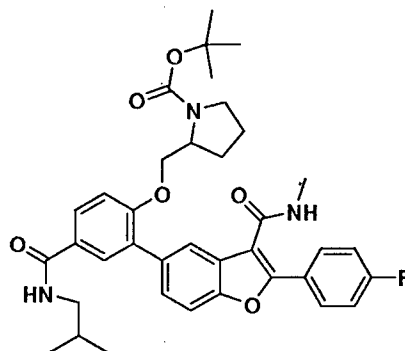
2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-(piperidin-2-yl)ethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

- 5 [00387] ^1H NMR (500 MHz, CD_3OD) δ ppm 0.92 - 1.04 (m, 6 H), 1.32 - 1.48 (m, 2 H), 1.59 (d, $J=14.34$ Hz, 1 H), 1.78 (br. s., 2 H), 1.88 - 2.06 (m, 3 H), 2.11 - 2.25 (m, 1 H), 2.85 (m, 1 H), 2.96 (s, 3 H), 3.11 - 3.27 (m, 4 H), 4.17 - 4.37 (m, 2 H), 7.23 (d, $J=8.85$ Hz, 1 H), 7.26 - 7.36 (m, 2 H), 7.55 (dd, $J=8.55$, 1.83 Hz, 1 H), 7.70 (d, $J=8.55$ Hz, 1 H), 7.83 - 8.01 (m, 5 H). LCMS m/z 572.33 ($\text{M}+\text{H}$), Rt 1.663 min.
- 10 HPLC Rt 7.638 min. (Sunfire C18), 98.8 % purity and 12.003 min. (XBridge phenyl C18), 97.3 % purity.



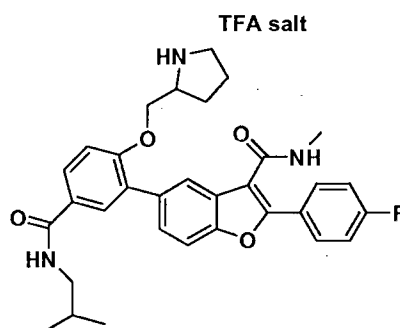
2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(pyridin-4-ylmethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

- 15 [00388] ^1H NMR (500 MHz, CD_3OD) δ ppm 0.98 (d, $J=6.71$ Hz, 6 H), 1.83 - 2.07 (m, 1 H), 2.92 (s, 3 H), 3.22 (d, $J=7.02$ Hz, 2 H), 5.54 (s, 2 H), 7.19 - 7.39 (m, 3 H), 7.62 (dd, $J=8.55$, 1.53 Hz, 1 H), 7.65 - 7.72 (m, 1 H), 7.88 - 7.99 (m, 5 H), 8.01 (d, $J=6.41$ Hz, 2 H), 8.79 (d, $J=6.71$ Hz, 2 H). LCMS m/z 552.28 ($\text{M}+\text{H}$), Rt 1.600 min.
- 20 HPLC Rt 6.831 min. (Sunfire C18), 99.5 % purity and 11.871 min. (XBridge phenyl C18), 99.3% purity.



tert-Butyl 2-((2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-(isobutylcarbamoyl)phenoxy)methyl)pyrrolidine-1-carboxylate

- 5 [00389] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.04 (d, $J=6.53$ Hz, 6 H), 1.48 (s, 9 H), 1.65 - 1.84 (m, 2 H), 1.91 - 2.12 (m, 3 H), 3.02 (s, 3 H), 3.06 - 3.21 (m, 1 H), 3.27 (d, $J=7.28$ Hz, 2 H), 3.29 - 3.34 (m, 1 H), 4.09 (br. s., 1 H), 4.18 - 4.30 (m, 2 H), 7.26 (d, $J=7.53$ Hz, 1 H), 7.29 - 7.37 (m, 2 H), 7.58 (br. s., 1 H), 7.68 (d, $J=8.53$ Hz, 1 H), 7.82 - 7.96 (m, 3 H), 7.99 - 8.08 (m, 2 H). LCMS m/z 666.32 ($\text{M}+\text{Na}$), Rt 2.716 min.
- 10 HPLC Rt 11.711 min. (Sunfire C18), 98.4 % purity and 12.663 min. (XBridge phenyl C18), 98.8 % purity.

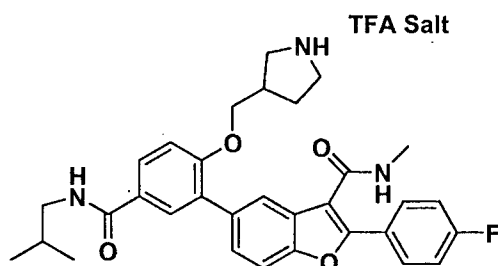


- 15 2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(pyrrolidin-2-ylmethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide, TFA.

- [00390] To a 10mL RBF was added dichloroethane (1 mL), *tert*-butyl 2-((2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-(isobutylcarbamoyl)phenoxy)methyl)pyrrolidine-1-carboxylate (10.2 mg, 15.8 μmol) and TFA, trifluoroacetic acid, (800 μL). The solution was stirred for 30 minutes at
- 20 room temperature, then evaporated on the rotovap.. The product was diluted with

dichloroethane and evaporated once more to give a white solid (99% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.04 (d, *J*=6.53 Hz, 6 H), 1.93 - 2.12 (m, 4 H), 2.24 - 2.37 (m, 1 H), 3.00 (s, 3 H), 3.13 - 3.22 (m, 1 H), 3.25 - 3.30 (m, 2 H), 3.30 - 3.36 (m, 1 H), 4.10 (dd, *J*=7.15, 2.89 Hz, 1 H), 4.29 (dd, *J*=10.67, 7.15 Hz, 1 H), 4.51 (dd, *J*=10.54, 3.26 Hz, 1 H), 7.28 (d, *J*=8.53 Hz, 1 H), 7.35 (t, *J*=8.78 Hz, 2 H), 7.60 (dd, *J*=8.53, 1.51 Hz, 1 H), 7.73 (d, *J*=8.53 Hz, 1 H), 7.92 - 8.08 (m, 5 H). LCMS *m/z* 544.22 (M+H), Rt 1.577 min. HPLC Rt 6.775 min. (Sunfire C18), 99.7 % purity and 11.724 min. (XBridge phenyl C18), 100 % purity.

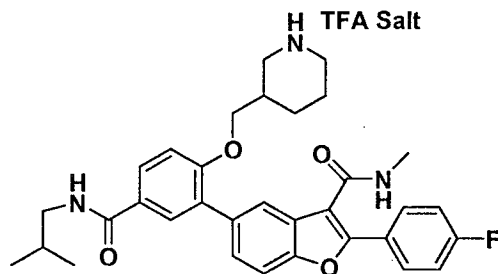
10



2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(pyrrolidin-3-ylmethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide, TFA

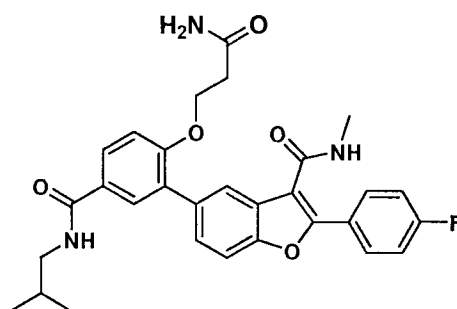
[00391] ¹H NMR (400 MHz, THF-*d*₈) δ ppm 0.93 (d, *J*=6.78 Hz, 6 H), 1.77 - 1.98 (m, 2 H), 2.10 (dd, *J*=13.05, 6.78 Hz, 1 H), 2.76 - 2.86 (m, 1 H), 2.88 - 2.98 (m, 3 H), 3.18 (t, *J*=6.40 Hz, 5 H), 3.55 (br. s., 1 H), 4.02 - 4.26 (m, 2 H), 7.08 (d, *J*=8.53 Hz, 1 H), 7.23 (t, *J*=8.78 Hz, 2 H), 7.48 (dd, *J*=8.53, 1.76 Hz, 1 H), 7.59 (d, *J*=8.53 Hz, 1 H), 7.70 (t, *J*=5.77 Hz, 1 H), 7.80 - 7.89 (m, 2 H), 7.94 (dd, *J*=9.79, 1.76 Hz, 2 H), 7.99 (dd, *J*=8.91, 5.40 Hz, 2 H). HPLC Rt 6.130 min. (Sunfire C18), 98.9 % purity and 10.184 min. (XBridge phenyl C18), 98.6 % purity. LCMS *m/z* 544.18 (M+H), Rt 1.557min.

20



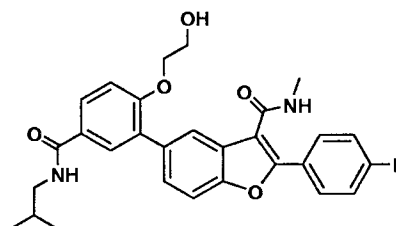
2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(piperidin-3-ylmethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide, TFA

[00392] ¹H NMR (400 MHz, THF-d₈) δ ppm 0.93 (d, *J*=6.78 Hz, 6 H), 1.40 - 1.57 (m, 1 H), 1.75 - 2.00 (m, 4 H), 2.33 (br. s., 1 H), 2.80 - 3.00 (m, 5 H), 3.18 (t, *J*=6.40 Hz, 2 H), 3.32 (d, *J*=12.05 Hz, 1 H), 3.45 (d, *J*=10.79 Hz, 1 H), 3.90 - 4.12 (m, 2 H), 7.03 (d, *J*=8.53 Hz, 1 H), 7.22 (t, *J*=8.78 Hz, 2 H), 7.47 (dd, *J*=8.53, 1.51 Hz, 1 H), 7.58 (d, *J*=8.53 Hz, 1 H), 7.71 (t, *J*=5.65 Hz, 1 H), 7.75 - 7.86 (m, 2 H), 7.92 (s, 2 H), 8.01 (dd, *J*=8.78, 5.52 Hz, 2 H). LCMS *m/z* 558.20 (M+H), Rt 1.595min. HPLC Rt 6.443 min. (Sunfire C18), 99.2 % purity and 10.418 min. (XBridge phenyl C18), 99.2 % purity.



5-(2-(3-Amino-3-oxopropoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

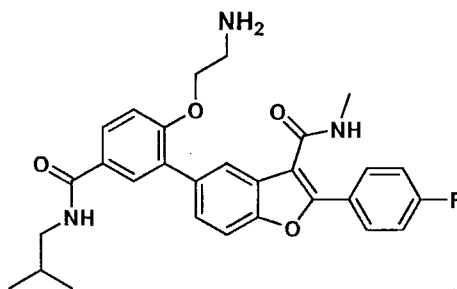
[00393] ¹H NMR (400 MHz, THF-d₈) δ ppm 0.88 - 0.97 (m, 6 H), 1.77 (dt, *J*=6.71, 3.29 Hz, 1 H), 1.89 (dt, *J*=13.36, 6.74 Hz, 1 H), 2.65 (br. s., 1 H), 2.96 (s, 3 H), 3.10 - 3.21 (m, 3 H), 3.60 - 3.65 (m, 1 H), 6.90 (d, *J*=8.28 Hz, 1 H), 7.16 - 7.25 (m, 2 H), 7.48 - 7.56 (m, 1 H), 7.66 - 7.73 (m, 2 H), 7.73 - 7.80 (m, 2 H), 7.84 (t, *J*=5.40 Hz, 1 H), 7.89 (br. s., 1 H), 7.92 - 8.03 (m, 3 H). LCMS Rt 1.835min., *m/z* 532.26 (M+H). HPLC Rt 7.465 min. (Sunfire C18), 100 % purity and 10.929 min. (XBridge phenyl C18), 92.9 % purity.



2-(4-Fluorophenyl)-5-(2-(2-hydroxyethoxy)-5-(isobutylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00394] To a small screw cap vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(isobutylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide (92 mg, 0.2 mmol) in DMF (4 mL), (2-Bromoethoxy)-*tert*-butyldimethylsilane (0.129 mL, 0.600 mmol), and DBU (0.121 mL, 0.800 mmol). The vial was capped and shaken at 80 °C overnight. The DMF was removed under a stream of nitrogen to give a tan oil which was taken up in 6 mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/10mM ammonium acetate where solvent A was 5% acetonitrile / 95% H₂O / 10mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10mM ammonium acetate with a PHENOMENEX® Luna 10µm C18 30x100mm column at a gradient of 40-100% B and a flow rate of 30 mL/min. over 8 minutes with a 10 minute hold. The solvent was removed on the rotovap to give 44mgs of the TBS protected alcohol as a clear colorless oil. LCMS *m/z* 619.47 (M+H), Rt 3.123 min., 96% purity. To the TBS protected alcohol was then added 2.5mL of tetrahydrofuran along with 2 eq. of 1 M HCl solution (0.14mmol, 140µL). The mixture was stirred for 1 hour at room temperature. The reaction mixture was transferred to a separatory funnel, diluted with ethyl acetate, washed with sodium bicarbonate, brine and dried over magnesium sulfate. The organic solvent was evaporated and the product placed under vacuum. The crude product was diluted with 2mL of acetonitrile, and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ammonium acetate where solvent A was 5% acetonitrile / 95% H₂O / 10mM ammonium acetate and solvent B was 5% H₂O / 95% acetonitrile / 10mM ammonium acetate with a XBridge C18 5µm OBD 19 x 100mm column at a gradient of 30-100% B and a flow rate of 20 mL/min. over 7 minutes with a 13 minute hold. 18.3mgs of a white solid (17% yield, 2 steps) was obtained after solvent evaporation. ¹H NMR (400 MHz, THF-*d*₈) δ ppm 0.93 (d, *J* = 6.78 Hz, 6 H), 1.80 - 1.98 (m, 1 H), 2.91 (d, *J* = 4.77 Hz, 3 H), 3.13 - 3.23 (m, 2 H), 3.79 (t, *J* = 4.89 Hz, 2 H), 4.10 (t, *J* = 4.89 Hz, 2 H), 7.08 (d, *J* = 8.53 Hz, 1 H), 7.21 (t, *J* = 8.78 Hz, 2 H), 7.52 (br. s., 1 H), 7.52 - 7.54 (m, 2 H), 7.59 (br. s., 1 H), 7.84 (dd, *J* = 8.53, 2.26 Hz, 1 H), 7.92 (d, *J* = 2.26 Hz, 1 H), 8.02 (s, 1 H), 8.09 - 8.20 (m, 2 H). LCMS *m/z* 505.36 (M+H), Rt 2.013min. HPLC Rt 8.901 min. (Sunfire C18), 92.5 % purity and 11.479

min. (XBridge phenyl C18), 92.0 % purity. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute.

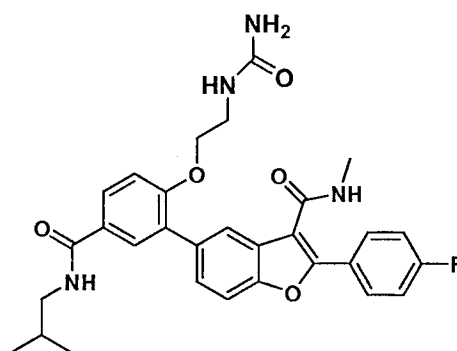


5-(2-(2-Aminoethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00395] To a 2 dram vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide (92.0 mg, 0.20 mmol) in 3 mL of DMF along with 2-(2-bromoethyl) isoindoline-1,3-dione (152 mg, 0.600 mmol) and DBU (0.120 mL, 0.800 mmol). The vial was capped and shaken at 75 °C over night. The crude reaction mixture was then evacuated to near dryness,

taken up in 6 mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5 μ m C18 30x100mm column at a gradient of 40-100% B and a flow rate of 40 mL/min. over 10 minutes with a 10 minute hold to give 5-(2-(2-(1,3-dioxoisindolin-2-yl)ethoxy)-5-(isobutyl carbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide as a white solid (30mgs, 23% yield). ¹H NMR (400 MHz, DMF-d₇) δ ppm 0.93 (d, J =6.78 Hz, 6 H), 1.86 - 1.99 (m, 1 H), 2.97 (d, J =4.77 Hz, 3 H), 3.14 - 3.26 (m, 2 H), 4.06 (t, J =5.90 Hz, 2 H), 4.47 (t, J =5.90 Hz, 2 H), 7.33 (d, J =9.29 Hz, 1 H), 7.36 - 7.49 (m, 4 H), 7.74 - 7.86 (m, 5 H), 7.97 - 8.02 (m, 2 H), 8.11 - 8.17 (m, 2 H), 8.20 (d, J =4.27 Hz, 1 H), 8.42 (s, 1 H). LCMS m/z 634.25 (M+H), Rt 2.408 min. HPLC Rt 9.339 min. (Sunfire C18), 100 % purity and 11.696 min. (Gemini C18), 98.9 % purity. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 30-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 30-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10 mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. To a 100mL RBF fitted with a reflux condenser was added 5-(2-(2-(1,3-dioxoisindolin-2-yl)ethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-

fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (26.4 mg, 0.042 mmol) in methanol and anhydrous hydrazine (1.308 μ L, 0.042 mmol) solution (Aldrich, 215155-50G). The flask was placed in a pre-equilibrated oil bath and refluxed for 2 hours. The crude product was concentrated on the rotovap to remove methanol, diluted with dichloromethane, washed with a 0.5M sodium hydroxide solution and extracted. The solvent was removed and the crude product was purified using the Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA mentioned above with a gradient of 20-100%B to give (13mgs, 58%) of a white solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.94 (d, *J*=6.78 Hz, 6 H), 1.91 (dt, *J*=13.55, 6.78 Hz, 1 H), 2.91 (s, 3 H), 3.18 (d, *J*=7.28 Hz, 2 H), 3.33 (t, *J*=5.02 Hz, 2 H), 4.30 (t, *J*=5.14 Hz, 2 H), 7.21 (d, *J*=8.78 Hz, 1 H), 7.26 (t, *J*=8.78 Hz, 2 H), 7.50 - 7.59 (m, 1 H), 7.60 - 7.68 (m, 1 H), 7.81 - 8.00 (m, 5 H). LCMS *m/z* 504.31 (M+H), Rt 1.538 min. HPLC Rt 6.435 min. (Sunfire C18), 97.1 % purity and 11.376 min. (XBridge phenyl C18), 100 % purity.



2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-ureidoethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00396] To a 2 dram vial was added 5-(2-(2-aminoethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (22.7 mg, 0.045 mmol) in ethanol (2 mL) along with water (0.667 mL) and potassium cyanate (5.34 μ L, 0.135 mmol). The vial was sealed and the mixture heated to 80 °C with shaking for 24 hours. 3 additional equivalents of potassium cyanate was added to the reaction mixture and the vial re-capped and heated for 3 days. The crude reaction mixture was evaporated, diluted with acetonitrile, filtered and purified using a Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA where solvent

A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5 μ m C18 30x100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 8 minutes with a 6 minute hold. The solvent was evaporated to give 10mgs

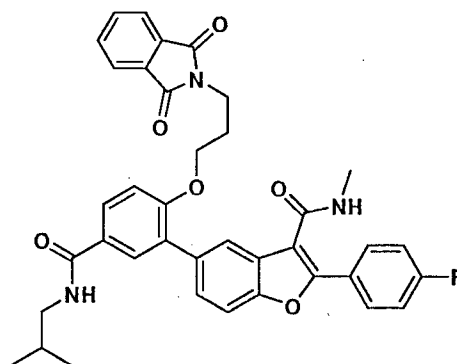
5 (40%) of a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% TFA/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% TFA/ 10% HPLC grade acetonitrile), in 3 minutes with a 1

10 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/ 0.1%TFA with a gradient of 20-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile),

15 in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a PHENOMENEX® Gemini C18 3 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 20-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC

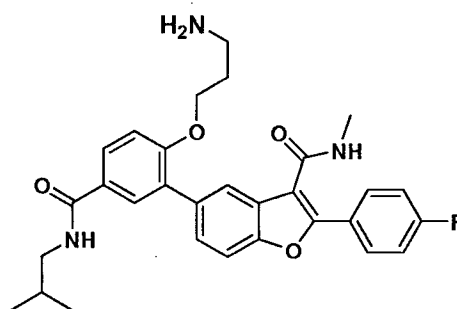
20 grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 0.94 (d, *J*=6.53 Hz, 6 H), 1.82 - 1.98 (m, 1 H), 2.88 (d, *J*=4.77 Hz, 3 H), 3.14 - 3.23 (m, 2 H), 3.47 (q, *J*=4.94 Hz, 2 H), 4.03 (t, *J*=4.52 Hz, 2 H), 5.55 (br. s., 1 H), 6.18 (br. s., 1 H), 7.03 (d, *J*=8.53 Hz, 1 H),

25 7.21 - 7.32 (m, 2 H), 7.46 - 7.51 (m, 1 H), 7.51 - 7.56 (m, 1 H), 7.56 - 7.62 (m, 1 H), 7.80 (dd, *J*=8.53, 2.26 Hz, 1 H), 7.84 (d, *J*=4.52 Hz, 1 H), 7.91 - 8.02 (m, 3 H), 8.22 (d, *J*=1.25 Hz, 1 H). LCMS Rt 1.988 min., *m/z* 547.24 (M+H). HPLC Rt 8.126 min. (Sunfire C18), 99.7 % purity and 11.214 min. (Gemini C18), 99.5 % purity.



5-(2-(3-(1,3-Dioxoisindolin-2-yl)propoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

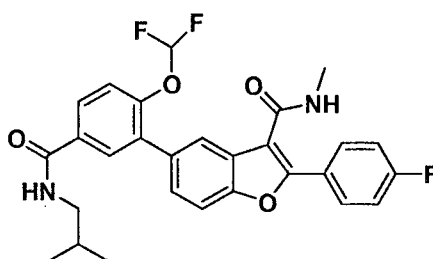
- [00397] ¹H NMR (400 MHz, THF-d₈) δ ppm 0.93 (d, *J*=6.78 Hz, 6 H), 1.81 - 1.97 (m, 1 H), 2.09 (m, 2 H), 2.90 (d, *J*=4.77 Hz, 3 H), 3.12 - 3.26 (m, 2 H), 3.79 (t, *J*=6.65 Hz, 2 H), 4.11 (t, *J*=5.90 Hz, 2 H), 7.03 (d, *J*=8.78 Hz, 1 H), 7.16 - 7.28 (m, 2 H), 7.45 (d, *J*=4.27 Hz, 1 H), 7.48 - 7.51 (m, 1 H), 7.51 - 7.56 (m, 1 H), 7.59 (dd, *J*=8.78, 1.76 Hz, 1 H), 7.65 - 7.74 (m, 4 H), 7.79 - 7.90 (m, 3 H), 8.08 - 8.24 (m, 2 H). LCMS *m/z* 648.19 (M+H), Rt 2.458 min. HPLC Rt 10.158 min. (Sunfire C18), 99.4 %
- 10 purity and 12.111 min. (Gemini C18), 99.7 % purity.



5-(2-(2-Aminoethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- 15 [00398] ¹H NMR (400 MHz, THF-d₈) δ ppm 0.93 (d, *J*=6.53 Hz, 6 H), 1.82 - 1.93 (m, 1 H), 2.15 (m, 2 H), 2.91 (d, *J*=4.52 Hz, 3 H), 3.08 - 3.24 (m, 4 H), 4.17 (t, *J*=5.65 Hz, 2 H), 7.06 (d, *J*=8.53 Hz, 1 H), 7.18 - 7.28 (m, 2 H), 7.47 (dd, *J*=8.53, 1.76 Hz, 1 H), 7.53 - 7.66 (m, 2 H), 7.82 (dd, *J*=8.53, 2.26 Hz, 2 H), 7.90 (d, *J*=2.26 Hz, 1 H), 7.95 (d, *J*=1.51 Hz, 1 H), 7.97 - 8.05 (m, 2 H), 8.28 (br. s., 2 H). LCMS Rt 1.537
- 20 min., *m/z* 518.16 (M+H). HPLC Rt 10.734 min. (Sunfire C18), 99.2 % purity and

10.881 min. (Gemini C18), 99.3 % purity. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a PHENOMENEX® Gemini C18 3µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute.



5-(2-(Difluoromethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00399] To a small microwave vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(isobutylcarbamoyl) phenyl)-*N*-methylbenzofuran-3-carboxamide (23.02 mg, 0.05 mmol), acetonitrile (400 µL), water (400 µL), and 2-chloro-2,2-difluoro-1-phenylethanone (47.6 mg, 0.250 mmol). The vial was sealed and the reaction mixture subjected to microwave heating (BIOTAGE® Initiator) at 110 °C for 8 minutes. The crude reaction mixture was further diluted with acetonitrile, filtered, and purified

using a Shimadzu preparative HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5µm C18 30x100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 10 minutes with a 10 minute hold. The solvent was evaporated to give product (35%) as a white solid. ¹H NMR (500 MHz, THF-d₈) δ ppm 0.86 - 1.01 (m, 6 H), 1.89 (dt, *J* = 13.50, 6.83 Hz, 1 H), 2.90 (d, *J* = 4.58 Hz, 3 H), 3.12 - 3.28 (m, 2 H), 6.61 - 7.04 (m, 1 H), 7.18 - 7.27 (m, 2 H), 7.31 (d, *J* = 8.54 Hz, 1 H), 7.49 (dd, *J* = 8.55, 1.83 Hz, 1 H), 7.53 (d, *J* = 4.27 Hz, 1 H), 7.59 (d, *J* = 8.55 Hz, 1 H), 7.78 (t, *J* = 5.49 Hz, 1 H), 7.82 (d, *J* = 1.22 Hz, 1 H), 7.91 (dd, *J* = 8.55, 2.44 Hz, 1 H), 7.98 (d, *J* = 2.14 Hz, 1 H), 8.09 - 8.17 (m, 2 H). LCMS *m/z* 511.21 (M+H), Rt 2.393 min. HPLC Rt 12.213 min. (Sunfire C18), 99.3 % purity and 15.427 min. (XBridge C18), 99.8 % purity. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:

Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 30-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters Phenyl XBridge C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 30-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute.

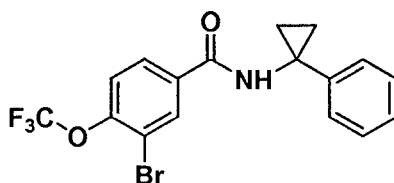
3-Bromo-*N*-isobutyl-5-isopropoxybenzamide

[00400] To a large screw top vial was added 3-bromo-5-hydroxybenzoic acid (1 g, 4.61 mmol), pyridine (10 mL), *N*1-((ethylimino)methylene)-*N*3,*N*3-dimethylpropane-1,3-diamine, HCl (0.972 g, 5.07 mmol) (EDAC) along with 2-methylpropan-1-amine (0.504 mL, 5.07 mmol). The vial was capped and the mixture shaken over night. The reaction mixture was acidified with 10 mL of an ice cold 1 M HCl solution. The mixture was diluted with dichloromethane, extracted, washed with brine and dried over magnesium sulfate. The reaction mixture was filtered then added to the top of a 240g Thomson silica gel cartridge. The product was eluted with 0-12% (3000mL) methanol in dichloromethane to give 3-bromo-5-hydroxy-*N*-isobutylbenzamide (95%) as a yellow solid. LCMS Rt 1.632 min., *m/z* 273.99 (M+H), 93% purity. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 30-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. To a sealed tube was added 3-bromo-5-hydroxy-*N*-isobutylbenzamide (380.4 mg, 1.398 mmol), DMF (15 mL), 2-iodopropane (0.210 mL, 2.097 mmol), and potassium carbonate (290 mg, 2.097 mmol). The tube was sealed and heated to 90 °C overnight. The reaction mixture was cooled, transferred to a separatory funnel, diluted with ethyl acetate and extracted. The organic solution was washed with 1M HCl, brine, dried over magnesium sulfate, filtered and evaporated to dryness. The resulting orange oil was taken up in dichloromethane and purified using the BIOTAGE® Horizon with a 110g Thomson silica gel column employing 0-5% methanol and 2000mL of solvent to give a near quantitative yield of 3-bromo-*N*-isobutyl-5-isopropoxybenzamide as a light yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:

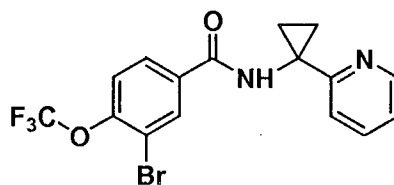
Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was
5 determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 30-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1
10 mL/minute. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.87 - 1.04 (m, 6 H), 1.23 - 1.37 (m, 6 H), 1.79 - 2.00 (m, 1 H), 3.25 (t, *J*=6.40 Hz, 2 H), 4.57 (dt, *J*=12.05, 6.02 Hz, 1 H), 6.29 (br. s., 1 H), 7.08 - 7.19 (m, 1 H), 7.21 - 7.26 (m, 1 H), 7.38 (s, 1 H). LCMS Rt 2.413 min., *m/z* 315.01 (M+H), 95% purity.

15 3-Bromo-*N*-isobutyl-4-(trifluoromethoxy)benzamide
[00401] To a large screw top vial was added previously synthesized 3-bromo-4-(trifluoromethoxy)benzoic acid (100 mg, 0.351 mmol), pyridine (5 mL), 2-methylpropan-1-amine (0.038 mL, 0.386 mmol), *N*1-((ethylimino)methylene)-*N*3,*N*3-dimethylpropane-1,3-diamine, HCl (EDAC) (74.0 mg, 0.386 mmol) and
20 HATU, 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (400 mg, 1.053 mmol). The vial was capped and shaken overnight at room temperature. The crude reaction mixture was diluted with methanol and purified using a Shimadzu preparative HPLC employing methanol/water/0.1%TFA where solvent A was 10% methanol / 90% water / 0.1%
25 trifluoroacetic acid and solvent B was 10% water / 90% methanol / 0.1% trifluoroacetic acid with a PHENOMENEX® Luna 10 μ m C18 30x100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 9 minutes with a 11 minute hold to give 75mgs (62%) of a yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the
30 following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/

10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a PHENOMENEX® Gemini C18 3 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.98 - 1.11 (m, 6 H), 1.91 - 2.09 (m, 1 H), 3.22 - 3.30 (m, 2 H), 7.57 (dd, *J*=8.53, 1.51 Hz, 1 H), 7.96 (dd, *J*=8.53, 2.26 Hz, 1 H), 8.25 (d, *J*=2.01 Hz, 1 H), 8.68 (br. s., 1 H). HPLC Rt 17.141 min. (Sunfire C18), 99.5 % purity and 15.912 min. (Gemini C18), 100 % purity. LCMS Rt 2.367 min., *m/z* 341.99 (M+H).

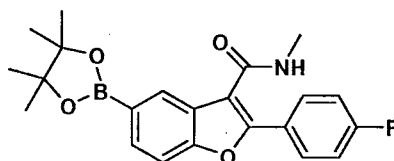


20 3-Bromo-N-(1-phenylcyclopropyl)-4-(trifluoromethoxy)benzamide
[00402] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.40 (d, *J* = 4.52 Hz, 4 H), 7.16 - 7.30 (m, 1 H), 7.32 - 7.41 (m, 4 H), 7.58 (dd, *J* = 8.66, 1.38 Hz, 1 H), 7.99 (dd, *J* = 8.66, 2.13 Hz, 1 H), 8.28 (d, *J* = 2.01 Hz, 1 H), 9.42 (br. s., 1 H). LCMS Rt 2.56 min., *m/z* 401.97 (M+H). HPLC Rt 15.171 min. (Sunfire C18), 98.8 % purity and 16.066 min. (Gemini C18), 100 % purity.



3-Bromo-N-(1-(pyridin-2-yl)cyclopropyl)-4-(trifluoromethoxy)benzamide

[00403] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.70 - 1.80 (m, 2 H), 1.80 - 1.91 (m, 2 H), 7.57 (dd, $J=8.78, 1.25$ Hz, 1 H), 7.76 - 7.88 (m, 2 H), 8.03 (dd, $J=8.53, 2.26$ Hz, 1 H), 8.33 (d, $J=2.01$ Hz, 1 H), 8.43 (t, $J=8.03$ Hz, 1 H), 8.63 (d, $J=5.52$ Hz, 1 H). LCMS Rt 1.420 min, m/z 402.95 (M+H). HPLC Rt 5.611 min. (Sunfire C18), 93.8 % purity and 11.206 min. (Gemini C18), 98.4 % purity.



10 2-(4-Fluorophenyl)-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide

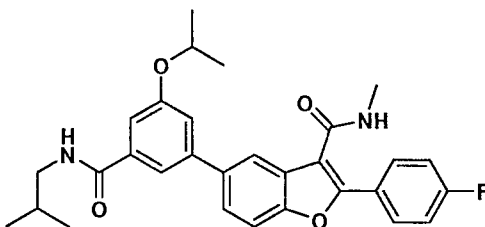
[00404] To a sealed tube was added 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoro methanesulfonate (2.000 g, 4.79 mmol), dioxane (20 mL), triethylamine (1.993 mL, 14.38 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.87 g, 19.17 mmol), and finally PdCl₂(dppf) (0.235 g, 0.144 mmol). The vial was flushed with N₂, sealed and heated overnight in an oil bath at 80 °C. The reaction mixture was cooled, diluted with dichloromethane, and washed with a 0.1M HCl solution then brine. The brown mixture was pulled through a plug of 1:1 magnesium sulfate/CELITE® to give a dark brown solid after solvent evaporation. The crude product was taken up in 50mL of dichloromethane and added to the top of a pre-equilibrated 240g Thomson silica gel cartridge. The product was eluted with 0-2% methanol in dichloromethane to give a 80% yield of 2-(4-fluorophenyl)-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide as a tan solid. ^1H NMR (400 MHz, THF-d₈) δ ppm 1.34 (s, 12 H), 2.92 - 2.95 (m, 3 H), 7.20 (t, $J=8.91$ Hz, 2 H), 7.50 (d, $J=8.28$ Hz, 2

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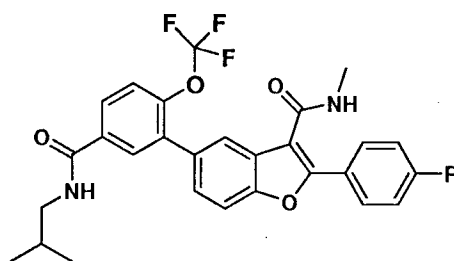
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H), 7.74 (dd, $J=8.28$, 1.00 Hz, 1 H), 8.08 - 8.13 (m, 2 H), 8.14 (s, 1 H). LCMS m/z 396.18 (M+H), Rt 2.455 min., 90% purity.



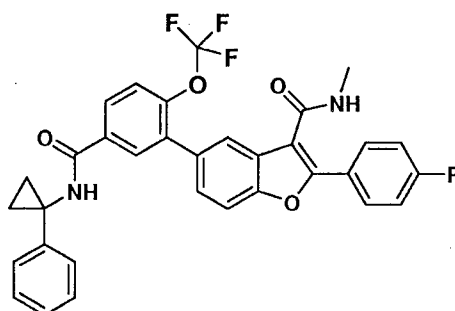
5 2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-isopropoxyphenyl)-*N*-methylbenzofuran-3-carboxamide

[00405] To a medium sized microwave vial was added 1 (465 mg, 1.0 mmol), dioxane (15 mL), water (1.500 mL), 3-bromo-*N*-isobutyl-5-isopropoxybenzamide (377 mg, 1.200 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (82 mg, 0.200 mmol), potassium phosphate, tribasic (849 mg, 4.00 mmol) and finally
 10 palladium(II) acetate (44.9 mg, 0.200 mmol). The vial was capped and subjected to microwave heating (150 °C) in a BIOTAGE® Initiator for 13 minutes. The reaction mixture was diluted with 150mL of dichloromethane, washed with a 1M HCl solution, then water and finally brine. The solution was filtered through pad of 1:1
 15 CELITE®/magnesium sulfate then evaporated to give a brown oil. The crude product was taken up in dichloromethane and added to the top of a pre-equilibrated 100g BIOTAGE® silica gel cartridge. The product was eluted with a 0-3% methanol in dichloromethane solvent mixture to give product as a light tan solid (51%). ¹H NMR (400 MHz, THF-*d*₈) δ ppm 0.95 (d, $J=6.53$ Hz, 6 H), 1.35 (d, $J=6.02$ Hz, 6 H), 1.83 - 1.98 (m, 1 H), 2.90 - 2.98 (m, 3 H), 3.14 - 3.29 (m, 2 H), 4.66 - 4.82 (m, 1 H), 7.18 - 7.25 (m, 2 H), 7.26 - 7.29 (m, 1 H), 7.38 - 7.42 (m, 1 H), 7.48 (m, 1 H), 7.58 - 7.65 (m, 2 H), 7.65 - 7.72 (m, 2 H), 7.96 (d, $J=1.00$ Hz, 1 H), 8.08 - 8.16 (m, 2 H). LCMS
 20 Rt 2.588 min., m/z 503.25 (M+H), 98% purity.



2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(trifluoromethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

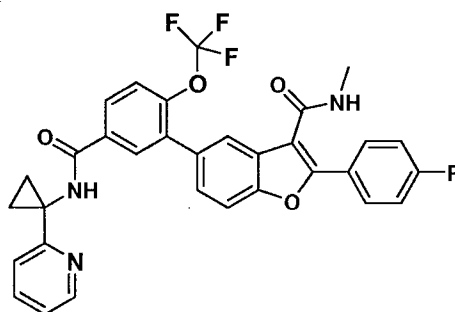
- [00406] The LC/MS data was obtained on a Shimadzu analytical LC /
- 5 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% TFA/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% TFA/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu
- 10 analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5mm 4.6 x 150mm column employing water/acetonitrile/ 0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was
- 15 then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a PHENOMENEX® Phenyl XBridge C18 3.5mm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate /
- 20 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 0.94 (dd, *J*=6.78, 2.26 Hz, 6 H), 1.82 - 1.97 (m, 1 H), 2.90 (d, *J*=4.77 Hz, 3 H), 3.12 - 3.24 (m, 2 H), 7.17 - 7.29 (m, 2 H), 7.47 (dd, *J*=8.53, 1.76 Hz, 2 H), 7.61 (d, *J*=8.53 Hz, 1 H), 7.71 - 7.81 (m, 2 H), 7.83 (d, *J*=1.26 Hz, 1 H), 7.92 - 7.98 (m, 1 H), 7.99 - 8.05 (m, 1 H), 8.07 - 8.15 (m, 2
- 25 H). LCMS Rt 2.565min., *m/z* 529.13 (M+H). HPLC Rt 11.166 min. (Sunfire C18), 99.5 % purity and 11.813 min. (Phenyl XBridge C18), 86.7 % purity.



2-(4-Fluorophenyl)-*N*-methyl-5-(5-(1-phenylcyclopropylcarbamoyl)-2-(trifluoromethoxy)phenyl)benzofuran-3-carboxamide

[00407] ¹H NMR (400 MHz, THF-d₈) δ ppm 1.20 - 1.39 (m, 4 H), 2.89 (d, *J*=4.52 Hz, 3 H), 7.06 - 7.15 (m, 1 H), 7.17 - 7.27 (m, 4 H), 7.29 - 7.35 (m, 2 H), 7.44 (br. s., 1 H), 7.47 (m, 2 H), 7.61 (d, *J*=8.53 Hz, 1 H), 7.83 (d, *J*=1.26 Hz, 1 H), 7.98 (dd, *J*=8.66, 2.38 Hz, 1 H), 8.05 (d, *J*=2.01 Hz, 1 H), 8.08 - 8.15 (m, 2 H), 8.50 (br. s., 1 H). LCMS Rt 2.796 min., *m/z* 589.23 (M+H). HPLC Rt 11.419 min. (Sunfire C18), 98.9 % purity and 12.424 min. (Phenyl XBridge C18), 100 % purity.

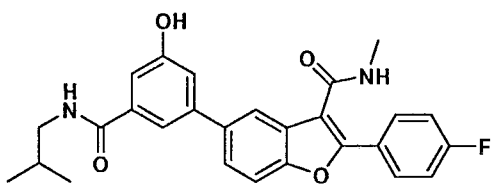
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2-(4-Fluorophenyl)-*N*-methyl-5-(5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)-2-(trifluoromethoxy)phenyl)benzofuran-3-carboxamide

[00408] ¹H NMR (400 MHz, THF-d₈) δ ppm 1.21 - 1.33 (m, 2 H), 1.62 - 1.70 (m, 2 H), 2.89 (d, *J*=4.77 Hz, 3 H), 7.01 (m, 1 H), 7.18 - 7.28 (m, 2 H), 7.40 (d, *J*=8.03 Hz, 1 H), 7.43 (br. s., 1 H), 7.46 - 7.58 (m, 3 H), 7.62 (d, *J*=8.53 Hz, 1 H), 7.86 (d, *J*=1.26 Hz, 1 H), 8.04 (dd, *J*=8.66, 2.38 Hz, 1 H), 8.07 - 8.17 (m, 3 H), 8.36 - 8.42 (m, 1 H), 8.57 (br. s., 1 H). LCMS Rt 1.768 min., *m/z* 590.13 (M+H). HPLC Rt 7.645 min. (Sunfire C18), 99.0 % purity and 12.041 min. (Phenyl XBridge C18), 99.9 %

20 purity.



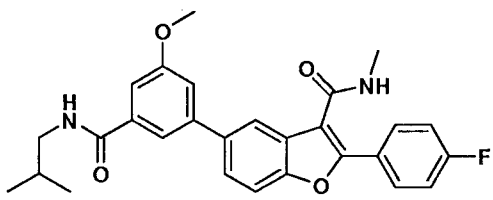
2-(4-Fluorophenyl)-5-(3-hydroxy-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00409] To a 250mL RBF was added 2-(4-fluorophenyl)-5-(3-

5 (isobutylcarbamoyl)-5-isopropoxyphenyl)-N-methylbenzofuran-3-carboxamide (1.3409 g, 2.67 mmol) in dichloromethane (20 mL). The flask was sealed with a septa, placed under N₂ and stirred for 5 minutes. To this mixture was then added (cold) 1M trichloroborane (8.00 mL, 8.00 mmol) in dichloromethane. The solution was stirred at room temperature for 6 hours. The reaction mixture was cooled to 0 °C

10 and methanol was added to quench the reaction. The flask was allowed to warm to room temperature and the volatiles were removed to give a quantitative yield of a tan solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.06 (d, *J* = 6.78 Hz, 6 H), 1.97 - 2.12 (m, 1 H), 3.01 - 3.12 (m, 3 H), 3.29 (t, *J* = 6.53 Hz, 2 H), 7.27 - 7.40 (m, 4 H), 7.64 (s, 1 H), 7.72 (s, 2 H), 7.98 (s, 1 H), 8.03 (dd, *J* = 8.66, 5.40 Hz, 2 H), 8.56 (br. s., 1 H).

15 LCMS Rt 2.157 min., *m/z* 461.03 (M+H), 97.6% purity.

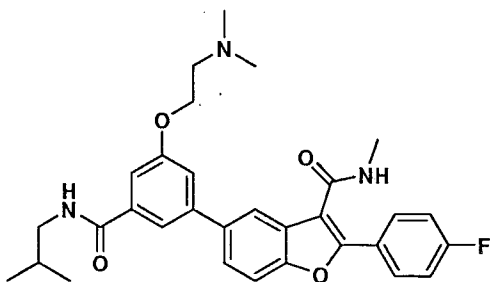


2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-methoxyphenyl)-N-methylbenzofuran-3-carboxamide

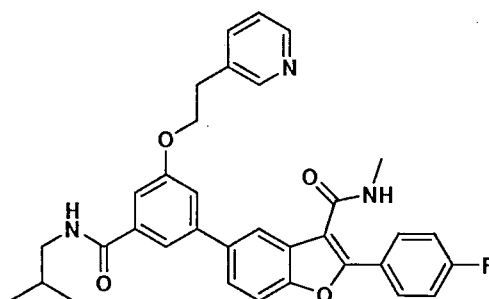
20 [00410] The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5μm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in

25 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters

Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%TFA with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters Phenyl XBridge C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 0.87 - 1.03 (m, 6 H), 1.83 - 1.99 (m, 1 H), 2.93 (d, *J*=4.77 Hz, 3 H), 3.16 - 3.25 (m, 2 H), 3.88 (s, 3 H), 7.18 - 7.26 (m, 2 H), 7.29 - 7.32 (m, 1 H), 7.42 (dd, *J*=2.38, 1.38 Hz, 1 H), 7.50 (br. s., 1 H), 7.57 - 7.66 (m, 2 H), 7.71 (br. s., 2 H), 7.97 (d, *J*=1.25 Hz, 1 H), 8.08 - 8.16 (m, 2 H). LCMS *m/z* 475.22 (M+H), Rt 2.373 min.. HPLC Rt 10.268 min. (Sunfire C18), 96.7 % purity and 12.104 min. (XBridge phenyl C18), 99.2 % purity.

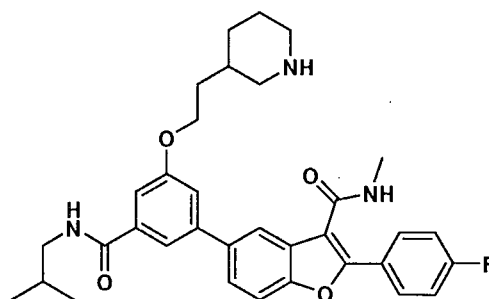


5-(3-(2-(Dimethylamino)ethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-
N-methylbenzofuran-3-carboxamide
[00411] ¹H NMR (400 MHz, THF-d₈) δ ppm 0.95 (d, *J* = 6.78 Hz, 6 H), 1.87 - 1.98 (m, 1 H), 2.89 (s, 6 H), 2.93 (d, *J* = 4.52 Hz, 3 H), 3.21 (t, *J* = 6.40 Hz, 2 H), 3.47 - 3.54 (m, 2 H), 4.54 - 4.64 (m, 2 H), 7.22 (t, *J* = 8.66 Hz, 2 H), 7.42 (s, 1 H), 7.51 (br. s., 1 H), 7.58 (d, *J* = 5.27 Hz, 1 H), 7.61 (s, 1 H), 7.62 - 7.69 (m, 1 H), 7.80 (s, 1 H), 7.83 (br. s., 1 H), 7.98 (s, 1 H), 8.12 (dd, *J* = 8.91, 5.40 Hz, 2 H). LCMS Rt 1.543 min., *m/z* 532.28 (M+H). HPLC Rt 6.816 min. (Sunfire C18), 96.0 % purity and 12.073 min. (Phenyl XBridge C18), 98.2 % purity.



2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(2-(pyridin-3-yl)ethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

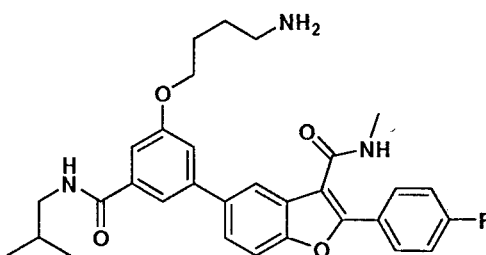
- 5 [00412] ^1H NMR (400 MHz, THF-d_8) δ ppm 0.94 (d, $J = 6.53$ Hz, 6 H), 1.83 - 1.98 (m, 1 H), 2.92 (d, $J = 4.27$ Hz, 3 H), 3.13 - 3.30 (m, 4 H), 4.32 - 4.47 (m, 2 H), 7.22 (t, $J = 8.66$ Hz, 2 H), 7.32 (s, 1 H), 7.41 - 7.53 (m, 3 H), 7.55 - 7.67 (m, 2 H), 7.72 (br. s., 2 H), 7.91 - 8.01 (m, 2 H), 8.11 (dd, $J = 8.03, 5.52$ Hz, 2 H), 8.55 (br. s., 1 H), 8.72 (br. s., 1 H). LCMS Rt 1.632 min., m/z 566.26 ($\text{M}+\text{H}$). HPLC Rt 7.216 min. (Sunfire
- 10 C18), 98.1 % purity and 12.073 min. (Phenyl XBridge C18), 99.0 % purity.



2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(2-(piperidin-3-yl)ethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

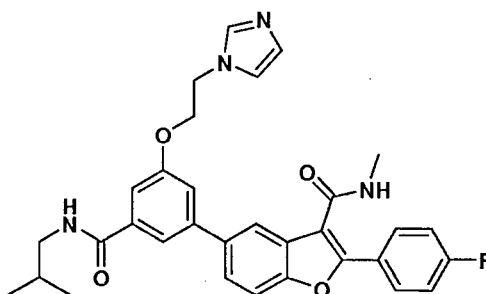
- 15 [00413] The LC/MS data was obtained on a Waters Acquity SDS analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Acquity UPLC BEH 1.7 μm C18, 2.1 x 50mm column, with a gradient of 2-98%B (B = 100% HPLC grade acetonitrile/ 0.05% TFA), (A = 100% HPLC grade water / 0.05% TFA), in 2.2 minutes at a rate of 0.8 mL/minute. HPLC purity was
- 20 determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μm 4.6 x 150mm column employing water/acetonitrile/ 0.1%TFA with a gradient of 20-100% B (B = 95% HPLC grade acetonitrile/ 0.1%

trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.99 (d, *J*=6.78 Hz, 6 H), 1.36 (dd, *J*=12.30, 3.01 Hz, 1 H), 1.69 - 1.89 (m, 3 H), 1.91 - 2.16 (m, 4 H), 2.77 (t, *J*=12.17 Hz, 1 H), 2.87 - 2.95 (m, 1 H), 3.23 (d, *J*=7.03 Hz, 2 H), 3.29 - 3.40 (m, 4 H), 3.43 - 3.52 (m, 1 H), 4.19 (t, *J*=6.02 Hz, 2 H), 7.24 (t, *J*=8.78 Hz, 2 H), 7.36 (dd, *J*=10.54, 1.51 Hz, 2 H), 7.58 - 7.68 (m, 2 H), 7.70 (s, 1 H), 7.87 - 7.98 (m, 3 H). LCMS *m/z* 572.16 (M+H). HPLC Rt 6.518 min. (Sunfire C18), 98% purity.



5-(3-(4-Aminobutoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

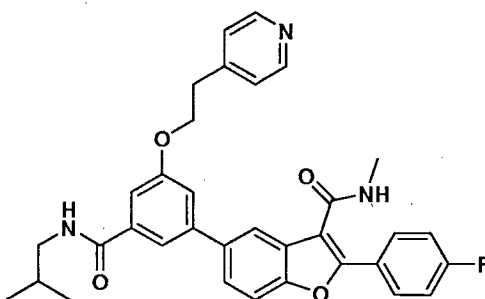
[00414] ¹H NMR (400 MHz, CD₃OD) δ ppm 0.99 (d, *J*=6.78 Hz, 6 H), 1.86 - 2.04 (m, 5 H), 2.95 - 3.00 (m, 3 H), 3.06 (t, *J*=7.15 Hz, 2 H), 3.21 - 3.27 (m, 2 H), 4.19 (t, *J*=5.40 Hz, 2 H), 7.23 - 7.31 (m, 2 H), 7.38 (dd, *J*=3.76, 1.25 Hz, 2 H), 7.64 - 7.70 (m, 2 H), 7.71 (s, 1 H), 7.91 - 7.99 (m, 3 H), 8.60 (br. s., 1 H). LCMS *m/z* 532.00 (M+H). HPLC Rt 6.386 min. (Sunfire C18), 100 % purity.



5-(3-(2-(1*H*-Imidazol-1-yl)ethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00415] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.06 (d, *J*=6.78 Hz, 6 H), 2.03 (d, *J*=6.78 Hz, 1 H), 3.05 (s, 3 H), 3.31 (d, *J*=7.03 Hz, 2 H), 4.62 (t, *J*=4.77 Hz, 2 H),

4.79 (br. s., 2 H), 7.35 (t, $J=8.78$ Hz, 2 H), 7.49 (d, $J=2.76$ Hz, 2 H), 7.68 (s, 1 H), 7.73 - 7.77 (m, 2 H), 7.83 (s, 1 H), 7.88 (s, 1 H), 7.98 - 8.07 (m, 3 H), 9.17 (s, 1 H). LCMS m/z 555.00 (M+H). HPLC Rt 6.295 min. (Sunfire C18), 95.2% purity.

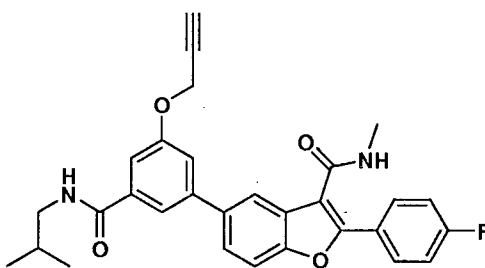


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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(2-(pyridin-4-yl)ethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00416] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.05 (d, $J=6.53$ Hz, 6 H), 1.95 - 2.09 (m, 1 H), 3.04 (s, 3 H), 3.24 - 3.33 (m, 2 H), 3.54 (t, $J=5.90$ Hz, 2 H), 4.60 (t, $J=5.77$ Hz, 2 H), 7.27 - 7.38 (m, 2 H), 7.41 - 7.49 (m, 2 H), 7.71 - 7.75 (m, 2 H), 7.78 (t, $J=1.51$ Hz, 1 H), 7.96 - 8.05 (m, 3 H), 8.12 (d, $J=6.53$ Hz, 2 H), 8.80 (d, $J=6.78$ Hz, 2 H). LCMS m/z 566.00 (M+H). HPLC Rt 6.4921 min. (Sunfire C18), 98.6% purity.

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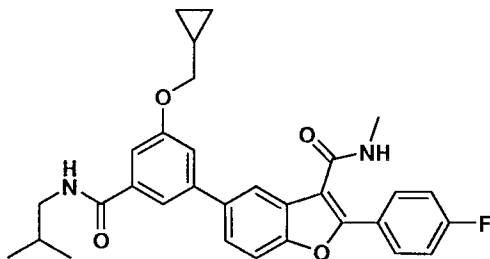


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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(prop-2-ynyloxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00417] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.07 (d, $J=6.78$ Hz, 6 H), 1.94 - 2.18 (m, 1 H), 3.00 - 3.13 (m, 4 H), 3.30 (d, $J=7.03$ Hz, 2 H), 4.94 - 4.98 (m, 2 H), 7.27 - 7.42 (m, 2 H), 7.47 - 7.59 (m, 2 H), 7.68 - 7.79 (m, 2 H), 7.82 (t, $J=1.51$ Hz, 1 H), 7.98 - 8.11 (m, 3 H). LCMS m/z 499.00 (M+H). HPLC Rt 9.984min. (Sunfire C18), 99.4% purity.

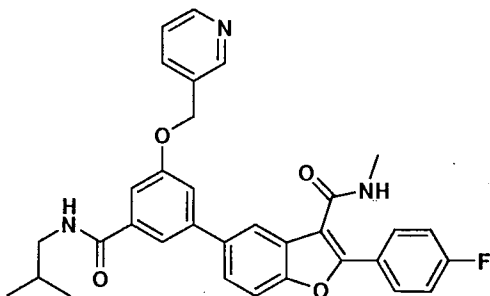
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5-(3-(Cyclopropylmethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00418] ¹H NMR (400 MHz, CD₃OD) δ ppm 0.48 (d, *J*=14.81 Hz, 2 H), 0.72 (d, *J*=7.78 Hz, 2 H), 1.06 (d, *J*=6.53 Hz, 6 H), 1.51 - 1.59 (m, 1 H), 1.98 - 2.10 (m, 1 H), 3.05 (s, 3 H), 3.30 (d, *J*=7.03 Hz, 2 H), 4.04 (d, *J*=6.78 Hz, 2 H), 7.33 (t, *J*=8.66 Hz, 2 H), 7.43 (s, 2 H), 7.49 (br. s., 1 H), 7.75 (d, *J*=9.04 Hz, 3 H), 7.97 - 8.09 (m, 3 H).

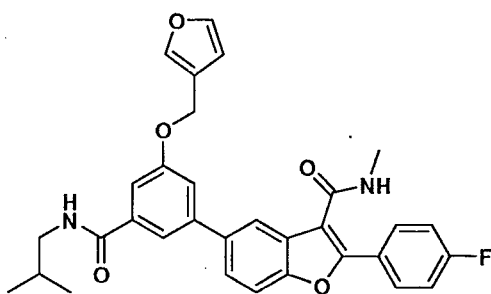
LCMS *m/z* 515.17 (M+H). HPLC Rt 10.878 min. (Sunfire C18), 91.4% purity.



2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(pyridin-3-ylmethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

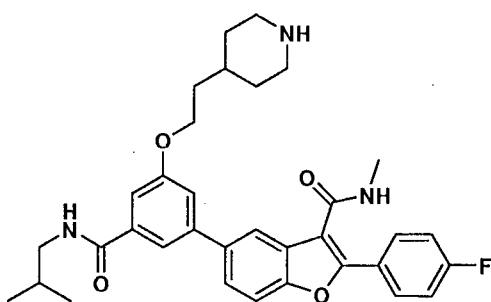
[00419] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.06 (d, *J*=6.78 Hz, 6 H), 2.03 (dt, *J*=13.55, 6.78 Hz, 1 H), 3.04 (s, 3 H), 3.30 (d, *J*=7.03 Hz, 2 H), 5.52 (s, 2 H), 7.33 (t, *J*=8.78 Hz, 2 H), 7.59 (dd, *J*=6.40, 1.38 Hz, 2 H), 7.69 - 7.80 (m, 2 H), 7.84 (s, 1 H), 7.96 - 8.09 (m, 4 H), 8.64 (d, *J*=8.28 Hz, 1 H), 8.83 (d, *J*=4.52 Hz, 1 H), 9.02 (s, 1 H).

LCMS *m/z* 552.05 (M+H). HPLC Rt 6.401 min. (Sunfire C18), 100% purity.



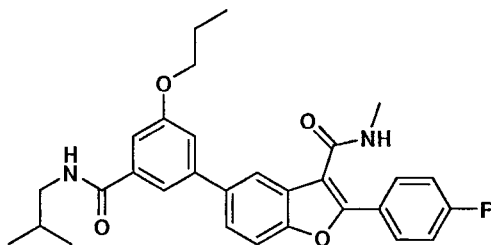
2-(4-Fluorophenyl)-5-(3-(furan-3-ylmethoxy)-5-(isobutylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00420] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.06 (d, *J*=6.53 Hz, 6 H), 1.96 - 2.14 (m, 1 H), 3.06 (s, 3 H), 3.30 (d, *J*=7.03 Hz, 2 H), 5.19 (s, 2 H), 6.64 (s, 1 H), 7.33 (t, *J*=8.78 Hz, 2 H), 7.51 (s, 2 H), 7.59 (br. s., 1 H), 7.70 - 7.82 (m, 4 H), 8.01 (d, *J*=11.54 Hz, 3 H). LCMS *m/z* 541.00 (M+H). HPLC Rt 10.426 min. (Sunfire C18), 90.0% purity.



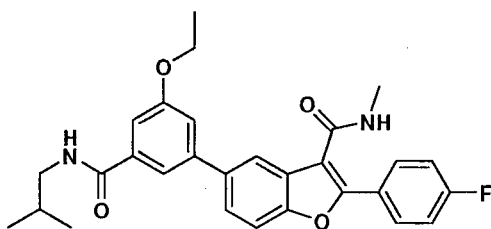
2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(2-(piperidin-4-yl)ethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00421] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.06 (d, *J*=6.53 Hz, 6 H), 1.96 - 2.14 (m, 1 H), 3.06 (s, 3 H), 3.30 (d, *J*=7.03 Hz, 2 H), 5.19 (s, 2 H), 6.64 (s, 1 H), 7.33 (t, *J*=8.78 Hz, 2 H), 7.51 (s, 2 H), 7.59 (br. s., 1 H), 7.70 - 7.82 (m, 4 H), 8.01 (d, *J*=11.54 Hz, 3 H). LCMS *m/z* 572.17 (M+H). HPLC Rt 6.571 min. (Sunfire C18), 95.8 % purity.



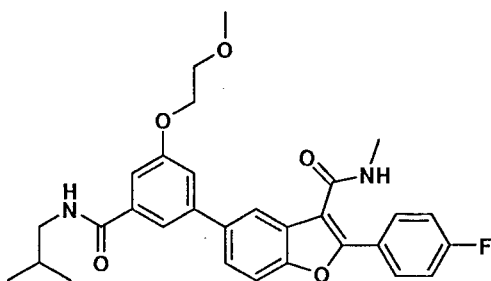
2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-propoxyphenyl)-*N*-methylbenzofuran-3-carboxamide

[00422] ^1H NMR (400 MHz, THF- d_8) δ ppm 0.87 - 0.98 (m, 6 H), 1.07 (t, $J=7.40$ Hz, 3 H), 1.79 - 1.96 (m, 3 H), 2.93 (d, $J=4.52$ Hz, 3 H), 3.21 (t, $J=6.40$ Hz, 2 H), 4.05 (t, $J=6.53$ Hz, 2 H), 7.22 (t, $J=8.66$ Hz, 2 H), 7.30 (br. s., 1 H), 7.39 - 7.56 (m, 2 H), 7.56 - 7.79 (m, 4 H), 7.97 (s, 1 H), 8.12 (dd, $J=8.53, 5.52$ Hz, 2 H). LCMS m/z 503.15 (M+H). HPLC Rt 11.141 min. (Sunfire C18), 98.9 % purity.



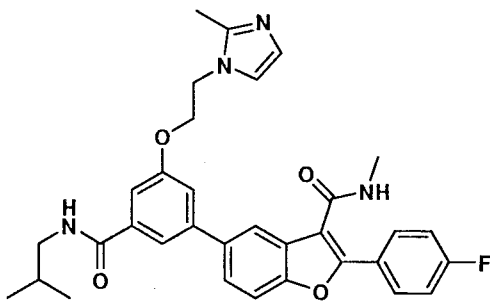
2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-ethoxyphenyl)-*N*-methylbenzofuran-3-carboxamide

[00423] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.06 (d, $J=6.78$ Hz, 6 H), 1.47 - 1.62 (m, 3 H), 1.92 - 2.15 (m, 1 H), 3.05 (s, 3 H), 3.30 (d, $J=7.03$ Hz, 2 H), 4.26 (q, $J=6.94$ Hz, 2 H), 7.33 (t, $J=8.78$ Hz, 2 H), 7.43 (s, 2 H), 7.70 - 7.83 (m, 3 H), 7.97 - 8.09 (m, 3 H). LCMS m/z 489.00 (M+H). HPLC Rt 10.464 min. (Sunfire C18), 93.7% purity.



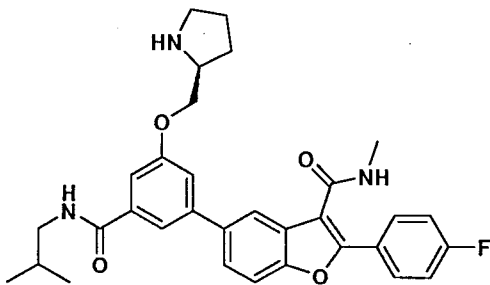
2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(2-methoxyethoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

[00424] ¹H NMR (400 MHz, THF-d₈) δ ppm 0.86 - 1.05 (m, 6 H), 1.82 - 2.02 (m, 1 H), 2.86 - 3.04 (m, 3 H), 3.21 (t, *J*=6.40 Hz, 2 H), 3.34 - 3.45 (m, 3 H), 3.72 (t, *J*=4.77 Hz, 2 H), 4.21 (t, *J*=4.77 Hz, 2 H), 7.22 (t, *J*=8.78 Hz, 2 H), 7.33 (s, 1 H), 7.42 (s, 1 H), 7.49 (br. s., 1 H), 7.55 - 7.83 (m, 4 H), 7.97 (s, 1 H), 8.12 (dd, *J*=8.78, 5.52 Hz, 2 H). LCMS *m/z* 519.10 (M+H). HPLC Rt 9.676min. (Sunfire C18), 100% purity.



2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(2-(2-methyl-1H-imidazol-1-yl)ethoxy)phenyl)-N-methylbenzofuran-3-carboxamide

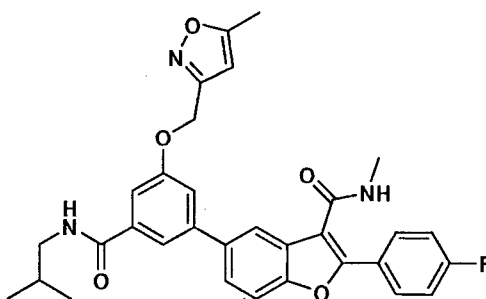
[00425] ¹H NMR (400 MHz, CD₃OD) δ ppm 0.99 (d, *J*=6.53 Hz, 6 H), 1.90 - 2.03 (m, 1 H), 2.78 (s, 3 H), 2.94 - 3.02 (m, 3 H), 3.23 (d, *J*=7.03 Hz, 2 H), 4.53 (t, *J*=4.89 Hz, 2 H), 4.65 (t, *J*=4.89 Hz, 2 H), 7.22 - 7.32 (m, 2 H), 7.38 (d, *J*=1.51 Hz, 2 H), 7.46 (d, *J*=2.01 Hz, 1 H), 7.63 - 7.69 (m, 3 H), 7.75 (t, *J*=1.51 Hz, 1 H), 7.91 - 8.00 (m, 3 H). LCMS *m/z* 569.12 (M+H). HPLC Rt 6.340 min. (Sunfire C18), 100% purity.



(S)-2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-(pyrrolidin-2-ylmethoxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00426] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.06 (d, *J*=6.78 Hz, 6 H), 1.98 - 2.12 (m, 2 H), 2.16 - 2.32 (m, 2 H), 2.34 - 2.48 (m, 1 H), 3.04 (s, 3 H), 3.31 (d, *J*=7.03 Hz, 2 H), 3.44 - 3.55 (m, 2 H), 4.12 - 4.22 (m, 1 H), 4.34 (dd, *J*=10.54, 8.28 Hz, 1 H),

4.51 - 4.62 (m, 1 H), 7.27 - 7.42 (m, 2 H), 7.49 - 7.59 (m, 2 H), 7.71 - 7.82 (m, 2 H), 7.85 (s, 1 H), 7.97 - 8.10 (m, 3 H). LCMS m/z 544.12 (M+H). HPLC Rt 6.326 min. (Sunfire C18), 95.8 % purity.

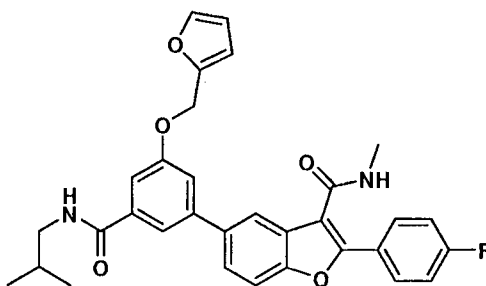


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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-((5-methylisoxazol-3-yl)methoxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00427] ^1H NMR (400 MHz, THF- d_8) δ ppm 0.92 - 0.99 (m, 6 H), 1.83 - 1.99 (m, 1 H), 2.40 (s, 3 H), 2.90 - 2.98 (m, 3 H), 3.17 - 3.27 (m, 2 H), 5.18 - 5.25 (m, 1 H), 6.17 - 6.25 (m, 1 H), 7.17 - 7.27 (m, 2 H), 7.41 - 7.46 (m, 1 H), 7.47 - 7.54 (m, 2 H), 7.57 - 7.68 (m, 3 H), 7.68 - 7.74 (m, 1 H), 7.76 (d, $J=1.51$ Hz, 1 H), 7.98 (d, $J=1.26$ Hz, 1 H), 8.07 - 8.19 (m, 2 H). LCMS m/z 556.00 (M+H). HPLC Rt 10.106 min. (Sunfire C18), 90.0% purity.

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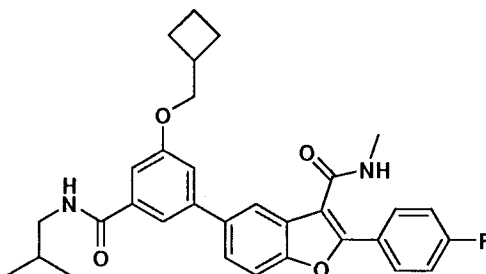
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2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-((5-methylisoxazol-3-yl)methoxy)phenyl)-N-methylbenzofuran-3-carboxamide

[00428] ^1H NMR (500 MHz, THF- d_8) δ ppm 0.98 (d, $J=6.71$ Hz, 6 H), 1.88 - 2.01 (m, 1 H), 2.92 - 3.00 (m, 3 H), 3.20 - 3.27 (m, 2 H), 5.17 (s, 2 H), 6.42 (dd, $J=3.05$, 1.83 Hz, 1 H), 6.53 (d, $J=3.36$ Hz, 1 H), 7.21 - 7.30 (m, 3 H), 7.43 (d, $J=1.53$ Hz, 1 H), 7.55 (d, $J=12.51$ Hz, 1 H), 7.59 - 7.66 (m, 3 H), 7.67 - 7.71 (m, 1 H), 7.78 (s, 1

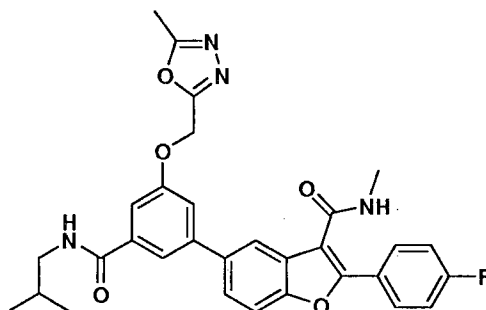
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H), 8.02 (s, 1 H), 8.13 - 8.18 (m, 2 H). LCMS m/z 541.17 (M+H). HPLC Rt 10.401 min. (Sunfire C18), 90.0% purity.



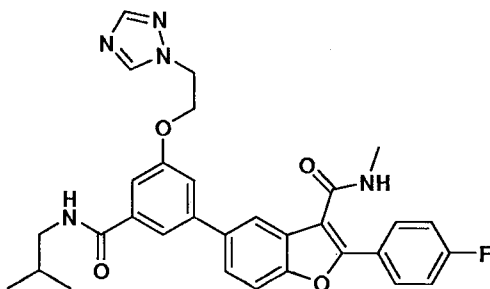
- 5 5-(3-(Cyclobutylmethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00429] ^1H NMR (500 MHz, THF- d_8) δ ppm 0.95 (d, $J=6.71$ Hz, 6 H), 1.86 - 2.02 (m, 6 H), 2.10 - 2.21 (m, 2 H), 2.87 - 2.97 (m, 3 H), 3.20 (d, $J=6.71$ Hz, 2 H), 4.07 (d, $J=6.71$ Hz, 2 H), 7.23 (t, $J=8.85$ Hz, 2 H), 7.32 (s, 1 H), 7.43 (s, 1 H), 7.57 - 7.63 (m, 2 H), 7.63 - 7.68 (m, 1 H), 7.73 (s, 1 H), 7.79 - 7.86 (m, 1 H), 7.99 (s, 1 H), 8.09 - 8.16 (m, 2 H). LCMS m/z 529.00 (M+H). HPLC Rt 11.771 min. (Sunfire C18), 94.2% purity.



- 15 2-(4-Fluorophenyl)-5-(3-(isobutylcarbamoyl)-5-((5-methyl-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-*N*-methylbenzofuran-3-carboxamide

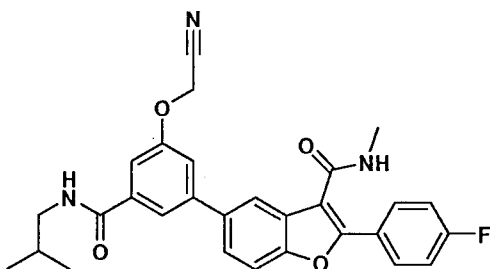
[00430] ^1H NMR (400 MHz, THF- d_8) δ ppm 0.90 - 1.02 (m, 6 H), 1.84 - 2.00 (m, 1 H), 2.50 (s, 3 H), 2.94 (d, $J=4.77$ Hz, 3 H), 3.17 - 3.27 (m, 2 H), 5.39 (s, 2 H), 7.18 - 7.29 (m, 2 H), 7.46 - 7.56 (m, 3 H), 7.58 - 7.68 (m, 2 H), 7.71 (br. s., 1 H), 7.79 (s, 1 H), 8.00 (d, $J=1.51$ Hz, 1 H), 8.08 - 8.21 (m, 2 H). LCMS m/z 557.11 (M+H). HPLC Rt 8.964 min. (Sunfire C18), 92.0% purity.



5-(3-(2-(1H-1,2,4-Triazol-1-yl)ethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00431] ¹H NMR (400 MHz, THF-d₈) δ ppm 0.87 - 1.01 (m, 6 H), 1.83 - 1.98 (m, 1 H), 2.93 (d, *J*=4.52 Hz, 3 H), 3.13 - 3.26 (m, 2 H), 4.49 (t, *J*=5.14 Hz, 2 H), 4.61 (t, *J*=5.02 Hz, 2 H), 7.19 - 7.27 (m, 2 H), 7.28 - 7.33 (m, 1 H), 7.39 - 7.42 (m, 1 H), 7.43 - 7.52 (m, 1 H), 7.57 - 7.66 (m, 2 H), 7.71 - 7.77 (m, 1 H), 7.81 (s, 1 H), 7.96 (d, *J*=1.00 Hz, 1 H), 8.06 - 8.17 (m, 3 H), 8.30 (s, 1 H). LCMS *m/z* 556.11 (M+H). HPLC Rt 7.969 min. (Sunfire C18), 92.0% purity.

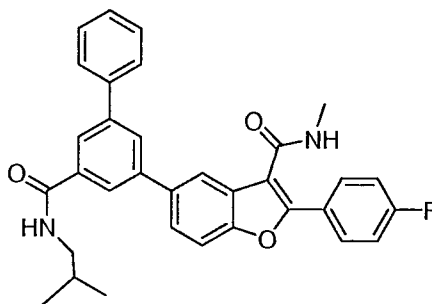
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5-(3-(Cyanomethoxy)-5-(isobutylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00432] ¹H NMR (500 MHz, THF-d₈) δ ppm 0.96 (d, *J*=6.71 Hz, 6 H), 1.85 - 1.98 (m, 1 H), 2.85 - 2.98 (m, 3 H), 3.16 - 3.27 (m, 2 H), 5.11 (s, 2 H), 7.18 - 7.29 (m, 2 H), 7.42 - 7.49 (m, 1 H), 7.54 (s, 1 H), 7.60 - 7.71 (m, 2 H), 7.79 - 7.88 (m, 2 H), 8.00 (s, 1 H), 8.08 - 8.19 (m, 2 H). LCMS *m/z* 500.00 (M+H). HPLC Rt 9.584 min. (Sunfire C18), 95.9% purity.

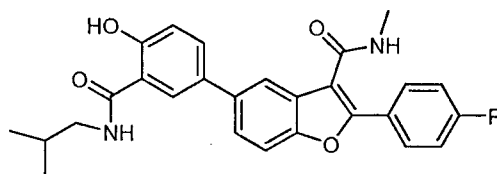
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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)biphenyl-3-yl)-N-methylbenzofuran-3-carboxamide

[00433] To a BIOTAGE® microwave vial was added 1,4-dioxane (2.0 mL), water (200 µL), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (16.42 mg, 0.040 mmol), 5-(3-chloro-5-(isobutylcarbamoyl) phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (96 mg, 0.2 mmol), potassium phosphate tribasic (170 mg, 0.800 mmol), palladium(II) acetate (8.98 mg, 0.040 mmol), and phenylboronic acid (73.2 mg, 0.600 mmol). The vial was capped, degassed, flushed with N₂ and heated in the microwave for 15 minutes at 150 °C. The solvent was removed in a Thermo/Savant SPEEDVAC® and the crude product was dissolved in DMF (1.8 mL) and purified by preparative HPLC using a Shimadzu Prep HPLC employing acetonitrile/water/0.1%TFA where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5µm C18 30x100mm column at a gradient of 30-100% B and a flow rate of 40 mL/min. over 8 minutes with a 10 minute hold. The tubes with desired product were evaporated overnight in a Savant/Thermo SPEEDVAC®. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% TFA/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% TFA/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/ 0.1%TFA with a gradient of 20-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5%

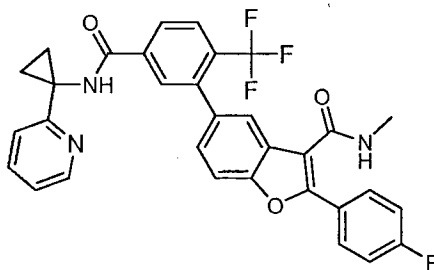
HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 20-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.99 (d, *J*=6.78 Hz, 6 H), 1.92 - 2.05 (m, 1 H), 2.91 - 3.03 (m, 3 H), 3.21 - 3.27 (m, 2 H), 7.25 (t, *J*=8.78 Hz, 2 H), 7.36 - 7.42 (m, 1 H), 7.49 (t, *J*=7.53 Hz, 2 H), 7.65 - 7.70 (m, 1 H), 7.75 (d, *J*=8.28 Hz, 3 H), 7.91 - 7.98 (m, 2 H), 8.00 (d, *J*=1.51 Hz, 1 H), 8.03 - 8.10 (m, 3 H). LCMS *m/z* 521.33 (M+H), Rt 2.715 min. HPLC (Sunfire C18) Rt 11.531 min, 95% purity and (XBridge phenyl C18) Rt 12.868 min., 92 % purity.



2-(4-Fluorophenyl)-5-(4-hydroxy-3-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00434] To a 350mL sealed tube was added 2-(4-fluorophenyl)-5-(3-(isobutylcarbamoyl)-4-methoxyphenyl)-N-methylbenzofuran-3-carboxamide (1.14 g, 2.4 mmol), dichloroethane (250 mL) and boron tribromide-methyl sulfide complex (6.0 g, 19.2 mmol). The vessel was sealed and the mixture heated with stirring at 90 °C overnight. The reaction mixture was cooled to 0 °C and 100mL of cold methanol was added and the mixture stirred for 30minutes then evaporated to near dryness. The addition of methanol followed by evaporation was repeated to give a tan solid (78%). The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% TFA/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% TFA/ 10% HPLC grade acetonitrile), in 3 minutes with a 1

minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/ 0.1%TFA with a gradient of 40-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Gemini C18 3 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 50-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10 mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (500 MHz, THF-d₈) δ ppm 0.97 (d, *J*=6.71 Hz, 6 H), 1.83 - 2.07 (m, 1 H), 2.92 (d, *J*=4.88 Hz, 3 H), 3.24 (t, *J*=6.41 Hz, 2 H), 6.96 (d, *J*=8.55 Hz, 1 H), 7.23 (t, *J*=8.70 Hz, 2 H), 7.50 - 7.55 (m, 1 H), 7.55 - 7.59 (m, 2 H), 7.67 (dd, *J*=8.55, 2.14 Hz, 1 H), 7.89 (s, 1 H), 7.99 (d, *J*=2.14 Hz, 1 H), 8.09 (dd, *J*=8.70, 5.34 Hz, 2 H), 8.35 (br. s., 1 H). LCMS *m/z* 461.18 (M+H), Rt 2.613 min. HPLC (Sunfire C18) Rt 10.033 min., 100% purity and (Gemini C18) Rt 9.748 min., 100 % purity.

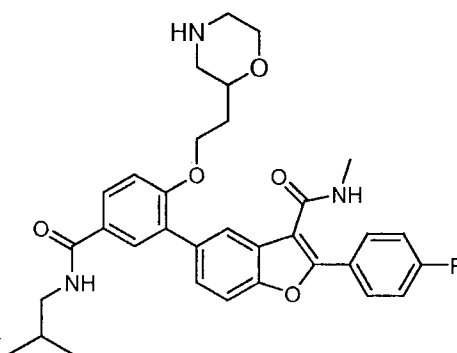


20 2-(4-Fluorophenyl)-*N*-methyl-5-(5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)-2-(trifluoromethyl)phenyl)benzofuran-3-carboxamide

[00435] To a BIOTAGE® microwave vial was added 2-(4-fluorophenyl)-*N*-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide (39.5 mg, 0.1 mmol), dioxane (2 mL), water (0.200 mL), 3-chloro-*N*-(1-(pyridin-2-yl)cyclopropyl)-4-(trifluoromethyl)benzamide (37.5 mg, 0.110 mmol) (prepared from the coupling of 3-chloro-4-(trifluoromethyl)benzoic acid with 1-(pyridin-2-

yl)cyclopropanamine dihydrochloride using HATU and N,N-Diisopropylethylamine in DMF at r.t.), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos, 8.21 mg, 0.020 mmol), tribasic potassium phosphate, (85 mg, 0.400 mmol) and finally palladium(II) acetate (4.49 mg, 0.020 mmol). The vial was capped and subjected to microwave heating (100 °C) for 10 minutes. After cooling the reaction mixture, the solvent was removed and the crude product was purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5µm C18 19 x 150mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 20 minutes with a 5 minute hold. The solvent was removed yielding 11.2mgs (20% yield) of the desired pyridylcarboxamide as a yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade methanol), in 4 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/ 0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Gemini C18 3.0µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.22 - 1.33 (m, 2 H), 1.63 - 1.69 (m, 2 H), 2.87 (d, J=4.77 Hz, 3 H), 7.03 (dd, J=7.40, 4.89 Hz, 1 H), 7.23 (t, J=8.66 Hz, 2 H), 7.33 (d, J=8.28 Hz, 1 H), 7.40 (d, J=7.53 Hz, 2 H), 7.52 - 7.63 (m, 2 H), 7.73 (d, J=1.25 Hz, 1 H),

7.90 (d, $J=8.03$ Hz, 1 H), 7.97 (s, 1 H), 8.05 - 8.16 (m, 3 H), 8.40 (d, $J=4.77$ Hz, 1 H), 8.69 (s, 1 H). LCMS R_t = 2.193min., m/z 574.3 (M+H). HPLC R_t = 7.435 min. (Sunfire C18), 97.5 % purity and 11.823 min. (Gemini C18), 100 % purity.



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2-(4-Fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-(morpholin-2-yl)ethoxy)phenyl)-
N-methylbenzofuran-3-carboxamide, TFA

[00436] To a 2 dram vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(isobutylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide (46.0 mg, 0.1 mmol), DMF (2 mL), 4.0 equivalents (60 μ L, 0.400 mmol) of DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.4 mmol) and 4.0 equivalents of *tert*-butyl 2-(2-bromoethyl)morpholine-4-carboxylate (236 mg, 0.400 mmol). The vial was capped and the reaction mixture heated for eighteen hours at 85 °C. The crude product was purified using a Shimadzu preparative HPLC employing

15 acetonitrile/water/trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5 μ m C18 19 x 150 mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 20 minutes with a 10 minute hold. The solvent mixture was removed on the rotovap and the resulting

20 white solid (19.2mgs) was taken up in 2mL of dichloroethane containing 200 μ L of trifluoroacetic acid. The acid mixture was stirred for 60minutes. The volatiles were then removed, the process repeated again giving 20mgs (29% yield, 2 steps) of 2-(4-fluorophenyl)-5-(5-(isobutylcarbamoyl)-2-(2-(morpholin-2-yl)ethoxy)phenyl)-N-methylbenzofuran-3-carboxamide, TFA as a white solid. The NMR spectrum was

25 recorded at room temperature using a Bruker DRX400 spectrometer. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC

(ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 0.93 (d, *J*=6.53 Hz, 6 H), 1.87 (m, 3 H), 2.90 (d, *J*=4.77 Hz, 3 H), 3.08 - 3.12 (m, 2 H), 3.16 - 3.20 (m, 2 H), 3.31 (d, *J*=9.54 Hz, 2 H), 3.95 - 4.11 (m, 3 H), 4.23 - 4.31 (m, 1 H), 4.35 (br. s., 1 H), 7.08 (d, *J*=8.78 Hz, 1 H), 7.25 (t, *J*=8.66 Hz, 2 H), 7.45 (dd, *J*=8.53, 1.76 Hz, 1 H), 7.54 (t, *J*=5.65 Hz, 1 H), 7.62 (d, *J*=8.53 Hz, 1 H), 7.84 (dd, *J*=8.53, 2.26 Hz, 1 H), 7.88 (d, *J*=2.01 Hz, 1 H), 7.91 (d, *J*=4.02 Hz, 1 H), 7.98 - 8.07 (m, 3 H). LCMS *m/z* 574.5 (M+H), *R*_t = 2.390 min. HPLC (Sunfire C18) *R*_t = 6.870 min., 99.3% purity and (XBridge phenyl C18) *R*_t = 10.973 min., 99.2% purity.

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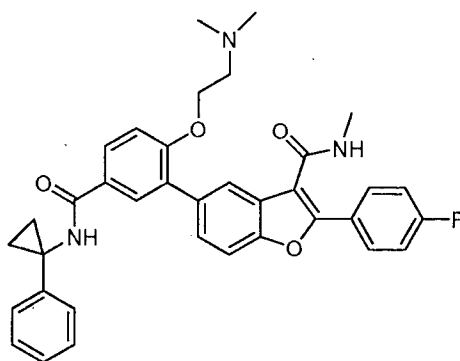
tert-Butyl 2-(2-bromoethyl)morpholine-4-carboxylate

[00437] To a 25mL round-bottomed flask was added 2-(morpholin-2-yl)ethanol (100 mg, 0.762 mmol), DCM (1 mL), and triethylamine (0.106 mL, 0.762 mmol). Di-*tert*-butyl dicarbonate (0.177 mL, 0.762 mmol) in DCM (1 mL) was then added dropwise via syringe. The mixture was stirred at room temperature under nitrogen for 3 hours. Volatiles were removed and NMR was taken of the colorless oil (176 mgs, 100% yield, 96% purity). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.39 (s, 9 H),

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1.47 - 1.61 (m, 2 H), 2.83 (br. s., 1 H), 3.28 - 3.42 (m, 3 H), 3.46 (q, $J=6.10$ Hz, 2 H), 3.68 (d, $J=11.29$ Hz, 1 H), 3.76 (d, $J=10.38$ Hz, 2 H), 4.45 (t, $J=5.04$ Hz, 1 H).

[00438] To a 25mL round-bottomed flask at 0 °C was added *tert*-butyl 2-(2-hydroxyethyl)morpholine-4-carboxylate (0.176 g, 0.762 mmol), DCM (4 mL), 1H-imidazole (0.104 g, 1.524 mmol), perbromomethane (0.379 g, 1.143 mmol), and triphenylphosphine (0.190 g, 0.723 mmol). The mixture was stirred overnight slowly reaching room temperature. The yellow solution was further diluted with 50 mL of DCM, washed with water, brine, dried over sodium sulfate, and filtered. The crude product was then pushed through a plug of silica gel and the solvent was removed to give 213mgs of a light yellow oil. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.40 (s, 9 H), 1.94 (q, $J=6.86$ Hz, 1 H), 2.56 - 2.66 (m, 1 H), 2.76 - 2.91 (m, 1 H), 3.35 - 3.47 (m, 4 H), 3.50 - 3.61 (m, 1 H), 3.68 (br. s., 1 H), 3.74 - 3.86 (m, 2 H).

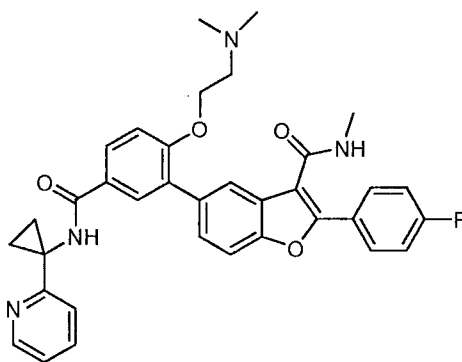


15 5-(2-(2-(Dimethylamino)ethoxy)-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide, TFA

[00439] To a small microwave vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(1-phenylcyclopropyl carbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide (11.3mgs, 0.022 mmol) (obtained from the de-methylation of the methoxy precursor using Boron tribromide-methyl sulfide complex (1,2-dichloroethane, 90 °C)), dioxane (2 mL), triphenylphosphine (105 mg, 0.400 mmol), 2-(dimethylamino)ethanol (0.025 mL, 0.250 mmol), and di-*tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol). The vial was crimped and the reaction mixture subjected to microwave heating (140 °C) for 20 minutes in a BIOTAGE® Initiator. The solvent was removed under a stream of nitrogen, the crude product taken up in 2mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where

solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Sunfire 5 μ m C18 19 x 150mm column at a gradient of 20-100% B and a flow rate of 20 mL/min. over 20 minutes with a 5 minute hold. The solvent was removed to give 14.5mgs (90% yield) of 5-(2-(2-(dimethylamino)ethoxy)-5-(1-phenylcyclopropyl carbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide, TFA salt as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% TFA/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% TFA/ 10% HPLC grade methanol), in 4 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/ 0.1% trifluoroacetic ac with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Gemini C18 3.0 μ m 4.6 x 150mm column employing water/methanol/ 10 mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10 mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10 mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The NMR spectrum was recorded at room temperature using a Bruker DRX400 spectrometer. Chemical shifts were reported in ppm relative to the deuterated solvent used. Coupling constants were reported in hertz. Peak multiplicity was reported using the following abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), br (broad). ¹H NMR (400 MHz, THF-d₈) δ ppm 1.22 - 1.27 (m, 2 H), 1.28 - 1.33 (m, 2 H), 2.70 (s, 6 H), 2.90 (d, *J*=4.52 Hz, 3 H), 3.41 - 3.46 (m, 2 H), 4.47 - 4.53 (m, 2 H), 7.06 - 7.12 (m, 1 H), 7.14 - 7.27 (m, 5 H), 7.28 - 7.35 (m, 2 H), 7.47 (dd, *J*=8.53, 1.76 Hz, 1 H), 7.54 - 7.61 (m, 2 H), 7.89 (dd, *J*=8.53, 2.26 Hz, 1 H), 7.94 (dd, *J*=4.02, 2.01 Hz, 2 H), 8.03 - 8.10 (m, 2 H), 8.28 (s, 1 H). LCMS *m/z*

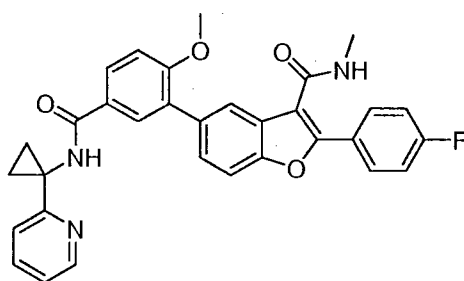
592.4 (M+H), Rt = 2.065 min. HPLC Rt = 7.025 min. (Sunfire C18), 95.2 % purity and 11.979 min. (Gemini C18), 95.7 % purity.



- 5 5-(2-(2-(Dimethylamino)ethoxy)-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-
2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide, TFA

[00440] The LC/MS data was obtained on a Shimadzu analytical LC /
MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:
Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC
10 grade methanol/ 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90%
HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade methanol), in 4
minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was
determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters
Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/ 0.1%
15 trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/
0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water /
0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10
minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an
orthogonal solvent system and column using a Shimadzu analytical LC with a
20 PHENOMENEX® Gemini C18 3.0µm 4.6 x 150mm column employing
water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B =
95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water),
(A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade
methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR
25 (400 MHz, THF-d₈) δ ppm 1.32 - 1.37 (m, 2 H), 1.59 - 1.65 (m, 2 H), 2.77 (s, 6 H),
2.90 (d, J=4.77 Hz, 3 H), 3.47 - 3.54 (m, 2 H), 4.48 - 4.55 (m, 2 H), 7.17 (d, J=8.53

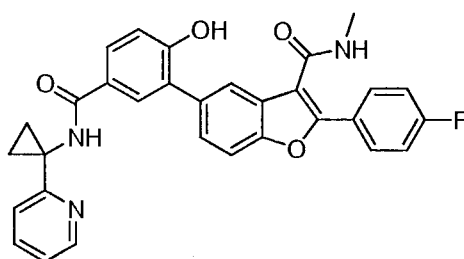
Hz, 1 H), 7.20 - 7.27 (m, 2 H), 7.31 (dd, $J=6.90, 5.65$ Hz, 1 H), 7.49 - 7.59 (m, 2 H), 7.61 - 7.70 (m, 2 H), 7.86 (td, $J=7.78, 1.51$ Hz, 1 H), 7.94 (dd, $J=8.53, 2.26$ Hz, 1 H), 7.97 (d, $J=1.00$ Hz, 1 H), 7.99 - 8.09 (m, 3 H), 8.54 (d, $J=4.27$ Hz, 1 H), 9.07 (s, 1 H). LCMS $R_t = 2.412$ min., m/z 593.4 (M+H). HPLC $R_t = 5.185$ min. (Sunfire C18), 96.4
 5 % purity and 11.558 min. (Gemini C18), 98.2 % purity.



2-(4-Fluorophenyl)-5-(2-methoxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-
 N-methylbenzofuran-3-carboxamide

- 10 [00441] The LC/MS data was obtained on a Shimadzu analytical LC /
 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:
 PHENOMENEX® Luna 10 μ M C18, 3.0 x 50mm column, with a gradient of 0-
 100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid / 10% HPLC
 grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC
 15 grade methanol), in 4 minutes with a 1 minute hold at a rate of 5 mL/minute. HPLC
 purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a
 Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/ 0.1%
 trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/
 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water /
 20 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10
 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an
 orthogonal solvent system and column using a Shimadzu analytical LC with a
 PHENOMENEX® Gemini C18 3.0 μ m 4.6 x 150mm column employing
 water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B =
 25 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water),
 (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade
 methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ^1H NMR

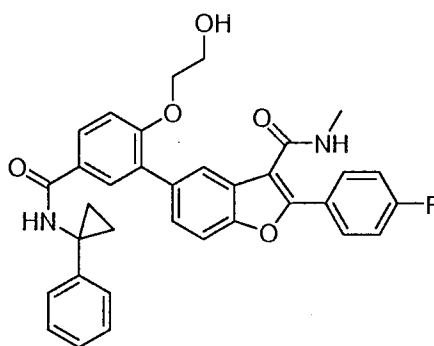
(400 MHz, DMSO- d_6) δ ppm 1.31 - 1.40 (m, 2 H), 1.56 - 1.65 (m, 2 H), 2.82 (d, $J=4.52$ Hz, 3 H), 3.85 (s, 3 H), 7.24 (d, $J=8.53$ Hz, 1 H), 7.30 (dd, $J=6.78, 5.52$ Hz, 1 H), 7.39 (t, $J=8.91$ Hz, 2 H), 7.46 (d, $J=8.03$ Hz, 1 H), 7.52 (dd, $J=8.53, 1.76$ Hz, 1 H), 7.68 - 7.75 (m, 2 H), 7.86 (s, 1 H), 7.93 - 8.02 (m, 4 H), 8.45 (d, $J=4.52$ Hz, 1 H), 8.49 (d, $J=4.27$ Hz, 1 H), 9.23 (s, 1 H). LCMS R_t = 2.557 min., m/z 536.10 (M+H). HPLC R_t = 6.683 min. (Sunfire C18), 96.3 % purity and 11.493 min. (Gemini C18), 99.5 % purity.



10 2-(4-Fluorophenyl)-5-(2-hydroxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-
N-methylbenzofuran-3-carboxamide

[00442] To a 100mL round-bottomed flask equipped with a reflux condenser was added 2-(4-fluorophenyl)-5-(2-methoxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide (400 mg, 0.747 mmol), DCE (42 mL) and boron tribromide-methyl sulfide complex (1868 mg, 5.97 mmol). The solution was placed under nitrogen and stirred overnight at 90 °C. The reaction mixture was cooled to room temperature, quenched with methanol and evaporated to near dryness. The mixture was taken up in 10 mL of methanol and purified using a Shimadzu preparative HPLC employing methanol/water/0.1% trifluoroacetic acid where solvent A was 10% methanol / 90% water / 0.1% trifluoroacetic acid and solvent B was 10% water / 90% methanol / 0.1% trifluoroacetic acid with a PHENOMENEX® Luna 10 μ m C18 30x100mm column at a gradient of 40-100% B and a flow rate of 40 mL/min. over 10 minutes with a 5 minute hold. The solvent was evaporated giving 234mgs (60% yield) of 2-(4-fluorophenyl)-5-(2-hydroxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Sunfire 5 μ m C18, 4.6 x 50mm column, with a gradient

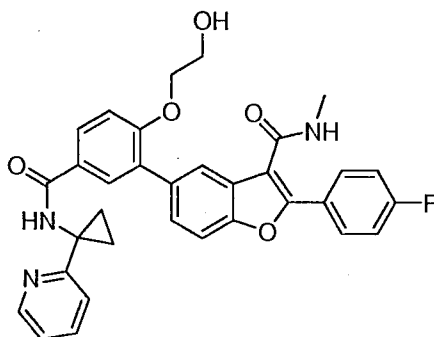
of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade methanol), in 4 minutes with a 1 minute hold at a rate of 4 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.25 - 1.31 (m, 2 H), 1.59 - 1.66 (m, 2 H), 2.90 (d, *J*=4.52 Hz, 3 H), 6.91 (d, *J*=8.53 Hz, 1 H), 7.08 (dd, *J*=6.90, 5.40 Hz, 1 H), 7.17 - 7.24 (m, 2 H), 7.45 - 7.65 (m, 5 H), 7.79 (dd, *J*=8.41, 2.13 Hz, 1 H), 7.88 (d, *J*=1.25 Hz, 1 H), 7.93 (d, *J*=2.01 Hz, 1 H), 8.08 - 8.17 (m, 2 H), 8.39 - 8.45 (m, 1 H), 8.49 (br. s., 1 H). LCMS Rt = 1.495 min., *m/z* 522.33 (M+H), 94% purity.



2-(4-Fluorophenyl)-5-(2-(2-hydroxyethoxy))-5-(1-phenylcyclopropylcarbamoyl)phenyl-N-methylbenzofuran-3-carboxamide

[00443] To a small screw cap vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(1-phenylcyclopropyl carbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide (19.5 mg, 0.037 mmol) in DMF (1.3 mL), (2-bromoethoxy)(*tert*-butyl)dimethylsilane (0.024 mL, 0.112 mmol), and DBU (1,8-diazabicyclo [5.4.0]undec-7-ene, 0.023 mL, 0.150 mmol). The vial was capped and shaken at 80 °C for 18 hours. The DMF was removed under a stream of nitrogen to give 5-(2-(2-(*tert*-butyldimethylsilyloxy)ethoxy))-5-(1-phenylcyclopropyl carbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide as a tan oil. To the mixture was then added 1.3mL of tetrahydrofuran along with 2 eq. of 1 M HCl (0.075 mL, 0.075 mmol). The solution was stirred for 1 hour at room temperature. The reaction mixture was transferred to a separatory funnel, diluted with ethyl acetate, washed sequentially with sodium bicarbonate, brine and dried over magnesium sulfate. The product mixture was filtered and the solvent was evaporated. The crude product was taken up in 1.8 mL of acetonitrile and 200μL of DMF and purified using a Shimadzu preparative

HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Sunfire C18 19 x 150mm column at a gradient of 20-100% B and a flow rate of 20 mL/min. over 20 minutes with a 5
5 minute hold. 15.2mgs of 2-(4-fluorophenyl)-5-(2-(2-hydroxyethoxy)-5-(1-phenylcyclopropyl carbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide (70% yield, 2 steps) was obtained after solvent evaporation. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Sunfire 5µm C18, 4.6 x 50mm column, with a
10 gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade methanol), in 4 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing
15 water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu
20 analytical LC with a Gemini C18 3.0µm 4.6 x 150mm column employing water/methanol / 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR
25 (400 MHz, THF-d₈) δ ppm 1.20 - 1.27 (m, 2 H), 1.28 - 1.36 (m, 2 H), 2.87 - 2.96 (m, 3 H), 3.75 - 3.83 (m, 3 H), 4.10 (t, *J*=4.89 Hz, 2 H), 7.04 - 7.13 (m, 2 H), 7.16 - 7.25 (m, 4 H), 7.29 - 7.35 (m, 2 H), 7.43 (d, *J*=4.27 Hz, 1 H), 7.51 - 7.59 (m, 2 H), 7.87 (dd, *J*=8.53, 2.26 Hz, 1 H), 7.94 (d, *J*=2.26 Hz, 1 H), 8.02 (s, 1 H), 8.11 - 8.18 (m, 2 H), 8.25 (s, 1 H). LCMS Rt = 2.671min., *m/z* 565.3 (M+H). HPLC Rt = 9.454 min.
30 (Sunfire C18), 95.0 % purity and 11.611 min. (Gemini C18), 99.7 % purity.

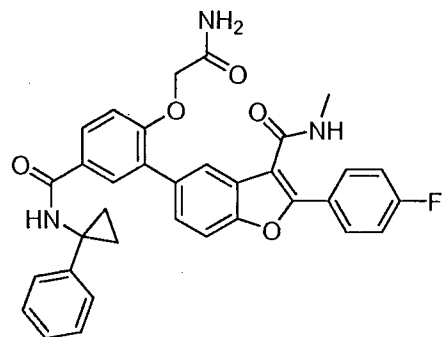


2-(4-Fluorophenyl)-5-(2-(2-hydroxyethoxy)-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00444] The LC/MS data was obtained on a Shimadzu analytical LC /

- 5 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC
- 10 purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5mm 4.6 x 150mm column employing water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10
- 15 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC
- 20 grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.23 - 1.29 (m, 2 H), 1.62 - 1.68 (m, 2 H), 2.91 (d, J=4.77 Hz, 3 H), 3.80 (t, J=4.77 Hz, 2 H), 4.13 (t, J=4.89 Hz, 2 H), 6.99 (m, 1 H), 7.14 (d, J=8.53 Hz, 1 H), 7.17 - 7.25 (m, 2 H), 7.37 - 7.47 (m, 2 H), 7.49 - 7.61 (m, 3 H), 7.93 (dd, J=8.53, 2.26
- 25 Hz, 1 H), 8.00 (d, J=2.26 Hz, 1 H), 8.03 - 8.06 (m, 1 H), 8.11 - 8.18 (m, 2 H), 8.33 (s, 1 H), 8.35 - 8.41 (m, 1 H). LCMS m/z 566.4 (M+H), Rt = 2.038 min. HPLC (Sunfire

C18) Rt = 5.916min., 100% purity and (XBridge phenyl C18) Rt = 10.474min., 100% purity.



5 5-(2-(2-Amino-2-oxoethoxy)-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00445] To a small screw cap vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(1-phenylcyclopropyl carbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide (15.6 mg, 0.030 mmol) in DMF (2 mL), 2-bromoacetamide (41.4 mg, 0.300 mmol), and

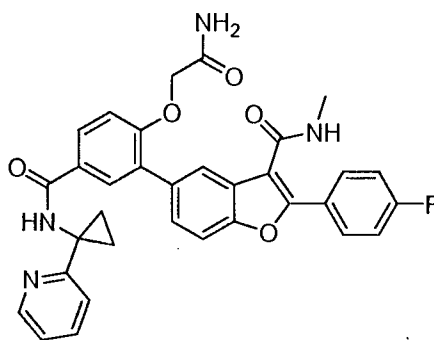
10 DBU (1,8-diazabicyclo [5.4.0]undec-7-ene, 0.060 mL, 0.400 mmol). The vial was capped and shaken at 75 °C overnight. The crude reaction mixture was cooled, evaporated, taken up in 2 mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10%

15 water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a XTERRA® C18 19 x 100mm column at a gradient of 25-100% B and a flow rate of 25 mL/min. over 12 minutes with a 8 minute hold. The solvent was evaporated overnight giving 9.9mgs (54.9% yield) of carboxamide as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the

20 following set of conditions: Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile / 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm

25 with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/ 0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade

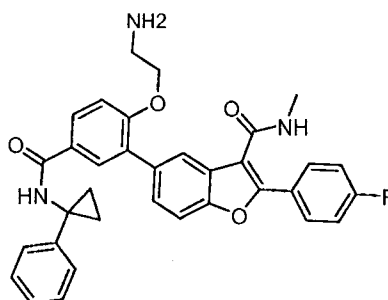
acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Gemini C18 3.0 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10 mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.21 - 1.26 (m, 2 H), 1.26 - 1.33 (m, 2 H), 2.87 - 2.92 (m, 3 H), 4.47 (s, 2 H), 7.05 - 7.13 (m, 2 H), 7.15 - 7.25 (m, 4 H), 7.27 - 7.34 (m, 2 H), 7.45 - 7.51 (m, 1 H), 7.52 - 7.61 (m, 2 H), 7.84 - 7.92 (m, 2 H), 7.93 - 8.00 (m, 2 H), 8.09 - 8.20 (m, 3 H), 8.29 (s, 1 H). LCMS Rt = 2.522min., *m/z* 578.3(M+H). HPLC Rt = 8.693 min. (Sunfire C18), 91.0 % purity and 11.423 min. (Gemini C18), 92 % purity.



5-(2-(2-Amino-2-oxoethoxy)-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00446] The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3 μ m C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile / 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/ 0.1%

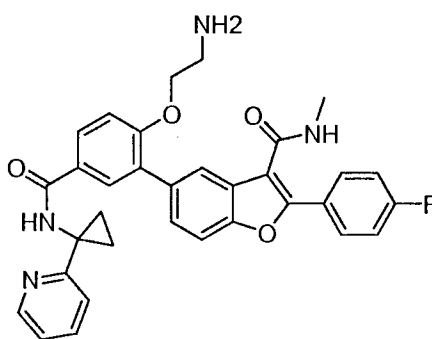
trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/
0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water /
0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10
minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an
5 orthogonal solvent system and column using a Shimadzu analytical LC with a
PHENOMENEX® Gemini C18 3.0 μ m 4.6 x 150mm column employing
water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B =
95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water),
(A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade
10 methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR
(400 MHz, THF-d₈) δ ppm 1.25 - 1.37 (m, 2 H), 1.57 - 1.67 (m, 2 H), 2.88 - 2.96 (m,
3 H), 4.49 (s, 2 H), 6.51 (br. s., 1 H), 6.79 (br. s., 1 H), 7.10 (d, *J*=8.78 Hz, 1 H), 7.17
- 7.27 (m, 3 H), 7.52 - 7.66 (m, 4 H), 7.72 - 7.82 (m, 1 H), 7.94 (dd, *J*=8.53, 2.26 Hz,
1 H), 7.99 (s, 1 H), 8.03 (d, *J*=2.26 Hz, 1 H), 8.08 - 8.18 (m, 2 H), 8.50 (d, *J*=4.27 Hz,
15 1 H), 8.91 (br. s., 1 H). LCMS Rt = 2.578min., *m/z* 580.3 (M + 2H). HPLC Rt = 9.368
min. (Sunfire C18), 96.0 % purity and 10.756 min. (Gemini C18), 97.9 % purity.



5-(2-(2-Aminoethoxy)-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-
20 fluorophenyl)-*N*-methylbenzofuran-3-carboxamide, TFA
[00447] To a 2 dram vial was added 2-(4-fluorophenyl)-5-(2-hydroxy-5-(1-
phenylcyclopropylcarbamoyl) phenyl)-*N*-methylbenzofuran-3-carboxamide (40.2 mg,
0.078 mmol) in 3 mL of DMF along with 3 eq. of 2-(2-bromoethyl)isoindoline-1,3-
dione (58.8 mg, 0.232 mmol) and 4 eq. of DBU (1,8-diaza bicyclo [5.4.0]undec-7-
25 ene, 0.046 mL, 0.308 mmol). The vial was capped and shaken at 75 °C over night.
The crude reaction mixture was evaporated, taken up in 2 mL of acetonitrile and
purified using a Shimadzu preparative HPLC employing acetonitrile/water/ 0.1%

trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a XTERRA® C18 19 x 100mm column at a gradient of 25-100% B and a flow rate of 25 mL/min. over 12 minutes with a 8 minute hold. The solvent was evaporated yielding 10.7mgs of the phthalimide intermediate as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade methanol), in 4 minutes with a 1 minute hold at a rate of 4 mL/minute. LCMS *m/z* 694.4 (M+H), *Rt* = 3.128 min., 93.7% purity. To a small screw cap vial was added the phthalimide intermediate, 5-(2-(2-(1,3-dioxoisindolin-2-yl)ethoxy)-5-(1-phenylcyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (10.7 mg, 0.015 mmol) in 2mL of methanol and anhydrous hydrazine (0.780 µL, 0.025 mmol). The vial was placed in a pre-equilibrated oil bath set to 75°C and the solution refluxed for 90minutes. The product was cooled to room temperature and the solvent was evaporated. The resulting oil was diluted with 10mL of DCM, washed with 1mL of 0.5M NaOH and extracted. The solvent was evaporated and the crude product was taken up in 1.8 mL of acetonitrile and 200µL of DMF and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Sunfire C18 19 x 150mm column at a gradient of 20-100% B and a flow rate of 20 mL/min. over 20 minutes with a 5 minute hold. The solvent was evaporated giving 7.0 mgs (14% yield, 2 steps) of 5-(2-(2-aminoethoxy)-5-(1-phenyl cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide, TFA as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Sunfire 5µm C18, 4.6 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC

grade methanol), in 4 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/ 0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Gemini C18 3.0 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.21 - 1.27 (m, 2 H), 1.28 - 1.35 (m, 2 H), 2.89 (d, *J*=4.77 Hz, 3 H), 3.39 (t, *J*=4.77 Hz, 2 H), 4.38 (t, *J*=5.02 Hz, 2 H), 7.05 - 7.13 (m, 1 H), 7.16 - 7.28 (m, 5 H), 7.29 - 7.35 (m, 2 H), 7.49 - 7.60 (m, 2 H), 7.62 (br. s., 1 H), 7.87 (dd, *J*=8.53, 2.26 Hz, 1 H), 7.96 - 8.05 (m, 3 H), 8.07 (d, *J*=1.00 Hz, 1 H), 8.30 (s, 1 H). LCMS Rt = 2.023 min., *m/z* 564.3 (M+H). HPLC Rt = 6.931 min. (Sunfire C18), 100 % purity and 11.423 min. (Gemini C18), 98.9 % purity.



5-(2-(2-Aminoethoxy)-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide, 2 TFA

[00448] The LC/MS data was obtained on a Shimadzu analytical LC /
 25 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:
 PHENOMENEX® Luna 3 μ m C18, 2 x 50mm column, with a gradient of 0-100%B

(B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a

5 Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1%trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was

10 then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5%

15 HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.23 - 1.33 (m, 2 H), 1.60 - 1.67 (m, 2 H), 2.89 (d, *J*=4.77 Hz, 3 H), 3.41 (t, *J*=5.14 Hz, 2 H), 4.40 (t, *J*=5.14 Hz, 2 H), 6.58 (br. s., 2 H), 7.01 - 7.11 (m, 1 H), 7.16 - 7.29 (m, 3 H), 7.46 (d, *J*=8.03 Hz, 1 H), 7.52 - 7.70 (m, 4 H), 7.93 (dd, *J*=8.53, 2.26 Hz, 1 H), 7.98 - 8.05 (m, 3 H), 8.07 (s, 1 H),

20 8.41 (d, *J*=4.77 Hz, 1 H), 8.56 (s, 1 H). LCMS *m/z* 565.4 (M+H), *R*_t = 1.628 min. HPLC (Sunfire C18) *R*_t = 5.048 min., 99.9% purity and (XBridge phenyl C18) *R*_t = 10.531 min., 100% purity.

5-Bromo-2,4-dimethoxy-*N*-(1-(pyridin-2-yl)cyclopropyl)benzamide

25 [00449] To a 250mL round-bottomed flask was added chloroform (60 mL) along with 2,4-dimethoxybenzoic acid (2.0 g, 10.98 mmol). The solution was cooled to 0 °C and bromine (0.566 mL, 10.98 mmol) was added dropwise over 5 minutes. The solution was allowed to warm to room temperature and stirred overnight. The resulting solid was filtered, washed with cold chloroform and dried under vacuum to

30 give 2.49g (8.6mmol, 78% yield) of 5-bromo-2,4-dimethoxybenzoic acid as a yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:

PHENOMENEX® Luna 3µm C18, 2 x 30mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 2 minutes with a 1 minute hold at a rate of 1.0 mL/minute. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.88 (s, 3 H), 3.95 (s, 3 H), 6.78 (s, 1 H), 7.86 (s, 1 H). LCMS Rt = 1.453min., m/z 262.99 (M+H), 93% purity.

[00450] To a 2 dram vial was added 5-bromo-2,4-dimethoxybenzoic acid (1.044 g, 4mmol), DMF (48.2 mL), *N,N*-Diisopropylethylamine (2.79 mL, 16.00 mmol), 1-(pyridin-2-yl)cyclopropanamine, 2 HCl (0.911 g, 4.40 mmol), and finally HATU (2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethyl isouronium hexafluorophosphate(V), 6.08 g, 16.00 mmol). The vial was capped and shaken for 16 hours at room temperature. The crude reaction mixture was diluted with 10mL of DCM, washed with 5mL of 1M HCl, extracted, washed with 20mL of brine, and dried over magnesium sulfate. The solution was pushed through a plug of silica gel and evaporated to dryness. Trituration with 20mL of diethyl ether gave 1.6grams of 5-bromo-2,4-dimethoxy-*N*-(1-(pyridin-2-yl)cyclopropyl)benzamide as a tan solid (76% yield). ¹H NMR (400 MHz, THF-d₈) δ ppm 1.22 - 1.32 (m, 2 H), 1.59 - 1.67 (m, 2 H), 3.94 (s, 3 H), 4.02 (s, 3 H), 6.72 (s, 1 H), 7.09 (m, 1 H), 7.47 (d, *J*=8.03 Hz, 1 H), 7.62 (td, *J*=7.72, 1.88 Hz, 1 H), 8.20 (s, 1 H), 8.39 - 8.52 (m, 2 H). LCMS Rt = 2.162 min., m/z 379.2 (M+2H), 96 % purity.

5-Bromo-2-methoxy-4-methylbenzoic acid

[00451] The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:

25 Waters Sunfire 5µm C18, 4.6 x 30mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 2 minutes with a 1 minute hold at a rate of 4 mL/minute. Yellow solid, 63.5% yield. LCMS Rt = 1.545 min., m/z 246.99 (M+H), 90 % purity. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.21 - 2.44 (m, 3 H), 3.82 (s, 3 H), 7.17 (s, 1 H), 7.78 (s, 1 H), 12.72 (br. s., 1 H).

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5-Bromo-2-methoxy-4-methyl-*N*-(1-(pyridin-2-yl)cyclopropyl)benzamide

[00452] The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2.0 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. Tan solid, 68% yield, 100% purity. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.34 - 1.42 (m, 2 H), 1.58 - 1.66 (m, 2 H), 2.39 (s, 3 H), 3.96 (s, 3 H), 7.05 (s, 1 H), 7.40 (dd, *J*=6.90, 5.90 Hz, 1 H), 7.76 (d, *J*=8.03 Hz, 1 H), 7.97 (td, *J*=7.78, 1.76 Hz, 1 H), 8.10 (s, 1 H), 8.60 (d, *J*=5.27 Hz, 1 H), 8.88 (s, 1 H). LCMS Rt = 3.525 min., *m/z* 362.88 (M+H), 98 % purity.

Methyl 4-hydroxy-2-methoxybenzoate

15 [00453] To a 250mL Erlenmeyer flask was added methyl 4-amino-2-methoxybenzoate (7.5 g, 41.4 mmol) and a 25% solution of sulfuric acid (40 mL, 188 mmol). The solution was cooled to 0°C and a saturated solution of sodium nitrite (4.29 g, 62.2 mmol) was added drop wise. The orange mixture was stirred for 15 minutes. The resulting diazonium solution was then very slowly poured into a 1L
20 flask containing 500mL of 3% sulfuric acid. The solution was stirred for 5 minutes then transferred to a separatory funnel. The reaction mixture was diluted with 150mL of DCM, extracted, dried over magnesium sulfate and concentrated. to a red solid. The resulting solid was triturated with hexane to give 5.71 grams of the desired phenol as a red powder (73% yield). The LC/MS data was obtained on a Shimadzu
25 analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 30mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 2 minutes with a 1 minute hold at a rate of 4 mL/minute. ¹H
30 NMR (400 MHz, DMSO-d₆) δ ppm 3.67 - 3.72 (m, 3 H), 3.74 (s, 3 H), 6.39 (dd, *J*=8.66, 2.13 Hz, 1 H), 6.45 (d, *J*=2.13 Hz, 1 H), 7.59 (d, *J*=8.66 Hz, 1 H). LCMS Rt = 1.070 min., *m/z* 183.09 (M+H), 96% purity.

Methyl 4-(2-amino-2-oxoethoxy)-5-bromo-2-methoxybenzoate

[00454] To a sealed tube was added 2-bromoacetamide (2.272 g, 16.47 mmol), DMF (50 mL), cesium carbonate (7.15 g, 21.96 mmol) and methyl 4-hydroxy-2-methoxybenzoate (1.00 g, 5.49 mmol). The tube was sealed and heated for 16 hours at 85 °C. The reaction mixture was diluted with DCM, washed sequentially with 10mL of 1M HCl, water, and brine. The solution was dried over sodium sulfate, filtered and the solvent removed to give 1.2 grams of methyl 4-(2-amino-2-oxoethoxy)-2-methoxybenzoate (78% yield) as a yellow powder. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 30mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 2 minutes with a 1 minute hold at a rate of 4 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 3.71 - 3.76 (m, 3 H), 3.80 - 3.84 (m, 3 H), 4.45 (s, 2 H), 6.56 (dd, *J*=8.66, 2.38 Hz, 1 H), 6.65 (d, *J*=2.26 Hz, 1 H), 6.77 (br. s., 1 H), 6.92 (br. s., 1 H), 7.75 (d, *J*=8.78 Hz, 1 H). LCMS Rt = 1.385 min., *m/z* 240.2 (M+H), 92% purity.

[00455] To a 250mL round-bottomed flask was added methyl 4-(2-amino-2-oxoethoxy)-2-methoxybenzoate (1.2 g, 5.14 mmol) and chloroform (40 mL). The mixture was placed under a nitrogen atmosphere and cooled to 0 °C. Bromine (0.263 mL, 5.14 mmol) was added drop wise (in 3mL of chloroform) and the solution was allowed to warm to room temperature overnight. The orange solid was cooled with an ice bath, filtered, washed sequentially with cold chloroform, then diethyl ether. The product was dried under vacuum giving 1.7 grams (91% yield) of methyl 4-(2-amino-2-oxoethoxy)-5-bromo-2-methoxybenzoate as an orange solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 30mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 2 minutes with a 1 minute hold at a rate of 4 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 3.76 (s, 3 H), 3.88 (s,

3 H), 4.63 (s, 2 H), 6.76 (s, 1 H), 7.10 (br. s., 2 H), 7.96 (s, 1 H). LCMS Rt = 1.793 min., m/z 319.1 (M+H), 90% purity.

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5-(2,4-Dimethoxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00456] To a microwave vial was added 5-bromo-2,4-dimethoxy-*N*-(1-(pyridin-2-yl)cyclopropyl)benzamide (41.5 mg, 0.110 mmol), 2-(4-fluorophenyl)-*N*-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide (39.5 mg, 0.1 mmol), dioxane (2.00 mL), water (0.200 mL), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos, 8.21 mg, 0.020 mmol), tribasic potassium phosphate (85 mg, 0.400 mmol) and palladium(II) acetate (4.49 mg, 0.020 mmol). The solvent was removed and the crude reaction mixture was taken up in 2 mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 3.5 μ m C18 4.6x150mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 20 minutes with a 10 minute hold. The solvent was evaporated giving 18.1mgs (30.4% yield) of the desired pyridylcarboxamide as a yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 10 μ m C18, 3.0 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 4 minutes with a 1 minute hold at a rate of 5 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a PHENOMENEX® Gemini C18 3.0 μ m 4.6 x

150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute
 5 hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.26 - 1.37 (m, 2 H), 1.60 - 1.67 (m, 2 H), 2.89 (d, *J*=4.77 Hz, 3 H), 3.87 (s, 3 H), 4.07 (s, 3 H), 6.78 (s, 1 H), 7.10 - 7.23 (m, 3 H), 7.39 - 7.44 (m, 1 H), 7.46 - 7.52 (m, 2 H), 7.57 (d, *J*=7.78 Hz, 1 H), 7.68 (td, *J*=7.72, 1.63 Hz, 1 H), 7.74 (d, *J*=1.25 Hz, 1 H), 8.09 (s, 1 H), 8.11 - 8.19 (m, 2 H), 8.47 (d, *J*=4.52 Hz, 1 H), 8.59 (s, 1 H). LCMS *m/z* 566.2 (M+H), Rt
 10 = 2.608 min. HPLC (Sunfire C18) Rt = 6.816min, 93.9% purity and (Gemini C18) Rt = 11.676min., 95.8% purity.

2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide

15 [00457] Alternative synthesis. To a sealed tube was added 5-bromo-2-methoxy-4-methyl-*N*-(1-(pyridin-2-yl)cyclopropyl) benzamide (1.9024 g, 5.27 mmol), dioxane (70 mL), 2-(4-fluorophenyl)-*N*-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide (2.529 g, 6.40 mmol), cesium carbonate (2.57 g, 7.90 mmol), water (14.00 mL) and finally tetrakis(triphenylphosphine)palladium(0) (0.304
 20 g, 0.263 mmol). The vessel was sealed and heated for 16 hours at 85 °C in an oil bath. The mixture was cooled to room temperature, diluted with 20 ml of DCM and pushed through a plug of CELITE®. The resulting dark solution was concentrated to a grey oil. To this residue was added 20 ml of 0.5N HCl, followed by 20 ml of water. The flask was cooled in an ice bath for 30minutes and the resulting solids were
 25 collected by filtration and washed with 10 ml of water and dried under vacuum. The crude product was taken up in 1:1 ethyl acetate/ hexane and pushed through a plug of silica gel. Solvent was removed giving 1.65grams of the product as a light tan solid.

Methyl 4-(2-amino-2-oxoethoxy)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoate

30 [00458] To a sealed tube was added methyl 4-(2-amino-2-oxoethoxy)-5-bromo-2-methoxybenzoate (318 mg, 1.0 mmol), dioxane (30 mL), water (6.00 mL), 2-(4-

fluorophenyl)-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide (593 mg, 1.500 mmol), cesium carbonate (489 mg, 1.500 mmol), and tetrakis(triphenylphosphine)palladium(0) (23.11 mg, 0.020 mmol). The vessel was sealed and the mixture heated overnight at 85 °C. The reaction mixture was cooled, 5 diluted with 200mL of DCM, washed sequentially with 50mL of 1M HCl then brine. The product was extracted and the resulting yellow solution was evaporated to dryness. The aqueous layers were combined, cooled for 5minutes in an ice bath and the solids that formed were filtered and dried under vacuum. The solids were then combined and triturated sequentially with diethyl ether then ice cold acetonitrile 10 (10mL each) giving 171.6mgs (30% yield) of methyl 4-(2-amino-2-oxoethoxy)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoate as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B 15 (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/ 0.1% 20 trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters 25 Phenyl XBridge C18 3.5µm 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, 30 CD₃OD) δ ppm 3.04 (s, 3 H), 3.92 (s, 3 H), 4.03 (s, 3 H), 4.71 (s, 2 H), 6.85 (s, 1 H), 7.33 (t, *J*=8.78 Hz, 2 H), 7.57 - 7.64 (m, 1 H), 7.66 - 7.73 (m, 1 H), 7.87 (s, 1 H), 7.96 (s, 1 H), 8.00 - 8.08 (m, 2 H). LCMS *m/z* 507.3 (M+H), *Rt* = 2.635 min. HPLC *Rt* =

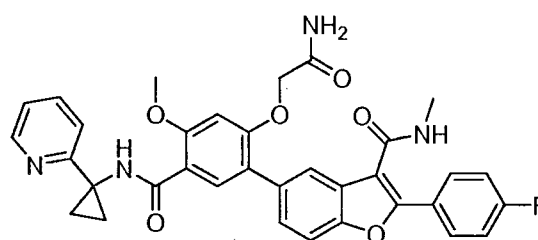
8.193 min. (Sunfire C18), 100 % purity and Rt = 10.678 min. (Phenyl XBridge C18), 100 % purity.

4-(2-Amino-2-oxoethoxy)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoic acid

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[00459] To a 50mL round-bottomed flask was added methyl 4-(2-amino-2-oxoethoxy)-5-(2-(4-fluorophenyl)-3-(methyl carbamoyl)benzofuran-5-yl)-2-methoxybenzoate (171.6 mg, 0.295 mmol) in a 1:1 mixture of methanol (7mL) and THF (7 mL). To this solution was then added 4 eq. of 1M aqueous sodium hydroxide
10 (1.2 mL, 1.2 mmol). The reaction mixture was stirred overnight at room temperature. Solvent was removed and the crude product was diluted with 50mL of 1:1 DCM/ethyl acetate, washed sequentially with 10mL of 1M HCl then brine. The product solution was dried over sodium sulfate, filtered and evaporated to dryness. The aqueous layers were combined, cooled in an ice bath and the product that formed on the sides of the
15 flask were filtered and dried under vacuum. The solids were combined, taken up in 10mL of DMF and purified using a Shimadzu preparative HPLC employing methanol/water/ trifluoroacetic acid where solvent A was 10% methanol / 90% water / 0.1% trifluoroacetic acid and solvent B was 10% water / 90% methanol / 0.1% trifluoroacetic acid with a PHENOMENEX® Luna 10µm C18 30x100mm column at
20 a gradient of 40-100% B and a flow rate of 40 mL/min. over 12 minutes with a 10 minute hold. Solvent was removed giving 87mgs (60% yield) of 4-(2-amino-2-oxoethoxy)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxybenzoic acid as a white powder. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the
25 following set of conditions: Waters Sunfire 5µm C18, 4.6 x 30mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 2 minutes with a 1 minute hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm
30 and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/ 0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A =

95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile),
 in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was
 then confirmed with an orthogonal solvent system and column using a Shimadzu
 analytical LC with a Waters XBridge phenyl C18 3.5µm 4.6 x 150mm column
 5 employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-
 100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC
 grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5%
 HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1
 mL/minute. ¹H NMR (400 MHz, DMF-d₇) δ ppm 2.97 (d, *J*=4.52 Hz, 3 H), 4.02 (s, 3
 10 H), 4.79 (s, 2 H), 6.97 (s, 1 H), 7.31 (br. s., 1 H), 7.38 - 7.46 (m, 2 H), 7.51 (br. s., 1
 H), 7.67 - 7.77 (m, 2 H), 7.92 (s, 1 H), 7.95 (s, 1 H), 8.09 - 8.16 (m, 2 H), 8.35 (d, 1
 H). LCMS *m/z* 493.00 (M+H), *R*_t = 1.618 min. HPLC (Sunfire C18) *R*_t = 7.108 min,
 100% purity and (XBridge phenyl C18) *R*_t = 6.383 min., 99.3% purity.

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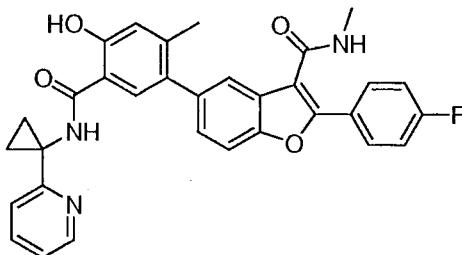


5-(2-(2-Amino-2-oxoethoxy)-4-methoxy-5-(1-(pyridin-2-
 yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-
 carboxamide

[00460] To a 25mL flask was added 4-(2-amino-2-oxoethoxy)-5-(2-(4-
 20 fluorophenyl)-3-(methyl carbamoyl)benzofuran-5-yl)-2-methoxybenzoic acid (48.8
 mg, 0.099 mmol), DMF (2 mL), *N*-ethyl-*N*-diisopropylpropan-2-amine (0.069 mL,
 0.396 mmol), 1-(pyridin-2-yl)cyclopropanamine (19.94 mg, 0.149 mmol) and finally
 HATU (2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethyl isouronium
 hexafluorophosphate(V), 151 mg, 0.396 mmol). The flask was sealed with a septa,
 25 placed under N₂ and stirred at room temperature overnight. The crude product was
 purified using a Shimadzu preparative HPLC employing acetonitrile/water/
 trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1%
 trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1%

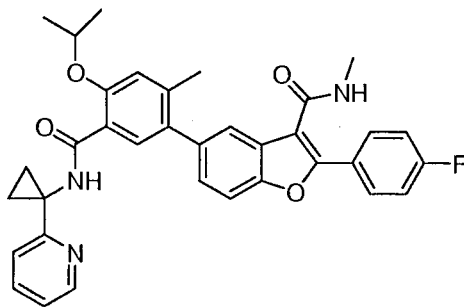
trifluoroacetic acid with a Waters Sunfire 5 μ m C18 19 x 150mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 22 minutes with a 8 minute hold. The solvent was removed giving 53.0mgs (87% yield) of 5-(2-(2-amino-2-oxoethoxy)-4-methoxy-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl) phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide as a yellow powder. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3 μ m C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, DMF-d₇) δ ppm 1.46 - 1.53 (m, 2 H), 1.69 - 1.76 (m, 2 H), 2.96 (d, *J*=4.77 Hz, 3 H), 4.16 (s, 3 H), 4.82 (s, 2 H), 7.04 (s, 1 H), 7.34 (br. s., 1 H), 7.36 - 7.48 (m, 3 H), 7.52 (br. s., 1 H), 7.66 - 7.78 (m, 3 H), 7.92 - 8.01 (m, 2 H), 8.03 (d, *J*=2.76 Hz, 1 H), 8.08 - 8.14 (m, 2 H), 8.36 (d, *J*=4.77 Hz, 1 H), 8.57 - 8.62 (m, 1 H), 8.94 (s, 1 H). LCMS *m/z* 609.5 (M+H), *Rt* = 2.030 min. HPLC (Sunfire C18) *Rt* = 5.800 min, 99.4% purity and (XBridge phenyl C18) *Rt* = 9.546 min., 99.7% purity.

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2-(4-Fluorophenyl)-5-(4-hydroxy-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide

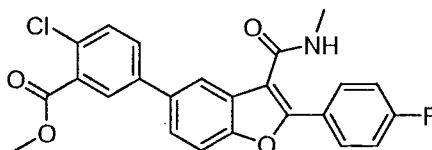
- [00461] To a 250mL round-bottomed flask was added 2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide (1.0008 g, 1.821 mmol), and DCM (18 mL). The solution was placed under an atmosphere of nitrogen and cooled to 0 °C. To the tan mixture was added dropwise 1M trichloroborane (9.10 mL, 9.10 mmol). The mixture was allowed to slowly warm to room temperature overnight. The reaction mixture was cooled to 0 °C and 100mL of cold methanol was added and the mixture stirred for 30minutes then evaporated to near dryness. The addition of methanol followed by evaporation was repeated to give a tan solid (82% yield). The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 95% HPLC grade acetonitrile/ 10mM Ammonium acetate/ 5% HPLC grade water), (A = 95% HPLC grade water / 10mM Ammonium acetate/ 5% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.26 - 1.37 (m, 2 H), 1.57 - 1.66 (m, 2 H), 2.28 (s, 3 H), 3.02 (d, *J*=4.02 Hz, 3 H), 6.77 (s, 1 H), 7.18 (t, *J*=8.78 Hz, 3 H), 7.32 (d, *J*=8.28 Hz, 1 H), 7.51 (d, *J*=8.53 Hz, 1 H), 7.69 - 7.79 (m, 1 H), 7.83 - 7.97 (m, 3 H), 8.08 (s, 1 H), 8.22 - 8.39 (m, 4 H), 8.66 (br. s., 1 H). LCMS *m/z* 536.5 (M+H), 534.4 (M - H), *R*_t = 3.446 min., 90% purity.



2-(4-Fluorophenyl)-5-(4-isopropoxy-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide, TFA

- [00462] To a microwave vial was added 2-(4-fluorophenyl)-5-(4-hydroxy-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide (16.6 mg, 0.031 mmol), dioxane (2 mL), triphenylphosphine (32.5 mg, 0.124 mmol), (*E*)-di-*tert*-butyl diazene-1,2-dicarboxylate (21.41 mg, 0.093 mmol) and propan-2-ol (5.92 μ L, 0.077 mmol). The vial was sealed and subjected to microwave heating (140°C) for 20 minutes. The crude product was purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5 μ m C18 19 x 150mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 20 minutes with a 5 minute hold. The solvent was removed giving 6mgs (25% yield) of 2-(4-fluorophenyl)-5-(4-isopropoxy-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-*N*-methylbenzofuran-3-carboxamide as a colorless powder. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3 μ m C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5 μ m 4.6 x 150mm column employing water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10

minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/ 10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 1.24 - 1.31 (m, 2 H), 1.46 (d, *J*=6.02 Hz, 6 H), 1.64 - 1.69 (m, 2 H), 2.29 (s, 3 H), 2.89 (d, *J*=4.52 Hz, 3 H), 4.83 - 4.95 (m, 1 H), 6.98 - 7.04 (m, 1 H), 7.07 (s, 1 H), 7.16 - 7.24 (m, 2 H), 7.26 (dd, *J*=8.28, 1.76 Hz, 1 H), 7.47 (d, *J*=8.03 Hz, 2 H), 7.52 - 7.59 (m, 2 H), 7.62 (d, *J*=1.26 Hz, 1 H), 7.95 (s, 1 H), 8.11 - 8.19 (m, 2 H), 8.36 - 8.43 (m, 1 H), 8.61 (s, 1 H). LCMS *m/z* 578.4 (M+H), *Rt* = 2.746 min. HPLC (Sunfire C18) *Rt* = 7.695 min, 98.38% purity and (XBridge phenyl C18) *Rt* = 12.003 min., 95.9 % purity.

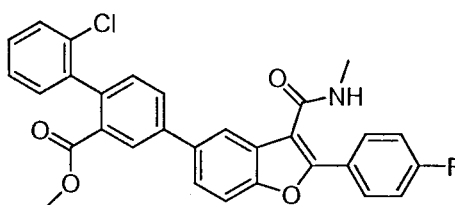


Methyl 2-chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate

[00463] To a 150mL sealed tube was added 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (0.5 g, 1.198 mmol), dioxane (7.18 mL), water (1.437 mL), tetrakis (triphenylphosphine)palladium(0) (0.028 g, 0.024 mmol), 4-chloro-3-(methoxycarbonyl) phenyl boronic acid (0.385 g, 1.797 mmol), and cesium carbonate (0.586 g, 1.797 mmol). The tube was sealed and heated in an oil bath overnight at 85 °C. The reaction mixture was cooled; the crude product was diluted with 100mL of ethyl acetate, washed sequentially with 50mL of water then brine. The product solution was dried over magnesium sulfate and filtered. Solvent was evaporated to give a crude yellow solid. The solid was triturated with diethyl ether (30mL x2) and hexane (30mL x1) then dried under vacuum to give 394mgs of a ivory colored solid (53% yield). The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at

220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute
 5 hold at a rate of 0.8 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 2.92 (d, *J*=4.77 Hz, 3 H), 3.91 (s, 3 H), 7.18 - 7.27 (m, 2 H), 7.52 - 7.55 (m, 1 H), 7.57 (d, *J*=8.53 Hz, 1 H), 7.63 (d, *J*=1.25 Hz, 2 H), 7.82 (dd, *J*=8.41, 2.38 Hz, 1 H), 7.96 - 8.00 (m, 1 H), 8.09 - 8.17 (m, 3 H). LCMS *m/z* 438.3 (M+H), *Rt* = 3.518 min., 90 %purity.

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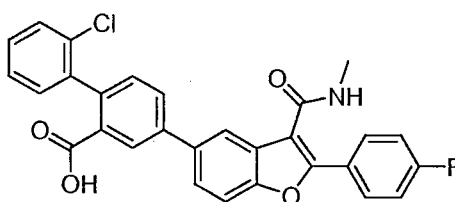


Methyl 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylate

[00464] To a microwave vial was added dioxane (6 mL), water (0.600 mL), dicyclohexyl(2',6'-dimethoxy biphenyl-2-yl)phosphine (S-Phos, 16.42 mg, 0.040
 15 mmol), methyl 2-chloro-5-(2-(4-fluorophenyl)-3-(methyl carbamoyl)benzofuran-5-yl)benzoate (87.6 mg, 0.2 mmol), tribasic potassium phosphate (0.170 g, 0.800 mmol), palladium(II) acetate (8.98 mg, 0.040 mmol), and 2-chlorophenylboronic acid (0.094 g, 0.600 mmol). The vial was capped, degassed, flushed with N₂ and heated in the microwave for 10 minutes at 130 °C. The solvent was removed and the crude
 20 reaction mixture was taken up in 4 mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5µm C18 19x150mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 20
 25 minutes with a 10 minute hold. The solvent was removed to give 43.8mgs (80%yield) of methyl 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylate as a yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna

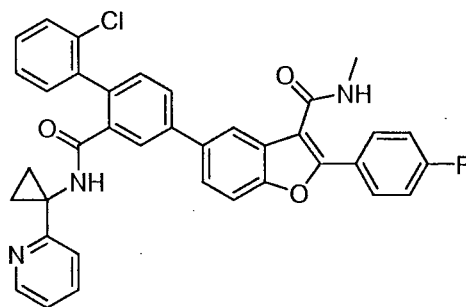
3 μ m C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm
 5 2.92 - 2.97 (m, 3 H), 3.60 - 3.62 (m, 3 H), 7.19 - 7.26 (m, 2 H), 7.27 - 7.34 (m, 3 H), 7.37 (d, *J*=8.03 Hz, 1 H), 7.41 - 7.45 (m, 1 H), 7.46 - 7.52 (m, 1 H), 7.62 - 7.67 (m, 1 H), 7.68 - 7.73 (m, 1 H), 7.92 (dd, *J*=7.91, 2.13 Hz, 1 H), 8.05 (d, *J*=1.25 Hz, 1 H), 8.12 - 8.19 (m, 2 H), 8.29 (d, *J*=2.01 Hz, 1 H). LCMS *m/z* 514.2 (M+H), *Rt* = 3.908 min., 93% purity.

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2'-Chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylic acid

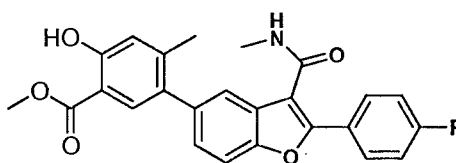
[00465] To a 25mL round-bottomed flask was added methyl 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylate (43.8
 15 mg, 0.079 mmol), methanol (1 mL), THF (1 mL) and 8 equivalents of a 1M solution of sodium hydroxide (0.63 mL, 0.63 mmol). The mixture was stirred at room temperature for 48 hours. The crude product was diluted with 20mL of ethyl acetate, made acidic with 0.5M HCl, extracted, washed with brine, dried over sodium sulfate,
 20 filtered and evaporated to dryness giving 47.2mgs (96% yield) of 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-methylbiphenyl-2-carboxylic acid as yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:
 25 (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. LCMS *m/z* 500.2 (M+H), *Rt* = 3.426 min., 90% purity.



5-(2'-Chloro-2-(1-(pyridin-2-yl)cyclopropylcarbamoyl)biphenyl-4-yl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

- [00466] To a 25mL flask was added 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylic acid (39.6 mg, 0.079 mmol), DMF (2 mL), *N*-ethyl-*N,N*-isopropylpropan-2-amine (0.055 mL, 0.317 mmol), 1-(pyridin-2-yl) cyclopropanamine (15.94 mg, 0.119 mmol), and finally HATU (2-(3H-[1,2,3]triazolo [4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (V), (120 mg, 0.317 mmol). The flask was sealed and the mixture stirred over night at room temperature. The crude product was purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5µm C18 19 x 150mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 20 minutes with a 10 minute hold. Solvent was removed giving 40.7mgs (70% yield) of 5-(2'-chloro-2-(1-(pyridin-2-yl)cyclopropylcarbamoyl)biphenyl-4-yl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A =

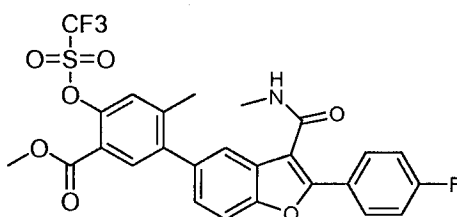
95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile),
 in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was
 then confirmed with an orthogonal solvent system and column using a Shimadzu
 analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column
 5 employing water/methanol/10mM ammonium bicarbonate with a gradient of 10-
 100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC
 grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5%
 HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1
 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 0.90 - 1.10 (m, 2 H), 1.42 - 1.53 (m,
 10 2 H), 2.94 (d, *J*=4.52 Hz, 3 H), 7.11 (dd, *J*=6.90, 5.40 Hz, 1 H), 7.18 - 7.27 (m, 2 H),
 7.30 - 7.43 (m, 5 H), 7.44 - 7.49 (m, 1 H), 7.52 - 7.58 (m, 1 H), 7.59 - 7.67 (m, 2 H),
 7.73 (dd, *J*=8.53, 1.76 Hz, 1 H), 7.81 (dd, *J*=7.78, 2.01 Hz, 1 H), 7.95 - 8.01 (m, 2 H),
 8.06 (d, *J*=1.51 Hz, 1 H), 8.09 - 8.17 (m, 2 H), 8.41 (d, *J*=4.02 Hz, 1 H). LCMS *m/z*
 617.3 (M+H), *R*_t = 2.765 min. HPLC (Sunfire C18) *R*_t = 7.823 min, 100% purity and
 15 (XBridge phenyl C18) *R*_t = 11.871min., 99.8% purity.



Methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-hydroxy-4-
 methylbenzoate

20 **[00467]** To a 100mL round-bottomed flask was added methyl 5-(2-(4-
 fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoate
 (350.5 mg, 0.783 mmol) in DCM (8 mL). To this solution was then added, under
 nitrogen, a 1M solution of boron trichloride (3.92 mL, 3.92 mmol) and the mixture
 was stirred overnight at room temperature. The reaction mixture was cooled in an ice
 25 bath and 10mL of methanol was slowly added. The solvent was removed under
 vacuum. The flask was again cooled, 25mL of ice cold methanol was added and the
 resulting solid was filtered to give 264.5mgs (78% yield) of methyl 5-(2-(4-
 fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-hydroxy-4-methylbenzoate as
 an ivory colored solid. The LC/MS data was obtained on a Shimadzu analytical LC /
 30 MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions:

PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. ¹H NMR (400 MHz, DMF-d₇) δ ppm 2.30 (s, 3 H), 2.95 (d, *J*=4.77 Hz, 3 H), 3.98 (s, 3 H), 7.02 (s, 1 H), 7.38 - 7.48 (m, 3 H), 7.68 - 7.73 (m, 2 H), 7.76 (d, *J*=8.53 Hz, 1 H), 8.08 - 8.15 (m, 2 H), 8.33 (br. s., 1 H). LCMS Rt = 3.636, *m/z* 434.3 (M+H), 100% purity.

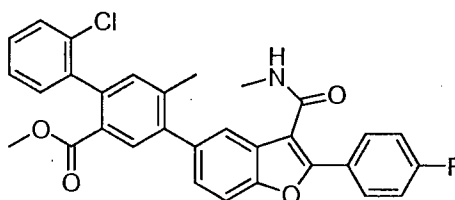


10 Methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methyl-2-(trifluoromethylsulfonyloxy)benzoate

[00468] To a 25mL round-bottomed flask was added methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-hydroxy-4-methylbenzoate (260 mg, 0.600 mmol), DCM (6 mL), triethylamine (0.166 mL, 1.200 mmol) and 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (321 mg, 0.900 mmol). The solution was stirred overnight at room temperature. To the reaction mixture was then added DMF (6mL) along with triethylamine (0.166 mL, 1.200 mmol) and 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (321 mg, 0.900 mmol). The mixture was heated to 65 °C for forty eight hours. The crude product mixture was returned to room temperature, diluted with 100mL of DCM, washed sequentially with 50mL of cold 0.1M HCl, water and brine. The solvent was evaporated and the resulting crude product was triturated with 10mL of diethyl ether (x2) to give 180.7mgs (44.7% yield) of an ivory colored solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute

hold at a rate of 0.8 mL/minute. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 2.37 (s, 3 H), 2.82 (d, *J*=4.58 Hz, 3 H), 3.88 (s, 3 H), 7.36 - 7.47 (m, 3 H), 7.56 - 7.65 (m, 2 H), 7.78 (d, *J*=8.54 Hz, 1 H), 7.91 (s, 1 H), 7.95 - 8.05 (m, 2 H), 8.47 (d, 1 H). LCMS *m/z* 566.3 (M+H), *R*_t = 3.913 min., 90% purity.

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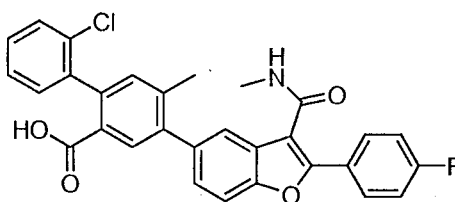


Methyl 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-methylbiphenyl-2-carboxylate

[00469] To a small sealed tube was added methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methyl-2-(trifluoromethylsulfonyloxy)benzoate (67.3 mg, 0.1 mmol), dioxane (3 mL), water (0.600 mL), 2-chlorophenylboronic acid (18.76 mg, 0.120 mmol), cesium carbonate (32.6 mg, 0.100 mmol) and tetrakis(triphenylphosphine)palladium(0) (2.311 mg, 2.000 μmol). The tube was sealed and heated overnight at 80 °C. The reaction was cooled to room temperature, filtered through a plug of CELITE® and concentrated to near dryness under a stream of nitrogen. The crude reaction mixture was taken up in 6 mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 3.5μm C18 19 x 150mm column at a gradient of 30-100% B and a flow rate of 25 mL/min. over 20 minutes with a 10 minute hold. The solvent was removed giving 48mgs (89% yield) of methyl 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-methylbiphenyl-2-carboxylate as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3μm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid / 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid / 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of

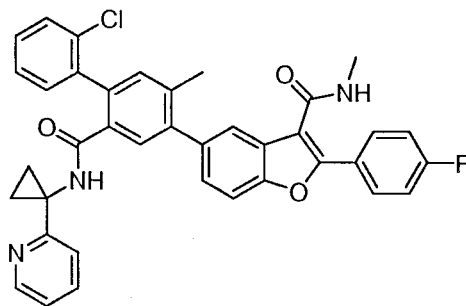
0.8 mL/minute. ^1H NMR (500 MHz, THF-d_8) δ ppm 2.35 (s, 3 H), 2.91 (d, $J=4.58$ Hz, 3 H), 3.57 (s, 3 H), 7.21 - 7.26 (m, 3 H), 7.27 - 7.30 (m, 1 H), 7.30 - 7.34 (m, 2 H), 7.38 (dd, $J=8.39$, 1.68 Hz, 1 H), 7.41 - 7.44 (m, 1 H), 7.50 (d, $J=4.27$ Hz, 1 H), 7.63 (d, $J=8.24$ Hz, 1 H), 7.75 (d, $J=1.53$ Hz, 1 H), 7.92 (s, 1 H), 8.13 - 8.19 (m, 2 H).

5 LCMS m/z 528.4 (M+H), R_t = 4.036 min., 98.3% purity.



2'-Chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-methylbiphenyl-2-carboxylic acid

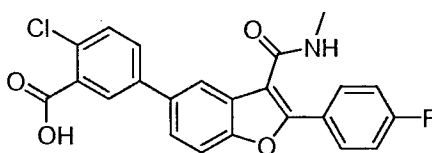
- 10 [00470] To a 25mL round-bottomed flask was added methyl 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-methylbiphenyl-2-carboxylate (48 mg, 0.091 mmol), THF (2.2 mL), methanol (2.2 mL), and aqueous 1M sodium hydroxide (0.728 mL, 0.728 mmol). The flask was sealed and stirred at room temperature for 48 hours. Volatiles were removed and the crude product was diluted
- 15 with 30mL of ethyl acetate, washed sequentially with 10mL of 1M HCl, brine, dried over sodium sulfate, filtered and evaporated to dryness. The resulting product was triturated with 10mL of diethyl ether giving 47.2mgs (96% yield) of 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-methylbiphenyl-2-carboxylic acid as a yellow solid. The LC/MS data was obtained on a Shimadzu
- 20 analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3 μ m C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8
- 25 mL/minute. ^1H NMR (400 MHz, DMF-d_7) δ ppm 2.42 (s, 3 H), 2.97 (d, $J=4.52$ Hz, 3 H), 7.30 (s, 1 H), 7.39 - 7.48 (m, 5 H), 7.50 - 7.57 (m, 2 H), 7.78 - 7.85 (m, 2 H), 7.99 (s, 1 H), 8.10 - 8.17 (m, 2 H), 8.35 - 8.43 (m, 1 H). LCMS m/z 514.3 (M+H), R_t = 3.950 min., 95.4% purity.



5-(2'-Chloro-5-methyl-2-(1-(pyridin-2-yl)cyclopropylcarbamoyl)biphenyl-4-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide, TFA

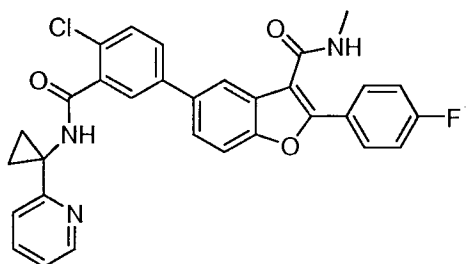
[00471] To a 25mL flask was added 2'-chloro-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-5-methylbiphenyl-2-carboxylic acid (47.2 mg, 0.087 mmol), DMF (2 mL), *N*-ethyl-*N,N*-diisopropyl propan-2-amine (0.061 mL, 0.349 mmol), 1-(pyridin-2-yl)cyclopropanamine (17.56 mg, 0.131 mmol) and finally HATU (2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V), 133 mg, 0.349 mmol). The flask was sealed with a septa, placed under N₂ and stirred at room temperature for 5 hours. The crude product was purified using a Shimadzu preparative HPLC employing acetonitrile/water/trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5μm C18 19 x 150mm column at a gradient of 30-100% B and a flow rate of 25 mL/min. over 20 minutes with a 10 minute hold. The solvent was evaporated to give 66.1mgs (92% yield) of 5-(2'-chloro-5-methyl-2-(1-(pyridin-2-yl)cyclopropyl carbamoyl)biphenyl-4-yl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide as a white solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3μm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5μm 4.6 x 150mm column employing water/acetonitrile/ trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95%

HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing
 5 water/methanol/10mM ammonium bicarbonate with a gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 0.85 - 0.96 (m, 1 H), 0.99 - 1.09 (m, 1 H), 1.38 - 1.53 (m, 2 H), 2.33 (s, 3 H), 2.90 (d, *J*=4.52 Hz, 3 H), 7.07 - 7.14 (m, 1 H), 7.20 - 7.28 (m, 3 H), 7.30 - 7.36 (m, 3 H), 7.37 - 7.42 (m, 2 H), 7.44 - 7.49 (m, 1 H), 7.56 (d, *J*=4.52 Hz, 1 H), 7.58 - 7.65 (m, 3 H), 7.77 (d, *J*=1.51 Hz, 1 H), 7.89 (s, 1 H), 8.10 - 8.18 (m, 2 H), 8.37 - 8.42 (m, 1 H). LCMS *m/z* 631.39 (M+H), *R*_t = 2.925 min. HPLC (Sunfire C18) *R*_t = 8.118 min, 99.9% purity and (XBridge phenyl C18) *R*_t =
 10 11.519min., 100% purity.



2-Chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid
[00472] Alternative Procedure: To a 150mL sealed tube was added 2-(4-
 20 fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (1.0 g, 2.4 mmol), dioxane (14.4 mL), water (2.9 mL), tetrakis(triphenyl phosphine)palladium(0) (0.055 g, 0.048 mmol), 5-borono-2-chlorobenzoic acid (0.720 g, 3.59 mmol), and cesium carbonate (1.171 g, 3.59 mmol). The tube was sealed and heated in an oil bath overnight at 85 °C. The reaction mixture was cooled,
 25 diluted with 150mL of ethyl acetate, washed sequentially with 20mL of 0.5M HCl then brine. The product solution was filtered through a plug of CELITE® then evaporated to dryness. The resulting solid was taken up in 10mL of 1:1 DMF and acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90%
 30 water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/

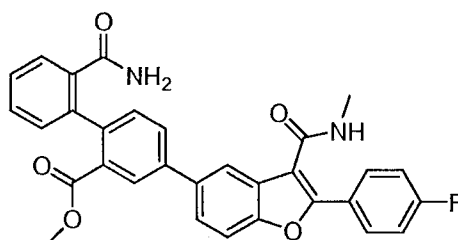
0.1% trifluoroacetic acid with a Waters Sunfire 3.5 μ m C18 4.6x150mm column at a gradient of 50-100% B and a flow rate of 40 mL/min. over 20 minutes with a 5 minute hold. Solvent was evaporated giving 319.5mgs (32.%yield) of 2-chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid as a white powder. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 10 μ m C18, 3.0 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade methanol/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade methanol), in 4 minutes with a 1 minute hold at a rate of 5 mL/minute. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.83 - 2.91 (m, 3 H), 7.35 - 7.45 (m, 2 H), 7.65 (d, *J*=8.53 Hz, 1 H), 7.69 - 7.75 (m, 1 H), 7.76 - 7.82 (m, 1 H), 7.85 - 7.93 (m, 2 H), 7.98 - 8.05 (m, 2 H), 8.08 (d, *J*=2.26 Hz, 1 H), 8.43 - 8.53 (m, 1 H), 13.50 (br. s., 1 H). LCMS *m/z* 424.0 (M+H), *Rt* = 3.105min., 100% purity.



5-(4-Chloro-3-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide

[00473] To a 250mL round-bottomed flask was added 2-chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (0.299 g, 0.705 mmol), 1-(pyridin-2-yl)cyclopropanamine (0.142 g, 1.058 mmol), DMF (8.50 mL), *N*-ethyl-*N*,*N*-diisopropylpropan-2-amine (0.493 mL, 2.82 mmol), and HATU (2-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V), 1.073 g, 2.82 mmol). The flask was sealed, placed under N₂ and stirred overnight at room temperature. The reaction mixture was diluted with 50mL of ethyl acetate, washed with 5mL of 1M HCl, extracted, dried over magnesium sulfate, filtered and evaporated to a red oil. The crude reaction mixture was then evacuated to near dryness, taken up in 8 mL of 1: 1 methanol and DMF and

purified using a Shimadzu preparative HPLC employing methanol/water/
trifluoroacetic acid where solvent A was 10% methanol / 90% water / 0.1%
trifluoroacetic acid and solvent B was 10% water / 90% methanol / 0.1%
trifluoroacetic acid with a PHENOMENEX® Luna 10µm C18 30x100mm column at
5 a gradient of 50-100% B and a flow rate of 40 mL/min. over 8 minutes with a 7
minute hold. Solvent was evaporated giving 261.3 mgs (66.4% yield) of 5-(4-chloro-
3-(1-(pyridin-2-yl)cyclopropyl carbamoyl)phenyl)-2-(4-fluorophenyl)-N-
methylbenzofuran-3-carboxamide as a light yellow solid. The LC/MS data was
obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at
10 220nm using the following set of conditions: Waters Sunfire 5µm C18, 4.6 x 50mm
column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1%
trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1%
trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 3 minutes with a 1 minute
hold at a rate of 4 mL/minute. HPLC purity was determined using a Shimadzu
15 analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm
column employing water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 20-
100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC
grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC
grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The
20 HPLC purity was then confirmed with an orthogonal solvent system and column
using a Shimadzu analytical LC with a PHENOMENEX® Gemini C18 3.0µm 4.6 x
150mm column employing water/methanol/ 10mM ammonium bicarbonate with a
gradient of 20-100% B (B = 95% HPLC grade methanol/ 10mM ammonium
bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM
25 ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute
hold at a rate of 1 mL/minute. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.33 - 1.40 (m,
2 H), 1.56 - 1.64 (m, 2 H), 2.83 - 2.91 (m, 3 H), 7.27 (dd, *J*=6.78, 5.27 Hz, 1 H), 7.35
- 7.45 (m, 2 H), 7.63 (d, *J*=8.28 Hz, 1 H), 7.69 - 7.96 (m, 7 H), 7.97 - 8.06 (m, 2 H),
8.50 (d, *J*=4.52 Hz, 2 H), 9.34 (s, 1 H). LCMS *m/z* 540.39 (M+H), *R*_t = 1.643min.,
30 94.2% purity. HPLC (Sunfire C18) *R*_t = 6.388min, 94% purity and (Gemini C18) *R*_t
= 11.238min., 99.6% purity.

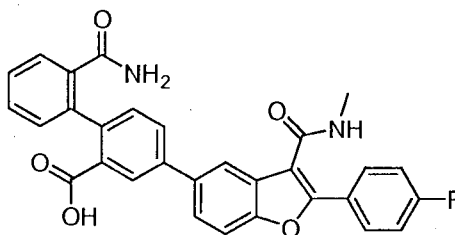


Methyl 2'-carbamoyl-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylate

- [00474] To a microwave vial was added dioxane (9 mL), water (0.900 mL), 2-carbamoylphenylboronic acid (148 mg, 0.900 mmol), methyl 2-chloro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate (131 mg, 0.3 mmol), tribasic potassium phosphate (255 mg, 1.200 mmol), dicyclohexyl (2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos, 24.63 mg, 0.060 mmol), and palladium(II) acetate (13.47 mg, 0.060 mmol). The vial was capped, degassed, flushed with N₂ and heated in the microwave for 13 minutes at 130 °C. The reaction mixture was filtered and solvent removed under a stream of nitrogen. The crude product was then taken up in 4 mL of acetonitrile and purified using a Shimadzu preparative HPLC employing acetonitrile/water/ trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5µm C18 19x150mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 20 minutes with a 10 minute hold. The solvent was removed giving 58.3mgs (36% yield) of methyl 2'-carbamoyl-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylate as a yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. ¹H NMR (400 MHz, THF-d₈) δ ppm 2.93 (d, *J*=4.52 Hz, 3 H), 3.62 (s, 3 H), 6.35 (br. s., 2 H), 7.09 - 7.15 (m, 1 H), 7.22 (t, *J*=8.91 Hz, 2 H), 7.31 - 7.43 (m, 3 H), 7.52 (d, *J*=4.27 Hz, 1 H), 7.58 - 7.71 (m, 3 H),

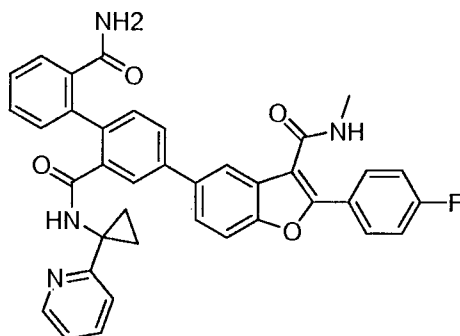
7.81 (dd, $J=8.03$, 2.01 Hz, 1 H), 8.01 (d, $J=1.25$ Hz, 1 H), 8.09 - 8.20 (m, 3 H).

LCMS m/z 523.3 (M+H), R_t = 3.051 min., 96% purity.



5 2'-Carbamoyl-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-
2-carboxylic acid

[00475] To a 25mL round-bottomed flask was added methyl 2'-carbamoyl-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylate (58.3 mg, 0.107 mmol), methanol (1 mL), THF (1 mL) and 8 equivalents of a 1M solution of sodium hydroxide (0.856 mL, 0.856 mmol). The mixture was diluted with 20mL of ethyl acetate, made acidic with 0.5M HCl and the crude product was extracted, washed with brine, and dried over sodium sulfate. The product solution was filtered and evaporated to dryness giving 52mgs (98% yield) of 2'-carbamoyl-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylic acid as a yellow solid. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. LCMS m/z 509.3 (M+H), R_t = 2.695 min., 90% purity.



4-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-N2-(1-(pyridin-2-yl)cyclopropyl) biphenyl-2,2'-dicarboxamide, TFA

[00476] To a 25mL round-bottomed flask was added 2'-carbamoyl-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)biphenyl-2-carboxylic acid (52mg, 0.104 mmol), DMF (2 mL), *N*-ethyl-*N*,*N*-isopropylpropan-2-amine (0.075 mL, 0.429 mmol), 1-(pyridin-2-yl)cyclopropanamine (21.57 mg, 0.161 mmol) and finally HATU (2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluoro phosphate (V), 163 mg, 0.429 mmol). The flask was sealed and the mixture stirred at room temperature over night. The crude product was purified using a Shimadzu preparative HPLC employing acetonitrile/water/trifluoroacetic acid where solvent A was 10% acetonitrile / 90% water/ 0.1% trifluoroacetic acid and solvent B was 10% water / 90% acetonitrile/ 0.1% trifluoroacetic acid with a Waters Sunfire 5µm C18 19 x 150mm column at a gradient of 20-100% B and a flow rate of 25 mL/min. over 20 minutes with a 10 minute hold. The solvent was evaporated giving 2 rotomers as shown above. The LC/MS data was obtained on a Shimadzu analytical LC / MICROMASS® Platform LC (ESI+) at 220nm using the following set of conditions: PHENOMENEX® Luna 3µm C18, 2 x 50mm column, with a gradient of 0-100%B (B = 90% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 10% HPLC grade water), (A = 90% HPLC grade water / 0.1% trifluoroacetic acid/ 10% HPLC grade acetonitrile), in 4 minutes with a 1 minute hold at a rate of 0.8 mL/minute. HPLC purity was determined using a Shimadzu analytical LC at 254nm and 256nm with a Waters Sunfire C18 3.5µm 4.6 x 150mm column employing water/acetonitrile/0.1% trifluoroacetic acid with a gradient of 10-100% B (B = 95% HPLC grade acetonitrile/ 0.1% trifluoroacetic acid/ 5% HPLC grade water), (A = 95% HPLC grade water / 0.1% trifluoroacetic acid/ 5% HPLC

grade acetonitrile), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute. The HPLC purity was then confirmed with an orthogonal solvent system and column using a Shimadzu analytical LC with a Waters XBridge phenyl C18 3.5 μ m 4.6 x 150mm column employing water/methanol/10mM ammonium bicarbonate with a
 5 gradient of 10-100% B (B = 95% HPLC grade methanol/ 10mM ammonium bicarbonate / 5% HPLC grade water), (A = 95% HPLC grade water / 10mM ammonium bicarbonate / 5% HPLC grade methanol), in 10 minutes with a 10 minute hold at a rate of 1 mL/minute.

[00477] Isomer A: ^1H NMR (400 MHz, THF- d_8) δ ppm 0.53 - 0.79 (m, 2 H), 1.36
 10 (d, $J=4.27$ Hz, 2 H), 2.95 (d, $J=4.52$ Hz, 3 H), 6.79 (br. s., 1 H), 6.88 - 7.00 (m, 2 H), 7.16 - 7.26 (m, 4 H), 7.39 (td, $J=7.72$, 1.88 Hz, 1 H), 7.46 - 7.53 (m, 3 H), 7.57 - 7.61 (m, 1 H), 7.61 - 7.65 (m, 2 H), 7.69 (ddd, $J=10.23$, 8.22, 1.88 Hz, 2 H), 7.91 (d, $J=2.01$ Hz, 1 H), 8.04 (d, $J=1.51$ Hz, 1 H), 8.13 - 8.19 (m, 2 H), 8.25 - 8.31 (m, 1 H), 9.01 (s, 1 H). LCMS m/z 625.4 (M+H), R_t = 2.310 min. HPLC (Sunfire C18) R_t =
 15 6.796 min, 100% purity and (XBridge phenyl C18) R_t = 10.793 min., 100% purity.

[00478] Isomer B: ^1H NMR (400 MHz, THF- d_8) δ ppm 0.64 - 0.92 (m, 2 H), 1.39
 (d, $J=4.02$ Hz, 2 H), 2.93 (d, $J=4.77$ Hz, 3 H), 6.76 (br. s., 1 H), 6.88 (dd, $J=6.90$,
 5.14 Hz, 1 H), 6.96 (d, $J=8.03$ Hz, 1 H), 7.11 - 7.18 (m, 1 H), 7.20 - 7.30 (m, 3 H),
 7.31 - 7.43 (m, 3 H), 7.50 (br. s., 1 H), 7.59 (dd, $J=7.15$, 1.88 Hz, 1 H), 7.62 - 7.67
 20 (m, 1 H), 7.68 - 7.76 (m, 2 H), 7.82 (dd, $J=7.78$, 2.01 Hz, 1 H), 7.92 (d, $J=1.76$ Hz, 1 H), 8.07 (d, $J=1.76$ Hz, 1 H), 8.09 - 8.17 (m, 2 H), 8.26 (d, $J=4.27$ Hz, 1 H), 8.98 (s, 1 H). LCMS m/z 625.4 (M+H), R_t = 2.275 min. HPLC (Sunfire C18) R_t = 6.688 min, 100% purity and (XBridge phenyl C18) R_t = 10.821 min., 100% purity.

25 Ethyl 4-fluoro-2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylate

[00479] To a mixture of ethyl 2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylate (500 mg, 1.665 mmol) in acetonitrile (10 mL) at r.t. under N_2 was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate (708 mg, 1.998 mmol). The mixture was stirred at r.t. (the mixture turned bright yellow in
 30 color) for 20 hours. The mixture was evaporated. The residue was added with 10 ml H_2O . The aqueous decanted, and the residue further washed with 2 x 5 ml H_2O . The mixture was dissolved in MeOH (about 10 ml), and the insoluble filtered. The filtrate

was purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 60, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.44 - 7.24 min. (UV detection at 220 nm). The desired fractions were combined and evaporated to give a yellow solid. The yellow solid was further purified by BIOTAGE® Horizon flash chromatography (0 to 70% EtOAc/Hexane, 3 x 80 g silica gel column) to give a light yellow solid (108.9 mg). ¹H NMR (500 MHz, CD₃OD) δ 7.95 (m, 2H), 7.26 (t overlapping with dd, 2H), 7.25 (dd, 1H), 7.03 (t, *J* = 8.39, 1H), 4.39 (q, *J* = 7.17, 2H), 1.36 (t, *J* = 7.17, 3H). ¹⁹F NMR (470.45 MHz, CD₃OD) δ 112.36, 142.29. The position of the F atom at C4 was confirmed by ¹H-¹H through bond correlation between H6 and H7, ¹H-¹³C HMBC and F-C4 coupling in ¹³C NMR (125.75 MHz, CD₃OD) (δ 144.8 ppm, d, *J* = 247, C4). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 319.14, HPLC *R*_t = 1.718 min. The minor fractions collected at about 7.69 - 8.20 min. was confirmed by ¹H-¹H through bond correlation, ¹H-¹³C HMBC and F-C6 coupling in ¹³C NMR (125.75 MHz, CD₃OD) (δ 152.5 ppm, d, *J* = 242 Hz, C6) to be the isomer of the F-atom at C6 (C4 : C6 about 3:1 based on preparative HPLC %area of the UV trace); ¹H NMR (500 MHz, CD₃OD) δ 8.04 (dd, *J* = 8.55, 5.49, 2H), 7.59 (d, *J* = 8.85, 1H), 7.38 (d, *J* = 10.07, 1H), 7.25 (t, *J* = 8.70, 2H), 4.40 (q, *J* = 7.17, 2H), 1.41 (t, *J* = 7.17, 3H). ¹⁹F NMR (470.45 MHz, CD₃OD) δ 112.29, 138.52. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 319.14, HPLC *R*_t = 1.798 min.

4-Fluoro-2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylic acid

[00480] To a mixture of ethyl 4-fluoro-2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylate (108.9 mg, 0.342 mmol) in a mixture of MeOH (2 mL)/THF (2 mL) at r.t. under N₂ was added sodium hydroxide (1.0 mL, 1.0 mmol) (1 M aq.). The mixture was stirred at 100 °C for 1.5 hours. The mixture was cooled to r.t., added with 1.5 ml 1N HCl, and then added 10 ml H₂O. The white precipitates were filtered and washed with 3 x 2 ml H₂O and dried (73 mg). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (m, 2H), 7.25 (t overlapping with dd, 2H), 7.24 (dd, 1H), 7.02 (t, *J* = 8.39, 1H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 291.01, HPLC *R*_t = 1.478 min.

4-Fluoro-2-(4-fluorophenyl)-5-hydroxy-N-methylbenzofuran-3-carboxamide
[00481] To a mixture of 4-fluoro-2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylic acid (73 mg, 0.252 mmol), methylamine, HCl (25.5 mg, 0.377 mmol), HOBT hydrate (65.5 mg, 0.428 mmol) and EDC hydrochloride (87 mg, 0.453 mmol) at r.t. under N₂ was added N,N-diisopropylethylamine (0.220 mL, 1.258 mmol). The mixture was stirred at r.t. for 16 hours. After concentration, the mixture was added with 5 ml 1N HCl, and then 14 ml H₂O. The white solid was filtered and washed with 3 x 5 ml H₂O and dried (64 mg). ¹H NMR (500 MHz, CD₃OD) δ 7.89 (dd, *J* = 8.09, 5.34, 2H), 7.25 (t overlapping with dd, 2H), 7.23 (dd, 1H), 6.99 (t, *J* = 8.55, 1H), 2.96 (s, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 304.06, HPLC *R*_t = 1.262 min.

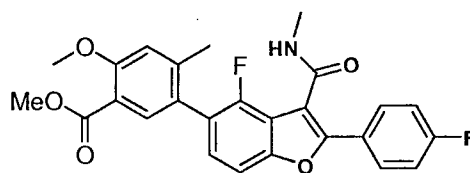
4-Fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl
trifluoromethanesulfonate

[00482] To a white suspension of 4-fluoro-2-(4-fluorophenyl)-5-hydroxy-N-methylbenzofuran-3-carboxamide (64 mg, 0.211 mmol) in CH₂Cl₂ (2 mL) at r.t. under N₂ was added triethylamine (0.059 mL, 0.422 mmol). The mixture was cooled to 0 °C, and then added 1,1,1-trifluoro-N-phenyl-N-

5 (trifluoromethylsulfonyl)methanesulfonamide (113 mg, 0.317 mmol). The mixture was then stirred at r.t. (the white suspension turned into a light yellow solution after stirring for about 10 min) for 2 hours 35 min. The mixture was left standing at r.t. overnight, and then evaporated. The residue was cooled in an ice-water bath, added with 2 ml H₂O. The solids were filtered and washed with 3 x 2 ml H₂O, and dried (94

10 mg). ¹H NMR (500 MHz, CD₃OD) δ 7.95 (m, 2H), 7.59 (dd, *J* = 9.00, 1.00, 1H), 7.50 (dd, *J* = 9.00, 7.50, 1H), 7.30 (t, *J* = 8.55, 2H), 2.99 (s, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100,

15 Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 436.04, HPLC *R*_t = 1.678 min.



20 Methyl 5-(4-fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoate

[00483] A mixture of the above prepared 4-fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (assumed 0.211 mmol), methyl 2-methoxy-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

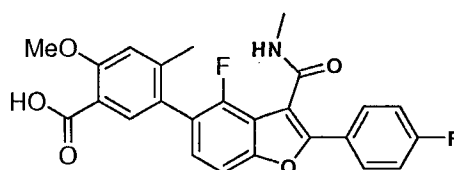
25 (0.078 g, 0.253 mmol), (Ph₃P)₄Pd (0.024 g, 0.021 mmol) and cesium carbonate (0.103 g, 0.317 mmol) in a mixture of H₂O (0.2 mL)/1,4-dioxane (1 mL) was stirred at 95 °C for 2 hours 30 min. The mixture was left standing at r.t. overnight. The mixture was diluted with 3.5 ml 1,4-dioxane, filtered through a Whatman PVDF 0.45 um disk (with 3 x 1 ml washing). The filtrate was concentrated. The mixture was added with

3.5 ml 1N HCl, and then 6 ml H₂O (yellow solid deposited on the wall of the flask).

The aqueous was decanted, and the residue washed with 3 x 2 ml H₂O and dried.

LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90%

- 5 H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 466.27, HPLC R_t = 1.708 min.



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5-(4-Fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoic acid

[00484] To the above prepared methyl 5-(4-fluoro-2-(4-fluorophenyl)-3-

(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoate (assumed 0.211

- 15 mmol) in a mixture MeOH (2 mL)/THF (2 mL) at r.t. under N₂ was added sodium hydroxide (0.84 mL, 0.84 mmol). The mixture was stirred at r.t. for 24 hours. The mixture was added with 2 ml 1N HCl, and concentrated until off white solids formed.

The mixture was added with 5 ml H₂O, the solids filtered and washed with 3 x 2 ml H₂O and dried (75.1 mg). ¹H NMR (500 MHz, CD₃OD) δ 7.95 (m, 2H), 7.73 (s, 1H),

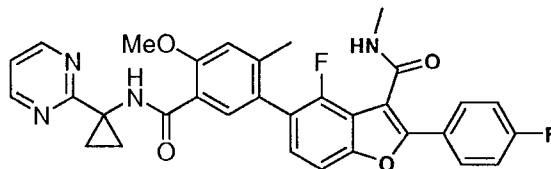
- 20 7.51 (d, *J* = 8.24, 1H), 7.30-7.25 (t overlapping with m, 3H), 7.13 (s, 1H), 3.99 (s, 3H), 2.96 (s, 3H), 2.28 (s, 3H). LC/MS were performed by using Shimadzu-VP

instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC

method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-

10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time

- 25 = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 452.23, HPLC R_t = 1.582.



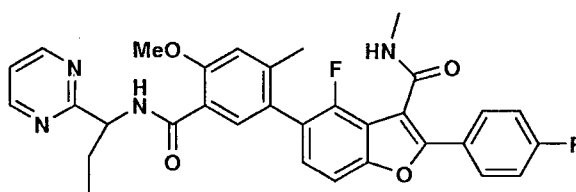
4-Fluoro-2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00485] To a mixture of 5-(4-fluoro-2-(4-fluorophenyl)-3-

- 5 (methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoic acid (30 mg, 0.066 mmol), 1-(pyrimidin-2-yl)cyclopropanamine, TFA (33.1 mg, about 75% pure, assumed 0.133 mmol,) and 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate (64.0 mg, 0.199 mmol) in DMF (1 mL) at r.t. under N₂ was added N,N-diisopropylethyl amine (0.058 mL, 0.332 mmol). The
- 10 mixture was stirred at r.t. for 20 hours. The mixture was diluted with MeOH and purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5,
- 15 UV detection at 220 nm, Fraction Collection: 7.25-7.73 min. The residue after evaporation of the combined fractions was further purified by preparative TLC (two of 500 um x 20 x 20 cm plates, 5% MeOH/CH₂Cl₂) to give 4-fluoro-2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide as a white
- 20 solid. Analytical TLC R_f = 0.32 (5% MeOH/CH₂Cl₂). ¹H NMR (500 MHz, CD₃OD) δ 8.65 (d, J = 4.88, 2H), 7.95 (m, 2H), 7.89 (s, 1H), 7.50 (d, J = 8.55, 1H), 7.28 (t, J = 8.70, 2H), 7.28-7.25 (m overlapping with t, 1H), 7.23 (t, J = 4.88, 1H), 7.17 (s, 1H), 4.09 (s, 3H), 2.95 (s, 3H), 2.30 (s, 3H), 1.79 (m, 2H), 1.51 (m, 2H). ¹⁹F NMR (470.45 MHz, CD₃OD) δ 112.81, 123.16. LC/MS were performed by using Shimadzu-VP
- 25 instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 mL/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 569.38, HPLC R_t = 1.660 min. Analytical HPLC were

performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 6.29 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 5.18 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 9.39 min.

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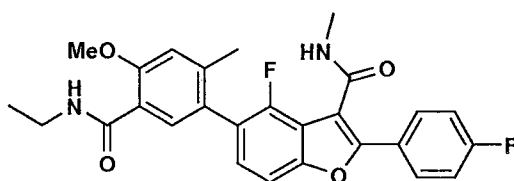
4-Fluoro-2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)propylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00486] 4-Fluoro-2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)propylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide was formed as a minor side product during the synthesis of 4-fluoro-2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide as described above, and was isolated during purification by preparative reverse phase HPLC (Fraction Collection: 7.82 - 8.48 min). ¹H NMR (500 MHz, DMSO-d₆) δ 9.08 (d, *J* = 7.32, 1H), 8.87 (d, *J* = 4.88, 2H), 8.70 (q, *J* = 4.58, 1H), 7.94 (m, 2H), 7.78 (s, 1H), 7.62 (d, *J* = 8.24, 1H), 7.46 (t, *J* = 4.88, 1H), 7.42 (t, *J* = 9.00, 2H), 7.30 (dd, *J* = 8.39, 7.17, 1H), 7.24 (s, 1H), 5.16 (m, 1H), 4.08 (s, 3H), 2.80 (d, *J* = 4.58, 3H), 2.24 (s, 3H), 1.97 (m, 2H), 0.82 (t, *J* = 7.32, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES⁺) *m/z* (M+H)⁺ = 571.35, HPLC R_t = 1.743 min. Analytical HPLC were performed by using Shimadzu-VP instrument with

UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μ m, 4.6 x 150 mm, R_t = 7.33 min; Column:

- 5 XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 5.69 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 10.23 min.

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5-(5-(Ethylcarbamoyl)-4-methoxy-2-methylphenyl)-4-fluoro-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00487] 5-(5-(Ethylcarbamoyl)-4-methoxy-2-methylphenyl)-4-fluoro-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide was formed as a minor side product during the synthesis of 4-fluoro-2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide as described above, and was isolated during purification by preparative TLC (the band right above the major product band). ¹H NMR (500 MHz, CD₃OD) δ 7.95 (m, 2H), 7.81 (s, 1H), 7.51 (d, *J* = 8.55, 1H), 7.30-7.25 (t overlapping with dd, 3H), (7.13 (s, 1H), 4.04 (s, 3H), 3.46 (q, *J* = 7.17, 2H), 2.95 (s, 3H), 2.28 (s, 3H), 1.25 (t, *J* = 7.17, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 479.30, HPLC R_t = 1.670 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95%
- 15
- 20
- 25

MeCN-5% H_2O -0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm , 4.6 x 150 mm, R_t = 6.94 min; Column: XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 5.31 min.

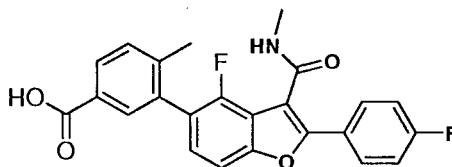
Analytical HPLC method: Solvent A = 5% MeOH-95% H_2O -10 mM NH_4HCO_3 ,

- 5 Solvent B = 95% MeOH-5% H_2O -10 mM NH_4HCO_3 , Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 9.20 min.

Methyl 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

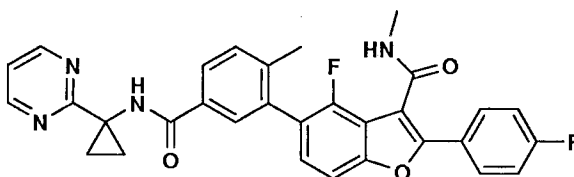
- 10 [00488] A mixture of methyl 5-iodo-2,4-dimethylbenzoate (1 g, 3.45 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.050 g, 4.14 mmol), potassium acetate (1.015 g, 10.34 mmol) and $\text{PdCl}_2(\text{dppf})(\text{Cl}_2\text{CH}_2)$ ([1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), dichloromethane) (0.284 g, 0.345 mmol) in DMF (25 mL) under N_2 was stirred at 100 $^\circ\text{C}$ for 20 hours. The
- 15 mixture was cooled to r.t., added with 30 ml H_2O . The dark solid was filtered and washed with 3 x 5 ml H_2O and dried. The solid was purified by BIOTAGE® Horizon flash chromatography (0 to 70% EtOAc/Hexane) to give the product as a white solid (442.7 mg). ^1H NMR (500 MHz, CD_3OD) δ 8.26 (s, 1H), 7.11 (s, 1H), 3.88 (s, 3H), 2.56 (s, 3H), 2.53 (s, 3H), 1.37 (s, 12H). LC/MS were performed by using Shimadzu-
- 20 VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 291.14, HPLC R_t = 1.933 min.

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3-(4-Fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid

[00489] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 422.19, HPLC R_t = 1.653 min.



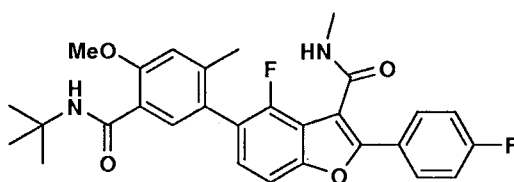
4-Fluoro-2-(4-fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00490] Purification was performed by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.80-7.18 min. (UV detection at 220 nm). The material obtained was further purified by preparative TLC (500 um x 20 x 20 cm plate, 5% MeOH/CH₂Cl₂). Analytical TLC R_f = 0.35 (5% MeOH/CH₂Cl₂). ¹H NMR (500 MHz, CD₃OD) δ 8.64 (d, *J* = 4.88, 2H), 7.96 (m, 2H), 7.90 (dd, *J* = 7.93, 1.83, 1H), 7.84 (d, *J* = 1.83, 1H), 7.54 (d, *J* = 8.54, 1H), 7.46 (d, *J* = 7.93, 1H), 7.34-7.27 (m overlapping with t, 3H), 7.22 (t, *J* = 4.88, 1H), 2.96 (s, 3H), 2.29 (s, 3H), 1.77 (m, 2H), 1.46 (m, 2H). ¹⁹F NMR (470.45 MHz, CD₃OD) δ 112.72, 123.10. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 539.32, HPLC R_t = 1.585 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95%

MeCN-5% H_2O -0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm , 4.6 x 150 mm, R_t = 5.64 min; Column: XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 4.66 min.

Analytical HPLC method: Solvent A = 5% MeOH-95% H_2O -10 mM NH_4HCO_3 ,

- 5 Solvent B = 95% MeOH-5% H_2O -10 mM NH_4HCO_3 , Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 8.43 min.



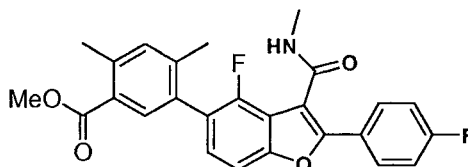
- 10 5-(5-(*tert*-Butylcarbamoyl)-4-methoxy-2-methylphenyl)-4-fluoro-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00491] Purification was performed by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 50, Final %B = 100,

- 15 Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.68 - 9.29 min. (UV detection at 220 nm). ^1H NMR (500 MHz, CD_3OD) δ 7.88 (dd, J = 8.55, 5.19, 2H), 7.72 (s, 1H), 7.43 (d, J = 8.55, 1H), 7.23–7.17 (overlapping m, 3H), 7.06 (s, 1H), 3.98 (s, 3H), 2.89 (s, 3H), 2.20 (s, 3H), 1.41 (s, 9H). LC/MS were performed by using Shimadzu-
20 VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H_2O -0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 507.33, HPLC R_t = 1.837 min. Analytical HPLC were
25 performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H_2O -0.1% TFA, Solvent B = 95% MeCN-5% H_2O -0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm , 4.6 x 150 mm, R_t = 10.19 min; Column: XBridge phenyl 3.5 μm , 4.6 x 150 mm, R_t = 7.50

min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 11.25 min.

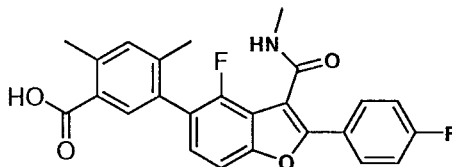
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Methyl 5-(4-fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2,4-dimethylbenzoate

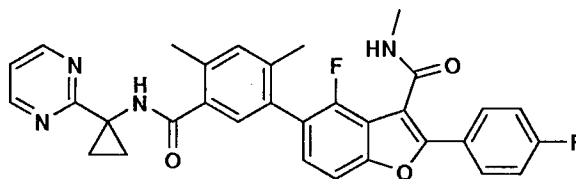
[00492] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 450.11, HPLC R_t = 1.852 min.

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5-(4-Fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2,4-dimethylbenzoic acid

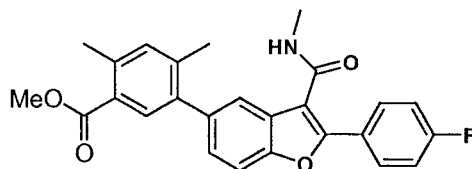
[00493] ¹H NMR (500 MHz, CD₃OD) δ 7.95 (m, 2H), 7.80 (s, 1H), 7.51 (d, *J* = 8.55, 1H), 7.30-7.25 (s and overlapping m, 4H), 2.96 (s, 3H), 2.63 (s, 3H), 2.23 (s, 3H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 436.09, HPLC R_t = 1.735 min.



5-(2,4-Dimethyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)-4-fluoro-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00494] Purification was performed by Shimadzu-VP preparative reverse phase

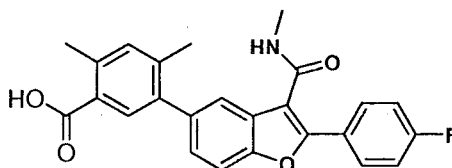
- 5 HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Sunfire Prep C18 19 x 100 5um, Fraction Collection: 6.93 - 7.43 min. (UV detection at 220 nm). ¹H NMR (500 MHz, DMSO-d₆, peaks were generally broad) δ 8.93 (s, 1H), 8.71 (broad s, 1H), 8.68 (m, 2H), 7.93 (m, 2H), 7.65 (m, 1H), 7.44 (m, 2H), 7.33 (m, 2H), 7.27 (m, 1H), 7.25 (m, 1H), 2.81 (s, 3H), 2.45 (s, 3H), 2.17 (s, 3H), 1.57 (s, 2H), 1.33 (s, 2H). ¹⁹F NMR (470.45 MHz, DMSO-d₆) δ 110.88, 121.61. LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 553.22, HPLC R_t = 1.645 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, R_t = 6.26 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 5.23 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 9.00 min.



Methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2,4-dimethylbenzoate

[00495] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 432.10, HPLC R_t = 1.928 min.

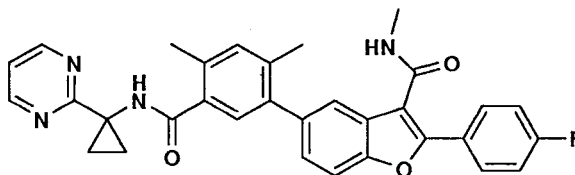
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5-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2,4-dimethylbenzoic acid

[00496] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 418.10, HPLC R_t = 1.810 min.

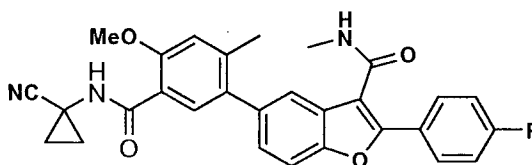
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5-(2,4-Dimethyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00497] Purification was performed by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column:
- 5 Sunfire Prep C18 19 x 100 5um, Fraction Collection: 7.75 - 8.16 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.67 (d, *J* = 4.88, 2H), 7.97 (m, 2H), 7.65 (s overlapped with d, 1H), 7.64 (d, *J* = 8.50, 1H), 7.50 (s, 1H), 7.38 (dd, *J* = 8.55, 1.83, 1H), 7.28 (t, *J* = 8.85, 2H), 7.24 (t, *J* = 4.88, 1H), 7.22 (s, 1H), 2.95 (s, 3H), 2.52 (s, 3H), 2.30 (s, 3H), 1.76 (m, 2H), 1.46 (m, 2H). LC/MS were performed by using
- 10 Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 535.23, HPLC *R*_t = 1.722 min. Analytical HPLC
- 15 were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, *R*_t = 7.24 min; Column: XBridge phenyl 3.5 um, 4.6 x
- 20 150 mm, *R*_t = 5.62 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, *R*_t = 9.24 min.

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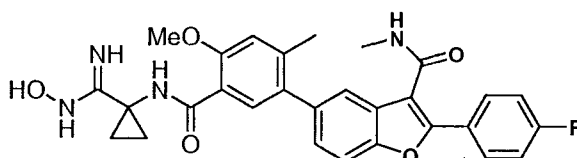


5-(5-(1-Cyanocyclopropylcarbamoyl)-4-methoxy-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- [00498] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10%

MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 498.21, HPLC R_t = 1.647 min.

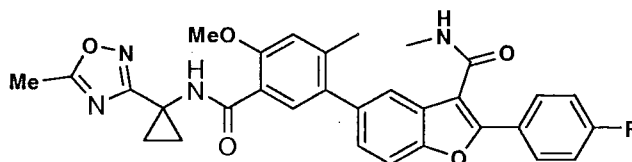
5



2-(4-Fluorophenyl)-5-(5-(1-(N-hydroxycarbamimidoyl)cyclopropylcarbamoyl)-4-methoxy-2-methylphenyl)-N-methylbenzofuran-3-carboxamide

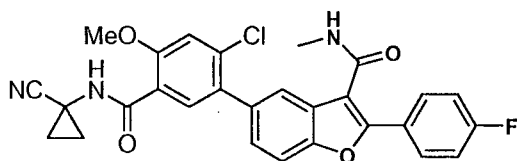
[00499] Purification was performed by Shimadzu-VP preparative reverse phase

- 10 HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 30, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 6.82 - 7.62 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 7.96 (dd, *J* = 8.24, 5.80, 2H), 7.88 (s, 1H), 7.63 (d, *J* = 8.24, 1H), 7.57 (s, 1H), 7.32 (d, *J* = 8.54, 1H), 7.28 (t, *J* = 8.70, 2H), 7.13 (s, 1H), 4.05 (s, 3H), 2.96 (s, 3H), 2.36 (s, 3H), 1.67 (m, 2H), 1.50 (m, 2H).
- 15 LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 531.22, HPLC R_t = 1.457 min.
- 20



- 25 2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(5-methyl-1,2,4-oxadiazol-3-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

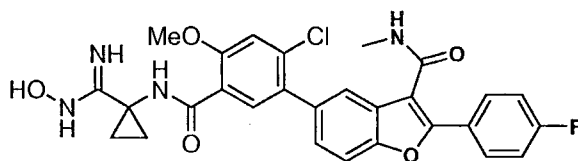
[00500] 2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(5-methyl-1,2,4-oxadiazol-3-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide was prepared from 2-(4-fluorophenyl)-5-(5-(1-(N-hydroxycarbamimidoyl)cyclopropylcarbamoyl)-4-methoxy-2-methylphenyl)-N-methylbenzofuran-3-carboxamide under similar conditions as described but using PhMe as a solvent. The crude mixture was purified by preparative TLC (20 x 20 cm x 500 um plates, 5% MeOH/CH₂Cl₂) to give the product, which was further purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 7.95 - 8.47 min. (UV detection at 220 nm). Analytical TLC R_f = 0.38 (5% MeOH/CH₂Cl₂). ¹H NMR (500 MHz, CD₃OD) δ 7.97 (dd, *J* = 7.93, 5.49, 2H), 7.87 (s, 1H), 7.62 (d, *J* = 8.24, 1H), 7.58 (s, 1H), 7.33 (d, *J* = 8.55, 1H), 7.27 (t, *J* = 8.39, 2H), 7.11 (s, 1H), 4.05 (s, 3H), 2.96 (s, 3H), 2.54 (s, 3H), 2.36 (s, 3H), 1.60 (m, 2H), 1.45 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 555.34, HPLC R_t = 1.735 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 um, 4.6 x 150 mm, R_t = 7.75 min; Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 5.93 min. Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃, Solvent B = 95% MeOH-5% H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: XBridge phenyl 3.5 um, 4.6 x 150 mm, R_t = 11.98 min.



5-(2-Chloro-5-(1-cyanocyclopropylcarbamoyl)-4-methoxyphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00501] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 518.20, 520.18, HPLC R_t = 1.692 min.

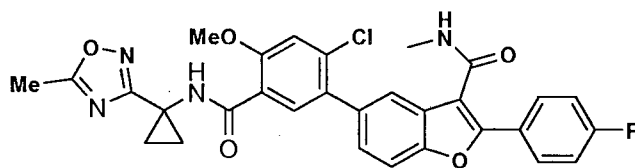
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5-(2-Chloro-5-(1-(N-hydroxycarbamimidoyl)cyclopropylcarbamoyl)-4-methoxyphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

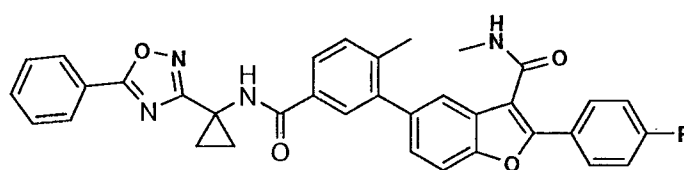
[00502] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 551.21, HPLC R_t = 1.478 min.

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5-(2-Chloro-4-methoxy-5-(1-(5-methyl-1,2,4-oxadiazol-3-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

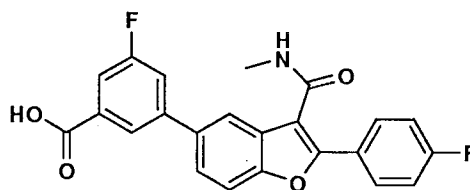
[00503] The mixture first purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 60, Final %B = 100, Gradient time = 5 min, Stop time = 6 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 50 mm S5, Fraction Collection: 3.85 - 4.21 min. (UV detection at 220 nm). The residue obtained after evaporation of the desired fractions was further purified by preparative TLC (5% MeOH/CH₂Cl₂, 20 cm x 20 cm x 0.5 mm plates). ¹H NMR (500 MHz, CD₃OD) δ 7.98 (dd overlapping with s, *J* = 5.19, 2H), 7.97 (s, 1H), 7.71 (d, *J* = 1.22, 1H), 7.65 (d, *J* = 8.55, 1H), 7.45 (dd, *J* = 8.55, 1.83, 1H), 7.36 (s, 1H), 7.28 (t, *J* = 8.85, 2H), 4.05 (s, 3H), 2.96 (s, 3H), 2.54 (s, 3H), 1.61 (m, 2H), 1.46 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 575.10, HPLC *R*_t = 1.817 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150 mm, *R*_t = 7.92 min; Column: XBridge phenyl 3.5 μm, 4.6 x 150 mm, *R*_t = 6.21 min.



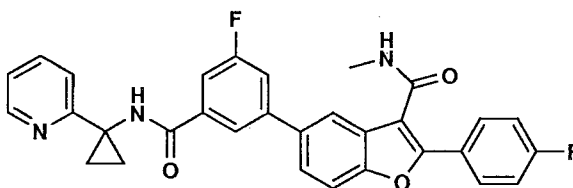
25 2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(5-phenyl-1,2,4-oxadiazol-3-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00504] The mixture was first purified by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 50, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column:

- Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 9.11 - 9.39 min. (UV detection at 220 nm) to isolate the desired product. The residue after evaporation of the desired fractions was further purified by preparative TLC (5% MeOH/CH₂Cl₂, 20 cm x 20 cm x 0.5 mm plate). Analytical TLC R_f = 0.52 (5% MeOH/CH₂Cl₂). ¹H NMR (500 MHz, CD₃OD) δ 8.11 (d, *J* = 7.02, 2H), 7.99 (m, 2H), 7.84 (s, 1H), 7.83 (m overlapping with s, 1H), 7.68–7.64 (overlapping m, 3 H), 7.60–7.57 (overlapping m, 2 H), 7.45 (d, *J* = 8.55, 1H), 7.40 (d, *J* = 8.24, 1.83, 1H), 7.28 (m, 2H), 2.96 (s, 3H), 2.36 (s, 3H), 1.72 (m, 2H), 1.50 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®.
- 10 HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 4 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 587.20, HPLC R_t = 1.950 min.

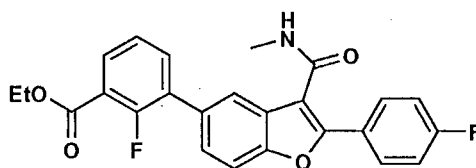


- 15 3-Fluoro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid
[00505] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 408.15, HPLC R_t = 1.757 min.



- 25 5-(3-Fluoro-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

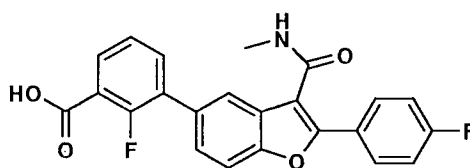
[00506] The product precipitated from the reaction mixture during the coupling of 3-fluoro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid (0.068 mmol scale) with 1-(pyridin-2-yl)cyclopropanamine dihydrochloride (TBTU, iPr₂NET, DMF, r.t.). The mixture was diluted with 4 ml H₂O, the off white solid
 5 filtered and washed with 3 x 2 ml H₂O. The solid was further washed with 3 x 1 ml MeOH and dried. ¹H NMR (500 MHz, DMSO-d₆) δ 9.50 (s, 1H), 8.52 (d, *J* = 4.58, 1H), 8.47 (d, *J* = 3.97, 1H), 8.17 (s, 1H), 8.03-8.00 (overlapping m, 3H), 7.83 (overlapping m, 3H), 7.73 (d, 1H), 7.70 (dt overlapping with d, 1H), 7.43-7.40 (overlapping m, 3H), 7.17 (dd, *J* = 6.87, 5.34, 1H), 2.88 (d, *J* = 4.27, 3H), 1.59 (m,
 10 2H), 1.32 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 524.25, HPLC *R_t* = 1.512 min.



Ethyl 2-fluoro-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate

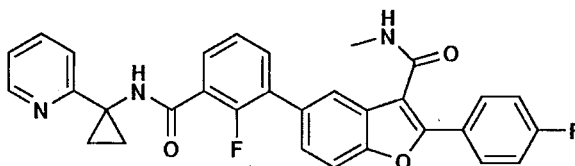
[00507] LC/MS were performed by using Shimadzu-VP instrument with UV
 20 detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 436.01, HPLC *R_t* = 1.820 min.

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2-Fluoro-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoic acid

[00508] LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 408.01, HPLC R_t = 1.623 min.



5-(2-Fluoro-3-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00509] The product was obtained as a TFA salt after purification by Shimadzu-VP preparative reverse phase HPLC using the separation method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10% H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 25 mL/min, Column: Waters-Sunfire 19 x 100 mm S5, Fraction Collection: 8.11 - 8.43 min. (UV detection at 220 nm). ¹H NMR (500 MHz, CD₃OD) δ 8.64 (d, *J* = 5.19, 1H), 8.42 (t, *J* = 7.78, 1H), 7.97 (dd, *J* = 8.24, 5.49, 2H), 7.91 (d, *J* = 8.24, 1H), 7.88 (s, 1H), 7.80 (q, *J* = 6.61, 2H), 7.76 (t, *J* = 7.17, 1H), 7.71 (d, *J* = 8.55, 1H), 7.60 (d, *J* = 8.24, 1H), 7.43 (t, *J* = 7.78, 1H), 7.29 (t, *J* = 8.55, 2H), 2.97 (s, 3H), 1.84 (m, 2H), 1.74 (m, 2H). LC/MS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH-90% H₂O-0.1% TFA, Solvent B = 90% MeOH-10%H₂O-0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 524.08, HPLC R_t = 1.417 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 220 nm and 254 nm. Analytical HPLC method: Solvent A = 5% MeCN-95% H₂O-0.1% TFA, Solvent B = 95% MeCN-5%H₂O-0.1% TFA, Start %B = 10, Final %B = 100, Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column: Sunfire C18, 3.5 μm, 4.6 x 150

mm, R_t = 8.57 min; Column: XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 9.09 min.

Analytical HPLC method: Solvent A = 5% MeOH-95% H₂O-10 mM NH₄HCO₃,

Solvent B = 95% MeOH-5%H₂O-10 mM NH₄HCO₃, Start %B = 50, Final %B = 100,

Gradient time = 15 min, Stop time = 18 min, Flow Rate = 1 ml/min, Column:

- 5 XBridge phenyl 3.5 μ m, 4.6 x 150 mm, R_t = 12.08 min.

Ethyl 3-(4-Fluorophenyl)-3-oxopropanoate

[00510] To a suspension of diethyl carbonate (7.69 g, 65.14 mmol, 1.8 eq) and NaH (hexane washed) (90.47 mmol, 2.5 eq) in dry THF (30 ml) p-

- 10 fluoroacetophenone (36.19 mmol) was added dropwise at 60 °C. The reaction was maintained at gentle reflux by adjusting the temperature and the addition rate (exothermic). After the addition was complete, the reaction was heated at reflux for 4 h, and then cooled to room temperature. The reaction mixture was poured carefully into ice cold acetic acid (6.0 ml) and water (20 ml). The product was extracted with
15 ether, and the combined ether layers were washed with saturated aqueous bicarbonate, brine and dried. Ether was evaporated and the crude product was purified by silica gel (60-120) column chromatography using 2 % EtOAc/hexane as eluent. Yield : 7.3 g (96 %). ¹H NMR (400MHz, CDCl₃): δ 1.27 (t, 3H, J = 7.12 Hz), 3.96 (s, 2H), 4.24 (q, 2H, J = 7.12 Hz), 7.17 (t, 2H, J = 7.59 Hz), 7.98 (m, 2H). LCMS :
20 (ES+) m/z = 211(M+H).

Ethyl 2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylate

- [00511] To a stirred solution of zinc chloride (8.39 g, 1.14 mmol, 1 eq) in toluene at ambient temperature, ethyl 3-(4-fluorophenyl)-3-oxopropanoate (13 g, 2.74 mmol,
25 1 eq) was added and stirred at 70 °C for 15 min. Benzoquinone (6.66 g, 0.72 mmol, 1 eq) was added portion wise into the reaction mixture and stirred at the same temperature for 15-20 min. Dean-stark apparatus was assembled and the reaction mixture was heated at 140 °C for 12 h and cooled to ambient temperature. Reaction completion was judged by TLC. EtOAc was added to the reaction mass and filtered
30 through the filter paper, to remove the inorganic material. Brine was added to the reaction mixture (filtrate) and extracted, dried over sodium sulphate and concentrated to get the crude material. Further it was purified by column chromatography using 10

% EtOAc/Hexane system. Yield : 8.0 g (43 %). ¹H NMR (400MHz, CDCl₃): δ 1.38-1.42 (t, 3H, *J* = 7.14 Hz), 4.37-4.42 (q, 2H, *J* = 7.13 Hz), 5.2 (br s, 1H), 6.87-6.9 (q, 1H, *J* = 3.81 Hz), 7.14-7.18 (q, 2H, *J* = 5.82 Hz), 7.36-7.39 (d, 1H, *J* = 8.80 Hz), 7.50-7.51 (d, 1H, *J* = 2.56 Hz), 8.00-8.03 (m, 2H). LCMS : (ES+) *m/z* = 301(M+H).

5

2-(4-Fluorophenyl)-5-hydroxybenzofuran-3-carboxylic acid

[00512] To a mixture of 2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylate (1 g, 3.5 mmol, 1 eq) in a 1:1 mixture of MeOH/THF at ambient temperature was added 5 eq. of NaOH and heated to 60 °C for 3 h. The mixture was cooled to ambient
10 temperature and to 0 °C in an ice-water bath, it was acidified slowly with 1.5 N HCl and then concentrated. The mixture with white precipitates was diluted with water and filtered to get the solid. It is further washed with water and dried in vacuum.
Yield : 0.9 g (94.6 %). ¹H NMR (400MHz, DMSO-*d*₆): δ 6.82-6.85 (m, 1H), 7.35-7.40 (m, 3H), 7.46-7.49 (d, 1H, *J* = 8.84 Hz), 8.02-8.05 (m, 2H), 9.4 (s, 1H), 13.05
15 (s, 1H). LCMS : (ES-) *m/z* = 271.1

2-(4-Fluorophenyl)-5-hydroxy-N-methylbenzofuran-3-carboxamide

[00513] To a mixture of 2-(4-fluorophenyl)-5-hydroxybenzofuran-3-carboxylic acid (1 g, 3.7mmol, 1 eq), methylamine in THF (2 M solution) (0.689 g, 21.5 mmol, 1
20 eq), HOBT (0.83 g, 6.2 mmol, 1.7 eq), EDC.HCl (1.24 g, 6.6 mmol, 1.8 eq) in DMF at ambient temperature under nitrogen was added Diisopropyl ethylamine (2.32 g, 18.5 mmol, 3.0 eq). The clear mixture was stirred at ambient temperature for 12 h. The LCMS indicated the desired product. The mixture was concentrated cooled in an ice-water bath, further diluted with water. The white solid was filtered and washed
25 with water and dried in vacuum. Yield : 0.85 g (90 %). ¹H NMR (400MHz, DMSO-*d*₆): δ 2.81-2.82 (d, 3H, *J* = 4.5Hz), 6.80-6.83 (m, 1H), 6.94-6.95 (d, 1H, *J* = 2.3 Hz), 7.34-7.38 (t, 2H, *J* = 8.7 Hz), 7.44-7.47 (d, 1H, *J* = 8.8 Hz), 7.90-7.93 (m, 2H), 8.39-8.40 (d, 1H, *J* = 4.4 Hz), 9.3 (s, 1H). LCMS : (ES+) *m/z* = 286.1(M+H).

30 2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate

[00514] To a mixture of 2-(4-fluorophenyl)-5-hydroxy-N-methylbenzofuran-3-carboxamide (5 g, 17.5 mmol, 1 eq) in Dichloromethane (50 ml) at ambient

temperature under N₂ was added triethylamine (2.6 g, 26 mmol, 1.5 eq). The mixture was cooled to 0 °C and then added 1,1,1-trifluoro-N-phenyl-N(trifluoromethylsulphonyl) methane sulphonamide (7.5 g, 21 mmol, 1.2 eq). The mixture was then stirred at ambient temperature for 12 h. The reaction mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer is further washed twice with water, dried over sodium sulphate and concentrated to get the product. The product was further purified by column chromatography using 230-400 silica gel and 50 % EtOAc/Hexane. Yield : 6.2 g (85 %). ¹H NMR (400MHz, DMSO-d₆): δ 2.83-2.84 (d, 3H, *J* = 4.6 Hz), 7.40-7.44 (t, 2H, *J* = 8.9 Hz), 7.51-7.53 (m, 1H), 7.75-7.76 (d, 1H, *J* = 2.52 Hz), 7.88-7.90 (d, 1H, *J* = 8.96 Hz), 7.94-7.98 (m, 2H), 8.51-8.52 (d, 1H, *J* = 4.6 Hz). LCMS : (ES+) *m/z* = 418(M+H).

3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoate [00515] To a mixture of 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (3.5 g, 8.4 mmol, 1 eq), boronic acid (1.95 g, 10.1 mmol, 1.2 eq), in 1,4-dioxane/H₂O (5:1) was added cesium carbonate (8.21 g, 26 mmol, 3 eq) and the nitrogen gas was passed through the mixture for 10 min. Then tetrakis(triphenyl)phosphine palladium (0.97 g, 0.8 mmol, 0.1 eq) was added to the reaction mixture and the nitrogen gas was again passed through the mixture for 10 min. The above reaction mixture was heated in microwave for one hour at 90 °C. About 50 ml of water is added to the reaction mixture and extracted with EtOAc. The organic layer was further washed twice with water and dried over sodium sulphate and concentrated to get the product. The product obtained was further purified by column chromatography using 40 % EtOAc/Hexane as eluent. Yield; 1.5 g (40 %) ¹H NMR (400MHz, DMSO-d₆): δ 2.32 (s, 3H), 2.81-2.82 (d, 3H, *J* = 4.56 Hz), 3.85 (s, 3H), 7.39-7.43 (t, 2H, *J* = 8.9 Hz), 7.39-7.43 (m, 1H), 7.49-7.51 (d, 1H, *J* = 8.16 Hz), 7.56 (s, 1H), 7.75-7.77 (d, 1H, *J* = 8.6), 7.83 (s, 1H), 7.89-7.91 (d, 1H, *J* = 7.82 Hz), 7.98-8.02 (m, 2H), 8.48-8.49 (d, 1H, *J* = 4.6 Hz). LCMS : (ES+) *m/z* = 418 (M+H).

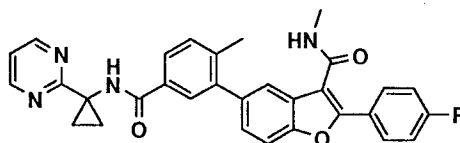
30 3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid [00516] To a mixture of methyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoate (1 g, 2.4 mmol, 1 eq) in a 1:1

mixture of MeOH/THF at ambient temperature was added 5 eq. of NaOH and heated to 60 °C for 5 h. The mixture was cooled to ambient temperature and then in an ice-water bath, quenched slowly with 1.5 N HCl and then concentrated. The mixture with white precipitates was diluted with water and filtered to get the solid. It is further
5 washed with water and dried in vacuum. Yield : 0.850 g (90 %). This acid was also prepared by the coupling of 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate with 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (Cs₂CO₃, (Ph₃)₄Pd, H₂O/1,4-dioxane (1:5), 90 °C) in a similar manner as described. ¹H NMR (400MHz, DMSO-d₆): δ 2.32 (s, 3H), 2.82-2.83 (d, 3H, *J* =
10 4.6 Hz), 7.36-7.48 (m, 6H), 7.56-7.57 (d, 1H, *J* = 1.44 Hz), 7.75-7.77 (d, 1H, *J* = 8.48 Hz), 7.81-8.03 (m, 2H), 8.46-8.48 (d, 1H, *J* = 4.7 Hz), 12.92 (s, 1H). LCMS : (ES+) *m/z* = 404.0 (M+H).

1-(Pyrimidin-2-yl)cyclopropanamine

15 [00517] 2-Cyano pyrimidine (5 g, 47.6 mmol, 1 eq) was taken in a Dry THF under Argon atmosphere, then titanium isopropoxide (17 ml, 57.1 mmol, 1.2 eq) was added slowly at ambient temperature and the reaction mixture was stirred for 15 mins. Ethyl magnesium bromide (1M solution) in THF (107 ml, 809 mmol, 2.5 eq) was added via syringe slowly at ambient temperature, (During the addition of EtMgBr reaction mass
20 becomes black). Then the reaction mass was stirred for an hour. BF₃.EtO (16.7 ml, 119.0 mmol, 2.5 eq) was added slowly through syringe at 0 °C. The mixture was allowed to attain ambient temperature and stirred for another one hour. 50 ml of Water was added to the reaction mixture and filtered through the CELITE® and washed the bed with water and Ethyl acetate. The reaction mass was basified with 10
25 % NaOH solution (pH = 9) then extracted with DCM and washed with brine solution. The required product was purified by silica gel (230-400) column chromatography using DCM/methanol as the eluent. Yield : 2.1 g (30 %). ¹H NMR (400MHz, DMSO-d₆): δ 1.49-1.52 (m, 2H), 1.59-1.62 (m, 2H), 7.47-7.49 (t, 1H, *J* = 4.80), 8.83-8.84 (d, 2H, *J* = 4.80).

30



2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

- [00518] To a mixture of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (0.1 g, 0.25 mmol, 1 eq), 1-(pyrimidin-2-yl)cyclopropanamine (0.041 g, 0.3 mmol, 1.2 eq) (60 % purity), HOBT (0.057 g, 0.42 mmol, 1.7 eq), EDC.HCl (0.086 g, 0.44 mmol, 1.8 eq) in DCM at ambient temperature under nitrogen was added Diisopropylethylamine (0.16 g, 1.3 mmol). The clear mixture was stirred at ambient temperature for 12 h. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer was further washed with water, dried over sodium sulphate and concentrated. The product obtained was further purified by column chromatography (neutral alumina) using 0.5 % Methanol/DCM and finally purified by preparative HPLC. Yield : 0.15 g (14 %). ¹H NMR (400MHz, DMSO-d₆): δ 1.33-1.36 (m, 2H), 1.59-1.61 (m, 2H), 2.31(s, 3H), 2.82-2.83 (d, 3H, *J* = 4.8 Hz), 7.26-7.29 (t, 1H, *J* = 4.8 Hz), 7.39-7.45 (m, 4H), 7.59 (s, 1H), 7.76-7.78 (d, 1H, *J* = 8.4 Hz), 7.86-7.87 (d, 2H, *J* = 4.4 Hz), 7.98-8.02 (m, 2H), 8.47-8.50 (m, 1H), 8.67-8.68 (d, 2H, *J* = 4.8 Hz), 9.20 (s, 1H). LCMS : (ES+) *m/z* = 521.2 (M+H). Column : Ascentis Express C18 (5X2.1mm-2.7μm). Mphase A : 2% MeCN -98% H₂O-10mM NH₄COOH. Mphase B : 98% MeCN – 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min.

Time	%A	%B
0.0	100.0	0
1.5	0.0	100.0
3.2	0.0	100.0
3.6	100.0	0.0

RT min : 1.908, wavelength:220nm.

HPLC Method:

Column : ZORBAX® C18 (4.6X150mm-5.0μm)

A : Buffer : 20mM Ammonium acetate
B : Methanol
Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :19.7

5 Wavelength : 220 nm, RT min :19.7

HPLC Method:
Sunfire C18 (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
10 Mobile Phase A : Buffer : MeCN (95:5)
Mobile Phase B : ACN :Buffer (95:5)
Flow : 1ml/min

Time	B%
0	10
12	100
15.	100

Wavelength : 254 nm, RT min :17.2

Wavelength : 220 nm, RT min :17.2

15

HPLC Method:
XBridge phenyl (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
Mobile Phase A : Buffer : MeCN (95:5)
20 Mobile Phase B : MeCN :Buffer (95:5)
Flow : 1ml/min

Time	B%
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Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :15.764

Wavelength : 220 nm, RT min :15.764

3-Fluoro-5-iodo-4-methylbenzoic acid

- 5 [00519] 3-Fluoro-4-methylbenzoic acid (1 g, 6.48 mmol, 1 eq) was dissolved in trifluoromethanesulphonic acid (10 ml) and the reaction was cooled to 0 °C. To the above solution *N*-iodosuccinimide (1.46 g, 6.48 mmol, 1 eq) was added in portion and the reaction was stirred at room temperature for 14 h. Later the above solution was poured into 50 ml of ice water, the solid obtained was filtered. The solid was
- 10 dissolved in ethylacetate, washed with sodiumthiosulphate solution and brine, the organic layer was concentrated to get the desired product as light brown solid. Yield : 1.5 g (83 %). ¹H NMR (400MHz, CDCl₃): δ 2.35 (s, 3H), 7.68 (d, 1H, *J* = 8 Hz), 8.14 (s, 1H). 13.50 (br, 1H).

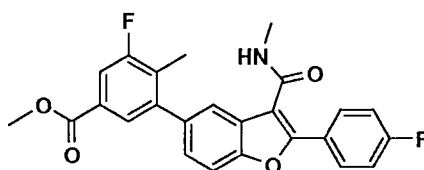
15 Methyl 3-fluoro-5-iodo-4-methylbenzoate

- [00520] 3-Fluoro-5-iodo-4-methylbenzoic acid (1.3 g, 4.6 mmol, 1 eq) was dissolved in methanol and treated with conc. Sulphuric acid (0.49 ml, 9.2 mmol, 2 eq). The above solution was stirred at 50 °C for 15 h. Later on solvent was removed and to the resulting residue diethylether was added and the organic layer was washed
- 20 with 10 % sodium bicarbonate solution and water. Finally, the organic layer was concentrated and purified by flash silica gel column chromatography using 240-400 silica gel and using 10 % EtOAc in hexane as the eluent. Yield : 1 g (77 %). ¹H NMR (400MHz CDCl₃). δ 2.39 (s, 3H), 3.90 (s, 3H), 7.64 (d, 1H, *J* = 8 Hz), 8.25 (s, 1H).

25 Methyl 3-fluoro-4-methyl-5-(3,3,4,4-tetramethylborolan-1-yl)benzoate

- [00521] A mixture of methyl 3-fluoro-5-iodo-4-methylbenzoate (0.85 g, 2.89 mmol, 1 eq), potassium acetate (1.41 g, 14.45 mmol, 5 eq), bispinacolatodiboron (1.1

g, 4.33 mmol, 1.5 eq) and 1,1-bis (diphenylphosphino)ferrocene)-dichloropalladium (II) (0.047 g, 0.057 mmol, 0.02 eq) were dissolved in DMF and the reaction was stirred at 90 °C for 18 h. Later solvent was removed, water was added and extracted with dichloromethane, organic layer was washed with 2 M HCl, 10 % lithium chloride and brine. The organic layer was concentrated and hexane was added. The solid obtained was filtered and dried to get the desired product as a white solid. Yield : 0.35 g, (41 %). ¹H NMR (400MHz CDCl₃): δ 1.35(s, 12H), 2.49 (s, 3H), 3.90 (s, 3H), 7.69-7.71 (d, 1H, *J* = 8 Hz), 8.18 (s, 1H).).

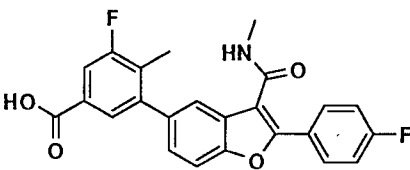


Methyl 3-fluoro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoate

[00522] To a mixture of 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (0.5 g, 1.2 mmol, 1 eq), boronic ester (0.42 g, 1.4 mmol, 1.2 eq) in 1,4-dioxane/H₂O (5:1) was added cesium carbonate (1.17 g, 3.6 mmol, 3 eq) and the nitrogen gas was passed through the solution for 10 min. Then tetrakis(triphenylphosphine) palladium (0.14 g, 0.12 mmol, 0.1 eq) was added to the reaction mixture and the nitrogen gas was passed again through the solution for 15 min. The above reaction mixture was heated in microwave for one hour at 90 °C. About 100 ml of water is added to the reaction mixture and extracted with EtOAc. The organic layer was further washed twice with water, dried and concentrated to get the product. The product obtained was further purified by column chromatography using 40 % EtOAc/Hexane as the eluent. Yield : 0.5 g (40 %). ¹H NMR (400MHz, DMSO-d₆): δ 2.23 (d, 3H, *J* = 1.9 Hz), 2.82-2.83 (d, 3H, *J* = 4.6 Hz), 3.8 (s, 3H), 7.39-7.43 (t, 2H, *J* = 8.4 Hz), 7.39-7.43 (1H, m), 7.61 (s, 1H), 7.70-7.72 (d, 2H, *J* = 7.2 Hz), 7.78-7.80 (d, 1H, *J* = 8.4 Hz), 7.99-8.03 (m, 2H), 8.49-8.51 (d, 1H, *J* = 4.7 Hz). LCMS : (ES⁺) *m/z* = 436 (M+H). PHENOMENEX® Luna C18 (4.6X3.0mm-5.0μm). Mphase A : 10% CH₃OH -90% H₂O-10mM NH₄OAc. Mphase B : 90% CH₃OH -10% H₂O-10mM NH₄OAc. Flow : 5 ml/Min.

Time	%B
0.0	0.0
2.0	100.0
3.0	0.0

RT min : 2.135, wavelength: 220nm



3-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid

5 [00523] To a mixture of methyl 3-fluoro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoate (0.3 g, 0.68 mmol, 1 eq) in a 1:1 mixture of MeOH/THF at ambient temperature was added 5 eq. of NaOH and heated to 60 °C for 5 h. The mixture was cooled to ambient temperature and then cooled in an ice-water bath. It was acidified slowly with 1.5 N HCl and then

10 concentrated. The mixture with white precipitates was diluted with water and filtered to get the solid. It is further washed with water and dried in vacuum. Yield : 0.2 g (60 %). ¹H NMR (400MHz, DMSO-d₆): δ 2.22 (s, 3H), 2.82-2.84 (d, 3H, J = 4.6 Hz), 7.39-7.43 (m, 3H), 7.61 (s, 1H), 7.66-7.70 (d, 1H, J = 8.6 Hz), 7.66-7.70 (m, 1H), 7.78-7.80 (d, 1H, J = 8.5 Hz), 8.01-8.03 (m, 2H), 8.49-8.51 (d, 1H, J = 4.76 Hz), 13.2

15 (s, 1H). LCMS : (ES-) m/z = 420.0 (M-H). CHROMOLITH® SpeedROD C18 (4.6X3.0mm-5.0µm). Mphase A : 10% CH₃OH -90% H₂O-0.1% TFA. Mphase B : 90% CH₃OH -10% H₂O-0.1% TFA. Flow : 5 ml/Min.

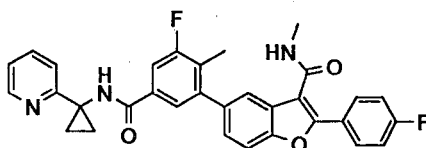
Time	%B
0.0	0.0
2.0	100.0
3.0	0.0

RT min : 2.040, wavelength: 220 nm.

20

1-(Pyridin-2-yl)cyclopropanamine

[00524] 2-Cyano pyridine (5 g, 48.0 mmol, 1 eq) was taken in dry THF under Argon atmosphere. To this mixture was added slowly Titanium isopropoxide (17 ml, 57.6 mmol, 1.2 eq) at ambient temperature. The reaction mass was stirred for 15 mins. Ethyl Magnesium Bromide (1 M solution) in THF (107 ml, 809 mmol, 2.5 eq) was added via syringe slowly at room temperature, (During the addition of EtMgBr reaction mass becomes black). Then the reaction mass stirred for an hour and BF₃.Et₂O (16.7 ml, 120.0 mmol, 2.5 eq) was added slowly at 0 °C. After the completion of addition process, reaction mass was allowed to attain ambient temperature and the stirring continued for one more hour. Finally, 50 ml of water was added and the reaction mass was filtered through the CELITE®. The bed was further washed with water and Ethyl acetate. The filtrate was basified with 10 % NaOH solution (pH = 9) then extracted with DCM and washed with brine solution, the required product was purified by silica gel (60-120) column chromatography using DCM/methanol as the eluent. Yield : 1.3 g (23 %). ¹H NMR (400MHz, CDCl₃): δ 1.12-1.14 (m, 2H), 1.27-1.29 (m, 2H), 2.12 (broad s, 2H), 7.03-7.07 (t, 1H), 7.33-7.35 (d, 1H), 7.60-7.62 (t, 1H), 8.48-8.49 (d, 1H).



5-(3-Fluoro-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00525] To a mixture of 3-fluoro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methyl benzoic acid (0.2 g, 0.47 mmol, 1 eq), 1-(pyridin-2-yl)cyclopropanamine (0.075 g, 5.5mmol, 1.2 eq) (60 % purity), HOBT (0.81 g, 0.015 mmol, 1.7 eq), EDC.HCl (0.16 g, 0.083 mmol, 1.8 eq) in DCM at ambient temperature and under nitrogen was added Diisopropylethylamine (0.30 g, 2.3 mmol, 5.0 eq). The clear mixture was stirred at ambient temperature for 12 h. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer is further washed with water, dried over sodium sulphate and concentrated. The product obtained was further purified by column chromatography (neutral alumina) using 0.5 % Methanol/DCM and further purification was done using preparative

HPLC. Yield : 0.1 g (50 %). ¹H NMR (400MHz, CDCl₃): δ 1.39-1.42 (m, 2H), 1.67-1.70(m, 2H), 2.21-2.22 (d, 3H, *J* = 2.24 Hz), 2.9-3.0 (d, 3H, *J* = 4.88 Hz), 5.98-5.99 (s, 1H), 7.06-7.09 (dd, 1H, *J* = 5.2, 7.2 Hz), 7.18-7.36 (m, 5H), 7.53-7.62 (m, 4H), 7.76 (d, 1H, *J* = 1.36 Hz), 7.94-7.97 (m, 2H), 8.4 (s, 1H). LCMS : (ES+) *m/z* = 538.2 (M+H). LCMS Method : Column : Atlantis dC18 (50X4.6mm-5μm). A: 10mM NH₄OAc. B : acetonitrile. Flow : 1mL/Min.

Time	%B
0.0-3.0	30-95
3.0-4.0	95
4.0-4.5	95-30
4.5-6.0	30

RT min : 3.665, wavelength:220nm

HPLC Method Info:

- 10
- Sunfire C18 (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
Mobile Phase A : Buffer : MeCN (95:5)
Mobile Phase B : MeCN :Buffer (95:5)
Flow : 1ml/min

Time	B%
0	10
12	100
15	100

- 15
- Wavelength : 254 nm, RT min :10.441
Wavelength : 220 nm, RT min :10.441
Purity : 96%

- XBridge phenyl (4.6X150)mm, 3.5 micron
- 20
- Buffer : 0.05% TFA in water pH 2.5
Mobile Phase A : Buffer : MeCN (95:5)
Mobile Phase B : MeCN : Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :9.592

Wavelength : 220 nm, RT min :9.592

Purity : 95.9 %

5

Methyl 3,5-dihydroxy-4-methylbenzoate

- [00526] 3,5-Dihydroxy-4-methylbenzoic acid (5.0 g, 29.79 mmol, 1.0 eq) and PTSA (1.13 g, 5.94 mmol, 0.2 eq) were dissolved in 50 ml of methanol, and the mixture was heated to reflux for 6 h. Methanol was evaporated. The resultant solid was washed with 10 % sodium bicarbonate solution. The aqueous solution was extracted thrice with ethyl acetate. The combined organic layer was dried over sodium sulphate and evaporated under vacuum. Yield : 5.25 g (96 %). ¹H NMR (400MHz, DMSO-d₆): δ 1.98 (s, 3H), 3.78 (s, 3H), 6.93(s, 2H), 9.53(s, 2H). LCMS : (ES+) m/z = 183 (M+H) Method: Column : PHENOMENEX® Luna C18 (4.6x30) mm, 5 micron. Mphase A : 10% MeOH – 90% H₂O – 10mM NH₄OAc. Mphase B : 90% MeOH –10% H₂O – 10mM NH₄OAc. Flow : 5 ml/min

Time (min.)	%A	%B
0.0	100.0	0.0
2.0	0.0	100.0
3.0	0.0	0.0

RT min : 0.956

Wavelength : 220 nm

20

Methyl 3-(benzyloxy)-5-hydroxy-4-methylbenzoate

- [00527] Methyl 3,5-dihydroxy-4-methylbenzoate (3.5 g, 19.22 mmol, 1.0 eq) was dissolved in 300 ml of DMF. To this solution potassium carbonate (2.52 g, 18.26 mmol, 0.95 eq) was added. To this stirred suspension, benzyl bromide (3.12 g, 18.26

mmol, 0.95 eq) (diluted with 50ml of DMF) was added dropwise over a period of 3 h. The solution was stirred overnight at ambient temperature. Then DMF was evaporated under reduced pressure. The residue was washed with water and the product was extracted thrice with DCM. The combined DCM layers was dried over sodium sulphate and evaporated under vacuum. The required product was purified by silica gel (240-400) column chromatography using 10 % ethyl acetate/hexane as the eluent. Yield : 1.6 g (30 %). ¹H NMR (400MHz, DMSO-d₆): δ 2.07 (s, 3H), 3.81 (s, 3H), 5.14 (s, 2H), 7.08 (s, 1H), 7.14 (s, 1H), 7.33-7.35 (d, 1H, *J* = 7.04 Hz), 7.39-7.42 (t, 2H, *J* = 7.40 Hz), 7.46-7.48 (d, 2H, *J* = 7.48 Hz), 9.78 (s, 1H).

10

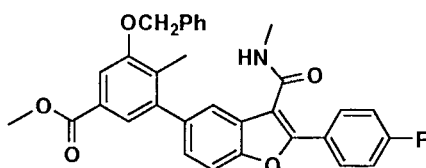
Methyl 3-(benzyloxy)-4-methyl-5-(trifluoromethylsulfonyloxy)benzoate
[00528] Methyl 3-(benzyloxy)-5-hydroxy-4-methylbenzoate (3.0 g, 11.02 mmol, 1.0 eq) was dissolved in DCM followed by *N*-phenyl bis (trifluoromethylsulphonimide) (5.9 g, 16.53 mmol, 1.5 eq). To this stirred solution TEA (3.34 g, 33.06 mmol, 3.0 eq) was added dropwise. The resultant solution was stirred overnight at ambient temperature. To this reaction mass water was added and the DCM layer was separated. The aqueous layer was extracted twice with DCM. The combined DCM layer was dried over sodium sulphate and evaporated. The resultant oil was purified by silica gel (60-120) column chromatography using 5 % ethyl acetate/hexane as the eluent. Yield : 4.0 g (80 %). ¹H NMR (400MHz, DMSO) : δ 2.26 (s, 3H), 3.90 (s, 3H), 5.77 (s, 2H), 7.36-7.39 (d, 1H, *J* = 8.20 Hz), 7.43-7.45 (t, 2H, *J* = 7.60 Hz), 7.51 (s, 3H), 7.70 (s, 1H).

25

Methyl 3-(benzyloxy)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
[00529] To the solution of methyl 3-(benzyloxy)-4-methyl-5-(trifluoromethylsulfonyloxy)benzoate (1.2 g, 2.96 mmol, 1.0 eq) in 1,4-dioxane was added PdCl₂(dppf) in DCM complex (242 mg, 0.296 mmol, 0.1 eq) followed by bis(pinacolato)diboron (1.5 g, 5.93 mmol, 2.0 eq). To this stirred solution TEA (1.5 g, 14.83 mmol, and 5.0 eq) was added. The reaction mixture was slowly heated to 110 °C and maintained for two days in a sealed tube. 1,4-Dioxane was evaporated under reduced pressure. To the residue water was added and the aqueous layer was

30

extracted thrice with DCM. The combined DCM layer was dried over sodium sulphate and evaporated under vacuum. The crude was purified by silica gel (60-120) column chromatography using 1% ethyl acetate/hexane as the eluent. Yield : 0.8 g (70 %). ¹H NMR (400MHz, CDCl₃): δ 1.39 (s, 12H), 2.53 (s, 3H), 3.91 (s, 3H), 5.17 (s, 2H), 7.33-7.35 (d, 1H, *J* = 7.36 Hz), 7.39-7.42 (t, 2H, *J* = 7.50 Hz), 7.48-7.50 (d, 2H, *J* = 7.40 Hz), 7.67-7.68 (d, 1H, *J* = 1.20 Hz), 8.00-8.01 (d, 1H, *J* = 1.40 Hz).



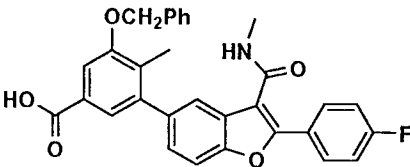
Methyl 3-(benzyloxy)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoate

[00530] To a mixture of 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (0.5 g, 1.2mmol, 1 eq), boronic ester (0.55 g, 1.4 mmol, 1.2 eq), in 1,4-dioxane/H₂O (5:1) was added cesium carbonate (1.37 g, 4.2 mmol, 3eq) and the nitrogen gas was passed through the solution for 10 min. Then tetrakis(triphenylphosphine)palladium (0.12 g, 0.16 mmol, 0.1 eq) was added to the reaction mixture and the nitrogen gas was passed again for 15 min. The above reaction mixture was heated in microwave for one hour at 90 °C. About 100 ml of water is added to the reaction mixture and extracted with EtOAc. The organic layer was further washed twice with water and dried over sodium sulphate and concentrated to get the product. The product obtained was further purified by column chromatography using 60-120 silica gel and 40 % EtOAc/Hexane system. Yield : 0.3 g (48 %). ¹H NMR (400MHz, DMSO-*d*₆): δ 2.20 (s, 3H), 2.82-2.83 (d, 3H, *J* = 4.6 Hz), 3.8 (s, 3H), 5.3 (s, 2H), 7.39-7.46 (m, 6H), 7.52-7.56 (m, 4H), 7.62 (s, 1H), 7.76-7.78 (d, 1H, *J* = 8.44 Hz), 7.99-8.03 (m, 2H), 8.49-8.50 (d, 1H, *J* = 4.52 Hz). LCMS : (ES+) *m/z* = 524.0 (M+H). CHROMOLITH® SpeedROD C18 (4.6X3.0mm-5.0μm). Mphase A : 10% CH₃OH -90% H₂O-0.1% TFA. Mphase B : 90% CH₃OH -10% H₂O-0.1% TFA. Flow : 5 ml/Min.

Time	%B
0.0	0.0

Time	%B
2.0	100.0
3.0	0.0

RT min : 2.303, wavelength : 220 nm



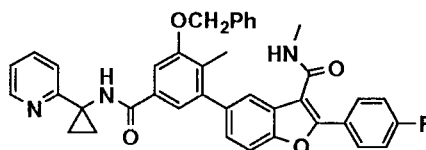
3-(Benzyloxy)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid

5
[00531] To a mixture of methyl 3-(benzyloxy)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoate (0.3 g, 0.57mmol, 1 eq) in a 1:1 mixture of MeOH/THF at ambient temperature was added 5 eq. of NaOH, and the resulting mixture was heated to 60 °C for 5h. The mixture was cooled to ambient
10 temperature and then cooled in ice-water bath. The reaction mixture was acidified with 1.5 N HCl and then concentrated. The mixture with white precipitates was diluted with water and filtered to get the solid. It is further washed with water and dried in vacuum. Yield : 0.2 g (70 %). ¹H NMR (400MHz, DMSO-d₆): δ 2.19 (s, 3H), 2.82-2.83 (d, 3H, *J* = 4.56 Hz), 5.27 (s, 2H), 7.34-7.46 (m, 6H), 7.50-7.55 (m, 4H),
15 7.60 (s, 1H), 7.75-7.77 (d, 1H, *J* = 8.44 Hz), 7.99-8.03 (m, 2H), 8.49-8.50 (d, 1H), 13.0 (s, 1H). LCMS : (ES+) *m/z* = 510 (M+H). Ascentis Express C18 (5.0X2.1-2.7μm). Mphase A : 2% MeCN -98% H₂O-10mM NH₄COOH. Mphase B : 98% MeCN -2% H₂O-10mM NH₄COOH. Flow : 5 ml/Min.

Time	%A	%B
0.0	100.0	0.0
1.5	0.0	100.0
3.2	0.0	100.0
3.6	100.0	0.0

RT min : 1.963, wavelength : 220 nm

20

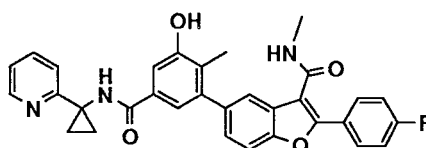


5-(3-(Benzyloxy)-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

[00532] To a mixture of 3-(benzyloxy)-5-(2-(4-fluorophenyl)-3-

- 5 (methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (0.2 g, 0.40 mmol, 1 eq),
1-(pyridin-2-yl)cyclopropanamine (0.064 g, 0.47 mmol, 1.2 eq) (60 % purity), HOBT
(0.68 g, 0.012 mmol, 1.7 eq), EDC.HCl (0.064 g, 0.72 mmol, 1.8 eq) in DCM at
ambient temperature under nitrogen was added Diisopropylethylamine (0.26 g, 2.0
mmol, 5.0 eq). The clear mixture was stirred at ambient temperature for 12 h. The
10 mixture was concentrated, diluted with water and extracted with EtOAc. The organic
layer was further washed with water, dried over sodium sulphate and concentrated.
The product obtained was further purified by column chromatography (neutral
alumina) using 0.5 % Methanol/DCM and preparative HPLC. Yield : 0.17 g (70 %).
¹H NMR (400MHz, DMSO-d₆): δ 1.26-1.27 (m, 2H), 1.54-1.56 (m, 2H), 2.18 (s, 3H),
15 2.81-2.82 (s, 3H), 5.26 (s, 2H) 7.13-7.15 (q, 1H, *J* = 4.4 Hz), 7.30-7.43 (m, 6H), 7.58
(d, 4H), 7.65-7.69 (t, 2H, *J* = 3.9 Hz), 7.74-7.79 (d, 1H, *J* = 8.0 Hz), 7.97-8.01 (m,
2H), 8.43-8.48 (dd, 2H, *J* = 4.89 Hz), 9.186 (s, 1H). LCMS : (ES+) *m/z* = 626 (M+H)
Ascentis Express C18 (5.0X2.1-2.7μm). Mphase A : 2% MeCN -98% H₂O-10mM
NH₄COOH. Mphase B : 98% MeCN -2% H₂O-10mM NH₄COOH. Flow : 5
20 ml/Min.

Time	%A	%B
0.0	100.0	0.0
1.5	0.0	100.0
3.2	0.0	100.0
3.6	100.0	0.0



2-(4-Fluorophenyl)-5-(3-hydroxy-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-N-ethylbenzofuran-3-carboxamide

[00533] To a solution of 3-(benzyloxy)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (0.17 g, 0.27 mmol, 1 eq) in DCM was added BCl₃ in DCM (0.32 g, 2.7 mmol, 10 eq). The clear mixture was stirred at ambient temperature for overnight. LCMS showed the desired product. The mixture was quenched with 10 % NaHCO₃ and extracted with EtOAc. The organic layer is further washed with water, dried over sodium sulphate and concentrated. The product obtained was further purified by column chromatography (neutral alumina) using 0.5 % Methanol/DCM and it was further purified with preparative HPLC. Yield : 0.048 g (33 %). ¹H NMR (400MHz, DMSO-d₆): δ 1.22-1.24 (m, 2H), 1.51-1.53 (m, 2H), 2.09 (s, 3H), 2.82-2.83 (s, 3H, J = 4.4 Hz), 7.12-7.15 (q, 1H), 7.30-7.32 (d, J = 8 Hz, 1H), 7.37-7.43 (m, 5H), 7.58 (s, 1H), 7.65-7.69 (t, 1H, J = 8 Hz), 7.74-7.76 (d, 1H, J = 8.8 Hz), 7.97-8.01 (m, 2H), 8.43-8.48 (dd, 2H, J = 16, 4.8 Hz), 9.18 (s, 1H), 9.77 (s, 1H). LCMS : (ES+) m/z = 536.2 (M+H). Column : Ascentis Express C18 (5X2.1mm-2.7µm). Mphase A : 2% MeCN -98% H₂O-10mM NH₄COOH. Mphase B : 98% MeCN – 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min.

Time	%A	%B
0.0	100.0	0
1.5	0.0	100.0
3.2	0.0	100.0
3.6	100.0	0.0

RT min : 1.862, wavelength:220nm

20 HPLC Method Info:
Sunfire C18 (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
Mobile Phase A : Buffer : MeCN (95:5)
Mobile Phase B : MeCN : Buffer (95:5)
25 Flow : 1ml/min

Time	B%
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Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :9.255

Wavelength : 220 nm, RT min :9.255

Purity : 95.2%

5 XBridge phenyl (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

10 Wavelength : 254 nm, RT min :9.046

Wavelength : 220 nm, RT min :9.046

Purity : 95.8%

2-Fluoro-3-iodo-4-methylbenzonitrile

15 [00534] A solution of 2,2,6,6-tetramethyl-4-piperidine (TMP) (550 mg, 3.93 mmol, 2.1 eq) in THF (5 ml) was cooled to -78 °C under nitrogen atmosphere. N-Butyl lithium (1.6 M in hexane, 1.52 ml, 3.96 mmol, 2.1 eq) was added slowly maintaining the temperature below -70 °C. After addition, the reaction mixture was warmed to -50 °C. and stirred for one hour. The clear solution became turbid indicating the salt

20 formation. The reaction mixture was cooled to -80 °C, and a solution of 2-fluoro-4-methylbenzonitrile (250 mg, 1.85 mmol, 1.0 eq) in THF (1 ml) was slowly added maintaining temperature below -70 °C. The mixture was then warmed to -50 °C. and stirred for 30 minutes. The mixture was re-cooled to -78 °C. and a saturated solution

of iodine (516 mg, 2.03 mmol, 1.1 eq) in THF (1 ml) was added slowly maintaining the temperature below -70 °C. After addition, the mixture was warmed to ambient temperature. The reaction mixture was poured into a saturated solution of Na₂S₂O₃ (10 ml) and stirred for 30 minutes. The organic layer was separated, and the aqueous
5 layer was extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over sodium sulphate. The volatiles were evaporated under reduced pressure. The crude product was purified under silica gel (60-120) column chromatography using 0.5 % ethyl acetate/hexane as eluent. Yield : 187 mg (38 %).
10 ¹H NMR (400MHz, CDCl₃): δ 2.55 (s, 3H), 7.13-7.15 (d, 1H, *J* = 7.92 Hz), 7.48-7.50 (t, 1H, *J* = 4.80 Hz).

2-Fluoro-3-iodo-4-methylbenzoic acid

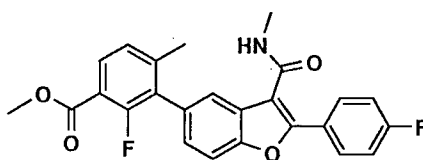
[00535] A mixture of 2-fluoro-3-iodo-4-methylbenzonitrile (450 mg, 1.71 mmol, 1.0 eq) in dioxane 2 ml and 60 % sulphuric acid (2 ml) was heated at 115 °C. in an oil
15 bath for 12 h. After the mixture was cooled to room temperature, it was poured on to 10 g of ice. The tan solid was filtered, washed with water followed by ethyl acetate. The solid collected was dried to afford 2-fluoro-3-iodo-4-methylbenzoic acid as a tan crystalline solid. The filtrate was transferred to a separatory funnel. The ethyl acetate layer was separated, washed with brine, dried over sodium sulphate and concentrated
20 to afford additional 2-fluoro-3-iodo-4-methylbenzoic acid. Yield : 450 mg (93 %). ¹H NMR (400MHz, DMSO-d₆): δ 2.48 (s, 3H), 7.27-7.29 (d, 1H, *J* = 8.00 Hz), 7.74-7.78 (t, 1H, *J* = 7.82 Hz), 13.2 (b, 1H).

Methyl 2-fluoro-3-iodo-4-methylbenzoate

25 [00536] To the solution of 2-fluoro-3-iodo-4-methylbenzoic acid (450 mg, 1.6 mmol, 1.0 eq) in methanol (5 ml), catalytic amount of conc.HCl (0.1 ml) was added. The resultant solution was heated to reflux at 80 °C for overnight. Methanol was evaporated. To this residue, water was added and the aqueous layer was extracted thrice with ethyl acetate. The combined ethyl acetate extracts were dried over sodium
30 sulphate, filtered and evaporated to afford methyl 2-fluoro-3-iodo-4-methylbenzoate. Yield: 450 mg (95 %). ¹H NMR (400MHz, DMSO): δ 2.49 (s, 3H), 3.85 (s, 3H),

7.30-7.32 (d, 1H, $J = 7.84$ Hz), 7.76-7.80 (t, 1H, $J = 7.82$ Hz). LCMS : (ES+) $m/z = 295$ (M+H).

- Methyl 2-fluoro-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
- 5 [00537] To the solution of methyl 2-fluoro-3-iodo-4-methylbenzoate (1.1 g, 3.74 mmol, 1.0 eq) in DMSO was added [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (305 mg, 0.37 mmol, 0.1 eq) followed by bis(pinacolato)diboron (1.9 g, 7.48 mmol, 2.0 eq). To this solution potassium acetate (1.83 g, 18.7 mmol, 5.0 eq) was added and nitrogen gas was passed through for 10 minutes. The resultant
- 10 solution was irradiated with microwave at 80 °C for 40 minutes. Reaction mixture was quenched with brine solution. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layer was dried over sodium sulphate and the clear ethyl acetate layer was evaporated under vacuum. The crude was purified by silica gel (60-120) column chromatography using 1 % ethyl acetate/hexane as eluent. Yield :
- 15 400 mg (36 %). ^1H NMR (400MHz, CDCl_3): δ 1.38 (s, 12H), 2.46 (s, 3H), 3.89 (s, 3H), 6.98-7.00 (d, 1H, $J = 7.84$ Hz), 7.81-7.85 (t, 1H, $J = 7.82$ Hz). LCMS : (ES+) $m/z = 295$ (M+H).



- 20 Methyl 2-fluoro-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoate
- [00538] To a mixture of 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (0.4 g, 0.96 mmol, 1 eq), boronic ester (0.366 g, 1.24 mmol, 1.3 eq), in 1,4-dioxane/ H_2O (5:1) was added cesium carbonate (0.938 g, 2.87
- 25 mmol, 3 eq) and the nitrogen gas was passed through for 10 min. Then tetrakis(triphenylphosphine) palladium (0.111 g, 0.095 mmol, 0.1 eq) was added to the reaction mixture and nitrogen gas was again passed through the mixture for 15 min. The above reaction mixture was heated in microwave for one hour at 90 °C. About 100 ml of water is added to the reaction mixture and extracted with EtOAc. The
- 30 organic layer was further washed twice with water and dried over sodium sulphate,

concentrated to get the product. The product obtained was further purified by column chromatography using 60-120 silica gel and 25 % EtOAc/Hexane as eluent. Yield :

0.320 g (76 %). ¹H NMR (400MHz, DMSO-d₆) : δ 2.19 (s, 3H), 2.81-2.82 (d, 3H, *J* = 4.64 Hz), 3.85 (s, 3H), 7.31-7.34 (d, 2H, *J* = 8.28 Hz), 7.39-7.44 (t, 2H, *J* = 8.90 Hz),

5 7.54 (s, 1H), 7.79-7.85 (m, 2H), 7.97-8.01 (m, 2H), 8.45-8.46 (d, 1H, *J* = 4.32 Hz

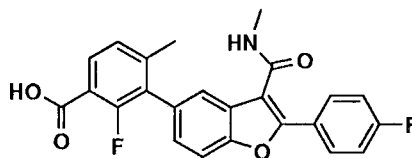
LCMS : (ES+) *m/z* = 436 (M+H). Method: Column : CHROMOLITH® SpeedRod C18 (4.6x30)mm, 5 micron. Mphase A : 10% MeOH – 90% H₂O – 0.1% TFA.

Mphase B : 90% MeOH – 10% H₂O – 0.1% TFA. Flow : 5 ml/min.

Time (min.)	%A	%B
0.0	100.0	0.0
2.0	0.0	100.0
3.0	0.0	0.0

RT min : 2.034

10 Wavelength : 220 nm



2-Fluoro-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid

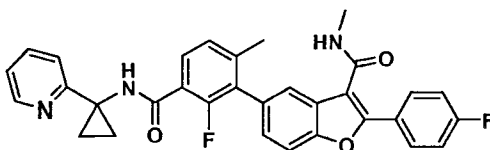
- 15 [00539] To a mixture of methyl 3-fluoro-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoate (0.320 g, 1 eq) in a 1:1 mixture of MeOH/THF, 1 M solution of NaOH (0.088 g, 2.20 mmol, 3.0 eq) was added and heated to 90 °C for 3h. The mixture was cooled to ambient temperature and then in an ice-water bath. It was acidified with 1.5 N HCl and then volatiles were
- 20 evaporated. The mixture with white precipitate was diluted with water and filtered to get the product. It was further washed with water and dried in vacuum. Yield : 0.220 g (71 %). ¹H NMR (400MHz, DMSO-d₆) : δ 2.17 (s, 3H), 2.81-2.82 (d, 3H, *J* = 4.60 Hz), 7.28-7.33 (m, 2H, *J* = 4.33 Hz), 7.39-7.44 (m, 2H, *J* = 8.88 Hz), 7.53 (d, 1H, *J* = 1.24 Hz), 7.78-7.83 (m, 2H, *J* = 5.93 Hz), 7.97-8.01 (m, 2H), 8.45-8.47 (d, 1H, *J* =
- 25 4.60 Hz), 13.13 (s, 1H). LCMS : (ES+) *m/z* = 422.0 (M+H). Method: Column :

CHROMOLITH® SpeedRod C18 (4.6x30)mm, 5 micron. Mphase A : 10% MeOH – 90% H₂O – 0.1% TFA. Mphase B : 90% MeOH – 10% H₂O – 0.1% TFA. Flow : 5 ml/min.

Time (min.)	%A	%B
0.0	100.0	0.0
2.0	0.0	100.0
3.0	0.0	0.0

RT min : 1.961

5 Wavelength : 220 nm



5-(2-Fluoro-6-methyl-3-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide

- 10 **[00540]** To the solution of 2-fluoro-3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (0.1 g, 0.273 mmol, 1.0 eq) in DMF (5.0 ml), 1-(pyridin-2-yl)cyclopropanamine (0.038 g, 0.285 mmol, 1.2 eq), TBTU (0.130 g, 0.403 mmol, 1.7 eq) and DIPEA (0.154 g, 1.187 mmol, 5.0 eq) were added. Mixture was stirred at ambient temperature for 12 h under nitrogen
- 15 atmosphere. DMF was concentrated and to this residue water was added and extracted with ethyl acetate. The combined organic layer was dried over sodium sulphate and ethyl acetate was evaporated. The crude was purified by preparative TLC eluted with hexane/EtOAc (5:5). The product was further purified by recrystallization with DCM and hexane. Yield : 0.045 g (39 %). ¹H NMR (400MHz, DMSO-d₆): δ 1.23-1.25 (m, 2H), 1.51-1.54 (m, 2H), 2.18 (s, 3H), 2.81-2.82 (d, 3H, *J* = 4.0 Hz), 7.13-7.15 (t, 1H, *J* = 3.78 Hz), 7.27-7.29 (d, 1H, *J* = 8.00 Hz), 7.33-7.35 (d, 1H, *J* = 4.26 Hz), 7.39-7.44 (m, 3H, *J* = 5.26 Hz), 7.56-7.60 (t, 2H, *J* = 7.56 Hz), 7.68-7.72 (m, 1H), 7.80-7.82 (d, 1H, *J* = 8.44 Hz), 7.96-8.00 (m, 2H), 8.43-8.49 (m, 2H), 9.12 (s, 1H). LCMS : (ES⁺) *m/z* = 538.0 (M+H). Method: Column : CHROMOLITH® SpeedRod C18
- 20

(4.6x30) mm, 5 micron. Mphase A : 10% MeOH – 90% H₂O – 0.1% TFA. Mphase B : 90% MeOH – 10% H₂O – 0.1% TFA. Flow : 5 ml/min.

Time (min.)	%A	%B
0.0	100.0	0.0
2.0	0.0	100.0
3.0	0.0	0.0

RT min : 1.813

Wavelength : 220 nm

5

HPLC Method:

Column : Sunfire C18 (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : MeCN (95:5)

10 Mobile Phase B : MeCN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :10.566 (Purity : 98.287%)

Wavelength : 220 nm, RT min :10.041 (Purity : 97.3%)

15 Column : XBridge phenyl (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100

Time	B%
15	100

Wavelength : 254 nm, RT min : 10.041 (Purity : 98.3%)

Wavelength : 220 nm, RT min : 10.041 (Purity : 97.3%)

2-Methyloxazole-4-carbonitrile

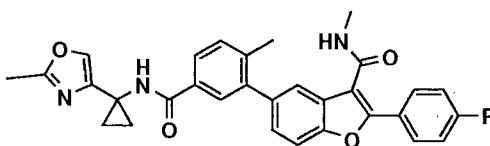
- 5 [00541] Ethylacetimidate hydrochloride (25 g, 340 mmol, 1 eq) and aminoacetonitrile (38.5 g, 410 mmol, 1.2 eq) were suspended in dichloromethane (300 ml) at room temperature. Triethylamine (148.4 ml, 380 mmol, 1.1 eq) was added dropwise over 1 h. After the completion of addition, the reaction mixture was cooled to 0 °C, water (125 ml) was added, organic layer was separated and the aq. layer was
- 10 extracted with 50 ml of dichloromethane. The combined dichloromethane mixture was concentrated to 50 ml. Diethyl ether (500 ml) was added to this solution, which was then cooled to 0 °C. To the above solution ethylformate (13.93 g, 190 mmol, 0.55 eq) was added followed by the addition of Potassium *tert*-butoxide (20.6 g, 172 mmol, 0.51 eq). The reaction was allowed to stir at room temperature for 90 minutes
- 15 and at 50 °C for 90 minutes. Chlorotrimethylsilane (56.5g, 520 mmol, 1.5 eq) was added at reflux condition and the reaction was stirred at 50 °C for 5 h. Later water was added and the product was extracted with dichloromethane and the organic layer was washed with water and purified by column chromatography yielding product as colorless oil. Yield : 6 g (16 %) overall yield. ¹H NMR (400MHz, DMSO-d₆): δ 2.5
- 20 (s, 3H), 8.07 (s, 1H).

1-(2-Methyloxazol-4-yl)cyclopropanamine

- [00542] 2-Methyloxazole-4-carbonitrile (5 g, 46.1 mmol, 1 eq) was dissolved in dry THF at room temperature, and to which titanium(IV) isopropoxide (16 ml, 655
- 25 mmol, 1.2 eq) was added dropwise over a period of 15 minutes. The resulting mixture was stirred for 10 min and ethyl magnesium bromide (85 ml, 17 volumes) was added slowly dropwise at ambient temperature and the reaction was stirred for 1 h. Later BF₃.etherate (16.7 ml, 115 mmol, 2.5 eq) was added slowly at ambient temperature and the above solution was stirred at ambient temperature for 3 h. Finally water was
- 30 added and the pH was brought to 10 using 10 % sodium hydroxide solution. The

reaction mixture was extracted with dichloromethane, concentrated and purified by combiflash chromatography. Yield : 1.5 g (20 %). ¹H NMR (400MHz, DMSO-d₆): δ 0.93 (m, 2H), 1.00 (m, 2H), 1.98 (br s, 2H), 2.39 (s, 3H), 7.33 (s, 1H). LCMS : (ES+) m/z = 138.9 (M+H).

5



2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(1-methyl-1H-pyrazol-3-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

- [00543] To a mixture of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (0.15 g, 0.37 mmol, 1 eq), 1-(2-methyloxazol-4-yl)cyclopropanamine (0.066 g, 0.47, 1.2 eq), HOBT (0.092 g, 0.68 mmol, 1.7 eq), EDC.HCl (0.14 g, 0.73 mmol, 1.8 eq) in DCM at ambient temperature under nitrogen was added Diisopropylethylamine (0.26 g, 2.2 mmol, 5.0 eq). The clear mixture was stirred at ambient temperature for 12 h. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer is further washed with water, dried over sodium sulphate and concentrated. The product obtained was further purified by column chromatography (neutral alumina) using 0.5 % Methanol/DCM as an eluent followed by preparative HPLC. Yield : 0.02 g (20 %). ¹H NMR (400MHz, DMSO-d₆): δ 1.10-1.13 (m, 2H), 1.21-1.24 (m, 2H), 2.29 (s, 3H), 2.33 (s, 3H), 2.81-2.82 (d, 3H, *J* = 4.6 Hz), 7.38-7.43 (m, 4H), 7.57 (s, 1H), 7.61 (s, 1H), 7.75-7.71 (d, 1H, *J* = 8.4 Hz), 7.80-7.81 (s and m, 2H), 7.97-8.01 (m, 2H), 8.47-8.48 (d, 1H, *J* = 4.76 Hz), 9.1 (s, 1H). LCMS : (ES+) m/z = 524.2 (M+H). LCMS Method : CHROMOLITH® SpeedROD C18 (4.6X3.0mm-5.0μm). Mphase A : 2% MeCN - 98% H₂O-10mM NH₄COOH. Mphase B : 98% MeCN - 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min.

Time	%B
0.0	0.0
2.0	100.0
3.0	100.0

WO 2010/030592

PCT/US2009/056166

RT min : 2.018, wavelength : 220 nm

HPLC Method:

Sunfire C18 (4.6X150) mm, 3.5 micron

5 Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :10.757

10 Wavelength : 220 nm, RT min :10.757

Purity: 96.7%

XBridge phenyl (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5

15 Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN : Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

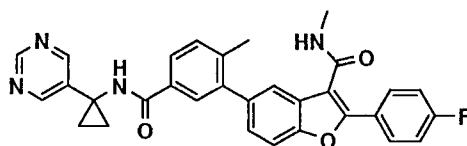
Wavelength : 254 nm, RT min :9.993

Wavelength : 220 nm, RT min :9.993

20 Purity: 96.7%

1-(Pyrimidin-5-yl)cyclopropanamine

[00544] 5-Cyano pyrimidine (5 g, 47.6 mmol, 1 eq) was taken in a Dry THF under Argon atmosphere, then Titanium isopropoxide (17 ml, 57.1 mmol, 1.2 eq) was added slowly at ambient temperature and the resulting mass was stirred for 15 mins. To the above stirred solution was added Ethyl magnesium bromide (1 M solution in THF, 107 ml, 809.3 mmol, 2.5 eq) slowly via syringe at ambient temperature. (During the addition of EtMgBr reaction mass turned black). Then the reaction mass was stirred for an hour, BF₃.EtO (16.7 ml, 119.0 mmol, 2.5 eq) was added slowly through syringe at 0 °C. Then the reaction was allowed to attain ambient temperature and the stirring was continued for another one hour. Finally the reaction was quenched by adding 50ml of water and the reaction mass was passed through CELITE® and the bed was washed with water and Ethyl acetate. The filtrate was basified with 10 % NaOH solution (pH = 9) and then extracted with DCM and washed with brine solution. The required product was purified by silica gel (60-120) column chromatography using DCM/methanol as the eluent. Yield: 0.1 g (5 %) ¹H NMR (400MHz, DMSO-d₆) : 1.04-1.08 (q, 2H, J = 3.96 Hz), 1.18-1.25 (q, 2H, J = 3.96 Hz), 8.26 (d, 2H), 9.05 (s, 1H). LCMS : (ES+) m/z = 136 (M+H).



2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyrimidin-5-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00545] To a mixture of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (0.1 g, 0.25 mmol, 1 eq), 1-(pyrimidin-5-yl)cyclopropanamine (0.041 g, 0.3 mmol, 1.2 eq) (60 % purity), HOBt (0.057 g, 0.42 mmol, 1.7 eq), EDC.HCl (0.086 g, 0.44 mmol, 1.8 eq) in DCM at ambient temperature under nitrogen was added Diisopropylethylamine (0.162 g, 1.2 mmol, 5.0 eq). The clear mixture was stirred at ambient temperature for overnight. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer is further washed with water, dried over sodium sulphate and concentrated. The product obtained was further purified by column chromatography (neutral alumina) using 0.5 % Methanol/DCM and finally it was purified by preparative HPLC. Yield :

0.02 g (20 %). ¹H NMR (400MHz, DMSO-d₆) : δ 1.34-1.35 (m, 2H), 1.41-1.42 (m, 2H), 2.29 (s, 3H), 2.81-2.82 (d, 3H, J = 4.56 Hz), 7.38-7.45 (m, 4H), 7.58 (d, 1H, J = 0.96 Hz), 7.75 (d, 1H, J = 8.4 Hz), 7.81 (s, 1H), 7.83 (m, 1H), 7.98-8.01 (m, 2H), 8.46-8.47 (d, 1H, J = 4.6 Hz), 8.64 (s, 2H), 9.01 (s, 1H), 9.31 (s, 1H). LCMS : (ES+) m/z = 521.2(M+H). LCMS Method : Column : Ascentis Express C18 (5X2.1mm-2.7μm). Mphase A : 2% ACN -98% H₂O-10mM NH₄COOH. Mphase B : 98% ACN - 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min.

Time	%A	%B
0.0	100.0	0
1.5	0.0	100.0
3.2	0.0	100.0
3.6	100.0	0.0

RT min : 1.825, wavelength: 220 nm

- 10 HPLC Method:
Sunfire C18 (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
Mobile Phase A : Buffer : MeCN (95:5)
Mobile Phase B : MeCN :Buffer (95:5)

- 15 Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :10.061
Wavelength : 220 nm, RT min :10.061
Purity : 92.3 %

- 20 XBridge phenyl (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

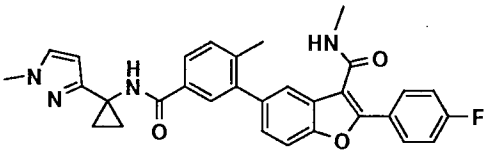
Wavelength : 254 nm, RT min :9.542

Wavelength : 220 nm, RT min :9.542

5 Purity : 92.5 %

1-(1-Methyl-1H-pyrazol-3-yl)cyclopropanamine

[00546] Ethyl magnesium bromide (2.5 mol, 1 M in ether) was added at -78 °C to a solution of a 1-methyl-1H-pyrazole-3-carbonitrile (0.5 g, 1 mmol) and Ti(Oi-Pr)₄ (1.1 mmol) in Et₂O (5 mL). The yellow solution was stirred for 10 min. After the solution was warmed to ambient temperature (1 h), BF₃.OEt₂ (2 mmol) was added. After the mixture was stirred for 1 h, 1 N HCl and ether were added. NaOH (10 %) was added to the resulting two clear phases and the mixture was extracted with ether. The combined ether layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Et₂O). ¹H NMR (400MHz, CDCl₃): δ 0.94-1.05 (m, 4H), 2.32 (s, 2H), 3.83 (s, 3H), 5.92 (d, 1H), 7.23-7.24 (d, 1H). LCMS : (ES+) m/z observed 137.7.



20 2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(1-methyl-1H-pyrazol-3-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00547] To a mixture of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (0.15 g, 0.37 mmol, 1 eq), 1-(1-methyl-1H-pyrazol-3-yl)cyclopropanamine (0.061 g, 0.44 mmol, 1.2 eq), HOBT (0.057 g, 0.42 mmol, 1.7 eq), EDC.HCl (0.086 g, 0.44 mmol, 1.8 eq) in DCM at ambient temperature under

25

nitrogen was added diisopropylehtylamine (0.16 g, 1.2mmol, 5.0 eq). The clear mixture was stirred at ambient temperature for 12 h. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer was further washed with water, dried over sodium sulphate and concentrated. The product obtained was

5 further purified by column chromatography (neutral alumina) using 0.5 % Methanol/DCM and finally by preparative HPLC. Yield : 0.06 g (40 %) ¹H NMR (400MHz, DMSO-d₆): δ 1.12-1.16 (m, 2H), 1.20-1.23 (m, 2H), 2.29 (s, 3H), 2.82-2.83 (d, 3H, *J* = 4.64 Hz), 3.37 (s, 3H), 5.9-6.0 (d, 1H, *J* = 2.12 Hz), 7.39-7.48 (m, 5H), 7.58 (d, 1H, *J* = 1.68 Hz), 7.75-7.77 (d, 1H, *J* = 9.7 Hz), 7.81-7.83 (t, 2H, *J* =

10 2.87 Hz), 7.98-8.46 (m, 2H), 8.47-8.48 (d, 1H, *J* = 4.52 Hz), 9.14 (s, 1H). LCMS : (ES+) *m/z* = 523.2 (M+H). LCMS Method : Column : Ascentis Express C18 (5X2.1mm-2.7μm). Mphase A : 2% MeCN -98% H₂O-10mM NH₄COOH. Mphase B : 98% MeCN – 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min.

Time	%A	%B
0.0	100.0	0.0
1.0	70.0	30.0
2.5	0.0	100.0
4.0	0.0	100.0

RT min : 1.882, wavelength : 220 nm

15

HPLC Method Info:
 Sunfire C18 (4.6X150)mm, 3.5 micron
 Buffer : 0.05% TFA in water pH 2.5
 Mobile Phase A : Buffer : MeCN (95:5)
 20 Mobile Phase B : MeCN :Buffer (95:5)
 Flow : 1ml/min

Time	B%
0	10
25	100
30	100

Wavelength : 254 nm, RT min :16.999

WO 2010/030592

PCT/US2009/056166

Wavelength : 220 nm, RT min :16.999

Purity: 96%

XBridge phenyl (4.6X150)mm, 3.5 micron

5 Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :15.556

10 Wavelength : 220 nm, RT min :15.556

Purity: 97 %

Methyl 2-methoxy-4-methylbenzoate

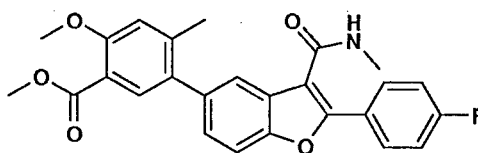
[00548] Methyl 2-methoxy-4-methylbenzoic acid (1.5 g, 9.0 mmol, 1 eq) was dissolved in DMF, methyl iodide (0.86 ml, 13.5 mmol, 1.5 eq) was added to it followed by the addition of potassium carbonate (3.11 g, 22.5 mmol, 2.5 eq). The above mixture was stirred at room temperature for 12 h. Finally, the reaction mixture was passed through CELITE®. The filtrate was evaporated and water was added and the product was extracted with ethyl acetate. The organic layer was washed with water and concentrated. Yield : 1.6 g (98 %). ¹H NMR (400MHz, CDCl₃): δ 2.31 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 6.77 (s, 1H), 6.79 (d, 1H), 7.14 (d, 1H).

Methyl 5-iodo-2-methoxy-4-methylbenzoate

[00549] Methyl 2-methoxy-4-methylbenzoate (1.5 g, 8.32 mmol, 1 eq) was dissolved in methanol. To this solution was added dropwise iodine monochloride (6.75 g, 41.6 mmol, 5 eq) in methanol at room temperature. The reaction mixture was heated at 50 °C for 15 h. Finally, methanol was concentrated, diluted with water and

extracted with ethyl acetate. The organic layer was washed with 0.1 N HCl (50 ml), water (100 ml) and brine solution (100 ml). The product was purified by column chromatography using 60-120 silica gel and using 5% ethyl acetate/hexane as eluent. Yield : 1.7 g (80 %). ¹H NMR (400MHz, CDCl₃): δ 2.44 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.86 (s, 1H), 8.20 (s, 1H). LCMS : (ES+) m/z = 307.0 (M+H).

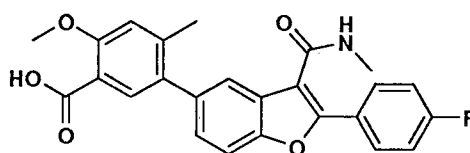
Methyl 2-methoxy-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
[00550] Methyl 5-iodo-2-methoxy-4-methylbenzoate (1.5 g, 4.9 mmol, 1 eq), Bispinacolatodiboron (1.49 g, 5.8 mmol, 1.2 eq), potassium acetate (1.44 g, 14.7 mmol, 3 eq) and Pd(dppf)Cl₂ (0.4 g, 0.49 mmol, 0.1 eq) were dissolved in DMF. Nitrogen gas was passed through the mixture for 10 minutes and the mixture was stirred at 90 °C for 14 hours. Later the solution was passed through CELITE®. The filtrate was evaporated and diluted with water and extracted with ethyl acetate and purified by column chromatography using 60-120 silica gel and using 20 % ethyl acetate/hexane as eluent. Yield : 1.2 g (80 %). ¹H NMR (400MHz, CDCl₃): δ 1.33 (s, 12H), 2.56 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 6.75 (s, 1H), 8.21 (s, 1H). LCMS : (ES+) m/z = 307.2 (M+H).



Methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoate

[00551] Methyl-2-methoxy-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.2 g, 3.92 mmol, 1 eq), 2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl trifluoromethanesulfonate (1.6 g, 3.92 mmol, 1 eq), Cesium carbonate (3.8 g, 11.7 mmol, 3 eq) and Tetrakis triphenylphosphinepalladium (0.13 g, 0.11 mmol, 0.03 eq) were dissolved in 1,4-dioxane/water and the above solution was stirred at 90 °C for 10 h. Then the reaction mixture was diluted with water and product was extracted with ethyl acetate and purified by combiflash chromatography using 40 % ethyl acetate/hexane as eluent. Yield : 0.95 g (55 %). ¹H NMR (400MHz, DMSO-d₆): δ 2.3 (s, 3H), 2.82 (d, J = 4.6

Hz, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 7.15 (s, 1H), 7.51 (s, 1H), 7.64 (m, 2H), 7.65 (m, 2H), 7.74 (d, 1H, $J = 8.48$ Hz), 8.00-8.01 (m, 2H), 8.48 (d, 1H). LCMS : (ES+) $m/z = 448$ (M+H).



5-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoic acid

[00552] Methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoate (0.9 g, 2 mmol, 1 eq) and sodium hydroxide (0.4 g, 10 mmol, 5 eq) were dissolved in methanol/water (20/5 ml) and the reaction was stirred at 50 °C for 10 h. Then the reaction mixture was concentrated and diluted with water and the pH of the solution was brought to 3 by using Conc HCl. The solid obtained was filtered and dried overnight. Yield : 0.72 g (82 %). ^1H NMR (400MHz, DMSO- d_6): δ 2.29 (s, 3H), 2.87 (d, 3H), 3.87 (s, 3H), 7.09 (s, 1H), 7.40-7.60 (m, 3H), 7.57 (m, 2H), 7.65 (d, 1H, $J = 8.74$ Hz), 7.98-8.01 (m, 2H), 8.46 (q, 1H, $J = 4.40$ Hz), 12.5 (br s, 1H). LCMS : (ES+) $m/z = 434$ (M+H) Method : Mphase A : water; Mphase B : 0.1% acetone in water; Flow : 2mL/Min.

Time	%B
0-20	100

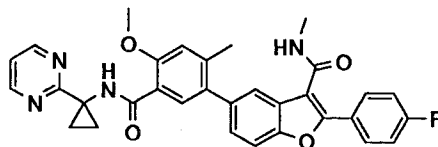
RT min : 1.741

Wavelength : 220 nm

20

[00553] Additional LCMS were performed by using Shimadzu-VP instrument with UV detection at 220 nm and Waters MICROMASS®. HPLC method: Solvent A = 10% MeOH 90% H_2O 0.1% TFA, Solvent B = 90% MeOH 10% H_2O 0.1% TFA, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: PHENOMENEX® Luna, 3.0 x 50 mm, S10; (ES+) m/z (M+H) $^+$ = 434.10, HPLC R_t = 1.653 min.

25



2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl) phenyl)-N-methylbenzofuran-3-carboxamide

- [00554] To a mixture of 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoic acid (0.2 g, 0.46 mmol, 1 eq), 1-(pyrimidin-2-yl)cyclopropanamine (0.074 g, 0.55 mmol, 1.2 eq), HOBT (0.105 g, 0.77 mmol, 1.7 eq), EDC.HCl (0.0158 g, 0.82 mmol, 1.8 eq), in DCM at ambient temperature and under nitrogen atmosphere was added diisopropylethylamine (0.297 g, 2.2 mmol, 5.0 eq). The clear mixture was stirred at ambient temperature for 12 h. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer was further washed with water, dried over sodium sulphate and concentrated. The product obtained was further purified by column chromatography (neutral alumina) using 0.5 % Methanol/DCM and preparative HPLC. Yield : 0.055 g (45%). ¹H NMR (400MHz, DMSO-d₆): δ 1.43-1.44 (m, 2H), 1.59-1.62 (m, 2H), 2.31 (s, 3H), 2.81-2.82 (d, 3H, *J* = 4.56 Hz), 4.01 (s, 3H), 7.17 (s, 1H), 7.26-7.29 (t, 1H, *J* = 4.8 Hz), 7.33-7.36 (dd, 1H, *J* = 8.4, 4 Hz), 7.38-7.43 (t, 2H, *J* = 8.8 Hz), 7.50-7.51 (d, 1H, *J* = 1.6 Hz), 7.72-7.76 (m, 2H), 7.97-8.01 (m, 2H), 8.48-8.49 (d, 1H, *J* = 4.4 Hz), 8.7 (d, 2H, *J* = 4.8 Hz), 8.87 (s, 1H). LCMS : (ES⁺) *m/z* = 551.2 (M+H). Column : Ascentis Express C18 (5X2.1mm-2.7μm). Mphase A : 2% MeCN -98% H₂O-10mM NH₄COOH.
- Mphase B : 98% MeCN – 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min

Time	%A	%B
0.0	100.0	0.0
1.0	70.0	30.0
2.5	0.0	100.0
4.0	0.0	100.0

RT min : 1.946, wavelength:220nm

HPLC Method:

Sunfire C18 (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5
 Mobile Phase A : Buffer : MeCN (95:5)
 Mobile Phase B : MeCN :Buffer (95:5)
 Flow : 1ml/min

Time	B%
0	10
25	100
30	100

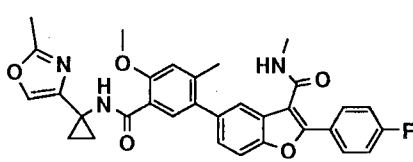
- 5 Wavelength : 254 nm, RT min :18.209
 Wavelength : 220 nm, RT min :18.209
 Purity: 99.4%

XBridge phenyl (4.6X150)mm, 3.5 micron

- 10 Buffer : 0.05% TFA in water pH 2.5
 Mobile Phase A : Buffer : MeCN (95:5)
 Mobile Phase B : MeCN :Buffer (95:5)
 Flow : 1ml/min

Time	B%
0	10
25	100
30	100

- Wavelength : 254 nm, RT min :16.549
- 15 Wavelength : 220 nm, RT min :16.549
 Purity: 99.5 %



- 20 2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(2-methyloxazol-4-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00555] 5-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoic acid (0.15 g, 0.34 mmol, 1 eq), 1-(2-methyloxazol-4-yl)cyclopropanamine (0.047 g, 0.34 mmol, 1 eq), EDCL.HCl (0.076 g, 0.4 mmol, 1.2 eq), HOBT (0.054 g, 0.4 mmol, 2 eq) and TEA (0.14 ml, 1.02 mmol, 3 eq) were dissolved in dichloromethane and the reaction was stirred at room temperature for 14 h. The reaction was diluted with water and the product was extracted with dichloromethane and purified by preparative HPLC yielding the desired product. Yield: 47 mg (25 %) ¹H NMR (400MHz, DMSO-d₆): δ 1.12-1.15 (m, 2H), 1.21-1.24 (m, 2H), 2.29 (s, 3H), 2.34 (s, 3H), 2.81-2.82 (d, 3H, *J* = 4.60 Hz), 3.95 (s, 3H), 7.12 (s, 1H), 7.31-7.32 (m, 1H), 7.34-7.40 (t, 2H, *J* = 3.21 Hz), 7.56 (s, 1H), 7.61 (s, 1H), 7.71 (s, 1H), 7.73 (s, 1H), 7.97-8.01 (m, 2H), 8.46-8.48 (m, 1H), 8.67 (s, 1H). LCMS : (ES+) *m/z* = 554.2 (M+H). Column : Ascentis Express C18 (5X2.1mm-2.7μm). Mphase A : 2% ACN -98% H₂O-10mM NH₄COOH. Mphase B : 98% ACN – 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min

Time	%A	%B
0.0	100.0	0
1.0	70.0	30.0
2.5	0.0	100.0
4.0	0.0	100.0

RT min : 1.964, wavelength : 220 nm

HPLC Method:
Sunfire C18 (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
Mobile Phase A : Buffer : MeCN (95:5)
Mobile Phase B : MeCN :Buffer (95:5)
Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :11.403

Wavelength : 220 nm, RT min :11.402

Purity: 98.8 %

5 XBridge phenyl (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN :Buffer (95:5)

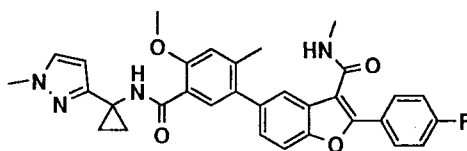
Flow : 1ml/min

Time	B%
0	10
12	100
15	100

10 Wavelength : 254 nm, RT min :10.588

Wavelength : 220 nm, RT min :10.588

Purity : 98.96 %



15 2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(1-methyl-1H-pyrazol-3-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00556] To a mixture of 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoic acid (0.15 g, 0.35 mmol, 1 eq), 1-(1-methyl-1H-pyrazol-3-yl)cyclopropanamine (0.058 g, 0.42 mmol, 1.2 eq), HOBT (0.08 g, 0.069

20 mmol, 1.7 eq), EDC.HCl (0.073 g, 0.014mmol, 1.8 eq), in DCM at ambient temperature under nitrogen was added Diisopropylethylamine (0.297 g, 2.2 mmol, 5.0 eq). The clear mixture was stirred at ambient temperature for 12 h. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer is further washed with water, dried over sodium sulphate and concentrated. The product
25 obtained was further purified by column chromatography (neutral alumina) using 0.5

% Methanol/DCM and the final purification was done by preparative HPLC. Yield : 0.06 g (45 %) ¹H NMR (400MHz, DMSO-d₆) : δ 1.18-1.20 (m, 4H), 2.29 (s, 3H), 2.81-2.82 (d, 3H, *J* = 4.64 Hz), 3.73 (s, 3H), 3.96 (s, 3H), 6.06-6.07 (d, 1H, *J* = 2.4 Hz), 7.12 (s, 1H), 7.32-7.34 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.38.-7.42 (t, 2H, *J* = 8.8 Hz), 7.48.-7.49 (d, 2H, *J* = 2.34 Hz), 7.59 (s, 1H), 7.71-7.73 (d, 1H, *J* = 8.4 Hz), 7.97-7.97-8.01 (m, 2H), 8.47-8.48 (d, 1H, *J* = 4.8 Hz), 8.69 (s, 1H). LCMS : (ES+) *m/z* = 553.2 (M+H). Column : Ascentis Express C18 (5X2.1mm-2.7µm). Mphase A : 2% MeCN -98% H₂O-10mM NH₄COOH. Mphase B : 98% MeCN – 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min.

Time	%A	%B
0.0	100.0	0
1.5	0.0	100.0
3.2	0.0	100.0

RT min : 1.937, wavelength : 220 nm

HPLC Method:

Sunfire C18 (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :11.289

Wavelength : 220 nm, RT min :11.289

Purity: 99.3 %

XBridge phenyl (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5

WO 2010/030592

PCT/US2009/056166

Mobile Phase A : Buffer : MeCN (95:5)

Mobile Phase B : MeCN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

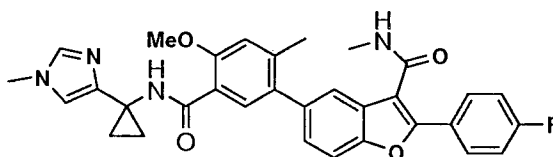
Wavelength : 254 nm, RT min :10.548

5 Wavelength : 220 nm, RT min :10.548

Purity: 99.5 %

1-(1-Methyl-1H-imidazol-4-yl) cyclopropanamine

- [00557] 1-Methyl-1H-imidazole-4-carbonitrile (0.5 g, 4.6 mmol, 1 eq) was dissolved in THF, and to which titanium isopropoxide (1.6 g, 5.6 mmol, 2.5 eq) was added dropwise over 15 minutes. The mixture was stirred for 15 minutes at room temperature, and then ethyl magnesium bromide (1.6 g, 11.5 mmol, 2.5 eq) was added at room temperature over 15 minutes. The reaction mixture was stirred for 1 h. BF₃ etherate (0.8 g, 5.6 mmol, 2.2 eq) was added and the mixture stirred at room temperature for 1 h. 1 N NaOH solution was added to the mixture to bring the pH to 9-10. Reaction mass was filtered through CELITE® and the filtrate washed with DCM. The organic mixture was concentrated and the residue purified by flash chromatography on silica gel using 10 % chloroform/ methanol. Yield: 0.6 g ¹H NMR (400MHz, CDCl₃): δ 0.97 (t, *J* = 3.4 Hz, 2H), 1.00 (t, *J* = 3.4 Hz, 2H), 3.63 (s, 3H), 7.28 (s, 1H), 7.31 (s, 1H). LCMS : (ES+) *m/z* = 138.2 (M+H).



2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(1-methyl-1H-imidazol-4-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

[00558] 5-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoic acid (0.2 g, 1 eq), 1-(1-methyl-1H-imidazol-4-yl) cyclopropanamine (0.07 g, 1.1 eq), EDCI.HCl (0.13 g, 1.5 eq), HOBT (0.094 g, 1.5 eq) and TEA (0.19 ml, 3 eq) were dissolved in dichloromethane and the above solution was stirred at
5 room temperature for 18 h. Later water was added and organic layer was separated. The organic layer was washed with water and the crude product was purified by Prep. HPLC. Yield : 24.69 mg (10 %) ¹H NMR (400MHz, CDCl₃): δ 1.39 (s, 4H), 2.30 (s, 3H), 2.99-3.01 (d, J = 4.6 Hz, 3H), 3.81 (s, 3H), 4.04 (s, 3H), 5.90 (s, 1H), 6.87 (s, 1H), 7.16-7.25 (m, 3H), 7.24 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.98-7.99
10 (m, 3H), 8.29 (s, 1H), 8.95 (s, 1H). LCMS : (ES+) m/z = 553.2 (M+H). Method: Column : Ascentis Express C18 (5X2.1mm-2.7μm). Mphase A : 2% ACN -98% H₂O-10mM NH₄COOH. Mphase B : 98% ACN – 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min.

Time	%A	%B
0.0	100.0	0
1.5	0.0	100.0
3.2	0.0	100.0

RT min : 1.854
15 Wavelength : 220 nm

HPLC Column:
Sunfire C18 (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
20 Mobile Phase A : Buffer : MeCN (95:5)
Mobile Phase B : MeCN :Buffer (95:5)
Flow : 1ml/min

Time	B%
0	10
25	100
30	100

Wavelength : 254 nm, RT min :11.685

Wavelength : 220 nm, RT min : 11.685
Purity : 99.1%

HPLC Column:

- 5 XBridge phenyl (4.6X150)mm, 3.5 micron
Buffer : 0.05% TFA in water pH 2.5
Mobile Phase A : Buffer: MeCN (95:5)
Mobile Phase B : 0.05% TFA in MeCN : Buffer (95:5)
Flow : 1ml/min

Time	B%
0	10
25	100
30	100

- 10 Wavelength : 254 nm, RT min :13.396
Wavelength : 220 nm, RT min : 13.396
Purity : 96.5%

Preparative HPLC Method:

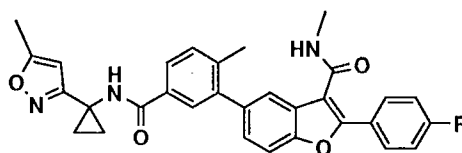
- 15 Column : Symmetry C18 (19X250X10μ)
Mobile Phase: 0.1% TFA (A), MeCN (B)
Gradient:

Time	Flow	A	B
0	15ml/min	95	5
10	15ml/min	55	45

RT: 10.5 min

- 20 1-(5-Methylisoxazol-3-yl)cyclopropanamine
[00559] 5-Methylisoxazole-3-carbonitrile (1.0 g, 1 mmol) was dissolved in THF. Ti (Oi-Pr) 4 (1.2 mmol) was added dropwise over a period of 5-10 min and the reaction mixture was stirred at r.t for 15 min. It was then cooled down to 0 °C and EtMgBr (2.5 mmol) was added dropwise over a period of 10-15min. It was stirred at

0 °C for 15 min. and then stirred at rt for 1 hr. The mixture was cooled again to 0 °C and BF₃OEt₂ (2 mmol) was added dropwise over a period of 5-10 min at 0 °C. After the mixture was stirred for 10min at 0 °C and 1hr at rt, 1 N NaOH was added at 0 °C. DCM was added to the reaction mixture which was then stirred for 5-10 min. This alkaline solution was filtered through CELITE® and washed with DCM. The organic layer was concentrated and residue purified by flash chromatography on silica gel using 10 % chloroform/ methanol. Yield: 0.6g ¹H NMR (400MHz, CDCl₃): δ 0.96-1.05 (m, 4H), 2.36 (s, 3H), 5.59 (s, 1H). LCMS : (ES+) m/z observed 138.7.



2-(4-Fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(5-methylisoxazol-3-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide

[00560] To a mixture of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (0.15 g, 0.37 mmol, 1 eq), amine (0.06 g, 0.43 mmol, 1.2 eq), HOBT (0.084 g, 0.62 mmol, 1.7 eq), EDC.HCl (0.127 g, 0.087 mmol, 1.8 eq) in DCM at ambient temperature under nitrogen was added Diisopropylethylamine (0.239 g, 1.8 mmol, 5.0 eq). The clear mixture was stirred at ambient temperature for 12 h. LCMS showed the desired product. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer is further washed with water, dried over sodium sulphate, filtered and then concentrated. The product obtained was further purified by column chromatography (neutral alumina) using 0.5% Methanol/DCM and preparative HPLC. Yield : 0.03 g (20 %). ¹H NMR (400MHz, DMSO-d₆): δ 1.24-1.29 (m, 4H), 2.29 (s, 3H), 2.32 (s, 3H), 2.81-2.82 (d, 3H, J = 4.6 Hz), 6.05 (s, 1H), 7.38-7.44 (m, 4H), 7.57 (d, 1H, J = 1.6 Hz), 7.75-7.82 (m, 3H), 7.97-8.0 (m, 2H), 8.46-8.47 (m, 1H), 9.24 (s, 1H). LCMS : (ES+) m/z = 524.2 (M+H). LCMS Method : Column : Ascentis Express C18 (5X2.1mm-2.7μm). Mphase A : 2% ACN -98% H₂O-10mM NH₄COOH. Mphase B : 98% ACN - 2% H₂O-10mM NH₄COOH. Flow : 1mL/Min

Time	%A	%B
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Time	%A	%B
0.0	100.0	0
1.5	0.0	100.0
3.2	0.0	100.0

RT min : 1.966, wavelength : 220nm

HPLC Method:

Column : Atlantis T3 (4.6X150mm-5.0µm)

5 A : Buffer : 20mM Ammonium acetate in Water

B : MeCN

Flow : 1ml/min

Time	B%
20	0
35	5
35	30
100	35
100	40

Wavelength : 254 nm, RT min :15.155

Wavelength : 220 nm, RT min :15.155

10

HPLC Method:

Sunfire C18 (4.6X150)mm, 3.5 micron

Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : MeCN (95:5)

15 Mobile Phase B : ACN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :18.678

Wavelength : 220 nm, RT min :18.678

Purity: 99.4%

XBridge phenyl (4.6X150)mm, 3.5 micron

5 Buffer : 0.05% TFA in water pH 2.5

Mobile Phase A : Buffer : ACN (95:5)

Mobile Phase B : ACN :Buffer (95:5)

Flow : 1ml/min

Time	B%
0	10
12	100
15	100

Wavelength : 254 nm, RT min :17.135

10 Wavelength : 220 nm, RT min :17.135

Purity: 99.5%

5-Methylthiazole-2-carbaldehyde

[00561] To a solution of BuLi (5 mmol) in ether at -78 °C was added dropwise a
 15 solution of 5-methylthiazole (5 mol) in ether at -78 °C for 1.5 hours. A solution of
 DMF (5 mmol) in ether was added at once and the reaction was allowed to warm to
 room temperature and stirred overnight. Ice was added to the mixture followed by the
 slow addition of 4 N HCl. The mixture was extracted with ether. The aq. layer was
 brought to pH 7.5 with solid NaHCO₃ and extracted with ether. The combined ethereal
 20 extracts was dried, filtered and concentrated to get crude residue, which was purified
 by flash chromatography on silica gel using 10 % EtOAc / Hexane. Yield: 6 g ¹H
 NMR (400MHz, CDCl₃): δ 2.56 (s, 3 H), 7.79 (s, 1H), 9.90 (s, 1H). LCMS : (ES+)
 m/z = 128 (M+H).

25

5-Methylthiazole-2-carbaldehyde oxime

[00562] To a solution of 5-methylthiazole-2-carbaldehyde (4.8 mmol) in DCM was
 added pyridine (4.8 mmol) and HONH₂.HCl (4.8 mmol). The reaction mixture was

stirred at ambient temperature for 12 hours, then diluted with DCM and extracted with water. The organic extract was dried, filtered and concentrated to obtain crude oxime. Yield: 6 g; LCMS : (ES+) m/z = 143 (M+H).

5 5-Mmethylthiazole-2-carbonitrile

[00563] 5-Methylthiazole-2-carbaldehyde oxime (4.2 mmol) was dissolved in DCM and added with CDI (4.3 mmol) portionwise. The reaction mixture and stir at rt overnight, and then added with water. The mixture was extracted with DCM, and the organic layer was dried and concentrated to get the crude residue, which was purified by flash chromatography on silica gel using 10 % EtOAc / Hexane. Yield : 3.2 g; ¹H NMR (400MHz, CDCl₃): δ 2.59 (s, 3 H), 7.71 (s, 1H).

1-(5-Methylthiazol-2-yl)cyclopropanamine

[00564] 5-Methylthiazole-2-carbonitrile (1.0 g, 1 mmol) was dissolved in THF. Ti(Oi-Pr)₄ (1.2 mmol) was added dropwise to the mixture over a period of 5-10 min and the reaction mixture was stirred at rt for 15 min. It was then cooled down to 0 °C and EtMgBr (2.5 mmol) was added dropwise over a period of 10-15 min. The reaction mixture was stirred again at 0 °C for 15 min, and then stirred at ambient temperature for 1 h. BF₃.OEt₂ (2.5 mmol) was then added dropwise over a period of 5-10 min to the mixture that was cooled again to 0 °C. After the mixture was stirred for 10 min at 0 °C and 1 h at ambient temperature, 1 N NaOH was added to the mixture cooled to 0 °C. DCM was added to the reaction mixture and stirred for 5-10 min. This alkaline solution was filtered through CELITE® and washed with DCM. The organic layer was concentrated and the residue purified by flash chromatography on silica gel using 10 % chloroform / methanol. Yield : 0.6 g; ¹H NMR (400MHz, CDCl₃): δ 1.20 (m, 2H) 1.31 (m, 2H), 2.40 (s, 3H), 7.26 (s, 1H). LCMS : (ES+) m/z observed 154.7.

2-(4-Fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(5-methylthiazol-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide

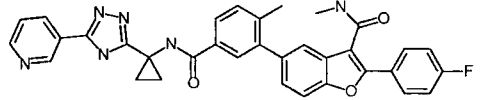
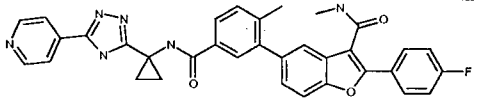
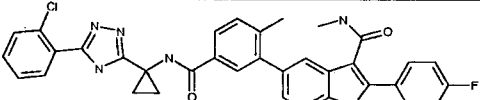
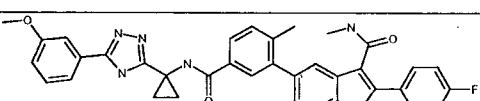
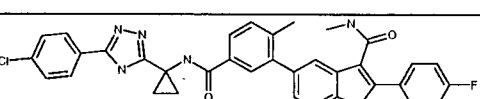
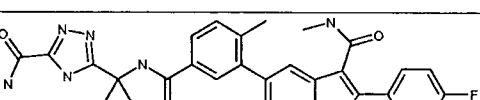
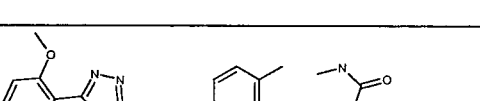
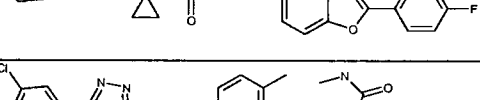
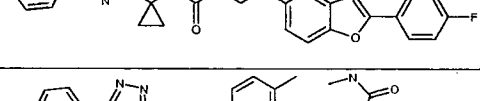
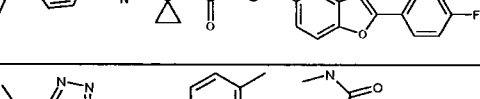
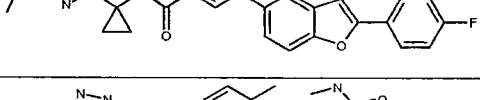
[00565] 5-(2-(4-Fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-2-methoxy-4-methylbenzoic acid (0.2 g, 1 eq), 1-(5-methylthiazol-2-yl)cyclopropanamine (0.07

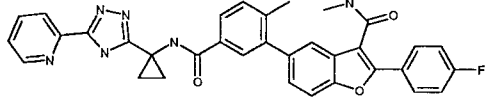
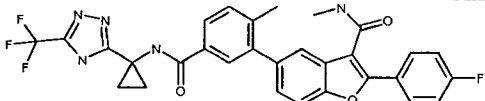
g, 1 eq), EDCI.HCl (0.13 g, 1.5 eq), HOBT (0.094 g, 1.5 eq) and TEA (0.19 ml, 3 eq) were dissolved in dichloromethane and the above solution was stirred at room temperature for 18 h. Then water was added to the mixture and the organic layer was separated. The organic layer was washed with water and the product was purified by
5 Prep. HPLC. Yield : 65 mg (25 %) ¹H NMR (400MHz, CDCl₃): δ 1.43-1.46 (m, 2H), 1.74-1.77 (m, 2H), 2.32 (s, 3H), 2.37 (s, 3H), 3.01-3.03 (d, J= 5.2 Hz, 3H), 4.04 (s, 3H), 5.89 (m, 1H), 6.91 (s, 1H), 7.16 (t, 2H), 7.27 (m, 2H), 7.51 (d, J= 4 Hz, 1H), 7.66 (s, 1H), 8.00 (m, 2H), 8.13 (s, 1H), 8.7 (s, 1H). LCMS : (ES+) m/z = 570.2 (M+H).

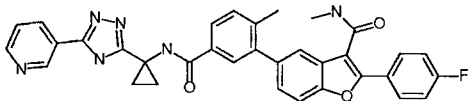
10 [00566] General procedure: 5-(5-(1-Cyanocyclopropylcarbamoyl)-2-methylphenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (448 mg) was dissolved in butan-1-ol (22.50 mL) and distributed evenly into 15 pre-weighed hydrazides in microwave vials (2-5mL size) and followed by adding K₂CO₃ (8.85 mg) as a solid. The vial was flashed with argon and capped, then heated at 165 °C for
15 30 minutes in a BIOTAGE® microwave reactor. The samples were dried by SPEEDVAC®, dissolved in DMF (1.8 mL) and purified by preparative HPLC. Purification method: Cw313a (19x100mm): Solvent A = 5:95 MeCN:Water; Solvent B = 95:5 MeCN:Water; Modifier = 10 mM NH₄OAc; 0' (25 mL/min) = 30% B, 0.5' (12.5 mL/min) = 30% B, 2' (12.5 mL/min) = 30% B, 2.5' = 30% B, 22' = 95% B, 36' = 95% B. HPLC purity was determined using a Waters ZQ with ESCi mass
20 spectrometer. Solvent A = 5:95 MeCN:Water; Solvent B = 95:5 MeCN:Water; Modifier = 10 mM NH₄OAc. Retention time was recorded in minutes.

Analytical Method A:
25 Waters XBridge 4.6x50mm 5 um C18v

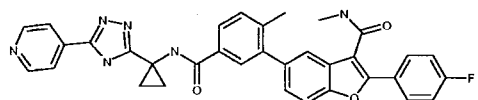
Time	B%	Flow (mL/min)
0.00'	5	2.00
8.00'	95	2.00
9.00'	95	2.00
9.01'	5	2.00
10.00	5	2.00

Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	4.73	89.3	587.33	A
	4.76	90.6	587.33	A
	5.44	88.5	620.37	A
	5.4	93.4	616.33	A
	5.37	100	620.187	A
	3.85	98.3	553.181	A
	5	100	616.218	A
	5.84	88.8	620.29	A
	4.86	100	616.166	A
	4.28	100	552.208	A
	4.32	100	552.207	A

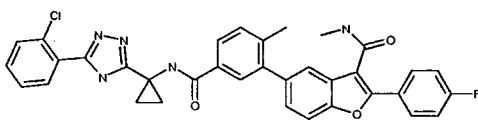
Structure	HPLC Rt	% Purity	Obs. MS Ion	HPLC Method
	4.37	95	587.153	A
	4.94	94.9	578.118	A



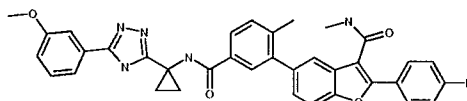
[00567] ¹H NMR (600 MHz, <DMSO-d₆_CDCl₃>) δ ppm 1.41 (br. s., 2 H) 1.62 (br. s., 2 H) 2.28 - 2.47 (m, 3 H) 2.89 (d, *J*=4.69 Hz, 3 H) 7.29 - 7.51 (m, 5 H) 7.66 (s, 1 H) 7.75 (d, *J*=8.79 Hz, 1 H) 7.86 - 7.99 (m, 2 H) 8.05 (dd, *J*=8.20, 5.86 Hz, 2 H) 8.44 (d, *J*=4.10 Hz, 1 H) 8.61 (br. s., 1 H) 9.17 (s, 1 H) 9.32 (br. s., 2 H).



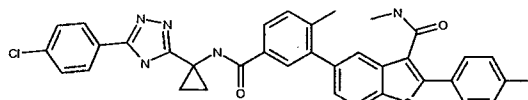
[00568] ¹H NMR (600 MHz, <DMSO-d₆_CDCl₃>) δ ppm 1.42 (br. s., 2 H) 1.61 (br. s., 2 H) 2.22 - 2.44 (m, 3 H) 2.56 - 2.63 (m, 3 H) 7.32 - 7.55 (m, 4 H) 7.66 (s, 1 H) 7.76 (d, *J*=8.79 Hz, 1 H) 7.89 - 8.03 (m, 2 H) 8.04 (dd, *J*=8.50, 5.57 Hz, 2 H) 8.44 (d, *J*=4.10 Hz, 1 H) 8.66 (d, *J*=4.10 Hz, 2 H) 9.33 (br. s., 1 H) 14.09 (br. s., 1 H).



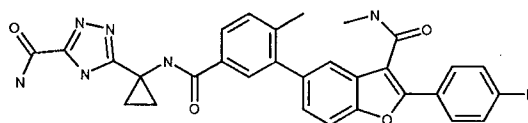
[00569] ¹H NMR (600 MHz, <DMSO-d₆_CDCl₃>) δ ppm 1.42 (br. s., 2 H) 1.60 (br. s., 2 H) 2.37 (s, 3 H) 2.89 (d, *J*=4.10 Hz, 3 H) 7.31 - 7.51 (m, 4 H) 7.51 - 7.59 (m, 1 H) 7.66 (s, 1 H) 7.75 (d, *J*=8.20 Hz, 1 H) 7.80 - 7.94 (m, 2 H) 8.05 (dd, *J*=8.20, 5.86 Hz, 2 H) 8.27 (s, 1 H) 8.44 (d, *J*=4.10 Hz, 1 H) 9.31 (br. s., 1 H) 13.93 (br. s., 1 H).



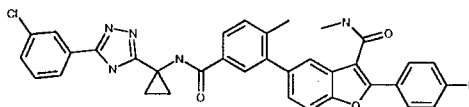
[00570] ^1H NMR (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 1.40 (br. s., 2 H) 1.60 (br. s., 2 H) 2.36 (s, 3 H) 2.89 (d, $J=4.69$ Hz, 3 H) 3.86 (s, 3 H) 7.23 - 7.49 (m, 5 H) 7.53 (br. s., 1 H) 7.55 - 7.62 (m, 1 H) 7.65 (s, 1 H) 7.75 (d, $J=8.20$ Hz, 1 H) 7.90 (d, $J=8.20$ Hz, 1 H) 8.05 (dd, $J=8.20$, 5.86 Hz, 1 H) 8.27 (s, 1 H) 8.44 (d, $J=4.69$ Hz, 1 H) 9.31 (br. s., 1 H) 13.77 (br. s., 1 H).



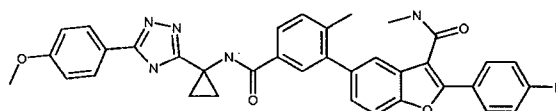
[00571] ^1H NMR (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 1.40 (br. s., 2 H) 1.60 (br. s., 2 H) 2.37 (s, 3 H) 2.89 (d, $J=4.69$ Hz, 3 H) 7.32 - 7.54 (m, 4 H) 7.65 (s, 1 H) 7.75 (d, $J=8.79$ Hz, 1 H) 7.85 - 7.96 (m, 1 H) 7.96 - 8.11 (m, 3 H) 8.27 (s, 1 H) 8.43 (br. s., 1 H) 9.31 (s, 1 H) 13.84 (br. s., 1 H).



[00572] ^1H NMR (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 1.39 (br. s., 2 H) 1.57 (br. s., 2 H) 2.36 (s, 3 H) 2.89 (d, $J=4.69$ Hz, 3 H) 7.36 - 7.60 (m, 3 H) 7.75 (d, $J=8.20$ Hz, 1 H) 7.85 - 7.96 (m, 1 H) 8.04 (dd, $J=8.20$, 5.27 Hz, 2 H) 8.27 (s, 1 H) 8.43 (d, $J=4.69$ Hz, 1 H) 9.27 (br. s., 1 H) 14.10 (br. s., 1 H).



[00573] ^1H NMR (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 1.41 (br. s., 2 H) 1.61 (br. s., 2 H) 2.37 (s, 3 H) 2.89 (d, $J=4.69$ Hz, 3 H) 7.28 - 7.58 (m, 4 H) 7.65 (s, 1 H) 7.75 (d, $J=8.79$ Hz, 1 H) 7.86 - 8.02 (m, 1 H) 8.02 - 8.18 (m, 3 H) 8.27 (s, 1 H) 8.44 (d, $J=4.10$ Hz, 1 H) 9.31 (br. s., 1 H) 13.90 (br. s., 1 H).



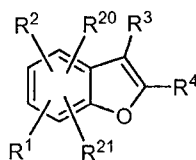
[00574] ¹H NMR (600 MHz, <DMSO-d₆_CDCl₃>) δ ppm 1.39 (br. s., 2 H) 1.59 (br. s., 2 H) 2.36 (br. s., 3 H) 2.89 (d, *J*=4.10 Hz, 3 H) 3.85 (s, 3 H) 6.99 (m, 2H) 7.29 - 7.54 (m, 4 H) 7.65 (s, 1 H) 7.75 (d, *J*=8.20 Hz, 1 H) 7.82 - 7.99 (m, 3 H) 7.99 - 8.14 (m, 2 H) 8.27 (s, 1 H) 8.43 (br. s., 1 H) 9.29 (s, 1 H) 13.63 (br. s., 1 H).

[00575] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

We claim:

- 5 1. A compound of formula I



I

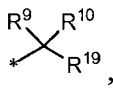
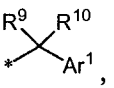
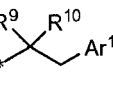
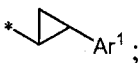
- R^1 is R^5R^6N ; alkoxy; (alkoxycarbonylamino)alkoxy; (alkylphenyl)alkoxy; (carboxy)alkenyl; (alkoxycarbonyl)alkenyl; (benzyloxycarbonyl)alkenyl; ((N-dimethylbenzyl)aminocarbonyl)alkenyl; or phenyl where said phenyl is substituted with 1-2 substituents selected from the group consisting of halo, cyano, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (carboxy)alkyl, alkoxy, hydroxyalkyloxy, alkoxyalkyloxy, benzyloxy, tetrahydropyranyloxy, carboxy, alkoxycarbonyl, alkylsulfonyl, (carboxy)alkenyl, (alkoxycarbonyl)alkenyl, alkylcarboxamido, alkoxy-carboxamido, alkylsulfamido, (alkylsulfamido)alkyl, Ar^5 , $SO_2NR^{15}R^{16}$, and $CONR^7R^8$; and where said phenyl is also substituted with 0-2 substituents selected from the group consisting of halo; nitro; alkyl; cycloalkyl; haloalkyl; aminoalkyl; hydroxyalkyl; alkoxyalkyl; hydroxy; alkoxy; OR^{17} ; cycloalkoxy; amino; alkylamino; dialkylamino; alkylcarboxamido; alkoxy-carboxamido; alkoxyalkylcarboxamido; furanyl, thienyl, or pyrazolyl substituted with 0-2 alkyl substituents; pyridinyl substituted with 0-2 halo, cyano, alkyl, hydroxy, alkoxy, amino, or alkylaminocarbonyl substituents; pyrimidinyl; pyrimidinedionyl; aminopyrimidinyl; indolyl; isoquinolinyl; and phenyl substituted with 0-2 substituents selected from the group consisting of halo, alkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, amino, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarboxamido, carboxyalkenyl, and phenyl;
- R^2 is hydrogen, halo, nitro, amino, phenyl, or R^5R^6N ;
- R^3 is cyano, alkoxycarbonyl, (cycloalkyl)oxycarbonyl, (alkylsulfonyl)aminocarbonyl, $CONR^{11}R^{12}$, $(R^{11})(R^{12})NCONH$, triazolyl, thiazolyl, or tetrazolyl;

R^4 is phenyl substituted with 0-2 halo substituents;

R^5 is hydrogen, alkyl, or alkylsulfonyl;

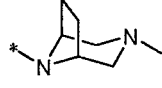
R^6 is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or alkylsulfonyl;

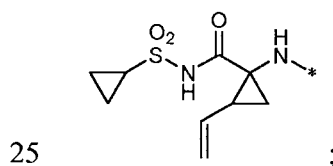
- R^7 is hydrogen, alkyl, alkenyl, alkynyl, cyanoalkyl, haloalkyl, hydroxyalkyl,
 5 dihydroxyalkyl, alkoxyalkyl, oxoalkyl, aminoalkyl, (alkylamino)alkyl,
 (dialkylamino)alkyl, (cycloalkyl)alkyl, cycloalkyl, (alkyl)cycloalkyl,
 (hydroxyalkyl)cycloalkyl, (tetrahydrofuranyl)alkyl, (tetrahydropyranyl)alkyl,
 (carboxy)alkyl, (alkoxycarbonyl)alkyl, (alkenyloxycarbonyl)alkyl,
 (alkoxycarbonyl)hydroxyalkyl, (CONR¹³R¹⁴)alkyl, (CONR¹³R¹⁴)(hydroxyalkyl)alkyl,
 10 (CONR¹³R¹⁴)cycloalkyl, (alkylcarbonyl)aminoalkyl, (phenyl)alkyl, (pyridinyl)alkyl,

alkylsulfonyl, phenylsulfonyl, Ar², Ar³, , , , or
 Ar¹;

R^8 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

- or R^7R^8N taken together is azetidiny, pyrrolidiny, piperidiny, piperazinyl,
 15 morpholinyl, dihydroindolyl, or isoindoliny, and is substituted with 0-2 substituents
 selected from alkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, carboxy,
 alkoxy carbonyl, dialkylcarboxamido, alkylcarbonylamino, alkoxy carbonylamino,
 pyridinyl, and phenyl where said phenyl is substituted with 0-2 halo or alkyl
 substituents;

- 20 or where R^7R^8N taken together is , (quinuclidinyl)amino,
 (quinuclidinyl)(alkyl)amino, (methylpyrrolidinyl)(alkyl)amino,
 ((imidazolyl)alkyl)(hydroxyalkyl)amino, (alkylthiazolyl)amino,
 ((carboxamido)cyclopentanyl)amino, ((halophenyl)cyclopentanyl)amino,
 3H-spiro(isobenzofuranyl)piperidiny, (hydroxyindanyl)amino, or



R^9 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

R^{10} is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

- or R⁹ and R¹⁰ taken together is ethylene, propylene, butylene, pentylene, or hexylene;
- R¹¹ is hydrogen, alkyl, or cycloalkyl;
- R¹² is hydrogen, alkyl, or cycloalkyl;
- 5 or R¹¹ and R¹² taken together with the nitrogen to which they are attached is azetidiny, pyrrolidiny, piperidiny, piperaziny, or morpholiny;
- R¹³ is hydrogen, alkyl, cyanoalkyl, haloalkyl, alkenyl, alkynyl, or thiazolyl;
- R¹⁴ is hydrogen or alkyl;
- R¹⁵ is hydrogen, alkyl, hydroxyalkyl, cycloalkyl, or benzyl;
- 10 R¹⁶ is hydrogen or alkyl;
- or R¹⁵ and R¹⁶ taken together with the nitrogen to which they are attached is azetidiny, pyrrolidiny, piperidiny, piperaziny, or morpholiny;
- R¹⁷ is haloalkyl, cyanoalkyl, (cycloalkyl)alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (R¹⁸)alkyl, (Ar⁴)alkyl, alkynyl, or aminocycloalkyl;
- 15 R¹⁸ is CONH₂, H₂NCONH, dibenzylamino, phthalimido, amino, alkylamino, dialkylamino, azetidiny, pyrrolidiny, piperidiny, piperaziny, or morpholiny where azetidiny, pyrrolidiny, piperidiny, piperaziny, or morpholiny is substituted with 0-3 alkyl or alkoxycarbonyl substituents;
- R¹⁹ is cyano, hydroxyalkyl, morpholinyalkyl, carboxy, alkoxycarbonyl, cycloalkylsulfoxamido, ((alkyl)pyrazolyl)amino, ((alkyl)isoxazolyl)amino, 20 (thiadiazolyl)amino, (triaziny)amino, or alkynylaminocarbonyl;
- R²⁰ is hydrogen, halo, alkyl, or alkoxy;
- R²¹ is hydrogen, halo, alkyl, or alkoxy;
- Ar¹ is phenyl, naphthalenyl, pyridiny, furanyl, thienyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, oxadiathiazolyl, 25 triazolyl, tetrazolyl, pyraziny, pyrimidiny, or benzothiazolyl, and is substituted with 0-2 substituents selected from halo, alkyl, cycloalkyl, haloalkyl, alkoxyalkyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, aminocarbonyl, pyridiny, phenyl, halophenyl, alkylphenyl, and alkoxyphenyl;
- 30 Ar² is phenyl, biphenyl, or pyridiny, and is substituted with 0-2 substituents selected from halo, alkyl, cyano, hydroxy, alkoxy, and carboxy;

Ar³ is pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, oxathiadiazolyl, pyrimidinyl, or pyrizinyl, and is substituted with 0-2 substituents selected from hydroxy, alkyl, hydroxyalkyl, and CONR¹³R¹⁴;

Ar⁴ is furanyl, thienyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridinyl, indolyl, or phenyl, and is substituted with 0-2 substituents selected from halo, alkyl, haloalkyl, hydroxyl, and alkoxy; and

Ar⁵ is pyrrolyl, imidazolyl, or oxadiazolyl, and is substituted with 0-2 substituents selected from alkyl, carboxy, alkoxycarbonyl, benzyl, and phenyl; or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 where R²⁰ and R²¹ are hydrogen.

3. A compound of claim 2 where R¹ is R⁵R⁶N; (carboxy)alkenyl; (alkoxycarbonyl)alkenyl; (benzyloxycarbonyl)alkenyl; or phenyl where said phenyl is substituted with 1-2 substituents selected from the group consisting of cyano, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, hydroxyalkyloxy, alkoxyalkyloxy, haloalkyl, benzyloxy, carboxy, alkoxycarbonyl, alkylsulfonyl, (carboxy)alkenyl, (alkoxycarbonyl)alkenyl, alkylcarboxamido, alkoxycarboxamido, alkylsulfamido, (alkylsulfamido)alkyl, tetrahydropyranyloxy, Ar⁵, SO₂NR¹⁵R¹⁶, and CONR⁷R⁸; and where said phenyl is also substituted with 0-1 substituents selected from the group consisting of halo; alkyl; hydroxyalkyl; alkoxyalkyl; hydroxyl; alkoxy; OR¹⁷; cycloalkoxy; amino; alkylamino; dialkylamino; alkylcarboxamido; alkoxyalkylcarboxamido; furanyl; indolyl; isoquinolinyl; pyridinyl substituted with 0-2 halo, alkyl, hydroxy, or alkoxy substituents; pyrazolyl substituted with 0-2 alkyl substituents; and phenyl substituted with 0-2 halo, alkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarboxamido, carboxyalkenyl, or phenyl substituents;

R² is hydrogen, nitro, or R⁵R⁶N;

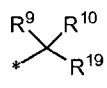
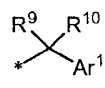
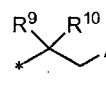
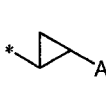
R^3 is cyano, alkoxycarbonyl, (cycloalkyl)oxycarbonyl, (alkylsulfonyl)aminocarbonyl, $\text{CONR}^{11}\text{R}^{12}$, $(\text{R}^{11})(\text{R}^{12})\text{NCONH}$, triazolyl, thiazolyl, or tetrazolyl;

R^4 is phenyl substituted with 0-2 halo substituents;

5 R^5 is hydrogen, alkyl, or alkylsulfonyl;

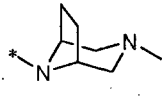
R^6 is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or alkylsulfonyl;

R^7 is hydrogen, alkyl, alkenyl, alkynyl, cyanoalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, oxoalkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkyl)alkyl, cycloalkyl, (alkyl)cycloalkyl, (hydroxyalkyl)cycloalkyl, 10 (tetrahydrofuranyl)alkyl, (tetrahydropyranyl)alkyl, (carboxy)alkyl, (alkoxycarbonyl)alkyl, (alkoxycarbonyl)hydroxyalkyl, $(\text{CONR}^{13}\text{R}^{14})\text{alkyl}$, (alkylcarbonyl)aminoalkyl, (phenyl)alkyl, (pyridinyl)alkyl, alkylsulfonyl,

phenylsulfonyl, Ar^2 , Ar^3 , , , , or .

R^8 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

15 or R^7R^8N taken together is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or dihydroindolyl, and is substituted with 0-2 substituents selected from alkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, carboxy, alkoxycarbonyl, dimethylcarboxamido, alkylcarbonylamino, alkoxycarbonylamino, pyridinyl, and phenyl where phenyl is substituted with 0-2 substituents selected from halo and alkyl;

20 or where R^7R^8N taken together is , (quinuclidinyl)(alkyl)amino, (methylpyrrolidinyl)(alkyl)amino, (alkylthiazolyl)amino, ((carboxamido)cyclopentanyl)amino, ((halophenyl)cyclopentanyl)amino, or (hydroxyindanyl)amino;

R^9 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

25 R^{10} is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

or R^9 and R^{10} taken together is ethylene, propylene, butylene, or pentylene;

R^{11} is hydrogen, alkyl, or cycloalkyl;

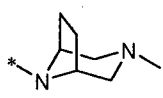
R^{12} is hydrogen, alkyl, or cycloalkyl;

30 or R^{11} and R^{12} taken together with the nitrogen to which they are attached is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

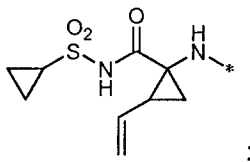
- R^{13} is hydrogen, alkyl, cyanoalkyl, alkenyl, or alkynyl;
 R^{14} is hydrogen or alkyl;
 R^{15} is hydrogen or alkyl;
 R^{16} is hydrogen or alkyl;
5 R^{17} is haloalkyl, hydroxyalkyl, alkoxyalkyl, alkynyl, (R^{18})alkyl or (Ar^4)alkyl;
 R^{18} is $CONH_2$, dibenzylamino, amino, alkylamino, dialkylamino, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl where azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl is substituted with 0-3 substituents selected from alkyl and alkoxycarbonyl;
10 R^{19} is cyano, ((alkyl)pyrazolyl)amino, ((alkyl)isoxazolyl)amino (thiadiazolyl)amino, or (triazinyl)amino;
 Ar^1 is phenyl, naphthalenyl, pyridinyl, thienyl, thiazolyl, or pyrazinyl, and is substituted with 0-2 substituents selected from alkyl, halo, hydroxy, alkoxy, amino, alkylamino, and dialkylamino;
15 Ar^2 is phenyl, biphenyl, or pyridinyl, and is substituted with 0-2 substituents selected from halo, alkyl, cyano, hydroxy, and alkoxy;
 Ar^3 is pyrazolyl isoxazolyl, thiazolyl, pyrimidinyl, or pyrizinyl, and is substituted with 0-2 substituents selected from alkyl and hydroxyalkyl;
 Ar^4 is pyrrolyl, imidazolyl, pyridinyl, indolyl, or phenyl, and is substituted
20 with 0-2 substituents selected from halo, alkyl, hydroxyl, and alkoxy; and
 Ar^5 is pyrrolyl, imidazolyl, or oxadiazolyl and is substituted with 0-2 substituents selected from alkyl, carboxy, alkoxycarbonyl, benzyl, and phenyl;
or a pharmaceutically acceptable salt thereof.
- 25 4. A compound of claim 2 where
 R^1 is alkoxy; (alkoxycarbonylamino)alkoxy; (alkylphenyl)alkoxy; (carboxy)alkenyl; ((N-dimethylbenzyl)aminocarbonyl)alkenyl; or phenyl where said phenyl is substituted with 1-2 substituents selected from the group consisting of halo, cyano, alkyl, haloalkyl, hydroxyalkyl, (carboxy)alkyl, alkoxy, hydroxyalkyloxy, tetrahydropyranyloxy, carboxy, alkoxycarbonyl, (carboxy)alkenyl, alkylcarboxamido,
30 alkoxycarboxamido, (alkylsulfamido)alkyl, Ar^5 , $SO_2NR^{15}R^{16}$, and $CONR^7R^8$; and where said phenyl is also substituted with 0-2 substituents selected from the group

consisting of halo; nitro; alkyl; cycloalkyl; haloalkyl; aminoalkyl; hydroxy; alkoxy; OR¹⁷; cycloalkoxy; amino; alkoxy-carboxamido; furanyl, thienyl, or pyrazolyl substituted with 0-2 alkyl substituents; pyridinyl substituted with 0-2 halo, cyano, alkyl, hydroxy, alkoxy, amino, or alkylaminocarbonyl substituents; pyrimidinyl; 5 pyrimidinedionyl; aminopyrimidinyl; indolyl; isoquinolinyl; and phenyl substituted with 0-2 substituents selected from halo, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, amino, carboxy, aminocarbonyl, alkylaminocarbonyl, alkylcarboxamido, and carboxyalkenyl;

- R² is hydrogen, halo, nitro, amino, phenyl, or R⁵R⁶N;
 10 R³ is CONR¹¹R¹²;
 R⁴ is phenyl substituted with 0-2 halo substituents;
 R⁵ is hydrogen or alkylsulfonyl;
 R⁶ is hydrogen, alkyl, hydroxyalkyl, or alkylsulfonyl;
 R⁷ is hydrogen, alkyl, alkynyl, cyanoalkyl, haloalkyl, hydroxyalkyl,
 15 dihydroxyalkyl, alkoxyalkyl, oxoalkyl, (dialkylamino)alkyl, (cycloalkyl)alkyl, cycloalkyl, (alkyl)cycloalkyl, (hydroxyalkyl)cycloalkyl, (tetrahydrofuranyl)alkyl, (tetrahydropyranyl)alkyl, (carboxy)alkyl, (alkoxycarbonyl)alkyl, (alkenyloxy-carbonyl)alkyl, (alkoxycarbonyl)hydroxyalkyl, (CONR¹³R¹⁴)alkyl, (CONR¹³R¹⁴)(hydroxyalkyl)alkyl, (CONR¹³R¹⁴)cycloalkyl,
 20 (alkylcarbonyl)aminoalkyl, (phenyl)alkyl, alkylsulfonyl, phenylsulfonyl, Ar², Ar³,
 $\begin{array}{c} R^9 \quad R^{10} \\ \diagdown \quad \diagup \\ * \quad C \\ \diagup \quad \diagdown \\ R^{19} \end{array}, \begin{array}{c} R^9 \quad R^{10} \\ \diagdown \quad \diagup \\ * \quad C \\ \diagup \quad \diagdown \\ Ar^1 \end{array}, \begin{array}{c} R^9 \quad R^{10} \\ \diagdown \quad \diagup \\ * \quad C \\ \diagup \quad \diagdown \\ CH_2 \end{array} Ar^1, \text{ or } \begin{array}{c} * \\ \diagdown \quad \diagup \\ \text{Cyclopropyl} \\ \diagup \quad \diagdown \\ Ar^1 \end{array};$
 R⁸ is hydrogen, alkyl, or alkoxyalkyl;
 or R⁷R⁸N taken together is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, dihydroindolyl, or isoindolinyl, and is substituted with 0-2 substituents
 25 selected from alkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy-carbonyl, dialkylcarboxamido, alkylcarbonylamino, pyridinyl, and phenyl where said phenyl is substituted with 0-2 halo or alkyl substituents;

or where R⁷R⁸N taken together is , (quinuclidinyl)amino, (quinuclidinyl)(alkyl)amino, (methylpyrrolidinyl)(alkyl)amino,
 30 ((imidazolyl)alkyl)(hydroxyalkyl)amino, (alkylthiazolyl)amino,

((carboxamido)cyclopentanyl)amino, ((halophenyl)cyclopentanyl)amino,
3H-spiro(isobenzofuranyl)piperidinyl, (hydroxyindanyl)amino, or



R⁹ is hydrogen, alkyl, or hydroxyalkyl;

5 R¹⁰ is hydrogen or alkyl;

or R⁹ and R¹⁰ taken together is ethylene or propylene;

R¹¹ is alkyl;

R¹² is hydrogen;

R¹³ is hydrogen, alkyl, cyanoalkyl, haloalkyl, alkenyl, or thiazolyl;

10 R¹⁴ is hydrogen or alkyl;

R¹⁵ is alkyl, hydroxyalkyl, cycloalkyl, or benzyl;

R¹⁶ is hydrogen;

or R¹⁵ and R¹⁶ taken together with the nitrogen to which they are attached is
azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

15 R¹⁷ is haloalkyl, cyanoalkyl, (cycloalkyl)alkyl, hydroxyalkyl, alkoxyalkyl,
aminoalkyl, (R¹⁸)alkyl, (Ar⁴)alkyl, alkynyl, or aminocycloalkyl;

R¹⁸ is CONH₂, H₂NCONH, dibenzylamino, phthalimido, amino,
dialkylamino, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl where azetidiny,
pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl is substituted with 0-3 alkyl or
20 alkoxy carbonyl substituents;

R¹⁹ is cyano, hydroxyalkyl, morpholinylalkyl, carboxy, alkoxy carbonyl,
cycloalkylsulfoxamido, ((alkyl)pyrazolyl)amino, ((alkyl)isoxazolyl)amino,
(thiadiazolyl)amino, (triazinyl)amino, or alkynylaminocarbonyl;

25 Ar¹ is phenyl, naphthalenyl, pyridinyl, furanyl, pyrazolyl, isoxazolyl,
imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyrazinyl,
pyrimidinyl, or benzothiazolyl, and is substituted with 0-2 substituents selected from
halo, alkyl, cycloalkyl, haloalkyl, alkoxyalkyl, hydroxy, alkoxy, amino,
aminocarbonyl, pyridinyl, phenyl, halophenyl, alkylphenyl, and alkoxyphenyl;

30 Ar² is phenyl, biphenyl, or pyridinyl, and is substituted with 0-2 substituents
selected from halo, alkyl, cyano, hydroxy, alkoxy, and carboxy;

Ar³ is pyrazolyl, isoxazolyl, thiazolyl, triazolyl, pyrimidinyl, or pyrizinyl, and is substituted with 0-2 substituents selected from hydroxy, alkyl, and CONR¹³R¹⁴;

Ar⁴ is furanyl, pyrrolyl, pyrazolyl, isoxazolyl, imidazolyl, oxadiazolyl, triazolyl, pyridinyl, indolyl, or phenyl, and is substituted with 0-2 substituents
5 selected from halo, alkyl, haloalkyl, and hydroxy; and

Ar⁵ is pyrrolyl, imidazolyl, or oxadiazolyl, and is substituted with 0-2 substituents selected from alkyl, alkoxycarbonyl, benzyl, and phenyl;
or a pharmaceutically acceptable salt thereof.

- 10 5. A compound of claim 2 where R¹ is phenyl substituted with 1
CONR⁷R⁸ substituent and also substituted with 0-2 halo, alkyl, or alkoxy substituents;
R² is hydrogen, halo, or R⁵R⁶N; R³ is CONR¹¹R¹²; R⁴ is monofluorophenyl; R⁵ is
alkylsulfonyl; R⁶ is hydroxyalkyl; R⁷ is ; R⁸ is hydrogen; R⁹ is alkyl; R¹⁰ is
alkyl or R⁹ and R¹⁰ taken together is ethylene or propylene; R¹¹ is alkyl; R¹² is
15 hydrogen; and Ar¹ is phenyl, pyridinyl, pyrimidinyl, isoxazolyl, oxazolyl, or
oxadiazolyl, and is substituted with 0-1 halo or alkyl substituents; or a
pharmaceutically acceptable salt thereof.

6. A compound of claim 1 where R¹ is phenyl substituted with 1-2
20 substituents selected from the group consisting of halo, cyano, alkyl, haloalkyl,
hydroxyalkyl, (carboxy)alkyl, alkoxy, hydroxyalkyloxy, tetrahydropyranyloxy,
carboxy, alkoxycarbonyl, (carboxy)alkenyl, alkylcarboxamido, alkoxycarboxamido,
(alkylsulfamido)alkyl, Ar⁵, SO₂NR¹⁵R¹⁶, and CONR⁷R⁸; and where said phenyl is
also substituted with 0-2 substituents selected from the group consisting of halo;
25 nitro; alkyl; cycloalkyl; haloalkyl; aminoalkyl; hydroxy; alkoxy; OR¹⁷; cycloalkoxy;
amino; alkoxycarboxamido; furanyl, thienyl, or pyrazolyl substituted with 0-2 alkyl
substituents; pyridinyl substituted with 0-2 halo, cyano, alkyl, hydroxy, alkoxy,
amino, or alkylaminocarbonyl substituents; pyrimidinyl; pyrimidinedionyl;
aminopyrimidinyl; indolyl; isoquinolinyl; and phenyl substituted with 0-2 substituents
30 selected from halo, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, amino, carboxy,
aminocarbonyl, alkylaminocarbonyl, alkylcarboxamido, and carboxyalkenyl.

7. A compound of claim 1 where R^1 is phenyl substituted with 1 $CONR^7R^8$ substituent and also substituted with 0-2 halo, alkyl, or alkoxy substituents.

8. A compound of claim 7 where R^7 is  and at least one of R^9 and R^{10} is not hydrogen.

9. A compound of claim 1 selected from the group consisting of
- 2-(4-fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide;
- 10 4-fluoro-2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide;
- 4-fluoro-2-(4-fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide;
- 2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide;
- 15 2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(3-methyl-1,2,4-oxadiazol-5-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide;
- 2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(5-methyl-1,2,4-oxadiazol-3-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide;
- 20 2-(4-fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide;
- 5-(3-fluoro-2-methyl-5-(1-(pyridin-2-yl)cyclopropylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide;
- 2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(5-methylthiazol-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide;
- 25 2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(5-methylisoxazol-3-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide;
- 2-(4-fluorophenyl)-5-(4-methoxy-2-methyl-5-(1-(5-methylloxazol-2-yl)cyclopropylcarbamoyl)phenyl)-N-methylbenzofuran-3-carboxamide;
- 30 2-(4-fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methyl-5-(3-(2-phenylpropan-2-ylcarbamoyl)phenyl)benzofuran-3-carboxamide

- 2-(4-fluorophenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methyl-5-(3-(1-phenylcyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide; and
- 2-(4-fluorophenyl)-5-(3-(1-(4-fluorophenyl)cyclopropylcarbamoyl)phenyl)-6-(N-(2-hydroxyethyl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide;
- 5 or a pharmaceutically acceptable salt thereof.

10. A composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

- 10 11. A method of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of claim 1 to a patient.

COMPUESTOS PARA EL TRATAMIENTO DE LA HEPATITIS C

REFERENCIA A SOLICITUDES DE PATENTE RELACIONADAS

Esta solicitud de patente reivindica la prioridad de la solicitud de patente
5 provisional de Estados Unidos con número de serie 61/096.005 presentada el
11 de septiembre de 2008.

ANTECEDENTES DE LA INVENCION

La descripción se refiere de forma general a los compuestos novedosos
10 de la fórmula I, incluyendo sus sales, que presentan actividad contra el virus de
la hepatitis C (HCV) y son útiles en el tratamiento de los infectados por HCV. La
descripción también se refiere a composiciones y procedimientos usar estos
compuestos.

El virus de la hepatitis C (VHC) es un importante patógeno humano, que
15 se estima que ha infectado a 170 millones de personas en todo el mundo -
aproximadamente cinco veces el número de personas infectadas por el virus de
la inmunodeficiencia humano de tipo 1. Una fracción sustancial de estos
individuos infectados por el VHC desarrollan una enfermedad hepática
progresiva grave, que incluye cirrosis y carcinoma hepatocelular (Lauer, G. M
20 et al., *N. Engl. J. Med.*, 345:41-52 (2001)).

El VHC es un virus de ARN de polaridad positiva. Basándose en una
comparación de la secuencia de aminoácidos deducida y la gran similitud en la

región 5' no traducida, el VHC ha sido clasificado como un género diferente de la familia Flaviviridae. Todos los miembros de la familia Flaviviridae presentan viriones encapsulados que contienen un genoma de ARN de polaridad positiva que codifica todas las proteínas específicas del virus conocidas mediante traducción de un marco de lectura abierto, ininterrumpido y único.

Se encuentra una heterogenicidad considerable en la secuencia de nucleótidos y de aminoácidos codificados por todo el genoma de VHC. Se han caracterizado al menos seis genotipos principales, y se han descrito más de 50 subtipos. Los genotipos principales de VHC difieren en su distribución por todo el mundo, y el significado clínico de la heterogeneidad genética de VHC sigue siendo esquivo a pesar de los numerosos estudios sobre el posible efecto de los genotipos sobre la patogénesis y el tratamiento.

El genoma de ARN monocatenario de VHC tiene una longitud de aproximadamente 9500 nucleótidos y tiene un único marco de lectura abierto (ORF) que codifica una única poliproteína grande de aproximadamente 3000 aminoácidos. En las células infectadas, esta poliproteína es escindida en múltiples sitios por proteasas celulares y víricas para producir las proteínas estructurales y no estructurales (NS). En el caso de VHC, la generación de proteínas no estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A, y NS5B) es realizada por dos proteasas víricas. Se cree que la primera es una metaloproteasa y escinde la unión entre NS2 y NS3; la segunda es una serina proteasa contenida en la región del extremo N de NS3 (también denominada

proteasa NS3) y actúa de mediadora de todas las escisiones posteriores
cadena abajo de NS3, tanto en cis, en el sitio de escisión de NS3 y NS4A,
como en trans, para el resto de los sitios NS4A-NS4B, NS4B-NS5A, NS5A-
NS5B. La proteína NS4A parece realizar funciones múltiples, actuando como
5 cofactor para la proteasa NS3 y posiblemente ayudando en la localización en la
membrana de NS3 y de otros componentes de las replicasas víricas. La
compleja formación de la proteína NS3 con NS4A parece necesaria para los
eventos de procesamiento, potenciando la eficacia proteolítica en todos los
sitios. La proteína NS3 también muestra actividades de nucleósido trifosfatasa
10 y ARN helicasa. La NS5B (también denominada VHC polimerasa) es una ARN
polimerasa dependiente de ARN que está implicada en la replicación de VHC.
La proteína NS5B de VHC se describe en "Structural Analysis of the Hepatitis C
Virus RNA Polymerase in Complex with Ribonucleotides (Bressanelli, S. et al.,
J. Virol., 3482-3492 (2002); y Defrancesco et al., *Clinics in Liver Disease*,
15 7:211-242 (2003)).

Actualmente, el tratamiento más eficaz contra VHC emplea una
combinación de alfa-interferón y ribavirina, que consigue una eficacia
mantenida en 40% de los pacientes (Poynard, T. et al., *Lancet*, 352:1426-1432
(1998)). Los resultados clínicos recientes demuestran que el alfa-interferón
20 pegilado es mejor que el alfa-interferón en monoterapia (Zeuzem, S. et al., *N.*
Engl. J. Med., 343:1666-1672 (2000)). Sin embargo, incluso con pautas
terapéuticas experimentales que emplean combinaciones de alfa-interferón

pegilado y ribavirina, una fracción sustancial de los pacientes no consigue una reducción mantenida de la carga vírica. Así, existe una necesidad clara e importante de desarrollar terapias eficaces para el tratamiento de la infección por VHC.

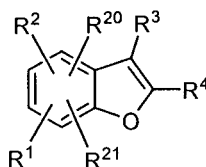
5 El VHC-796, un inhibidor de NS5B de HCV, demostró capacidad de reducir los niveles de ARN de VHC en los pacientes. Los niveles de ARN vírico descendieron de forma transitoria y después rebotaron durante la administración cuando el tratamiento se realizó con el compuesto como agente
10 único pero los niveles cayeron de forma más contundente cuando se combinó con el tratamiento estándar que es una forma de interferón y ribavirina. El desarrollo de este compuesto se suspendió debido a la toxicidad hepática que se observó durante la administración prolongada de las politerapias. La patente de Estados Unidos n.º 7.265.152 y la correspondiente solicitud de patente PCT WO 2004/041201 A2 describen compuestos de la clase VHC-796.

15 La invención proporciona ventajas técnicas, por ejemplo, los compuestos son novedosos y son eficaces contra la hepatitis C. Además, los compuestos proporcionan ventajas para usos farmacéuticos, por ejemplo, con respecto a uno o más de sus mecanismos de acción, unión, eficacia de inhibición, selectividad por la diana, solubilidad, perfiles de seguridad o biodisponibilidad.

20

DESCRIPCIÓN DE LA INVENCION

Un aspecto de la invención es un compuesto de la fórmula I.



I

R^1 es R^5R^6N ; alcoxi; (alcoxicarbonilamino)alcoxi; (alquilfenil)alcoxi; (carboxi)alquenilo; (alcoxicarbonil)alquenilo; (benciloxycarbonil)alquenilo; ((N-
 5 dimetilbencil)aminocarbonil)alquenilo; o fenilo, donde dicho fenilo está sustituido con 1-2 sustituyentes que se seleccionan a partir del grupo constituido por halo, ciano, alquilo, haloalquilo, hidroxialquilo, alcoxialquilo, (carboxi)alquilo, alcoxi, hidroxialquiloxi, alcoxialquiloxi, benciloxi, tetrahidropiraniloxi, carboxi, alcoxicarbonilo, alquilsulfonilo, (carboxi)alquenilo,
 10 (alcoxicarbonil)alquenilo, alquilcarboxamido, alcoxycarboxamido, alquilsulfamido, (alquilsulfamido)alquilo, Ar^5 , $SO_2NR^{15}R^{16}$, y $CONR^7R^8$; y donde dicho fenilo también está sustituido con 0-2 sustituyentes que se seleccionan a partir del grupo constituido por halo; nitro; alquilo; cicloalquilo; haloalquilo; aminoalquilo; hidroxialquilo; alcoxialquilo; hidroxil; alcoxi; OR^{17} ; cicloalcoxi;
 15 amino; alquilamino; dialquilamino; alquilcarboxamido; alcoxycarboxamido; alcoxialquilcarboxamido; furanilo, tienilo, o pirazolilo sustituido con 0-2 sustituyentes alquilo; piridinilo sustituido con 0-2 sustituyentes halo, ciano, alquilo, hidroxil, alcoxi, amino, o alquilaminocarbonilo; pirimidinilo; pirimidindionilo; aminopirimidinilo; indolilo; isoquinolinilo; o fenilo sustituido con
 20 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, cianoalquilo,

hidroxialquilo, alcoxialquilo, hidroxí, alcoxi, amino, carboxi, alcoxycarbonilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, alquilcarboxamido, carboxialquenilo, y fenilo;

R^2 es hidrógeno, halo, nitro, amino, fenilo, o R^5R^6N ;

5 R^3 es ciano, alcoxycarbonilo, (cicloalquil)oxycarbonilo, (alquilsulfonil)aminocarbonilo, $CONR^{11}R^{12}$, $(R^{11})(R^{12})NCONH$, triazolilo, tiazolilo, o tetrazolilo;

R^4 es fenilo sustituido con 0-2 sustituyentes halo;

R^5 es hidrógeno, alquilo, o alquilsulfonilo;

10 R^6 es hidrógeno, alquilo, hidroxialquilo, alcoxialquilo, o alquilsulfonilo;

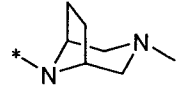
R^7 es hidrógeno, alquilo, alquenilo, alquinilo, cianoalquilo, haloalquilo, hidroxialquilo, dihidroxialquilo, alcoxialquilo, oxoalquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo, (cicloalquil)alquilo, cicloalquilo, (alquil)cicloalquilo, (hidroxialquil)cicloalquilo, (tetrahidrofuranil)alquilo, (tetrahidropiranil)alquilo, (carboxi)alquilo, (alcoxycarbonil)alquilo, (alqueniloxycarbonil)alquilo, (alcoxycarbonil)hidroxialquilo, $(CONR^{13}R^{14})$ alquilo, $(CONR^{13}R^{14})(hidroxialquil)$ alquilo, $(CONR^{13}R^{14})$ cicloalquilo, (alquilcarbonil)aminoalquilo, (fenil)alquilo, (piridinil)alquilo, alquilsulfonilo,

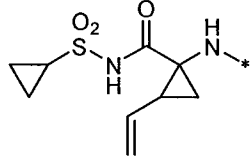
fenilsulfonilo, Ar^2 , Ar^3 , , , , O, ;

20 R^8 es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;

o R^7R^8N tomado conjuntamente es azetidínico, pirrolidinilo, piperidinilo,

piperazinilo, morfolinilo, dihidroindolilo, o isoindolinilo, y está sustituido con 0-2
sustituyentes que se seleccionan a partir de alquilo, hidroxialquilo, alcoxialquilo,
hidroxi, alcoxi, carboxi, alcoxicarbonilo, dialquilcarboxamido,
alquilcarbonilamino, alcoxicarbonilamino, piridinilo, y fenilo donde dicho fenilo
5 está sustituido con 0-2 sustituyentes halo o alquilo;

o cuando R^7R^8N tomado conjuntamente es ,
(quinuclidinil)amino, (quinuclidinil)(alquil)amino, (metilpirrolidinil)(alquil)amino,
((imidazolil)alquil)(hidroxialquil)amino, (alquiltiazolil)amino,
((carboxamido)ciclopentanil)amino, ((halofenil)ciclopentanil)amino, 3H-

10 espiro(isobenzofuranil)piperidinilo, (hidroxiindanil)amino, o  ;

R^9 es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;
 R^{10} es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;
o R^9 y R^{10} tomados conjuntamente son etileno, propileno, butileno,
pentileno, o hexileno;

15 R^{11} es hidrógeno, alquilo, o cicloalquilo;
 R^{12} es hidrógeno, alquilo, o cicloalquilo;
o R^{11} y R^{12} tomados conjuntamente con el nitrógeno al que están unidos
son azetidino, pirrolidinilo, piperidinilo, piperazinilo, o morfolinilo;
 R^{13} es hidrógeno, alquilo, cianoalquilo, haloalquilo, alqueno, alquino, o

tiazolilo;

R^{14} es hidrógeno o alquilo;

R^{15} es hidrógeno, alquilo, hidroxialquilo, cicloalquilo, o bencilo;

R^{16} es hidrógeno o alquilo;

- 5 o R^{15} y R^{16} tomados conjuntamente con el nitrógeno al que están unidos son azetidínilo, pirrolidínilo, piperidínilo, piperazinilo, o morfolínilo;

R^{17} es haloalquilo, cianoalquilo, (cicloalquil)alquilo, hidroxialquilo, alcoxialquilo, aminoalquilo, (R^{18})alquilo, (Ar^4)alquilo, alquinilo, o aminocicloalquilo;

- 10 R^{18} es $CONH_2$, H_2NCONH , dibencilamino, ftalimido, amino, alquilamino, dialquilamino, azetidínilo, pirrolidínilo, piperidínilo, piperazinilo, morfolínilo, donde azetidínilo, pirrolidínilo, piperidínilo, piperazinilo, o morfolínilo están sustituidos con 0-3 sustituyentes alquilo o alcóxicarbonilo;

- R^{19} es ciano, hidroxialquilo, morfolínialquilo, carboxi, alcóxicarbonilo, 15 cicloalquilsulfoxamido, ((alquil)pirazolil)amino, ((alquil)isoxazolil)amino, (tiadiazolil)amino, (triazinil)amino, o alquinilaminocarbonilo;

R^{20} es hidrógeno, halo, alquilo, o alcoxi;

R^{21} es hidrógeno, halo, alquilo, o alcoxi;

- Ar^1 es fenilo, naftalenilo, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, 20 isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, oxadiazolilo, triazolilo, tetrazolilo, pirazinilo, pirimidinilo, o benzotiazolilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo,

alquilo, cicloalquilo, haloalquilo, alcoxialquilo, hidroxilo, alcoxi, amino, alquilamino, dialquilamino, aminocarbonilo, piridinilo, fenilo, halofenilo, alquilfenilo, y alcoxifenilo;

Ar^2 es fenilo, bifenilo, o piridinilo y está sustituido con 0-2 sustituyentes
5 que se seleccionan a partir de halo, alquilo, ciano, hidroxilo, alcoxi, y carboxi;

Ar^3 es pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, triazolilo, oxadiazolilo, oxatiadiazolilo, pirimidinilo, o pirazinilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de hidroxilo, alquilo, hidroxialquilo, y $CONR^{13}R^{14}$;

10 Ar^4 es furanilo, tienilo, pirrolilo, pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piridinilo, indolilo, o fenilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, haloalquilo, hidroxilo, y alcoxi; y

Ar^5 es pirrolozilo, imidazolilo, u oxadiazolilo y está sustituido con 0-2
15 sustituyentes que se seleccionan a partir de alquilo, carboxi, alcoxycarbonilo, bencilo, y fenilo;

o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un compuesto de la fórmula I donde R^{20} y R^{21} son hidrógeno.

20 Otro aspecto de la invención es un compuesto de la fórmula I donde

R^1 es R^5R^6N ; (carboxi)alquenilo; (alcoxycarbonil)alquenilo; (benciloxycarbonil)alquenilo; o fenilo donde dicho fenilo está sustituido con 1-2

- sustituyentes que se seleccionan a partir del grupo constituido por ciano, alquilo, alcoxi, hidroxialquilo, alcoxialquilo, hidroxialquiloxi, alcoxialquiloxi, haloalquilo, benciloxi, carboxi, alcoxycarbonilo, alquilsulfonilo, (carboxi)alquenilo, (alcoxycarbonil)alquenilo, alquilcarboxamido, alcoxycarboxamido, alquilsulfamido, (alquilsulfamido)alquilo, tetrahidropiraniloxi, Ar^5 , $SO_2NR^{15}R^{16}$, y $CONR^7R^8$; y donde dicho fenilo también está sustituido con 0-1 sustituyentes que se seleccionan a partir del grupo constituido por halo; alquilo; hidroxialquilo; alcoxialquilo; hidroxilo; alcoxi; OR^{17} ; cicloalcoxi; amino; alquilamino; dialquilamino; alquilcarboxamido; alcoxialquilcarboxamido; furanilo; indolilo; isoquinolinilo; piridinilo sustituido con 0-2 sustituyentes halo, alquilo, hidroxilo, o alcoxi; pirazolilo sustituido con 0-2 sustituyentes alquilo; y fenilo sustituido con 0-2 sustituyentes halo, alquilo, cianoalquilo, hidroxialquilo, alcoxialquilo, hidroxilo, alcoxi, carboxi, alcoxycarbonilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, alquilcarboxamido, carboxialquenilo, o fenilo;

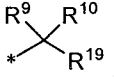
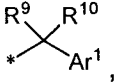
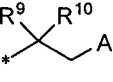
R^2 es hidrógeno, nitro, o R^5R^6N ;

R^3 es ciano, alcoxycarbonilo, (cicloalquil)oxycarbonilo, (alquilsulfonil)aminocarbonilo, $CONR^{11}R^{12}$, $(R^{11})(R^{12})NCONH$, triazolilo, tiazolilo, o tetrazolilo;

R^4 es fenilo sustituido con 0-2 sustituyentes halo;

R^5 es hidrógeno, alquilo, o alquilsulfonilo;

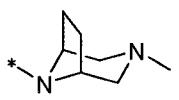
R^6 es hidrógeno, alquilo, hidroxialquilo, alcoxialquilo, o alquilsulfonilo;

R^7 es hidrógeno, alquilo, alquenilo, alquinilo, cianoalquilo, haloalquilo, hidroxialquilo, alcoxialquilo, oxoalquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo, (cicloalquil)alquilo, cicloalquilo, (alquil)cicloalquilo, (hidroxialquil)cicloalquilo, (tetrahidrofuranil)alquilo, (tetrahidropiranil)alquilo, (carboxi)alquilo, (alcoxicarbonil)alquilo, (alcoxicarbonil)hidroxialquilo, (CONR¹³R¹⁴)alquilo, (alquilcarbonil)aminoalquilo, (fenil)alquilo, (piridinil)alquilo, alquilsulfonilo, fenilsulfonilo, Ar², Ar³, , , , o



R^8 es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;

o R^7R^8N tomado conjuntamente es azetidínico, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, o dihidroindolilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, hidroxialquilo, alcoxialquilo, hidroxilo, alcoxi, carboxi, alcoxicarbonilo, dimetilcarboxamido, alquilcarbonilamino, alcoxicarbonilamino, piridinilo, y fenilo donde fenilo está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo y alquilo;

o donde R^7R^8N tomado conjuntamente es , (quinuclidinil)(alquil)amino, (metilpirrolidinil)(alquil)amino, (alquiltiazolil)amino, ((carboxamido)ciclopentanil)amino, ((halofenil)ciclopentanil)amino, o (hidroxiindanil)amino;

R^9 es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;

- R^{10} es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;
o R^9 y R^{10} tomados conjuntamente son etileno, propileno, butileno, o pentileno;
- R^{11} es hidrógeno, alquilo, o cicloalquilo;
- 5 R^{12} es hidrógeno, alquilo, o cicloalquilo;
o R^{11} y R^{12} tomados conjuntamente con el nitrógeno al que están unidos son azetidino, pirrolidino, piperidino, piperazino, o morfolino;
- R^{13} es hidrógeno, alquilo, cianoalquilo, alqueno, o alquino;
- R^{14} es hidrógeno o alquilo;
- 10 R^{15} es hidrógeno o alquilo;
- R^{16} es hidrógeno o alquilo;
- R^{17} es haloalquilo, hidroxialquilo, alcoxialquilo, alquino, (R^{18}) alquilo o (Ar^4) alquilo;
- R^{18} es $CONH_2$, dibencilamino, amino, alquilamino, dialquilamino, azetidino, pirrolidino, piperidino, piperazino, morfolino donde azetidino, pirrolidino, piperidino, piperazino, o morfolino están sustituidos con 0-3 sustituyentes que se seleccionan a partir de alquilo y alcoxycarbonilo;
- 15 R^{19} es ciano, ((alquil)pirazolil)amino, ((alquil)isoxazolil)amino (tiadiazolil)amino, o (triazinil)amino;
- 20 R^{20} y R^{21} son hidrógeno;
- Ar^1 es fenilo, naftalenilo, piridinilo, tienilo, tiazolilo, o pirazinilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, halo,

hidroxi, alcoxi, amino, alquilamino, y dialquilamino;

Ar² es fenilo, bifenilo, o piridinilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, ciano, hidroxi, y alcoxi;

Ar³ es pirazolilo, isoxazolilo, tiazolilo, pirimidinilo, o pirizinilo y está
5 sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo e hidroxialquilo;

Ar⁴ es pirrolilo, imidazolilo, piridinilo, indolilo, o fenilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, hidroxilo, y alcoxi;
y

10 Ar⁵ es pirrozolilo, imidazolilo, u oxadiazolilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, carboxi, alcoxicarbonilo, bencilo, y fenilo;

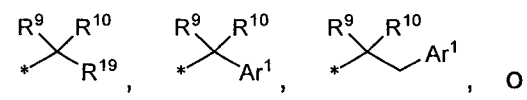
o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un compuesto de la fórmula I donde

15 R¹ es alcoxi; (alcoxicarbonilamino)alcoxi; (alquilfenil)alcoxi; (carboxi)alquenilo; ((N-dimetilbencil)aminocarbonil)alquenilo; o fenilo donde dicho fenilo está sustituido con 1-2 sustituyentes que se seleccionan a partir del grupo constituido por halo, ciano, alquilo, haloalquilo, hidroxialquilo, (carboxi)alquilo, alcoxi, hidroxialquiloxi, tetrahidropiraniloxi, carboxi,
20 alcoxicarbonilo, (carboxi)alquenilo, alquilcarboxamido, alcoxicarboxamido, (alquilsulfamido)alquilo, Ar⁵, SO₂NR¹⁵R¹⁶, y CONR⁷R⁸; y donde dicho fenilo también está sustituido con 0-2 sustituyentes que se seleccionan a partir del

grupo constituido por halo; nitro; alquilo; cicloalquilo; haloalquilo; aminoalquilo; hidrox; alcoxi; OR¹⁷; cicloalcoxi; amino; alcoxicarboxamido; furanilo, tienilo, o pirazolilo sustituido con 0-2 sustituyentes alquilo; piridinilo sustituido con 0-2 sustituyentes halo, ciano, alquilo, hidrox, alcoxi, amino, o alquilaminocarbonilo; 5 pirimidinilo; pirimidindionilo; aminopirimidinilo; indolilo; isoquinolinilo; y fenilo sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, cianoalquilo, hidroxialquilo, alcoxialquilo, alcoxi, amino, carboxi, aminocarbonilo, alquilaminocarbonilo, alquilcarboxamido, y carboxialqueno;

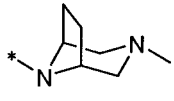
- R² es hidrógeno, halo, nitro, amino, fenilo, o R⁵R⁶N;
- 10 R³ es CONR¹¹R¹²;
- R⁴ es fenilo sustituido con 0-2 sustituyentes halo;
- R⁵ es hidrógeno o alquilsulfonilo;
- R⁶ es hidrógeno, alquilo, hidroxialquilo, o alquilsulfonilo;
- R⁷ es hidrógeno, alquilo, alquinilo, cianoalquilo, haloalquilo, 15 hidroxialquilo, dihidroxialquilo, alcoxialquilo, oxoalquilo, (dialquilamino)alquilo, (cicloalquil)alquilo, cicloalquilo, (alquil)cicloalquilo, (hidroxialquil)cicloalquilo, (tetrahidrofuranil)alquilo, (tetrahidropiranil)alquilo, (carboxi)alquilo, (alcoxicarbonil)alquilo, (alqueniloxicarbonil)alquilo, (alcoxicarbonil)hidroxialquilo, (CONR¹³R¹⁴)alquilo, (CONR¹³R¹⁴)(hidroxialquil)alquilo, 20 (CONR¹³R¹⁴)cicloalquilo, (alquilcarbonil)aminoalquilo, (fenil)alquilo, alquilsulfonilo, fenilsulfonilo, Ar², Ar³,

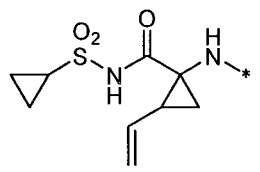




R^8 es hidrógeno, alquilo, o alcoxialquilo;

o R^7R^8N tomado conjuntamente es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, dihidroindolilo, o isoindolinilo, y está sustituido con 0-2
5 sustituyentes que se seleccionan a partir de alquilo, hidroxialquilo, alcoxialquilo, hidroxilo, alcoxycarbonilo, dialquilcarboxamido, alquilcarbonilamino, piridinilo, y fenilo donde dicho fenilo está sustituido con 0-2 sustituyentes halo o alquilo;

o donde R^7R^8N tomado conjuntamente es ,
(quinuclidinil)amino, (quinuclidinil)(alquil)amino, (metilpirrolidinil)(alquil)amino,
10 ((imidazolil)alquil)(hidroxialquil)amino, (alquiltiazolil)amino,
((carboxamido)ciclopentanil)amino, ((halofenil)ciclopentanil)amino, 3H-



espiro(isobenzofuranil)piperidinilo, (hidroxiindanil)amino, o

R^9 es hidrógeno, alquilo, o hidroxialquilo;

R^{10} es hidrógeno o alquilo;

15 o R^9 y R^{10} tomados conjuntamente son etileno o propileno;

R^{11} es alquilo;

R^{12} es hidrógeno;

R^{13} es hidrógeno, alquilo, cianoalquilo, haloalquilo, alquenilo, o tiazolilo;

R^{14} es hidrógeno o alquilo;

R^{15} es alquilo, hidroxialquilo, cicloalquilo, o bencilo;

R^{16} es hidrógeno;

o R^{15} y R^{16} tomados conjuntamente con el nitrógeno al que están unidos son azetidino, pirrolidino, piperidino, piperazino, o morfolino;

5 R^{17} es haloalquilo, cianoalquilo, (cicloalquil)alquilo, hidroxialquilo, alcoxialquilo, aminoalquilo, (R^{18})alquilo, (Ar^4)alquilo, alquino, o aminocicloalquilo;

R^{18} es $CONH_2$, H_2NCONH , dibencilamino, ftalimido, amino, dialquilamino, pirrolidino, piperidino, piperazino, morfolino donde azetidino, 10 pirrolidino, piperidino, piperazino, o morfolino están sustituidos con 0-3 sustituyentes alquilo o alcocarbonilo;

R^{19} es ciano, hidroxialquilo, morfolinalquilo, carboxi, alcocarbonilo, cicloalquilsulfoxamido, ((alquil)pirazolil)amino, ((alquil)isoxazolil)amino, (tiadiazolil)amino, (triazinil)amino, o alquilaminocarbonilo;

15 R^{20} y R^{21} son hidrógeno;

Ar^1 es fenilo, naftalenilo, piridinilo, furanilo, pirazolilo, isoxazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, triazolilo, tetrazolilo, pirazinilo, pirimidinilo, o benzotiazolilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, cicloalquilo, haloalquilo, alcoxialquilo, 20 hidroxilo, alcoxi, amino, aminocarbonilo, piridinilo, fenilo, halofenilo, alquilfenilo, y alcoxifenilo;

Ar^2 es fenilo, bifenilo, o piridinilo y está sustituido con 0-2 sustituyentes

que se seleccionan a partir de halo, alquilo, ciano, hidroxilo, alcoxi, y carboxi;

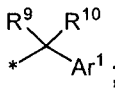
Ar^3 es pirazolilo, isoxazolilo, tiazolilo, triazolilo, pirimidinilo, o pirazinilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de hidroxilo, alquilo, y $CONR^{13}R^{14}$;

5 Ar^4 es furanilo, pirrolilo, pirazolilo, isoxazolilo, imidazolilo, oxadiazolilo, triazolilo, piridinilo, indolilo, o fenilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, haloalquilo, e hidroxilo; y

Ar^5 es pirrolozilo, imidazolilo, u oxadiazolilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, alcoxycarbonilo, bencilo, y
10 fenilo;

o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un compuesto de la fórmula I donde R^1 es fenilo sustituido con 1 sustituyente $CONR^7R^8$ y también sustituido con 0-2 sustituyentes halo, alquilo, o alcoxi; R^2 es hidrógeno, halo, o R^5R^6N ; R^3
15 $CONR^{11}R^{12}$; R^4 es monofluorofenilo; R^5 es alquilsulfonilo; R^6 es hidroxialquilo;

R^7 es ; R^8 es hidrógeno; R^9 es alquilo; R^{10} es alquilo o R^9 y R^{10} tomados conjuntamente son etileno o propileno; R^{11} es alquilo; R^{12} es hidrógeno; R^{20} y R^{21} son hidrógeno; Ar^1 es fenilo, piridinilo, pirimidinilo, isoxazolilo, oxazolilo, u oxadiazolilo, y está sustituido con 0-1 sustituyentes halo
20 o alquilo; o una sal farmacéuticamente aceptable del mismo.

Otro aspecto de la invención es un compuesto de la fórmula I donde R^1

- es fenilo sustituido con 1-2 sustituyentes que se seleccionan a partir del grupo constituido por halo, ciano, alquilo, haloalquilo, hidroxialquilo, (carboxi)alquilo, alcoxi, hidroxialquiloxi, tetrahidropiraniloxi, carboxi, alcoxycarbonilo, (carboxi)alquenilo, alquilcarboxamido, alcoxycarboxamido, (alquilsulfamido)alquilo, Ar^5 , $SO_2NR^{15}R^{16}$, y $CONR^7R^8$; y donde dicho fenilo también está sustituido con 0-2 sustituyentes que se seleccionan a partir del grupo constituido por halo; nitro; alquilo; cicloalquilo; haloalquilo; aminoalquilo; hidrox; alcoxi; OR^{17} ; cicloalcoxi; amino; alcoxycarboxamido; furanilo, tienilo, o pirazolilo sustituido con 0-2 sustituyentes alquilo; piridinilo sustituido con 0-2 sustituyentes halo, ciano, alquilo, hidrox, alcoxi, amino, o alquilaminocarbonilo; pirimidinilo; pirimidindionilo; aminopirimidinilo; indolilo; isoquinolinilo; y fenilo sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, cianoalquilo, hidroxialquilo, alcoxialquilo, alcoxi, amino, carboxi, aminocarbonilo, alquilaminocarbonilo, alquilcarboxamido, y carboxialquenilo.
- 15 Otro aspecto de la invención es un compuesto de la fórmula I donde R^1 es fenilo sustituido con 1 sustituyente $CONR^7R^8$ y también sustituido con 0-2 sustituyentes halo, alquilo, o alcoxi.
- Otro aspecto de la invención es compuesto de la fórmula I donde R^7 es
- $$\begin{array}{c} R^9 \quad R^{10} \\ \diagdown \quad \diagup \\ * \quad C \\ \diagup \quad \diagdown \\ Ar^1 \end{array}$$

y al menos uno de R^9 y R^{10} no es hidrógeno.
- 20 Otro aspecto de la invención es compuesto de la fórmula I donde R^2 es R^5R^6N .

Otro aspecto de la invención es compuesto de la fórmula I donde R^3 es $CONR^{11}R^{12}$.

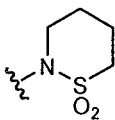
Otro aspecto de la invención es compuesto de la fórmula I donde R^4 es fenilo o monofluorofenilo.

5 A no ser que se especifique lo contrario, estos términos tienen los siguientes significados. "Alquilo" quiere decir un grupo alquilo lineal o ramificado compuesto por de 1 a 6 carbonos. "Alquenilo" quiere decir un grupo alquilo lineal o ramificado compuesto por de 2 a 6 carbonos con al menos un enlace doble. "Cicloalquilo" quiere decir un sistema de anillos monocíclico
10 compuesto por de 3 a 7 carbonos. "Hidroalquilo," "alcoxi" y otros términos con un resto alquilo sustituido incluyen isómeros lineales y ramificados compuestos por de 1 a 6 átomos de carbono para el resto alquilo. "Haloalquilo" y "haloalcoxi" incluyen todos los isómeros halogenados desde alquilo monohalosustituido a alquilo perhalosustituido. "Ariilo" incluye sustituyentes
15 aromáticos carbocíclicos y heterocíclicos. Los términos entre paréntesis y entre paréntesis múltiples se pretende que aclaren las relaciones de los enlaces a los expertos en la técnica. Por ejemplo, un término tal como ((R)alquilo) quiere decir un sustituyente alquilo sustituido además con el sustituyente R.

20 Los sustituyentes que se ilustran mediante las figuras de compuestos químicos como que se unen a posiciones variables en un sistema de anillos múltiples (por ejemplo un sistema de anillos bicíclico) se pretende que se unan

al anillo donde se dibuja que están unidos. Por ejemplo, los sustituyentes R^1 y R^2 de la fórmula I se pretende que estén unidos al anillo benceno de la fórmula I y no al anillo furano.

Etileno quiere decir etandiilo o $-\text{CH}_2\text{CH}_2-$; propileno quiere decir propandiilo o $-\text{CH}_2\text{CH}_2\text{CH}_2-$; butileno quiere decir butandiilo o $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$; pentileno quiere decir pentandiilo o $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$.



Dioxotiazinilo quiere decir

Cualquiera de los alcances de cualquier variable, que incluyen $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, \text{Ar}^1, \text{Ar}^2, \text{Ar}^3, \text{Ar}^4$, o Ar^5 puede usarse independientemente con el alcance de cualquier otro caso de una variable.

La invención incluye todas las formas salinas farmacéuticamente aceptables de los compuestos. Las sales farmacéuticamente aceptables son aquellas en las que los iones conjugados no contribuyen de forma significativa a la actividad fisiológica o a la toxicidad de los compuestos y como tal funcionan como equivalentes farmacológicos. Estas sales pueden prepararse de acuerdo con técnicas de química orgánica habituales que emplean reactivos disponibles comercialmente. Algunas formas salinas aniónicas incluyen acetato, acistrato, besilato, bromuro, cloruro, citrato, fumarato, glucouronato, bromhidrato, clorhidrato, yodhidrato, yoduro, lactato, maleato, mesilato, nitrato, pamoato, fosfato, succinato, sulfato, tartrato, tosilato, y xinofoato. Algunas

formas salinas catiónicas incluyen amonio, aluminio, benzatina, bismuto, calcio, colina, dietilamina, dietanolamina, litio, magnesio, meglumina, 4-fenilciclohexilamina, piperazina, potasio, sodio, trometamina y cinc.

Algunos de los compuestos de la invención poseen átomos de carbono
5 asimétricos. La invención incluye todas las formas estereoisoméricas, que incluyen enantiómeros y diastereómeros así como mezclas de estereoisómeros como por ejemplo racematos. Algunos estereoisómeros pueden prepararse usando procedimientos conocidos en la técnica. Las mezclas estereoisoméricas de los compuestos e intermedios relacionados pueden
10 separarse en los isómeros individuales de acuerdo con procedimientos conocidos en la técnica.

Se pretende que la invención incluya todos los isótopos de los átomos que aparecen en los presentes compuestos. Los isótopos incluyen los átomos que tienen el mismo número atómico pero diferentes números másicos. Como
15 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 marcados isotópicamente de la invención generalmente pueden prepararse mediante técnicas convencionales conocidas por los expertos en la técnica o mediante procesos análogos a los descritos en el presente documento, usando un
20 reactivo marcado isotópicamente apropiado en lugar del reactivo no marcado que se emplea en otros casos. Dichos compuestos pueden tener una variedad de usos potenciales, por ejemplo como patrones y reactivos para determinar la

actividad biológica. En el caso de los isótopos estables, dichos compuestos pueden tener el potencial de modificar favorablemente propiedades biológicas, farmacológicas o farmacocinéticas.

5

PROCEDIMIENTOS DE SÍNTESIS

Los compuestos pueden prepararse mediante procedimientos conocidos en la técnica que incluyen los que se describen más adelante e incluyen las variaciones que están dentro de la experiencia de la técnica. Algunos reactivos e intermedios son conocidos en la técnica. Otros reactivos e intermedios pueden prepararse mediante procedimientos conocidos en la técnica usando materiales fácilmente disponibles. Las variables (por ejemplo los sustituyentes "R" numerados) que se usan para describir la síntesis de los compuestos se pretende únicamente que ilustren cómo preparar los compuestos y no deben confundirse con las variables que se usan en las reivindicaciones ni en otras secciones de la memoria descriptiva. Los siguientes procedimientos tienen un fin ilustrativo y no se pretende que limiten el alcance de la invención.

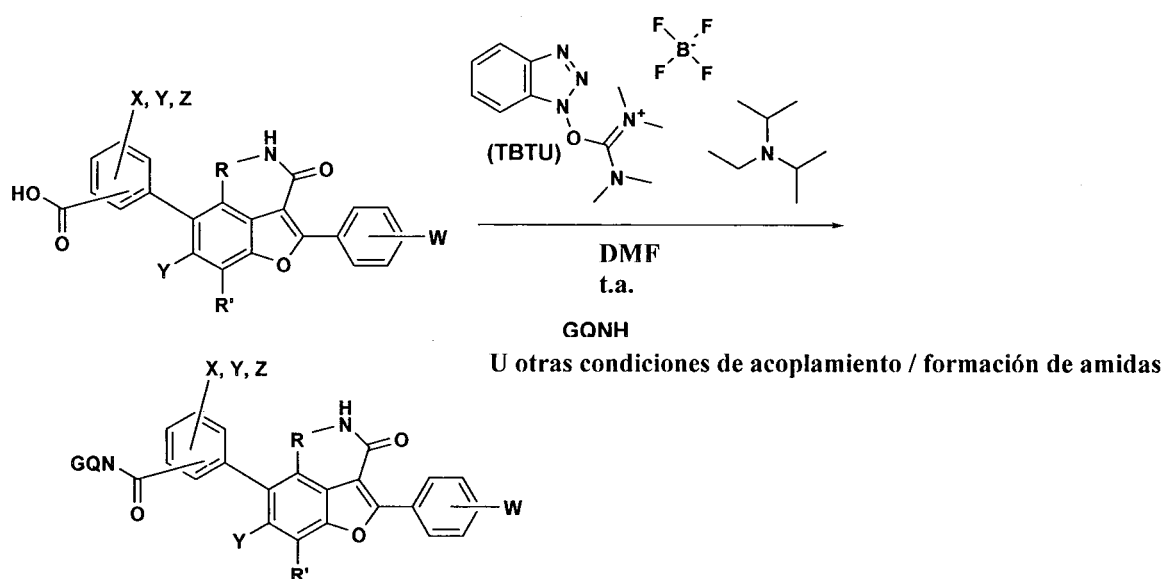
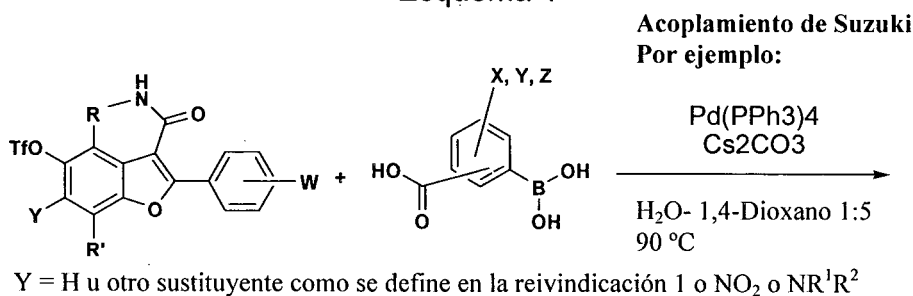
Las abreviaturas que se usan en los esquemas generalmente siguen las convenciones que se usan en la técnica. Las abreviaturas químicas que se usan en la especificación y los ejemplos se definen de la forma siguiente:

20 "NaHMDS" por bis(trimetilsilil)amida sódica; "DMF" por N,N-dimetilformamida; "MeOH" por metanol; "NBS" por N-bromosuccinimida; "Ar" por arilo; "TFA" por ácido trifluoroacético; "LAH" por hidruro de litio y aluminio; "BOC", "DMSO" por

dimetilsulfóxido; "h" por horas; "ta" por temperatura ambiente; "tr" por tiempo de retención (según el contexto); "min" por minutos; "EtOAc" por acetato de etilo; "THF" por tetrahidrofurano; "EDTA" por ácido etilendiaminotetraacético; "Et₂O" por dietiléter; "DMAP" por 4-dimetilaminopiridina; "DCE" por 1,2-dichloroetano; 5 "ACN" por acetonitrilo; "DME" por 1,2-dimetoxietano; "HOBt" por hidrato de 1-hidroxibenzotriazol; "DIEA" por diisopropiletilamina, "Nf" por CF₃(CF₂)₃SO₂-; y "TMOF" por ortoformiato de trimetilo.

Como se muestra en el Esquema 1, algunos compuestos de la invención pueden prepararse mediante acoplamiento de un triflato o haluro de 10 benzofurano a un ácido fenilborónico sustituido que en algunos ejemplos contiene un ácido carboxílico o un éster de ácido carboxílico. Otras técnicas y condiciones de acoplamiento también son conocidas en la técnica al igual que otras reacciones que forman enlaces carbono-carbono. Los ácidos y los ésteres pueden convertirse en amidas mediante procedimientos conocidos en 15 la técnica.

Esquema 1

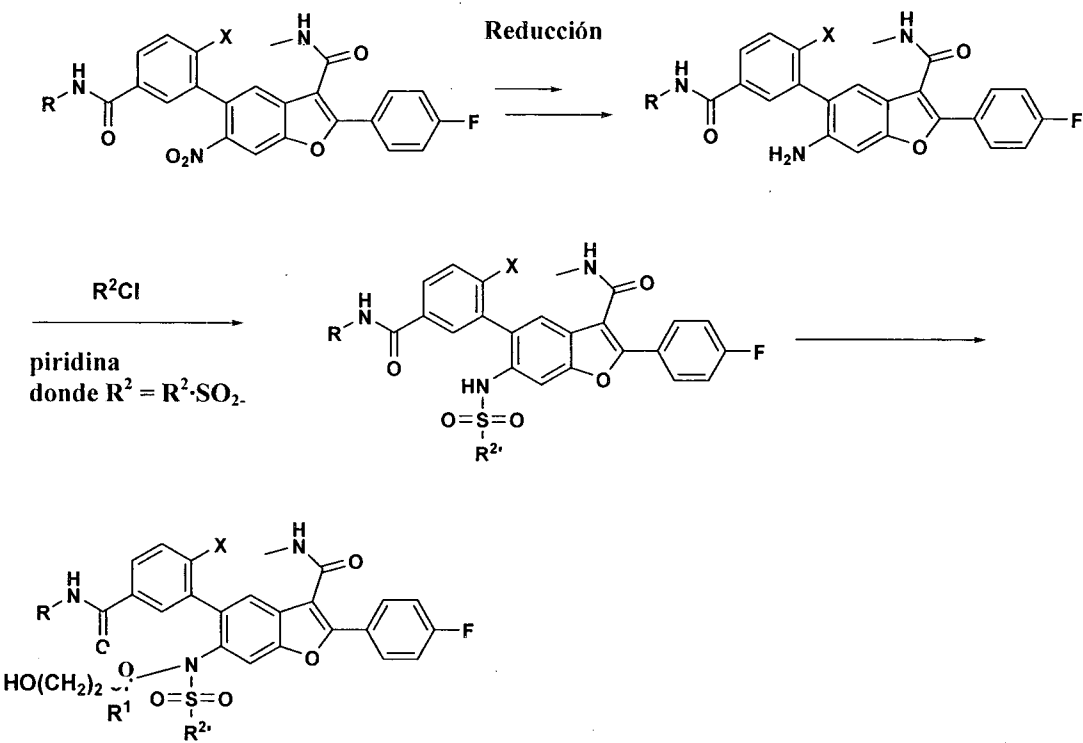


El Esquema 2 representa un ejemplo específico del Esquema 1.

- 5 Como se muestra en el Esquema 2, un grupo nitro del anillo de benzofurano puede reducirse y el grupo amino resultante puede funcionalizarse usando reacciones químicas conocidas. Por ejemplo, la amina puede convertirse en una monosulfonamida mediante reacción con un cloruro de sulfonilo o mediante preparación de una bis sulfonamida seguida de hidrólisis
- 10 selectiva. La monosulfonamida puede alquilarse de nuevo o bien con un alquilo simple o bien con uno funcionalizado. En el Esquema 3, el grupo hidroxietilo se

desprotege mediante eliminación ácida del grupo protector de sililo.

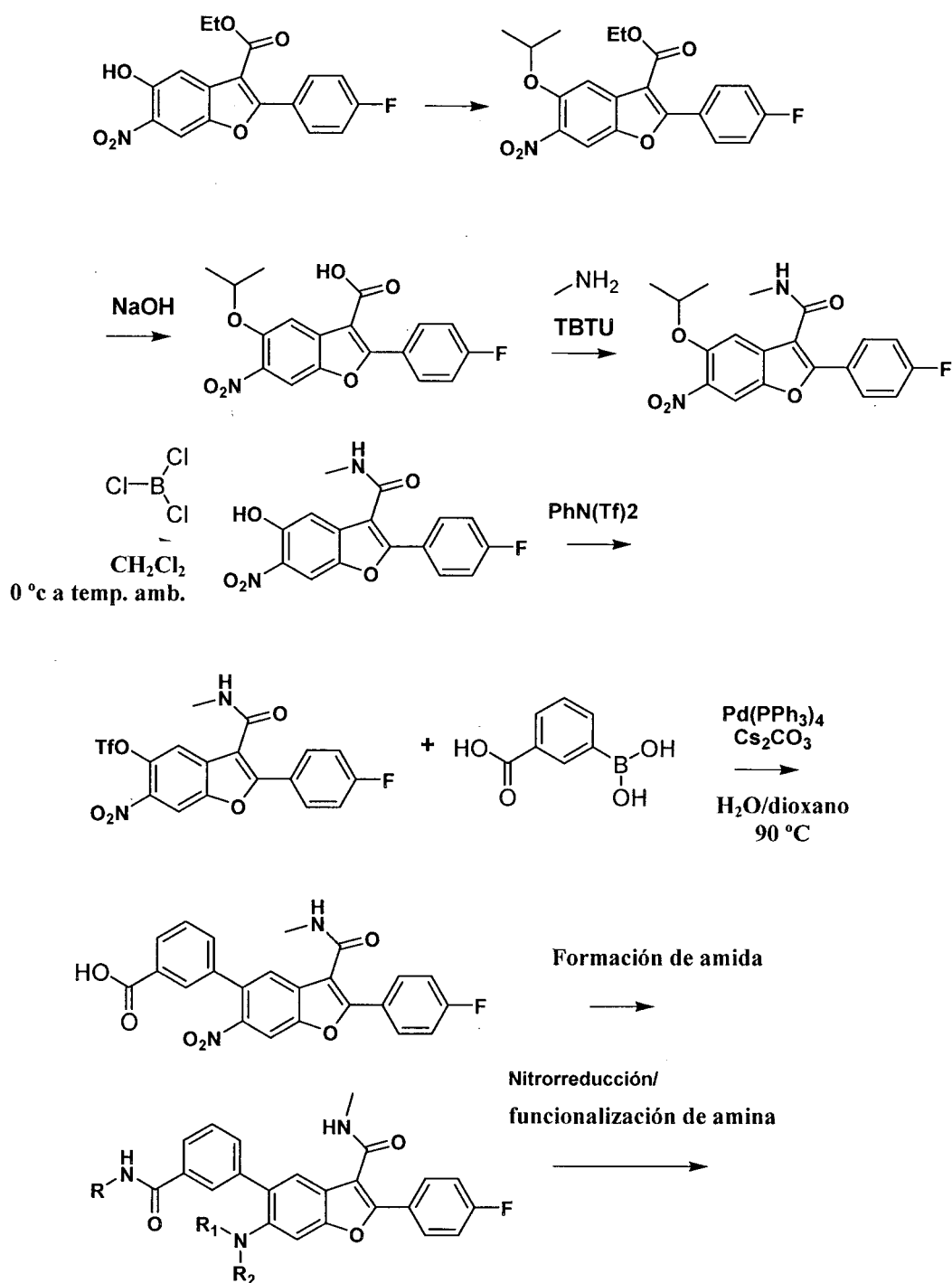
Esquema 2



5

El Esquema 3 representa la preparación de dos intermedios marcados como intermedio 1 y 2 comunes que pueden usarse para preparar algunos compuestos de la invención. El grupo isopropilo se usa para proteger temporalmente el grupo hidroxilo en C5 de forma que pueda construirse la metil amida a partir del éster etílico. El intermedio común más avanzado 2 permite funcionalizar la sulfonamida, la desprotección con ácido y la formación de algunos compuestos de amida después del acoplamiento de las aminos al ácido como se describe anteriormente.

10

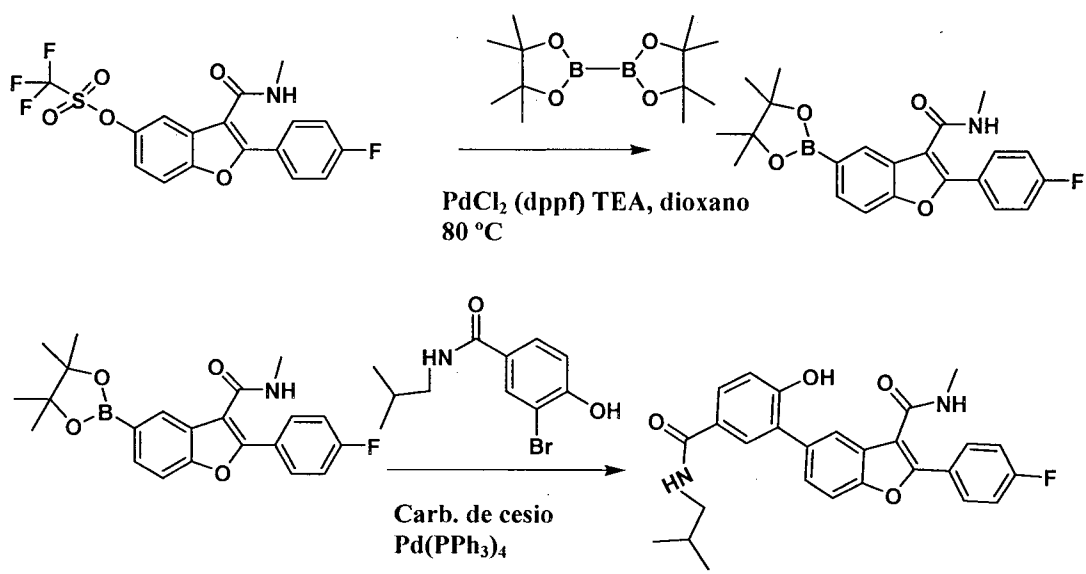


El Esquema 5 ilustra un procedimiento para preparar algunos compuestos preparando 2-(4-fluorofenil)-N-metil-5-(4,4,5,5-tetrametil-1,3,2-

dioxaborolan-2-il)benzofuran-3-carboxamida en la que el boro está unido al benzofurano y después acoplando a los restos arilo que contienen triflatos o halógeno.

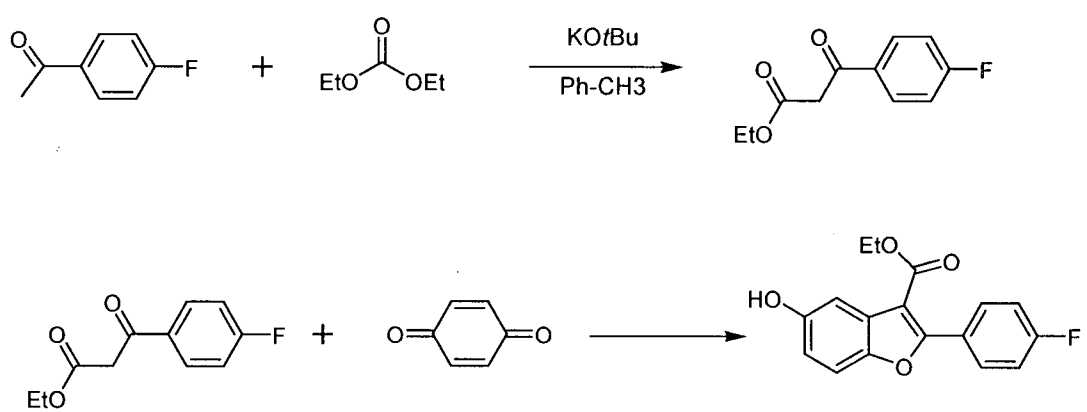
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Esquema 5

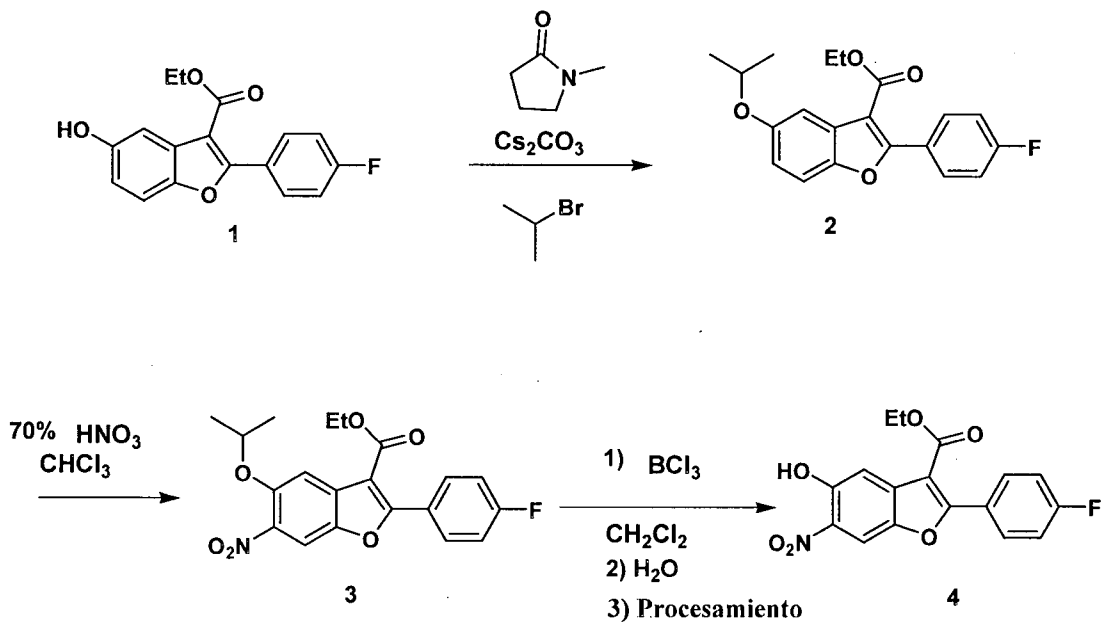


El Esquema 6 muestra una preparación del benzofurano funcionalizado y el Esquema 7 muestra un procedimiento para la instalación de una función de nitrógeno que después puede funcionalizarse como se describe en los anteriores Esquemas.

Esquema 6



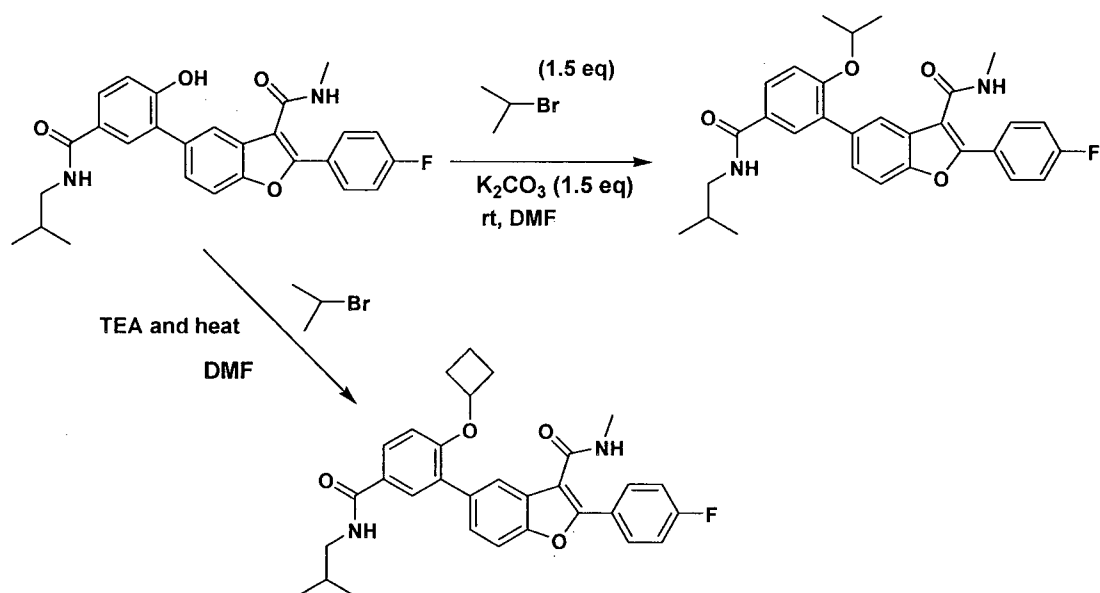
Esquema 7



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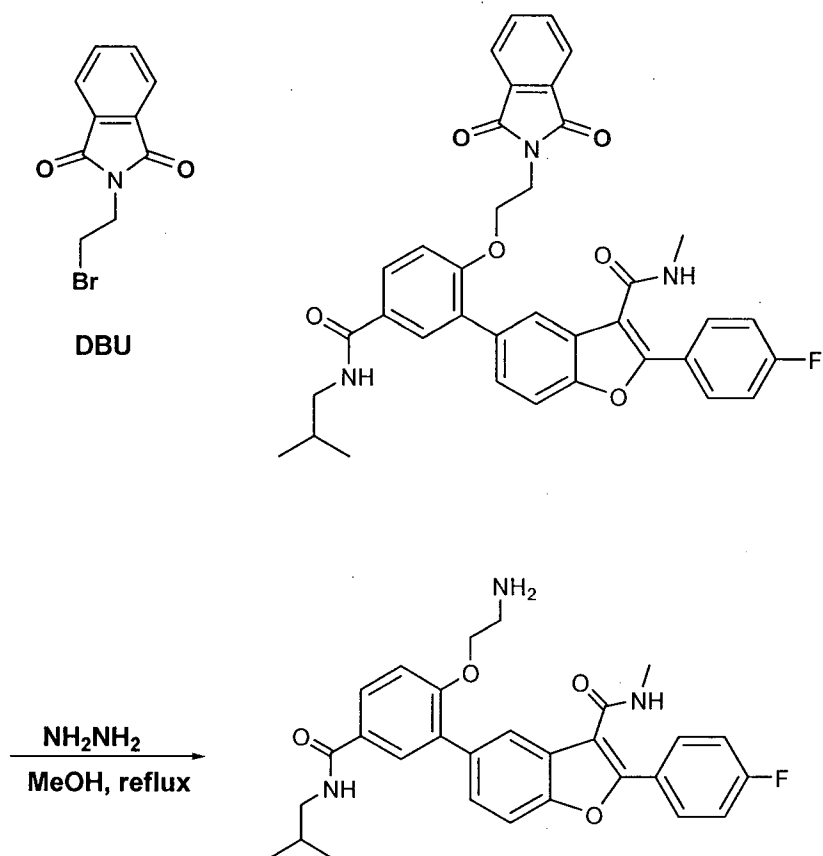
El Esquema 8 ilustra que puede usarse un grupo OH fenólico para formar algunos compuestos de éter. El Esquema 9 proporciona una alquilación para formar éteres en condiciones suaves o más extremas dependiendo de la reactividad del reactivo de alquilación.

10



El Esquema 10 muestra cómo puede unirse un éter con una amina protegida, y después de la posterior desprotección de la ftalimida, se libera una amina libre que puede incorporarse a los compuestos de la invención o derivarse más mediante reacciones químicas estándar proporcionando aminas o amidas o sulfonamidas secundarias o terciarias.

Esquema 10



PROCEDIMIENTOS BIOLÓGICOS

Los compuestos demostraron actividad contra NS5B de VHC según se
5 determinó en los siguientes ensayos con RdRp de VHC.

Clonación, expresión y purificación de RdRp de NS5B de VHC

El ADNc que codifica la proteína NS5B de VHC, genotipo 1b, se clonó
en el vector de expresión pET21a. La proteína se expresó con un truncado en
10 el extremo C de 18 aminoácidos para mejorar la solubilidad. Se usó la línea
celular competente BL21(DE3) de *E. coli* para la expresión de la proteína. Los

cultivos se cultivaron a 37 °C durante ~ 4 horas hasta que los cultivos alcanzaron una densidad óptica de 2,0 a 600 nm. Los cultivos se enfriaron a 20 °C y se indujeron con IPTG 1 mM. Se añadió ampicilina fresca a una concentración final de 50 µg/ml y las células se cultivaron toda la noche a 20 °C.

Se lisaron los sedimentos celulares (3 l) para purificar obteniendo 15-24 mg de NS5B purificada. El tampón de lisis estaba constituido por Tris-HCl 20 mM, a pH 7,4, NaCl 500 mM, 0,5% de triton X-100, DTT 1 mM, EDTA 1 mM, 20% de glicerol, 0,5 mg/ml de lisozima, MgCl₂ 10 mM, 15 µg/ml de desoxirribonucleasa I, y comprimidos inhibidores de proteasas CompleteTM (Roche). Tras la adición del tampón de lisis, se resuspendieron sedimentos celulares congelados usando un homogenizador tisular. Para reducir la viscosidad de la muestra, se sometieron a ultrasonidos alícuotas del lisado sobre hielo usando una microboquilla unida a un aparato de ultrasonidos Branson. El lisado sometido a ultrasonidos se centrifugó a 100.000 x g durante 1 hora a 4 °C y se filtró a través de una unidad de filtración de 0,2 µm (CORNING®).

La proteína se purificó usando tres etapas cromatográficas secuenciales: Heparina sefarosa CL-6B, poliU sefarosa 4B, y Hitrap® SP sefarosa (Pharmacia). Los tampones de cromatografía eran idénticos al tampón de lisado pero no contenían lisozima, desoxirribonucleasa I, MgCl₂ ni inhibidor de proteasas y la concentración de NaCl del tampón se ajustó de acuerdo con los

requisitos para cargar la proteína en la columna. Cada columna se eluyó con un gradiente de NaCl que variaba en longitud de 5-50 volúmenes de columna dependiendo del tipo de columna. Después de la etapa cromatográfica final, la pureza resultante de la enzima es >90% basándose en el análisis por SDS-PAGE. La enzima se dividió en alícuotas y se almacenó a -80°C .

Ensayo estándar de la enzima RdRp NS5B de VHC

Se realizaron ensayos de RdRp de VHC genotipo 1b en un volumen final de 60 μl en placas de 96 pocillos (Costar® 3912). El tampón de ensayo está compuesto por Hepes 20 mM, a pH 7,5, KCl 2,5 mM, MgCl_2 2,5 mM, DTT 1 mM, 1,6 U de inhibidor de RNAsa (Promega N2515), 0,1 mg/ml de BSA (Promega R3961), y 2% de glicerol. Se realizaron diluciones seriadas de todos los compuestos (3 veces) en DMSO y se diluyeron además en agua de tal forma que la concentración final de DMSO en el ensayo era de 2%. Se usó la enzima RdRp de VHC genotipo 1b a una concentración final de 28 nM. Se usó una plantilla de poliA a 6 nM, y un cebador de oligo-dT12 biotinilado a una concentración final de 180 nM. La plantilla se obtuvo comercialmente (Amersham 27-4110). El cebador biotinilado fue preparado por Sigma Genosys. Se usó ^3H -UTP a 0,6 μCi (UTP total 0,29 μM). Las reacciones se iniciaron mediante la adición de enzima, se incubaron a 30°C durante 60 minutos, y se terminaron mediante la adición de 25 μl de EDTA 50 mM que contenía perla de SPA (4 $\mu\text{g}/\mu\text{l}$, Amersham RPNQ 0007). Las placas se leyeron en un Packard

Top Count NXT después de incubar >1 hora a temperatura ambiente.

Ensayo de la enzima RdRp NS5B de VHC modificado

Se llevó a cabo un ensayo enzimático modificado esencialmente como se describe para el ensayo estándar de la enzima excepto por lo siguiente: El

5 cebador de oligo dT12 biotilado se capturó previamente sobre microesferas de SPA recubiertas con estreptavidina mezclando el cebador y las microesferas en tampón de ensayo e incubando a temperatura ambiente durante una hora. El cebador no unido se eliminó después de centrifugar. Las microesferas unidas al cebador se volvieron a suspender en tampón Hepes 20 mM, a pH 7,5

10 y se usaron en el ensayo a concentraciones finales de 20 nM para el cebador y 0,67 $\mu\text{g}/\mu\text{l}$ de microesferas. El orden de adición en el ensayo: la enzima (14 nM) se añadió al compuesto diluido y después se añadió una mezcla de plantilla (0,2 nM), ^3H -UTP (0,6 μCi , 0,29 μM), y las microesferas unidas al cebador, para iniciar la reacción; las concentraciones que se citan son las

15 finales. Se dejó que las reacciones siguieran su curso durante 4 horas a 30°C.

Los valores de CI_{50} para los compuestos se determinaron usando siete [I] diferentes. Los valores de CI_{50} se calcularon a partir de la inhibición usando la fórmula $y = A + ((B - A) / (1 + ((C/x)^D)))$.

20 Preparación del ensayo con FRET

Para realizar el ensayo de cribado con FRET de VHC, se usaron placas de cultivo celular de 96 pocillos. El péptido FRET (Anaspec, Inc.) (Taliani et al.,

Anal. Biochem., 240: 60-67 (1996)) contiene un donante de fluorescencia, EDANS, cerca de un extremo del péptido y un receptor, DABCILLO, cerca del otro extremo. La fluorescencia del péptido se inactiva mediante transferencia de energía por resonancia intermolecular (RET) entre el donante y el receptor, pero la proteasa NS3 al escindir el péptido, libera los productos de la inactivación de RET y la fluorescencia del donante se hace visible. El reactivo del ensayo se preparó de la forma siguiente: 5X reactivo de lisis de cultivo celular con luciferasa de Promega (#E153A) diluido a 1X con dH₂O, se añade NaCl a una concentración final de 150 mM, el péptido FRET diluido a una concentración final de 20 μ M a partir de una solución madre 2 mM.

Para preparar las placas, se tripsinizaron células con replicón de VHC, con o sin un gen testigo de luciferasa de Renilla, y se introdujeron en cada uno de los pocillos de una placa de 96 pocillos con compuestos de prueba titulados añadidos en las columnas 3 a 12; las columnas 1 y 2 contenían un compuesto de control (inhibidor de proteasa de VHC), y la fila inferior contenía células sin compuesto. Después las placas se introdujeron en una incubadora con CO₂ a 37°C.

Ensayos.

Posteriormente a la adición de los compuestos de prueba que se describen anteriormente (Preparación de ensayo con FRET), en tiempos diferentes se retiró la placa y se añadió solución azul de Alamar (Trek

Diagnostics, n.º 00-100) a cada pocillo para medir la toxicidad celular. Después de leer en un aparato CYTOFLUOR® 4000 (PE Biosystems), las placas se enjuagaron con PBS y después se usaron para un ensayo de FRET mediante la adición de 30 µl del reactivo del ensayo del péptido FRET que se describe
5 anteriormente (Preparación del ensayo con FRET) por pocillo. Después la placa se introdujo en el aparato CYTOFLUOR® 4000 que se había ajustado a 340 para excitación/490 para emisión, modo automático durante 20 ciclos y la placa se leyó en modo cinético. Habitualmente, la proporción entre señal y ruido usando un análisis de criterio de valoración después de las lecturas era
10 de al menos tres veces. De forma alternativa, después de la lectura con azul Alamar, las placas se enjuagaron con PBS, se añadieron 50 µl de DMEM (alto en glucosa) sin rojo fenol y las placas se usaron después para el ensayo con luciferasa usando el Sistema de ensayo de luciferasa Promega DUAL-GLO®.

El análisis de los compuestos se determinó mediante cuantificación de
15 los valores de la inhibición relativa del replicón de VHC y de citotoxicidad relativa. Para calcular los valores de la citotoxicidad, las señales de fluorescencia de azul Alamar medias de los pocillos de control se interpretaron como 100% no tóxicos. Las señales individuales de cada uno de los pocillos de prueba de los compuestos se dividieron después entre la señal de control
20 media y se multiplicaron por 100% para determinar la citotoxicidad porcentual. Para calcular los valores de inhibición del replicón de VHC, se obtuvo un valor de ruido de fondo medio a partir de los dos pocillos que contenían la mayor

cantidad de inhibidor de proteasa de VHC al final del periodo del ensayo. Estos números eran similares a los obtenidos con las células Huh-7 no expuestas.

Los números del ruido de fondo se restaron después de la señal media obtenida en los pocillos de control y este número se usó como 100% de actividad. Las señales individuales de cada uno de los pocillos de prueba de los compuestos se dividieron después entre el promedio de los valores de control después de restar el ruido de fondo y se multiplicaron por 100% para determinar la actividad. Los valores de CE_{50} para la valoración de un inhibidor de proteasas se calcularon en términos de la concentración que provocó una reducción del 50% de la actividad de FRET o de luciferasa. Los dos números generados para la placa de los compuestos, citotoxicidad porcentual y actividad porcentual se usaron para determinar los compuestos de interés para análisis ulteriores.

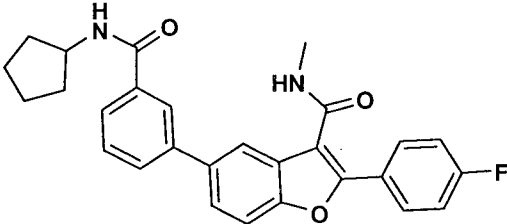
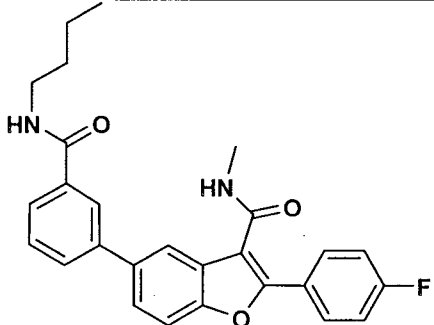
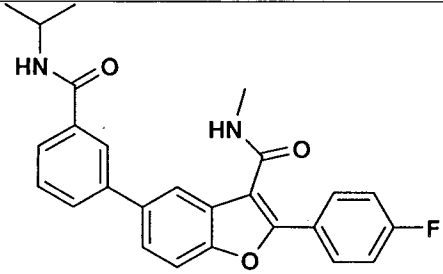
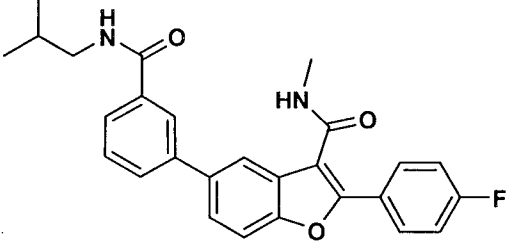
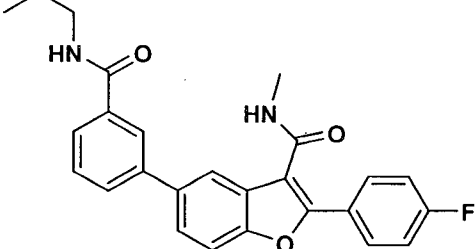
15 Ensayo de replicón de HCV con testigo de luciferasa

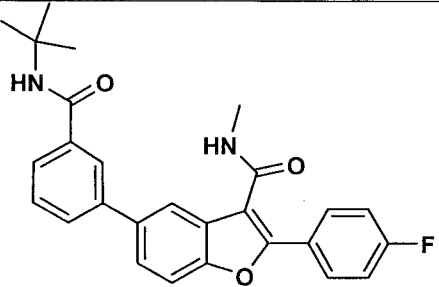
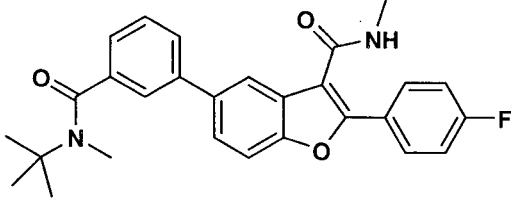
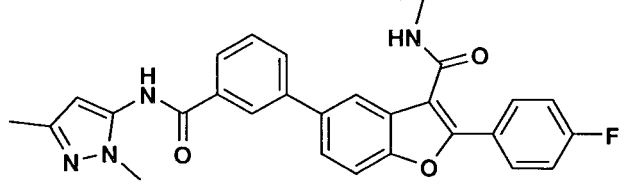
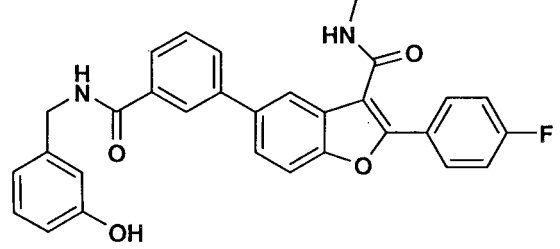
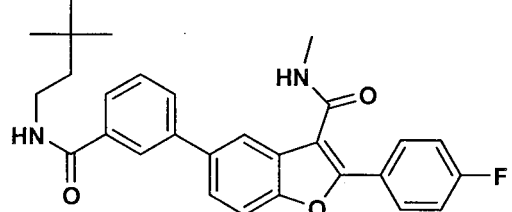
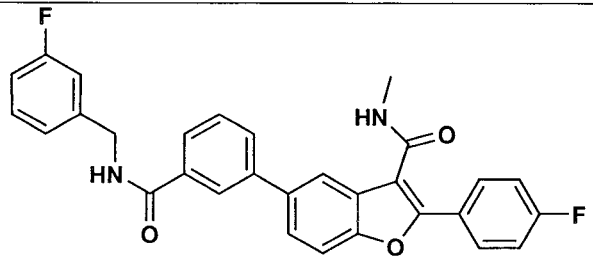
El ensayo de replicón de HCV con luciferasa se desarrolló para controlar los efectos inhibidores de los compuestos que se describen en la memoria sobre la replicación vírica de HCV. La utilización de un ensayo de replicón con testigo de luciferasa fue descrita por primera vez por Krieger et al (Krieger, N. et al., *J. Virol.*, 75(10):4614-4624 (2001)). Se cultivaron células HUH-7 que expresan el replicón de HCV de forma constitutiva, en medio de Eagle modificado por Dulbecco (DMEM) (Gibco-BRL) que contenía suero bovino fetal

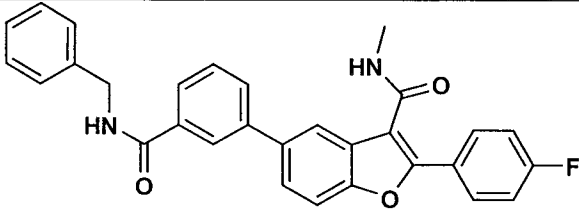
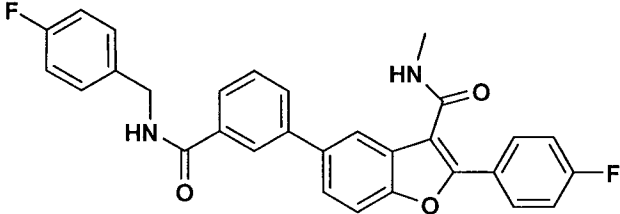
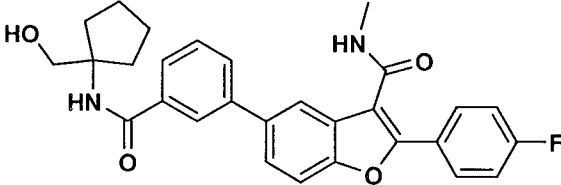
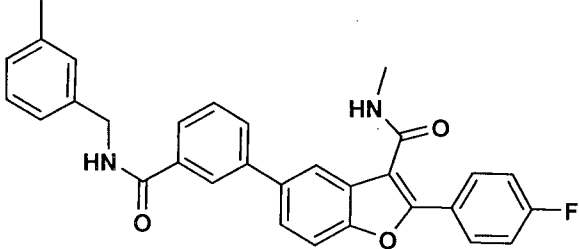
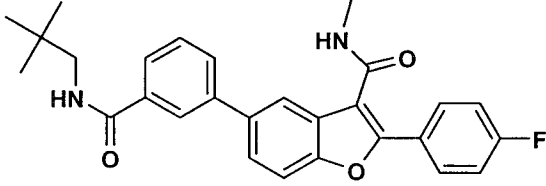
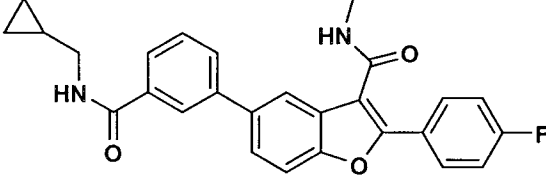
al 10% (FCS) (Sigma) y 1 mg/ml de G418 (Gibco-BRL). Se hicieron diluciones seriadas de factor 3 de los compuestos en DMSO para una valoración de veinte puntos y posteriormente se transfirieron a placas tratadas de cultivo tisular de 384 pocillos estériles (CORNING® n.º de cat. 3571). Las placas
5 después se sembraron con 50 µl de células a una densidad de $3,0 \times 10^3$ células/pocillo en DMEM que contenía 4% de FCS (concentración final de DMSO a 0,5%). Después de 3 días de incubación a 37 °C, las células se analizaron para determinar la actividad de la luciferasa de Renilla usando EnduRen como sustrato (Promega n.º de cat. E6485). El sustrato EnduRen se
10 diluyó en DMEM y después se añadió a las placas a una concentración final de 7,5 µM. Las placas se incubaron durante 2 horas a 37 °C y después se leyeron inmediatamente durante 30 segundos con VIEWLUX® Imager (PerkinElmer) usando un programa de luminiscencia. Para evaluar la citotoxicidad de los compuestos, se generaron los valores de CC₅₀ multiplexando las placas que
15 contenían EnduRen con CELLTITER-BLUE® (Promega, n.º de cat. G8082). Se añadieron 3 µl de CellTiter Blue a cada pocillo y se incubó durante 8 horas a 37 °C. Se leyó la señal de fluorescencia de cada pocillo, con una longitud de onda de excitación a 525/10 nm y una longitud de onda de emisión de 598/10 nm, usando el VIEWLUX® Imager.

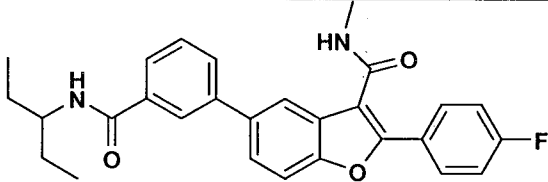
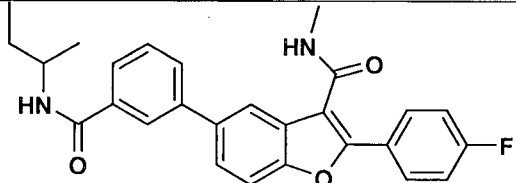
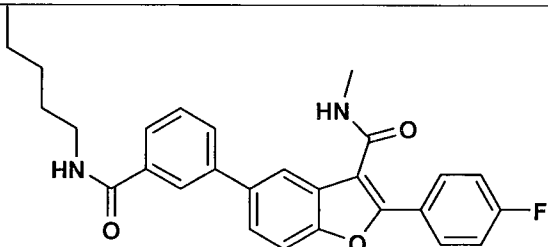
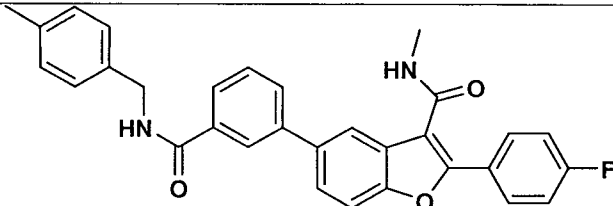
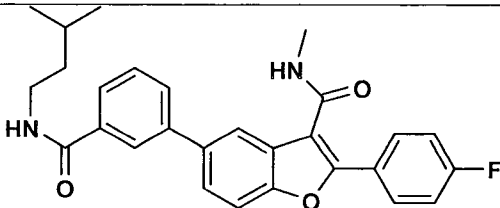
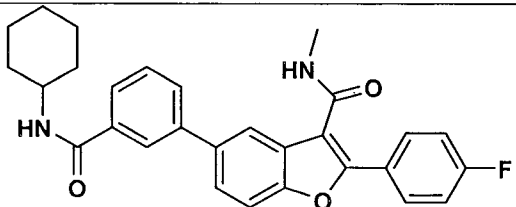
En las Tablas 1a, 1b y 1c se presentan datos representativos para compuestos.

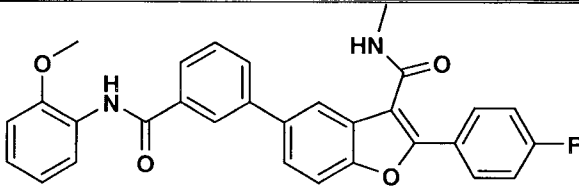
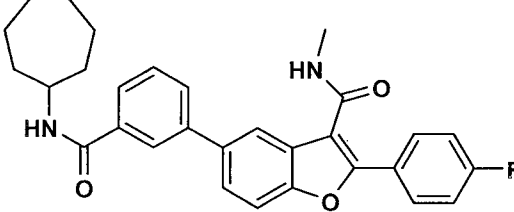
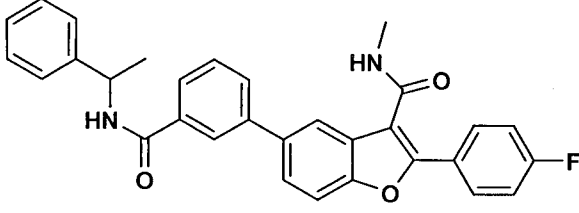
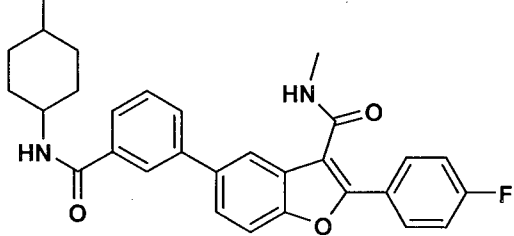
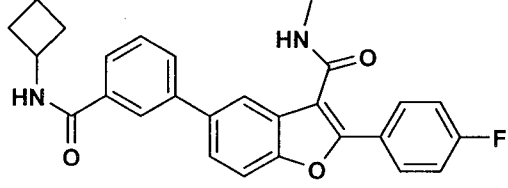
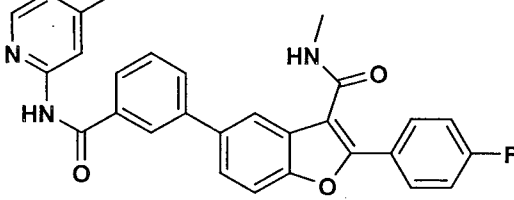
Tabla 1a

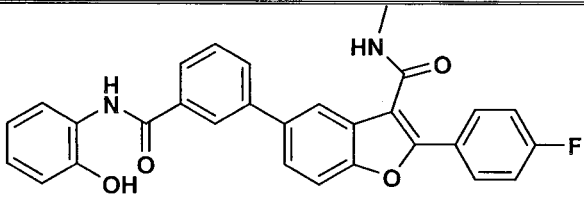
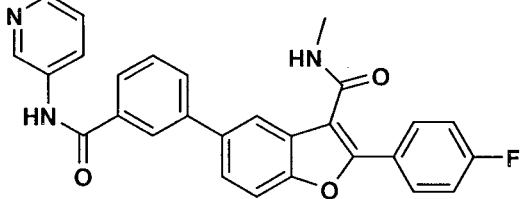
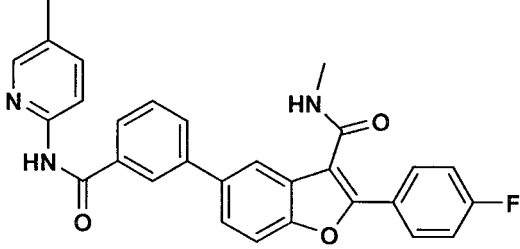
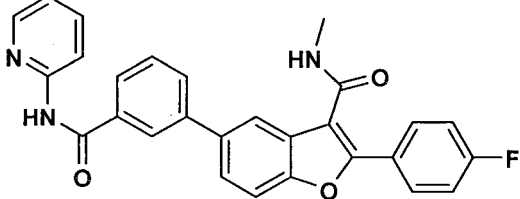
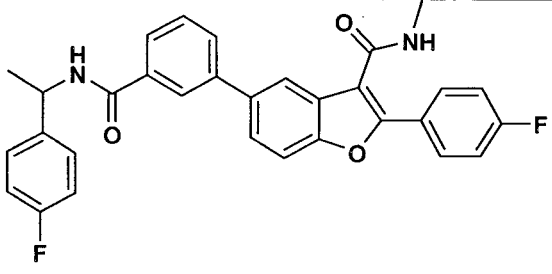
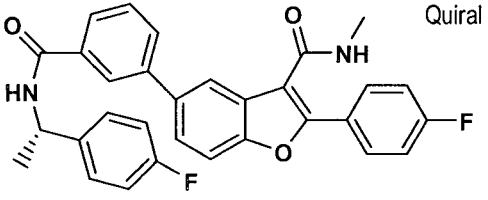
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	A	A
	A	A

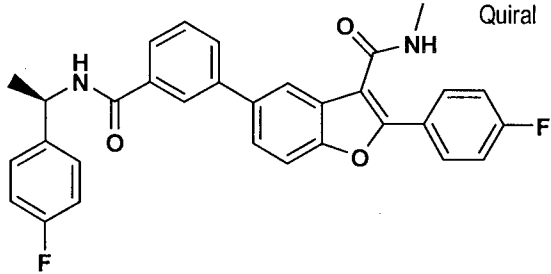
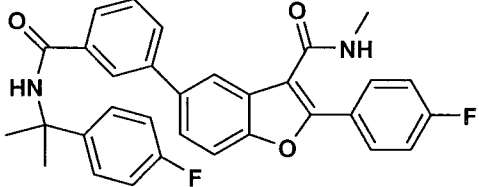
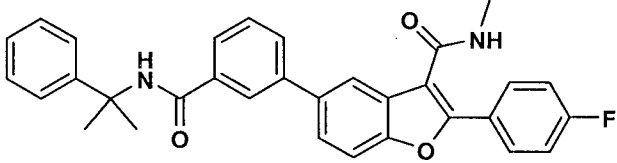
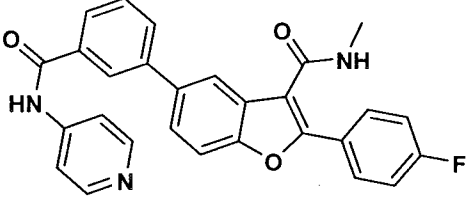
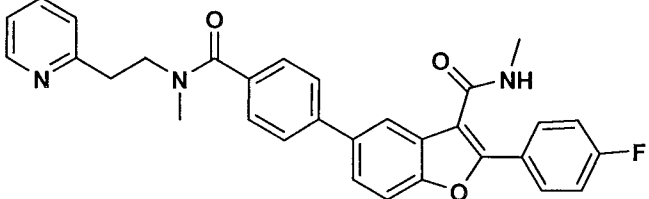
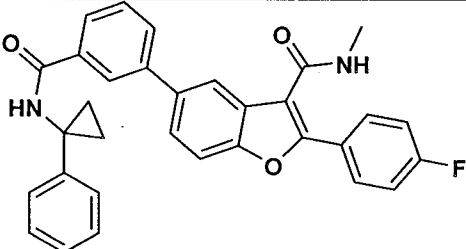
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	B	A
	A	A
	A	A

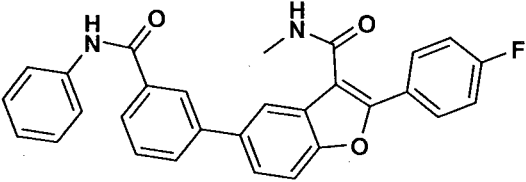
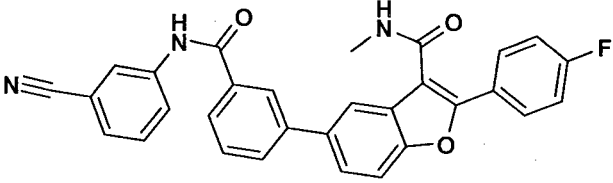
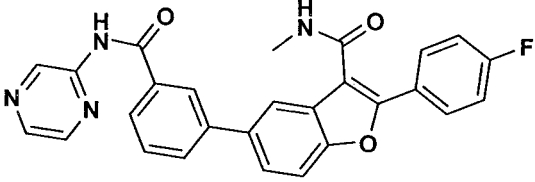
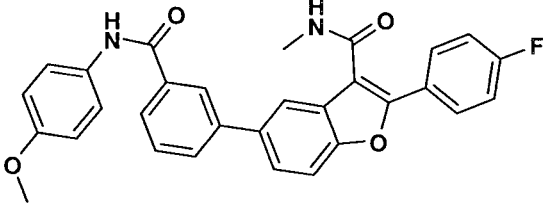
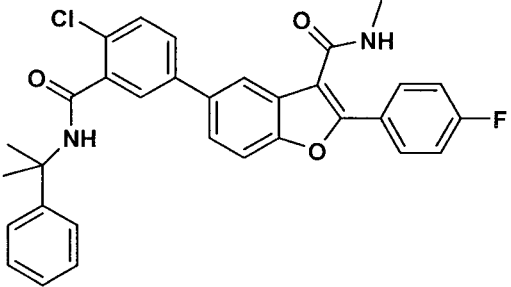
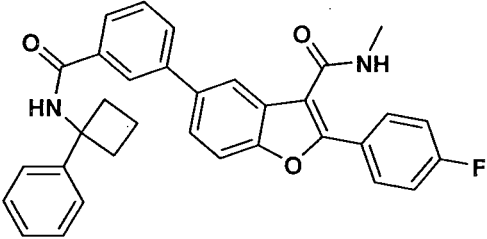
Estructura	Cl ₅₀	CE ₅₀
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	A	A
	A	A
	A	A
	A	A
	A	A

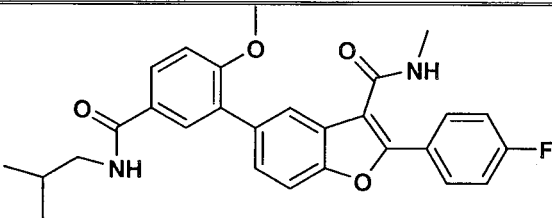
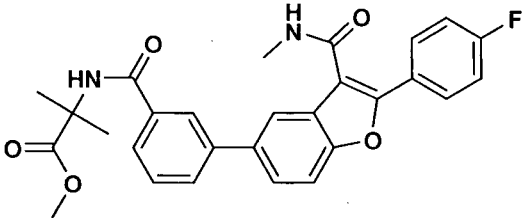
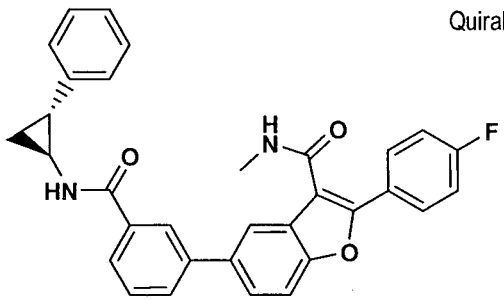
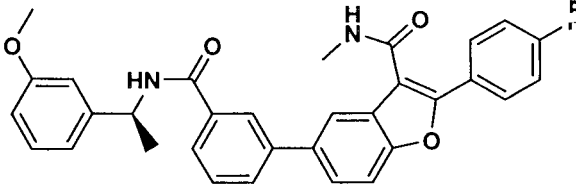
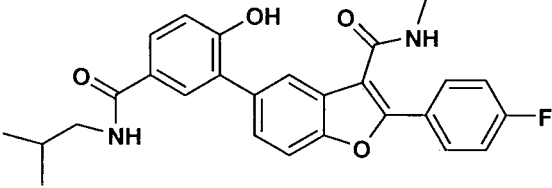
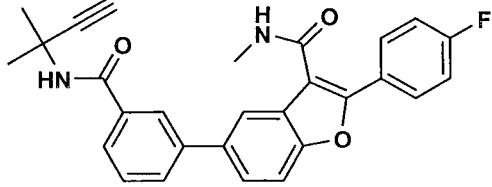
Estructura	Cl ₅₀	CE ₅₀
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	A	A
	A	A
	A	A
	B	A
	A	A

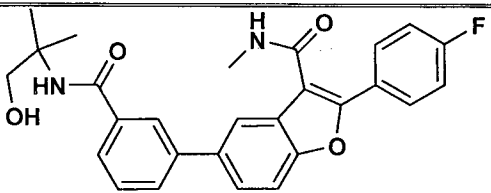
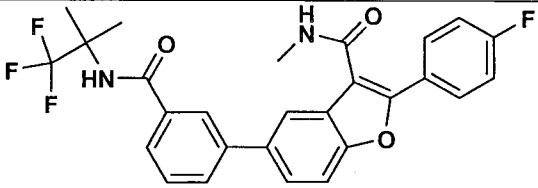
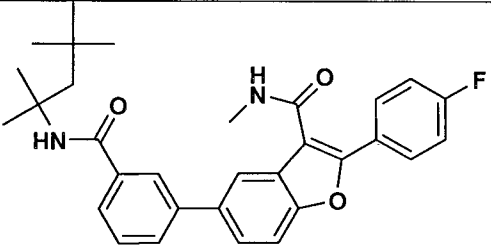
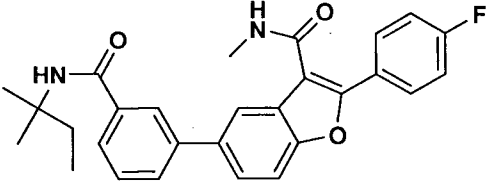
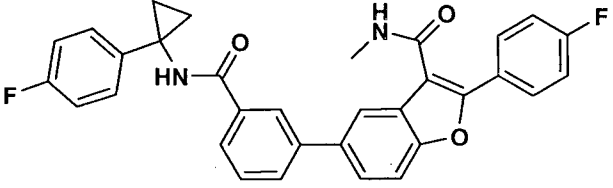
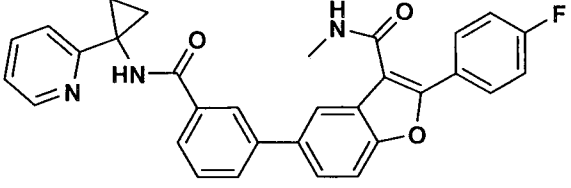
Estructura	Cl ₅₀	CE ₅₀
	B	A
	A	A
	A	A
	A	A
	A	A
	B	A

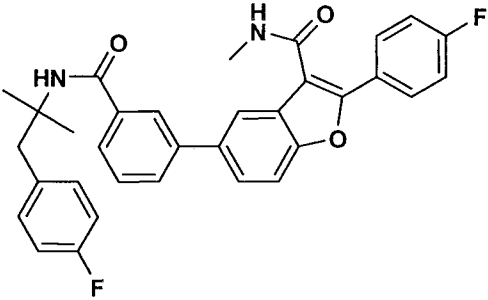
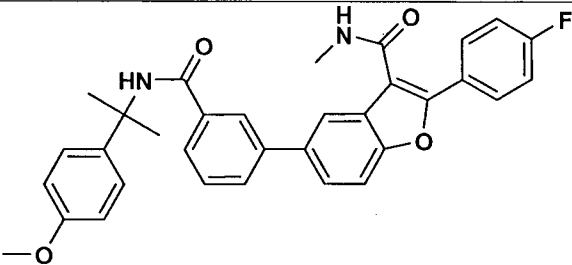
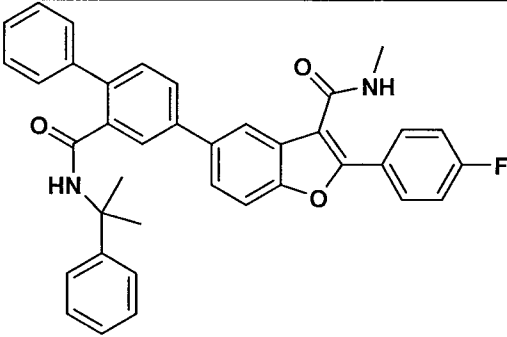
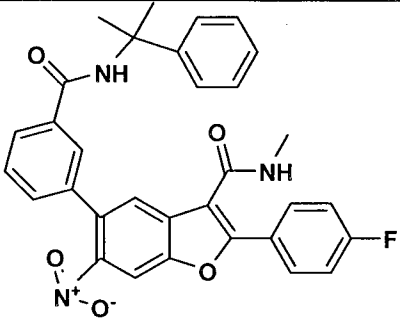
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	A	A
	A	A
 Quiral	A	A

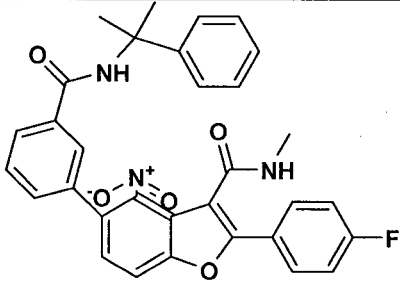
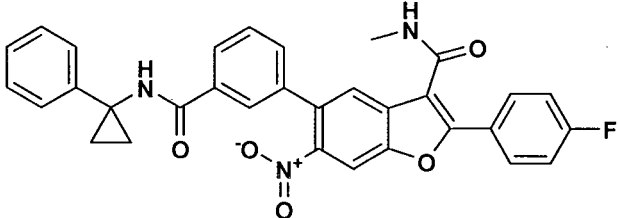
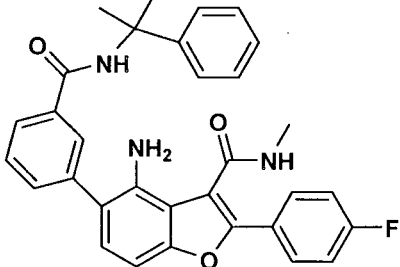
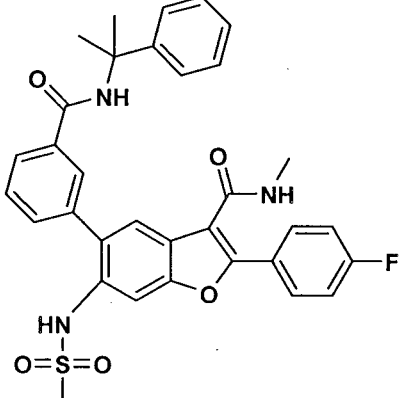
Estructura	Cl ₅₀	CE ₅₀
 <chem>CN1C(=O)c2cc(ccc2Oc3cc(ccc3C(=O)N[C@@H](C)Cc4ccc(F)cc4)C(=O)N[C@@H](C)Cc5ccc(F)cc5)cc1</chem> Quiral	A	A
 <chem>CN1C(=O)c2cc(ccc2Oc3cc(ccc3C(=O)N[C@@H](C)Cc4ccc(F)cc4)C(=O)N[C@@H](C)Cc5ccc(F)cc5)cc1</chem>	A	A
 <chem>CN1C(=O)c2cc(ccc2Oc3cc(ccc3C(=O)N[C@@H](C)Cc4ccc(F)cc4)C(=O)N[C@@H](C)Cc5ccc(F)cc5)cc1</chem>	A	A
 <chem>CN1C(=O)c2cc(ccc2Oc3cc(ccc3C(=O)N[C@@H](C)Cc4ccc(F)cc4)C(=O)N[C@@H](C)Cc5ccc(F)cc5)cc1</chem>	A	A
 <chem>CN1C(=O)c2cc(ccc2Oc3cc(ccc3C(=O)N[C@@H](C)Cc4ccc(F)cc4)C(=O)N[C@@H](C)Cc5ccc(F)cc5)cc1</chem>	A	A
 <chem>CN1C(=O)c2cc(ccc2Oc3cc(ccc3C(=O)N[C@@H](C)Cc4ccc(F)cc4)C(=O)N[C@@H](C)Cc5ccc(F)cc5)cc1</chem>	A	A

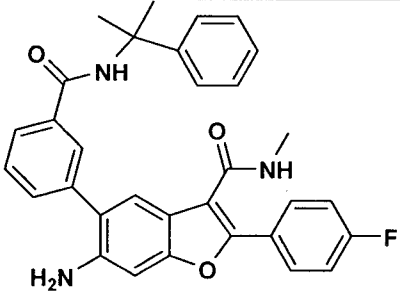
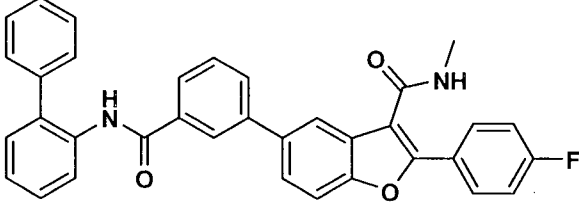
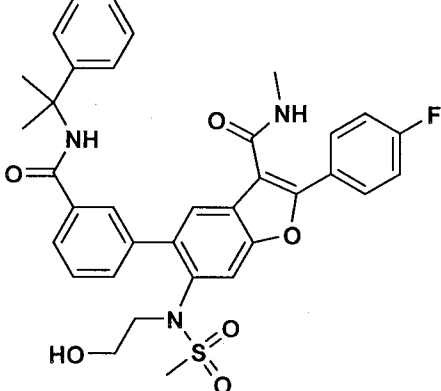
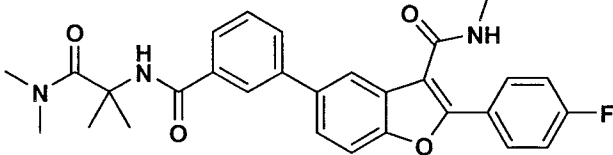
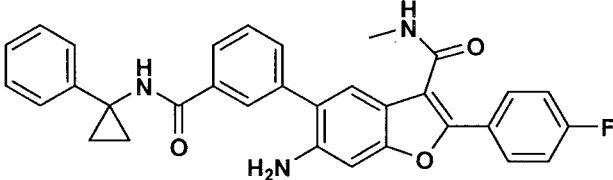
Estructura	Cl ₅₀	CE ₅₀
	A	A
	B	A
	A	A
	A	A
	A	A
	A	A

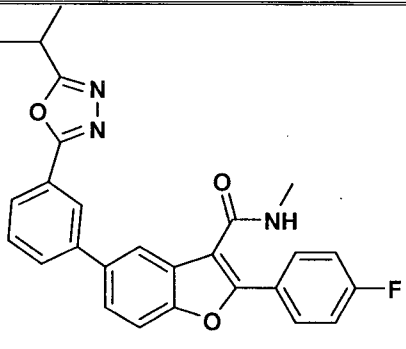
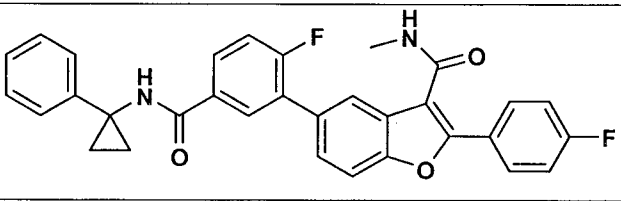
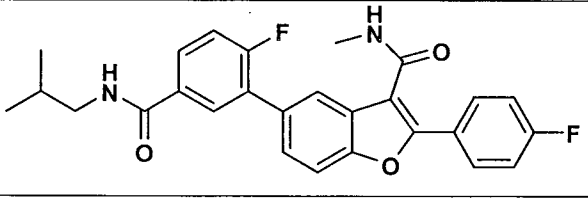
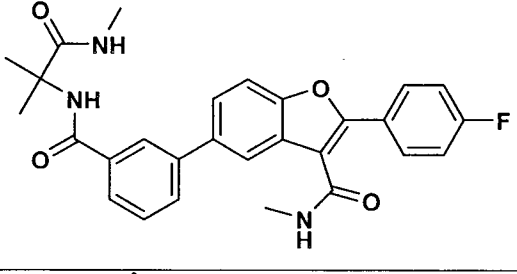
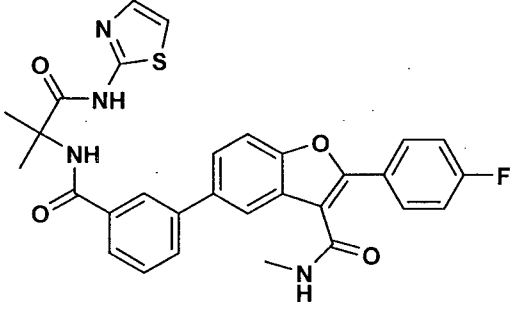
Estructura	Cl ₅₀	CE ₅₀
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	A	A
 Quiral	F	A
 Quiral	--	A
	A	A
	A	A

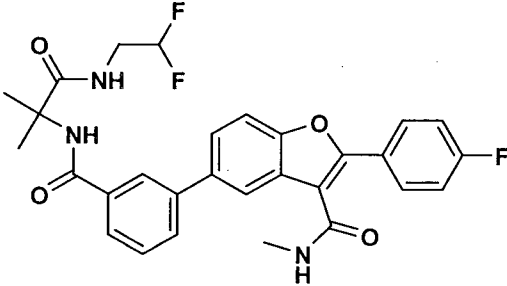
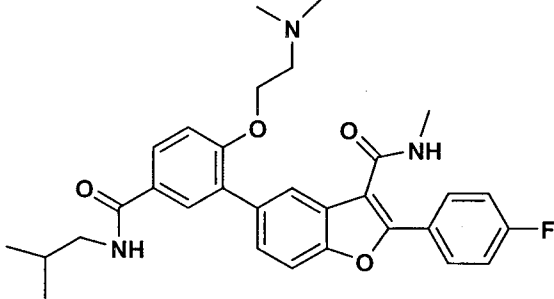
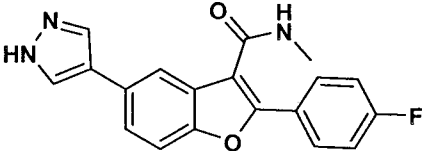
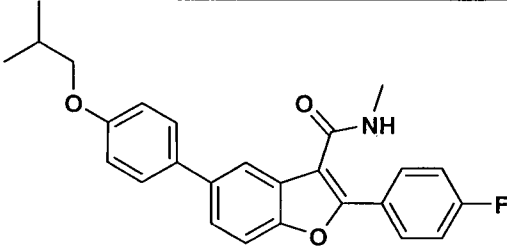
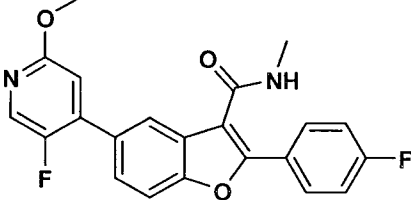
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	B	A
	A	A
	A	A
	A	A

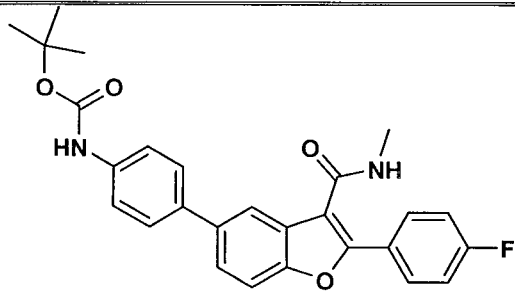
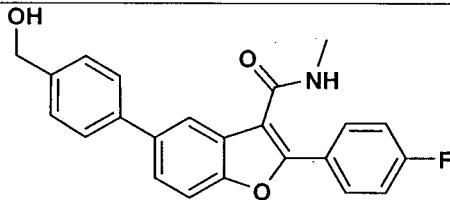
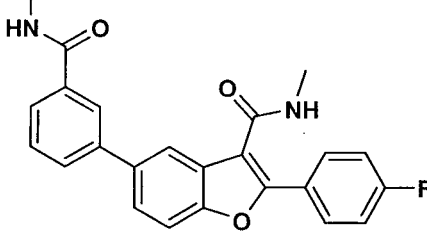
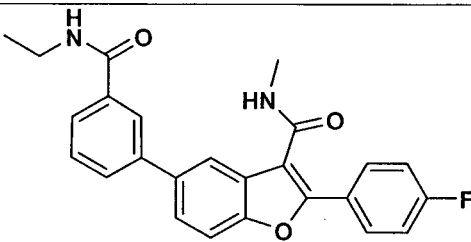
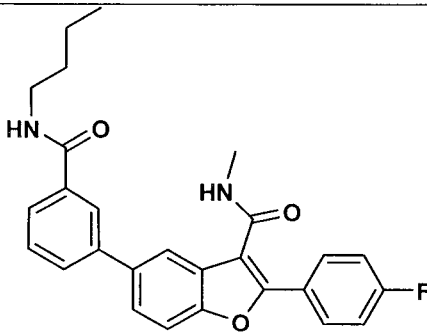
Estructura	Cl ₅₀	CE ₅₀
	B	A
	A	A
	A	A
	A	A

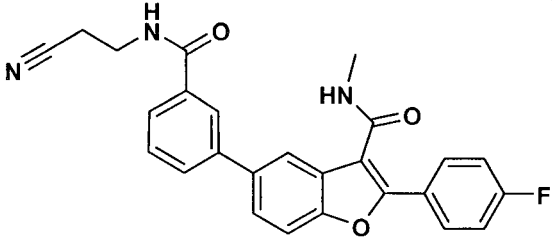
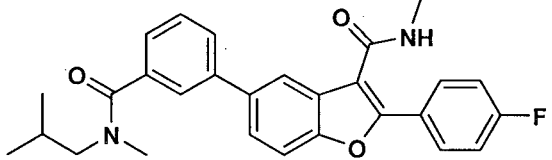
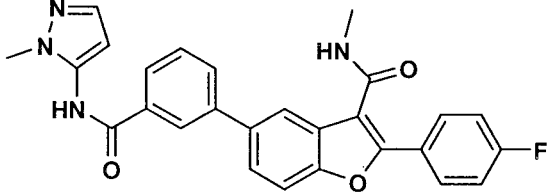
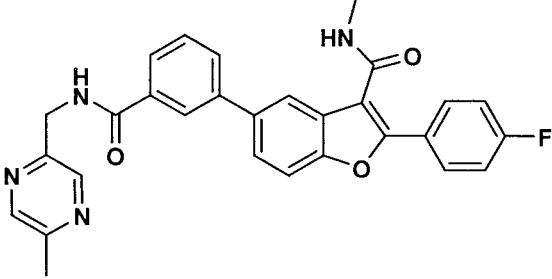
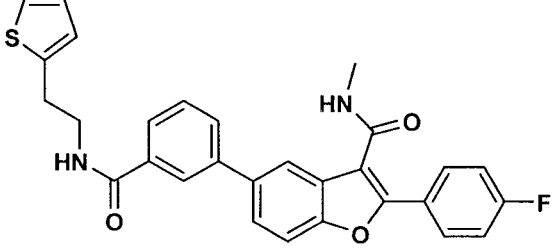
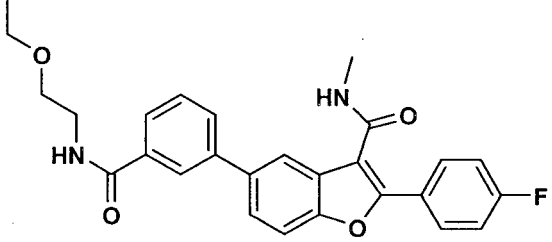
Estructura	Cl ₅₀	CE ₅₀
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	A	A
	A	A
	A	A

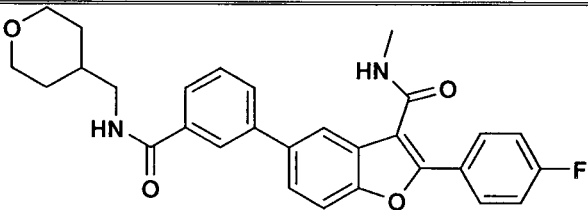
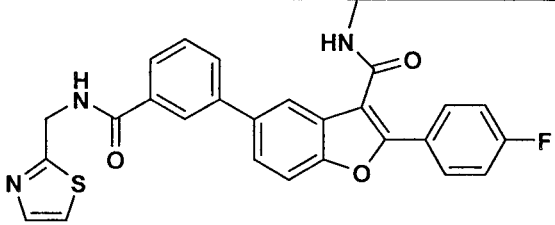
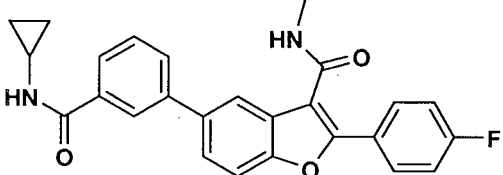
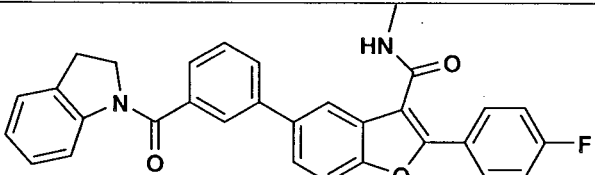
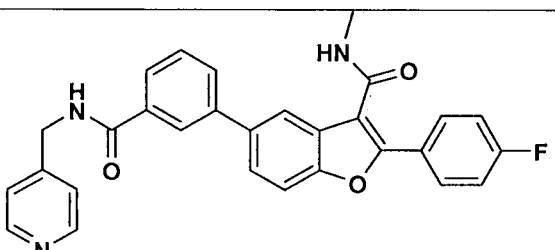
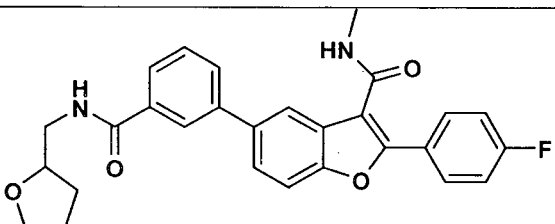
Estructura	Cl ₅₀	CE ₅₀
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	C	A
	A	A
	A	A
	A	A

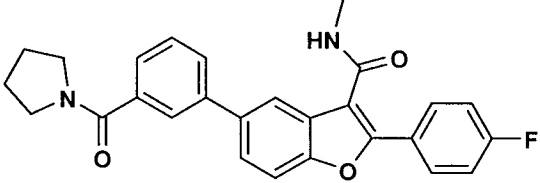
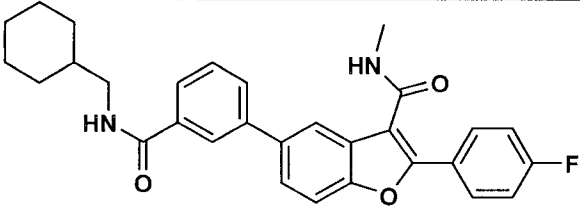
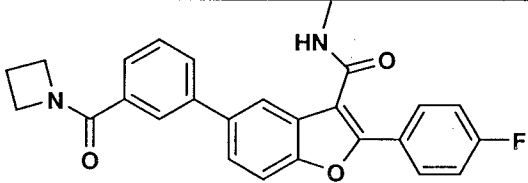
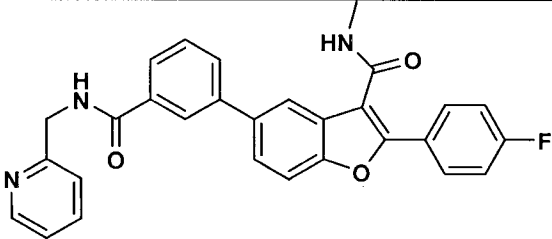
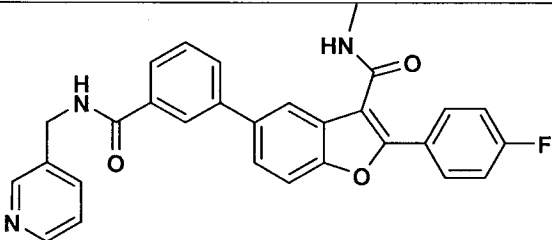
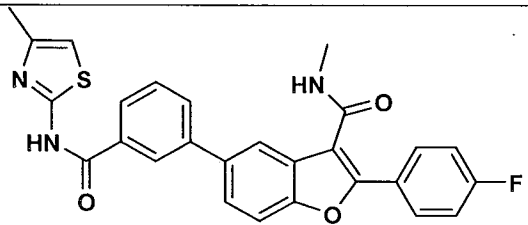
Estructura	Cl ₅₀	CE ₅₀
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	A	A
	A	A
	A	A
	A	A

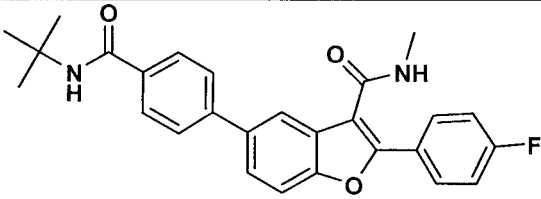
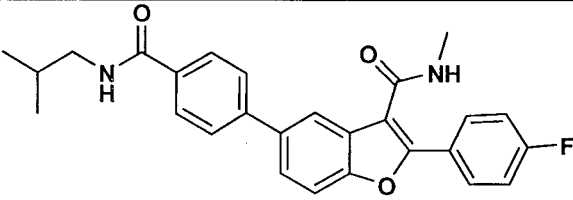
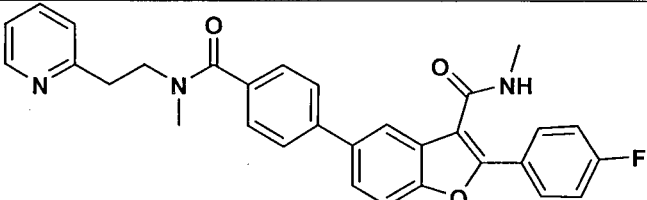
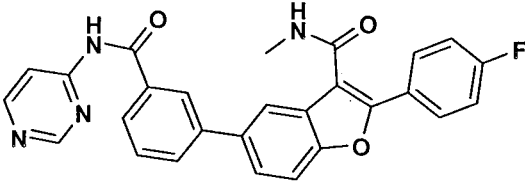
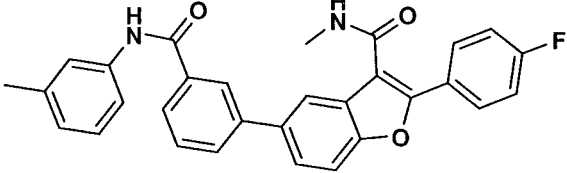
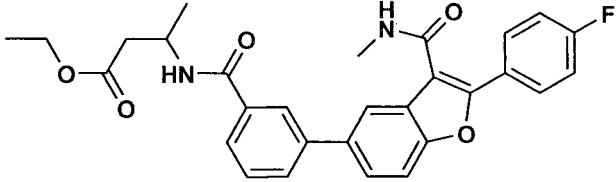
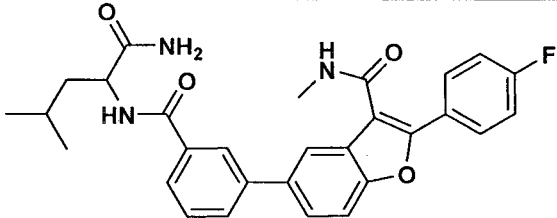
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	E	B
	E	F
	E	H

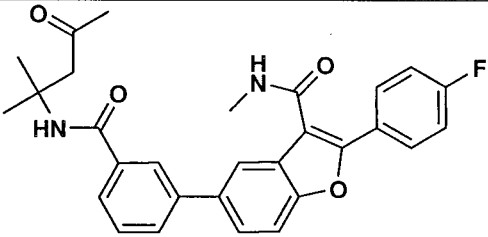
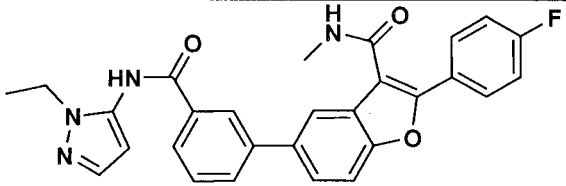
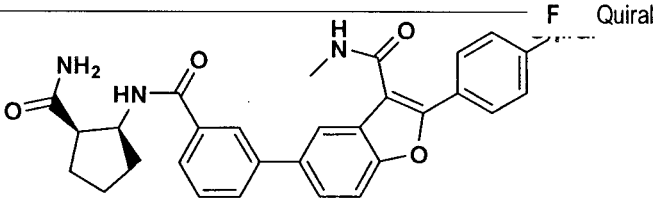
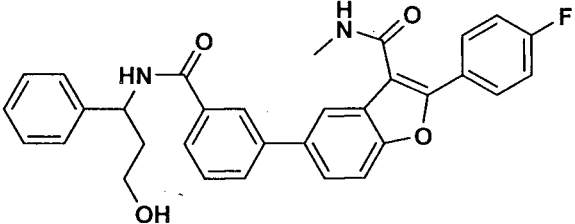
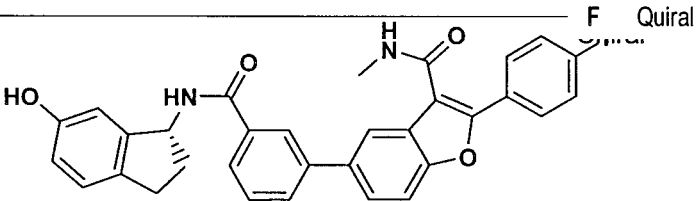
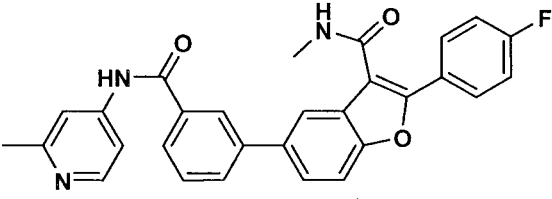
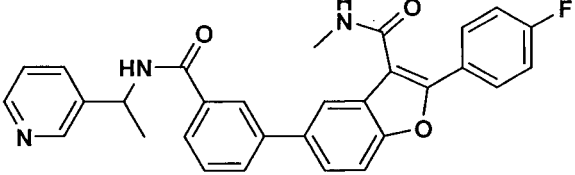
Estructura	Cl ₅₀	CE ₅₀
	E	F
	E	B
	C	B
	B	B
	A	A

Estructura	Cl ₅₀	CE ₅₀
	B	B
	A	B
	B	B
	B	B
	B	B
	A	B

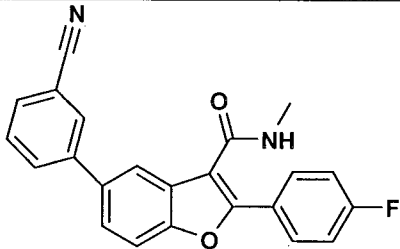
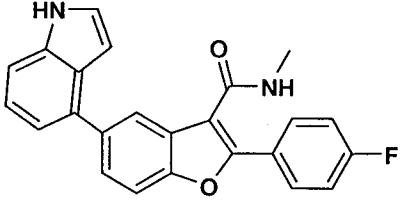
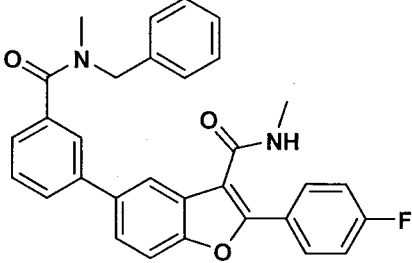
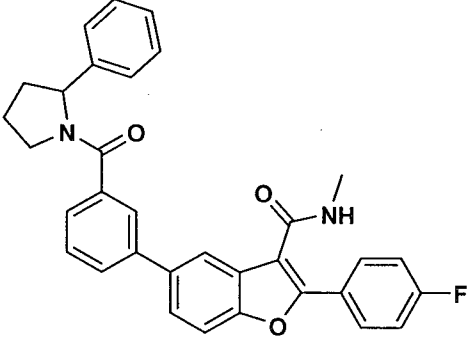
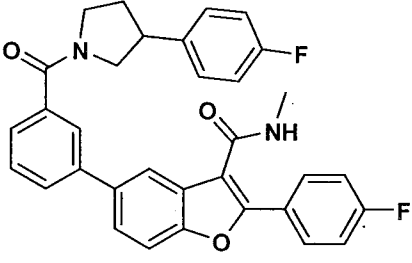
Estructura	Cl ₅₀	CE ₅₀
	A	B
	B	B
	B	B
	C	B
	A	B
	A	B

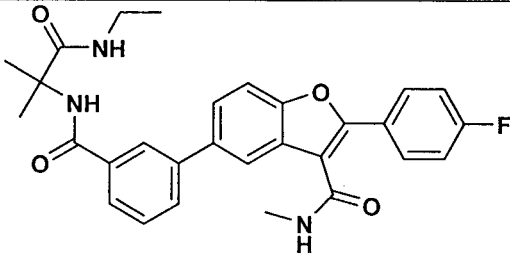
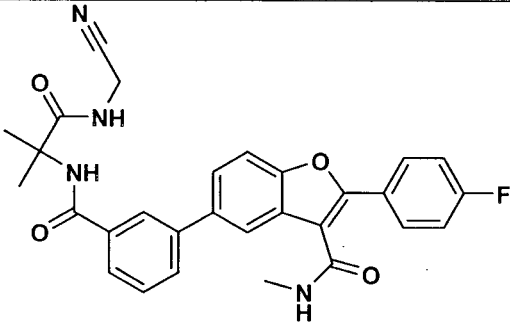
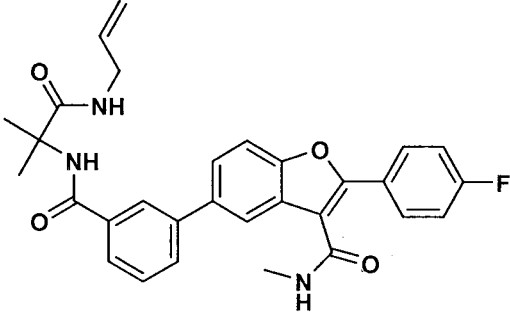
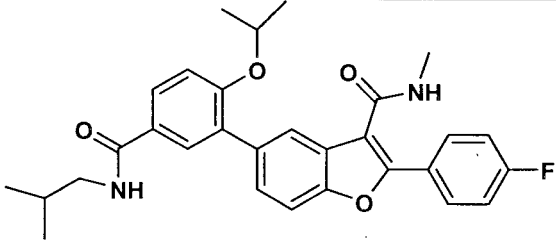
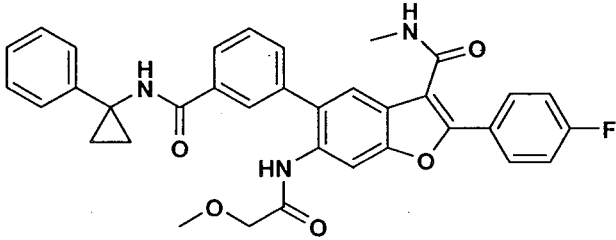
Estructura	Cl ₅₀	CE ₅₀
	B	B
	A	B
	B	B
	A	B
	A	B
	A	B

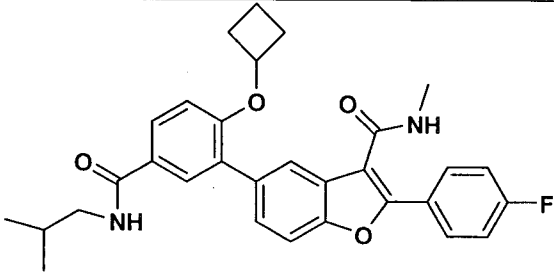
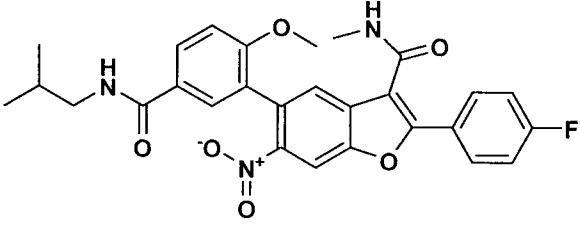
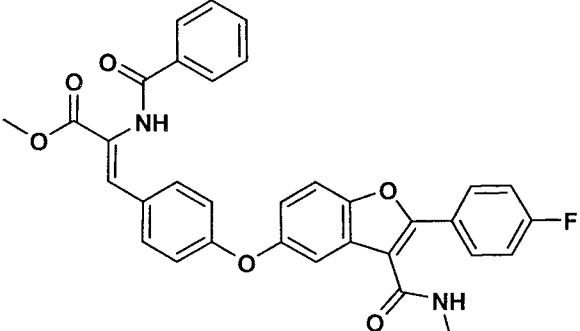
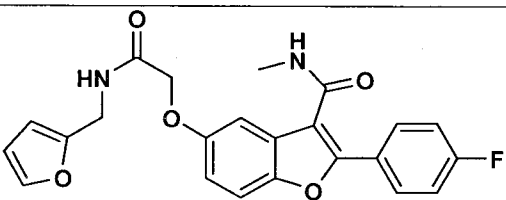
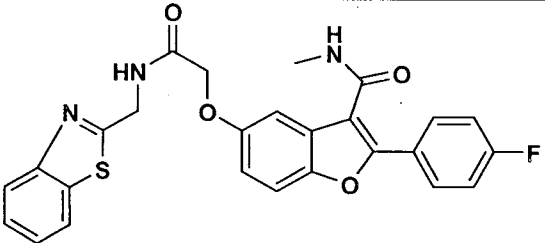
Estructura	Cl ₅₀	CE ₅₀
	C	B
	E	B
	A	A
	B	B
	B	B
	A	B
	B	B

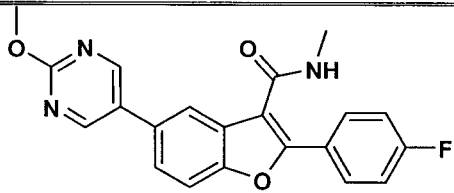
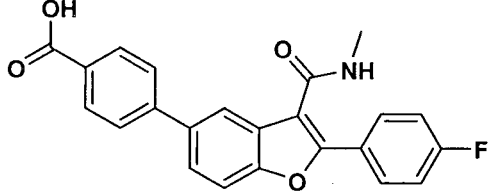
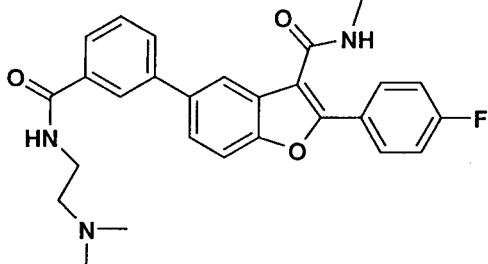
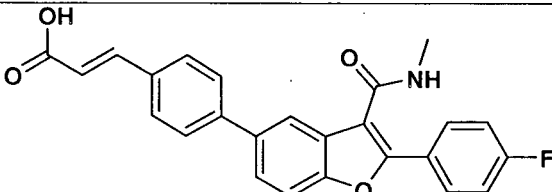
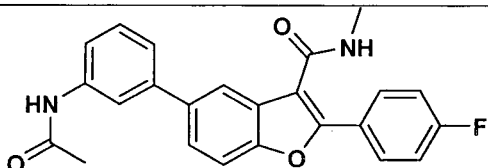
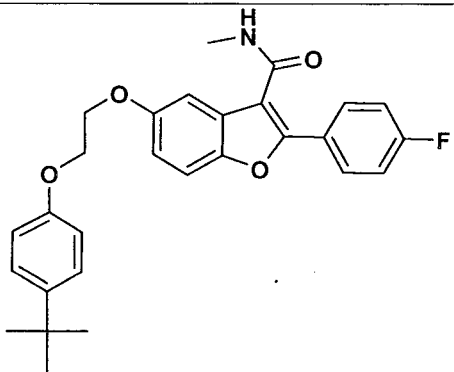
Estructura	Cl ₅₀	CE ₅₀
	B	B
	B	B
	B	B
	A	B
	G	B
	C	B
	A	B

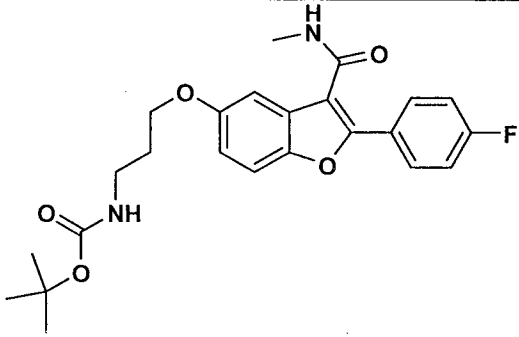
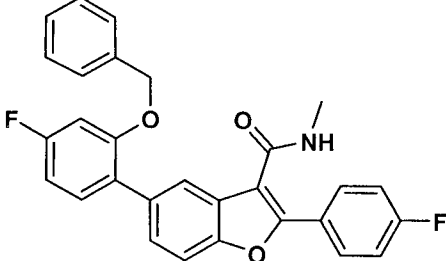
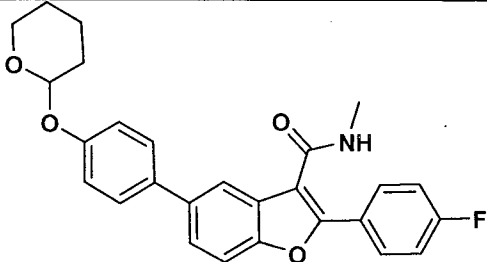
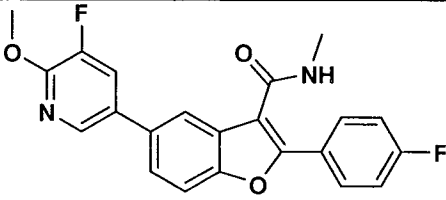
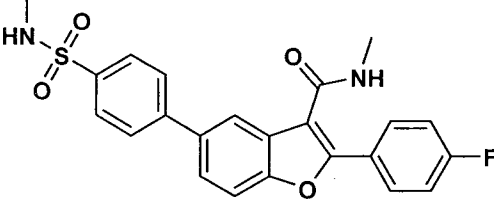
Estructura	Cl ₅₀	CE ₅₀
<chem>CN(C)[C@H]1CCCN1C(=O)c2ccc(cc2)-c3ccc4c(c3)oc(=C5C(=O)N(C)C(=O)c6ccc(F)cc6)cc45</chem> Quiral	B	B
<chem>CN(C)[C@H]1CCCN1C(=O)c2ccc(cc2)-c3ccc4c(c3)oc(=C5C(=O)N(C)C(=O)c6ccc(F)cc6)cc45</chem>	B	B
<chem>CC(C)CNC(=O)c1ccc(cc1)-c2ccc3c(c2)oc(=C4C(=O)N(C)C(=O)c5ccc(F)cc5)cc34</chem>	B	B
<chem>CC1(C)C2=CC=CC=C2C1NC(=O)c3ccc(cc3)-c4ccc5c(c4)oc(=C6C(=O)N(C)C(=O)c7ccc(F)cc7)cc56</chem>	B	B
<chem>c1cc[nH]c1C(=O)c2ccc(cc2)-c3ccc4c(c3)oc(=C5C(=O)N(C)C(=O)c6ccc(F)cc6)cc45</chem>	A	B
<chem>CN(C)C(=O)c1ccc(cc1)-c2ccc3c(c2)oc(=C4C(=O)N(C)C(=O)c5ccc(F)cc5)cc34</chem>	C	B

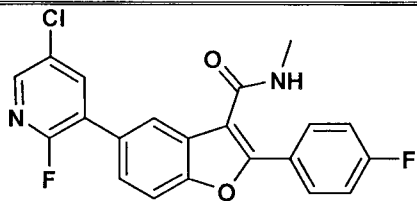
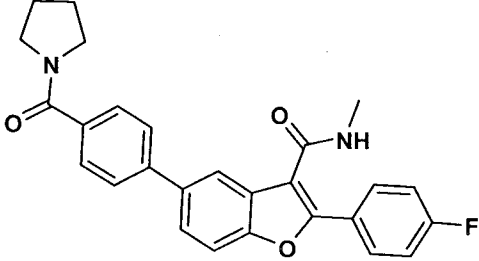
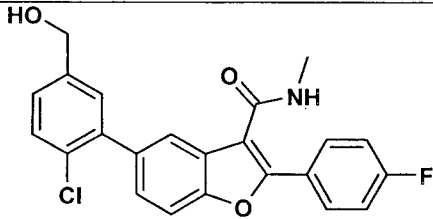
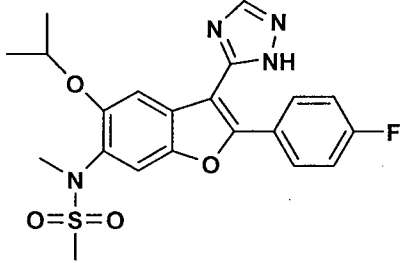
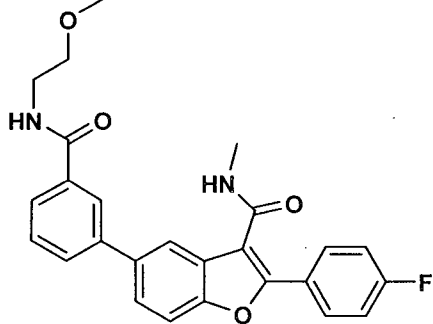
Estructura	Cl ₅₀	CE ₅₀
	E	B
	E	B
	B	B
	B	B
	B	B

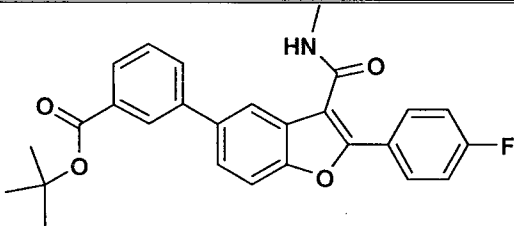
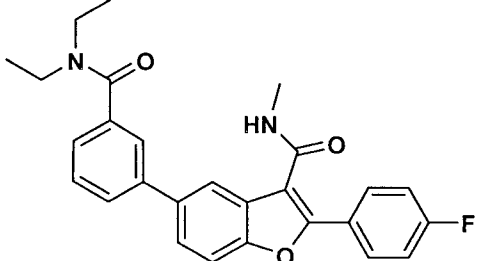
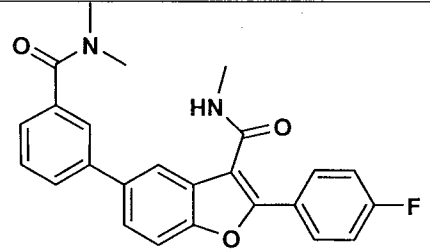
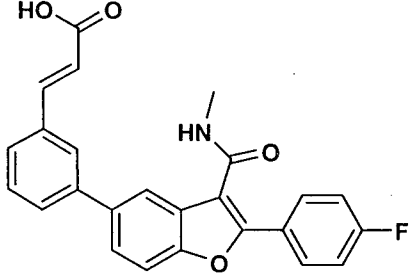
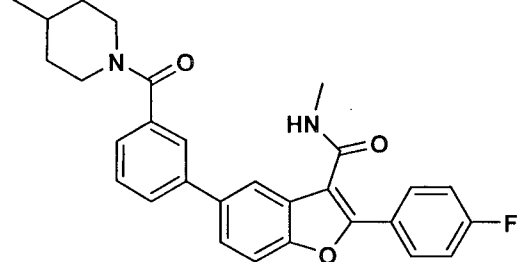
Estructura	Cl ₅₀	CE ₅₀
	B	B
	A	B
	B	B
	B	B
	B	B

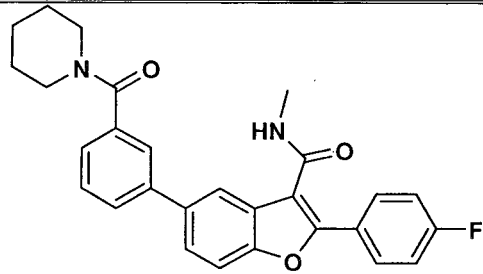
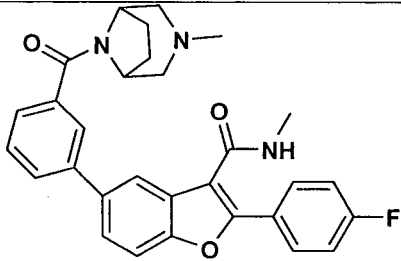
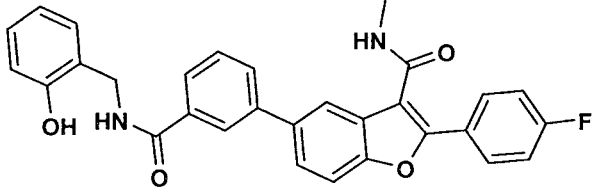
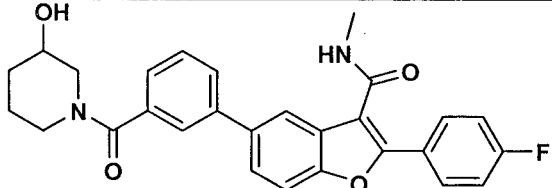
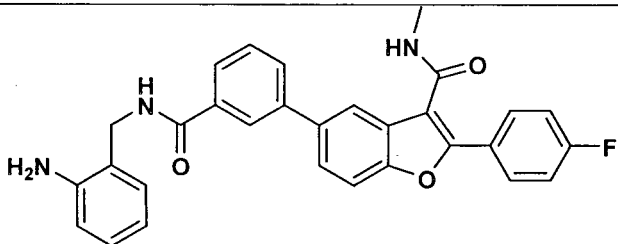
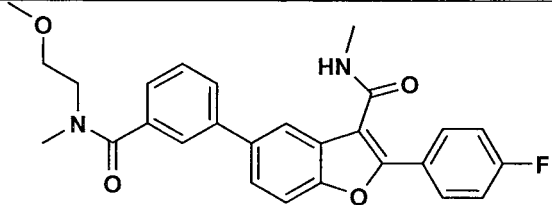
Estructura	Cl ₅₀	CE ₅₀
	G	B
	B	B
	C	C
		C
		C

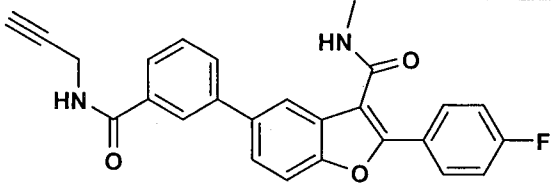
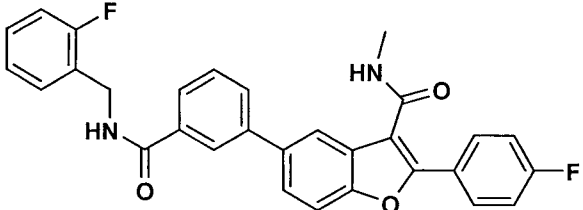
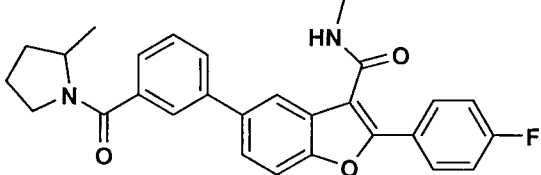
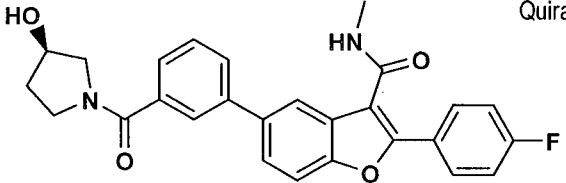
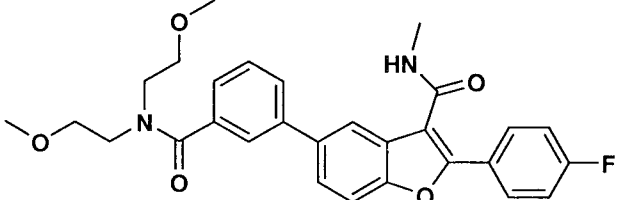
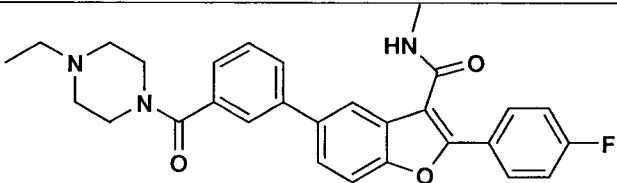
Estructura	Cl ₅₀	CE ₅₀
	C	C
	B	C
	C	C
	C	C
	C	C
	E	C

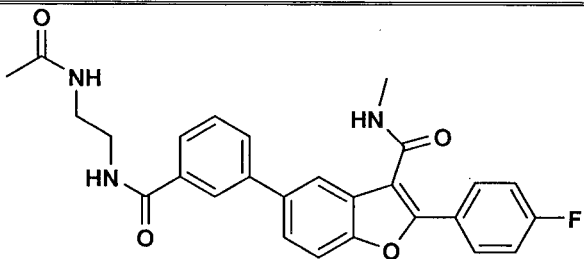
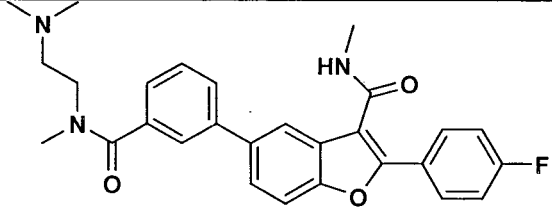
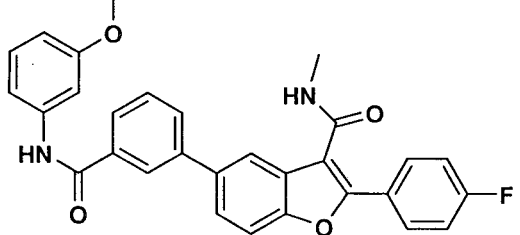
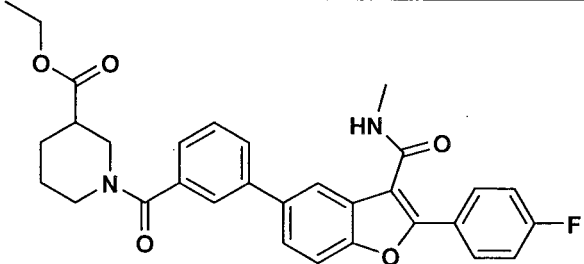
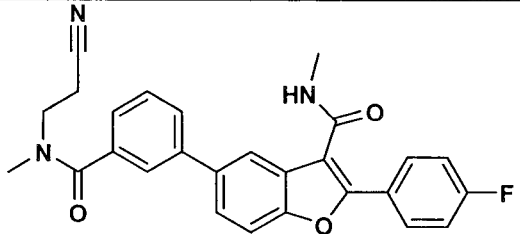
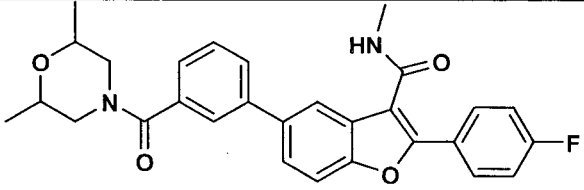
Estructura	Cl ₅₀	CE ₅₀
	C	C
	E	C
	E	C
	E	C
	E	C

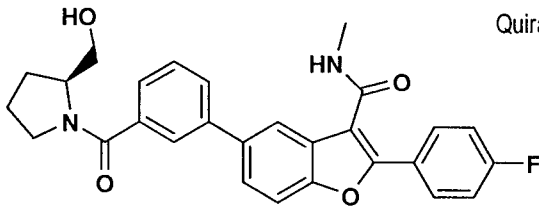
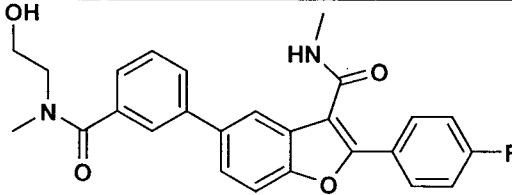
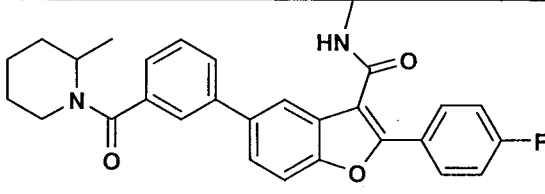
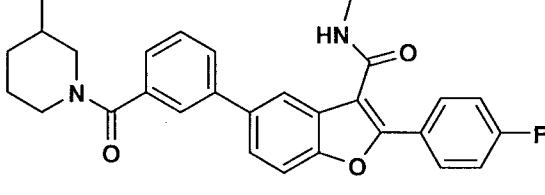
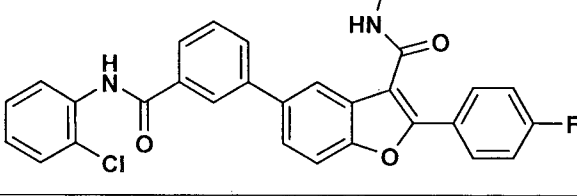
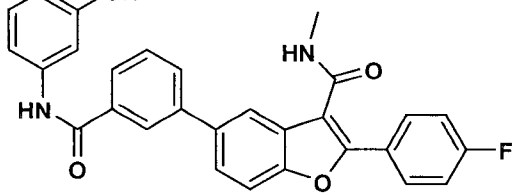
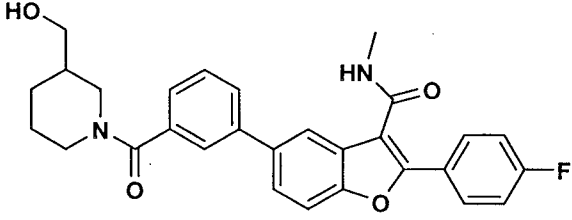
Estructura	Cl ₅₀	CE ₅₀
	E	C
	C	C
	E	C
	B	C
	C	C

Estructura	Cl ₅₀	CE ₅₀
	C	C
	C	C
	C	C
	B	C
	C	C

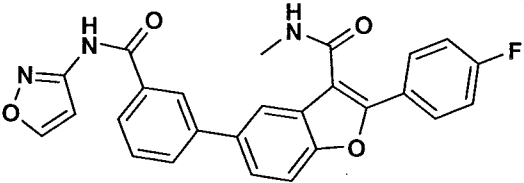
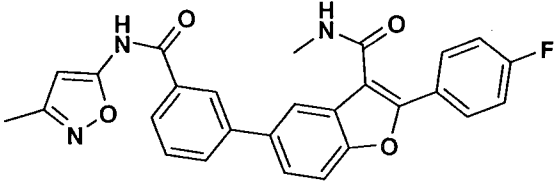
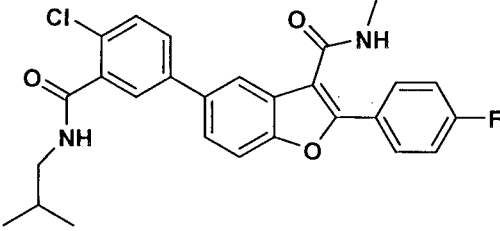
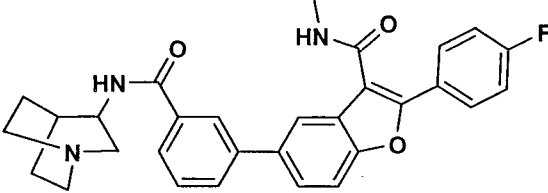
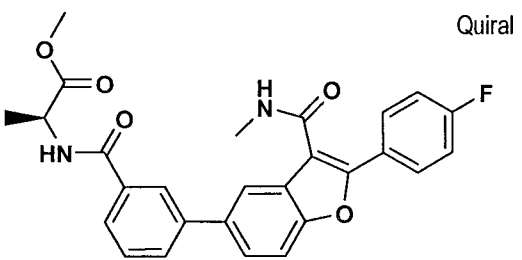
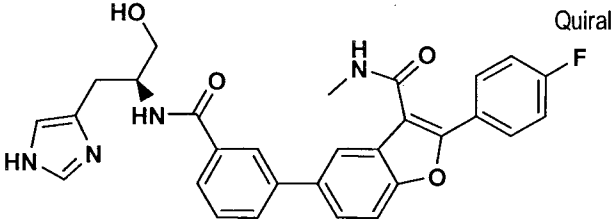
Estructura	Cl ₅₀	CE ₅₀
	B	C
	C	C
	B	C
	C	C
	C	C
	C	C

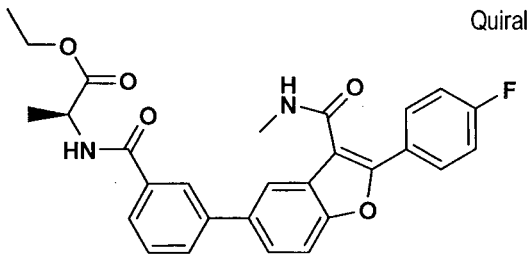
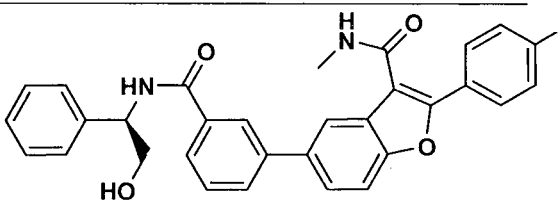
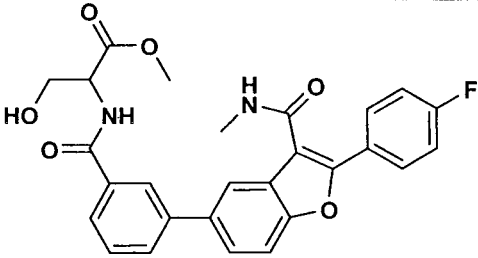
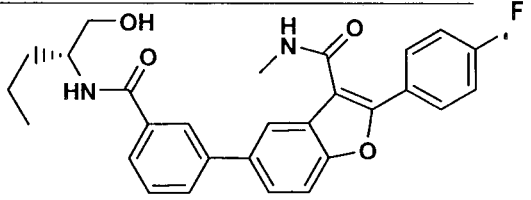
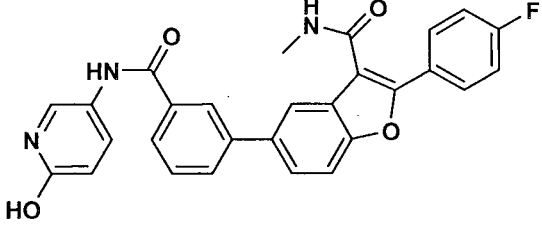
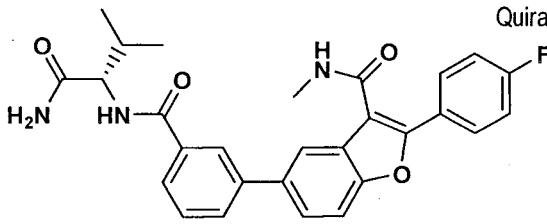
Estructura	Cl ₅₀	CE ₅₀
	B	C
	B	C
	B	C
 Quiral	C	C
	C	C
	C	C

Estructura	Cl ₅₀	CE ₅₀
	C	C
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	C	C
	C	C
	B	C
	C	C

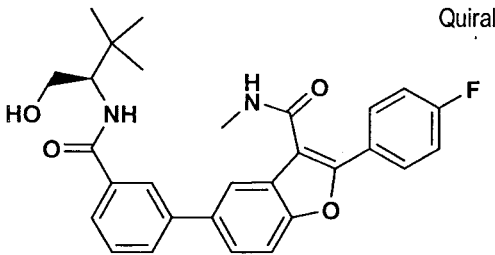
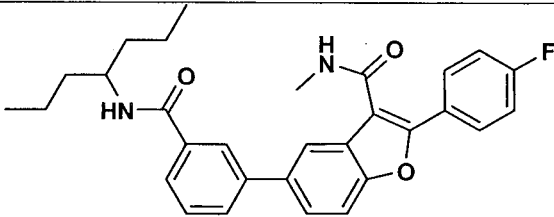
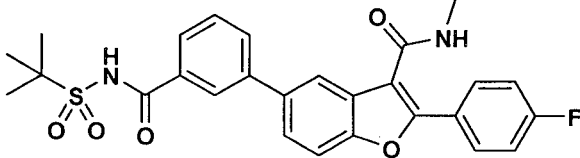
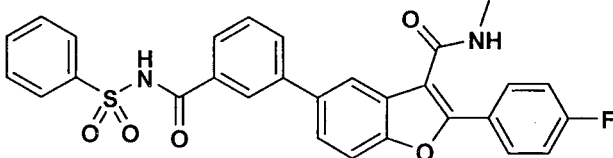
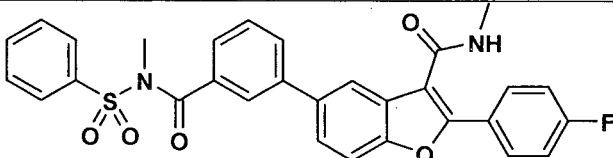
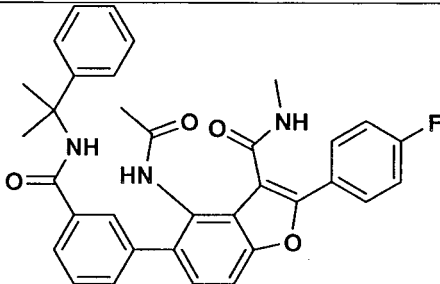
Estructura	Cl ₅₀	CE ₅₀
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 	B	C
 	C	C
 	C	C
 	C	C
 	C	C

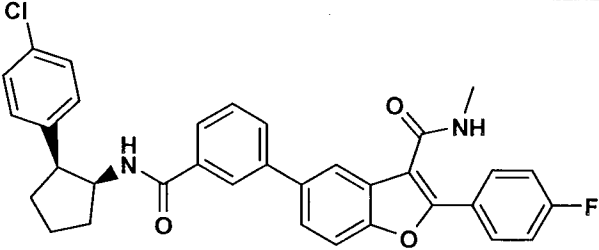
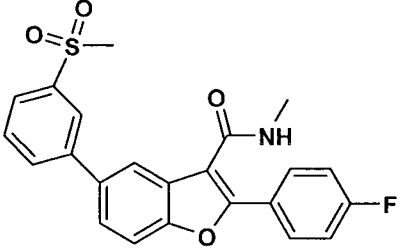
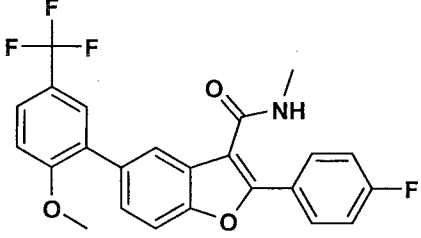
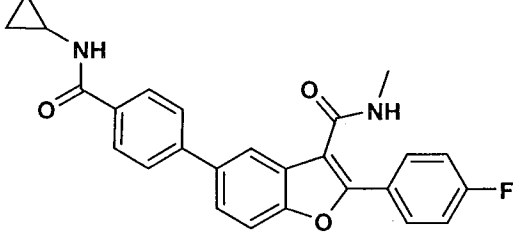
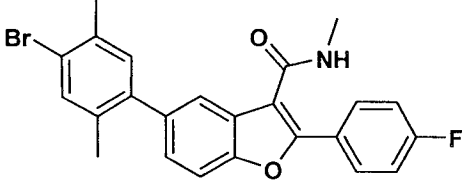
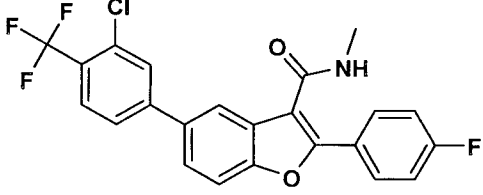
Estructura	Cl ₅₀	CE ₅₀
Quiral	C	C
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	E	C
	E	C
	E	C
	E	C

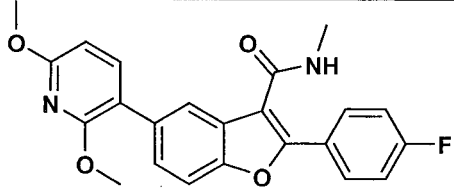
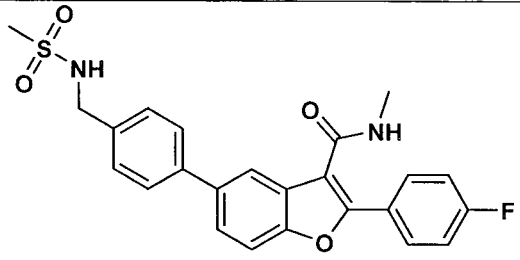
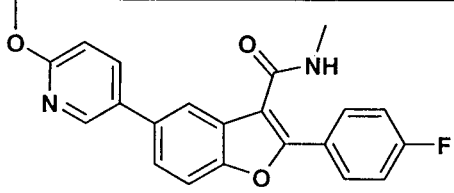
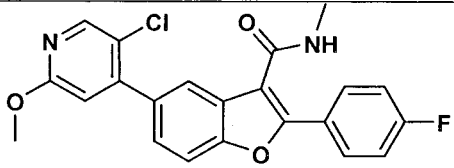
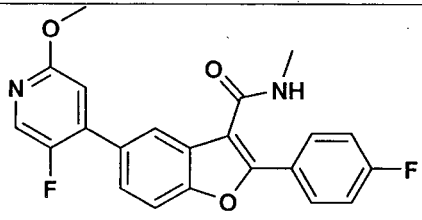
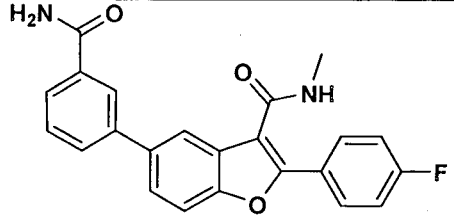
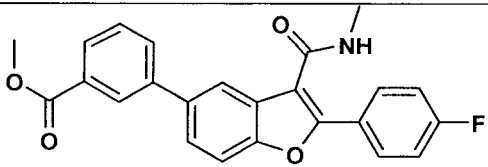
Estructura	Cl ₅₀	CE ₅₀
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	C	C
	C	C
	C	C
	A	C
	C	C

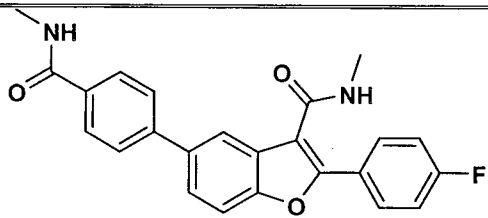
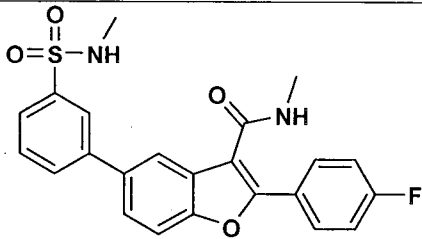
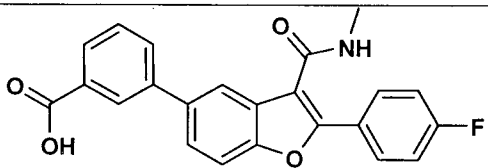
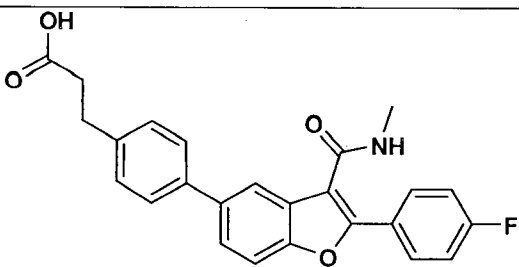
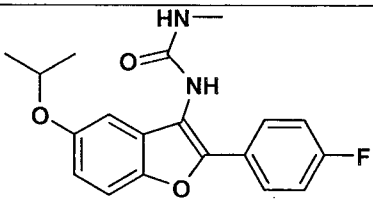
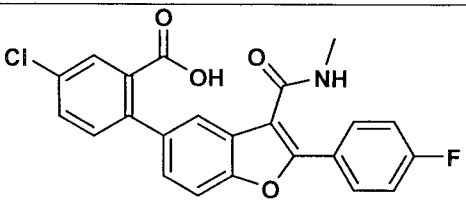
Estructura	Cl ₅₀	CE ₅₀
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 Quiral	B	C
	B	C
 Quiral	C	C
	C	C
 Quiral	B	C

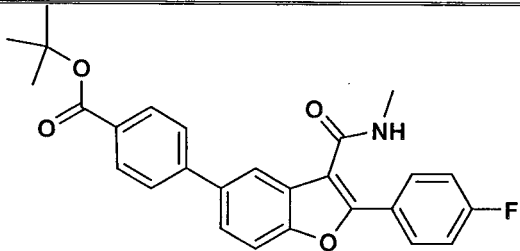
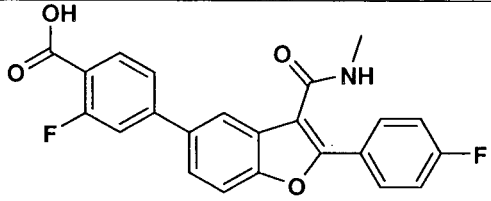
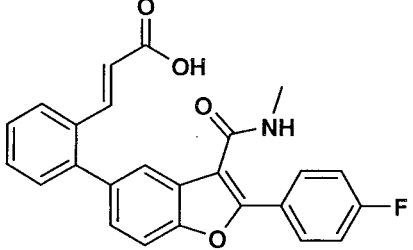
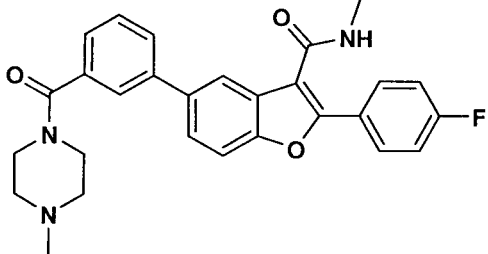
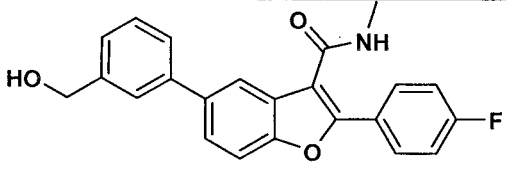
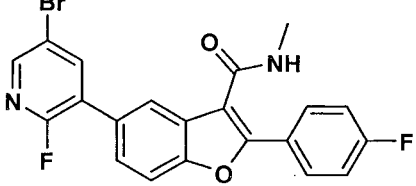
Estructura	Cl ₅₀	CE ₅₀
Quiral	B	C
Quiral	B	C
	B	C
Quiral	B	C
Quiral	B	C
Quiral	C	C

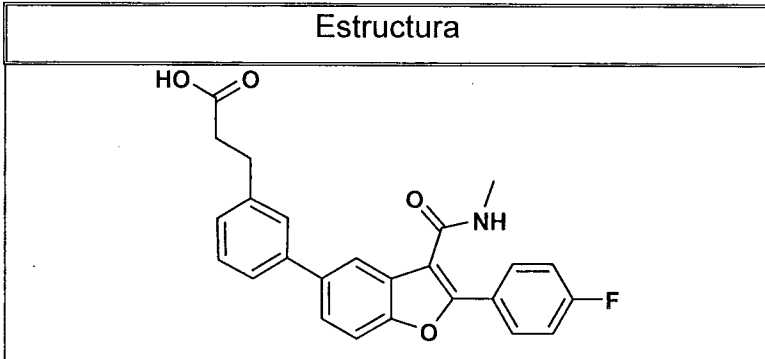
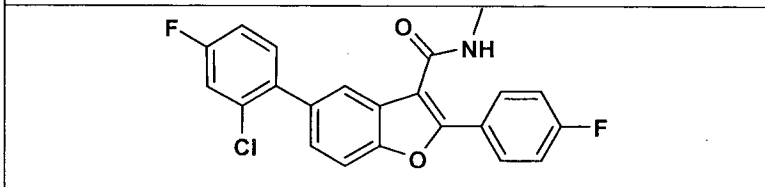
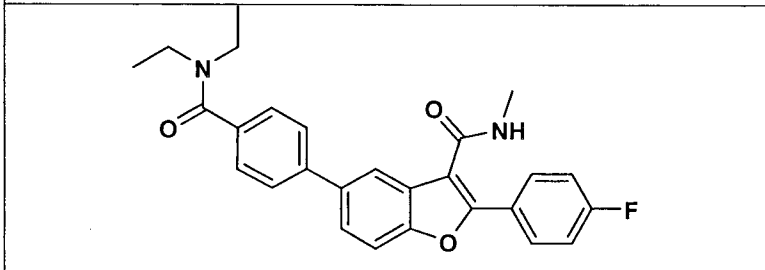
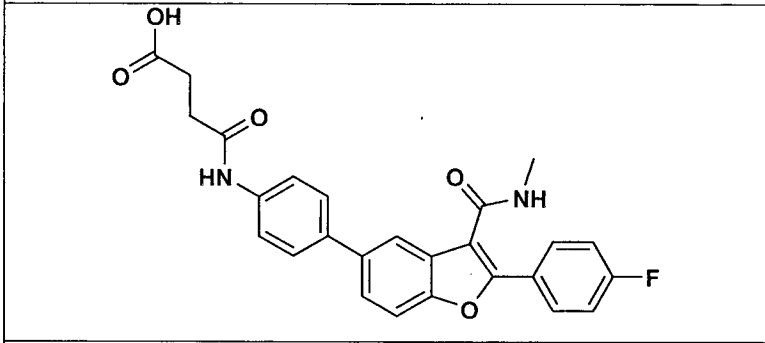
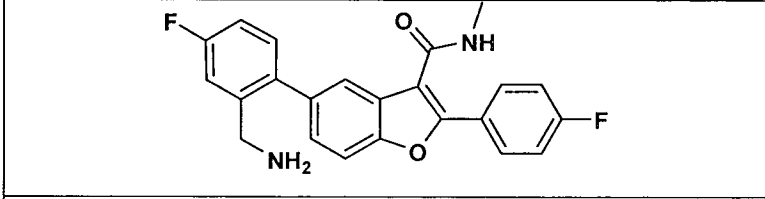
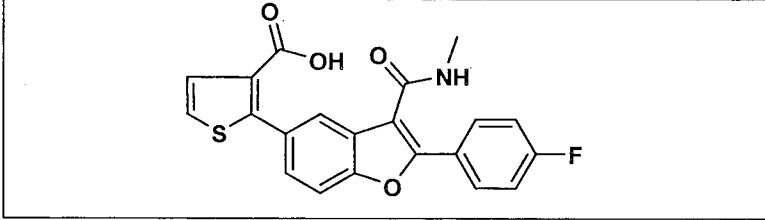
Estructura	Cl ₅₀	CE ₅₀
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	F	C
	A	C
	A	C
	G	C
	C	C

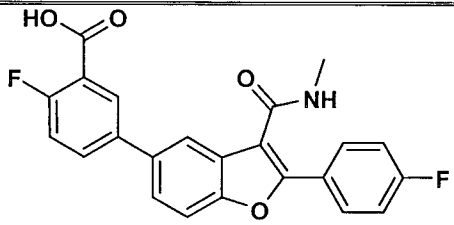
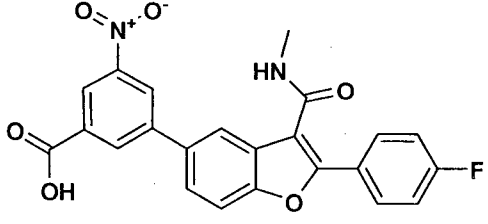
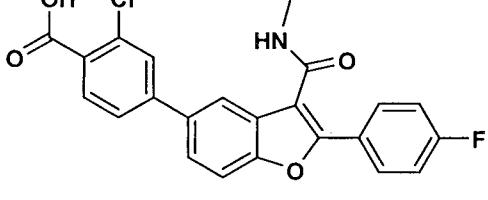
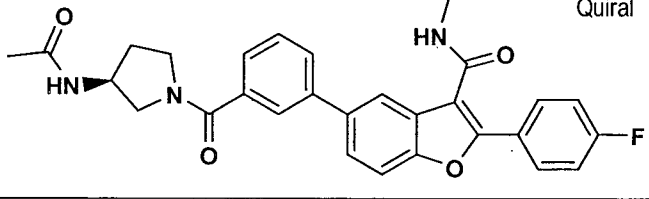
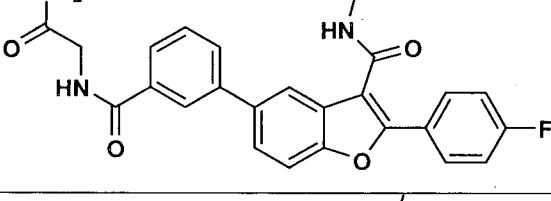
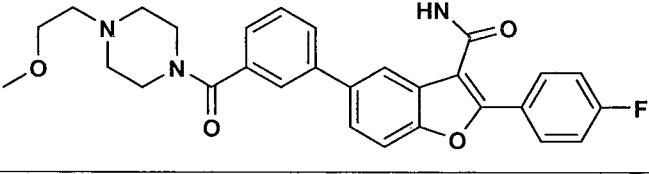
Estructura	Cl ₅₀	CE ₅₀
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	E	C
	E	J
	E	K
	E	J
	E	K

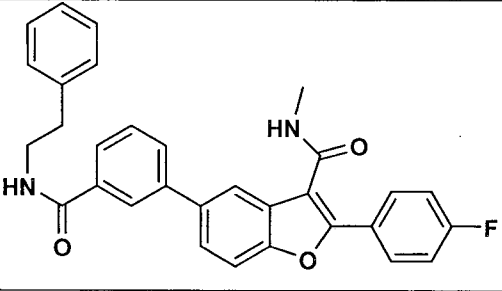
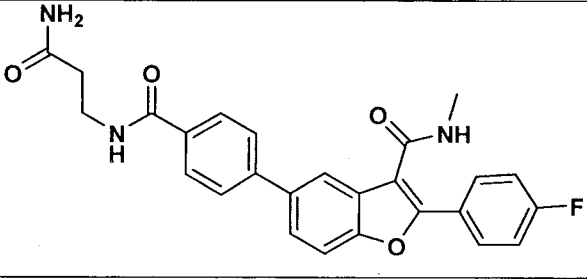
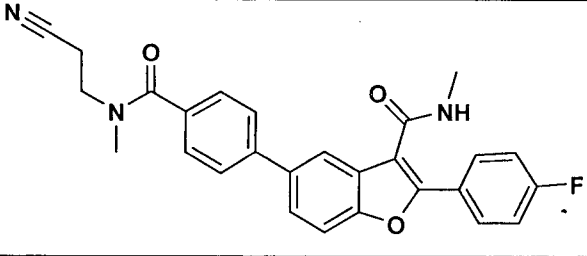
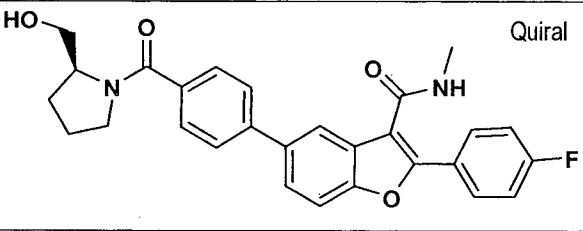
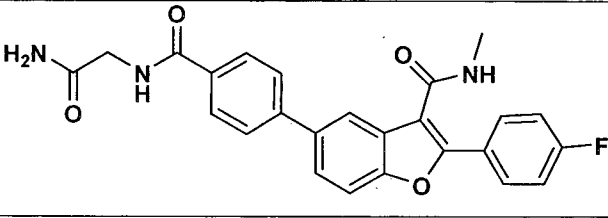
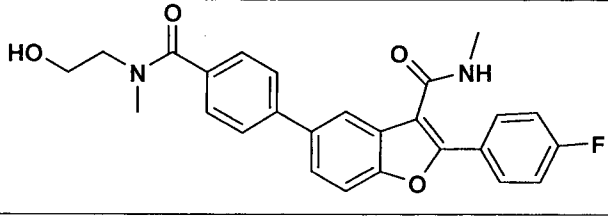
Estructura	Cl ₅₀	CE ₅₀
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	E	K
	E	K
	E	K
	E	H
	C	J
	E	J

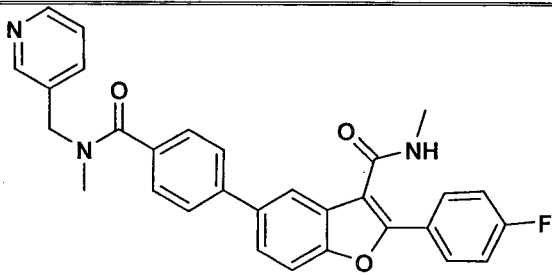
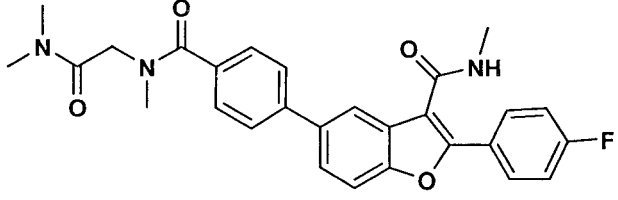
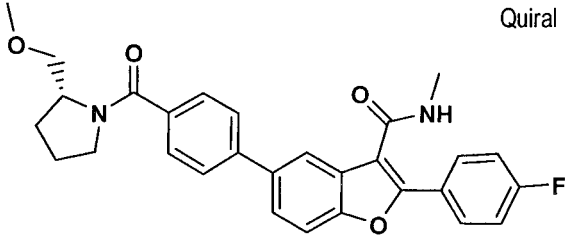
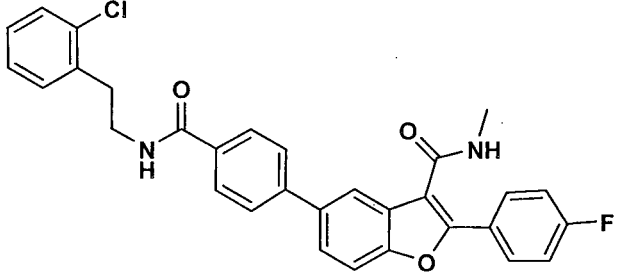
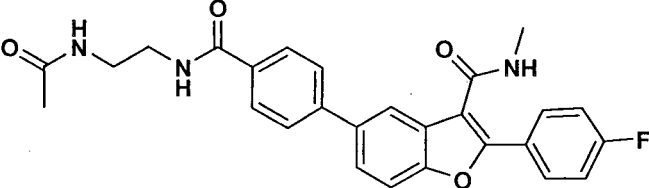
Estructura	Cl ₅₀	CE ₅₀
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	E	J
	C	E
	C	E
	E	E
	C	E

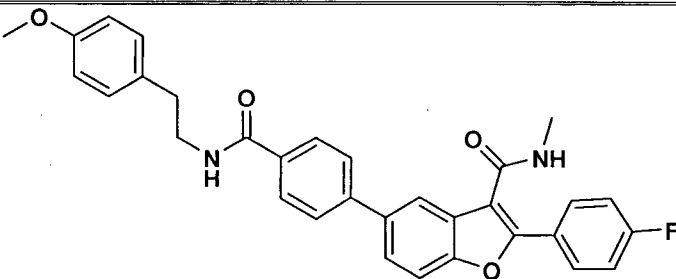
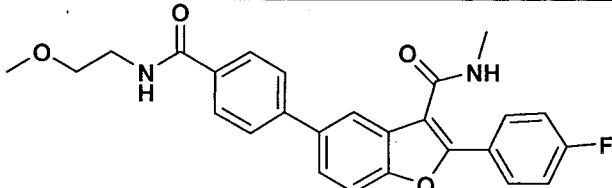
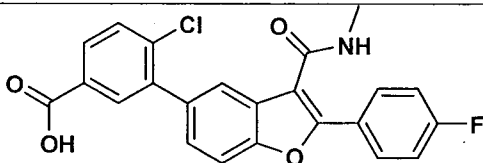
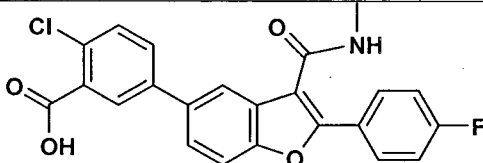
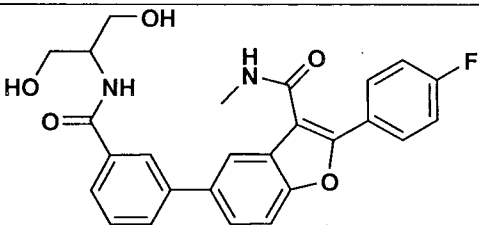
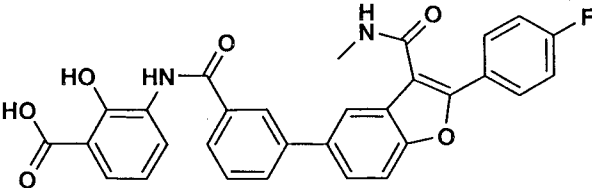
Estructura	Cl ₅₀	CE ₅₀
	E	E
	C	E
	C	E
	E	E
	E	E
	E	E

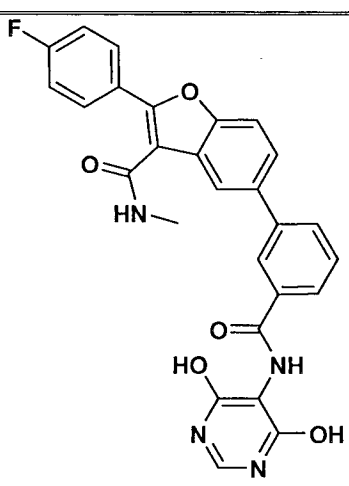
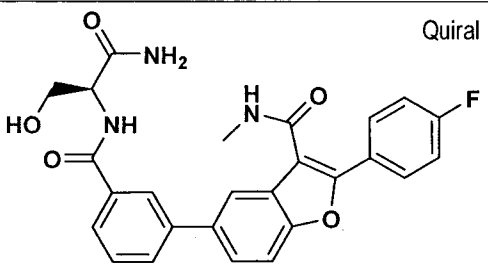
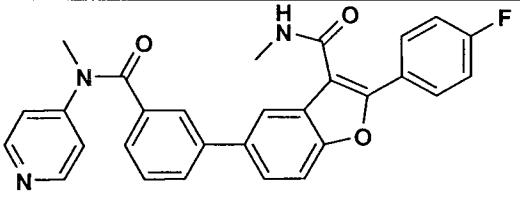
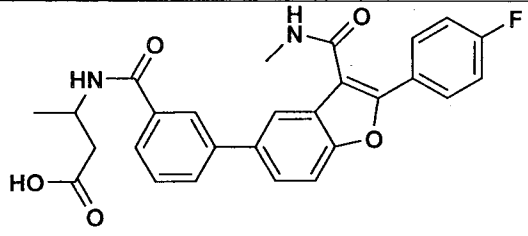
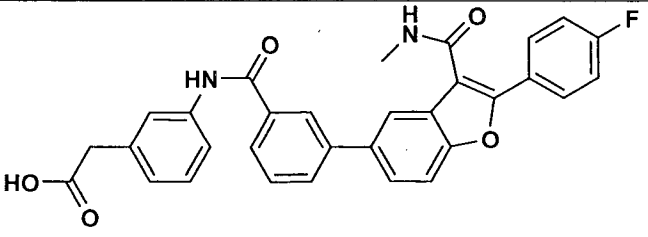
Estructura	Cl ₅₀	CE ₅₀
	C	E
	E	E
	C	E
	C	E
	E	E
	E	E

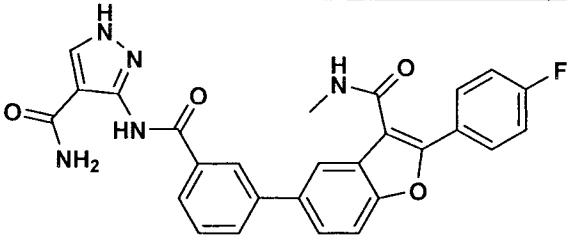
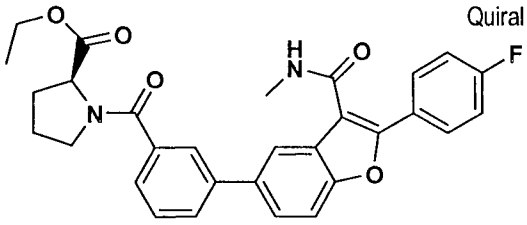
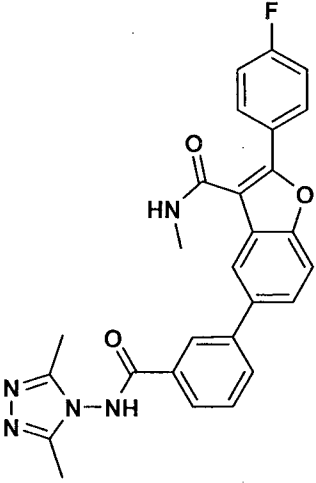
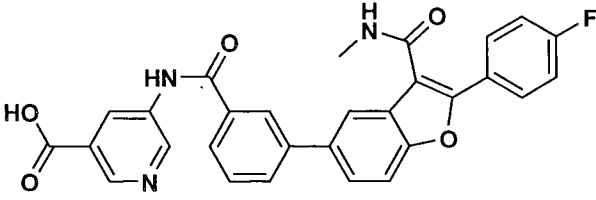
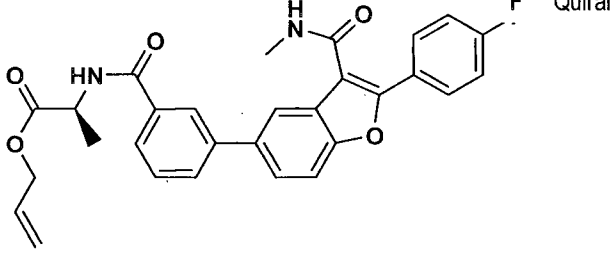
Estructura	Cl ₅₀	CE ₅₀
	C	E
	B	E
	C	E
 Quiral	C	E
	E	E
	E	E

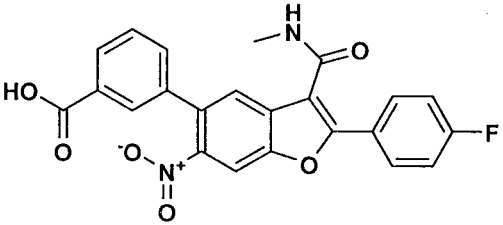
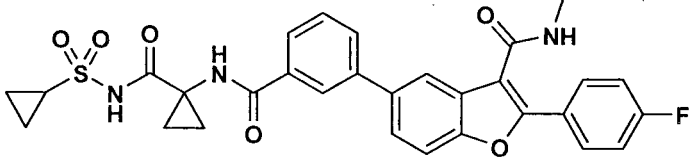
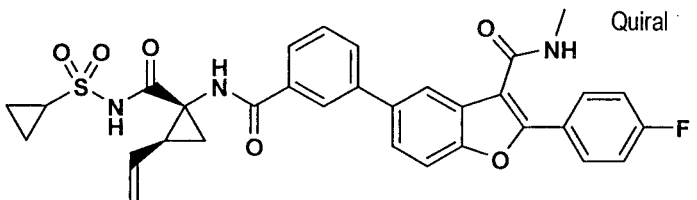
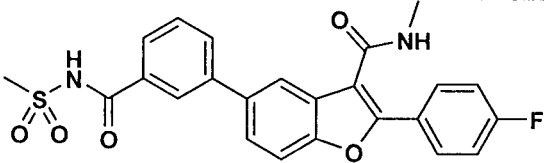
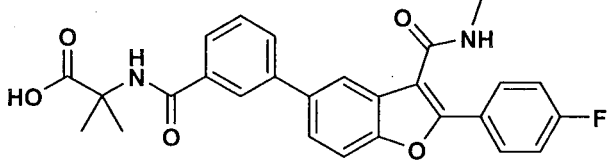
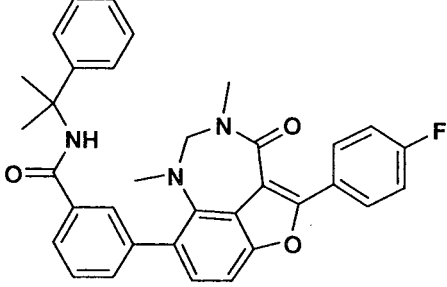
Estructura	Cl ₅₀	CE ₅₀
	E	E
	E	E
	C	E
	E	E
	E	E
	C	E

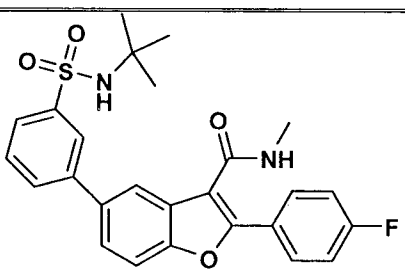
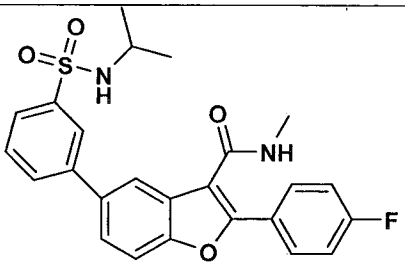
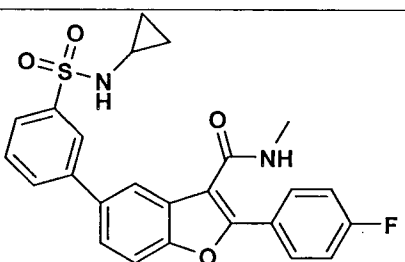
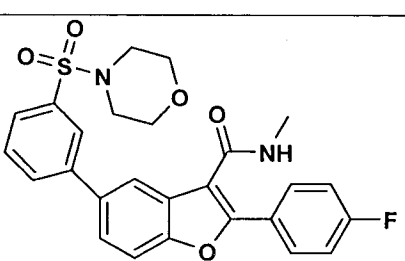
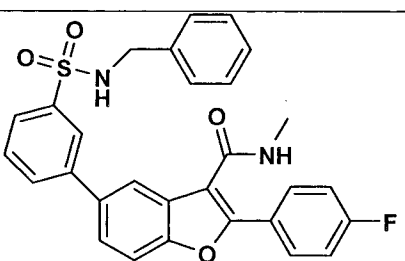
Estructura	Cl ₅₀	CE ₅₀
	C	E
	E	E
 Quiral	E	E
	E	E
	E	E

Estructura	Cl ₅₀	CE ₅₀
	E	E
	E	E
	C	E
	C	E
	C	E
	B	E

Estructura	Cl ₅₀	CE ₅₀
	B	E
	C	E
	C	E
	B	E
	A	E

Estructura	Cl ₅₀	CE ₅₀
	C	E
	C	E
	B	E
	B	E
	A	E

Estructura	Cl ₅₀	CE ₅₀
	C	E
	A	E
	B	E
	B	E
	B	E
	E	E

Estructura	Cl ₅₀	CE ₅₀
	I	E
	E	E
	E	E
	E	E
	E	E

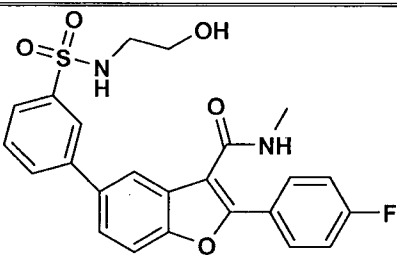
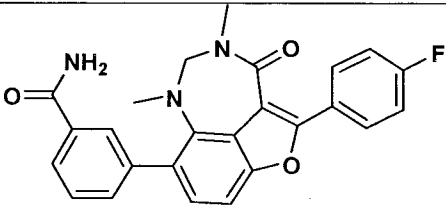
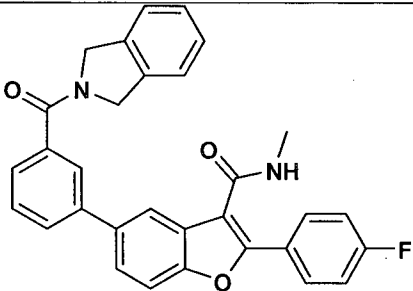
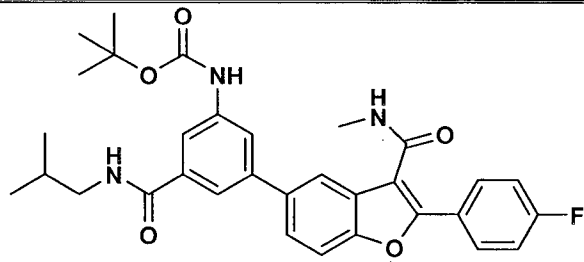
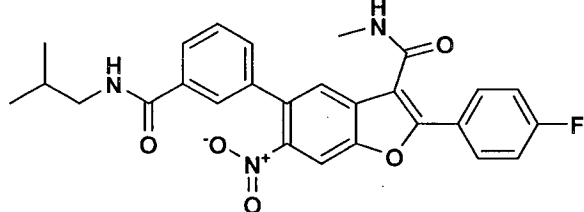
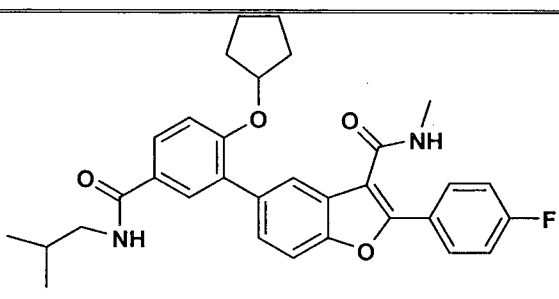
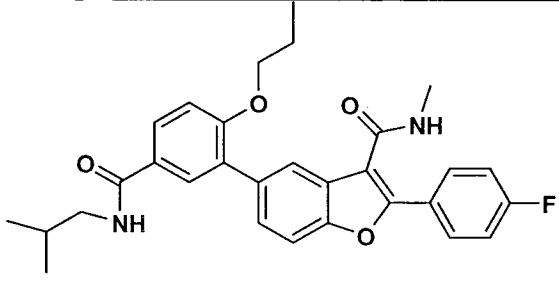
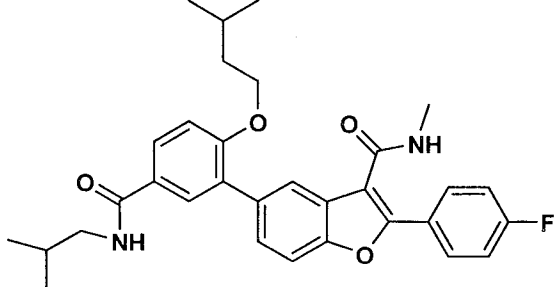
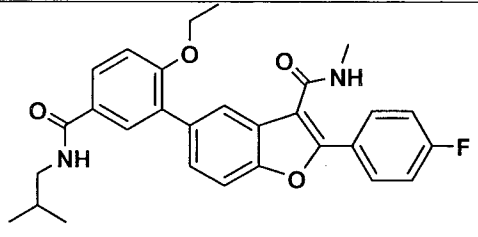
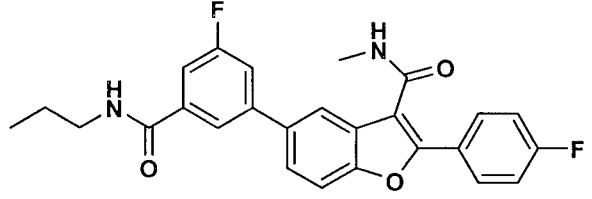
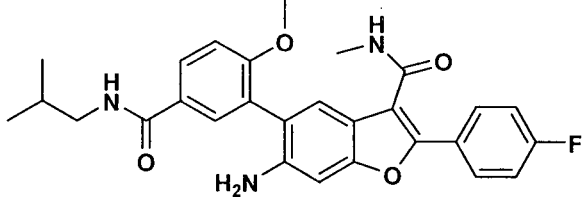
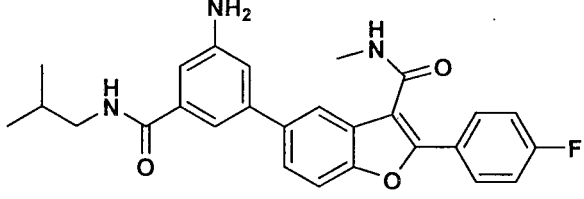
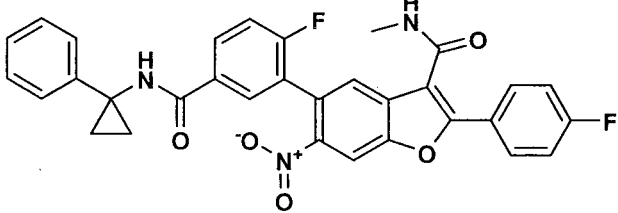
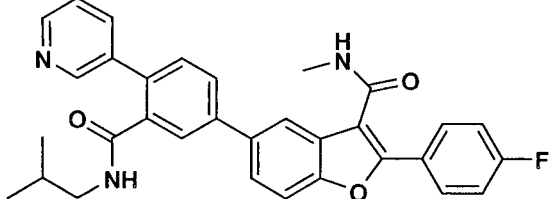
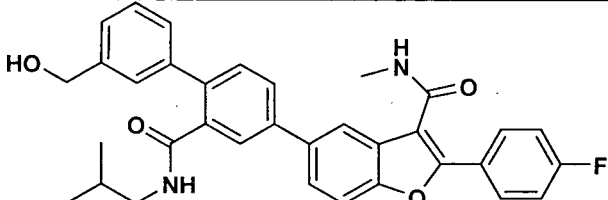
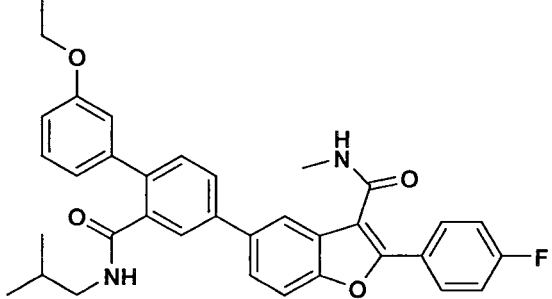
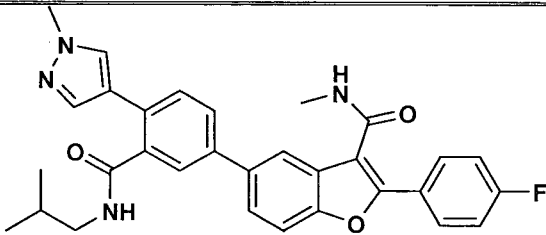
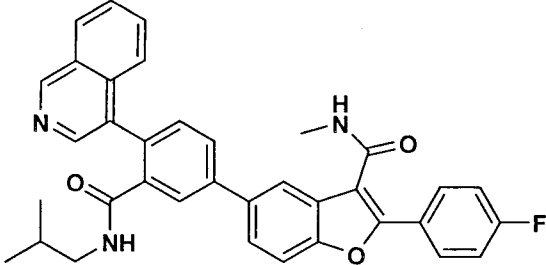
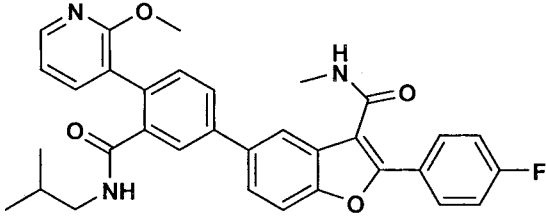
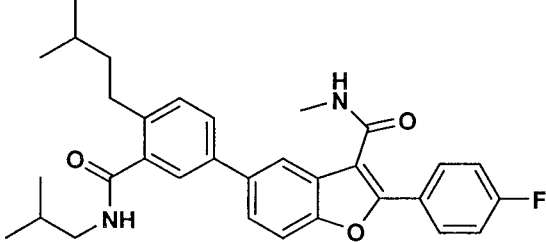
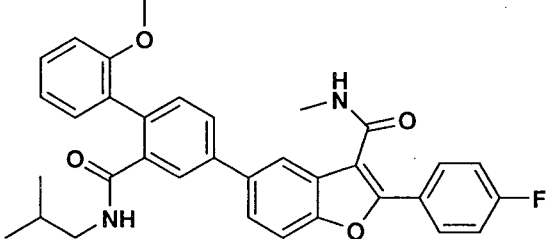
Estructura	Cl ₅₀	CE ₅₀
	C	E
	E	E
	F	E

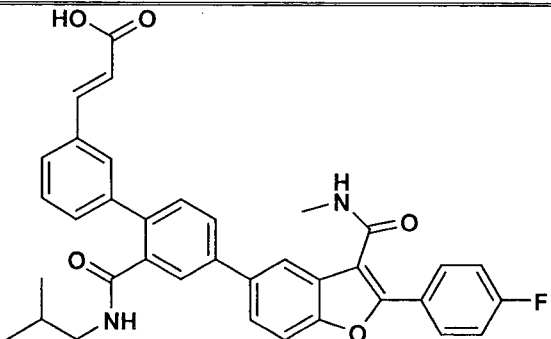
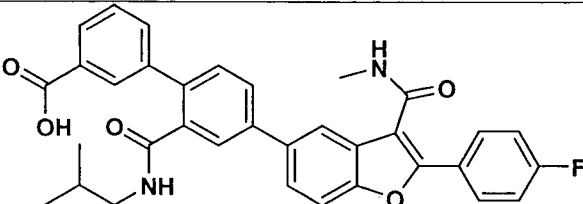
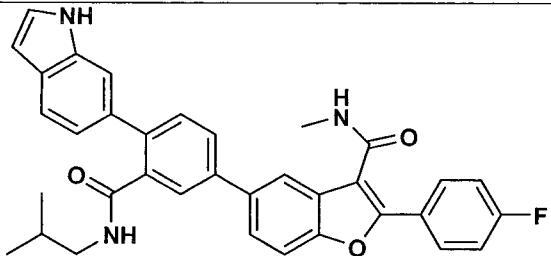
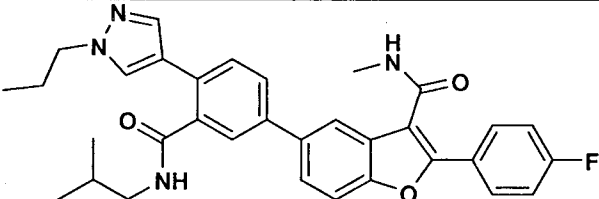
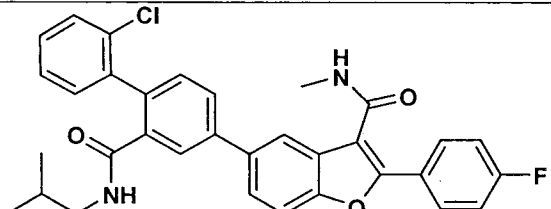
TABLA 1b

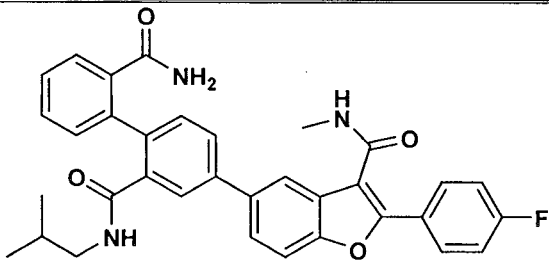
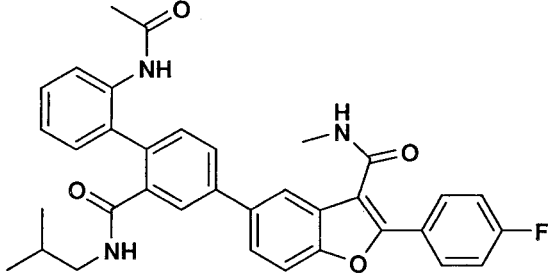
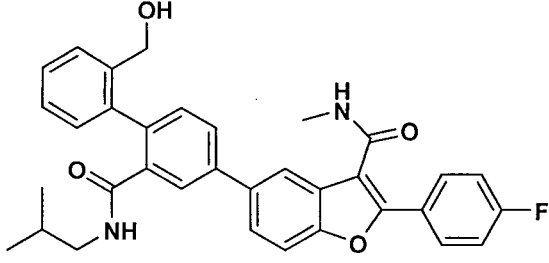
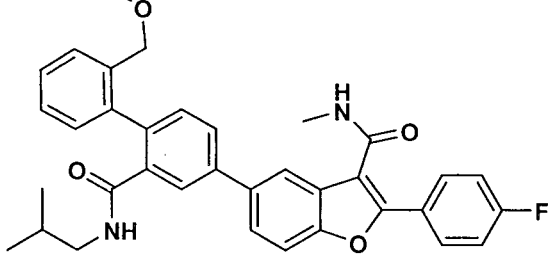
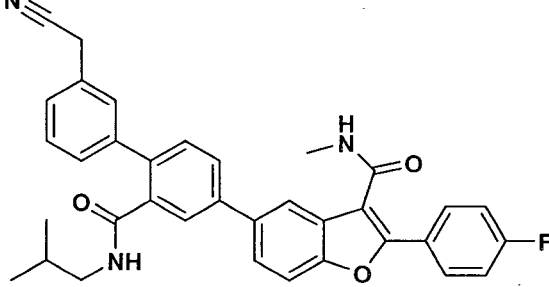
Estructura	Cl ₅₀	CE ₅₀
	B	A
	A	A

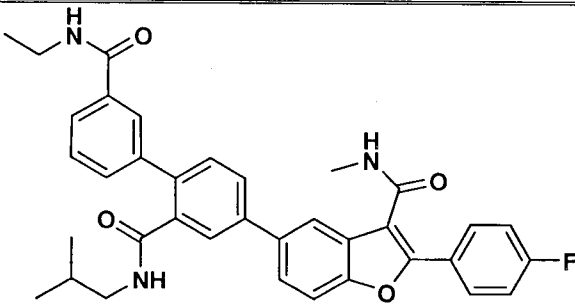
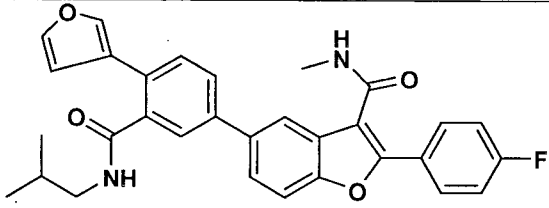
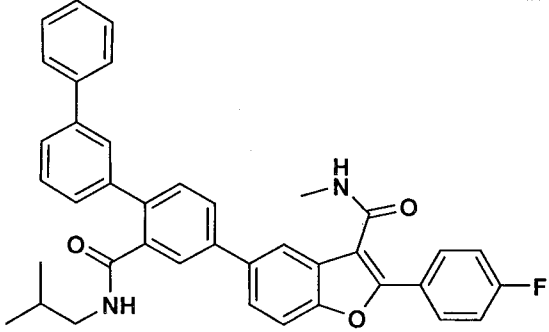
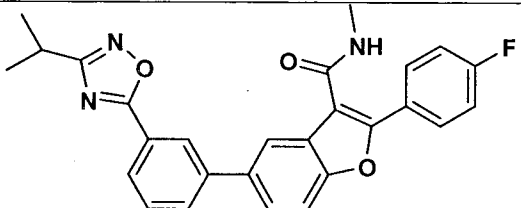
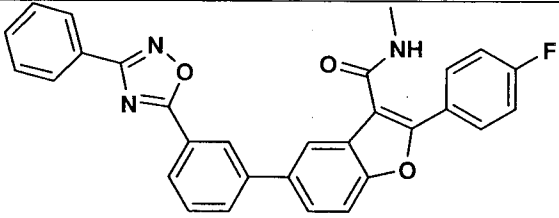
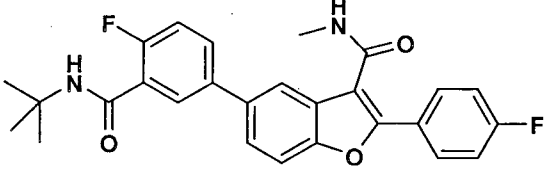
Estructura	Cl ₅₀	CE ₅₀
	E	C
	C	B
	E	C
		A
		

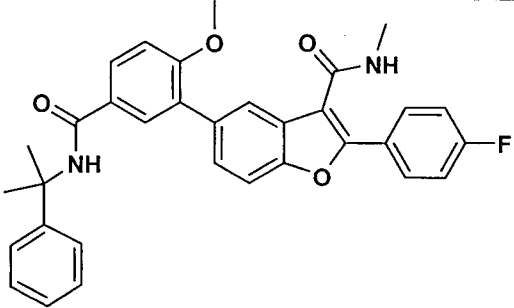
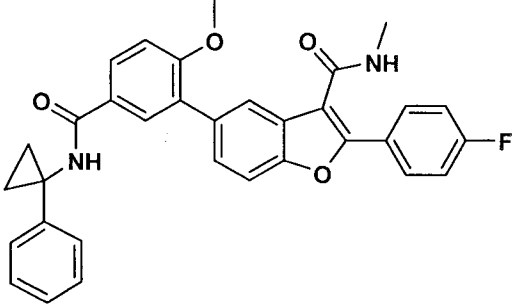
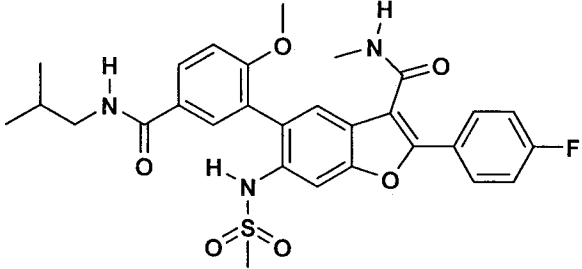
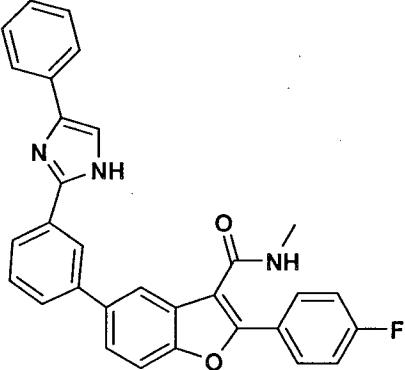
Estructura	Cl ₅₀	CE ₅₀
	A	A
		
	A	A
		A
	A	A
		A

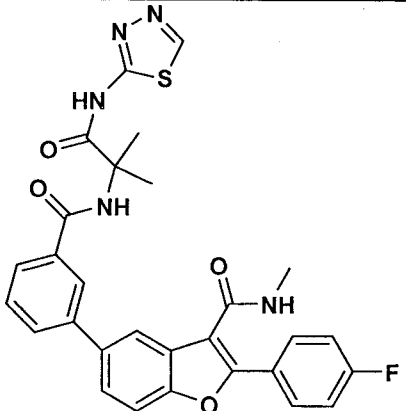
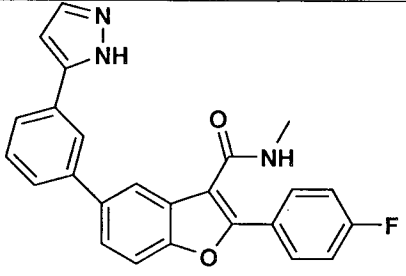
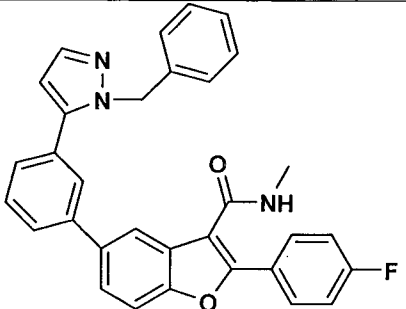
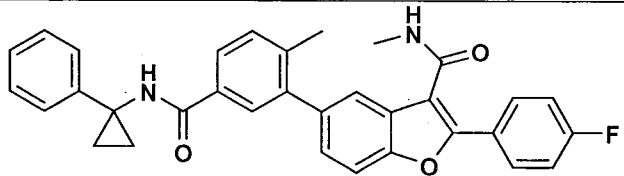
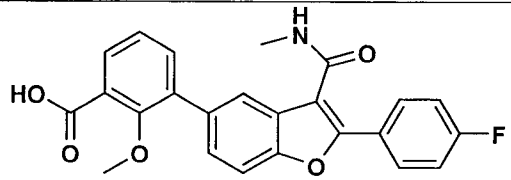
Estructura	Cl ₅₀	CE ₅₀
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	B	A
	A	A
		E
	A	A

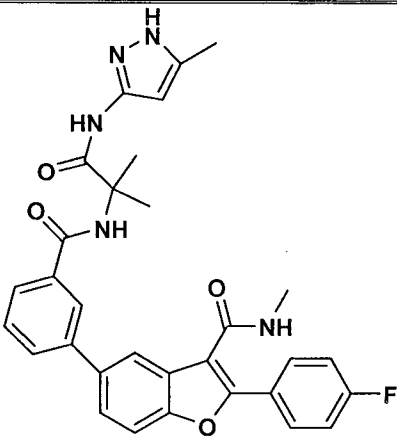
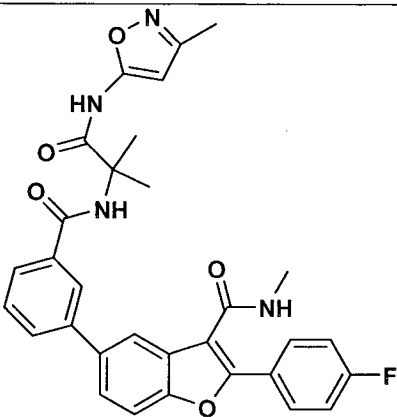
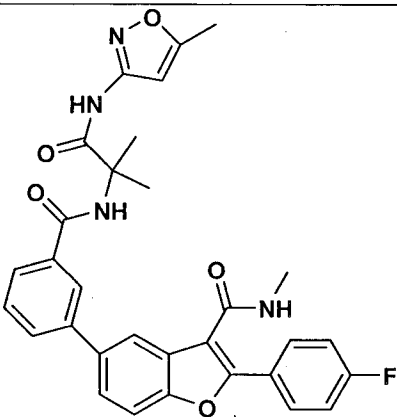
Estructura	Cl ₅₀	CE ₅₀
	A	B
		C
	B	A
		A
	A	A

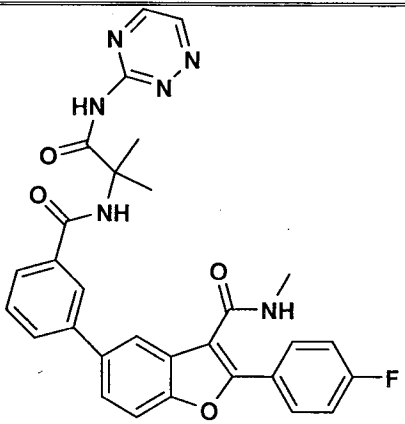
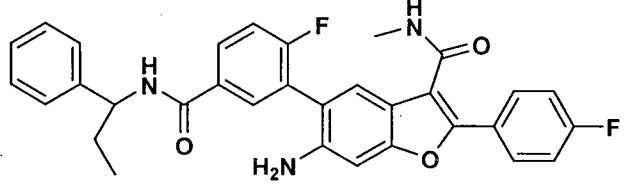
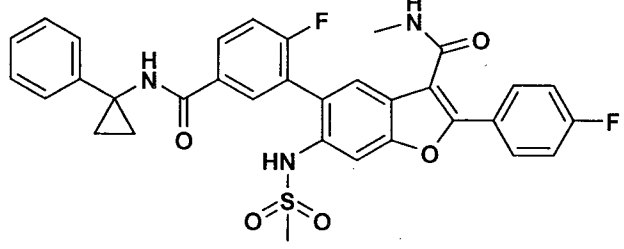
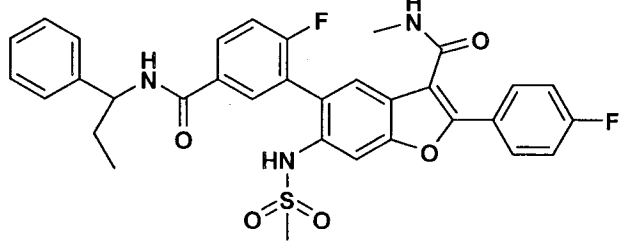
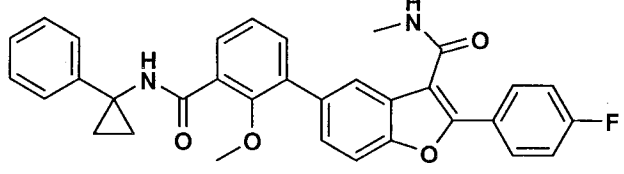
Estructura	Cl ₅₀	CE ₅₀
	A	A
	B	C
		A
	B	A
	A	A

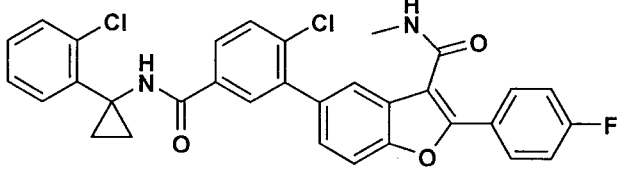
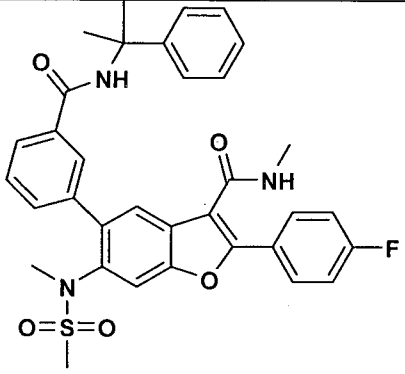
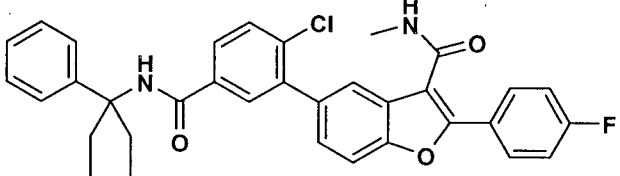
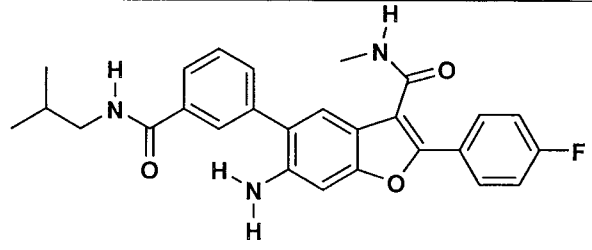
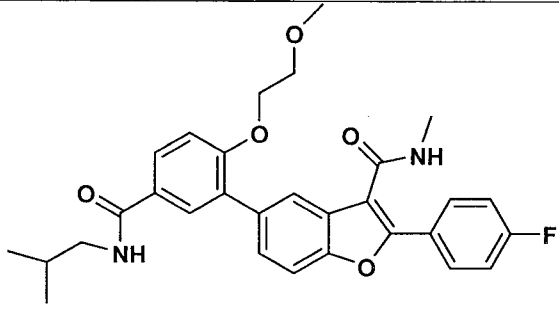
Estructura	Cl ₅₀	CE ₅₀
	A	A
		A
	E	B
	G	B
	E	A
	A	A

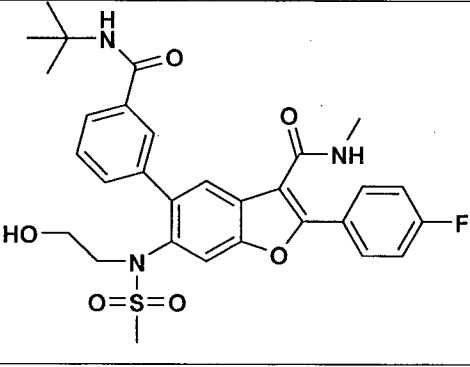
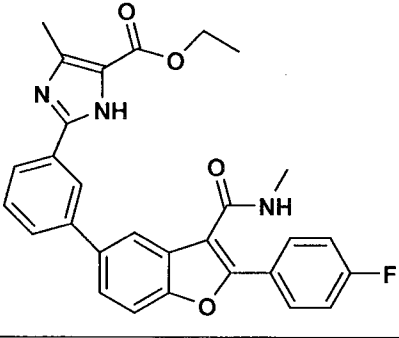
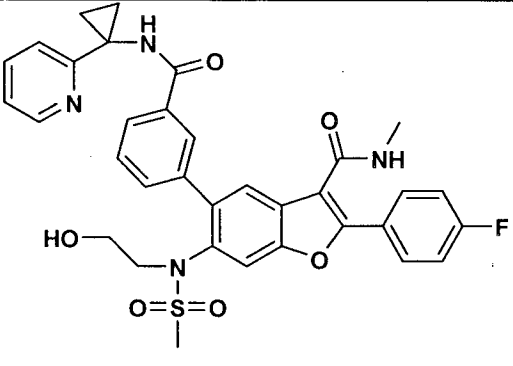
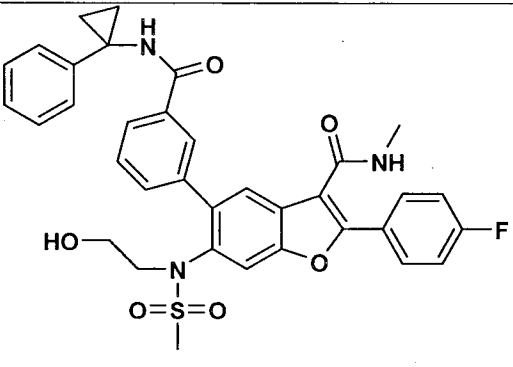
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	B	A

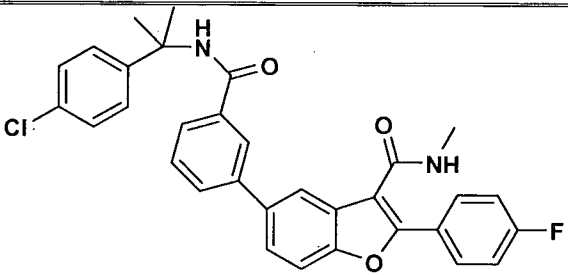
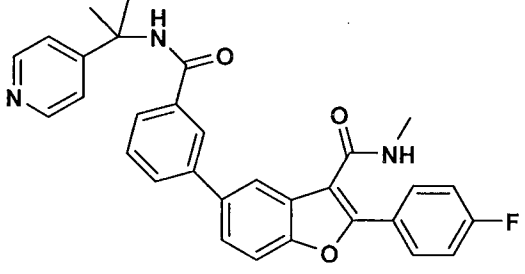
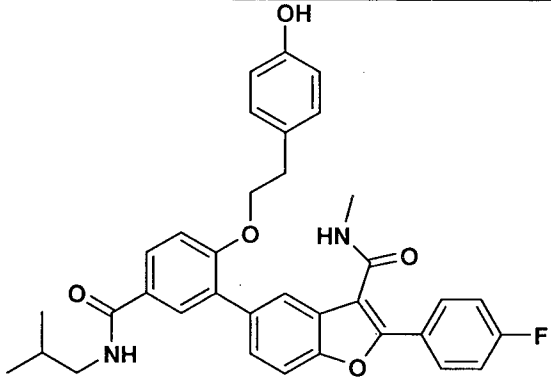
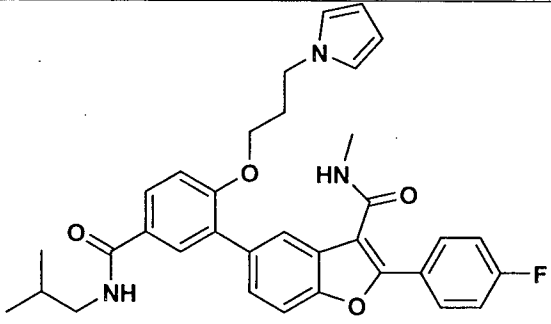
Estructura	Cl ₅₀	CE ₅₀
	A	A
	C	C
	A	A
	A	A
	C	E

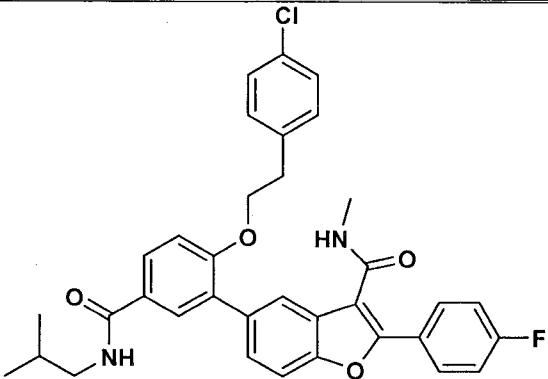
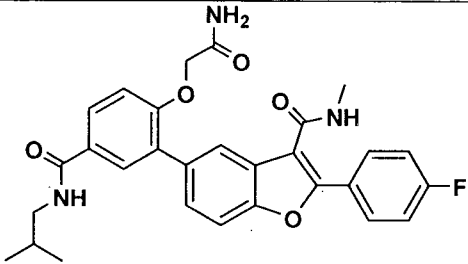
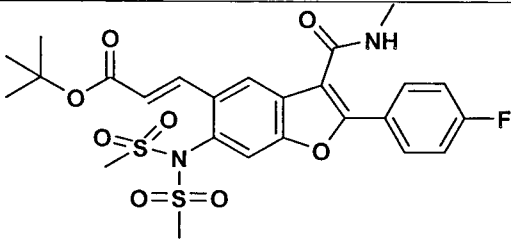
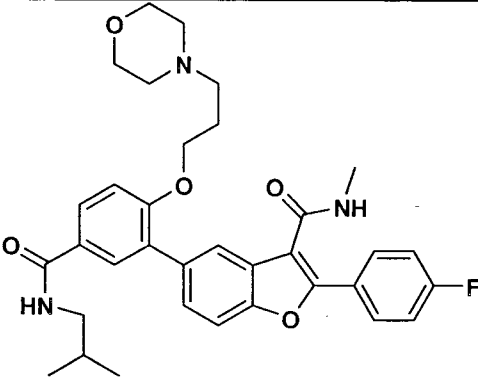
Estructura	Cl ₅₀	CE ₅₀
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	A	A
	A	A

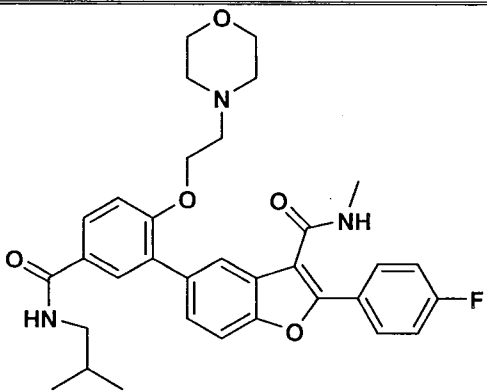
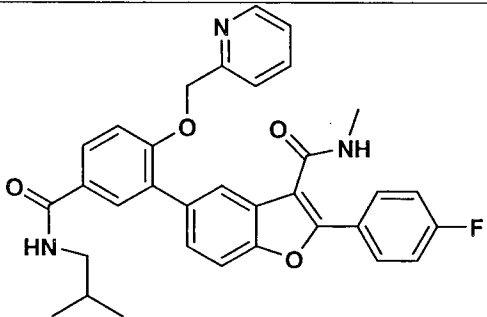
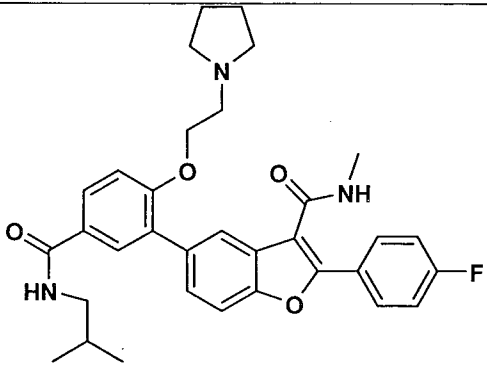
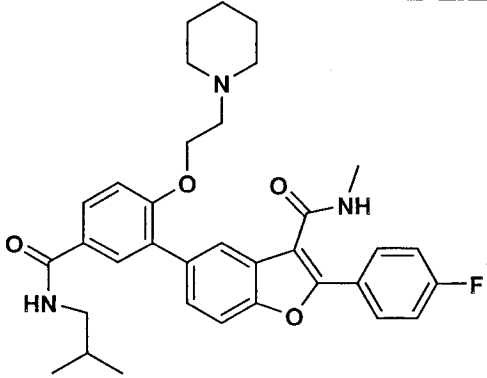
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	A	A
	E	E

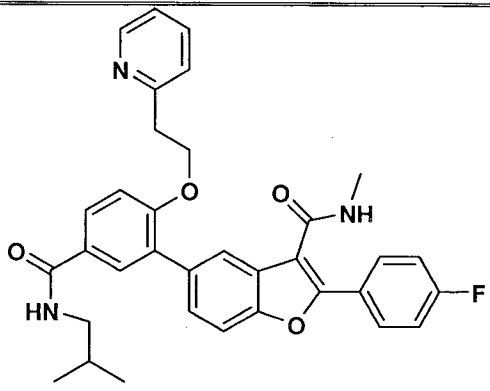
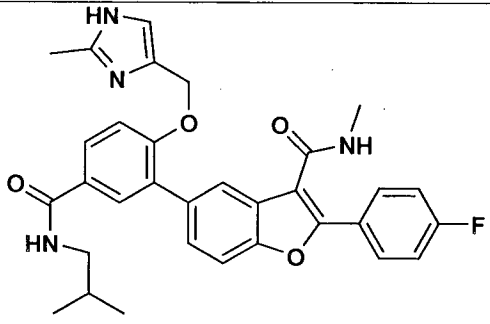
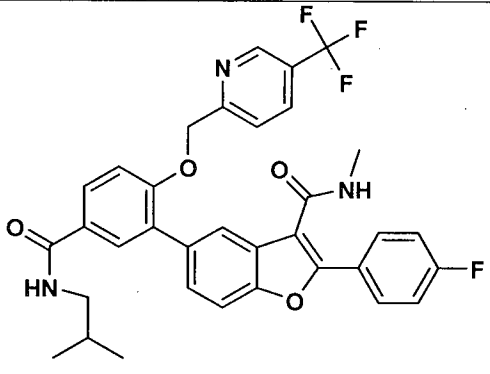
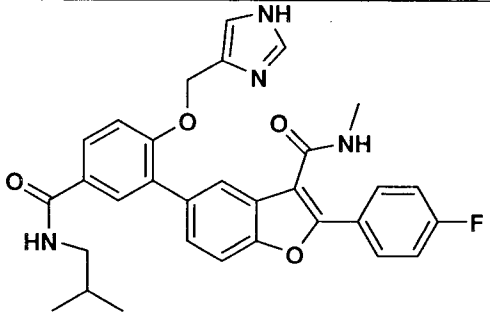
Estructura	Cl ₅₀	CE ₅₀
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	A	A
	A	A
	A	A
	B	A

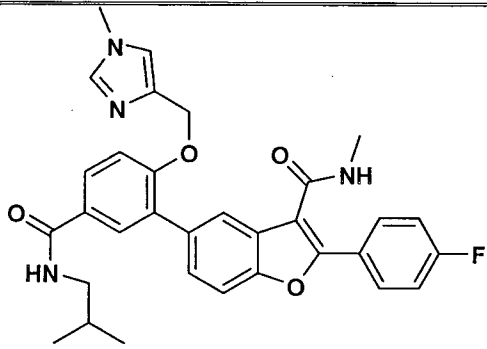
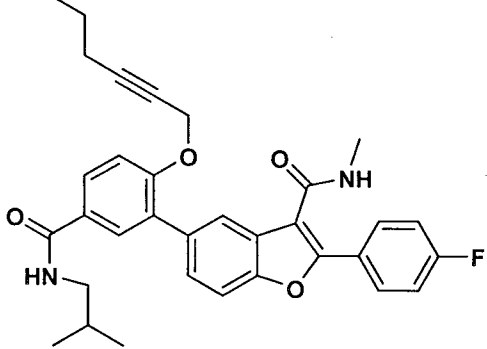
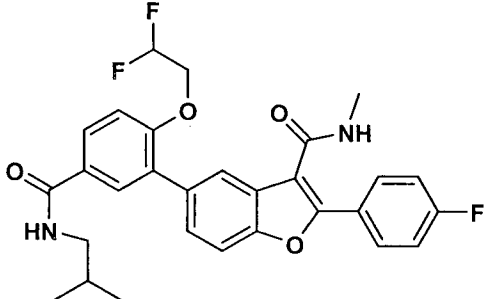
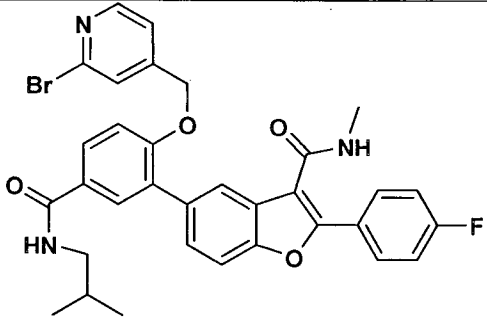
Estructura	Cl ₅₀	CE ₅₀
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	A	
	A	A
	A	A

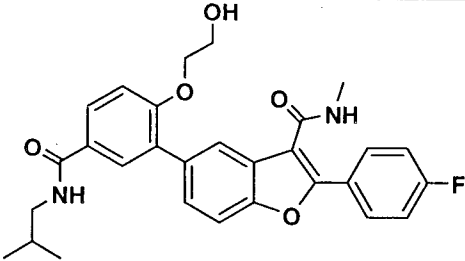
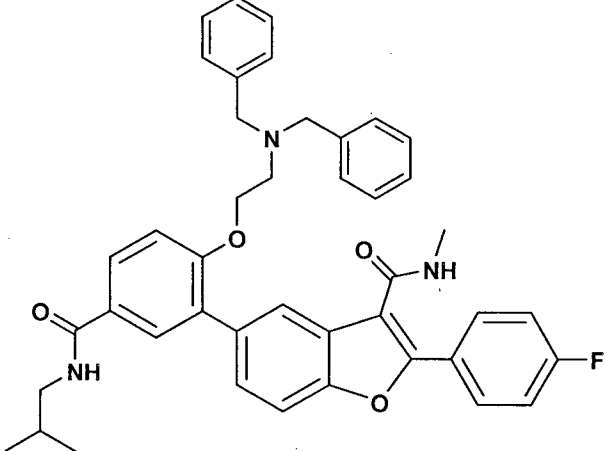
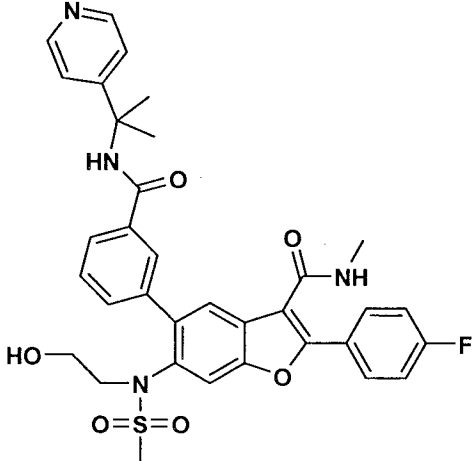
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	B	B
	C	B

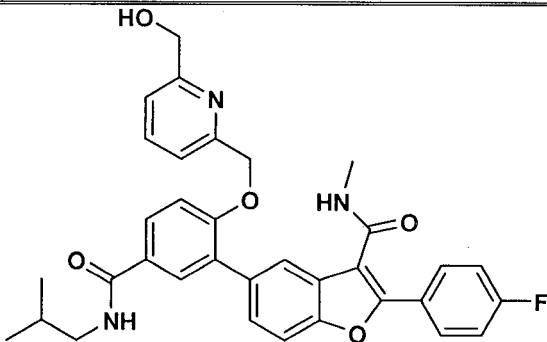
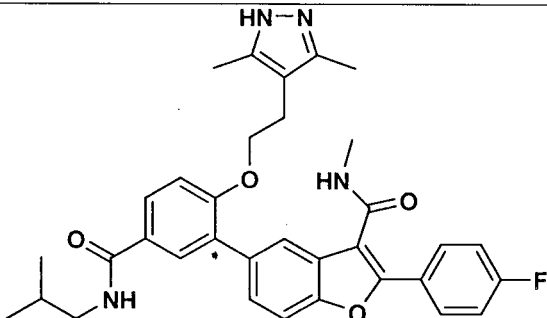
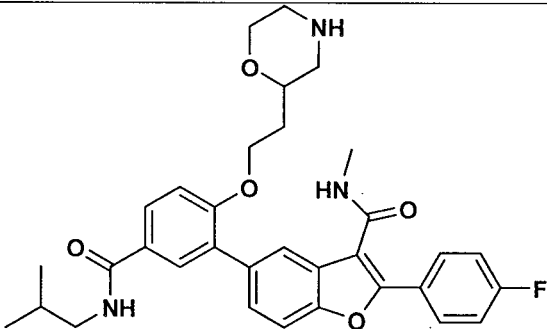
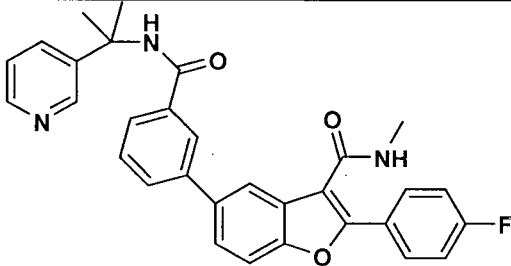
Estructura	Cl ₅₀	CE ₅₀
	E	E
	A	A
		
	A	A

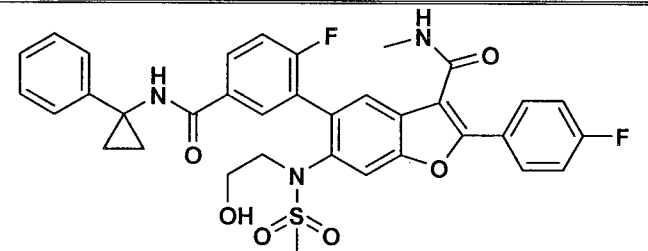
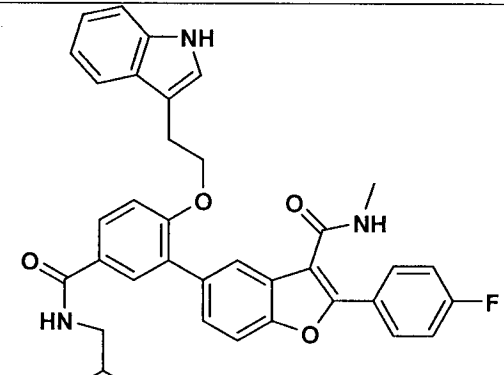
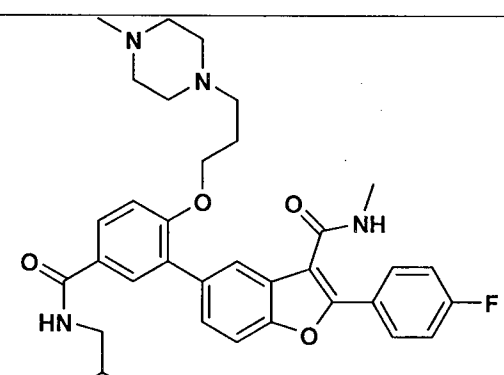
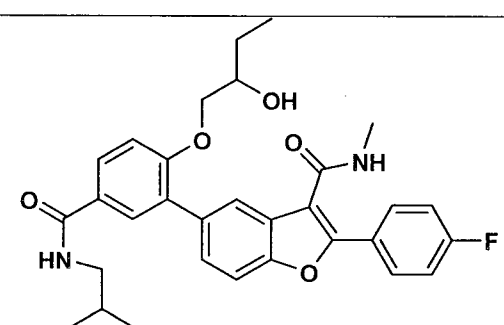
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	B	A

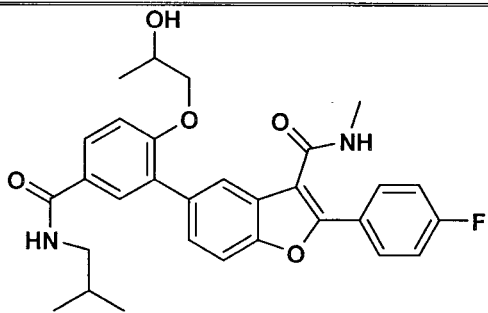
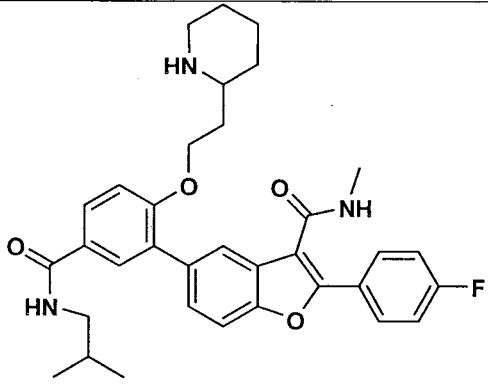
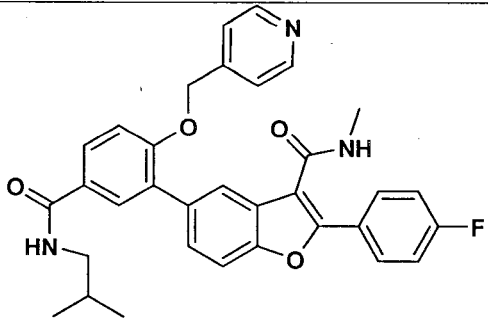
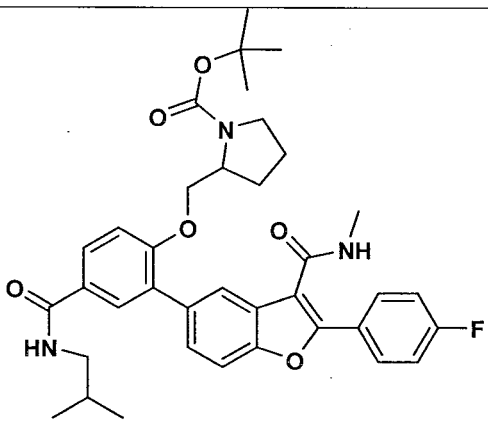
Estructura	Cl ₅₀	CE ₅₀
	B	A
	A	A
	E	E
	A	A

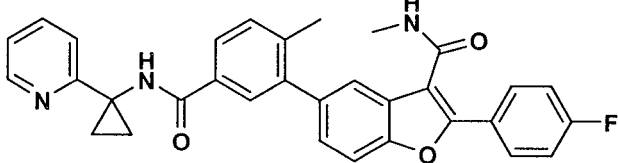
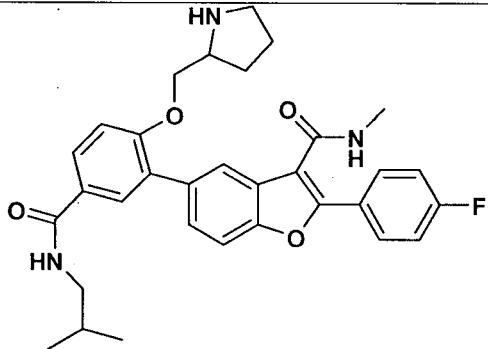
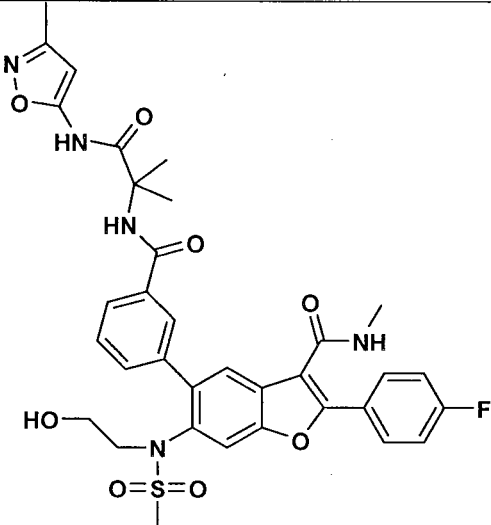
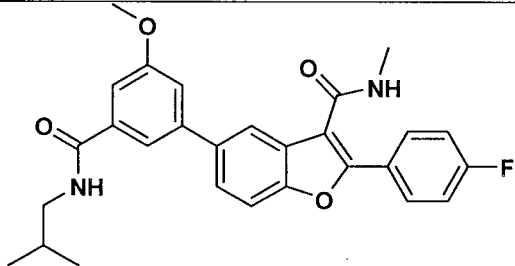
Estructura	Cl ₅₀	CE ₅₀
	C	B
	C	C
	B	A
	B	B

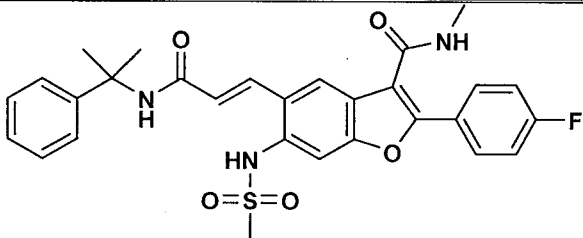
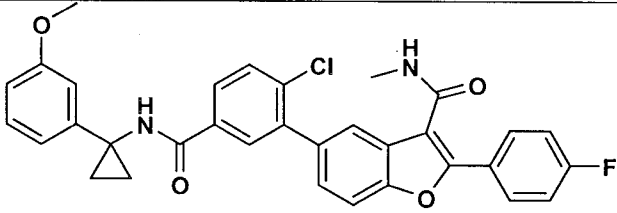
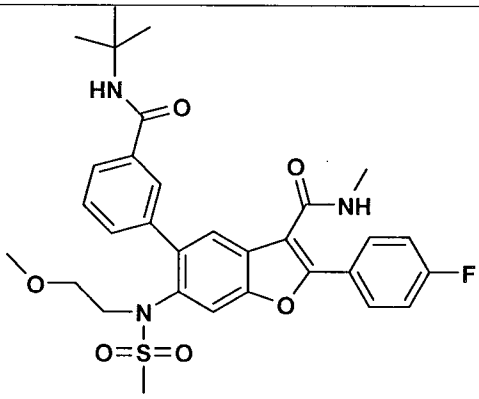
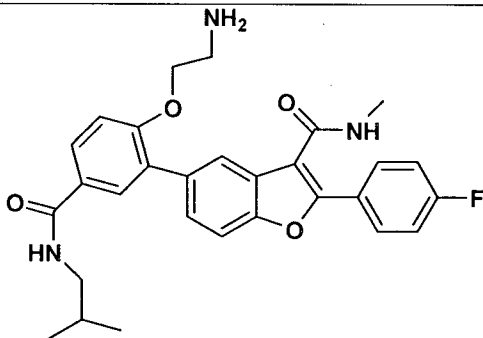
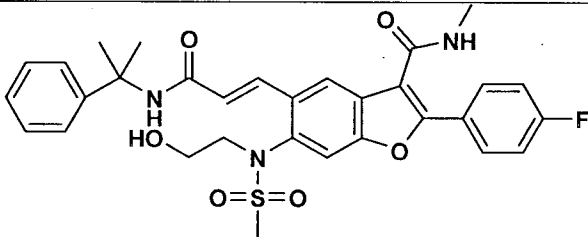
Estructura	Cl ₅₀	CE ₅₀
	A	A
		C
		A

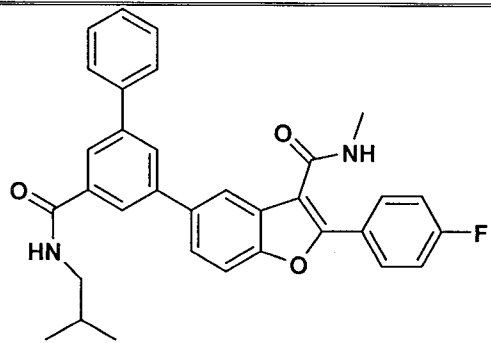
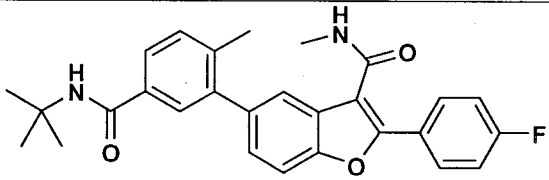
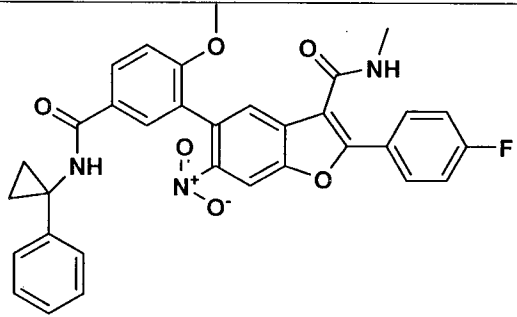
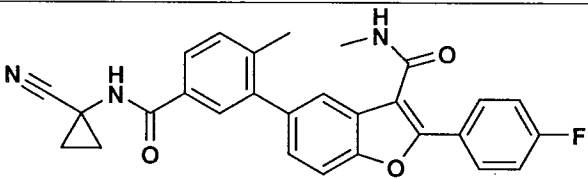
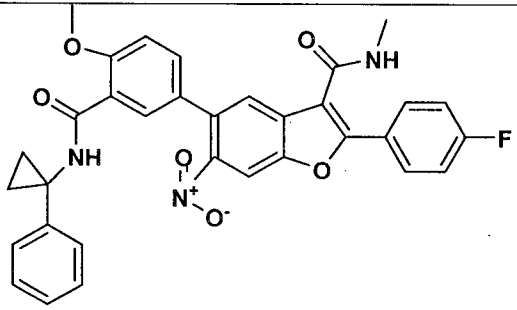
Estructura	Cl ₅₀	CE ₅₀
		
	A	A
	A	A
	A	A

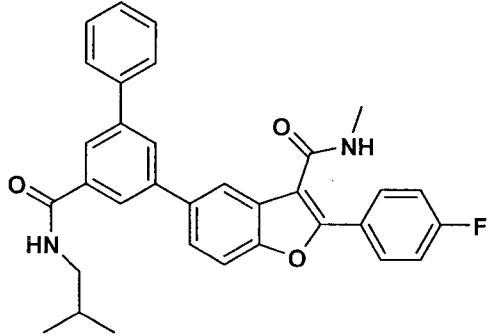
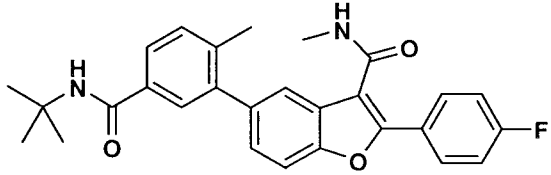
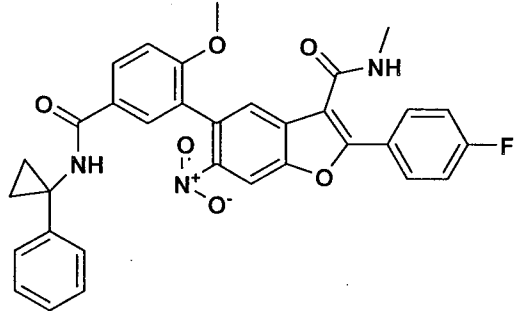
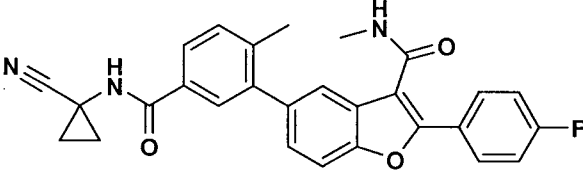
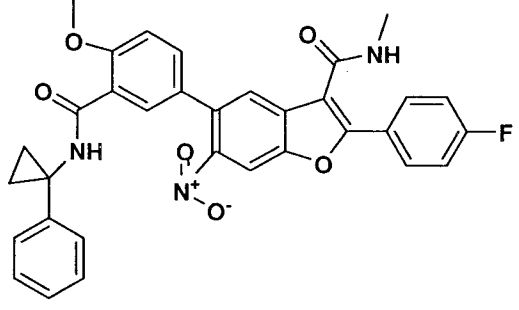
Estructura	Cl ₅₀	CE ₅₀
	A	A
	C	C
	A	A
	B	B

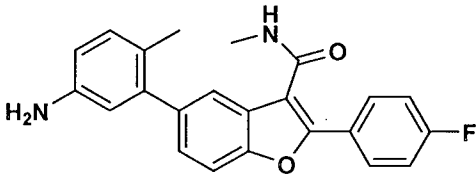
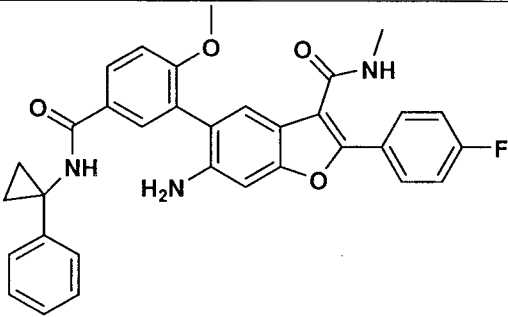
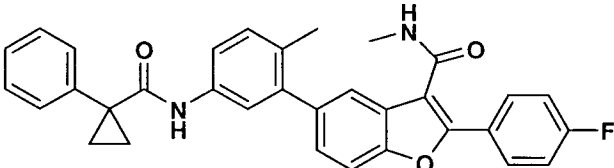
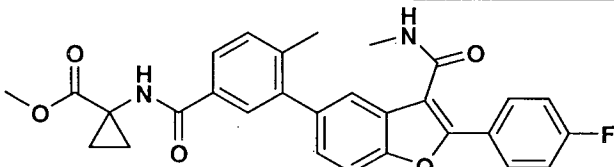
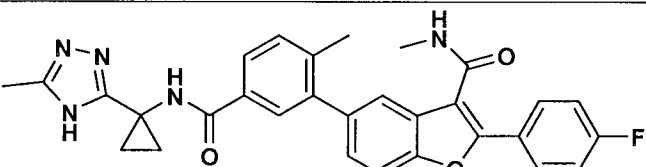
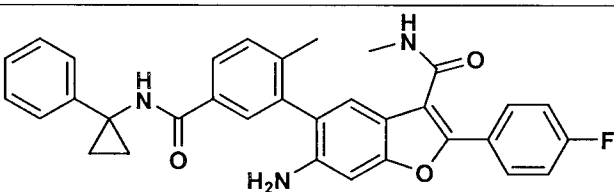
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	E	C

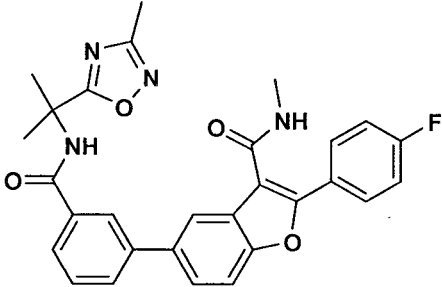
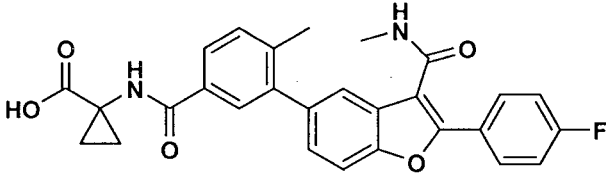
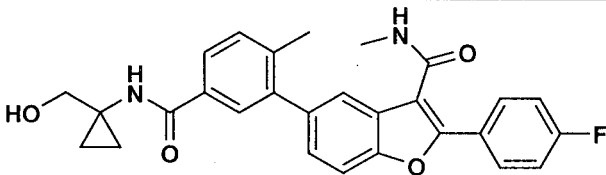
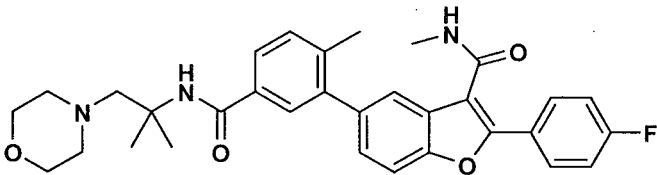
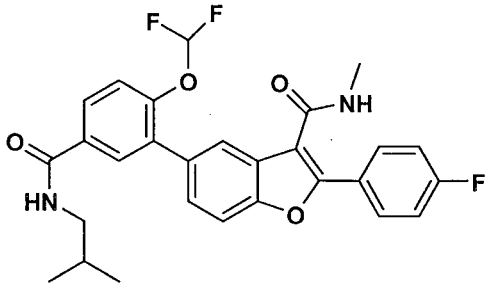
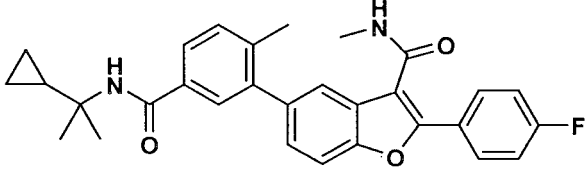
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	B
	A	A
	B	B

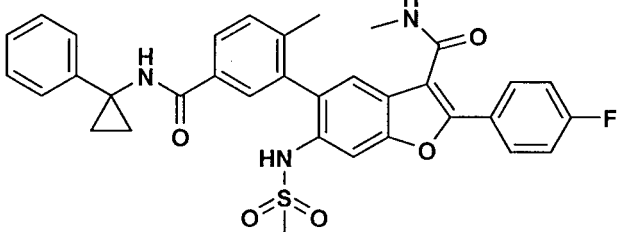
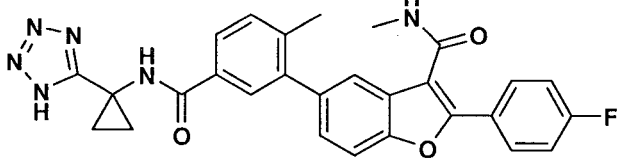
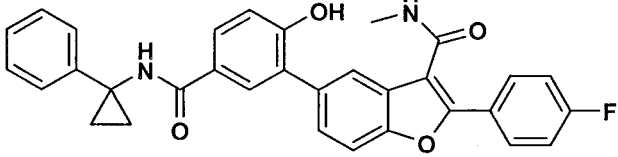
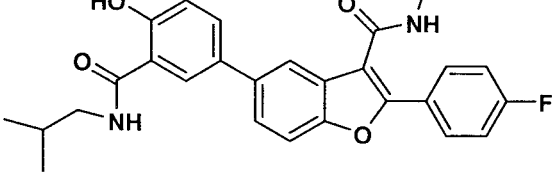
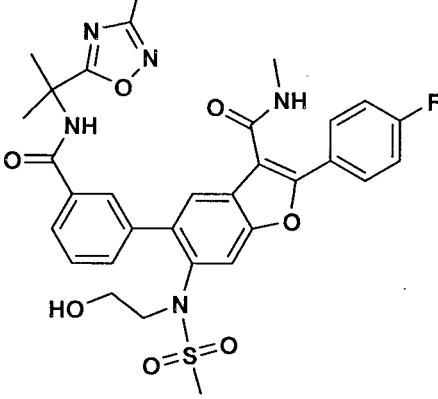
Estructura	Cl ₅₀	CE ₅₀
	C	
		
		
	A	A
	A	

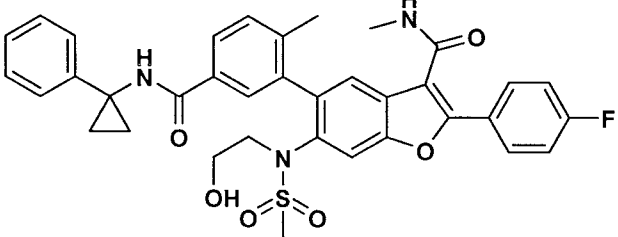
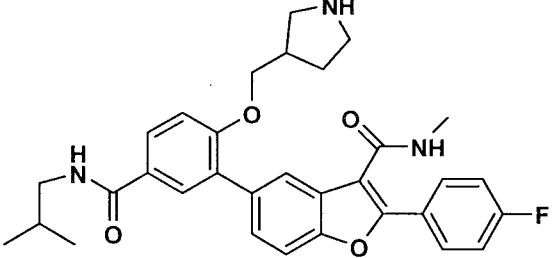
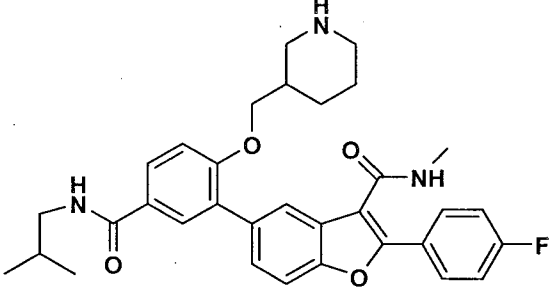
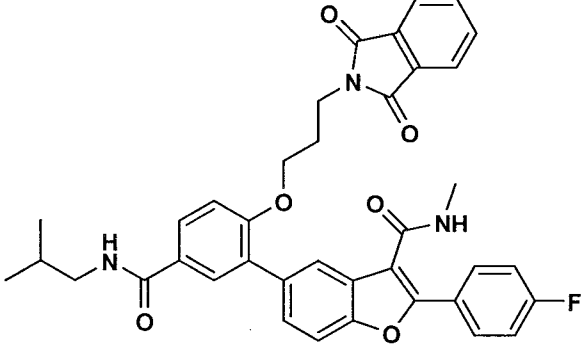
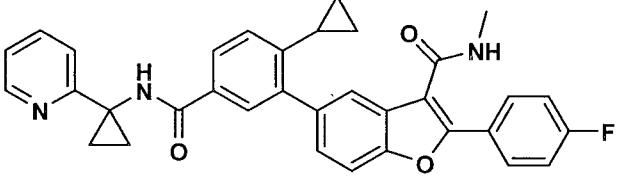
Estructura	Cl ₅₀	CE ₅₀
		
		
		
		
		

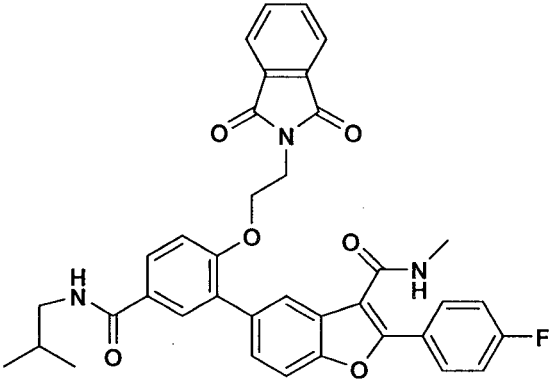
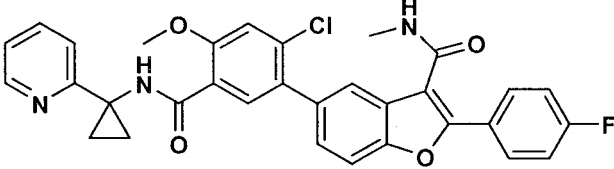
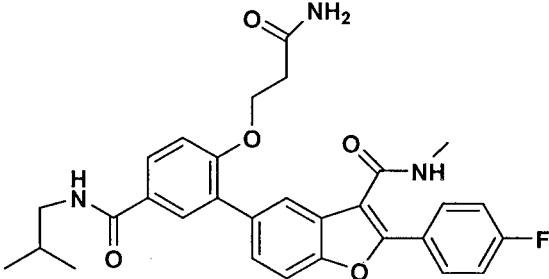
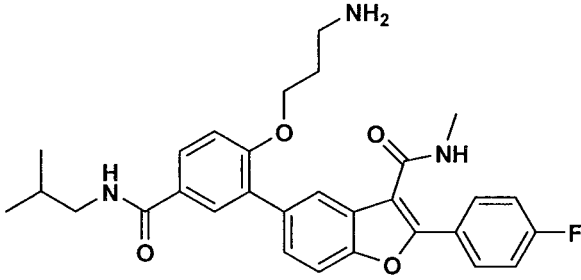
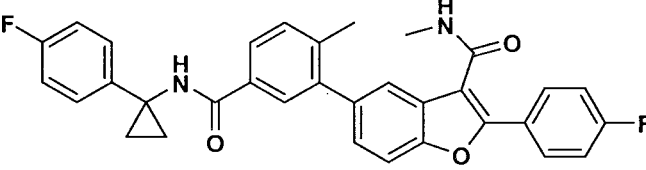
Estructura	Cl ₅₀	CE ₅₀
	E	E
	A	A
	A	B
	A	A
	A	A

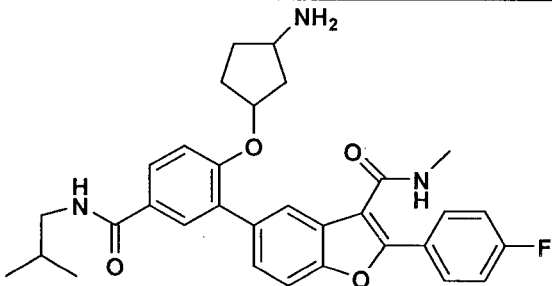
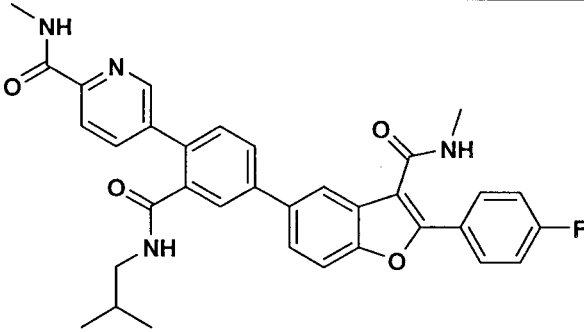
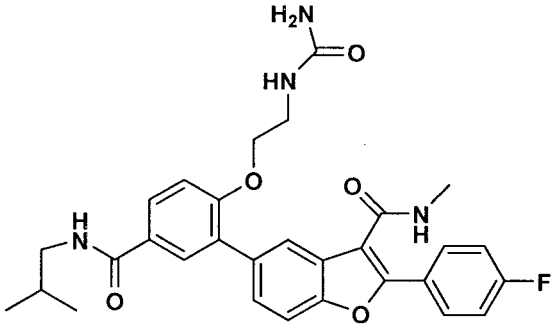
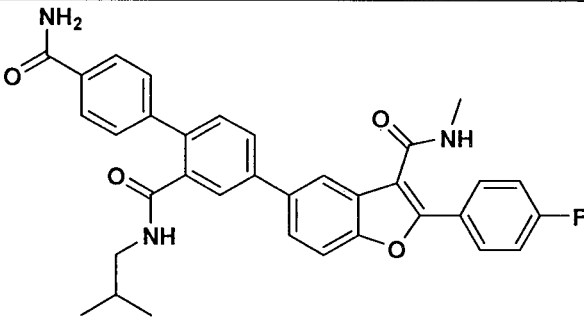
Estructura	Cl ₅₀	CE ₅₀
	C	C
	A	A
	C	B
	A	A
	A	A
	A	A

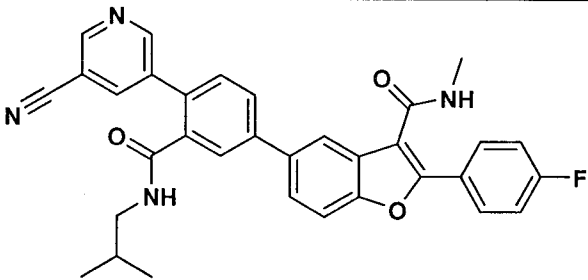
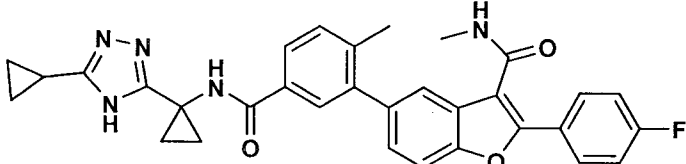
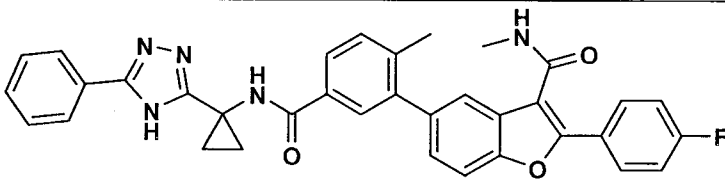
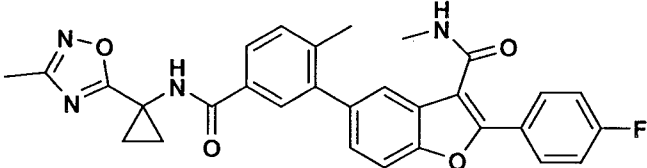
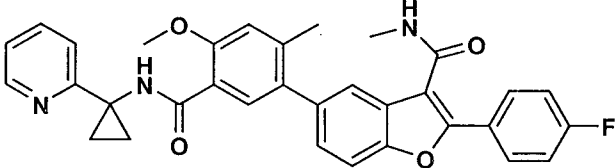
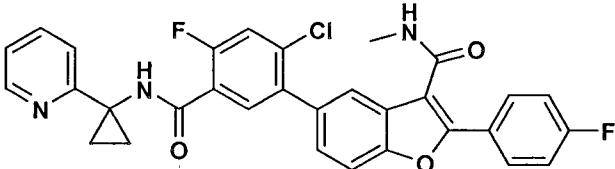
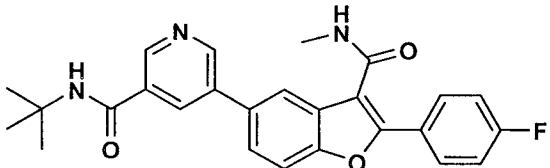
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	C
	C	C
	A	A
	A	A
	A	A

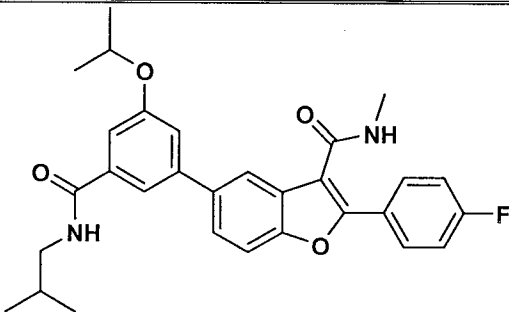
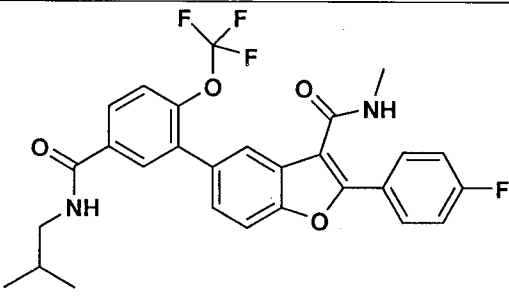
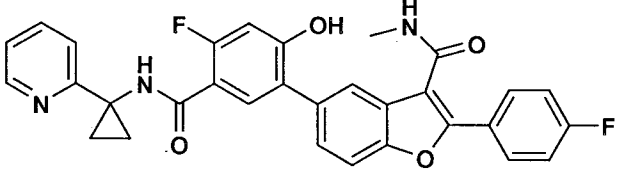
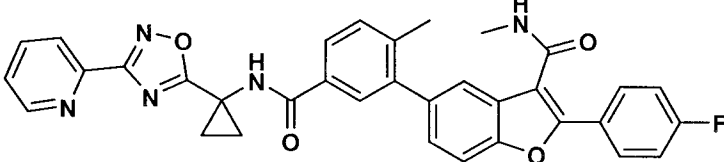
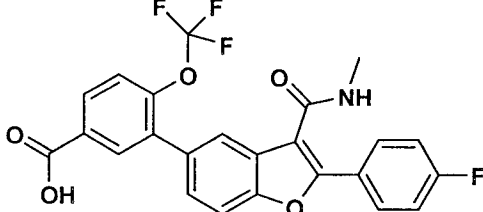
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	C
	A	A
	C	E
	A	A

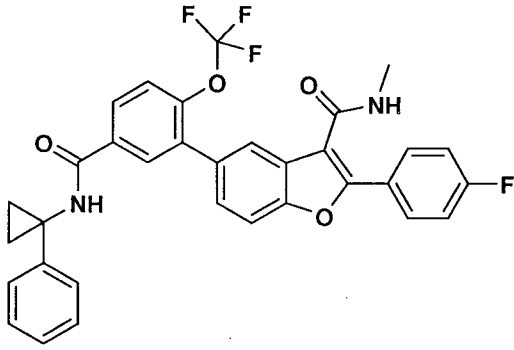
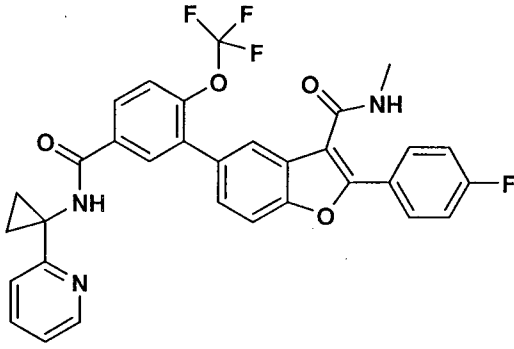
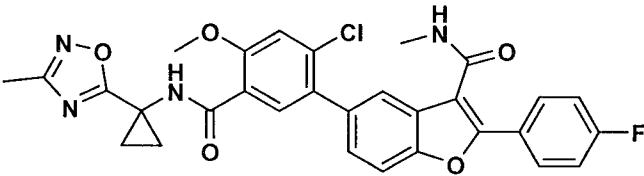
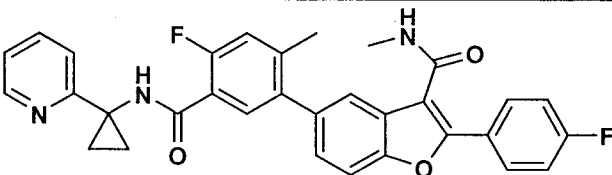
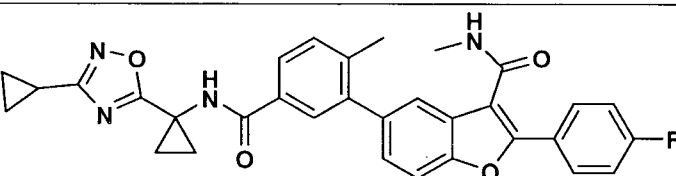
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
		E
		E

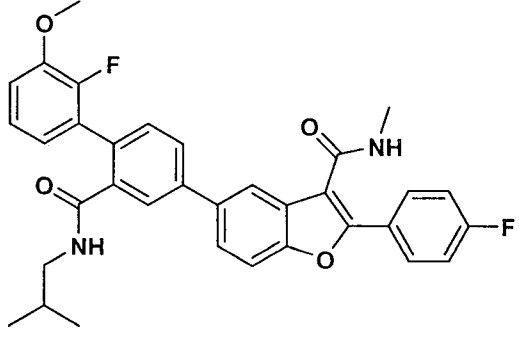
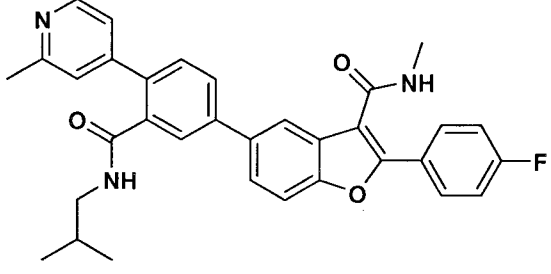
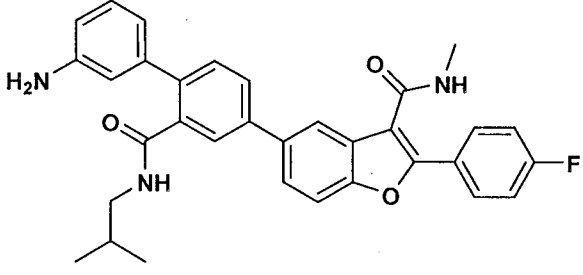
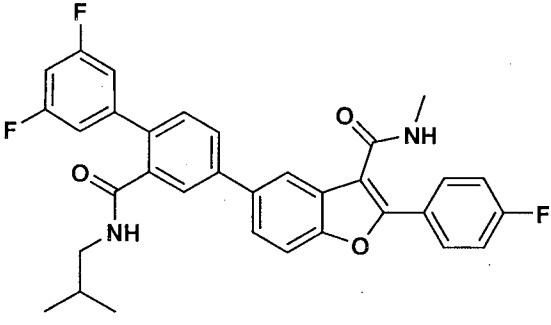
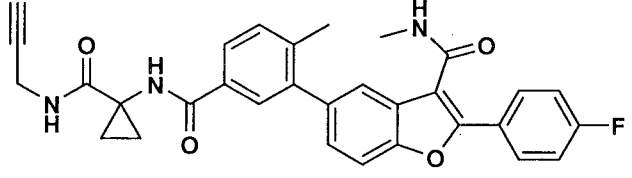
Estructura	Cl ₅₀	CE ₅₀
		
	A	A
	E	E
	A	A
	A	A

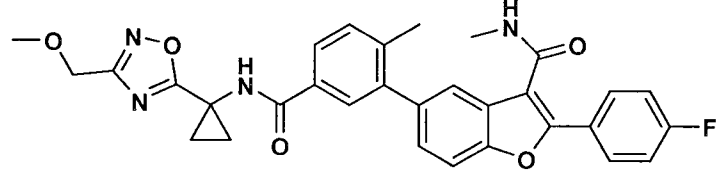
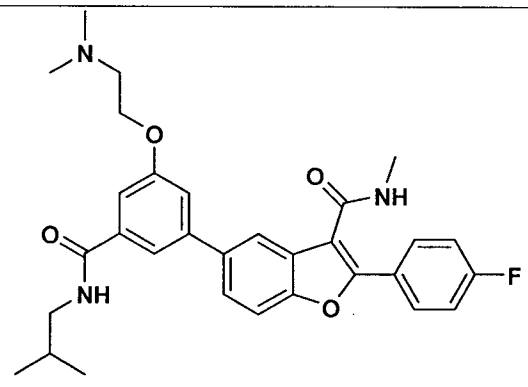
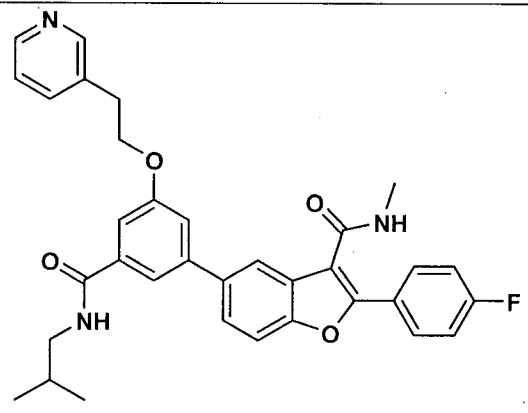
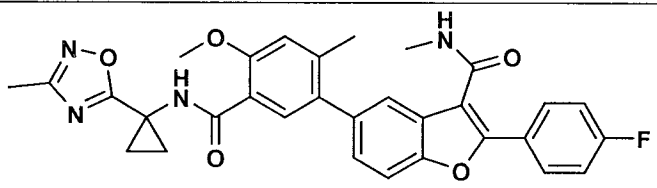
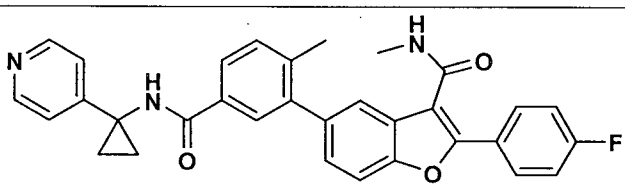
Estructura	Cl ₅₀	CE ₅₀
	A	A
	E	E
	A	A
	A	E

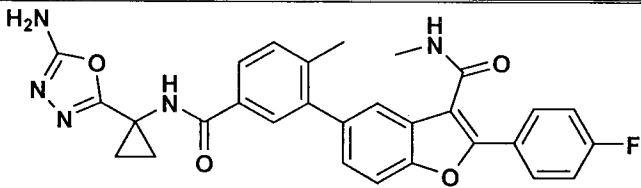
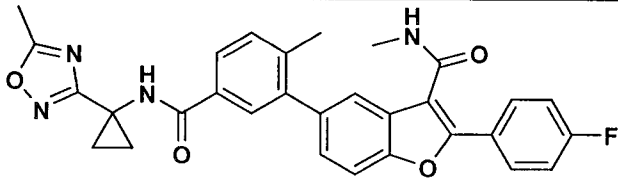
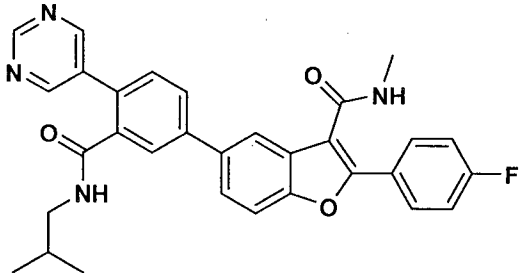
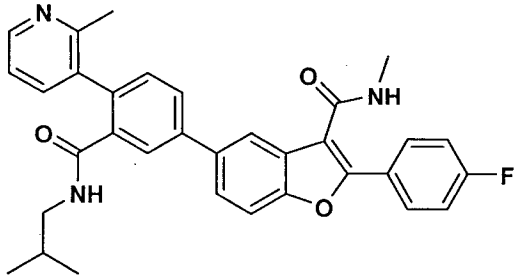
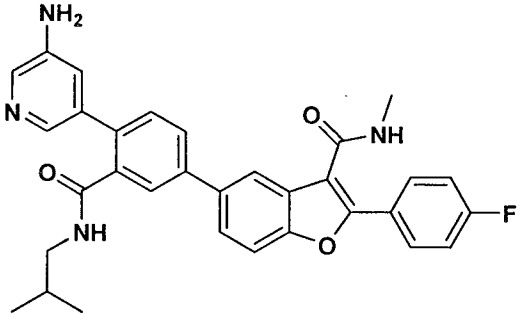
Estructura	Cl ₅₀	CE ₅₀
	A	B
	A	A
	A	A
		A
	A	A
	A	A
	A	A

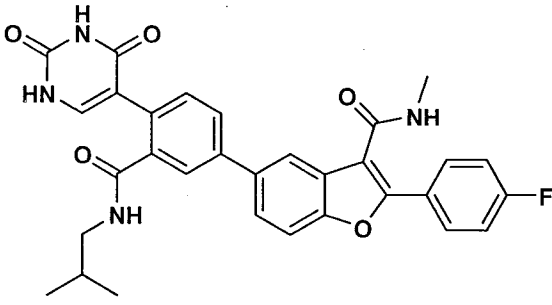
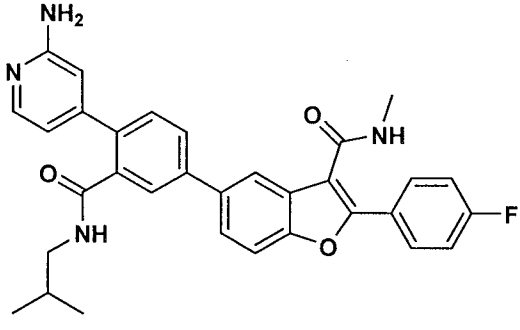
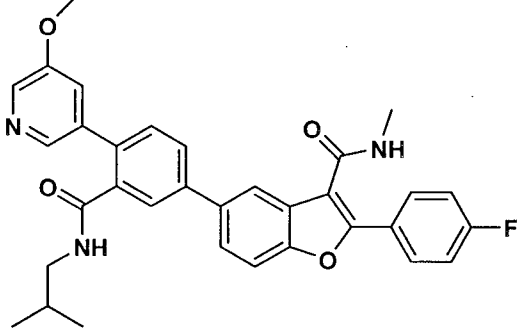
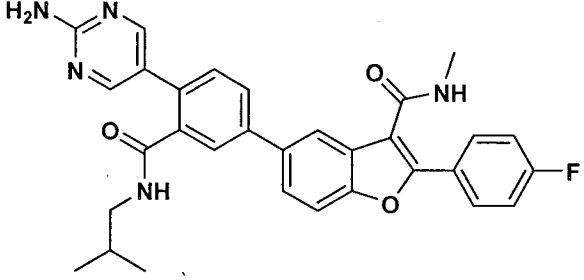
Estructura	Cl ₅₀	CE ₅₀
	C	E
	B	E
	A	B
	A	A
		E

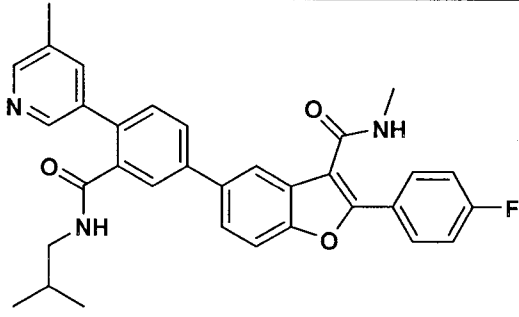
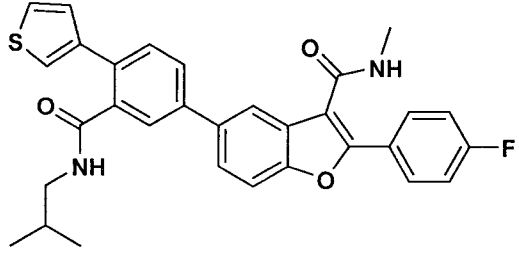
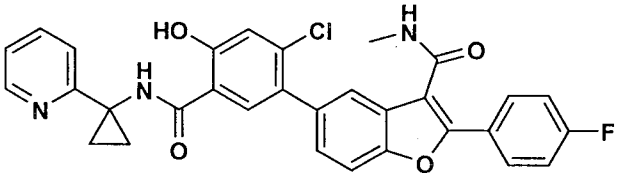
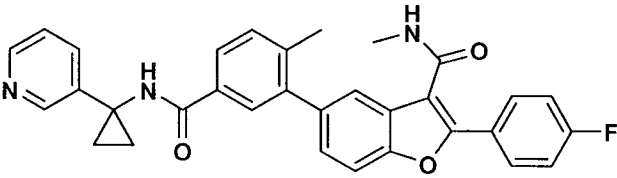
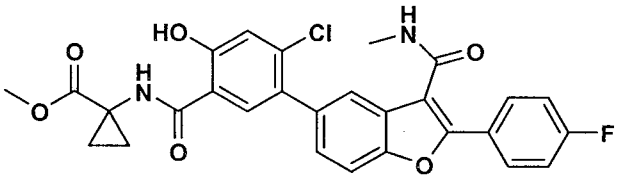
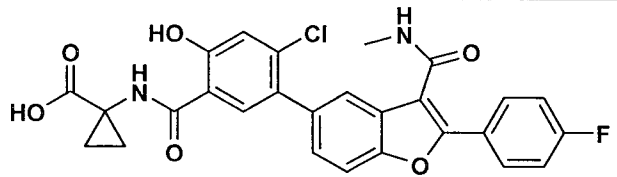
Estructura	Cl ₅₀	CE ₅₀
	B	A
	B	A
	A	A
	A	A
	A	A

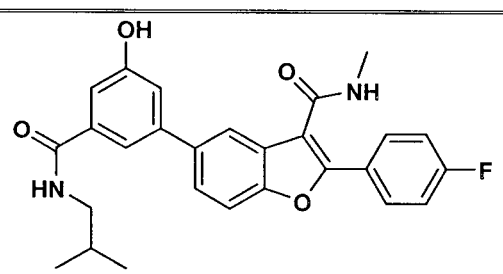
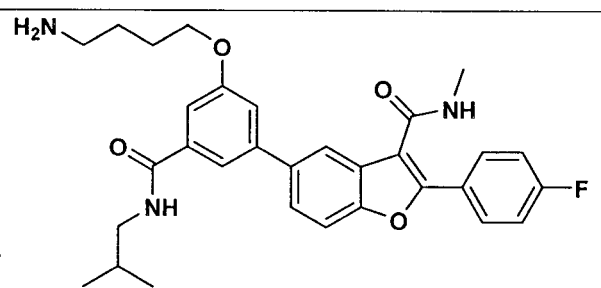
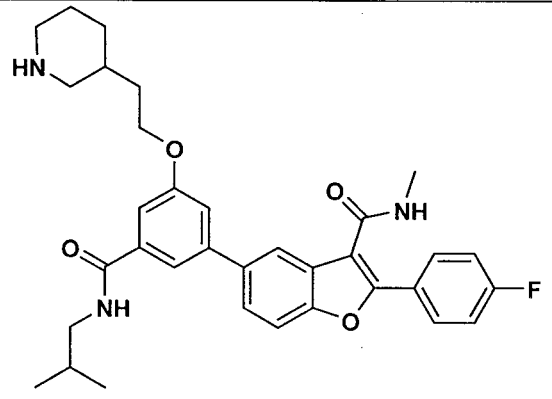
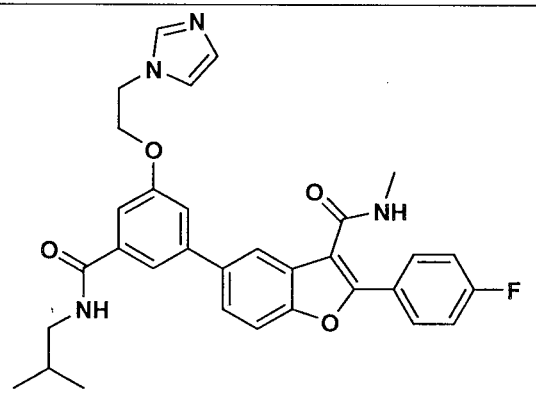
Estructura	Cl ₅₀	CE ₅₀
	E	B
	A	
	A	
	B	A
	A	A

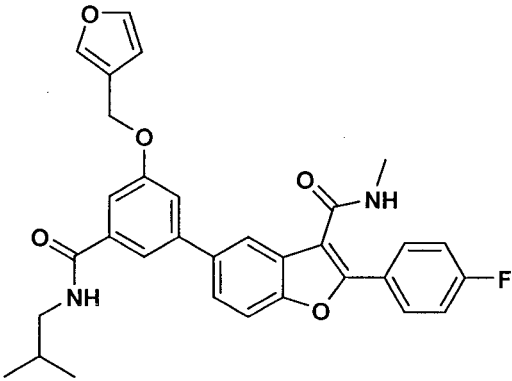
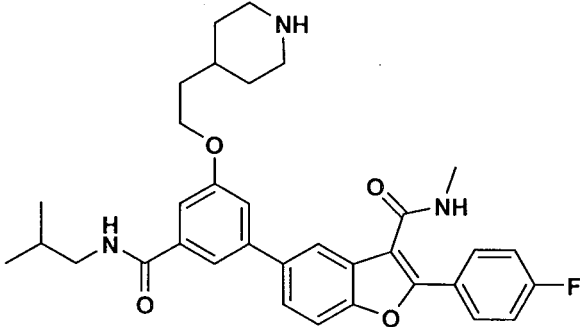
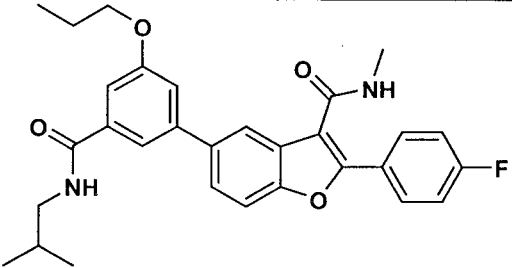
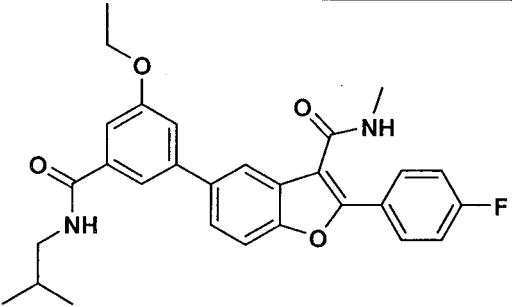
Estructura	Cl ₅₀	CE ₅₀
	A	A
	B	B
	E	C
	A	A
	A	A

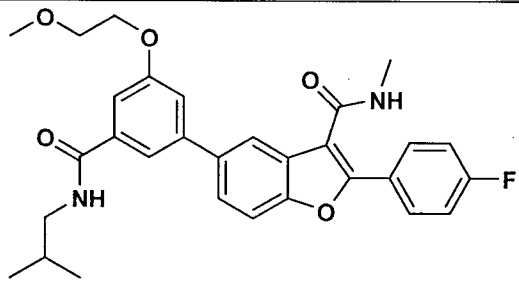
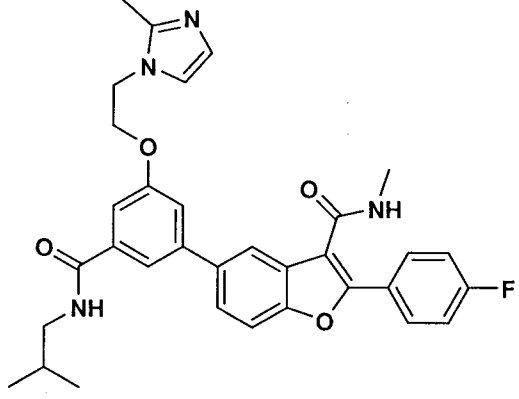
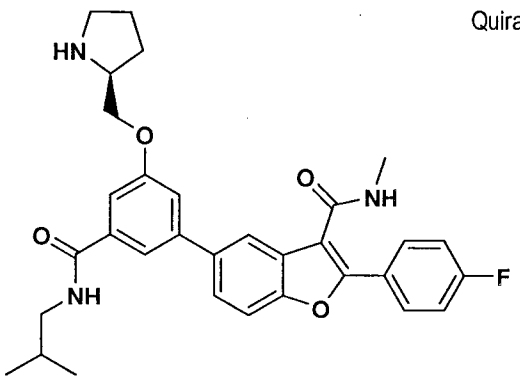
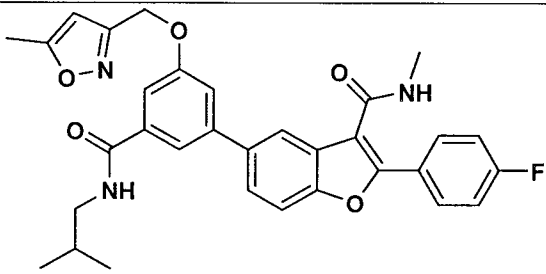
Estructura	Cl ₅₀	CE ₅₀
	A	A
	L	A
	A	
	A	A
	A	B

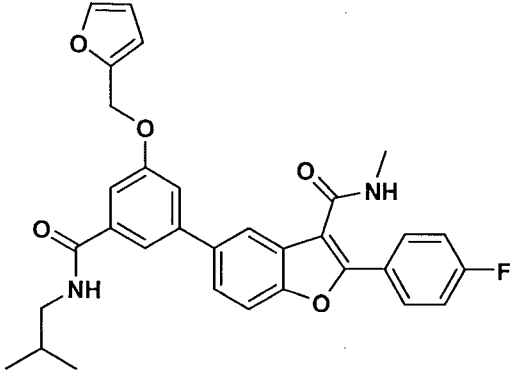
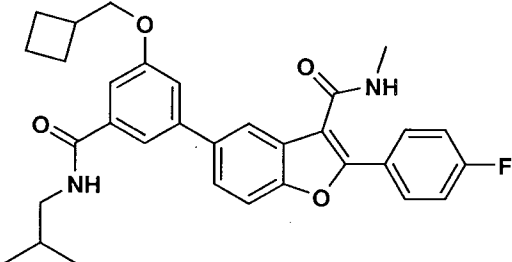
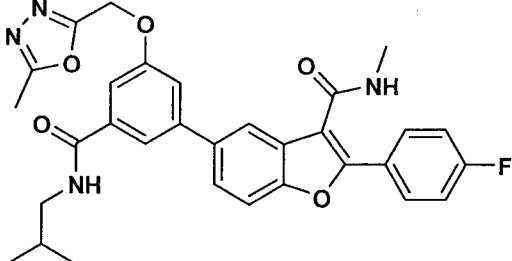
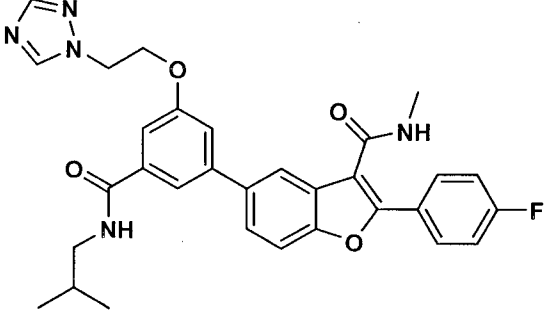
Estructura	Cl ₅₀	CE ₅₀
	A	
	L	A
	B	
	A	

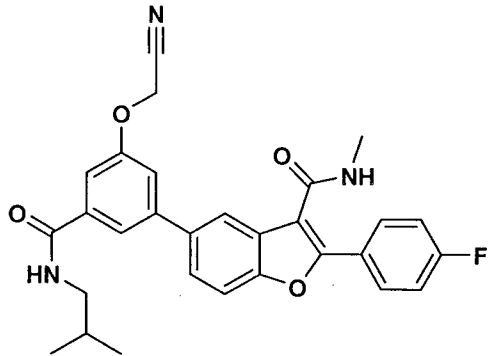
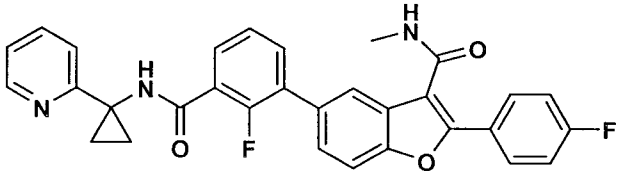
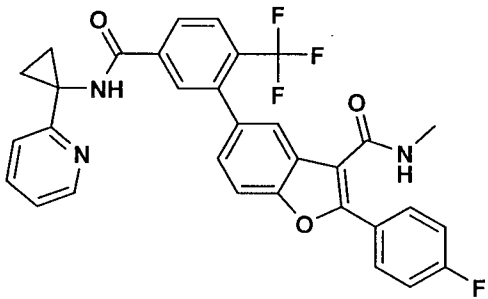
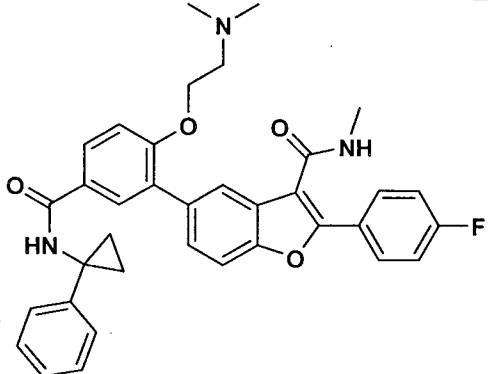
Estructura	Cl ₅₀	CE ₅₀
	B	
	A	
	A	B
	L	A
	B	
	B	

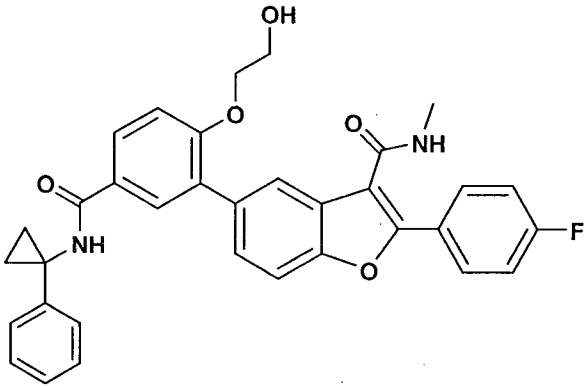
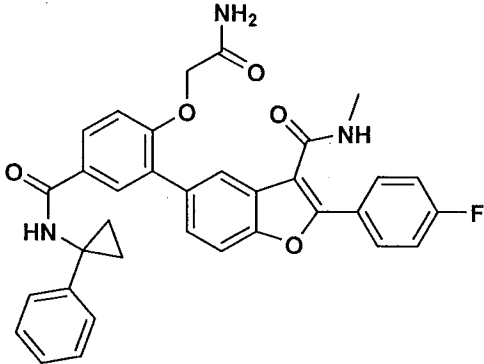
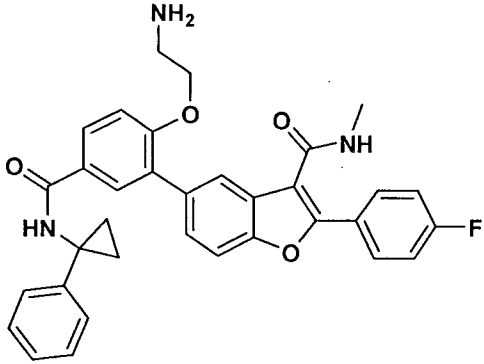
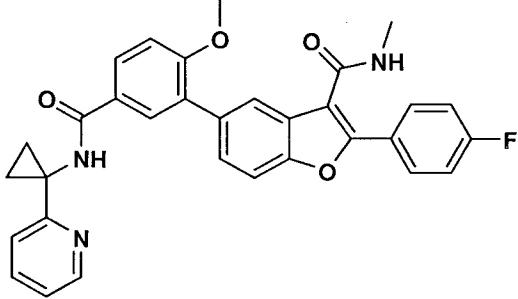
Estructura	Cl ₅₀	CE ₅₀
	A	B
	A	C
	A	A
	C	C

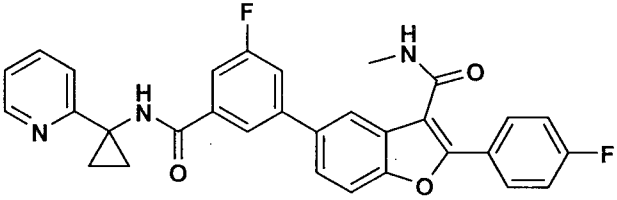
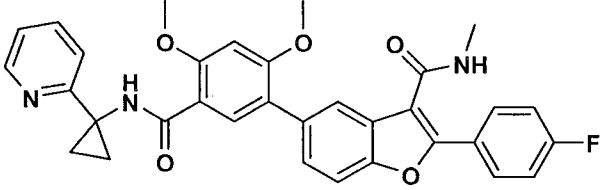
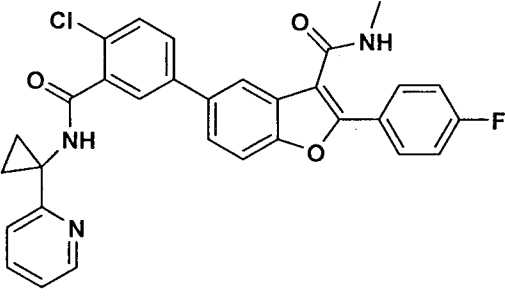
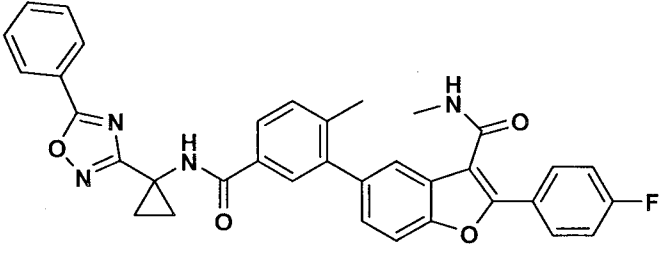
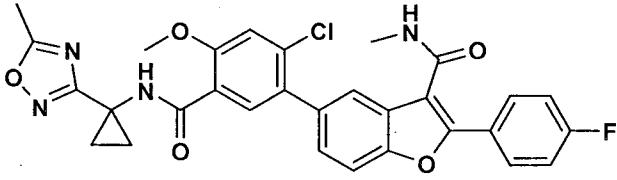
Estructura	Cl ₅₀	CE ₅₀
	C	C
	A	C
	E	C
	M	C

Estructura	Cl ₅₀	CE ₅₀
	M	C
	C	C
 Quiral	C	C
	G	C

Estructura	Cl ₅₀	CE ₅₀
	C	C
	E	C
	A	C
	B	C

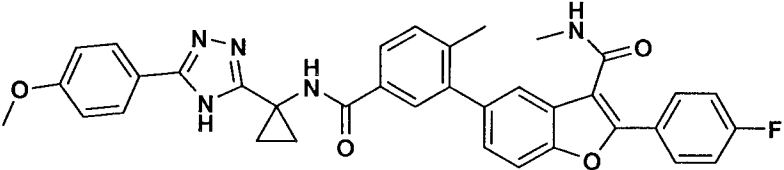
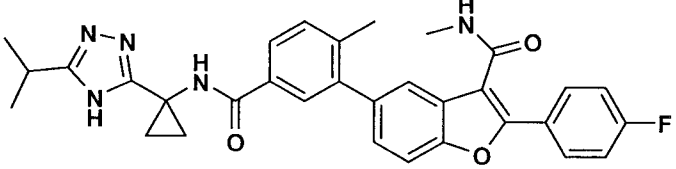
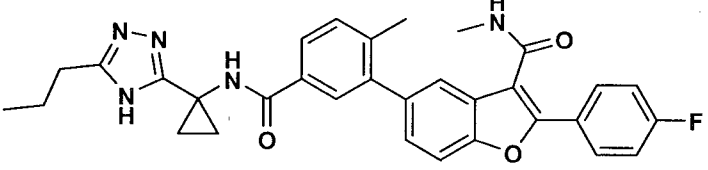
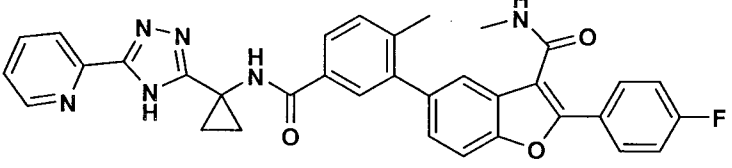
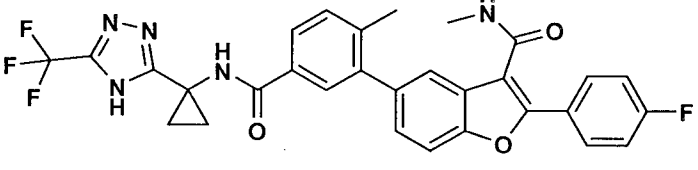
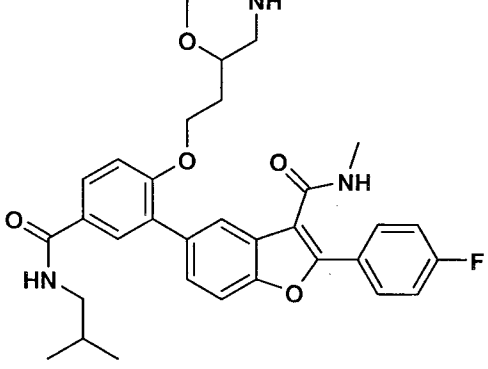
Estructura	Cl ₅₀	CE ₅₀
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	A	A
	A	A
	A	A

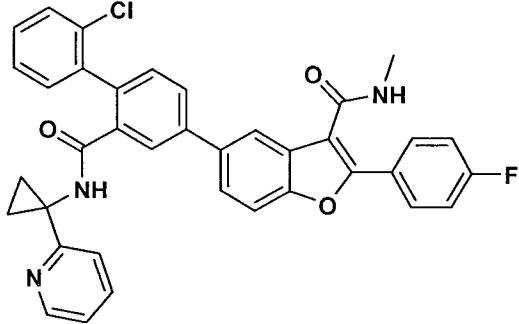
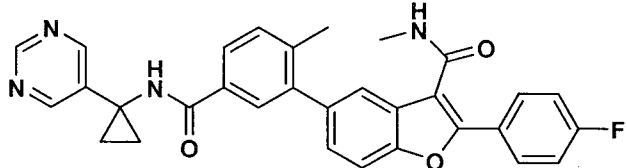
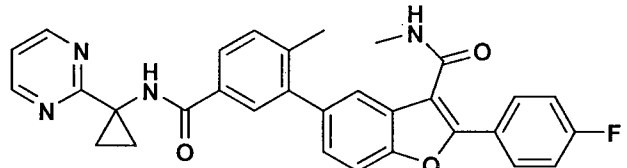
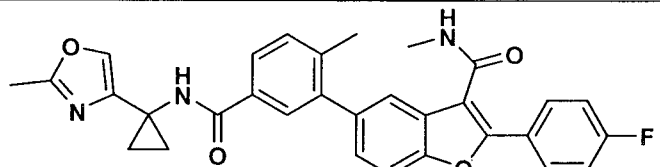
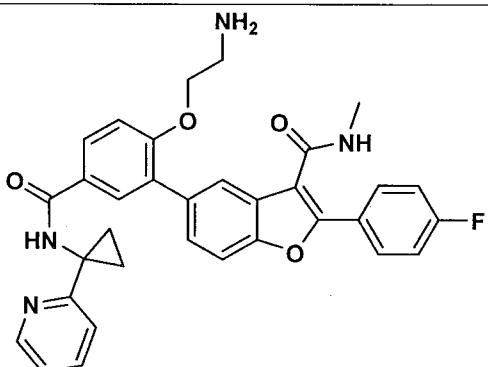
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	A	A

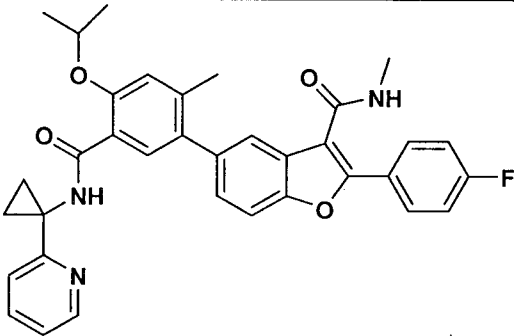
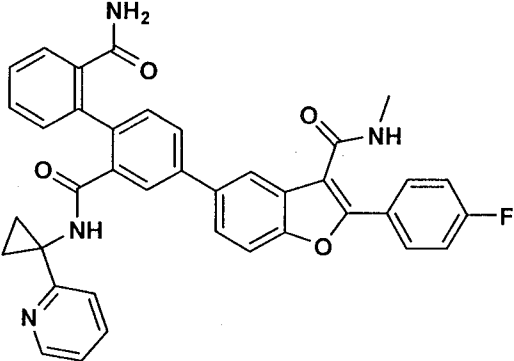
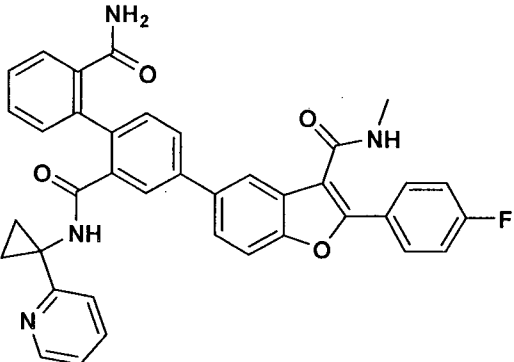
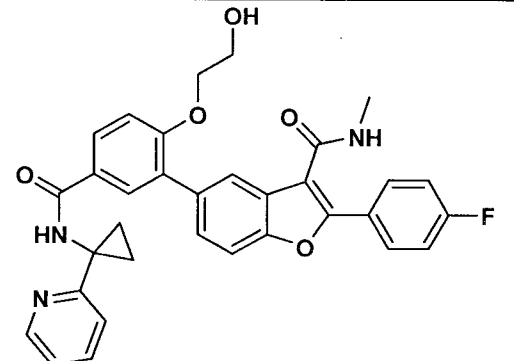
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	B	E
		A
		A

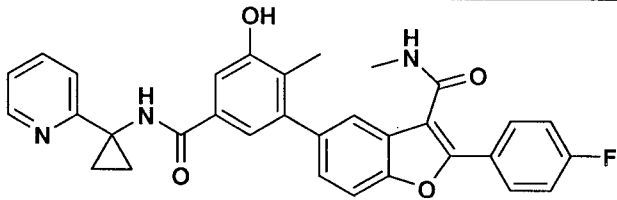
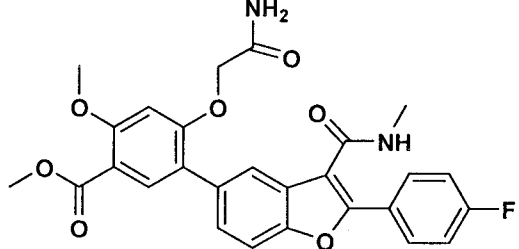
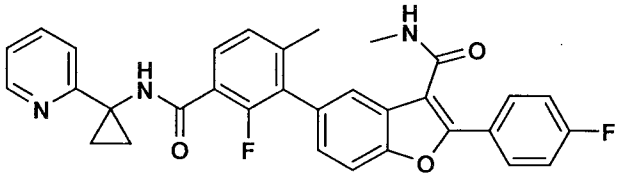
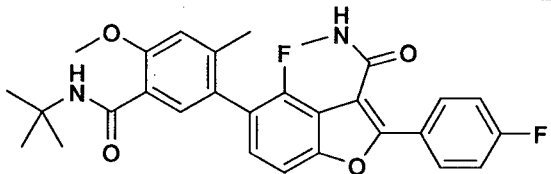
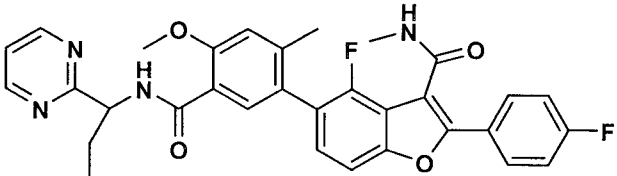
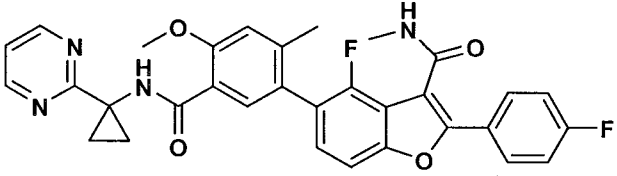
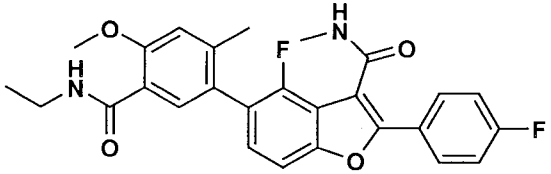
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
		A
	A	A
	A	A

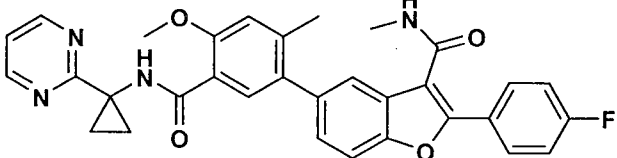
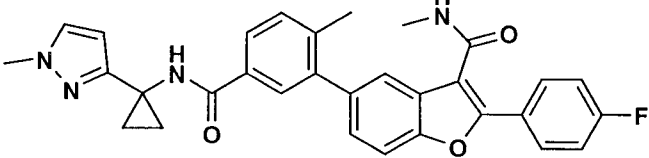
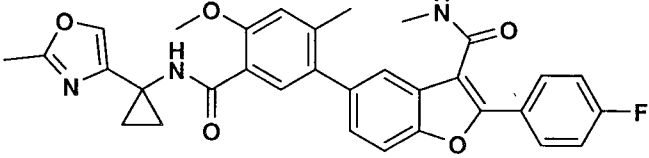
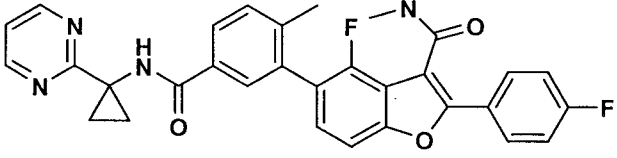
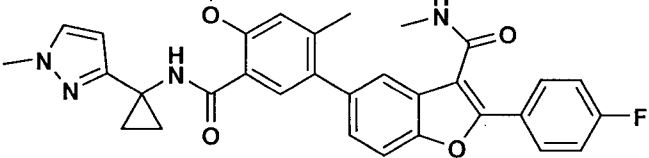
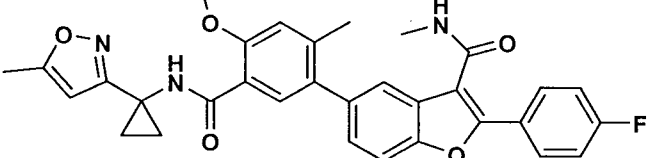
Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	A	A
	B	A
	A	B
		A

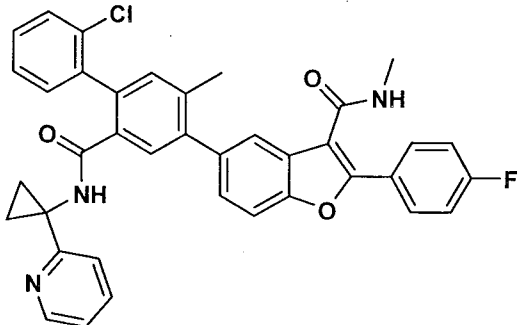
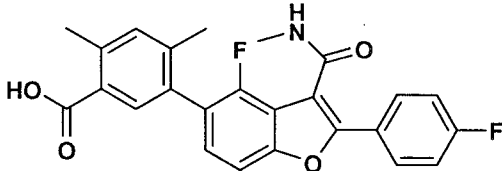
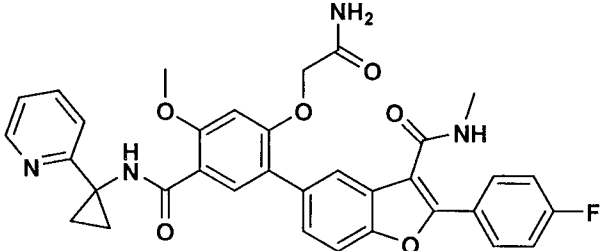
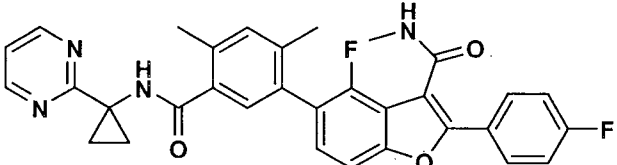
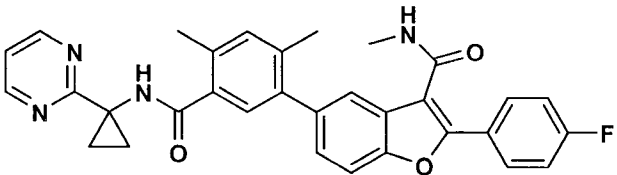
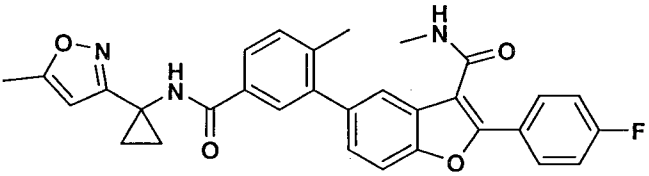
Estructura	Cl ₅₀	CE ₅₀
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	A	A
		A
	A	A
	A	A
		A

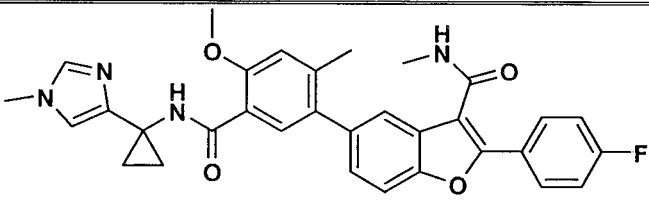
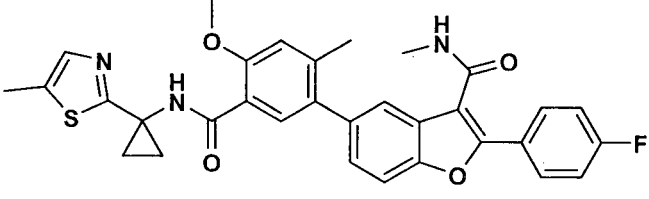
Estructura	Cl ₅₀	CE ₅₀
		A
		A
	A	A
	A	A
	N	A

Estructura	Cl ₅₀	CE ₅₀
	A	A
	A	A
	A	A
	A	A

Estructura	Cl ₅₀	CE ₅₀
	A	A
		C
	N	A
	A	A
	A	A
	A	A
		A

Estructura	Cl ₅₀	CE ₅₀
	A	A
	N	A
	A	A
	A	A
	A	A
	A	A

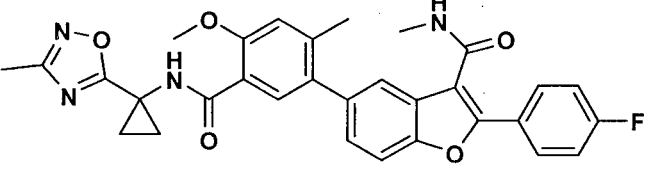
Estructura	Cl ₅₀	CE ₅₀
	A	A
	C	E
	N	A
	B	A
	A	A
		A

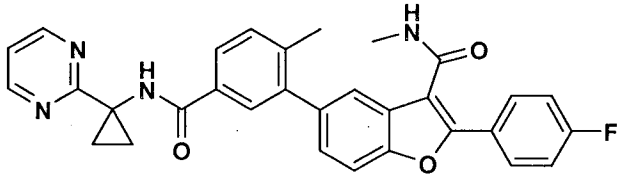
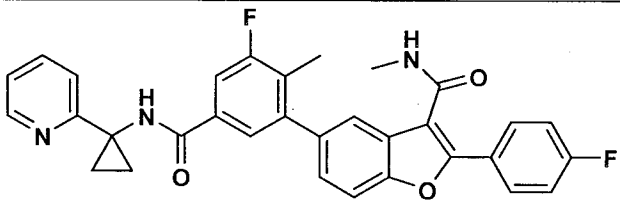
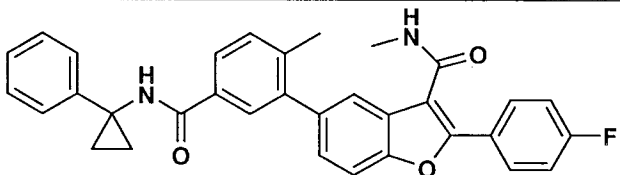
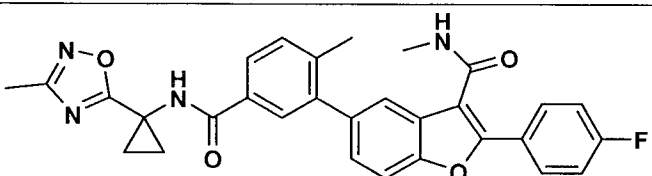
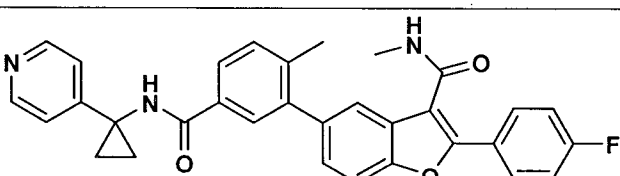
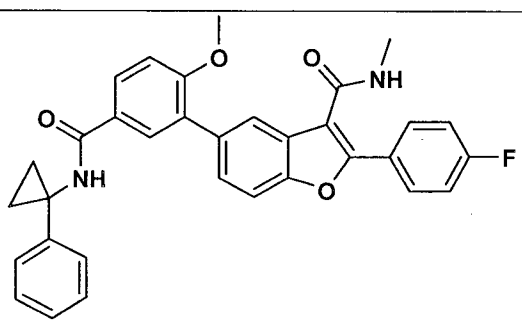
Estructura	Cl ₅₀	CE ₅₀
		A
		A

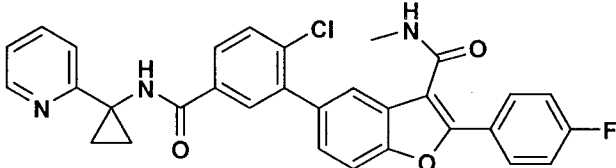
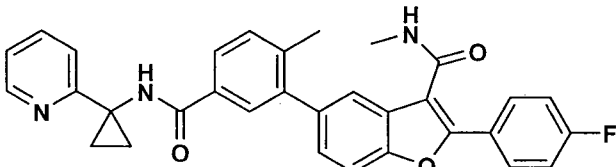
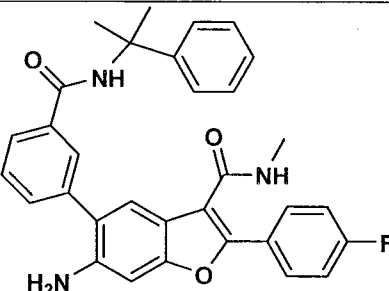
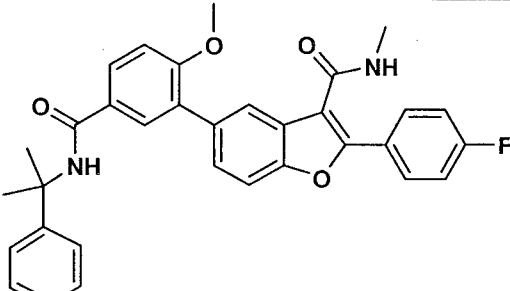
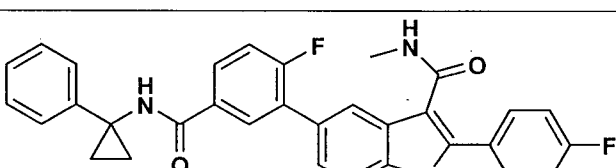
A 0,002 o menos hasta 0,25 µM; B >0,25 µM – <1,0 µM; C 1,0 µM – 10,0 µM; D >0,67 µM pero no se determinó un valor exacto; E >10,0 µM; F >0,4 µM; pero no se determinó un valor exacto; G > 1,39 µM pero no se determinó un valor exacto; H >0,62 µM pero no se determinó un valor exacto; I >4 µM pero no se determinó un valor exacto; J>3,7 µM pero no se determinó un valor exacto; K >1,23 µM pero no se determinó un valor exacto; L < 0,02 µM pero no se determinó un valor exacto; M >0,50 pero no se determinó un valor exacto. N <0,02 pero no se determinó un valor exacto.

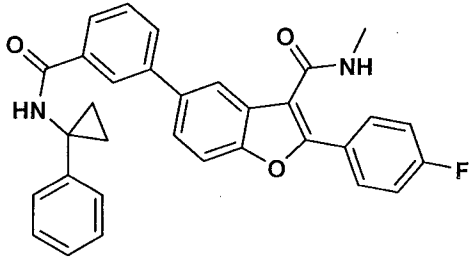
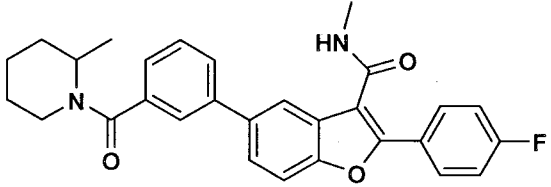
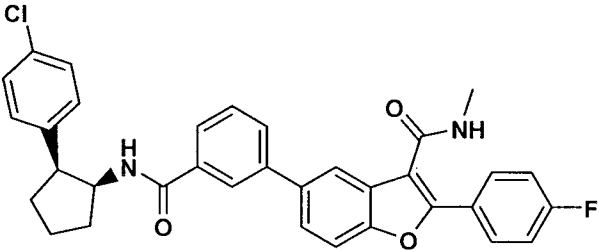
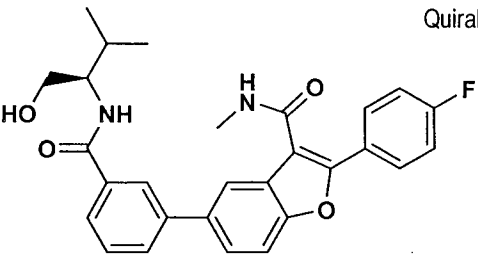
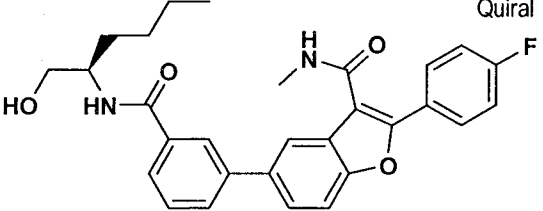
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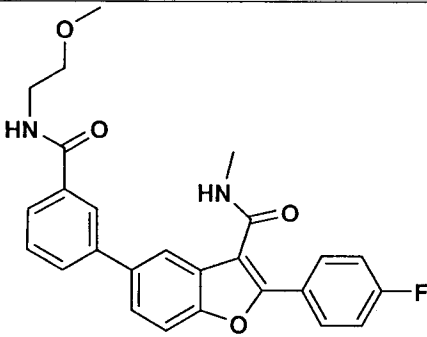
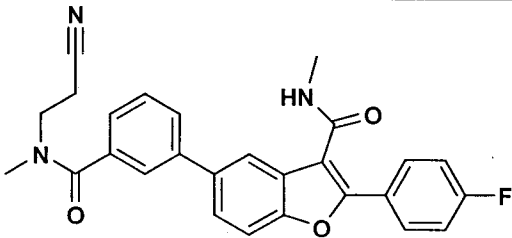
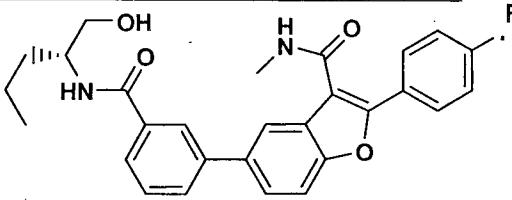
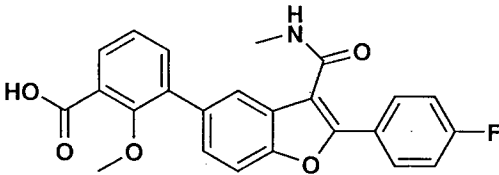
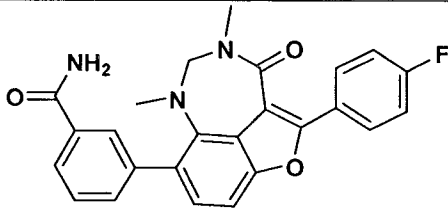
TABLA 1c

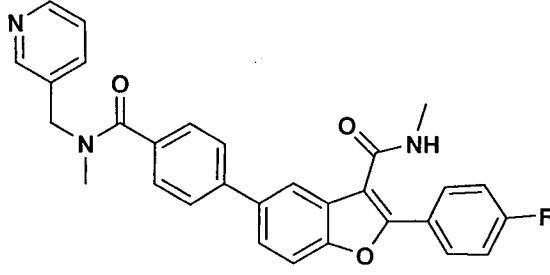
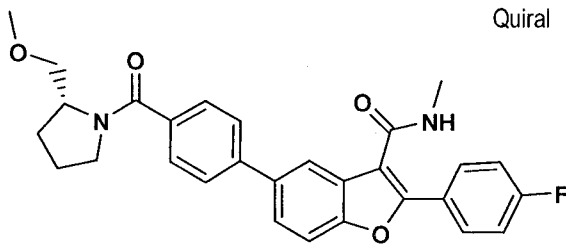
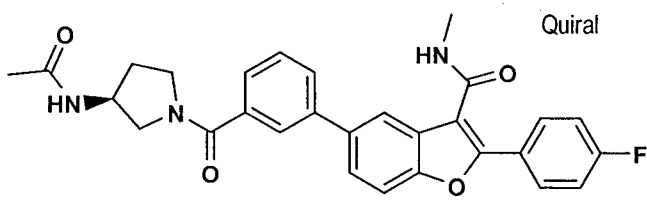
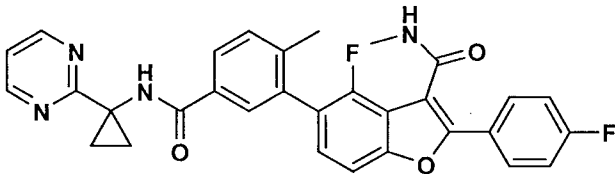
Estructura	CC ₅₀ (µM)	CE ₅₀ (µM)
	0,02	1,60E-03*

Estructura	CC ₅₀ (μM)	CE ₅₀ (μM)
	< 0,02	3,04E-04*
	0,01	4,25E-04*
	0,02	7,86E-04*
	7,20E-03	8,05E-04*
	3,95E-03	8,30E-04*
	9,95E-03	1,78E-03

Estructura	CC ₅₀ (μM)	CE ₅₀ (μM)
	0,01	1,83E-03
	8,60E-03	1,95E-03
	5,45E-03	2,47E-03
	9,65E-03	3,04E-03
	0,02	3,57E-03

Estructura	CC ₅₀ (μM)	CE ₅₀ (μM)
	5,90E-03	3,58E-03
	0,29	1,13
	> 12,50	1,13
 Quiral	0,80	1,25
 Quiral	0,60	1,26

Estructura	CC ₅₀ (μM)	CE ₅₀ (μM)
	1,71	1,34
	0,80	1,38
 Quiral	1,15	1,39
	4,75	13,26
	> 12,50	13,66

Estructura	CC ₅₀ (μM)	CE ₅₀ (μM)
	9,92	15,11
 Quiral	10,39	15,39
 Quiral	7,13	16,08
		5,68E-03*

* Las CE₅₀ se determinaron usando el procedimiento de placa de 384 pocillos

COMPOSICIONES FARMACÉUTICAS Y PROCEDIMIENTOS DE
TRATAMIENTO

5 Los compuestos demuestran actividad contra NS5B del VHC y pueden ser útiles para tratar VHC y la infección por VHC. Por tanto, otro aspecto de la invención es una composición que comprende un compuesto, o una de sus

sales farmacéuticamente aceptables, y un vehículo farmacéuticamente aceptable.

Otro aspecto de la invención es una composición que además comprende un compuesto que presenta actividad contra VHC.

5 Otro aspecto de la invención es una composición en la que el compuesto que tiene actividad contra VHC es un interferón. Otro aspecto de la invención es aquel en el que el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

10 Otro aspecto de la invención es una composición en la que el compuesto que tiene actividad contra VHC es una ciclosporina. Otro aspecto de la invención es aquel en el que la ciclosporina es ciclosporina A.

Otro aspecto de la invención es una composición en la que el compuesto que tiene actividad contra VHC se selecciona a partir del grupo constituido por
15 interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una respuesta de tipo 1 con linfocitos T cooperadores, ARN de interferencia, ARN no codificante, Imiqimod, ribavirina, un inhibidor de inosin 5'-monofosfato deshidrogenasa, amantadina, y rimantadina.

Otro aspecto de la invención es una composición en la que el compuesto
20 que tiene actividad contra VHC es eficaz para inhibir la función de una diana que se selecciona entre metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de

VHC, ensamblaje de VHC, salida de VHC, proteína NS5A de VHC, IMPDH, y un análogo nucleosídico para el tratamiento de una infección por VHC.

Otro aspecto de la invención es una composición que comprende un compuesto, o una de sus sales farmacéuticamente aceptables, un vehículo
5 farmacéuticamente aceptable, un interferón y ribavirina.

Otro aspecto de la invención es un procedimiento para inhibir la función del replicón de VHC que comprende poner en contacto el replicón de VHC con un compuesto de fórmula I o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un procedimiento para inhibir la función
10 de la proteína NS5B de VHC que comprende poner en contacto la proteína NS5B de VHC con un compuesto de fórmula I o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un procedimiento de tratar una infección por VHC en un paciente que comprende administrar al paciente una cantidad
15 terapéuticamente eficaz de un compuesto o una de sus sales farmacéuticamente aceptables. Otro aspecto de la invención es un procedimiento para inhibir la función del replicón del VHC. Otro aspecto de la invención es un procedimiento para inhibir la función de la proteína NS5B de VHC.

20 Otro aspecto de la invención es un procedimiento de tratar una infección por VHC en un paciente que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto o una de sus sales

farmacéuticamente aceptables, junto (antes, después, a la vez) con otro compuesto que tiene actividad contra VHC.

Otro aspecto de la invención es el procedimiento en el que el otro compuesto que tiene actividad contra VHC es un interferón.

5 Otro aspecto de la invención es el procedimiento en el que el interferón se selecciona entre interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

Otro aspecto de la invención es el procedimiento en el que el otro compuesto que tiene actividad contra VHC es una ciclosporina.

10 Otro aspecto de la invención es el procedimiento en el que la ciclosporina es ciclosporina A.

Otro aspecto de la invención es el procedimiento en el que el otro compuesto que tiene actividad contra VHC se selecciona entre interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una
15 respuesta de tipo 1 con linfocitos T cooperadores, ARN de interferencia, ARN no codificante, Imiqimod, ribavirina, un inhibidor de inosin 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

Otro aspecto de la invención es el procedimiento en el que el otro compuesto que tiene actividad contra VHC es eficaz para inhibir la función de
20 una diana que se selecciona del grupo constituido por metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamblaje de VHC, salida de VHC, proteína NS5A

de VHC, IMPDH, y un análogo nucleosídico para el tratamiento de una infección por VHC.

Otro aspecto de la invención es el procedimiento en el que el otro compuesto que tiene actividad contra VHC es eficaz para inhibir la función de la
5 diana en el ciclo vital de VHC que no sea la proteína NS5B de VHC.

“Terapéuticamente eficaz” quiere decir la cantidad de agente necesaria para proporcionar un beneficio significativo al paciente tal como lo entienden los expertos en el campo de la hepatitis y de la infección por VHC.

“Paciente” quiere decir una persona infectada por el virus VHC y
10 adecuado para ser tratado tal como lo entienden los expertos en el campo de la hepatitis y de la infección por VHC.

“Tratamiento,” “terapia,” “pauta,” “infección por VHC,” y los términos relacionados se usan tal como los entienden los expertos en el campo de la hepatitis y de la infección por VHC.

15 Los compuestos de esta invención generalmente se administran en forma de composiciones farmacéuticas compuestas por una cantidad terapéuticamente eficaz de un compuesto o su sal farmacéuticamente aceptable, y un vehículo farmacéuticamente aceptable y puede contener excipientes convencionales. Los vehículos farmacéuticamente aceptables son
20 aquellos vehículos conocidos convencionalmente que tienen perfiles de seguridad aceptables. Las composiciones engloban todas las formas sólidas y líquidas habituales que incluyen cápsulas, comprimidos, pastillas, y polvos así

como suspensiones, jarabes, elixires y soluciones líquidos. Las composiciones se preparan usando técnicas de formulación habituales y generalmente se usan excipientes convencionales (tales como aglutinantes y humectantes) y vehículos (tales como agua y alcoholes) para las composiciones. Véase, por ejemplo, *Remington's Pharmaceuticals Sciences*, 17^a edición, Mack Publishing Company, Easton, PA (1985).

Las composiciones sólidas habitualmente se formulan en monodosis y se prefieren las composiciones que proporcionan de aproximadamente 1 a aproximadamente 1000 mg del principio activo por dosis. Algunos ejemplos de dosis son 1 mg, 10 mg, 100 mg, 250 mg, 500 mg, y 1000 mg. Generalmente, habrá otros agentes presentes en un intervalo de unidades similar al de los agentes de esa clase que se usan en clínica. Habitualmente, éste es de 0,25-1000 mg/unidad.

Las composiciones líquidas habitualmente están en intervalos de unidades de dosis. Generalmente, la composición líquida estará en un intervalo de monodosis de 1-100 mg/ml. Algunos ejemplos de dosis son 1 mg/ml, 10 mg/ml, 25 mg/ml, 50 mg/ml, y 100 mg/ml. Generalmente, habrá otros agentes presentes en un intervalo de unidades similar al de los agentes de esa clase que se usan en clínica. Habitualmente, este es de 1-100 mg/ml.

La invención engloba todos los modos de administración convencionales; se prefieren los procedimientos orales y parenterales. Generalmente, la pauta será similar a otros agentes que se usan en clínica.

Habitualmente, la dosis diaria será 1-100 mg/kg peso corporal al día. Generalmente, es necesario más compuesto por vía oral y menos por vía parenteral. La posología específica, sin embargo, la determinará un médico usando el criterio médico fundado.

5 La invención también engloba procedimientos en los que el compuesto se administra en politerapia. Es decir, el compuesto puede usarse junto a otros agentes útiles en el tratamiento de la hepatitis y de la infección por VHC, pero de forma separada. En estos procedimientos de combinación, el compuesto generalmente se administrará en una dosis diaria de 1-100 mg/kg de peso
10 corporal al día junto con otros agentes. Los otros agentes generalmente se administrarán en las cantidades que se usan terapéuticamente. La posología específica, sin embargo, la determinará un médico usando el criterio médico fundado.

 En la Tabla 2 se enumeran algunos ejemplos de compuestos adecuados
15 para las composiciones y procedimientos.

TABLA 2.

Nombre comercial	Tipo de inhibidor o diana	Compañía suministradora
Omega IFN	IFN- ω	Intarcia Therapeutics
BILN-2061	Inhibidor de serina proteasas	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania

Nombre comercial	Tipo de inhibidor o diana	Compañía suministradora
Summetrel	Antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
Roferon A	IFN- α 2a	F. Hoffmann-La Roche Ltd., Basilea, Suiza
Pegasys	IFN- α 2a PEGilado	F. Hoffmann-La Roche Ltd., Basilea, Suiza
Pegasys y ribavirina	IFN- α 2a/ PEGilado/ribavirina	F. Hoffmann-La Roche Ltd., Basilea, Suiza
CELLCEPT®	Inmunosupresor IgG de VHC	F. Hoffmann-La Roche Ltd., Basilea, Suiza
Wellferon	IFN- α 1 linfoblastoide	GlaxoSmithKline plc, Uxbridge, Reino Unido
Albuferon - α	Albúmina IFN- α 2b	Human Genome Sciences Inc., Rockville, MD
Levovirina	Ribavirina	ICN Pharmaceuticals, Costa Mesa, CA
IDN-6556	Inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA
IP-501	Antifibrótico	Indevus Pharmaceuticals Inc., Lexington, MA
Actimmune	INF- γ	InterMune Inc., Brisbane, CA

Nombre comercial	Tipo de inhibidor o diana	Compañía suministradora
Infergen A	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
ISIS 14803	Hebra complementaria	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., Nueva York, NY
JTK-003	Inhibidor de RdRp	Japan Tobacco Inc., Tokio, Japón
Pegasys y Cepleno	IFN- α 2a/ PEGilado Inmunomodulador	Maxim Pharmaceuticals Inc., San Diego, CA
Ceplene	Inmunomodulador	Maxim Pharmaceuticals Inc., San Diego, CA
Civacir	Inmunosupresor IgG de VHC	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Intrón A y Zadaxin	IFN- α 2b/ α 1-timosina	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Levovirina	Inhibidor de IMPDH	Ribapharm Inc., Costa Mesa, CA
Viramidina	Profármaco de rivavirina	Ribapharm Inc., Costa Mesa, CA

Nombre comercial	Tipo de inhibidor o diana	Compañía suministradora
Heptazyme	Ribozima	Ribozyme Pharmaceuticals Inc., Boulder, CO
Intrón A	IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intrón	IFN- α 2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ
Rebetrón	IFN- α 2b/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Ribavirina	Ribavirina	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intrón / rivavirina	IFN- α 2b/ PEGilado/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Zadazim	Inmunomodulador	SciClone Pharmaceuticals Inc., San Mateo, CA
Rebif	IFN- β 1a	Serono, Ginebra, Suiza
IFN- β y EMZ701	IFN- β y EMZ701	Transition Therapeutics Inc., Ontario, Canadá
Batabulin (T67)	Inhibidor de β -tubulina	Tularik Inc., South San Francisco, CA

Nombre comercial	Tipo de inhibidor o diana	Compañía suministradora
Merimepodib (VX-497)	Inhibidor de IMPDH	Vertex Pharmaceuticals Inc., Cambridge, MA
Telaprevir (VX-950, LY-570310)	Inhibidor de la serina proteasasa NS3	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly y Co. Inc., Indianapolis, IN
Omniferon	IFN α - natural	Viragen Inc., Plantation, FL
XTL-6865 (XTL-002)	Anticuerpo monoclonal	XTL Biopharmaceuticals Ltd., Rehovot, Israel
HCV-796	Inhibidor de la replicasa NS5B	Wyeth / Viropharma
NM-283	Inhibidor de la replicasa NS5B	Idenix / Novartis
GL-59728	Inhibidor de la replicasa NS5B	Gene Labs / Novartis
GL-60667	Inhibidor de la replicasa NS5B	Gene Labs / Novartis
2'C MeA	Inhibidor de la replicasa NS5B	Gilead
PSI 6130	Inhibidor de la replicasa NS5B	Roche
R1626	Inhibidor de la replicasa NS5B	Roche

Nombre comercial	Tipo de inhibidor o diana	Compañía suministradora
SCH 503034	Inhibidor de serina proteasas	Schering Plough
NIM811	Inhibidor de ciclofilina	Novartis
Suvus	Azul de metileno	Bioenvision
Multiferon	IFN de duración prolongada	Viragen/Valentis
Actilon (CPG10101)	Agonista de TLR9	Coley
Interferón-β	Interferón-β-1a	Serono
Zadaxin	Inmunomodulador	Sciclone
Compuestos y sales de pirazolopirimidina A partir del documento WO-2005/047288	Inhibidores de VHC	Arrow Therapeutics Ltd.
2'C Metil adenosina	Inhibidor de la replicasa NS5B	Merck
GS-9132 (ACH-806)	Inhibidor de VHC	Achillion / Gilead

DESCRIPCIÓN DE REALIZACIONES ESPECÍFICAS

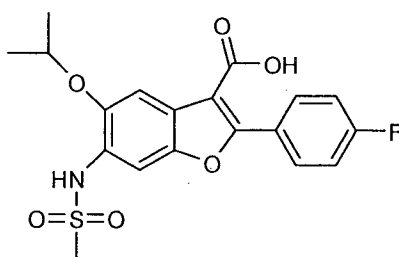
Las abreviaturas como se usan en la presente memoria descriptiva, se defienen como sigue: "1 x" para una vez, "2 x" para dos veces, "3 x" para tres veces, "°C" para grados Celsius, "eq" para equivalente o equivalentes, "g" para gramo o gramos, "mg" para miligramo o miligramos, "l" para litro o litros, "ml" para mililitro o mililitros, "μl" para microlitro o microlitros, "N" para normal, "M" para molar, "mmol" para milimol o milimoles, "min" para minuto o minutos, "h"

para hora u horas, "ta" para temperatura ambiente, "TR" para tiempo de retención, "atm" para atmósfera, "psi" para libras por pulgada cuadrada, "conc." para concentrado, "sat" o "sat'd" para saturado, "PM" para peso molecular, "mp" para punto de fusión, "ee" para exceso enantiomérico, "EM" o "Esp Masas

5 Spec" para espectrometría de masas, "ESI" para espectroscopía de masas de ionización por electropulverización, "HR" para alta resolución, "HREM" para espectrometría de masas de alta resolución, "LCEM" para espectrometría de masas con cromatografía líquida, "HPLC" para cromatografía líquida de alta presión, "HPLC FI" para HPLC de fase inversa, "TLC" o "tlc" para cromatografía

10 en capa fina, "RMN" para espectroscopía de resonancia magnética nuclear, "¹H" para protón, "δ" para delta, "s" para singlete, "d" para doblete, "t" para triplete, "c" para cuartete, "m" para multiplete, "a" para ancho, "Hz" para hertzio, y "α", "β", "R", "S", "E", y "Z" son designaciones estereoquímicas familiares para alguien experto en la técnica.

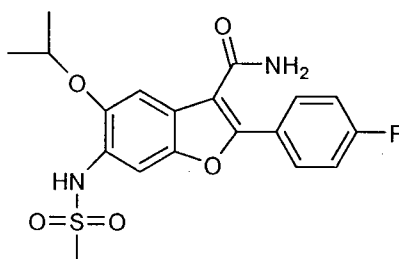
15



Ácido 2-(4-fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carboxílico

Se añadió NaOH en exceso (10 ml, 1N ac) a una solución agitada de 2-

(4-fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carboxilato de metilo (3,0 g, 6,89 mmol) en EtOH (34 ml) y THF (34 ml). Se dejó agitando a 60°C durante la noche. La mezcla se calentó entonces hasta 67°C y se dejó agitando durante 4 horas más. La mezcla se concentró y luego se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el compuesto del epígrafe (2,7 g, 96%). RMN de ¹H (300 MHz, DMSO-d₆) δ ppm 1,31 - 1,38 (m, 6 H) 2,99 (s, 3 H) 4,63 - 4,73 (m, 1 H) 7,32 - 7,41 (m, 2 H) 8,00 - 8,08 (m, 2 H) 8,88 (s, 2 H) 13,05 (s, 1 H). Tiempo de retención de LC-EM: 1,03 min; m/z (MH⁻): 406. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

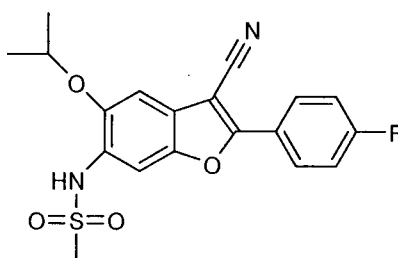


2-(4-Fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carboxamida

Se añadió amoníaco (6,1 ml, 12,2 mmol, 2M en MeOH) a una solución agitada de HATU (1,1 g, 2,95 mmol) y ácido 2-(4-fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carboxílico (1,0 g, 2,46 mmol) en DMF (20 ml) a 0°C. Se dejó agitando para calentar hasta temperatura ambiente y se agitó durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el compuesto del epígrafe (925 mg, 93%). RMN de ¹H (300 MHz, DMSO-d₆) δ ppm 1,30 - 1,37 (m, 6 H) 2,98 (s, 3 H) 4,64 - 4,77 (m, 1 H) 7,19 (s, 1 H) 7,30 - 7,41 (m, 2 H) 7,54 (s, 1 H) 7,63 - 7,71 (m, 1 H) 7,89 (s, 1 H) 7,93 - 8,02 (m, 2 H) 8,85 (s, 1 H). Tiempo de retención de LC-EM: 1,26 min; m/z (MH⁺) 407. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el

disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

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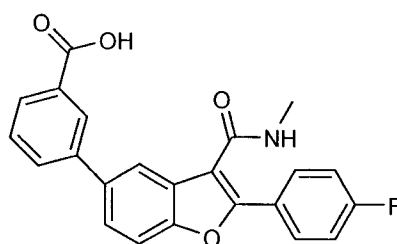


N-(3-Ciano-2-(4-fluorofenil)-5-isopropoxibenzofuran-6-il)metanosulfonamida

Se añadió anhídrido trifluoracético (375 µl, 2,66 mmol) a una solución agitada de DIEA (928 µl, 5,31 mmol), 2-(4-fluorofenil)-5-isopropoxi-6 (metilsulfonamido) benzofuran-3-carboxamida (300 mg, 0,738 mmol) en CH₂Cl₂ 10 (4 ml) y THF (4 ml) a 0 °C durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró. El residuo bruto se purificó sobre gel de sílice (BIOTAGE®, gradiente EtOAc/hexanos, recogida de la fracción a λ = 254 nm) 15 dando el compuesto del epígrafe (143 mg, 50%). RMN de ¹H (300 MHz, DMSO-d₆) δ ppm 1,28 - 1,41 (m, 6 H) 3,01 (s, 3 H) 4,77 - 4,95 (m, 1 H) 7,35 (s, 1 H) 7,44 - 7,57 (m, 2 H) 7,68 (s, 1 H) 8,04 - 8,20 (m, 2 H) 9,01 (s, 1 H). Tiempo de retención de LC-EM: 1,65 min; m/z (MH⁺): 387. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con

una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

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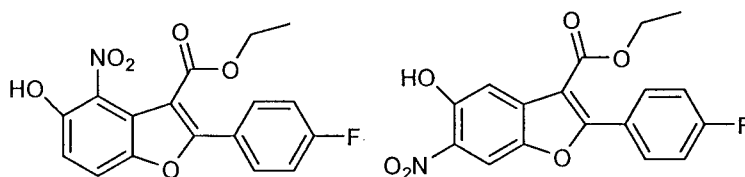


Ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

Se añadió carbonato de cesio (3,5 g, 10,7 mmol) a Pd(Ph₃P)₄ (108 mg, 0,093 mmol), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (3,0 g, 7,19 mmol), ácido 3-boronobenzoico (1,97 g, 11,86 mmol). Se añadieron dioxano (60 ml) y agua (12 ml) a temperatura ambiente. La reacción se desgasificó 3x y luego se calentó hasta 95 °C y se dejó agitando durante la noche. Se dejó enfriar hasta temperatura ambiente. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. El

15

precipitado formado se filtró y se secó durante la noche a 55 °C a vacío. La fase orgánica restante se concentró y se trituró con DCM, seguido por DCE caliente y finalmente MeOH caliente proporcionando el compuesto del epígrafe que se combinó con el precipitado previamente recogido (2,4 g, 87%). Tiempo de retención de LC-EM: 1,19 min; m/z (MH⁺): 390. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



2-(4-Fluorofenil)-5-hidroxi-4-nitrobenzofuran-3-carboxilato de etilo y

2-(4-Fluorofenil)-5-hidroxi-6-nitrobenzofuran-3-carboxilato de etilo

Se añadió ácido nítrico (21 µl, 0,33 mmol) a una solución agitada de 2-

(4-fluorofenil)-5-hidroxibenzofuran-3-carboxilato de etilo (100 mg, 0,33 mmol) en cloroformo (3,3 ml) a -20°C. Se dejó agitando durante 10 min. Se observó una relación 9:2 de 2-(4-fluorofenil)-5-hidroxi-4-nitrobenzofuran-3-carboxilato de etilo a 2-(4-fluorofenil)-5-hidroxi-6-nitrobenzofuran-3-carboxilato de etilo. La
5 reacción bruta se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a $\lambda = 254$ nm) dando el compuesto de los epígrafes:

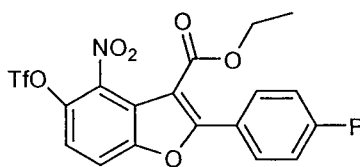
2-(4-Fluorofenil)-5-hidroxi-6-nitrobenzofuran-3-carboxilato de etilo

10 RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 10,92 (1 H, s), 8,33 (1 H, s), 8,03 - 8,11 (2 H, m), 7,69 (1 H, s), 7,43 (2 H, t, $J=8,85$ Hz), 4,34 (2 H, c, $J=7,22$ Hz), 1,33 (3 H, t, $J=7,17$ Hz). Tiempo de retención de LC-EM: 1,79 min; m/z (MH-): 344. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de
15 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el
20 disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC

en modo electropulverización.

2-(4-Fluorofenil)-5-hidroxi-4-nitrobenzofuran-3-carboxilato de etilo

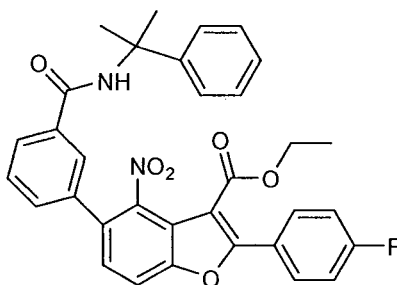
RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 11,03 (1 H, s), 7,92 - 8,01 (2 H, m), 7,86 (1 H, d, $J=9,16$ Hz), 7,42 (2 H, t, $J=8,85$ Hz), 7,17 (1 H, d, $J=8,85$ Hz), 4,20 (2 H, c, $J=7,12$ Hz), 1,21 (3 H, t, $J=7,17$ Hz). Tiempo de retención de LC-EM: 1,56 min; m/z (MH $^-$): 344. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



20 2-(4-Fluorofenil)-4-nitro-5-(trifluorometilsulfoniloxi)benzofuran-3-carboxilato de

etilo

Se añadió trietilamina (91 μ l, 0,652 mmol) a una solución agitada de 1,1,1-trifluoro-N-fenil-N-(trifluorometilsulfonil)metanosulfonamida (116 mg, 0,326 mmol) y 2-(4-fluorofenil)-5-hidroxi-4-nitrobenzofuran-3-carboxilato de etilo (75 mg, 0,217 mmol) en DCM (2,2 ml). La reacción bruta se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a λ = 254 nm) dando el compuesto del epígrafe (78 mg, 75%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 11,03 (1 H, s), 7,92 - 8,01 (2 H, m), 7,86 (1 H, d, $J=9,16$ Hz), 7,42 (2 H, t, $J=8,85$ Hz), 7,17 (1 H, d, $J=8,85$ Hz), 4,20 (2 H, c, $J=7,12$ Hz), 1,21 (3 H, t, $J=7,17$ Hz). Tiempo de retención de LC-EM: 1,91 min; m/z (MH $^+$): no se detectaron iones. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



2-(4-Fluorofenil)-4-nitro-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil) benzofuran-3-carboxilato de etilo

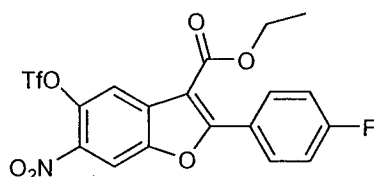
Etapa 1: Se añadió carbonato de cesio (333 mg, 1,021 mmol) a
5 Pd(Ph₃P)₄ (39 mg, 0,034 mmol), 2-(4-fluorofenil)-4-nitro-5-(trifluorometilsulfoniloxi)benzofuran-3-carboxilato de etilo (325 mg, 0,681 mmol), ácido 3-boronobenzoico (169 mg, 1,021 mmol). Se añadieron dioxano (5,6 ml) y agua (1,1 ml) a temperatura ambiente. La reacción se desgasificó 3x y se calentó hasta 90 °C durante la noche. Se dejó enfriar. La mezcla se diluyó con
10 EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el *m*-ácido.

Etapa 2: El *m*-ácido bruto se diluyó con DMF (5 ml) y se trató con HATU (388 mg, 1,021 mmol), 2-fenilpropan-2-amina (138 mg, 1,021 mmol) y DIEA (357 µl, 2,043 mmol) y se dejó agitando a temperatura ambiente durante 1
15 hora. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el compuesto del epígrafe que se purificó sobre gel de sílice (columna BIOTAGE® 25+M, gradiente de EtOH/hexanos; R_f ~0,2 para EtOH al 20% /hexanos; recogida de la fracción a λ = 254 nm) dando un sólido amarillo claro (294 mg,

76%). Tiempo de retención de LC-EM: 1,97 min; m/z (MH⁺): 567. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las

5 condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% /

10 acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

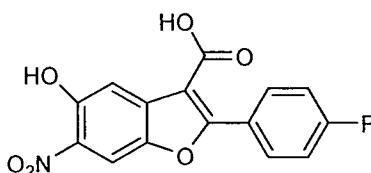


2-(4-Fluorofenil)-6-nitro-5-(trifluorometilsulfonilo)benzofuran-3-carboxilato de etilo

15 Se añadió trietilamina (121 µl, 0,869 mmol) a una solución agitada de 1,1,1-trifluoro-N-fenil-N-(trifluorometilsulfonil)metanosulfonamida (155 mg, 0,434 mmol) y 2-(4-fluorofenil)-5-hidroxi-6-nitrobenzofuran-3-carboxilato de etilo (100 mg, 0,290 mmol) en DCM (3 ml). Se dejó agitando durante la noche. La mezcla se concentró y se purificó sobre gel de sílice (BIOTAGE®, gradiente de

20 EtOH/hexanos, recogida de la fracción a $\lambda = 254$ nm) dando el compuesto del

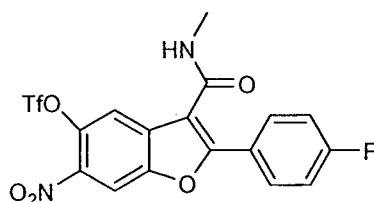
epígrafe (140 mg, 100%). RMN de ^1H (300 MHz, $\text{DMSO}-d_6$) δ ppm 8,91 (1 H, s), 8,10 - 8,19 (3 H, m), 7,48 (2 H, t, $J=8,97$ Hz), 4,37 (2 H, c, $J=7,07$ Hz), 1,34 (3 H, t, $J=6,95$ Hz). Tiempo de retención de LC-EM: 1,91 min; m/z (MH^+): no se detectaron iones. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



Ácido 2-(4-fluorofenil)-5-hidroxi-6-nitrobenzofuran-3-carboxílico

Se añadió NaOH en exceso (11 ml, 11,00 mmol, 1M ac) a una solución agitada de 2-(4-fluorofenil)-5-hidroxi-6-nitrobenzofuran-3-carboxilato de etilo (1,9 g, 5,50 mmol) en EtOH (55 ml) y THF (55 ml) y se dejó agitando a 64 °C durante la noche. La mezcla se concentró y se diluyó con EtOAc y se lavó con

HCl 1M y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró dando el compuesto del epígrafe (1,7 g, cuantitativo). RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 7,31 - 7,48 (m, 2 H) 7,71 (s, 1 H) 8,00 - 8,14 (m, 2 H) 8,29 (s, 1 H) 10,80 (s, 1 H) 13,35 (s, 1 H). Tiempo de retención de LC-EM: 0,99 min; m/z (MH⁻): 416. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



Trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)-6-nitrobenzofuran-5-ilo.

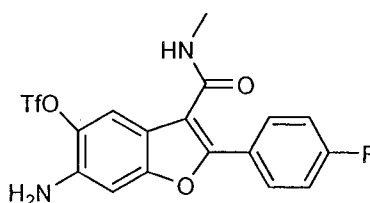
Etapa 1: Se añadió metanamina (4,4 ml, 8,83 mmol) a una solución agitada de DIEA (3 ml, 17,65 mmol), BOP (2,9 g, 6,62 mmol) y ácido 2-(4-

fluorofenil)-5-hidroxi-6-nitrobenzofuran-3-carboxílico (1,4 g, 4,41 mmol) en DMF (44 ml) a 0°C. Se dejó agitando para calentar hasta temperatura ambiente y se agitó durante 1 hora. La mezcla se concentró y se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando un producto bruto que se trituró con MeOH dando la metilamida, aducto de nitro fenol-hmpa (1,7 g, 78%).

Etapa 2: El aducto de hmpa (100 mg, 0,203 mmol) se recogió en EtOH y se trató con NaOH 1M (609 µl, 0,609 mmol) a 70 °C. Se dejó agitando durante la noche. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el nitro fenol (50 mg, 75%) como un sólido marrón. Tiempo de retención de LC-EM: 1,34 min; m/z (MH⁺): 331. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

Etapa 3: Se añadió trietilamina (422 μ l, 3,03 mmol) a una solución agitada de N-fenilbis(trifluorometano)sulfonimida (649 mg, 1,817 mmol) y 2-(4-fluorofenil)-5-hidroxi-N-metil-6-nitrobenzofuran-3-carboxamida (400 mg, 1,211 mmol) en DCM (24 ml) a temperatura ambiente. La suspensión se dejó
5 agitando durante la noche. La mezcla se diluyó con EtOAc y se lavó con NaHCO_3 sat y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró dando un residuo bruto que se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, $R_f \sim 0,2$ en EtOAc al 30%/hexanos, recogida de la fracción a $\lambda = 254$ nm) dando el compuesto del epígrafe (375
10 mg, 67%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 8,83 (1 H, s), 8,55 - 8,65 (1 H, m), 7,98 - 8,05 (2 H, m), 7,95 (1 H, s), 7,47 (2 H, t, $J=8,85$ Hz), 2,84 (3 H, d, $J=4,58$ Hz). Tiempo de retención de LC-EM: 1,96 min; m/z (MH $^-$): 461. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm
15 usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A
20 era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo

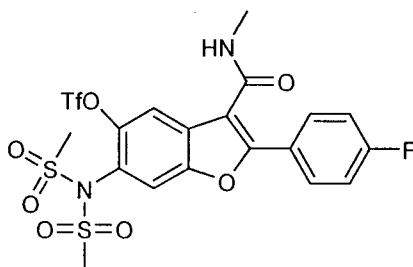
electropulverización.



Trifluorometanosulfonato de 6-amino-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo

- 5 Se añadió hierro (211 mg, 3,79 mmol) a una solución agitada de trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)-6-nitrobenzofuran-5-ilo (350 mg, 0,757 mmol) en EtOH (8,4 ml) y AcOH (8,4 ml) a temperatura ambiente y luego se calentó hasta 100 °C durante 10 min. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat seguido por
- 10 NaOH 1M y salmuera. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando un sólido blanco que era material de partida: producto 1:1. Este se volvió a someter a las condiciones de reacción durante 15 minutos y se volvió a tratar dando el compuesto del epígrafe (275 mg, 84%). Tiempo de retención de LC-EM: 1,47 min; m/z (MH⁺): 433. Los datos de LC se registraron
- 15 en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo
- 20 de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de

análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

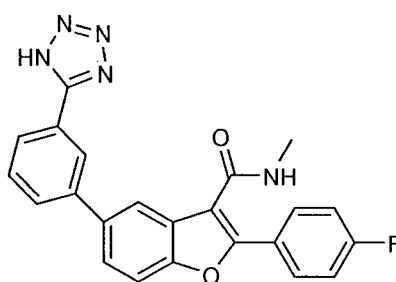


5

Trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)-6-(N-(metilsulfonyl)metilsulfonamido)benzofuran-5-ilo

Se añadió cloruro de metanosulfonilo (146 µl, 1,873 mmol) a una solución agitada de trifluorometanosulfonato de 6-amino-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (270 mg, 0,624 mmol) y DIEA (500 µl, 2,86 mmol) en DCM (6,3 ml) a 25 °C. Se dejó agitando durante 1 hora y luego se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró. Se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a λ = 254 nm) dando el compuesto del epígrafe (300 mg, 82%). Tiempo de retención de LC-EM: 1,49 min; m/z (MH⁺): 589. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución

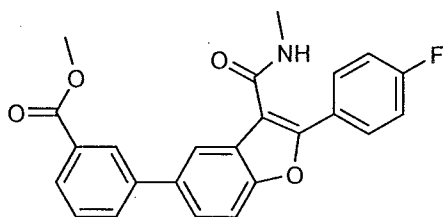
emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



10 5-(3-(1H-Tetrazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió azidotrimetilsilano (161 µl, 1,215 mmol) a una solución agitada de 5-(3-cianofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (225 mg, 0,607 mmol) y dibutilestananona (30 mg, 0,121 mmol) en tolueno (6 ml) a temperatura ambiente. Se calentó hasta 105 °C y se dejó agitando durante la noche. La reacción, que quedó como una suspensión, dio lugar a una conversión de ~70%. Se añadieron más equivalentes de reaccionantes y disolventes y se dejó agitando la mezcla durante la noche a 105 °C. La reacción se dejó enfriar y se filtró dando el compuesto del epígrafe (205 mg, 82%). Tiempo de retención de LC-EM: 1,03 min; m/z (MH⁺): 414. Los datos de

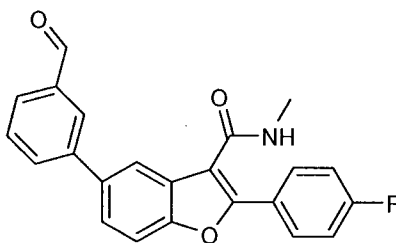
LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



3-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoato de metilo

Se añadió trimetilsilildiazometano (500 µl, 1,00 mmol, 2M en éter dietílico) a una solución agitada de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (100 mg, 0,257 mmol) en éter dietílico (2,5 ml) a 25 °C. Se dejó agitando durante 2 horas. La mezcla se concentró proporcionando el compuesto del epígrafe (100 mg, 97%). Tiempo de retención de LC-EM: 2,46 min; m/z (MH⁺): 404. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna

Waters SunFire 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min donde el disolvente A era acetonitrilo al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



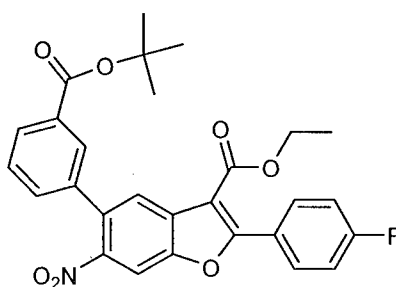
2-(4-Fluorofenil)-5-(3-formilfenil)-N-metilbenzofuran-3-carboxamida

Se añadió carbonato de cesio (176 mg, 0,539 mmol) a Pd(Ph₃P)₄ (20 mg, 0,018 mmol), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (150 mg, 0,359 mmol), ácido 3-formilfenilborónico (59 mg, 0,395 mmol). Se añadió dioxano (3 ml) y agua (600 µl) a temperatura ambiente. La reacción se calentó hasta 90°C durante la noche. La mezcla se diluyó con acetato de etilo y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se trituroó con DCM dando el compuesto del epígrafe (55 mg, 41%). Tiempo de

retención de LC-EM: 1,49 min; m/z (MH⁺): 374. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución

5 emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% /

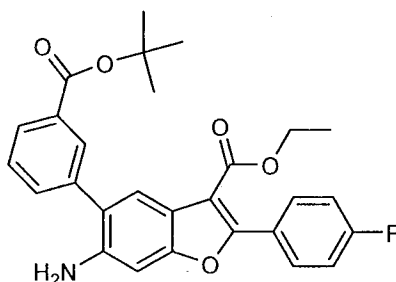
10 acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



5-(3-(terc-Butoxicarbonil)fenil)-2-(4-fluorofenil)-6-nitrobenzofuran-3-carboxilato
de etilo

15 Se añadió carbonato de cesio (1,54 g, 4,71 mmol) a Pd(Ph₃P)₄ (182 mg, 0,157 mmol), 2-(4-fluorofenil)-6-nitro-5-(trifluorometilsulfonilo)benzofuran-3-carboxilato de etilo (1500 mg, 3,14 mmol), ácido 3-(terc-butoxicarbonil)fenilborónico (768 mg, 3,46 mmol). Se añadieron dioxano (26 ml) y agua (5 ml) a temperatura ambiente. La reacción se calentó hasta 90°C

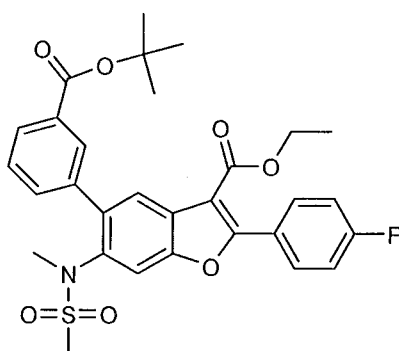
durante la noche. La reacción se dejó enfriar, se diluyó con EtOAc y se lavó con NaHCO_3 sat y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró y se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a $\lambda = 254$ nm) dando el compuesto del epígrafe (1,10 g, 69%). RMN de ^1H (300 MHz, $\text{DMSO}-d_6$) δ ppm 8,60 (1 H, s), 8,08 - 8,18 (2 H, m), 8,02 (1 H, s), 7,95 - 8,01 (1 H, m), 7,88 (1 H, s), 7,58 - 7,70 (2 H, m), 7,46 (2 H, t, $J=8,78$ Hz), 4,34 (2 H, c, $J=7,20$ Hz), 1,56 (9 H, s), 1,27 (3 H, t, $J=7,14$ Hz). Tiempo de retención de LC-EM: 2,13 min; m/z (MH^+): el principal no se ioniza. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



6-Amino-5-(3-(*tert*-butoxicarbonil)fenil)-2-(4-fluorofenil)benzofuran-3-carboxilato
de etilo

Se añadió hierro (28 mg, 0,495 mmol) a una solución agitada de 5-(3-
5 (*tert*-butoxicarbonil)fenil)-2-(4-fluorofenil)-6-nitrobenzofuran-3-carboxilato de
etilo (50 mg, 0,099 mmol) en EtOH (495 μ l) y AcOH (495 μ l) a 100 °C. Se dejó
agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con HCl 1M
y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró
dando el compuesto del epígrafe (45 mg, 96%). RMN de ¹H (400 MHz, DMSO-
10 d₆) δ ppm 7,99 - 8,06 (2 H, m), 7,89 - 7,96 (2 H, m), 7,65 - 7,72 (1 H, m), 7,61 (1
H, t, *J*=7,65 Hz), 7,55 (1 H, s), 7,31 - 7,40 (2 H, m), 7,00 (1 H, s), 5,10 (2 H, s
ancho), 4,29 (2 H, c, *J*=7,03 Hz), 1,56 (9 H, s), 1,26 (3 H, t, *J*=7,15 Hz). Tiempo
de retención de LC-EM: 2,03 min; *m/z* (MH⁺): el principal no se ioniza. Se
observó 420 (-tBu). Los datos de LC se registraron en un cromatógrafo de
15 líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u
C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de
onda de detección de 220nm. Las condiciones de elución emplearon un caudal
de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta
disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un

tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



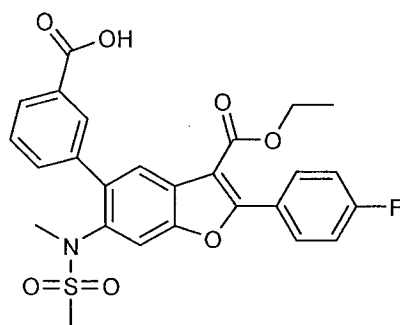
5-(3-(*tert*-Butoxicarbonil)fenil)-2-(4-fluorofenil)-6-(N-metilmetsulfonamido)benzofuran-3-carboxilato de etilo

Etapa 1: Se añadió cloruro de metanosulfonilo (16 µl, 0,208 mmol) a una solución agitada de 6-amino-5-(3-(*tert*-butoxicarbonil)fenil)-2-(4-fluorofenil)benzofuran-3-carboxilato de etilo (90 mg, 0,189 mmol) en piridina (2 ml) a temperatura ambiente. Se dejó agitando durante 6 horas, luego se añadieron 8 µl de MsCl y se dejó agitando la reacción durante la noche. La reacción se concentró y se diluyó con acetato de etilo y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando NH sulfonamida intermedia. Tiempo de retención de LC-EM: 1,93 min; m/z (MH⁻): 552. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de

4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

10 Etapa 2: El residuo bruto se diluyó con DMF (2ml) y se trató con DIEA (99 µl, 0,568 mmol) y Yodometano (18 µl, 0,284 mmol) seguido por Na₂CO₃ (20 mg). La reacción se dejó agitando durante 3 días. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el compuesto del epígrafe (100 mg, 15 93%). Tiempo de retención de LC-EM: 1,96 min; m/z (MH⁺): el principal no se ioniza. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el

disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

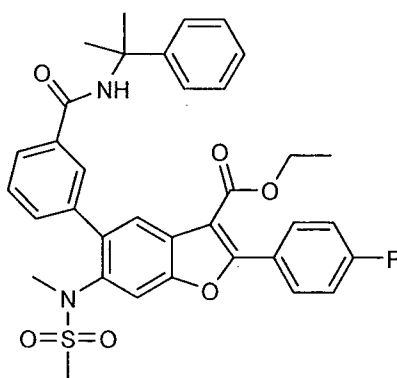


5

Ácido 3-(3-(etoxicarbonil)-2-(4-fluorofenil)-6-(N-metilmetsulfonamido)benzofuran-5-il)benzoico

Se añadió TFA (2 ml, 26,0 mmol) a una solución agitada de 5-(3-(*terc*-butoxicarbonil)fenil)-2-(4-fluorofenil)-6-(N-metilmetsulfonamido)benzofuran-3-carboxilato de etilo (100 mg, 0,176 mmol) en DCE (9 ml) a 25°C. Se dejó agitando durante varias horas y luego se concentró dando el compuesto del epígrafe (92 mg, cuant). RMN de ¹H (400 MHz, DMSO-*d*₆) δ ppm 8,05 - 8,12 (3 H, m), 7,92 - 8,03 (3 H, m), 7,65 - 7,75 (1 H, m), 7,53 - 7,64 (1 H, m), 7,44 (2 H, t, *J*=8,91 Hz), 4,33 (2 H, c, *J*=7,03 Hz), 3,12 (3 H, s), 2,93 (3 H, s), 1,26 (3 H, t, *J*=7,15 Hz). Tiempo de retención de LC-EM: 1,17 min; *m/z* (MH⁺): 510. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las

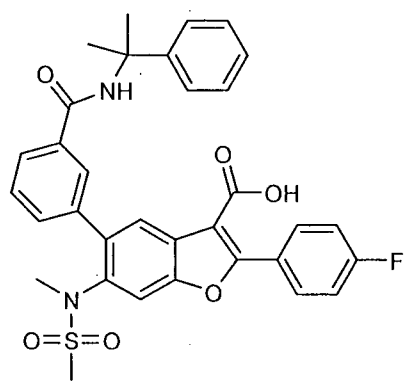
condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



10 2-(4-Fluorofenil)-6-(N-metilmetsulfonamido)-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxilato de etilo

Se añadió DIEA (51 µl, 0,293 mmol) a una solución agitada de ácido 3-(3-(etoxicarbonil)-2-(4-fluorofenil)-6-(N-metilmetsulfonamido)benzofuran-5-il)benzoico (50 mg, 0,098 mmol), 2-fenilpropan-2-amina (26 mg, 0,195 mmol),
15 HATU (56 mg, 0,147 mmol) en DMF (1 ml) a 25 °C. Se dejó agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el compuesto

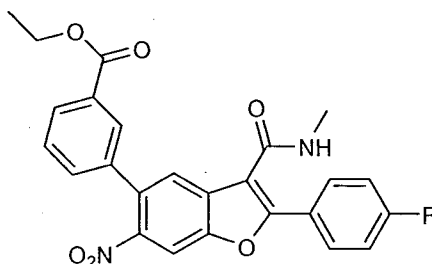
del epígrafe (50 mg, 81%). Tiempo de retención de LC-EM: 1,82 min; m/z (MH+): 629. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



15 Ácido 2-(4-fluorofenil)-6-(N-metilmetilulfonamido)-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxílico

Se añadió NaOH (500 µl, 0,500 mmol, 1M ac.) a una solución agitada de

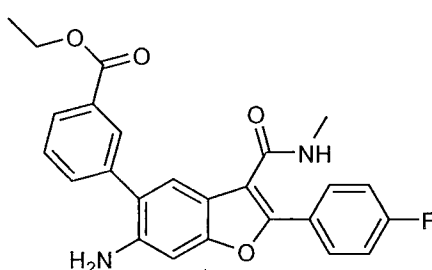
2-(4-fluorofenil)-6-(N-metilmetsulfonamido)-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxilato de etilo (50 mg, 0,080 mmol) en etanol (795 μ l) a 60 °C. La suspensión se dejó agitando durante la noche. Se añadió DMF (2 ml) junto con una porción adicional de NaOH y la mezcla se calentó hasta 70°C y se dejó agitando durante la noche. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el compuesto del epígrafe (49 mg, cuantitativo). Tiempo de retención de LC-EM: 2,36 min; m/z (MH⁺): 601. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters SunFire 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min donde el disolvente A era acetonitrilo al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



3-(2-(4-Fluorofenil)-3-(metilcarbamoil)-6-nitrobenzofuran-5-il)benzoato de etilo

Se añadió carbonato de cesio (1,69 g, 5,19 mmol) a $\text{Pd}(\text{Ph}_3\text{P})_4$ (250 mg, 0,216 mmol), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)-6-nitrobenzofuran-5-ilo (2,00 g, 4,33 mmol), ácido 3-(etoxicarbonil)fenilborónico (1,01 g, 5,19 mmol). Se añadieron dioxano (36 ml) y agua (7 ml) a temperatura ambiente y la mezcla se desgasificó 3x. La reacción se calentó hasta 90 °C durante la noche. Se dejó enfriar. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , filtro y se concentró. El sólido bruto se trituró con DCM dando el compuesto del epígrafe (1,70 g, 85%). RMN de ^1H (400 MHz, $\text{DMSO}-d_6$) $\delta\delta$ ppm 8,55 - 8,61 (1 H, m), 8,54 (1 H, s), 8,00 - 8,09 (3 H, m), 7,95 (1 H, s), 7,73 (1 H, s), 7,61 - 7,70 (2 H, m), 7,45 (2 H, t, $J=8,91$ Hz), 4,35 (2 H, c, $J=7,19$ Hz), 2,83 (3 H, d, $J=4,52$ Hz), 1,34 (3 H, t, $J=7,03$ Hz). Tiempo de retención de LC-EM: 1,62 min; m/z (MH $^+$): 463. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al

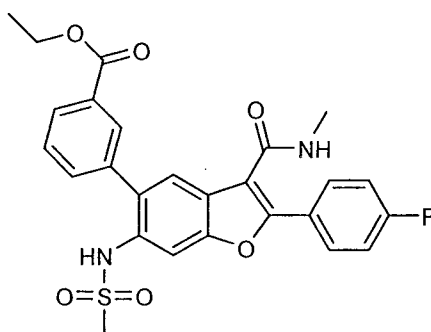
0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM
 5 se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



3-(6-Amino-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoato de etilo

10 Se añadió hierro (1,03 g, 18,4 mmol) a una solución agitada de 3-(2-(4-fluorofenil)-3-(metilcarbamoil)-6-nitrobenzofuran-5-il)benzoato de etilo (1,70 g, 3,68 mmol) en EtOH (37 ml) y AcOH (37 ml) a 90 °C. La suspensión se dejó agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat seguido por NaOH 1M y NaCl sat. La fase orgánica se secó sobre
 15 Na₂SO₄, se filtró y se concentró dando el compuesto del epígrafe (1,40 g 88%).
 RMN de ¹H (400 MHz, DMSO-d₆) δ ppm 8,25 - 8,34 (1 H, m), 8,00 - 8,03 (1 H, m), 7,87 - 7,99 (3 H, m), 7,69 - 7,75 (1 H, m), 7,63 (1 H, t, J=7,65 Hz), 7,26 - 7,37 (2 H, m), 7,20 (1 H, s), 6,98 (1 H, s), 5,07 (2 H, s), 4,35 (2 H, c, J=7,03 Hz), 2,78 (3 H, d, J=4,52 Hz), 1,34 (3 H, t, J=7,03 Hz). Tiempo de retención de LC-

EM: 1,46 min; m/z (MH⁺): 433. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución
5 emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% /
10 acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



3-(2-(4-Fluorofenil)-3-(metilcarbamoil)-6-(metilsulfonamido)benzofuran-5-
15 il)benzoato de etilo

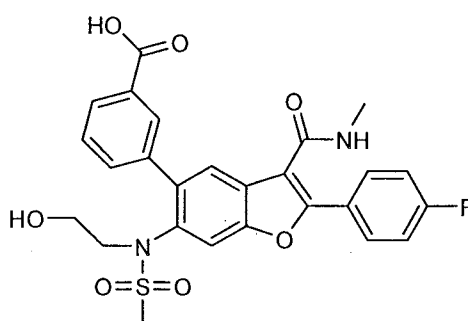
Se añadió cloruro de metanosulfonilo (303 µl, 3,88 mmol) a una solución agitada de 3-(6-amino-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoato de etilo (1,40 g, 3,24 mmol) en piridina (32 ml) a 25 °C. Se dejó

agitando durante la noche a temperatura ambiente. La reacción se concentró y se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a $\lambda = 254$ nm) dando el compuesto del epígrafe (1,01 g, 61%). Tiempo de retención de LC-EM: 1,53 min; m/z (MH⁺): 511. Los datos de

5 LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de

10 disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

15



Ácido 3-(2-(4-fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-3-(metilcarbamoil)benzofuran-5-il)benzoico

Etapa 1: Se añadió (2-bromoetoxi)(*terc*-butil)dimetilsilano (189 μ l, 0,881 mmol) a una suspensión agitada de Na_2CO_3 (311 mg, 2,94 mmol) y 3-(6-(N-(2-(*terc*-butildimetilsililoxi)etil)metilsulfonamido)-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoato de etilo en DMF (6 ml) a 100 °C. Se dejó agitando durante 5 horas y luego se dejó enfriar hasta temperatura ambiente y se agitó durante la noche. La mezcla se diluyó con EtOAc y se lavó con NaHCO_3 sat y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró. Tiempo de retención de LC-EM: 2,12 min; m/z (MH^+): 669. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

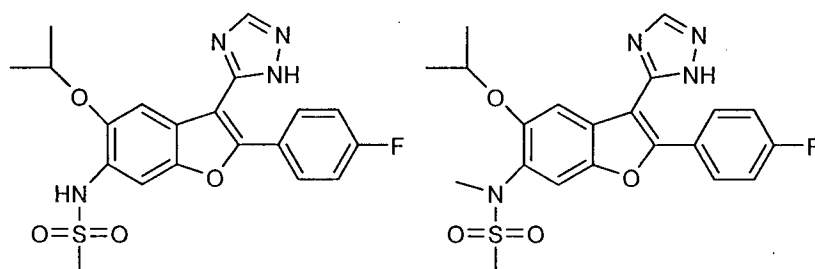
Etapa 2: El residuo se diluyó con EtOH (10 ml) y se trató con NaOH (2938 μ l, 2,94 mmol) y se dejó agitando a 60°C durante 4 horas. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró.

Etapa 3: El residuo bruto se recogió en THF y se trató con HCl 1M (haciendo el 30% en THF). La reacción se dejó agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró dando el compuesto del epígrafe

5 (300 mg, 97%). Tiempo de retención de LC-EM: 1,09 min; m/z (MH⁺): 527. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de

10 disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron

15 usando una Plataforma MICROMASS® para LC en modo electropulverización.



N-(2-(4-Fluorofenil)-5-isopropoxi-3-(1H-1,2,4-triazol-5-il)benzofuran-6-il)metanosulfonamida, y

N-(2-(4-fluorofenil)-5-isopropoxi-3-(1H-1,2,4-triazol-5-il)benzofuran-6-il)-N-metilmetanosulfonamida

Se combinaron dimetil acetal de N,N-dimetilformamida (500 μ l, 3,76 mmol) y 2-(4-fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carboxamida (100 mg, 0,246 mmol) y se calentó hasta 85 °C. Se añadió DMF (1 ml). Se dejó agitando durante 1 hr. La mezcla se concentró y se diluyó con dioxano (200 μ l), ácido acético (1 ml) y se trató con hidrazina (154 μ l, 4,92 mmol) y se calentó a 85 °C durante varias horas. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró. El residuo bruto se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente tamponado adecuadamente y se concentró dando N-(2-(4-fluorofenil)-5-isopropoxi-3-(1H-1,2,4-triazol-5-il)benzofuran-6-il)metanosulfonamida (25 mg, 0,058 mmol) y N-(2-(4-fluorofenil)-5-isopropoxi-3-(1H-1,2,4-triazol-5-il)benzofuran-6-il)-N-metilmetanosulfonamida (11 mg, 0,025 mmol).

N-(2-(4-Fluorofenil)-5-isopropoxi-3-(1H-1,2,4-triazol-5-il)benzofuran-6-il)metanosulfonamida

RMN de ¹H (300 MHz, DMSO-d₆) δ ppm 1,30 - 1,42 (m, 6 H) 2,99 (s, 3 H) 4,57 - 4,73 (m, 1 H) 7,24 - 7,40 (m, 2 H) 7,57 (s, 1 H) 7,67 (s, 1 H) 8,06 - 8,22 (m, 2 H) 8,68 (s, 1 H). Tiempo de retención de LC-EM: 1,30 min; m/z (MH⁺): 431. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu

LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Las HPLC adicionales se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 10,71 min, pureza = 94%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 9,74 min, pureza = 97%.

N-(2-(4-Fluorofenil)-5-isopropoxi-3-(1H-1,2,4-triazol-5-il)benzofuran-6-il)-N-metilmetanosulfonamida

RMN de ¹H (300 MHz, DMSO-d₆) δ ppm 1,29 - 1,41 (m, 6 H) 3,04 (s, 3 H) 3,19 - 3,24 (m, 3 H) 4,61 - 4,80 (m, 1 H) 7,28 - 7,39 (m, 2 H) 7,61 (s, 1 H)

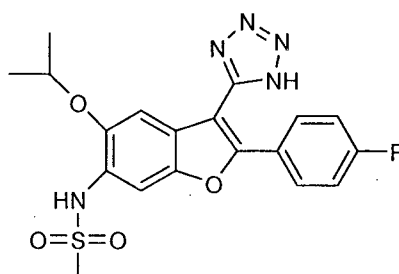
7,76 (s, 1 H) 8,08 - 8,27 (m, 2 H) 8,78 (s, 1 H) 14,34 (s, 1 H). Tiempo de retención de LC-EM: 1,36 min; m/z (MH⁺) 345. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a

5 una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% /

10 acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10,

15 %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 11,30 min, pureza = >95%; Columna: columna Waters XBridge Phenyl 4,6 x

150 mm, 3,5 µm, Tr = 10,21 min, pureza = >95%.



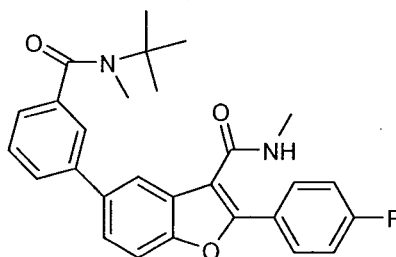
N-(2-(4-Fluorofenil)-5-isopropoxi-3-(1H-tetrazol-5-il)benzofuran-6-il)metanosulfonamida

Se añadió azidotrimetilsilano (34,2 μ l, 0,257 mmol) a una solución
5 agitada de óxido de dibutil estaño (6,41 mg, 0,026 mmol) y N-(3-ciano-2-(4-fluorofenil)-5-isopropoxibenzofuran-6-il)metanosulfonamida (50 mg, 0,129 mmol) en dioxano (1,3 ml) a temperatura ambiente. Se sometió a irradiación en microondas durante 15 min a 150°C. Se trató con más equivalentes de reaccionantes y se volvió a someter durante 30 minutos seguido por 60 min. La
10 mezcla se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente tamponado adecuadamente y se concentró dando el compuesto del epígrafe (12 mg, 22%). RMN de ^1H (300 MHz, DMSO- d_6) δ ppm 1,29 - 1,39 (m, 6 H) 3,01 (s, 3 H) 4,62 - 4,81 (m, 1 H) 7,28 - 7,45 (m, 3 H) 7,65 (s, 1 H) 7,84 - 7,98 (m, 2 H) 8,92 (s, 1 H). Tiempo de retención de LC-
15 EM: 1,04 min; m/z (MH $^+$): 432. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% /

disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 11,56 min, pureza = 94%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 10,55 min, pureza = 96%.

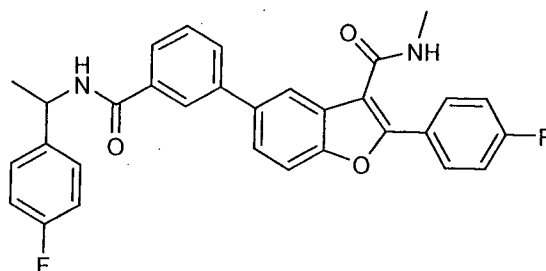
Procedimiento General: Acoplamiento de *m*-amida

Se añadió DIEA (36 µl, 0,205 mmol) a una solución agitada de HATU (59 mg, 0,154 mmol), la amina apropiada (0,164 mmol) y ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (40 mg, 0,103 mmol) en DMF (1 ml) a temperatura ambiente. Se dejó agitando durante la noche. La reacción se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el producto esperado. Este procedimiento general se aplicó a los Ejemplos KP4 a KP14.



5-(3-(*tert*-Butil(metil)carbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

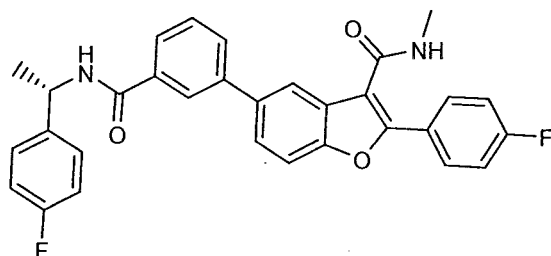
- 5 RMN de ^1H (500 MHz, CD_3OD) δ ppm 1,54 - 1,57 (m, 9 H) 2,94 - 2,99 (m, 6 H) 7,25 (t, 2 H) 7,35 - 7,40 (m, 1 H) 7,53 (t, 1 H) 7,64 - 7,67 (m, 2 H) 7,67 - 7,68 (m, 1 H) 7,72 - 7,77 (m, 1 H) 7,88 - 7,90 (m, 1 H) 7,92 - 7,97 (m, 2 H). Tiempo de retención de LC-EM: 1,71 min; m/z (MH^+): 459. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con
- 10 una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de
- 15 análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.



2-(4-Fluorofenil)-5-(3-(1-(4-fluorofenil)etilcarbamoyl)fenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (500 MHz, CD_3OD) δ ppm 8,10 - 8,15 (1 H, m), 7,90 - 7,99 (3 H, m), 7,84 (2 H, t, $J=9,61$ Hz), 7,63 - 7,72 (2 H, m), 7,56 (1 H, t, $J=7,78$ Hz), 7,40 - 7,47 (2 H, m), 7,22 - 7,29 (2 H, m), 7,03 - 7,10 (2 H, m), 5,24 - 5,30 (1 H, m), 2,97 (3 H, s), 1,59 (3 H, d, $J=7,02$ Hz). Tiempo de retención de LC-EM: 1,67 min; m/z (MH $^-$): 509. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/ H_2O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al

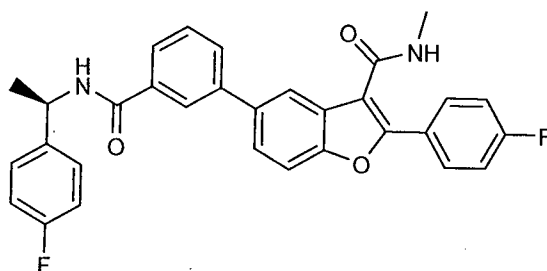
95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C1 C-18, 4,6 x 150 mm, 3 µm, Tr = 15,64 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 15,63 min, pureza = 98%.



(S)-2-(4-Fluorofenil)-5-(3-(1-(4-fluorofenil)etilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

- 10 RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,13 (1 H, s), 7,91 - 7,99 (3 H, m), 7,84 (2 H, t, J=9,31 Hz), 7,64 - 7,72 (2 H, m), 7,56 (1 H, t, J=7,78 Hz), 7,41 - 7,48 (2 H, m), 7,26 (2 H, t, J=8,85 Hz), 7,02 - 7,10 (2 H, m), 5,28 (1 H, c, J=7,22 Hz), 2,97 (3 H, s), 1,59 (3 H, d, J=7,02 Hz). Tiempo de retención de LC-EM: 1,67 min; m/z (MH⁻): 509. Los datos de LC se registraron en un cromatógrafo
- 15 de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un

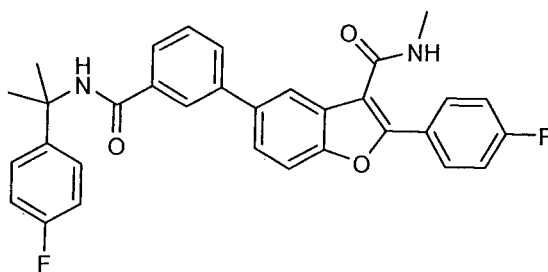
tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C1 C-18, 4,6 x 150 mm, 3 µm, Tr = 15,55 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 15,34 min, pureza = 98%.



(R)-2-(4-Fluorofenil)-5-(3-(1-(4-fluorofenil)etilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,14 (1 H, s), 7,92 - 7,99 (3 H, m), 7,81 - 7,87 (2 H, m), 7,65 - 7,72 (2 H, m), 7,57 (1 H, t, J=7,63 Hz), 7,42 - 7,47 (2 H, m), 7,23 - 7,29 (2 H, m), 7,04 - 7,10 (2 H, m), 5,28 (1 H, c, J=7,02 Hz), 2,97 (3 H, s), 1,59 (3 H, d, J=7,02 Hz). Tiempo de retención de LC-EM: 1,66 min;

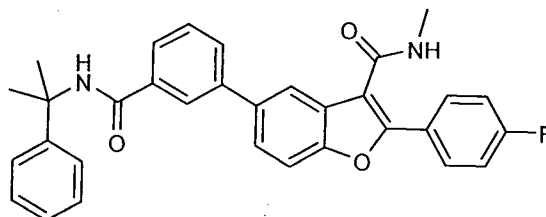
m/z (MH⁻): 509. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C1 C-18, 4,6 x 150 mm, 3 µm, Tr = 15,56 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 15,33 min, pureza = 97%.



2-(4-Fluorofenil)-5-(3-(2-(4-fluorofenil)propan-2-ilcarbamoil)fenil)-N-
metilbenzofuran-3-carboxamida

RMN de ^1H (500 MHz, CD_3OD) δ ppm 8,04 - 8,10 (1 H, m), 7,89 - 7,99 (3 H, m), 7,76 - 7,86 (2 H, m), 7,63 - 7,73 (2 H, m), 7,56 (1 H, t, $J=7,78$ Hz), 7,42 - 7,51 (2 H, m), 7,26 (2 H, t, $J=8,70$ Hz), 6,98 - 7,06 (2 H, m), 2,98 (3 H, s), 1,78 (6 H, s). Tiempo de retención de LC-EM: 1,72 min; m/z (MH $^-$): 523. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/ H_2O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/ H_2O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C1 C-18, 4,6 x 150 mm, 3 μm , Tr = 15,73 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm,

3,5 μ m, Tr = 15,53 min, pureza = 99%.

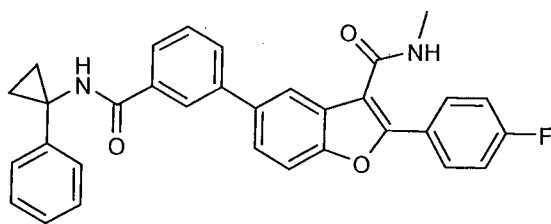


2-(4-Fluorofenil)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoi)fenil)benzofuran-3-carboxamida

5

- RMN de ^1H (500 MHz, CD_3OD) δ ppm 8,09 (1 H, s), 7,90 - 7,99 (3 H, m), 7,74 - 7,89 (1 H, m), 7,63 - 7,72 (2 H, m), 7,55 (1 H, t, $J=7,63$ Hz), 7,47 (2 H, d, $J=7,32$ Hz), 7,31 (2 H, t, $J=7,78$ Hz), 7,22 - 7,28 (2 H, m), 7,19 (1 H, t, $J=7,32$ Hz), 2,97 (3 H, s), 1,79 (6 H, s). Tiempo de retención de LC-EM: 1,71 min; m/z (MH $^-$): 505. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC

en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1
 5 ml/min. Columna: PHENOMENEX® Gemini C1 C-18, 4,6 x 150 mm, 3 µm, Tr = 15,79 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 15,53 min, pureza = 98%.



10 2-(4-Fluorofenil)-N-metil-5-(3-(1-fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 9,35 (1 H, s), 8,48 - 8,56 (1 H, m), 8,24 (1 H, s), 7,96 - 8,04 (2 H, m), 7,87 - 7,96 (3 H, m), 7,75 - 7,82 (2 H, m), 7,59 (1 H, t, *J*=7,63 Hz), 7,40 (2 H, t, *J*=8,70 Hz), 7,21 - 7,29 (4 H, m), 7,16 (1
 15 H, t, *J*=7,17 Hz), 2,86 (3 H, d, *J*=4,58 Hz), 1,25 - 1,35 (4 H, m). Tiempo de retención de LC-EM: 1,63 min; *m/z* (MH⁻): 503. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución

emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una

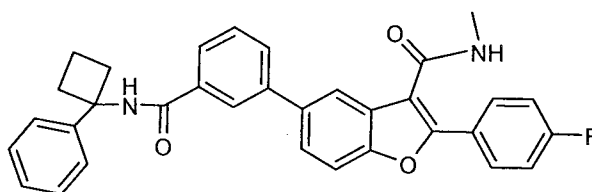
5 Plataforma MICROMASS® para LC en modo electropulverización.

Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al

10 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min.

Columna: PHENOMENEX® Gemini C1 C-18, 4,6 x 150 mm, 3 µm, Tr = 15,91 min, pureza = 96%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 15,79 min, pureza = 95%.

15



2-(4-Fluorofenil)-N-metil-5-(3-(1-fenilciclobutilcarbamoi)fenil)benzofuran-3-carboxamida

RMN de ¹H (500 MHz, DMSO-d₆) δ ppm 9,18 (1 H, s), 8,53 (1 H, c, J=4,48 Hz), 8,20 (1 H, s), 8,01 (2 H, dd, J=8,85, 5,49 Hz), 7,92 (1 H, d, J=1,22

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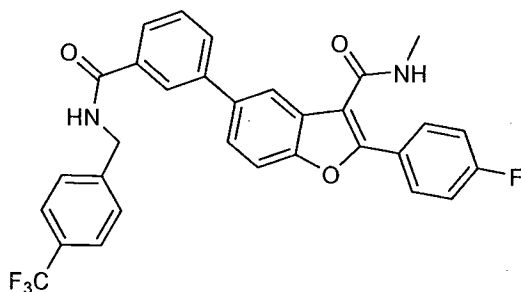
Hz), 7,87 (2 H, dd, $J=7,63, 1,53$ Hz), 7,73 - 7,83 (2 H, m), 7,57 (1 H, t, $J=7,78$ Hz), 7,52 (2 H, d, $J=7,32$ Hz), 7,40 (2 H, t, $J=9,00$ Hz), 7,33 (2 H, t, $J=7,78$ Hz), 7,20 (1 H, t, $J=7,32$ Hz), 2,87 (3 H, d), 2,61 - 2,71 (2 H, m), 2,54 - 2,58 (2 H, m), 2,01 - 2,11 (1 H, m), 1,82 - 1,92 (1 H, m). Tiempo de retención LC-EM 2,42 min;

5 m/z (MH⁺): 519. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta

10 disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC

15 en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 μm, Tr = 14,66 min, pureza = 97%; Columna:

20 columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μm, Tr = 13,13 min, pureza = 97%.

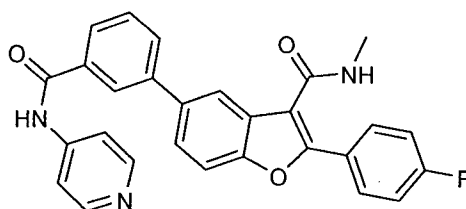


2-(4-Fluorofenil)-5isopropoxi-3-(1H-1,2,4-triazol-5-il)benzofuran-6-il)metanosulfonamida

RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 11,03 (1 H, s), 7,92 - 8,01 (2 H, m), 7,86 (1 H, d, $J=9,16$ Hz), 7,42 (2 H, t, $J=8,85$ Hz), 7,17 (1 H, d, $J=8,85$ Hz), 4,20 (2 H, c, $J=7,12$ Hz), 1,21 (3 H, t, $J=7,17$ Hz).). Tiempo de retención de LC-EM: 1,70 min; m/z (MH^+): 547. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH_3CN al 5%/ H_2O al 95%/TFA

al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 14,86 min, pureza = 99%; Procedimiento HPLC adicional 2: Disolvente A = 5 MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C-18, 4,6 x 150 mm, 3 µm, Tr = 17,53 min, pureza = 99%.

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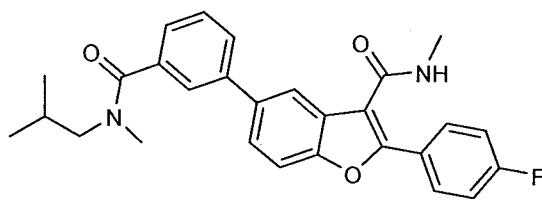


2-(4-Fluorofenil)-N-metil-5-(3-(piridin-4-ilcarbamoil)fenil)benzofuran-3-carboxamida

RMN de ¹H (500 MHz, DMSO-d₆) δ ppm 11,15 (1 H, s), 8,64 (2 H, d, J=6,41 Hz), 8,48 - 8,55 (1 H, m), 8,30 (1 H, s), 8,05 - 8,08 (2 H, m), 7,97 - 8,03 (6 H, m), 7,76 - 7,85 (2 H, m), 7,71 (1 H, t, J=7,78 Hz), 7,41 (2 H, t, J=8,70 Hz), 2,83 - 2,92 (3 H, m). Tiempo de retención de LC-EM: 1,45 min; m/z (MH⁺): 466. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando

un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C-18, 4,6 x 150 mm, 3 µm, Tr = 15,11 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 14,81 min, pureza = 96%.



2-(4-Fluorofenil)-5-(3-(isobutil(metil)carbamoil)fenil)-N-metilbenzofuran-3-carboxamida

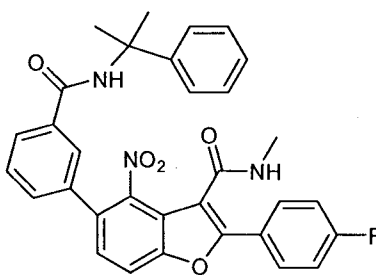
RMN de ¹H (500 MHz, CD₃OD) δ ppm 7,93 - 7,98 (2 H, m), 7,88 - 7,91 (1

H, m), 7,74 - 7,81 (1 H, m), 7,63 - 7,70 (3 H, m), 7,51 - 7,60 (1 H, m), 7,32 - 7,41 (1 H, m), 7,25 (2 H, t), 3,43 (1 H, d), 3,21 (1 H, d), 3,10 (2 H, s), 3,03 (2 H, s), 2,96 (3 H, s), 2,10 - 2,21 (1 H, m), 1,92 - 2,07 (1 H, m), 1,01 (3 H, d), 0,78 (3 H, d). Tiempo de retención de LC-EM: 1,65 min; m/z (MH⁺): 459. Los datos de

5 LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente

10 B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

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2-(4-Fluorofenil)-N-metil-4-nitro-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida

Etapa 1: Se diluyó 2-(4-fluorofenil)-4-nitro-5-(3-(2-fenilpropan-2-

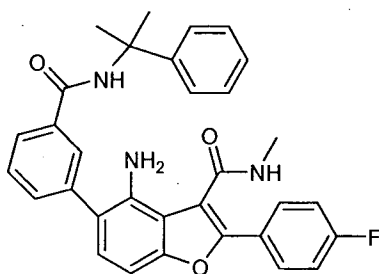
ilcarbamoil)fenil)benzofuran-3-carboxilato de etilo (300 mg, 0,529 mmol) con EtOH (10 ml) y se trató con NaOH (2,1 ml, 2,12 mmol, 1N ac.) y la mezcla, que se convirtió en una suspensión, se dejó agitando durante la noche a 60°C. La reacción se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase
5 orgánica se secó sobre Na₂SO₄, se filtró y se concentró.

Etapa 2: Se añadió EDC (128 mg, 0,668 mmol) a una solución agitada del ácido 2-(4-fluorofenil)-4-nitro-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxílico bruto (300 mg, 0,557 mmol), metanamina (306 µl, 0,613 mmol), 1-hidroxi-7-azabenzotriazol (83 mg, 0,613
10 mmol), DIEA (204 µl, 1,170 mmol) en DCM (5,5 ml) a temperatura ambiente. Se dejó agitando durante 3 días. La suspensión se convirtió en una solución durante dicho período de tiempo. La mezcla se concentró y se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a $\lambda = 254$ nm) dando el compuesto del epígrafe (220 mg, 95%). RMN de ¹H (500
15 MHz, CD₃OD) δ ppm 7,90 - 7,99 (3 H, m), 7,85 - 7,90 (1 H, m), 7,82 - 7,84 (1 H, m), 7,49 - 7,56 (3 H, m), 7,45 (2 H, d, $J=7,32$ Hz), 7,27 - 7,34 (4 H, m), 7,19 (1 H, t, $J=7,32$ Hz), 2,87 (3 H, s), 1,76 (6 H, s). Tiempo de retención de LC-EM: 1,62 min; m/z (MH⁺): 552. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u
20 C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta

disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los

5 datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters

10 Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 13,60 min, pureza = 94%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 12,66 min, pureza = 96%.

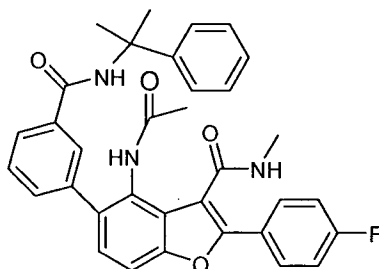


15 4-Amino-2-(4-fluorofenil)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida

Se añadió hierro (25 mg, 0,453 mmol) a una solución agitada de 2-(4-fluorofenil)-N-metil-4-nitro-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida (50 mg, 0,091 mmol) en etanol (1 ml) y AcOH (1 ml) a

temperatura ambiente. Se colocó en un bloque de reacción ajustado a 100 °C. Se dejó agitando durante 1 hora. La mezcla se dejó enfriar y se diluyó con EtOAc y se lavó con HCl 1M, seguido por NaOH 1N y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se trituró con Et₂O dando el compuesto del epígrafe (28 mg, 56%). RMN de ¹H (300 MHz, CD₃OD) δ ppm 7,83 - 7,89 (1 H, m), 7,73 - 7,81 (3 H, m), 7,52 - 7,64 (2 H, m), 7,42 - 7,49 (2 H, m), 7,10 - 7,35 (6 H, m), 6,98 (1 H, d, J=8,42 Hz), 2,87 (3 H, s), 1,76 (6 H, s). Tiempo de retención de LC-EM: 2,33 min; m/z (MH⁺): 522. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x

150 mm, 3,5 μ m, Tr = 14,17 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μ m, Tr = 12,84 min, pureza = 98%.



4-Acetamido-2-(4-fluorofenil)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoyl)fenil)benzofuran-3-carboxamida

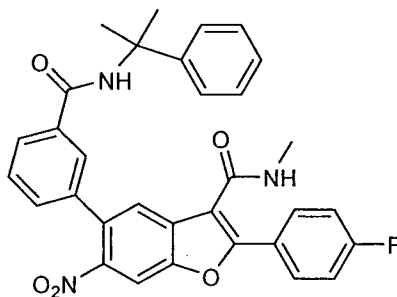
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Se diluyó 4-amino-2-(4-fluorofenil)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoyl)fenil)benzofuran-3-carboxamida (20 mg, 0,038 mmol) en piridina (1 ml) y se trató con cloruro de acetilo en exceso (10 μ l). La reacción se dejó agitando durante 2 horas. La mezcla se concentró y se diluyó con MeOH (1ml).

- 10 El producto comenzó a fragmentarse, se sometió a ultrasonidos, se filtró y se lavó con MeOH proporcionando el compuesto del epígrafe (8 mg, 34%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 9,41 (1 H, s), 8,43 (1 H, s), 8,31 - 8,38 (1 H, m), 7,88 - 7,92 (1 H, m), 7,82 - 7,87 (2 H, m), 7,80 (1 H, d, $J=7,63$ Hz), 7,71 (1 H, d, $J=8,55$ Hz), 7,54 - 7,60 (1 H, m), 7,43 - 7,49 (2 H, m), 7,36 - 7,43 (5 H, m), 7,28 (2 H, t, $J=7,78$ Hz), 7,17 (1 H, t, $J=7,32$ Hz), 2,76 (3 H, d), 1,79 (3 H, s), 1,69 (6 H, s). Tiempo de retención LC-EM 1,42 min; m/z 564 (MH^+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las
- 15

condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 12,00 min, pureza = 96%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 11,26 min, pureza = 95%.



2-(4-Fluorofenil)-N-metil-6-nitro-5-(3-(2-fenilpropan-2-ilcarbamoyl)fenil)benzofuran-3-carboxamida

Etapas 1: Se añadió carbonato de cesio (143 mg, 0,440 mmol) a

Pd(Ph₃P)₄ (17 mg, 0,015 mmol), 2-(4-fluorofenil)-6-nitro-5-(trifluorometilsulfonilo)benzofuran-3-carboxilato de etilo (140 mg, 0,293 mmol), ácido 3-boronobenzoico (73 mg, 0,440 mmol). Se añadieron dioxano (2,5 ml) y agua (500 µl) a temperatura ambiente. La reacción se desgasificó 3x y se calentó hasta 90 °C durante la noche. Se dejó enfriar. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró.

Etapa 2: El residuo se diluyó con DMF y se trató con HATU (167 mg, 0,440 mmol), 2-fenilpropan-2-amina (60 mg, 0,440 mmol) y DIEA (154 µl, 0,880 mmol) y se dejó agitando a temperatura ambiente durante la noche. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró, se concentró y se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a λ = 254 nm) dando 2-(4-fluorofenil)-6-nitro-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxilato de etilo. (Tiempo de retención de LC-EM: 1,97 min; m/z (MH⁺): 567. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de

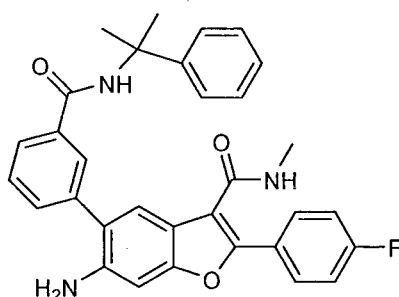
análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización).

5 Etapa 3: Este material se trató con NaOH (1 ml, 1,000 mmol) en etanol (2,93 ml) a 60°C durante 2 horas y luego se dejó agitando durante la noche mientras se enfriaba hasta temperatura ambiente. La reacción se calentó hasta 60°C durante 3 horas. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró.

10 Etapa 4: Se añadieron EDC (58 mg, 0,301 mmol), metanamina (1 ml, 2,000 mmol), 1-hidroxi-7-azabenzotriazol (38 mg, 0,276 mmol), DIEA (92 µl, 0,526 mmol) al residuo en DCE (2,5 ml) a temperatura ambiente. Se dejó agitando durante 3 días. La suspensión se convirtió en una solución durante dicho período de tiempo. La reacción bruta se purificó sobre gel de sílice
15 (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a λ = 254 nm) dando el compuesto del epígrafe (112 mg, 81%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,32 (1 H, s), 7,97 - 8,06 (2 H, m), 7,82 - 7,90 (2 H, m), 7,75 (1 H, s), 7,47 - 7,56 (2 H, m), 7,45 (2 H, d, J=7,32 Hz), 7,31 (4 H, t, J=8,09 Hz), 7,18 (1 H, t, J=7,32 Hz), 2,94 (3 H, s), 1,77 (6 H, s). Tiempo de retención de LC-
20 EM: 3,10 min; m/z (MH⁺): 552. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis

SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 14,12 min, pureza = 96%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 12,98 min, pureza = 97%.

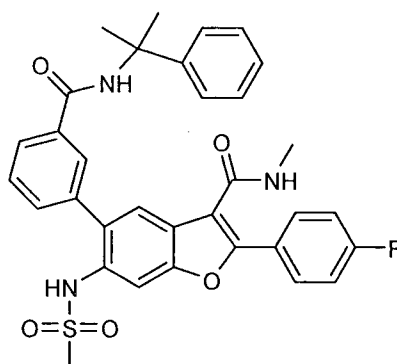
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6-Amino-2-(4-fluorofenil)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoyl)fenil)benzofuran-3-carboxamida

Se añadió hierro (68 mg, 1,22 mmol) a una solución agitada de 2-(4-fluorofenil)-N-metil-6-nitro-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida (112 mg, 0,203 mmol) en etanol (2,3 ml) y AcOH (2,3 ml) a temperatura ambiente. Se colocó en un bloque de reacción ajustado a 100 °C y se dejó agitando durante 1 hora. La mezcla se dejó enfriar y se diluyó con EtOAc y se lavó con HCl 1M, seguido por NaOH 1N y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se trituró con Et₂O dando el compuesto del epígrafe (52 mg, 47%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 6,58 - 6,65 (3 H, m), 6,52 (1 H, d, J=7,63 Hz), 6,37 (1 H, d, J=7,93 Hz), 6,30 (1 H, t, J=7,63 Hz), 6,18 (2 H, d, J=7,32 Hz), 6,08 (1 H, s), 6,03 (2 H, t, J=7,78 Hz), 5,88 - 5,97 (3 H, m), 5,73 (1 H, s), 1,65 (3 H, s), 0,50 (6 H, s). Tiempo de retención LC-EM 1,54 min; m/z (MH⁺): 520. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

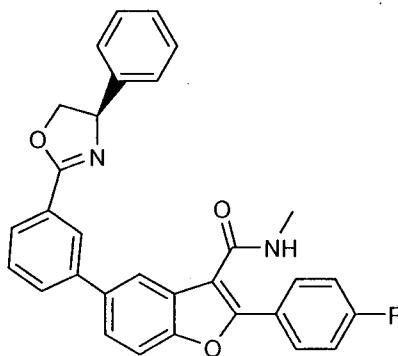
Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 μm, Tr = 15,11 min, pureza = 95%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μm, Tr = 11,11 min, pureza = 94%.



2-(4-Fluorofenil)-N-metil-6-(metilsulfonamido)-5-(3-(2-fenilpropan-2-ilcarbamoyl)fenil)benzofuran-3-carboxamida

Etapa 1: Se añadió DIEA (134 μl, 0,765 mmol) a Pd(Ph₃P)₄ (30 mg, 0,025 mmol), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoyl)-6-(N-(metilsulfonil)metilsulfonamido)benzofuran-5-ilo (150 mg, 0,255 mmol), ácido 3-(etoxicarbonil)fenilborónico (74 mg, 0,382 mmol). Se añadieron dioxano (5 ml) y agua (1 ml) a temperatura ambiente. La reacción se desgasificó 3x y se calentó hasta 90°C durante la noche. Se dejó enfriar y se dejó agitando durante 3 días a temperatura ambiente.

8,49 - 8,57 (1 H, m), 8,34 (1 H, s), 8,08 (1 H, d, $J=7,32$ Hz), 7,99 - 8,05 (2 H, m), 7,87 - 7,94 (2 H, m), 7,79 - 7,83 (1 H, m), 7,72 - 7,78 (1 H, m), 7,70 (1 H, t, $J=7,78$ Hz), 7,41 (2 H, t, $J=8,70$ Hz), 5,17 - 5,27 (1 H, m), 2,87 (3 H, d, $J=4,58$ Hz), 1,66 (6 H, d, $J=6,71$ Hz). Tiempo de retención de LC-EM: 2,02 min; m/z (MH⁺): 456. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 μ m, Tr = 15,35 min, pureza = 96%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μ m, Tr = 13,39 min, pureza = 97%.



(R)-2-(4-Fluorofenil)-N-metil-5-(3-(4-fenil-4,5-dihidrooxazol-2-il)fenil)benzofuran-3-carboxamida

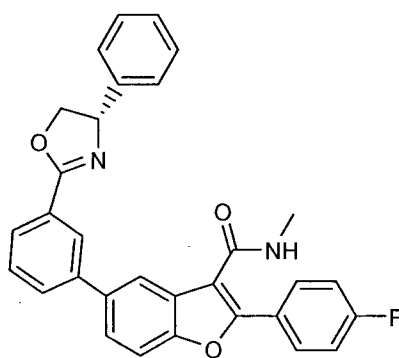
Se añadió cloruro de cinc (8 mg, 0,054 mmol) a una solución agitada de

5 5-(3-cianofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (40 mg, 0,108 mmol) y (R)-2-amino-2-feniletanol (148 mg, 1,080 mmol) en PhCl (3 ml) a temperatura ambiente. Se sometió a dos iteraciones de irradiación en microondas a 200 °C durante 1 hora. El material se concentró y se purificó por

10 HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (7 mg, 13%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,33 (1 H, s), 7,94 - 8,00 (4 H, m), 7,91 (1 H, d, J=7,94 Hz), 7,64 - 7,73 (2 H, m), 7,61 (1 H, t, J=7,78 Hz), 7,32 - 7,42 (6 H, m), 7,26 (2 H, t, J=8,55 Hz), 5,45 (1 H, t, J=9,16 Hz), 4,94 (1 H, t, J=9,31 Hz), 4,36 (1 H, t, J=8,24 Hz), 2,97 (3 H, s). Tiempo de

15 retención LC-EM 1,75 min; m/z (MH⁺): 491. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución

emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C-18, 4,6 x 150 mm, 3 µm, Tr = 18,32 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 18,11 min, pureza = 97%.

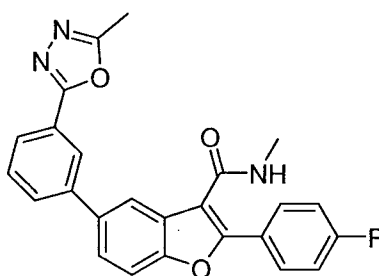


(S)-2-(4-Fluorofenil)-N-metil-5-(3-(4-fenil-4,5-dihidrooxazol-2-il)fenil)benzofuran-

3-carboxamida

Se añadió cloruro de cinc (9 mg, 0,067 mmol) a una solución agitada de 5-(3-cianofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (50 mg, 0,135 mmol) y (S)-2-amino-2-feniletanol (93 mg, 0,675 mmol) en PhCl (3 ml) a temperatura ambiente. Se sometió a dos iteraciones de irradiación en microondas a 200 °C durante 1 hora. El material se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (16 mg, 23%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,33 (1 H, s), 7,94 - 8,00 (4 H, m), 7,91 (1 H, d, J=7,94 Hz), 7,64 - 7,73 (2 H, m), 7,61 (1 H, t, J=7,78 Hz), 7,32 - 7,42 (6 H, m), 7,26 (2 H, t, J=8,55 Hz), 5,45 (1 H, t, J=9,16 Hz), 4,94 (1 H, t, J=9,31 Hz), 4,36 (1 H, t, J=8,24 Hz), 2,97 (3 H, s). Tiempo de retención LC-EM 1,76 min; m/z (MH⁺): 491. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una

Plataforma MICROMASS® para LC en modo electropulverización.
 Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de
 5 gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min.
 Columna: PHENOMENEX® Gemini C-18, 4,6 x 150 mm, 3 µm, Tr = 18,32 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 18,10 min, pureza = 99%.

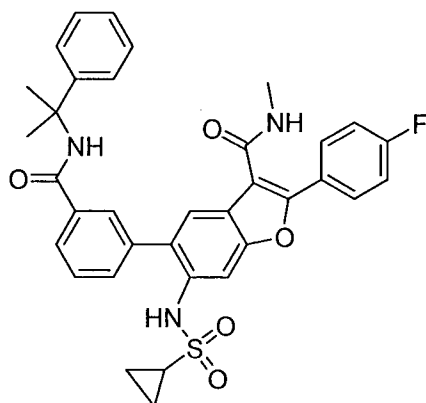


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2-(4-Fluorofenil)-N-metil-5-(3-(5-metil-1,3,4-oxadiazol-2-il)fenil)benzofuran-3-carboxamida

Se añadió DIEA (50 µl, 0,288 mmol) a Pd(Ph₃P)₄ (6 mg, 4,79 µmol), trifluorometanosulfonato de -(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-ilo
 15 (40 mg, 0,096 mmol), ácido 3-(5-metil-1,3,4-oxadiazol-2-il)fenilborónico (29 mg, 0,144 mmol). Se añadieron dioxano (1 ml) y agua (200 µl) a temperatura ambiente. La reacción se calentó hasta 90 °C durante la noche. La mezcla se enfrió y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se

concentró dando el compuesto del epígrafe (16 mg, 37%). RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,49 - 8,56 (1 H, m), 8,24 (1 H, s), 7,98 - 8,05 (4 H, m), 7,93 (1 H, s), 7,79 - 7,83 (1 H, m), 7,68 - 7,76 (2 H, m), 7,41 (2 H, t, $J=8,70$ Hz), 2,87 (3 H, d, $J=4,58$ Hz), 2,62 (3 H, s). Tiempo de retención de LC-EM: 1,41 min; m/z (MH $^-$): 426. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH_3CN al 5%/ H_2O al 95%/TFA al 0,1%, Disolvente B = CH_3CN al 95%/ H_2O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 12,96 min, pureza = 95% ; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 11,53 min, pureza = 94% .

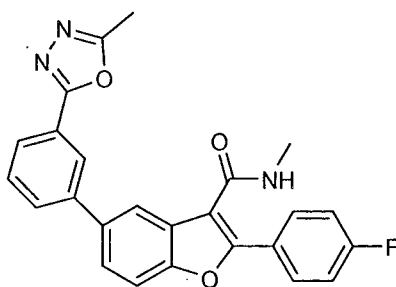


6-(Ciclopropanosulfonamido)-2-(4-fluorofenil)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida

Se añadió cloruro de ciclopropanosulfonilo (8 μ l, 0,058 mmol) a una
 5 solución agitada de 6-amino-2-(4-fluorofenil)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida (20 mg, 0,038 mmol) en piridina (,5 ml) a temperatura ambiente. Se dejó agitando durante 2 horas. La mezcla se concentró, se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se
 10 concentró dando el compuesto del epígrafe (17 mg, 70%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,41 (1 H, s ancho), 7,91 - 8,01 (3 H, m), 7,78 - 7,86 (2 H, m), 7,61 - 7,71 (2 H, m), 7,58 (1 H, t, J=7,63 Hz), 7,41 - 7,49 (2 H, m), 7,24 - 7,33 (4 H, m), 7,18 (1 H, t, J=6,87 Hz), 2,94 (3 H, s), 2,34 - 2,43 (1 H, m), 1,77 (6 H, s), 0,80 - 1,03 (4 H, m). Tiempo de retención de LC-EM: 1,53 min; m/z
 15 (MH⁺): 626. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de

detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el
5 disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al
10 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 15,40 min, pureza = 99% ; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 12,65 min, pureza = 99%.

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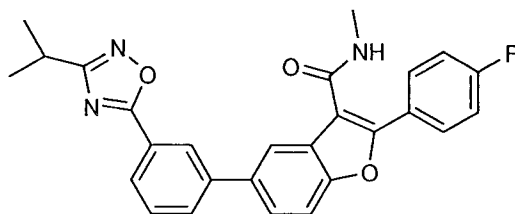


2-(4-Fluorofenil)-N-metil-5-(3-(5-metil-1,3,4-oxadiazol-2-il)fenil)benzofuran-3-carboxamida

Se añadió DIEA (50 µl, 0,288 mmol) a Pd(Ph₃P)₄ (6 mg, 4,79 µmol),

trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (40 mg, 0,096 mmol), ácido 3-(5-metil-1,3,4-oxadiazol-2-il)fenilborónico (29 mg, 0,144 mmol). Se añadieron dioxano (799 µl) y agua (160 µl) a temperatura ambiente. La reacción se calentó hasta 90 °C durante la noche. La mezcla se
5 enfrió y se purificó por HPLC prep dando el compuesto del epígrafe (16 mg, 37%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 8,49 - 8,56 (1 H, m), 8,24 (1 H, s), 7,98 - 8,05 (4 H, m), 7,93 (1 H, s), 7,79 - 7,83 (1 H, m), 7,68 - 7,76 (2 H, m), 7,41 (2 H, t, *J*=8,70 Hz), 2,87 (3 H, d, *J*=4,58 Hz), 2,62 (3 H, s). Tiempo de retención de LC-EM: 1,41 min; *m/z* (MH⁻): 426. Los datos de LC se registraron
10 en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo
15 de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una
Plataforma MICROMASS® para LC en modo electropulverización.
20 Procedimiento HPLC analítico: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min,

Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 μ m, Tr = 12,96 min, pureza = 95%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μ m, Tr = 11,53 min, pureza = 94%.



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2-(4-Fluorofenil)-5-(3-(3-isopropil-1,2,4-oxadiazol-5-il)fenil)-N-metilbenzofuran-3-carboxamida

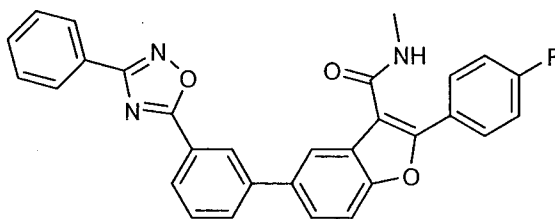
Se añadió metóxido sódico (33 mg, 0,620 mmol) a una suspensión agitada de 3-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)benzoato de metilo (50 mg, 0,124 mmol) y (Z)-N'-hidroxiiisobutirimidamida (38 mg, 0,372 mmol) en EtOH (2,5 ml) a temperatura ambiente. La mezcla se sometió a irradiación en microondas durante 5 min a 160 °C. La mezcla se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (11 mg, 20%). RMN de ¹H (400 MHz, DMSO-d₆) δ ppm 8,46 - 8,54 (1 H, m), 8,35 (1 H, s), 8,11 (1 H, d, J=7,78 Hz), 7,97 - 8,08 (3 H, m), 7,92 - 7,97 (1 H, m), 7,73 - 7,84 (3 H, m), 7,40 (2 H, t, J=8,91 Hz), 3,12 - 3,23 (1 H, m), 2,87 (3 H, d, J=4,52 Hz), 1,36 (6 H, d, J=7,03 Hz). Tiempo de retención de LC-EM: 1,80 min; m/z (MH⁺): 456. Los datos de LC se registraron en un

cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% /

5 disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una

10 Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr =

15 16,33 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 13,72 min, pureza = 99%.



2-(4-Fluorofenil)-N-metil-5-(3-(3-fenil-1,2,4-oxadiazol-5-il)fenil)benzofuran-3-

carboxamida

Se añadió metóxido sódico (33 mg, 0,620 mmol) a una suspensión agitada de 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoato de metilo (50 mg, 0,124 mmol) y (Z)-N'-hidroxibenzimidamida (51 mg, 0,372 mmol) en EtOH (2,5 ml) a temperatura ambiente. La mezcla se sometió a irradiación en microondas durante 5 min a 160 °C. La mezcla se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (8,7 mg, 14%). RMN de ¹H (400 MHz, DMSO-*d*₆) δ ppm

8,49 - 8,56 (1 H, m), 8,44 - 8,49 (1 H, m), 8,19 - 8,25 (1 H, m), 8,13 - 8,18 (2 H, m), 8,07 - 8,12 (1 H, m), 8,00 - 8,07 (2 H, m), 7,98 (1 H, s), 7,76 - 7,86 (3 H, m), 7,59 - 7,68 (3 H, m), 7,41 (2 H, t, *J*=8,91 Hz), 2,88 (3 H, d, *J*=4,77 Hz). Tiempo de retención de LC-EM: 1,94 min; *m/z* (MH⁺): 490. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una

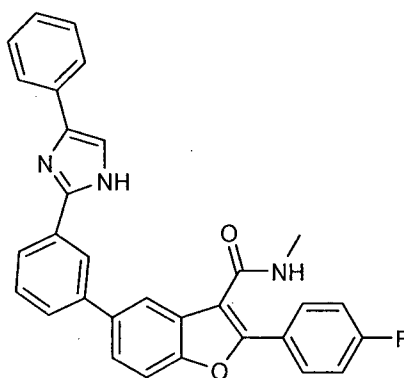
Plataforma MICROMASS® para LC en modo electropulverización.

Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA

al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10,

%B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min,

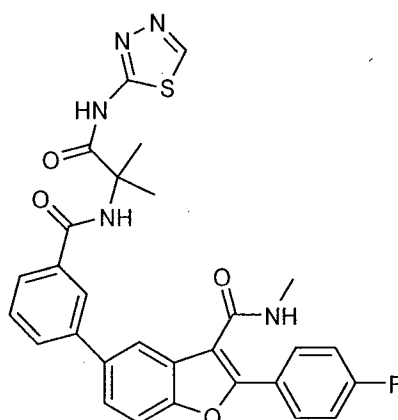
- 5 Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 17,39 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 14,58 min, pureza = 98%.



- 10 2-(4-Fluorofenil)-N-metil-5-(3-(4-fenil-1H-imidazol-2-il)fenil)benzofuran-3-carboxamida

- Se añadió 2-oxo-2-fenilacetaldehído hidrato (10 mg, 0,066 mmol) en MeOH (1 ml) a una solución agitada de 2-(4-fluorofenil)-5-(3-formilfenil)-N-metilbenzofuran-3-carboxamida (20 mg, 0,054 mmol) y acetato amónico (25 mg, 0,324 mmol) en MeOH (1 ml) a temperatura ambiente. Se dejó agitando durante la noche. La reacción se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente
- 15

tamponado y se concentró dando el compuesto del epígrafe (6,5 mg, 24%).
RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 12,82 (1 H, s ancho), 8,51 - 8,58 (1 H, m), 8,35 (1 H, s ancho), 7,98 - 8,07 (3 H, m), 7,93 - 7,97 (1 H, m), 7,76 - 7,90 (4 H, m), 7,72 (1 H, d, $J=7,63$ Hz), 7,60 (1 H, t, $J=7,78$ Hz), 7,36 - 7,45 (4 H, m),
5 7,19 - 7,29 (1 H, m), 2,88 (3 H, d, $J=4,58$ Hz). Tiempo de retención de LC-EM: 1,57 min; m/z (MH^+): 488. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución
10 emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H_2O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H_2O al 10% / MeOH al 90% / ácido
15 trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH_3CN al 5%/ H_2O al 95%/TFA al 0,1%, Disolvente B = CH_3CN al 95%/ H_2O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min,
20 Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 9,54 min, pureza = 96%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 10,41 min, pureza = 97%.



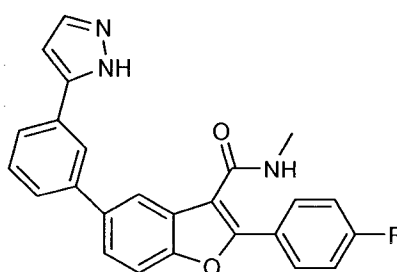
5-(3-(1-(1,3,4-Tiadiazol-2-ilamino)-2-metil-1-oxopropan-2-ilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 5 Se añadió DIEA (44 μ l, 0,253 mmol) a una solución agitada de ácido 2-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzamido)-2-metilpropanoico (40 mg, 0,084 mmol), 1,3,4-tiadiazol-2-amina (17,05 mg, 0,169 mmol) en DMF (843 μ l) a temperatura ambiente. Se añadió NaH (17 mg, 0,422 mmol) y la suspensión se convirtió en una solución transparente después de 10
- 10 min. Se dejó agitando durante la noche. La reacción se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H_2O/CH_3CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (22 mg, 45%). RMN de 1H (500 MHz, $DMSO-d_6$) δ ppm 12,44 (1 H, s ancho), 9,14 (1 H, s ancho), 8,78 (1 H, s ancho), 8,47 - 8,57 (1 H, m), 8,30 (1
- 15 H, s), 7,97 - 8,04 (2 H, m), 7,88 - 7,95 (3 H, m), 7,75 - 7,84 (2 H, m), 7,61 (1 H, t, $J=7,78$ Hz), 7,41 (2 H, t), 2,86 (3 H, d, $J=4,88$ Hz), 1,57 (6 H, s). Tiempo de retención de LC-EM: 1,57 min; m/z (MH^+): 488. Los datos de LC se registraron

en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una

10 Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr =

15 11,23 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 10,56 min, pureza = 96%.

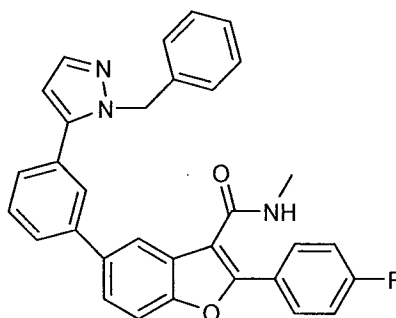


5-(3-(1H-Pirazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió carbonato de cesio (234 mg, 0,719 mmol) a $\text{Pd}(\text{Ph}_3\text{P})_4$ (20,77 mg, 0,018 mmol), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (150 mg, 0,359 mmol), 5-(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-pirazol (146 mg, 0,539 mmol). Se añadieron
5 dioxano (3 ml) y agua (599 μl) a temperatura ambiente. La reacción se calentó hasta 90 °C durante la noche. La mezcla se diluyó con EtOAc y se lavó con NaHCO_3 sat y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró y se purificó triturando con Et_2O dando el compuesto del epígrafe (140 mg, 92%). RMN de ^1H (400 MHz, $\text{DMSO}-d_6$) δ ppm 13,40 (1 H, s ancho),
10 12,91 (1 H, s ancho), 8,45 - 8,55 (1 H, m), 8,13 (1 H, s), 7,97 - 8,08 (2 H, m), 7,85 - 7,95 (1 H, m), 7,73 - 7,85 (4 H, m), 7,59 - 7,67 (1 H, m), 7,49 - 7,58 (1 H, m), 7,35 - 7,45 (2 H, m), 6,84 (1 H, s ancho), 2,87 (3 H, d, $J=4,52$ Hz). Tiempo de retención de LC-EM: 1,41 min; m/z (MH^+): 412. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con
15 una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de
20 análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una

Plataforma MICROMASS® para LC en modo electropulverización.

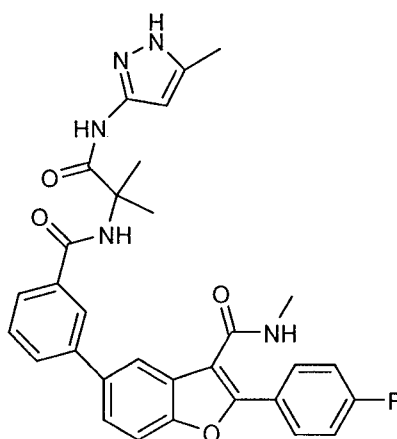
Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 11,86 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 10,97 min, pureza = 99%.



10 5-(3-(1-benzil-1H-pirazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió (bromometil)benceno (17 mg, 0,097 mmol) a una solución agitada de Na₂CO₃ (11 mg, 0,097 mmol) y 5-(3-(1H-pirazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (20 mg, 0,049 mmol) en DMF (486 µl) a 100 °C. Se dejó agitando durante la noche, se filtró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (8,6 mg, 35%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 8,49 - 8,57

(1 H, m), 8,06 - 8,11 (1 H, m), 7,98 - 8,04 (2 H, m), 7,92 (1 H, d, $J=2,44$ Hz), 7,86 - 7,89 (1 H, m), 7,75 - 7,83 (2 H, m), 7,69 - 7,75 (1 H, m), 7,63 (1 H, d, $J=8,24$ Hz), 7,51 (1 H, t, $J=7,63$ Hz), 7,34 - 7,43 (4 H, m), 7,27 - 7,32 (3 H, m), 6,89 (1 H, d, $J=2,44$ Hz), 5,41 (2 H, s), 2,86 (3 H, d, $J=4,58$ Hz). Tiempo de retención de LC-EM: 2,00 min; m/z (MH^+): 502. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 15,47 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 13,77 min, pureza = 100%.



2-(4-Fluorofenil)-N-metil-5-(3-(2-metil-1-(5-metil-1H-pirazol-3-ilamino)-1-oxopropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida

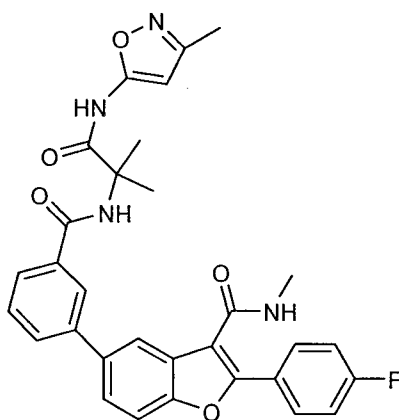
Se añadió DIEA (28 μ l, 0,158 mmol) a una solución agitada de ácido 2-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzamido)-2-metilpropanoico (25 mg, 0,053 mmol), 5-metil-1H-pirazol-3-amina (11 mg, 0,105 mmol) en DMF (527 μ l) a temperatura ambiente. Se dejó agitando durante 30 min. Se añadió NaH (11 mg, 0,263 mmol) y la reacción se dejó agitando durante la noche. La mezcla se trató con una gota de MeOH y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (6,4 mg, 21%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 11,90 (1 H, s ancho), 9,84 (1 H, s ancho), 8,51 - 8,56 (1 H, m), 8,41 (1 H, s ancho), 8,23 - 8,28 (1 H, m), 7,98 - 8,03 (2 H, m), 7,86 - 7,93 (3 H, m), 7,76 - 7,83 (2 H, m), 7,59 (1 H, t, *J*=7,63 Hz), 7,37 - 7,43 (2 H, m), 6,28 (1 H, s ancho), 2,87 (3 H, d, *J*=4,88 Hz), 2,17 (3 H, s), 1,54 (6 H, s). Tiempo de retención de LC-EM: 1,56

min; m/z (MH⁺): 554. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución

5 emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido

10 trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min,

15 Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 10,47 min, pureza = 97% ; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 9,58 min, pureza = 96%.

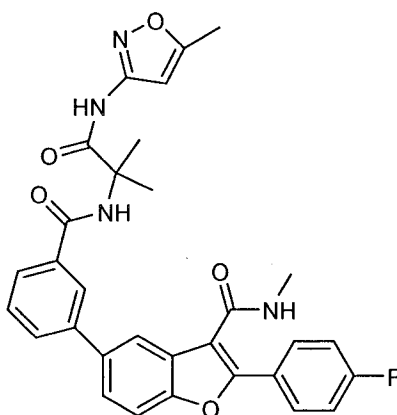


2-(4-Fluorofenil)-N-metil-5-(3-(2-metil-1-(3-metilisoxazol-5-ilamino)-1-oxopropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida

- Se añadió DIEA (28 μ l, 0,158 mmol) a una solución agitada de ácido 2-
- 5 (3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzamido)-2-metilpropanoico (25 mg, 0,053 mmol), 3-metilisoxazol-5-amina (11 mg, 0,105 mmol) en DMF (527 μ l) a temperatura ambiente. Se dejó agitando durante 30 min. Se añadió NaH (11 mg, 0,263 mmol) y la reacción se dejó agitando durante la noche. La mezcla se trató con una gota de MeOH y se purificó por
- 10 HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H_2O/CH_3CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (3,3 mg, 11%). RMN de 1H (500 MHz, CD_3OD) δ ppm 8,18 - 8,24 (1 H, m), 7,93 - 8,00 (3 H, m), 7,84 - 7,91 (2 H, m), 7,65 - 7,74 (2 H, m), 7,58 (1 H, t, $J=7,78$ Hz), 7,23 - 7,31 (2 H, m), 2,98 (3 H, s), 2,24 (3 H, s), 1,65 (6 H, s).
- 15 Tiempo de retención de LC-EM: 1,69 min; m/z (MH^+): 555. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un

detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 12,09 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 11,18 min, pureza = 99%.

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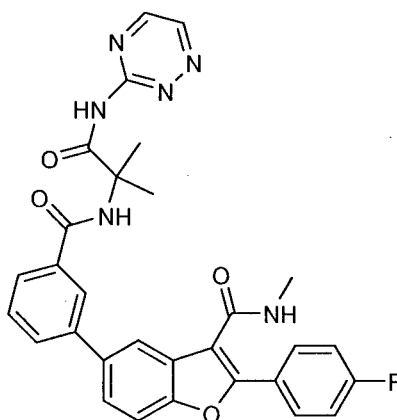


2-(4-Fluorofenil)-N-metil-5-(3-(2-metil-1-(5-metilisoxazol-3-ilamino)-1-

oxopropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida

Se añadió DIEA (28 µl, 0,158 mmol) a una solución agitada de ácido 2-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzamido)-2-metilpropanoico (25 mg, 0,053 mmol), 5-metilisoxazol-3-amina (11 mg, 0,105 mmol) en DMF (527 µl) a temperatura ambiente. Se dejó agitando durante 30 min. Se añadió NaH (11 mg, 0,263 mmol) y la reacción se dejó agitando durante la noche. La mezcla se trató con una gota de MeOH y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (2,8 mg, 9%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,17 - 8,25 (1 H, m), 7,92 - 8,00 (3 H, m), 7,83 - 7,91 (2 H, m), 7,66 - 7,76 (2 H, m), 7,58 (1 H, t, J=7,78 Hz), 7,27 (2 H, t, J=8,85 Hz), 6,63 (1 H, s), 2,98 (3 H, s), 2,39 (3 H, s), 1,65 (6 H, s). Tiempo de retención de LC-EM: 1,69 min; m/z (MH⁺): 555. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM

se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo
5 de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 12,20 min, pureza = 95%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 11,30 min, pureza = 90%.

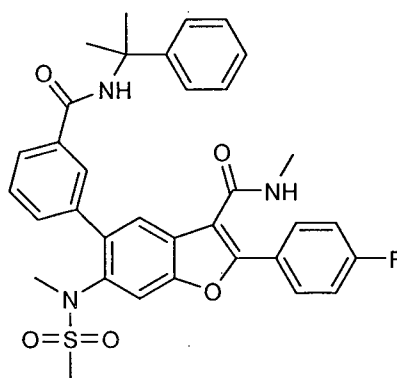


5-(3-(1-(1,2,4-Triazin-3-ilamino)-2-metil-1-oxopropan-2-ilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió DIEA (28 μ l, 0,158 mmol) a una solución agitada de ácido 2-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzamido)-2-metilpropanoico (25 mg, 0,053 mmol), 1,2,4-triazin-3-amina (11 mg, 0,105 mmol) en DMF (527 μ l) a temperatura ambiente. Se dejó agitando durante 30 min. Se añadió NaH (11 mg, 0,263 mmol) y la reacción se dejó agitando durante la noche. La mezcla se trató con una gota de MeOH y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ adecuadamente tamponado y se concentró dando el compuesto del epígrafe (7,4 mg, 25%). RMN de ^1H (500 MHz, CD_3OD) δ ppm 8,58 - 8,63 (1 H, m), 8,22 - 8,26 (1 H, m), 7,93 - 8,00 (3 H, m), 7,85 - 7,93 (2 H, m), 7,66 - 7,75 (2 H, m), 7,59 (1 H, t, $J=7,63$ Hz), 7,27 (2 H, t, $J=8,85$ Hz), 2,98 (3 H, s), 1,72 (6 H, s). Tiempo de retención de LC-EM: 1,56 min; m/z (MH^+): 553. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm

usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 9,65 min, pureza = 97% ; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 9,58 min, pureza = 97%.

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2-(4-Fluorofenil)-N-metil-6-(N-metilmetilsulfonamido)-5-(3-(2-fenilpropan-2-

ilcarbamoil)fenil)benzofuran-3-carboxamida

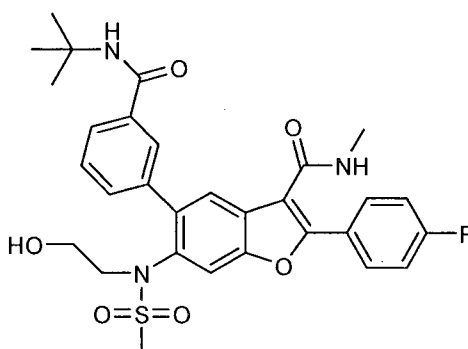
Se añadió cloruro de oxalilo (22 μ l, 0,250 mmol) a una solución agitada de ácido 2-(4-fluorofenil)-6-(N-metilmetilsulfonamido)-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxílico (50 mg, 0,083 mmol) en DCE (832 μ l) a temperatura ambiente. Se añadió DMF (3 μ l, 0,042 mmol). La mezcla se dejó agitando durante 30 minutos, se concentró y se diluyó con THF. Se añadieron DIEA (59 μ l, 0,333 mmol) y metanamina (208 μ l, 0,416 mmol, 2M en THF). Se dejó agitando durante la noche. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (11 mg, 20%). RMN de ¹H (400 MHz, DMSO-*d*₆) δ ppm 8,46 - 8,56 (1 H, m), 8,36 (1 H, s), 7,97 - 8,05 (3 H, m), 7,94 (1 H, s), 7,86 (1 H, d, *J*=7,78 Hz), 7,59 - 7,67 (2 H, m), 7,53 (1 H, t, *J*=7,65 Hz), 7,35 - 7,42 (4 H, m), 7,29 (2 H, t, *J*=7,78 Hz), 7,17 (1 H, t, *J*=7,28 Hz), 3,06 (3 H, s), 3,01 (3 H, s), 2,82 (3 H, d, *J*=4,52 Hz), 1,69 (6 H, s). Tiempo de retención de LC-EM: 1,51 min; *m/z* (MH⁺): 614. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo

de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una

5 Plataforma MICROMASS® para LC en modo electropulverización.

Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr =

10 12,89 min, pureza = 92% ; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 12,11 min, pureza = 91%.



5-(3-(*tert*-Butilcarbamoil)fenil)-2-(4-fluorofenil)-6-(N-(2-
15 hidroxietil)metilsulfonamido)-N-metilbenzofuran-3-carboxamida

Se añadió *tert*-butilamina (21 µl, 0,195 mmol) a una solución agitada de HATU (45 mg, 0,117 mmol), DIEA (41 µl, 0,234 mmol) y ácido 3-(6-(N-(2-(*tert*-butildimetilsililoxi)etil)metilsulfonamido)-2-(4-fluorofenil)-3-

(metilcarbamoil)benzofuran-5-il)benzoico (50 mg, 0,078 mmol) en DMF (780 μ l) a temperatura ambiente. Se dejó agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con NaHCO_3 sat y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró y se purificó por HPLC preparativa en

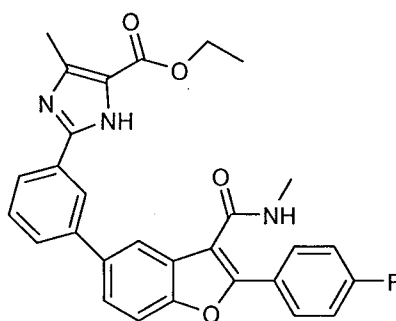
5 fase inversa en una columna C18 usando un gradiente de $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ adecuadamente tamponado y se concentró dando el compuesto del epígrafe (11 mg, 23%). RMN de ^1H (500 MHz, CD_3OD) δ ppm 8,04 (1 H, s ancho), 7,94 - 8,02 (2 H, m), 7,77 - 7,86 (2 H, m), 7,66 - 7,73 (2 H, m), 7,49 - 7,59 (2 H, m), 7,24 - 7,34 (2 H, m), 3,56 - 3,66 (1 H, m), 3,35 - 3,43 (2 H, m), 3,27 (3 H, s),

10 2,94 (3 H, s), 2,78 - 2,87 (1 H, m), 1,47 (9 H, s). Tiempo de retención de LC-EM: 1,57 min; m/z (MH^+): 582. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución

15 emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% /

20 acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH_3CN al 5%/ H_2O al 95%/TFA

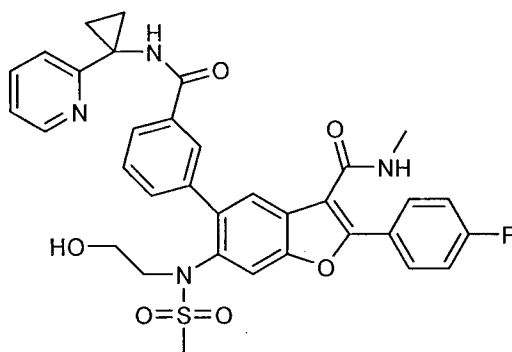
al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 10,88 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150
5 mm, 3,5 mm, Tr = 10,27 min, pureza = 96%.



2-(3-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)fenil)-4-metil-1H-imidazol-5-carboxilato de etilo

- 10 Se añadió carbonato de cesio (234 mg, 0,719 mmol) a Pd(Ph₃P)₄ (27,7 mg, 0,024 mmol), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (200 mg, 0,479 mmol), 4-metil-2-(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-5-carboxilato de etilo (171 mg, 0,479 mmol). Se añadieron dioxano (4 ml) y agua (800 µl) a temperatura
15 ambiente. La reacción se calentó hasta 90 °C durante la noche. La mezcla se diluyó con acetato de etilo y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se purificó sobre gel de sílice gel (BIOTAGE®, gradiente de EtOAc/hexanos, recogida de la fracción

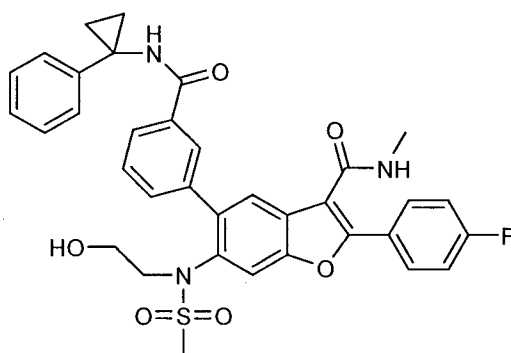
a $\lambda = 254$ nm) dando el compuesto del epígrafe (6,8 mg, 3%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 13,16 (0,34 H, s), 12,96 (0,66 H, s), 8,54 (1 H, c, $J=4,48$ Hz), 8,50 (0,32 H, s), 8,24 (0,68 H, s), 8,10 (0,31 H, d, $J=7,93$ Hz), 7,97 - 8,04 (2 H, m), 7,89 - 7,97 (2 H, m), 7,79 - 7,84 (1,35 H, m), 7,70 - 7,79 (2 H, m), 7,54 - 7,63 (1 H, m), 7,37 - 7,44 (2 H, m), 4,33 (0,65 H, c, $J=7,22$ Hz), 4,25 (1,42 H, c, $J=7,22$ Hz), 2,87 (3 H, d, $J=4,88$ Hz), 2,55 (2 H, s), 2,45 (1 H, s), 1,34 (1 H, t, $J=7,02$ Hz), 1,31 (2 H, t, $J=7,17$ Hz). Tiempo de retención de LC-EM: 1,46 min; m/z (MH^+): 498. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH_3CN al 5%/ H_2O al 95%/TFA al 0,1%, Disolvente B = CH_3CN al 95%/ H_2O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 9,90 min, pureza = 99%.



2-(4-Fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metil-5-(3-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

- 5 Se añadió diclorhidrato de 1-(piridin-2-il)ciclopropanamina (24 mg, 0,114 mmol) a una solución agitada de HATU (54 mg, 0,142 mmol), DIEA (50 μ l, 0,285 mmol) y ácido 3-(2-(4-fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-3-(metilcarbamoil)benzofuran-5-il)benzoico (50 mg, 0,095 mmol) en DMF (950 μ l) a temperatura ambiente. Se dejó agitando durante 1 hora. La mezcla se diluyó
- 10 con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (20 mg, 32%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 9,20 (1 H, s), 8,49 -
- 15 8,57 (1 H, m), 8,45 (1 H, d, *J*=3,97 Hz), 7,97 - 8,05 (3 H, m), 7,96 (1 H, s), 7,94 (1 H, d, *J*=7,93 Hz), 7,80 (1 H, d, *J*=7,93 Hz), 7,64 - 7,69 (1 H, m), 7,63 (1 H, s), 7,56 (1 H, t, *J*=7,63 Hz), 7,37 - 7,47 (3 H, m), 7,15 (1 H, dd, *J*=6,41, 4,88 Hz), 4,91 (1 H, s ancho), 3,51 - 3,60 (1 H, m), 3,22 (3 H, s), 2,89 - 2,98 (3 H, m),

2,81 (3 H, d), 1,50 - 1,60 (2 H, m), 1,23 - 1,33 (2 H, m). Tiempo de retención de LC-EM: 1,37 min; m/z (MH⁺): 643. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 7,17 min, pureza = 98% ; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 7,89 min, pureza = 99%.



2-(4-Fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metil-5-(3-(1-fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

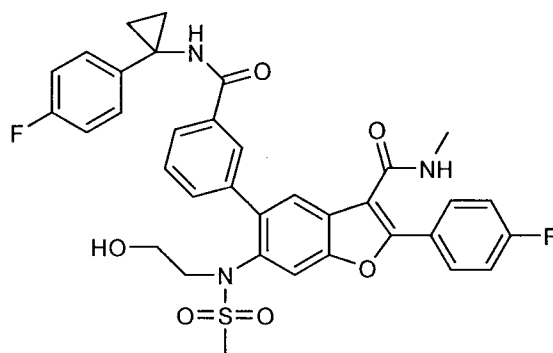
Se añadió clorhidrato de 1-fenilciclopropanamina (16 mg, 0,091 mmol) a
 5 una solución agitada de HATU (43 mg, 0,114 mmol), DIEA (40 μ l, 0,228 mmol)
 y ácido 3-(2-(4-fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-3-(
 (metilcarbamoil)benzofuran-5-il)benzoico (40 mg, 0,076 mmol) en DMF (760 μ l)
 a temperatura ambiente. Se dejó agitando durante 1 hora. La mezcla se diluyó
 con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó
 10 sobre Na₂SO₄, se filtró y se concentró y se purificó por HPLC preparativa en
 fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN
 adecuadamente tamponado y se concentró dando el compuesto del epígrafe
 (22 mg, 44%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 9,12 (1 H, s), 8,49 -
 8,56 (1 H, m), 7,97 - 8,05 (3 H, m), 7,95 (1 H, s), 7,90 (1 H, d, *J*=7,93 Hz), 7,78
 15 (1 H, d, *J*=7,93 Hz), 7,62 (1 H, s), 7,54 (1 H, t, *J*=7,78 Hz), 7,37 - 7,46 (2 H, m),
 7,28 (2 H, t, *J*=7,63 Hz), 7,19 - 7,24 (2 H, m), 7,15 (1 H, t, *J*=7,32 Hz), 4,90 (1
 H, t, *J*=5,19 Hz), 3,50 - 3,58 (1 H, m), 3,25 - 3,28 (1 H, m), 3,21 (3 H, s), 2,88 -
 2,96 (2 H, m), 2,82 (3 H, d, *J*=4,58 Hz), 1,22 - 1,32 (4 H, m). Tiempo de

retención de LC-EM: 1,57 min; m/z (MH⁺): 642. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución

5 emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% /

10 acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min,

15 Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 11,28 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 10,86 min, pureza = 98%.



2-(4-Fluorofenil)-5-(3-(1-(4-fluorofenil)ciclopropilcarbamoil)fenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metilbenzofuran-3-carboxamida

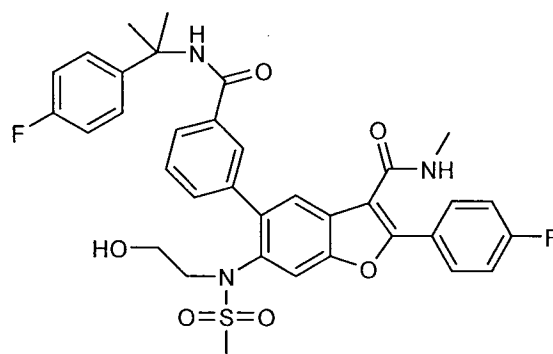
Se añadió clorhidrato de 1-(4-fluorofenil)ciclopropanamina (22 mg, 0,114 mmol) a una solución agitada de HATU (54 mg, 0,142 mmol), DIEA (50 μ l, 0,285 mmol) y ácido 3-(2-(4-fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-3-(metilcarbamoil)benzofuran-5-il)benzoico (50 mg, 0,095 mmol) en DMF (950 μ l) a temperatura ambiente. Se dejó agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (30 mg, 47%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 9,14 (1 H, s), 8,49 - 8,55 (1 H, m), 7,99 - 8,04 (2 H, m), 7,97 - 7,98 (1 H, m), 7,95 (1 H, s), 7,88 (1 H, d, *J*=8,24 Hz), 7,78 (1 H, d, *J*=7,93 Hz), 7,61 (1 H, s), 7,53 (1 H, t, *J*=7,78 Hz), 7,39 - 7,45 (2 H, m), 7,22 - 7,32 (2 H, m), 7,05 - 7,13 (2 H, m), 4,90 (1 H, t, *J*=5,04 Hz), 3,50 - 3,58 (1 H, m), 3,24 - 3,28 (1 H, m), 3,20 (3 H, s), 2,93 (2 H, s ancho), 2,81 (3 H, d, *J*=4,58 Hz), 1,25 (4 H, d, *J*=9,77 Hz). Tiempo de retención

de LC-EM: 1,60 min; m/z (MH⁺): 660. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución

5 emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% /

10 acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min,

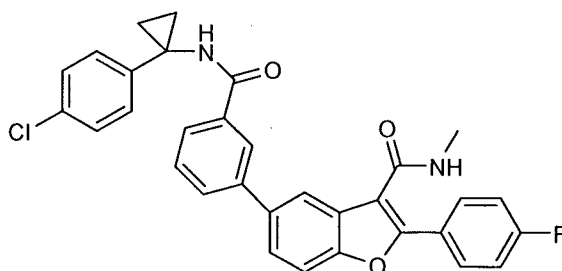
15 Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 11,49 min, pureza = 99% ; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 11,04 min, pureza = 99%.



2-(4-Fluorofenil)-5-(3-(2-(4-fluorofenil)propan-2-ilcarbamoil)fenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metilbenzofuran-3-carboxamida

Se añadió 2-(4-fluorofenil)propan-2-amina (18 mg, 0,114 mmol) a una
 5 solución agitada de HATU (54 mg, 0,142 mmol), DIEA (50 µl, 0,285 mmol) y 2-(4-fluorofenil)propan-2-amina (18 mg, 0,114 mmol) en DMF (950 µl) a temperatura ambiente. Se dejó agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se purificó por HPLC preparativa en
 10 fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (18 mg, 28%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 8,50 - 8,56 (1 H, m), 8,31 (1 H, s), 7,98 - 8,05 (3 H, m), 7,96 (1 H, s), 7,83 (1 H, d, *J*=7,63 Hz), 7,73 (1 H, d, *J*=7,63 Hz), 7,62 (1 H, s), 7,53 (1 H, t, *J*=7,78 Hz), 7,38 - 7,47 (4 H, m),
 15 7,09 (2 H, t, *J*=8,85 Hz), 4,90 (1 H, t, *J*=5,19 Hz), 3,50 - 3,58 (1 H, m), 3,26 - 3,29 (1 H, m), 3,23 (3 H, s), 2,87 - 2,93 (2 H, m), 2,82 (3 H, d, *J*=4,58 Hz), 1,67 (6 H, s). Tiempo de retención de LC-EM: 1,66 min; *m/z* (MH⁺): 662. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS

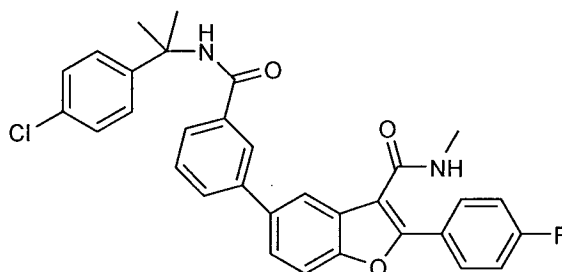
- equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente
- 5 B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.
- 10 Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 12,11 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150
- 15 mm, 3,5 mm, Tr = 11,48 min, pureza = 100%.



5-(3-(1-(4-Clorofenil)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió clorhidrato de 1-(4-clorofenil)ciclopropanamina (25 mg, 0,123 mmol) a una solución agitada de HATU (59 mg, 0,154 mmol), DIEA (54 μ l, 0,308 mmol) y ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (40 mg, 0,103 mmol) en DMF (1 ml) a temperatura ambiente. Se dejó agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con NaHCO_3 sat y NaCl sat. La fase orgánica se secó sobre Na_2SO_4 , se filtró y se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ adecuadamente tamponado y se concentró dando el compuesto del epígrafe (8 mg, 14%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 9,37 (1 H, s), 8,46 - 8,55 (1 H, m), 8,22 (1 H, s), 7,95 - 8,05 (2 H, m), 7,86 - 7,95 (3 H, m), 7,74 - 7,83 (2 H, m), 7,59 (1 H, t, $J=7,63$ Hz), 7,38 - 7,44 (2 H, m), 7,30 - 7,36 (2 H, m), 7,20 - 7,28 (2 H, m), 2,86 (3 H, d, $J=4,58$ Hz), 1,26 - 1,36 (4 H, m). Tiempo de retención de LC-EM: 1,92 min; m/z (MH^+): 539. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H_2O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H_2O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los

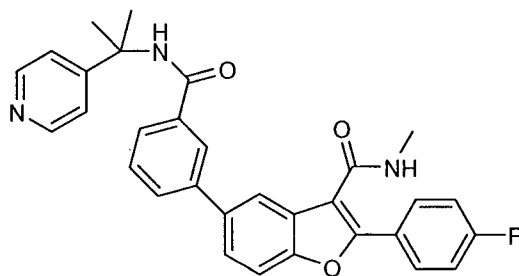
datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 14,56 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 13,20 min, pureza = 97%.



5-(3-(2-(4-Clorofenil)propan-2-ilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió 2-(4-clorofenil)propan-2-amina (21 mg, 0,123 mmol) a una solución agitada de HATU (59 mg, 0,154 mmol), DIEA (54 µl, 0,308 mmol) y ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (40 mg, 0,103 mmol) en DMF (1 ml) a temperatura ambiente. Se dejó agitando durante 1 hora. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un

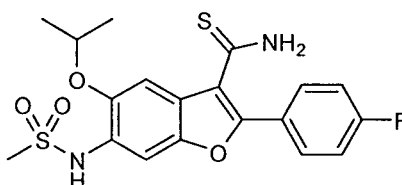
gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (32 mg, 57%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 8,64 (1 H, s), 8,47 - 8,55 (1 H, m), 8,14 (1 H, s), 7,99 - 8,04 (2 H, m), 7,92 (1 H, s), 7,74 - 7,89 (4 H, m), 7,57 (1 H, t, *J*=7,78 Hz), 7,37 - 7,45 (4 H, m), 7,34 (2 H, d, *J*=8,85 Hz), 2,87 (3 H, d, *J*=4,58 Hz), 1,69 (6 H, s). Tiempo de retención de LC-EM: 1,95 min; *m/z* (MH⁺): 541. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 15,18 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 13,66 min, pureza = 99%.



2-(4-Fluorofenil)-N-metil-5-(3-(2-(piridin-4-il)propan-2-ilcarbamoi)fenil)benzofuran-3-carboxamida

- 5 Se añadió diclorhidrato de 2-(piridin-4-il)propan-2-amina (26 mg, 0,123 mmol) a una solución agitada de HATU (59 mg, 0,154 mmol), DIEA (54 μ l, 0,308 mmol) y ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoi)benzofuran-5-il)benzoico (40 mg, 0,103 mmol) en DMF (1 ml) a temperatura ambiente. Se dejó agitando durante 1 hora. La reacción se purificó por HPLC preparativa en
- 10 fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (15 mg, 27%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 8,73 (1 H, s), 8,50 - 8,55 (1 H, m), 8,48 (2 H, dd, *J*=4,58, 1,53 Hz), 8,16 (1 H, s), 7,97 - 8,04 (2 H, m), 7,91 - 7,94 (1 H, m), 7,88 (1 H, d, *J*=7,63 Hz), 7,85 (1 H, d, *J*=7,93 Hz), 7,75 - 7,82 (2 H, m), 7,58 (1 H, t, *J*=7,63 Hz), 7,36 - 7,43 (4 H, m), 2,86 (3 H, d, *J*=4,58 Hz), 1,68 (6 H, s). Tiempo de retención de LC-EM: 1,59 min; *m/z* (MH⁺):
- 15 508. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de

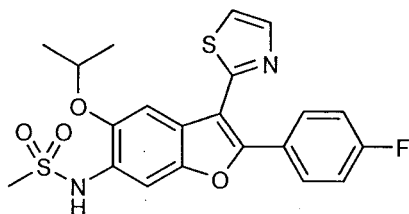
220nM. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 mm, Tr = 8,60 min, pureza = 95%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 mm, Tr = 9,26 min, pureza = 96%.



2-(4-Fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carbotioamida.

La reacción se desarrolló en dos lotes y se combinaron para el tratamiento. En el primer lote, se añadió reactivo de Lawesson (27 mg, 0,067 mmol) a una solución de 2-(4-fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carboxamida (35 mg, 0,086 mmol) en THF (1,2

ml). La reacción se agitó a temperatura ambiente durante 2 horas, punto en el que se añadió más reactivo de Lawesson (8 mg, 0,020 mmol). En el segundo lote, se añadió reactivo de Lawesson (129 mg, 0,32 mmol) a una solución de 2-(4-fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carboxamida (125 mg, 0,31 mmol) en THF (3 ml) y se agitó a temperatura ambiente durante 1,5 h. Se reunieron entonces los dos lotes y se repartió entre EtOAc (50 ml) y agua (10 ml). La fase orgánica se lavó con NaHCO₃ saturado y salmuera, se secó sobre Na₂SO₄, se filtró y se concentró dando un aceite amarillo. El residuo se purificó por cromatografía sobre gel de sílice (Cartucho de gel de sílice BIOTAGE® 25+S, gradiente de elución: 20% hasta 80% de EtOAc/hexanos sobre 20 volúmenes de columna, recogida de la fracción a $\lambda = 320$ nm) dando 48 mg (29% de rendimiento) del compuesto del epígrafe. RMN de ¹H (300 MHz, CDCl₃) δ ppm 7,76 - 7,87 (m, 2 H) 7,71 (d, $J = 5,86$ Hz, 2 H) 7,53 (s ancho, 1 H) 7,13 - 7,23 (m, 2 H) 6,97 (s, 1 H) 6,90 (s ancho, 1 H) 4,74 (dt, $J = 12,08, 6,04$ Hz, 1 H) 2,93 (s, 3 H) 1,40 (d, $J = 6,22$ Hz, 6 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 5%/H₂O al 95%/NH₄OAc al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/NH₄OAc al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 5 ml/min, Columna: XBridge C18 5 μ m 4,6 x 50 mm; HPLC Tr = 1,39 min, (ES+) m/z (MH⁺) = 423.

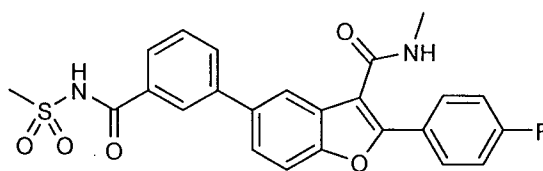


N-(2-(4-Fluorofenil)-5-isopropoxi-3-(tiazol-2-il)benzofuran-6-il)metanosulfonamida

Se añadió cloroacetaldehído (solución al 50% en agua, 100 μ l, 0,79 mmol) a una suspensión agitada del intermedio 2-(4-fluorofenil)-5-isopropoxi-6-(metilsulfonamido)benzofuran-3-carbotioamida (48 mg, 0,11 mmol) en etanol (1,5 ml) y la reacción se llevó a reflujo (temperatura de baño de aceite 100 $^{\circ}$ C). Después de 4 h, se añadió más solución de cloroacetaldehído (200 μ l, 1,6 mmol) y se continuó calentando durante la noche. La reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc (75 ml), se lavó con agua (10 ml), NaHCO₃ saturado (2 x 5 ml) y salmuera, se secó sobre Na₂SO₄, se filtró y se concentró dando un aceite marrón. El residuo se purificó sobre gel de sílice (columna BIOTAGE® 12+M, gradiente de elución 10% hasta 40% de EtOAc/hexanos sobre 20 volúmenes de columna, recogida de la fracción a λ = 320 nm) dando un aceite incoloro, 38 mg (75% de rendimiento). RMN de ¹H (300 MHz, CDCl₃) δ ppm 7,96 (d, J = 3,29 Hz, 1 H) 7,73 - 7,86 (m, 3 H) 7,56 (s, 1 H) 7,37 (d, J = 3,29 Hz, 1 H) 7,07 - 7,19 (m, 2 H) 6,98 (s, 1 H) 4,73 (spt, J = 6,04 Hz, 1 H) 2,96 (s, 3 H) 1,40 (d, J = 5,86 Hz, 7 H). Se obtuvo una muestra analíticamente pura por precipitación en Et₂O/hexanos dando un precipitado

amarillo, que se trituro con Et₂O y se seco al aire. La LC/EM se realizo usando un instrumento Shimadzu-VP con deteccion UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 5%/H₂O al 95%/NH₄OAc al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/NH₄OAc al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de deteccion = 3 min, Caudal = 5 ml/min, Columna: XBridge C18 5 µm 4,6 x 50 mm; HPLC Tr = 1,69 min, (ES+) m/z (MH⁺) = 447. Se realizo una HPLC analitica usando un instrumento Shimadzu-VP con deteccion UV a 220 nm y 254 nm. Procedimiento HPLC analitico: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de deteccion = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 14,74 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 12,86 min, pureza = 98%.

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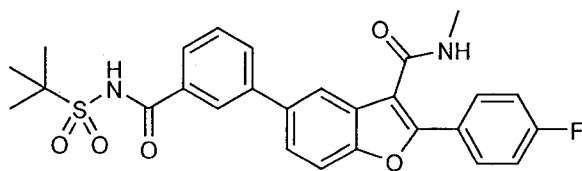


2-(4-Fluorofenil)-N-metil-5-(3-(metilsulfonilcarbamoil)fenil)benzofuran-3-carboxamida

En un vial de 1,77 cm³ (1 dracma) con barra de agitacion se combinaron
ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (35 mg,

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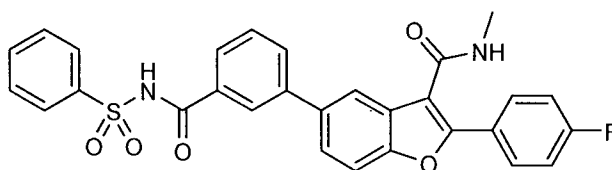
0,090 mmol), DMAP (33 mg, 0,27 mmol), clorhidrato de EDC (26 mg, 0,14 mmol) y metanosulfonamida (25 mg, 0,26 mmol). Se añadió DMF (0,5 ml), se tapó el vial y se agitó la reacción a temperatura ambiente durante la noche. La reacción se filtró, se purificó por HPLC prep y se concentró dando 30 mg (72% de rendimiento) del compuesto del epígrafe como un polvo blanco. RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 12,36 (s ancho, 1 H) 8,53 (d, $J = 4,58$ Hz, 1 H) 8,27 (s, 1 H) 7,97 - 8,05 (m, 2 H) 7,84 - 7,96 (m, 3 H) 7,77 - 7,82 (m, 1 H) 7,71 - 7,76 (m, 1 H) 7,56 (t, $J = 7,78$ Hz, 1 H) 7,40 (t, $J = 8,85$ Hz, 2 H) 3,17 (s, 3 H) 2,86 (d, $J = 4,58$ Hz, 3 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH_3CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH_3CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 μm 4,6 x 50 mm; HPLC Tr = 1,56 min, (ES+) m/z (MH^+) = 467. Se realizó una HPLC analítica usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = CH_3OH al 5%/H₂O al 95%/NH₄CO₃ 10 mM, Disolvente B = CH_3OH al 95%/H₂O al 5%/NH₄CO₃ 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C18, 4,6 mm, 3 μm , Tr = 11,93 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μm , Tr = 13,97 min, pureza = 99%.



5-(3-(*tert*-Butilsulfonilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 5 En un vial de 1,77 cm³ (1 dracma) con barra de agitación se combinaron ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (35 mg, 0,090 mmol), DMAP (33 mg, 0,27 mmol), clorhidrato de EDC (26 mg, 0,14 mmol) y *tert*-butilsulfonamida (37 mg, 0,27 mmol). Se añadieron 1,2-dicloroetano (1 ml) y DMF (0,3 ml), se tapó el vial y la reacción se agitó a
- 10 temperatura ambiente durante la noche. La reacción se concentró, se filtró, se purificó por HPLC prep y se concentró en un SPEEDVAC® dando 14 mg (31% de rendimiento) del compuesto del epígrafe como un polvo blanco. RMN de ¹H (500 MHz, CDCl₃) δ ppm 8,12 (s, 1 H) 7,97 (s, 1 H) 7,91 (dd, *J* = 8,55, 5,19 Hz, 2 H) 7,84 (d, *J* = 7,63 Hz, 1 H) 7,79 (d, *J* = 7,32 Hz, 1 H) 7,46 - 7,59 (m, 3 H)
- 15 7,19 (t, *J* = 8,55 Hz, 2 H) 6,04 (s ancho, 1 H) 2,99 (d, *J* = 4,58 Hz, 3 H) 1,54 (s, 9 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH₃CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min,
- 20 Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 μm

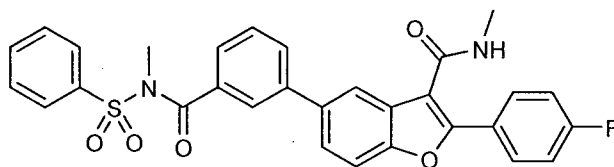
4,6 x 50 mm; HPLC Tr = 1,71 min, (ES+) m/z (MH⁺) = 509. Se realizó una HPLC analítica usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = CH₃OH al 5%/H₂O al 95%/NH₄CO₃ 10 mM, Disolvente B = CH₃OH al 95%/H₂O al 5%/NH₄CO₃ 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C18, 4,6 mm, 3 µm, Tr = 16,49 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 15,35 min, pureza = 100%.



2-(4-fluorofenil)-N-metil-5-(3-(fenilsulfonilcarbamoil)fenil)benzofuran-3-carboxamida

En un vial de 1,77 cm³ (1 dracma) con barra de agitación se combinaron ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (35 mg, 0,090 mmol), DMAP (33 mg, 0,27 mmol), Clorhidrato de EDC (26 mg, 0,14 mmol) y bencenosulfonamida (43 mg, 0,27 mmol). Se añadieron 1,2-dicloroetano (1 ml) y DMF (0,3 ml), el vial se tapó y la suspensión se agitó a temperatura ambiente durante la noche, tiempo durante el cual se disolvieron los sólidos. La reacción se concentró, se filtró, se purificó por HPLC prep y se concentró dando 32 mg (67% de rendimiento) del compuesto del epígrafe como

un polvo blanco. RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 12,78 (s ancho, 1 H) 8,52 (c, $J = 4,48$ Hz, 1 H) 8,24 (s, 1 H) 7,97 - 8,06 (m, 4 H) 7,90 - 7,97 (m, 2 H) 7,85 (d, $J = 7,94$ Hz, 1 H) 7,74 - 7,81 (m, 2 H) 7,66 - 7,73 (m, 1 H) 7,63 (t, $J = 7,63$ Hz, 2 H) 7,58 (t, $J = 7,63$ Hz, 1 H) 7,40 (t, $J = 8,85$ Hz, 2 H) 2,87 (d, $J = 4,58$ Hz, 3 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH_3CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH_3CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 μm 4,6 x 50 mm; HPLC Tr = 1,77 min, (ES+) m/z (MH^+) = 529. Se realizó una HPLC analítica usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = CH_3OH al 5%/H₂O al 95%/NH₄CO₃ 10 mM, Disolvente B = CH_3OH al 95%/H₂O al 5%/NH₄CO₃ 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C18, 4,6 mm, 3 μm , Tr = 15,70 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μm , Tr = 14,90 min, pureza = 99%.

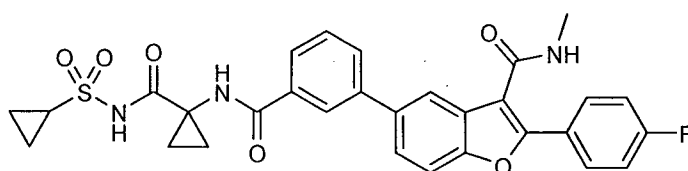


2-(4-Fluorofenil)-N-metil-5-(3-(metil(fenilsulfonil)carbamoil)fenil)benzofuran-3-carboxamida

En un vial de 1,77 cm³ (1 dracma) con barra de agitación se combinaron ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (35 mg, 0,090 mmol), DMAP (33 mg, 0,27 mmol), clorhidrato de EDC (26 mg, 0,14 mmol) y *N*-metilbencenosulfonamida (50 µl, 0,26 mmol). Se añadieron 1,2-dicloroetano (0,5 ml) y DMF (0,5 ml), el vial se tapó y la reacción se agitó a temperatura ambiente durante la noche. La reacción se filtró, se purificó por HPLC prep y se concentró en un SPEEDVAC® dando 27 mg (55% de rendimiento) del compuesto del epígrafe como un polvo blanco. RMN de ¹H (500 MHz, CDCl₃) δ ppm 7,91 - 8,02 (m, 5 H) 7,75 - 7,82 (m, 2 H) 7,65 (t, *J* = 7,48 Hz, 1 H) 7,47 - 7,60 (m, 6 H) 7,15 - 7,24 (m, 2 H) 5,91 (d, *J* = 4,27 Hz, 1 H) 3,36 (s, 3 H) 3,04 (d, *J* = 4,88 Hz, 3 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH₃CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 µm 4,6 x 50 mm; HPLC Tr = 1,89 min, (ES+) *m/z* (MH⁺) = 543. Se realizó una HPLC analítica usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = CH₃OH al 5%/H₂O al 95%/NH₄CO₃ 10 mM, Disolvente B = CH₃OH al 95%/H₂O al 5%/NH₄CO₃ 10

mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C18, 4,6 mm, 3 μ m, Tr = 17,42 min, pureza = 92%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μ m, Tr = 17,86 min, pureza >90%.

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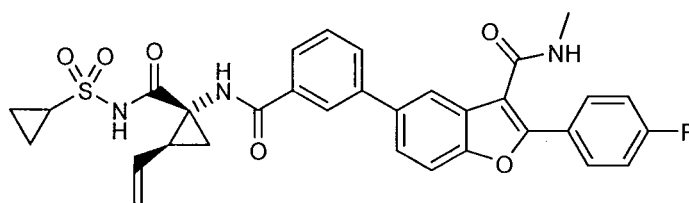


5-(3-(1-(Ciclopropilsulfonilcarbamoyl)ciclopropilcarbamoyl)fenil)-2-(4-fluorofenil)-
N-metilbenzofuran-3-carboxamida

En un vial de centelleo de 7 ml se combinaron ácido 3-(2-(4-fluorofenil)-
10 3-(metilcarbamoyl)benzofuran-5-il)benzoico (30 mg, 0,077 mmol), clorhidrato de
1-amino-N-(ciclopropilsulfonil)ciclopropanocarboxamida (20 mg, 0,083 mmol) y
HATU (40 mg, 0,10 mmol). Se añadieron DMF (0,4 ml) y DIPEA (0,1 ml, 0,57
mmol), el vial se tapó y la solución se agitó a temperatura ambiente durante 45
min. La reacción se diluyó con MeOH, se filtró, se purificó por HPLC prep y las
15 fracciones recogidas se concentraron en un SPEEDVAC® proporcionando el
compuesto del epígrafe (23 mg, 52% de rendimiento) como un polvo blanco.
RMN de ^1H (500 MHz, DMSO- d_6) δ ppm 8,99 (s ancho, 1 H) 8,53 (c, J = 4,78
Hz, 1 H) 8,25 (s ancho, 1 H) 8,00 (dd, J = 8,85, 5,49 Hz, 2 H) 7,93 (s, 1 H) 7,89
(t, J = 7,78 Hz, 2 H) 7,72 - 7,83 (m, 2 H) 7,58 (t, J = 7,48 Hz, 1 H) 7,40 (t, J =
20 8,85 Hz, 2 H) 7,07 (s ancho, 1 H) 2,89 - 2,98 (m, 1 H) 2,87 (d, J = 4,58 Hz, 3 H)

1,35 - 1,56 (m, 2 H) 0,77 - 1,28 (m, 6 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH₃CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 µm 4,6 x 50 mm; HPLC Tr = 1,59 min, (ES+) m/z (MH⁺) = 576. Se realizó una HPLC analítica usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = CH₃OH al 5%/H₂O al 95%/NH₄CO₃ 10 mM, Disolvente B = CH₃OH al 95%/H₂O al 5%/NH₄CO₃ 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C18, 4,6 mm, 3 µm, Tr = 15,39 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 14,50 min, pureza = 100%.

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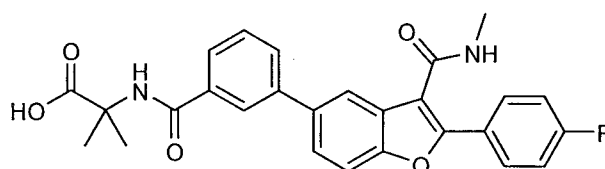


5-(3-((1R,2S)-1-(Ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

En un vial de centelleo de 7 ml se combinaron ácido 3-(2-(4-fluorofenil)-

3-(metilcarbamoil)benzofuran-5-il)benzoico (30 mg, 0,077 mmol), 4-metilbencenosulfonato de (1R,2S)-1-amino-*N*-(ciclopropilsulfonil)-2-vinilciclopropanocarboxamida (30 mg, 0,075 mmol) y HATU (40 mg, 0,10 mmol). Se añadieron DMF (0,4 ml) y DIPEA (0,1 ml, 0,57 mmol), el vial se tapó y la solución se agitó a temperatura ambiente durante 45 min. La reacción se diluyó con MeOH, se filtró, se purificó por HPLC prep y las fracciones recogidas se concentraron en un SPEEDVAC® proporcionando el compuesto del epígrafe (25 mg, 54% de rendimiento) como un polvo blanco. RMN de ^1H (500 MHz, CDCl_3) δ ppm 8,01 (s, 1 H) 7,97 (s, 1 H) 7,88 (dd, $J = 8,85, 5,19$ Hz, 2 H) 7,80 (d, $J = 7,63$ Hz, 1 H) 7,74 (d, $J = 7,63$ Hz, 1 H) 7,59 (s ancho, 1 H) 7,52 (s, 2 H) 7,48 (t, $J = 7,63$ Hz, 1 H) 7,18 (t, $J = 8,55$ Hz, 2 H) 6,00 (d, $J = 3,97$ Hz, 1 H) 5,61 - 5,73 (m, 1 H) 5,39 (d, $J = 17,09$ Hz, 1 H) 5,20 (d, $J = 10,99$ Hz, 1 H) 3,02 (d, $J = 4,88$ Hz, 3 H) 2,91 - 2,99 (m, 1 H) 2,34 (c, $J = 8,44$ Hz, 1 H) 2,05 - 2,09 (m, 1 H) 1,49 (dd, $J = 9,31, 5,95$ Hz, 1 H) 1,41 (dd, $J = 5,80, 4,58$ Hz, 1 H) 1,30 - 1,35 (m, 1 H) 1,22 - 1,30 (m, 1 H) 1,04 - 1,12 (m, 1 H) 0,96 - 1,04 (m, 1 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH_3CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH_3CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 μm 4,6 x 50 mm; HPLC Tr = 1,73 min, (ES+) m/z (MH^+) = 602. Se realizó una HPLC analítica usando un instrumento Shimadzu-VP con detección UV a 220 nm y

254 nm. Procedimiento HPLC analítico: Disolvente A = CH₃OH al 5%/H₂O al 95%/NH₄CO₃ 10 mM, Disolvente B = CH₃OH al 95%/H₂O al 5%/NH₄CO₃ 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: PHENOMENEX® Gemini C18, 4,6 mm, 3 μm, Tr = 16,26 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μm, Tr = 15,28 min, pureza = 100%.



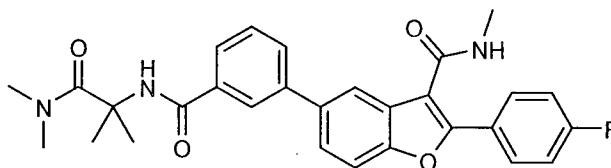
Ácido 2-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzamido)-2-metilpropanoico

Se añadió HATU (450 mg, 1,18 mmol) a una suspensión de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (400 mg, 1,03 mmol), clorhidrato de 2-amino-2-metilpropanoato de metilo (180 mg, 1,17 mmol) y DIPEA (0,6 ml, 3,4 mmol) en DCE (10 ml). Después de 5 min, los sólidos no se habían disuelto. Se añadió DMF (0,5 ml) y se continuó agitando la suspensión a temperatura ambiente durante la noche. La reacción se concentró a continuación dando una suspensión densa (quedaba DMF después de concentrar). Se añadieron agua y Et₂O y el matraz se removió hasta que se formó una suspensión fina color gris. El precipitado se recogió por filtración, se lavó con HCl 1N, agua y éter y se secó al aire proporcionando 550 mg (110%

de rendimiento) del compuesto del epígrafe como un sólido gris. La LC/EM se llevó a cabo en un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 5%/H₂O al 95%/NH₄OAc 10 mM, Disolvente B = CH₃CN al 95%/H₂O al 5%/NH₄OAc 10 mM, %B inicial = 0, final %B = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 5 ml/min, Columna: XBridge C18 5 μm 4,6 x 50 mm; HPLC Tr = 1,49 min, (ES+) m/z (MH⁺) = 489.

A una suspensión del éster bruto anterior (~0,1 mmol) en MeOH (7 ml)/H₂O (2,1 ml) en un vial de centelleo de 20 ml con una barra de agitación se añadió solución 10 N de NaOH (0,4 ml, 4,00 mmol). El vial se tapó, se agitó a temperatura ambiente durante la noche, luego se inactivó vertiendo en 8 ml de HCl 1 N. Se formó un precipitado blanco. La suspensión se extrajo con EtOAc y el sólido gris insoluble se recogió por filtración y se secó al aire (61 mg). La fase orgánica se lavó con salmuera, se secó sobre Na₂SO₄, se filtró y se concentró dando un polvo blanco. Este se trituroó con Et₂O y se recogió por filtración dando 360 mg del polvo blanco. Ambas tandas de precipitado eran idénticas por LC/EM y se reunieron dando 421 mg (86% para las dos etapas) del compuesto del epígrafe como un polvo blanquecino. RMN de ¹H (300 MHz, CD₃OD) δ ppm 8,59 (s, 1 H) 8,50 (d, J = 3,29 Hz, 1 H) 8,10 - 8,16 (m, 1 H) 7,91 - 8,01 (m, 3 H) 7,83 (dd, J = 12,99, 7,87 Hz, 2 H) 7,64 - 7,74 (m, 2 H) 7,56 (t, J = 7,68 Hz, 1 H) 7,27 (t, J = 8,78 Hz, 2 H) 2,95 - 3,02 (m, 3 H) 1,62 (s, 6 H). La LC/EM se llevó a cabo en un instrumento Shimadzu-VP con detección UV a

220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 5%/H₂O al 95%/NH₄OAc 10 mM, Disolvente B = CH₃CN al 95%/H₂O al 5%/NH₄OAc 10 mM, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 5 ml/min, Columna: XBridge C18 5
 5 µm 4,6 x 50 mm; HPLC Tr = 1,06 min, (ES+) m/z (MH⁺) = 475. Se realizó una HPLC analítica usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de
 10 detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 3,5 µm 4,6 x 150 mm, Tr = 10,91 min, pureza = 98%; Columna: columna Waters XBridge Phenyl 3,5 µm 4,6 x 150 mm, Tr = 10,21 min, pureza = 98%.



15 5-(3-(1-(Dimetilamino)-2-metil-1-oxopropan-2-ilcarbamoil)fenil)-2-(4-fluorofenil)-
 N-metilbenzofuran-3-carboxamida

Se añadió una solución de dimetilamina en THF (2 molar, 0,10 ml, 0,20 mmol) a ácido 2-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzamido)-2-metilpropanoico (17 mg, 0,036 mmol) y HATU (15 mg, 0,039
 20 mmol) en un vial de 1,77 cm³ (1 dracma). Se añadió DMF (0,3 ml), el vial se

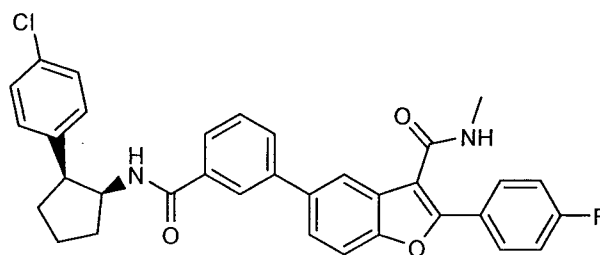
tapó y la solución homogénea se agitó a temperatura ambiente durante 1 h, punto en el que se añadió DIPEA (50 μ l, 0,29 mmol). Se continuó agitando durante 3 h, punto en el que la reacción se filtró y se purificó directamente por HPLC prep. La concentración de las fracciones recogidas proporcionó el

5 compuesto del epígrafe como un sólido blanco (13 mg, 71% de rendimiento). RMN de ^1H (500 MHz, CD_3OD) δ ppm 8,09 - 8,17 (m, 1 H) 7,90 - 7,98 (m, 3 H) 7,86 (d, J = 7,94 Hz, 1 H) 7,79 - 7,84 (m, 1 H) 7,63 - 7,72 (m, 2 H) 7,57 (t, J = 7,63 Hz, 1 H) 7,20 - 7,32 (m, 2 H) 3,14 (s ancho, 3 H) 2,98 (s, 6 H) 1,61 (s, 6 H). La LC/EM se llevó a cabo en un instrumento Shimadzu-VP con detección

10 UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH_3CN al 5%/H₂O al 95%/NH₄OAc 10 mM, Disolvente B = CH_3CN al 95%/H₂O al 5%/NH₄OAc 10 mM, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 5 ml/min, Columna: XBridge C18 5 μ m 4,6 x 50 mm; HPLC Tr = 1,29 min, (ES+) m/z (MH^+) = 502. Procedimiento

15 HPLC analítico: Disolvente A = CH_3CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH_3CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 3,5 μ m 4,6 x 150 mm, Tr = 14,80 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 3,5 μ m 4,6 x 150

20 mm, Tr = 10,37 min, pureza = 100%.

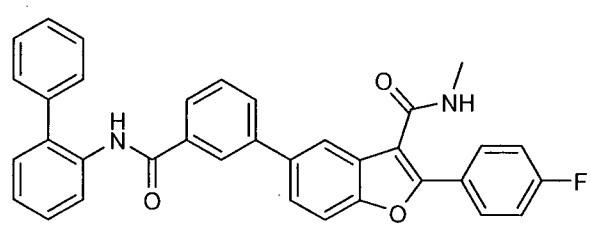


5-(3-((Cis)-2-(4-clorofenil)ciclopentilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

En un vial de 1,77 cm³ (1 dracma) se combinaron ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (20 mg, 0,051 mmol), *cis*-2-(4-clorofenil)ciclopentanamina (14 mg, 0,072 mmol) y HATU (31 mg, 0,082 mmol). Se añadieron DMF (0,4 ml) y DIPEA (50 µl, 0,29 mmol) y el vial se tapó y se agitó a temperatura ambiente durante 2 h, luego se diluyó con MeOH, se filtró y se purificó directamente por HPLC prep. La concentración proporcionó el compuesto del epígrafe (15 mg, 52% de rendimiento) como un sólido blanco apelmusado. RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 8,47 - 8,59 (m, 1 H) 8,06 (d, *J* = 8,85 Hz, 1 H) 7,97 - 8,03 (m, 2 H) 7,86 (d, *J* = 1,83 Hz, 1 H) 7,75 - 7,82 (m, 2 H) 7,68 (s, 1 H) 7,65 (dd, *J* = 8,55, 1,83 Hz, 1 H) 7,45 - 7,53 (m, 2 H) 7,40 (t, *J* = 8,85 Hz, 2 H) 7,27 (s, 4 H) 4,60 - 4,71 (m, *J* = 7,67, 7,67, 7,55, 7,32 Hz, 1 H) 3,33 - 3,41 (m, 1 H) 2,87 (d, *J* = 4,58 Hz, 3 H) 1,99 - 2,15 (m, 3 H) 1,89 - 1,98 (m, 1 H) 1,72 - 1,82 (m, 1 H) 1,57 - 1,71 (m, 1 H). La LC/EM se llevó a cabo en un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH₃CN al 90%/H₂O al

10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 µm 4,6 x 50 mm; HPLC Tr = 2,02 min, (ES+) m/z (MH⁺) = 567. Procedimiento HPLC analítico: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%,
5 Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 3,5 µm 4,6 x 150 mm, Tr = 15,42 min, pureza = 98%; Columna: columna Waters XBridge Phenyl 3,5 µm 4,6 x 150 mm, Tr = 13,74 min, pureza = 97%.

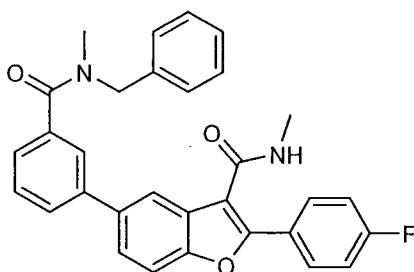
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5-(3-(Bifenil-2-ilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

En un vial de 1,77 cm³ (1 dracma) se combinaron ácido 3-(2-(4-
15 fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)benzoico (30 mg, 0,077 mmol), bifenil-2-amina (17 mg, 0,10 mmol) y HATU (40 mg, 0,105 mmol). Se añadieron DMF (0,4 ml) y DIPEA (50 µl, 0,29 mmol) y el vial se tapó y se agitó a temperatura ambiente durante la noche, luego se diluyó con MeOH, se filtró y se purificó directamente por HPLC prep. La concentración proporcionó el

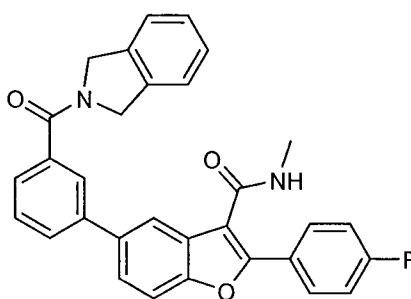
compuesto del epígrafe (17 mg, 41% de rendimiento) como un sólido blanco
apelusado. RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 9,96 (s, 1 H) 8,53 (c, J =
4,58 Hz, 1 H) 7,96 - 8,06 (m, 3 H) 7,85 - 7,91 (m, 2 H) 7,80 (d, J = 8,55 Hz, 1 H)
7,77 (d, J = 7,32 Hz, 1 H) 7,70 (dd, J = 8,55, 1,83 Hz, 1 H) 7,57 - 7,61 (m, 1 H)
5 7,56 (d, J = 6,10 Hz, 1 H) 7,48 (d, J = 7,32 Hz, 2 H) 7,36 - 7,46 (m, 7 H) 7,31 (t,
 J = 7,48 Hz, 1 H) 2,87 (d, J = 4,88 Hz, 3 H). La LC/EM se realizó usando un
instrumento Shimadzu-VP con detección UV a 220 nm y Waters
MICROMASS®. Procedimiento LC/EM: Disolvente A = CH_3CN al 10%/H₂O al
90%/TFA al 0,1%, Disolvente B = CH_3CN al 90%/H₂O al 10%/TFA al 0,1%, %B
10 inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección =
3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 μm 4,6 x 50 mm; HPLC Tr =
2,02 min, (ES+) m/z (MH^+) = 541. Procedimiento HPLC analítico: Disolvente A
= CH_3CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH_3CN al 95%/H₂O al
5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15
15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters
Sunfire C-18, 3,5 μm 4,6 x 150 mm, Tr = 15,37 min, pureza = 100%; Columna:
columna Waters XBridge Phenyl 3,5 μm 4,6 x 150 mm, Tr = 13,75 min, pureza
= 100%.



5-(3-(Bencil(metil)carbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadieron DIPEA (50 μ l, 0,29 mmol) y *N*-metilbencilamina (20 μ l, 0,16 mmol) a una suspensión agitada de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (20 mg, 0,051 mmol) y HATU (25 mg, 0,066 mmol) en DMF (0,5 ml) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se diluyó entonces con MeOH, se filtró, se purificó por HPLC prep y se concentró dando el compuesto del epígrafe como un polvo color castaño (12 mg, 47% de rendimiento). RMN de ^1H (500 MHz, DMSO- d_6) δ ppm 8,50 (s ancho, 1 H) 8,01 (dd, J = 8,39, 5,65 Hz, 2 H) 7,66 - 7,93 (m, 5 H) 7,58 (s ancho, 1 H) 7,42 - 7,50 (m, 1 H) 7,35 - 7,42 (m, 4 H) 7,31 (d, J = 5,80 Hz, 1 H) 7,23 (d, J = 4,58 Hz, 1 H) 4,72 (s ancho, 1 H) 4,54 (s ancho, 1 H) 2,83 - 3,00 (m, 6 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH₃CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 μ m 4,6 x 50 mm; HPLC Tr = 1,85 min, (ES+)

m/z (MH^+) = 493. Procedimiento HPLC analítico: Disolvente A = CH_3CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH_3CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 3,5 μm 4,6 x 150 mm, Tr = 16,26 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 3,5 μm 4,6 x 150 mm, Tr = 12,81 min, pureza = 98%.



2-(4-Fluorofenil)-5-(3-(isoindolin-2-carbonil)fenil)-N-metilbenzofuran-3-carboxamida

10

Se añadió isoindolina (20 μl , 0,18 mmol) a una suspensión agitada de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (20 mg, 0,051 mmol), HATU (25 mg, 0,066 mmol) y DIPEA (50 μl , 0,29 mmol) en DMF (0,5 ml). La reacción se agitó a temperatura ambiente durante la noche. La reacción se diluyó entonces con MeOH y se formó un precipitado blanquecino. El precipitado se recogió por filtración, se trituroó con MeOH y se secó al aire proporcionando el compuesto del epígrafe (17 mg, 68% de rendimiento). RMN de 1H (500 MHz, DMSO- d_6) δ ppm 8,50 (c, J = 4,58 Hz, 1 H) 7,99 - 8,05 (m, 2

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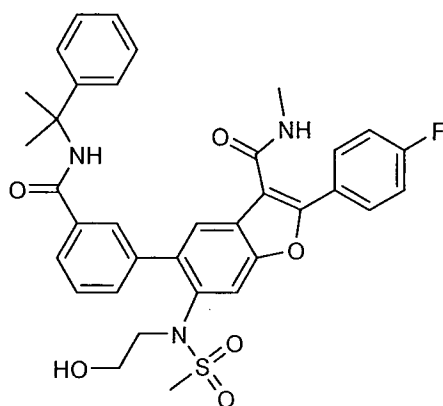
Etapa 2: La mezcla se concentró y se diluyó con EtOH (5 ml) y se trató con NaOH 1N en exceso (~1 ml) y se dejó agitando a temperatura ambiente durante la noche dando el meta-ácido. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y HCl 1M. La fase orgánica se secó sobre Na₂SO₄, se filtró y se
5 concentró.

Etapa 3: El residuo bruto se diluyó con DMF (5 ml) y se trató con HATU (145 mg, 0,382 mmol), 2-fenilpropan-2-amina (52 mg, 0,382 mmol) y DIEA (134 µl, 0,765 mmol) y se dejó agitando a temperatura ambiente durante la noche. La mezcla se concentró y se purificó por HPLC preparativa en fase inversa en
10 una columna C18 usando un gradiente tamponado adecuadamente y se concentró. El compuesto del epígrafe aislado se volvió a purificar sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, R_f ~0,2 50% EtOAc/hexanos, recogida de la fracción a λ = 254 nm) dando el compuesto del epígrafe (7 mg, 4%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 7,94 - 8,01 (2 H, m), 7,92 (1 H, s),
15 7,83 (1 H, d, J=7,63 Hz), 7,77 (1 H, s), 7,63 - 7,68 (2 H, m), 7,59 (1 H, t, J=7,63 Hz), 7,46 (2 H, d, J=7,32 Hz), 7,24 - 7,32 (4 H, m), 7,18 (1 H, t, J=7,32 Hz), 2,94 (3 H, s), 2,88 (3 H, s), 1,77 (6 H, s). Tiempo de retención de LC-EM: 2,25 min; m/z (MH⁺): 600. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters SunFire 5u C18 de
20 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta

disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / 0,1% TFA y el disolvente B era H₂O al 5% / acetonitrilo al 95% / 0,1% TFA. Los datos de EM se

5 determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x

10 150 mm, 3,5 µm, Tr = 12,87 min, pureza = 96%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 11,97 min, pureza = 98%.



2-(4-Fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida

15

Etapa 1: Se añadió cloruro de metanosulfonilo (10 µl, 0,128 mmol) a una solución agitada de 6-amino-2-(4-fluorofenil)-N-metil-5-(3-(2-fenilpropan-2-

ilcarbamoil)fenil)benzofuran-3-carboxamida (50 mg, 0,096 mmol) en piridina (1 ml) a temperatura ambiente. Se dejó agitando durante 2 horas y luego se concentró y diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró.

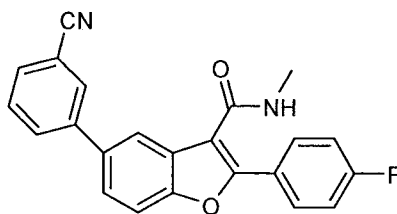
5 Etapa 2: El residuo bruto se disolvió en DMF (1 ml) y se trató con (2-bromoetoxi)(*terc*-butil)dimetilsilano (102 µl, 0,479 mmol) y Na₂CO₃ (31 mg, 0,288 mmol) a temperatura ambiente. Se calentó hasta 100°C durante 4 horas y luego se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró.

10 Etapa 3: El residuo bruto se recogió en THF (2 ml) y se trató con 2 ml de HCl 1N y se dejó agitando a temperatura ambiente durante 1 hr. La mezcla se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se trituró con Et₂O dando el compuesto del epígrafe (25 mg, 39%). RMN de ¹H (500 MHz, CD₃OD) δ ppm

15 8,14 - 8,21 (1 H, m), 7,95 - 8,04 (2 H, m), 7,83 - 7,87 (1 H, m), 7,76 - 7,81 (1 H, m), 7,66 - 7,74 (2 H, m), 7,56 (1 H, t, *J*=7,63 Hz), 7,41 - 7,49 (2 H, m), 7,24 - 7,33 (4 H, m), 7,17 (1 H, t, *J*=7,32 Hz), 2,94 (3 H, s), 1,76 (6 H, s). Tiempo de retención LC-EM 1,42 min; *m/z* (MH⁺): 644. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna

20 Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% /

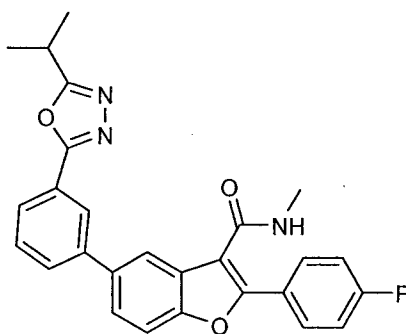
- disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una
- 5 Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min,
- 10 Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 12,26 min, pureza = 96%; Procedimiento HPLC adicional: Disolvente A = MeOH al 5%/H₂O al 95%/bicarbonato amónico 10 mM, Disolvente B = MeOH al 95%/H₂O al 5%/bicarbonato amónico 10 mM, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1
- 15 ml/min. Columna: PHENOMENEX® Gemini C-18, 4,6 x 150 mm, 3 µm, Tr = 13,61 min, pureza = 94%.



5-(3-Cianofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió carbonato de cesio (187 mg, 0,575 mmol) a Pd(Ph₃P)₄ (22 mg, 0,019 mmol), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (160 mg, 0,383 mmol), ácido 3-cianofenilborónico (85 mg, 0,575 mmol). Se añadieron dioxano (3 ml) y agua (600 µl) a temperatura ambiente. La reacción se desgasificó 3x y se calentó hasta 90 °C durante la noche. Se dejó enfriar. La mezcla se diluyó con EtOAc y se lavó con HCl 1M y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró. El residuo bruto se recogió en DCM. Se formó un precipitado blanco que se filtró dando el compuesto del epígrafe. El filtrado se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, R_f ~0,4: 50% EtOAc/Hex, recogida de la fracción a λ = 254 nm) dando el compuesto del epígrafe que se combinó con el precipitado previamente recogido (85 mg, 60%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 8,46 - 8,53 (1 H, m), 8,24 (1 H, s), 8,09 (1 H, d, *J*=7,93 Hz), 7,99 - 8,05 (2 H, m), 7,96 (1 H, d, *J*=1,53 Hz), 7,85 (1 H, d, *J*=7,63 Hz), 7,74 - 7,82 (2 H, m), 7,70 (1 H, t, *J*=7,78 Hz), 7,40 (2 H, t, *J*=8,85 Hz), 2,87 (3 H, d, *J*=4,58 Hz). Tiempo de retención de LC-EM: 2,17 min; *m/z* (MH⁺): 371. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un

tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 13,59 min, pureza = 99%; Columna: 10 columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 12,29 min, pureza = 99%.



2-(4-Fluorofenil)-5-(3-(5-isopropil-1,3,4-oxadiazol-2-il)fenil)-N-metilbenzofuran-3-carboxamida

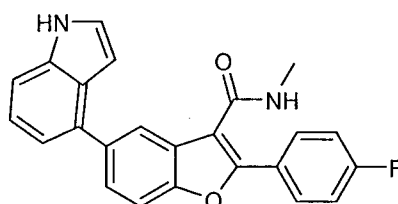
15 Se añadió cloruro de isobutirilo (90 mg, 0,847 mmol) a una solución agitada de 5-(3-(1H-tetrazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (50 mg, 0,085 mmol) en piridina (1 ml) a 100°C. Se dejó agitando durante la noche. La reacción se concentró y se diluyó con EtOH (3 ml) y se

trató con NaOH 1N en exceso (500 µl) y se agitó a 60°C durante 2 horas para hidrolizar la amida acilada. La mezcla se filtró y el filtrado se diluyó con EtOAc y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a λ = 254 nm) dando el compuesto del epígrafe (8 mg, 20%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,31 - 8,35 (1 H, m), 8,03 (1 H, d, *J*=7,94 Hz), 7,95 - 8,00 (3 H, m), 7,93 (1 H, d, *J*=7,93 Hz), 7,67 - 7,74 (3 H, m), 7,25 - 7,30 (2 H, m), 3,37 - 3,40 (1 H, m), 2,99 (3 H, s), 1,49 (6 H, d, *J*=7,02 Hz). Tiempo de retención de LC-EM: 2,28 min; *m/z* (MH⁺):

456. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15

min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 μ m, Tr = 14,30 min, pureza = 94%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μ m, Tr = 12,50 min, pureza = 93%.

5



2-(4-Fluorofenil)-5-(1H-indol-4-il)-N-metilbenzofuran-3-carboxamida

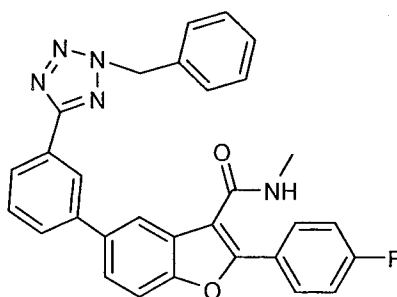
Se añadió carbonato de cesio (176 mg, 0,539 mmol) a Pd(Ph₃P)₄ (20,77 mg, 0,018 mmol), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-ilo (150 mg, 0,359 mmol), ácido 1H-indol-4-ilborónico (87 mg, 0,539 mmol). Se añadieron dioxano (3 ml) y agua (600 μ l) a temperatura ambiente. La reacción se desgasificó 3x y luego se calentó hasta 90°C durante la noche. Se dejó enfriar. La mezcla se diluyó con acetato de etilo y se lavó con NaHCO₃ sat y NaCl sat. La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró y se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, recogida de la fracción a λ = 254 nm) dando el compuesto del epígrafe (66 mg, 46%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 11,28 (1 H, s ancho), 8,48 - 8,57 (1 H, m), 7,98 - 8,07 (2 H, m), 7,86 (1 H, s ancho), 7,79 (1 H, d, *J*=8,24 Hz), 7,69 (1 H, d, *J*=7,93 Hz), 7,37 - 7,47 (4 H, m), 7,21 (1 H, t,

$J=7,63$ Hz), 7,14 (1 H, d, $J=7,02$ Hz), 6,60 (1 H, s ancho), 2,84 (3 H, d, $J=4,27$ Hz). Tiempo de retención de LC-EM: 1,53 min; m/z (MH⁺): 385. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector

5 UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al

10 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10,

15 %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 μ m, Tr = 13,46 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 μ m, Tr = 12,27 min, pureza = 97%.



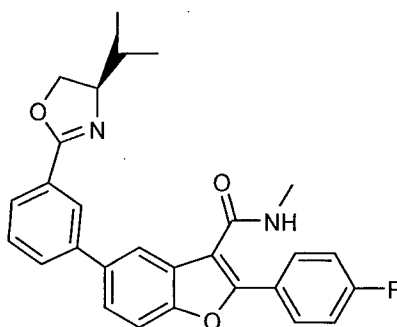
5-(3-(2-Bencil-2H-tetrazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió bromuro de bencilo (29 μ l, 0,242 mmol) a una solución
 5 agitada de 5-(3-(1H-tetrazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (50 mg, 0,121 mmol) y Na_2CO_3 (26 mg, 0,242 mmol) en DMF (1,2 ml) a 100 °C. Se dejó agitando durante la noche. La mezcla se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ adecuadamente tamponado y se concentró dando el
 10 compuesto del epígrafe (12 mg, 19%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 8,48 - 8,56 (1 H, m), 8,30 - 8,35 (1 H, m), 8,06 (1 H, d, $J=7,63$ Hz), 7,98 - 8,03 (2 H, m), 7,90 - 7,93 (2 H, m), 7,78 - 7,83 (1 H, m), 7,72 - 7,77 (1 H, m), 7,69 (1 H, t, $J=7,78$ Hz), 7,36 - 7,46 (7 H, m), 6,04 (2 H, s), 2,86 (3 H, d, $J=4,58$ Hz).
 Tiempo de retención de LC-EM: 1,78 min; m/z (MH^+): 504. Los datos de LC se
 15 registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100%

/ disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una

5 Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min,

10 Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 15,69 min, pureza = 97%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 13,95 min, pureza = 98%.

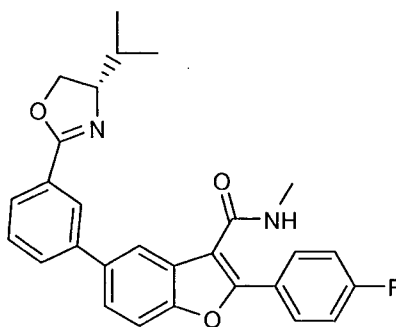


15 (R)-2-(4-fluorofenil)-5-(3-(4-isopropil-4,5-dihidrooxazol-2-il)fenil)-N-metilbenzofuran-3-carboxamida

Se añadió cloruro de cinc (8 mg, 0,054 mmol) a una solución agitada de 5-(3-cianofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (40 mg,

0,108 mmol) y (R)-2-amino-3-metilbutan-1-ol (111 mg, 1,08 mmol) en PhCl (3 ml) a temperatura ambiente. Se sometió durante dos iteraciones a irradiación en microondas durante 1 hora a 200°C. La mezcla se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un
5 gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (13 mg, 25%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,24 (1 H, s), 7,93 - 7,99 (2 H, m), 7,89 - 7,93 (2 H, m), 7,86 (1 H, d, J=7,63 Hz), 7,63 - 7,69 (2 H, m), 7,56 (1 H, t, J=7,78 Hz), 7,26 (2 H, t, J=8,55 Hz), 4,52 (1 H, t, J=9,31 Hz), 4,30 (1 H, t, J=8,09 Hz), 4,14 - 4,22 (1 H, m), 2,98 (3 H, s),
10 1,87 - 1,97 (1 H, m), 1,04 (3 H, d, J=7,02 Hz), 0,97 (3 H, d, J=6,71 Hz). Tiempo de retención LC-EM 1,64 min; m/z (MH⁺): 457. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de
15 elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido
20 trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA

al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 10,13 min, pureza = 95%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 10,58 min, pureza = 94%.



(S)-2-(4-Fluorofenil)-5-(3-(4-isopropil-4,5-dihidrooxazol-2-il)fenil)-N-metilbenzofuran-3-carboxamida

- 10 Se añadió cloruro de cinc (8 mg, 0,054 mmol) a una solución agitada de 5-(3-cianofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (40 mg, 0,108 mmol) y (S)-2-amino-3-metilbutan-1-ol (111 mg, 1,080 mmol) en PhCl (3 ml) a temperatura ambiente. Se sometió durante dos iteraciones de 1 hora a irradiación en microondas a 200°C. La reacción se concentró y se purificó por
- 15 HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (9 mg, 17%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,24 (1 H, s), 7,93 - 7,99 (2 H, m), 7,89 - 7,93 (2 H, m), 7,86 (1 H, d, J=7,63 Hz), 7,63 - 7,69

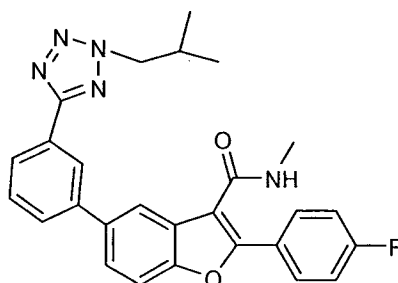
(2 H, m), 7,56 (1 H, t, $J=7,78$ Hz), 7,26 (2 H, t, $J=8,70$ Hz), 4,52 (1 H, t, $J=9,31$ Hz), 4,30 (1 H, t, $J=8,09$ Hz), 4,15 - 4,22 (1 H, m), 2,98 (3 H, s), 1,86 - 1,96 (1 H, m), 1,04 (3 H, d, $J=6,71$ Hz), 0,97 (3 H, d, $J=6,71$ Hz). Tiempo de retención de LC-EM: 1,63 min; m/z (MH^+): 457. Los datos de LC se registraron en un

5 cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo

10 de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización.

15 Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 μ m, Tr = 10,06 min, pureza = 95%; Columna: columna Waters XBridge Phenyl 4,6 x 150

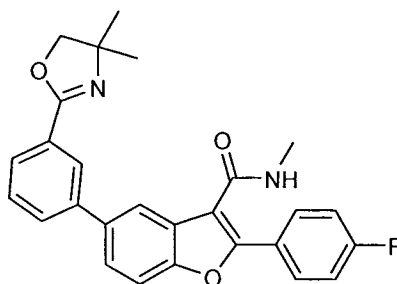
20 mm, 3,5 μ m, Tr = 10,53 min, pureza = 95%.



2-(4-Fluorofenil)-5-(3-(2-isobutil-2H-tetrazol-5-il)fenil)-N-metilbenzofuran-3-carboxamida

Se añadió 1-bromo-2-metilpropano (23 mg, 0,169 mmol) a una solución
5 agitada de 5-(3-(1H-tetrazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (35 mg, 0,085 mmol) y Na_2CO_3 (18 mg, 0,169 mmol) en DMF (1 ml) a 100 °C. Se dejó agitando durante la noche. La mezcla se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ adecuadamente tamponado y se concentró dando el
10 compuesto del epígrafe (15 mg, 38%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ ppm 8,49 - 8,56 (1 H, m), 8,34 (1 H, s), 8,08 (1 H, d, $J=7,63$ Hz), 7,99 - 8,04 (2 H, m), 7,87 - 7,94 (2 H, m), 7,79 - 7,84 (1 H, m), 7,73 - 7,78 (1 H, m), 7,70 (1 H, t, $J=7,63$ Hz), 7,41 (2 H, t, $J=8,70$ Hz), 4,62 (2 H, d, $J=7,32$ Hz), 2,87 (3 H, d, $J=4,27$ Hz), 2,31 - 2,39 (1 H, m), 0,95 (6 H, d, $J=6,71$ Hz). Tiempo de retención
15 de LC-EM: 2,09 min; m/z (MH^+): 470. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3,0x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de

elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era MeOH al 10% / H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 16,08 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 13,89 min, pureza = 99%.



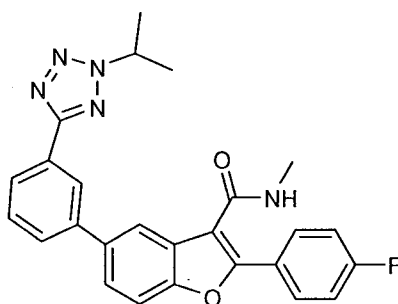
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5-(3-(4,4-Dimetil-4,5-dihidrooxazol-2-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió cloruro de cinc (1 mg) a una solución agitada de 5-(3-

cianofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (40 mg, 0,108 mmol) y 2-amino-2-metilpropan-1-ol (10 mg, 0,108 mmol) en PhCl (3 ml) a 130 °C. Se dejó agitando durante 7 días. Se observó una conversión ~20%. Se añadieron cantidades adicionales de ZnCl (8 mg) y 2-amino-2-metilpropan-1-ol (50 mg) y la reacción se calentó en microondas durante 1 hora a 200°C. La reacción había progresado hasta ~ 50%. La mezcla se concentró y se purificó sobre gel de sílice (BIOTAGE®, gradiente de EtOH/hexanos, Rf ~,2 en 50% EtOAc/hexanos; recogida de la fracción a $\lambda = 254$ nm) seguido por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (7 mg, 14%). RMN de ¹H (500 MHz, CD₃OD) δ ppm 8,24 (1 H, s), 7,97 (2 H, dd, J=8,09, 5,65 Hz), 7,93 (1 H, s), 7,88 (2 H, dd, J=11,44, 8,39 Hz), 7,68 (2 H, s), 7,57 (1 H, t, J=7,78 Hz), 7,27 (2 H, t, J=8,55 Hz), 4,25 (2 H, s), 2,99 (3 H, s), 1,42 (6 H, s). Tiempo de retención LC-EM 1,60 min; m/z (MH⁺): 443. Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters XBridge 5u C18 de 4,6x50mm usando un detector UV-Vis SPD-10AV a una longitud de onda de detección de 220nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de disolvente A al 100% / disolvente B al 0% hasta disolvente A al 0% / disolvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10 mM y el disolvente B

era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para LC en modo electropulverización. Procedimiento HPLC adicional: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 µm, Tr = 12,24 min, pureza = 95%; Columna: columna Waters XBridge Phenyl 4,6 x 150 mm, 3,5 µm, Tr = 10,02 min, pureza = 95%.



10 2-(4-Fluorofenil)-5-(3-(2-isopropil-2H-tetrazol-5-il)fenil)-N-metilbenzofuran-3-carboxamida

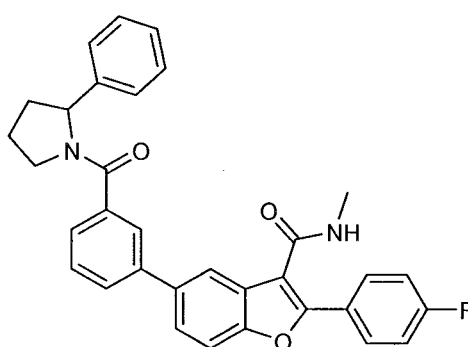
Se añadió 2-yodopropano (29 mg, 0,169 mmol) a una solución agitada de 5-(3-(1H-tetrazol-5-il)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (35 mg, 0,085 mmol) y Na₂CO₃ (18 mg, 0,169 mmol) en DMF (1 ml) a 100 °C. Se dejó agitando durante la noche. La mezcla se concentró y se purificó por HPLC preparativa en fase inversa en una columna C18 usando un gradiente de H₂O/CH₃CN adecuadamente tamponado y se concentró dando el compuesto del epígrafe (12 mg, 30%). RMN de ¹H (500 MHz, DMSO-d₆) δ ppm

H) 7,90 - 7,95 (m, 2 H) 7,85 (dt, $J = 6,10, 2,44$ Hz, 1 H) 7,77 - 7,81 (m, 1 H) 7,73 - 7,77 (m, 1 H) 7,58 - 7,64 (m, 2 H) 7,36 - 7,45 (m, 3 H) 7,30 - 7,34 (m, 1 H) 7,29 (s, 2 H) 4,91 (s, 2 H) 4,84 (s, 2 H) 2,86 (d, $J = 4,88$ Hz, 3 H). La LC/EM se llevó a cabo en un instrumento Shimadzu-VP con detección UV a 220 nm y

5 Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH₃CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 3 min, Tiempo de detección = 4 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 µm 4,6 x 50 mm; HPLC Tr = 2,48 min, (ES+) m/z (MH⁺) = 491. Procedimiento HPLC

10 analítico: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 3,5 µm 4,6 x 150 mm, Tr = 13,81 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 3,5 µm 4,6 x 150 mm, Tr =

15 13,81 min, pureza = 100%.

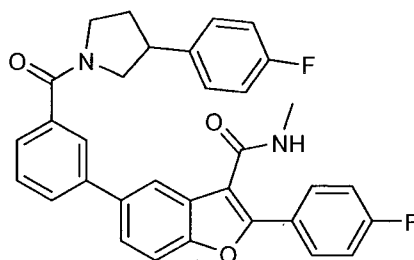


2-(4-Fluorofenil)-N-metil-5-(3-(2-fenilpirrolidin-1-carbonil)fenil)benzofuran-3-

carboxamida

Se añadió 2-fenilpirrolidina (20 mg, 0,14 mmol) a una suspensión agitada de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (20 mg, 0,051 mmol), HATU (25 mg, 0,066 mmol) y DIPEA (50 μ l, 0,29 mmol) en DMF (0,5 ml). La reacción se agitó a temperatura ambiente durante la noche. La reacción se diluyó entonces con MeOH, se filtró y se purificó por HPLC prep. La concentración proporcionó el compuesto del epígrafe (21 mg, 78% de rendimiento) como un sólido rosa claro. RMN de ^1H (~3:2 relación de rotámeros amida, 500 MHz, DMSO- d_6) δ ppm 8,44 - 8,56 (m, 1 H) 7,96 - 8,07 (m, 2 H) 7,74 - 7,89 (m, 3 H) 7,56 - 7,67 (m, 2 H) 7,30 - 7,45 (m, 5,4 H) 7,16 - 7,29 (m, 2,6 H) 7,09 (d, J = 7,02 Hz, 1 H) 5,19 (t, J = 6,71 Hz, 0,6 H) 4,98 (d, J = 6,41 Hz, 0,4 H) 3,75 - 3,92 (m, 1,4 H) 3,53 - 3,64 (m, 0,6 H) 2,87 (m, 3 H) 2,40 (dd, J = 12,36, 6,56 Hz, 0,6 H) 2,30 - 2,38 (m, 0,4 H) 1,73 - 1,92 (m, 3 H). La LC/EM se realizó usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH_3CN al 10%/H $_2\text{O}$ al 90%/TFA al 0,1%, Disolvente B = CH_3CN al 90%/H $_2\text{O}$ al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 3 min, Tiempo de detección = 4 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 μ m 4,6 x 50 mm; HPLC Tr = 1,86 min, (ES+) m/z (MH^+) = 519. Procedimiento HPLC analítico: Disolvente A = CH_3CN al 5%/H $_2\text{O}$ al 95%/TFA al 0,1%, Disolvente B = CH_3CN al 95%/H $_2\text{O}$ al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal =

1 ml/min. Columna: Waters Sunfire C-18, 3,5 μ m 4,6 x 150 mm, Tr = 14,38 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 3,5 μ m 4,6 x 150 mm, Tr = 13,01 min, pureza = 99%.



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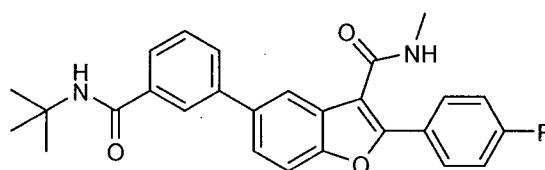
2-(4-Fluorofenil)-5-(3-(3-(4-fluorofenil)pirrolidin-1-carbonil)fenil)-N-metilbenzofuran-3-carboxamida

Se añadió clorhidrato de 3-(4-fluorofenil)pirrolidina (25 mg, 0,12 mmol) a una suspensión agitada de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)benzoico (20 mg, 0,051 mmol), HATU (25 mg, 0,066 mmol) y DIPEA (50 μ l, 0,29 mmol) en DMF (0,5 ml). La reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con MeOH, se filtró y se purificó por HPLC prep. La concentración proporcionó el compuesto del epígrafe (22 mg, 79% de rendimiento) como un sólido rosa. RMN de ^1H (~1:1 relación de rotámeros amida, 500 MHz, DMSO- d_6) δ ppm 8,44 - 8,54 (m, 1 H) 7,98 - 8,06 (m, 2 H) 7,66 - 7,91 (m, 5 H) 7,52 - 7,61 (m, 2 H) 7,36 - 7,44 (m, 3 H) 7,33 (dd, J = 8,55, 5,49 Hz, 1 H) 7,18 (t, J = 8,85 Hz, 1 H) 7,12 (t, J = 8,85 Hz, 1 H) 4,01 (dd, J = 11,14, 7,17 Hz, 0,5 H) 3,72 - 3,82 (m, 1,5 H) 3,56 - 3,69 (m, 1,5 H) 3,36 - 3,55 (m, 1,5 H) 2,87 (d, J = 4,58 Hz, 1,5 H) 2,84 (d, J = 4,58

15

Hz, 1,5 H) 2,27 - 2,34 (m, 0,5 H) 2,24 (dd, $J = 6,56, 3,51$ Hz, 0,5 H) 2,04 - 2,12 (m, 0,5 H) 2,00 (dd, $J = 19,84, 10,38$ Hz, 0,5 H). La LC/EM se llevó a cabo en un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento LC/EM: Disolvente A = CH₃CN al 10%/H₂O al 90%/TFA al 0,1%, Disolvente B = CH₃CN al 90%/H₂O al 10%/TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 3 min, Tiempo de detección = 4 min, Caudal = 4 ml/min, Columna: Sunfire C18 5 µm 4,6 x 50 mm; HPLC Tr = 1,89 min, (ES+) m/z (MH⁺) = 537. Procedimiento HPLC analítico: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 3,5 µm 4,6 x 150 mm, Tr = 14,43 min, pureza = 99%; Columna: columna Waters XBridge Phenyl 3,5 µm 4,6 x 150 mm, Tr = 13,18 min, pureza = 99%.

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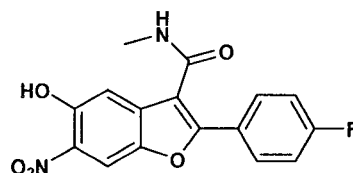
5-(3-(*tert*-butilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Se añadió DIEA (50 µl, 0,29 mmol) a una suspensión de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (50 mg, 0,13 mmol) y

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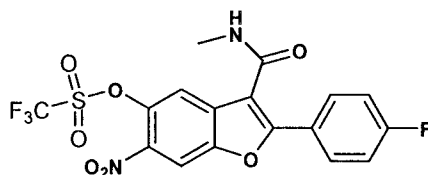
HATU (60 mg, 0,16 mmol) en DMF (0,5 ml). Los sólidos se disolvieron durante 5 minutos, punto en el que se añadió *tert*-butilamina (20 μ l, 0,19 mmol). La solución se agitó a temperatura ambiente durante 1 h, luego se diluyó con CH₃CN (1 ml), se filtró, se purificó por HPLC prep, se concentró y se secó en un horno de vacío durante el fin de semana a 40 °C dando el compuesto del epígrafe (39 mg, 69% de rendimiento) como un polvo blanco. RMN de ¹H (500 MHz, DMSO-*d*₆) δ ppm 8,53 (c, *J* = 4,37 Hz, 1 H) 8,08 (s, 1 H) 8,01 (dd, *J* = 8,24, 5,80 Hz, 2 H) 7,92 (d, *J* = 7,93 Hz, 2 H) 7,84 (d, *J* = 7,63 Hz, 1 H) 7,77 - 7,82 (m, 2 H) 7,73 - 7,77 (m, 1 H) 7,55 (t, *J* = 7,63 Hz, 1 H) 7,40 (t, *J* = 8,85 Hz, 2 H) 2,87 (d, *J* = 4,58 Hz, 3 H) 1,42 (s, 9 H). RMN de ¹³C (125 MHz, DMSO-*d*₆) δ ppm 166,20 (s) 163,22 (s) 162,66 (d, *J* = 246 Hz) 152,56 (s) 152,52 (s) 140,06 (s) 136,53 (s) 135,76 (s) 129,38 (d, *J* = 12 Hz) 129,36 (s) 128,70 (s) 127,86 (s) 126,27 (s) 125,86 (s) 125,70 (d, *J* = 2,5 Hz) 124,83 (s) 118,90 (s) 115,93 (d, *J* = 20 Hz) 113,88 (s) 111,60 (s) 50,85 (s) 28,60 (s) 26,19 (s). Procedimiento LC/EM: Disolvente A = CH₃CN al 5%/H₂O al 95%/NH₄OAc 10 mM, Disolvente B = CH₃CN al 95%/H₂O al 5%/NH₄OAc 10 mM, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 5 ml/min, Columna: XBridge C18 5 μ m 4,6 x 50 mm; HPLC Tr = 1,57, (ES-) *m/z* (*M*⁻) = 443. Procedimiento HPLC analítico: Disolvente A = CH₃CN al 5%/H₂O al 95%/TFA al 0,1%, Disolvente B = CH₃CN al 95%/H₂O al 5%/TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min. Columna: Waters Sunfire C-18, 3,5 μ m

4,6 x 150 mm, Tr = 11,71 min, pureza = 100%; Columna: columna Waters XBridge Phenyl 3,5 μ m 4,6 x 150 mm, Tr = 9,53 min, pureza = 100%.



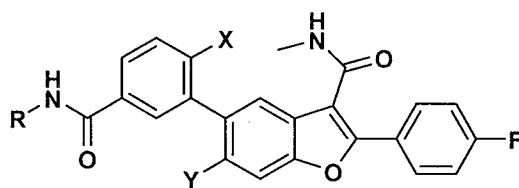
5 2-(4-Fluorofenil)-5-hidroxi-N-metil-6-nitrobenzofuran-3-carboxamida

A una mezcla de 2-(4-fluorofenil)-5-isopropoxi-N-metil-6-nitrobenzofuran-3-carboxamida (210,5 mg, 0,565 mmol) en CH_2Cl_2 (14 ml) a 0 °C en N_2 se añadió tricloroborano (1,70 ml, 1,7 mmol) (solución 1M en CH_2Cl_2). La mezcla se agitó a continuación a temperatura ambiente durante 17 hr. La mezcla se evaporó. Al residuo naranja rojizo se añadieron 7 ml de H_2O y luego 3,5 ml de HCl 1N y se dejó reposar hasta que el sólido viró a amarillo. El producto sólido se filtró entonces y se lavó con 3 x 3 ml H_2O y se secó (182 mg, 93%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ 10,18 (s ancho, 1H), 8,53 (m, 1H), 8,31 (s, 1H), 7,98 (dd aparente, J = 8,85, 5,49, 2H), 7,43 (t aparente, J = 8,85, 2H), 7,28 (s, 1H), 2,84 (aparece como d, J = 4,58, 3H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0

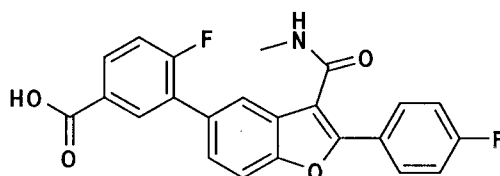


Trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)-6-nitrobenzofuran-5-ilo

A una mezcla de 2-(4-fluorofenil)-5-hidroxi-N-metil-6-nitrobenzofuran-3-carboxamida (100 mg, 0,303 mmol) en CH_2Cl_2 (4 ml) a temperatura ambiente en N_2 se añadió trietilamina (0,084 ml, 0,606 mmol). La mezcla se enfrió entonces hasta 0 °C y luego se añadió 1,1,1-trifluoro-N-fenil-N-(trifluorometilsulfonil)metanosulfonamida (162 mg, 0,454 mmol). La suspensión naranja se agitó entonces a temperatura ambiente durante 23 hr. La mezcla se evaporó. Al residuo verde grisáceo se añadieron 3 ml de H_2O , el producto sólido se filtró y se lavó con 3 x 3 ml H_2O y se secó (130,8 mg, 89%). RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ 8,84 (s, 1H), 8,62 (s ancho, 1H), 8,02 (td, $J = 5,65$, 2,44, 2H), 7,96 (s, 1H), 7,48 (td, $J = 8,77$, 2,59, 2H), 2,85 (aparece como d, $J = 3,97$, 3H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z $(\text{M}+\text{H})^+ = 463,25$, HPLC Tr = 1,700 min.

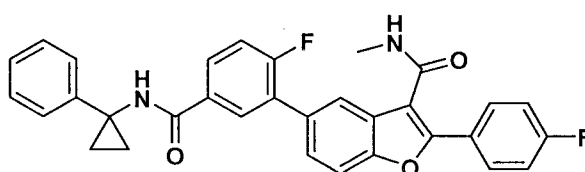


Procedimiento General: Se agitó a 90 °C durante aproximadamente 1,5 a 5 horas una mezcla de trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (o el análogo 6-nitro) (0,3 mmol, 1 equiv.), ácido 3-boronobenzoico (1,5 equiv.), carbonato de cesio (1,7 equiv.) y Pd(PPh₃)₄ (0,1 equiv.) en una mezcla de H₂O (0,6 ml)/1,4-dioxano (3,00 ml) en N₂. La mezcla se enfrió hasta temperatura ambiente y se diluyó con 3 ml de 1,4-dioxano. La mezcla se filtró a través de un disco Whatman PTFE 4,5 µm y se concentró. A la mezcla se añadieron 4 ml de HCl 1N, se diluyó con 5 ml de H₂O. Los precipitados se filtraron y se lavaron con 3 x 4 ml de H₂O y se secó. El material bruto se purificó como se ha indicado o se usó para la etapa de acoplamiento de amida sin purificación posterior. A una mezcla del derivado ácido 3-(benzofuran-5-il)benzoico obtenido antes (0,074 mmol, 1 equiv.), amina (1,5 equiv.) y tetrafluorborato de 2-(1H-benzo[d][1,2,3]triazol-1-il)-1,1,3,3-tetrametilisouronio (2 equiv.) en DMF (1 ml) a temperatura ambiente en N₂ se añadió N,N-diisopropiletilamina (3 equiv.). La mezcla se agitó a temperatura ambiente durante aproximadamente 23 hr. La mezcla se diluyó con MeOH y se purificó como se ha indicado, por ejemplo, por HPLC de fase inversa preparativa Shimadzu-VP.



Ácido 4-fluoro-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico.

RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ 13,17 (s, 1H), 8,51 (c, $J = 4,27$, 1H), 8,13 (dd, $J = 7,78$, 1,98, 1H), 8,01 (dd aparente, $J = 8,70$, 5,34, 3H), 7,81 (d, $J =$
 5 8,54, 1H), 7,80 (s, 1H), 7,61 (d, $J = 8,54$, 1H), 7,49 (dd, $J = 10,07$, 8,85, 1H), 7,41 (t aparente, $J = 8,85$, 2H), 2,85 (aparece como d, $J = 4,58$, 3H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10%
 10 - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z $(\text{M}+\text{H})^+ = 408,29$, HPLC Tr = 1,693 min.



15 5-(2-Fluoro-5-(1-fenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

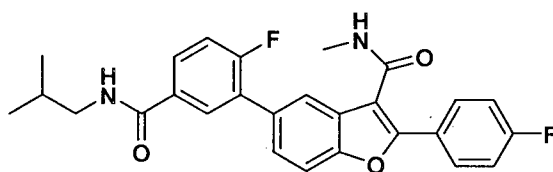
Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%- H_2O al 90%-TFA

al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,79 - 9,35 min. (Detección UV a 220 nm). **RMN de ¹H** (500

5 MHz, DMSO-*d*₆) δ 9,33 (s, 1H), 8,51 (c, *J* = 4,58, 1H), 8,15 (dd, *J* = 7,48, 2,29, 1H), 8,00 (dd, *J* = 9,00, 5,34, 2H), 7,97 (m, 1H), 7,83 (s, 1H), 7,82 (d, *J* = 8,60, 1H), 7,64 (d, *J* = 8,55, 1H), 7,46 (dd, *J* = 10,22, 8,70, 1H), 7,41 (t, *J* = 9,00, 2H), 7,29 (t, *J* = 7,63, 1H), 7,28 (d, *J* = 7,32, 1H), 7,23 (dd aparente, *J* = 7,10, 2H), 7,17 (t, *J* = 7,17, 1H), 2,85 (aparece como d, *J* = 4,58, 3H), 1,30 (aparece como

10 d, 4H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min,

15 Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 523,44, HPLC Tr = 1,803 min.



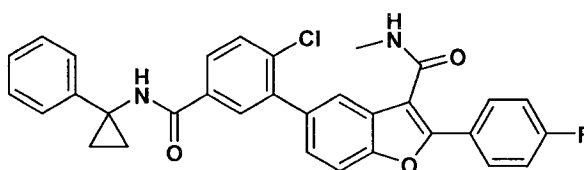
5-(2-Fluoro-5-(isobutylcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-

20 carboxamida

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,47 - 9,09 min. (Detección UV a 220 nm). **RMN de ¹H** (500 MHz, CD₃OD, aparece como una mezcla de dos isómeros) δ 8,06–8,04 (m, 1H), 8,00–7,97 (m, 2H), 7,90–7,87 (m, 2H), 7,70 (d, J = 8,50, mayoritario) y 7,69 (d, J = 8,50, minoritario) (1H), 7,63–7,62 (m, 1H), 7,36–7,27 (m solapando, 3H), 3,23 (d, J = 7,02, mayoritario) y 3,23–3,22 (d, minoritario) (2H), 2,98 (s, mayoritario) y 2,97 (s, minoritario) (3H), 1,97 (m, 1H), 1,00 (d, J = 6,71, mayoritario) y 0,99 (d, J = 6,71, minoritario) (6H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 463,38, HPLC Tr = 1,772 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo

de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 8,85 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 6,44 min.

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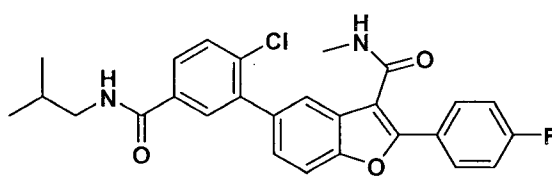


5-(2-Cloro-5-(1-fenilciclopropilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 9,28 - 9,85 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD, aparece como una mezcla de dos isómeros) δ 9,36 (s ancho, 1H), 7,98–7,94 (m solapando, 3H), 7,85 (dd, J = 8,39, 2,29, mayoritario) y 7,86–7,83 (dd, minoritario) (1H), 7,75 (d, J = 1,83, mayoritario) y 7,75–7,74 (d, minoritario) (1H), 7,66 (d, J = 8,55, mayoritario) y 7,66–7,64 (d, minoritario) (1H), 7,633 (d, J = 8,00, mayoritario) y 7,626 (d, J = 8,50, minoritario) (1H), 7,48 (dd, J = 8,55, 1,83, mayoritario) y 7,49–7,47 (dd, minoritario) (1H), 7,29–7,25 (m solapando, 6H), 7,17 (m, 1H), 2,95 (s, mayoritario) y 2,94 (s, minoritario) (3H),

1,36–1,34 (aparece como d, 4H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%,
5 %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 539,37, 541,38, HPLC Tr = 1,868 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5%
10 - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 10,84 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 8,37 min.

15



5-(2-Cloro-5-(isobutilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando
20 el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA

al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 9,01 - 9,47 min. (Detección UV a 220 nm). RMN de ¹H (500

5 MHz, CD₃OD, aparece como una mezcla de dos isómeros) δ 7,98 (mayoritario) y 7,97 (minoritario) (dd, 2H), 7,91 (d, J = 2,14, mayoritario) y 7,91–7,90 (d, minoritario) (1H), 7,82 (dd, J = 8,24, 2,14, mayoritario) y 7,82–7,80 (dd, minoritario) (1H), 7,75 (m, 1H), 7,65 (dd, J = 16, 8,39, mayoritario) y 7,64 (dd, J = 16,5, 8,55, minoritario) (2H), 7,49 (dd, J = 8,24, 1,83, mayoritario) y 7,49–7,47

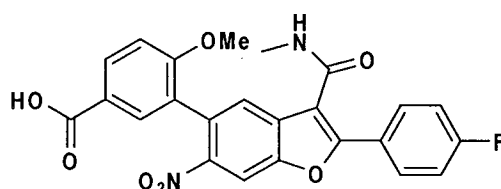
10 (dd, minoritario) (1H), 7,27 (t, J = 8,85, mayoritario) y 7,29–7,25 (m aparente, minoritario) (2H), 3,22 (d, J = 7,02, mayoritario) y 3,21 (d, J = 7,02, mayoritario) (2H), 2,96 (s, mayoritario) y 2,95 (s, minoritario) (3H), 1,95 (m, 1H), 0,98 (d, J = 6,71, mayoritario) y 0,97 (d, J = 6,71, minoritario) (6H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters

15 MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 479,33, 481,36, HPLC Tr = 1,830 min. Las HPLC

20 analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al

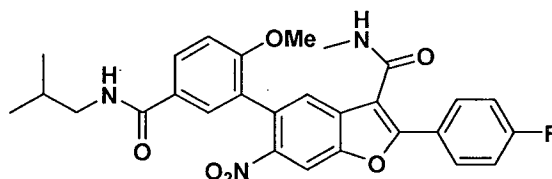
0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 9,66 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 7,19 min.

5



Ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)-6-nitrobenzofuran-5-il)-4-metoxibenzoico

Las LC/EM se realizaron usando un instrumento Shimadzu-VP con
 10 detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC:
 Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B =
 MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100,
 Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min,
 Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 465,31,
 15 HPLC Tr = 1,568 min.

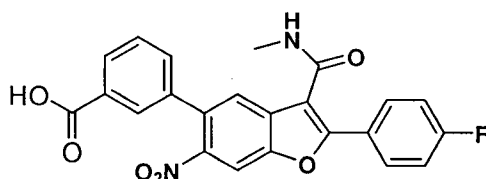


2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-metoxifenil)-N-metil-6-

nitrobenzofuran-3-carboxamida

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,79 - 8,36 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, DMSO-*d*₆) δ 8,62 (c, *J* = 4,48, 1H), 8,48 (s, 1H), 8,46 (t, *J* = 5,80, 1H), 8,05 (dd, *J* = 9,00, 5,34, 2H), 7,96 (dd, 1H), 7,95 (s aparente, 1H), 7,68 (s, 1H), 7,46 (t, *J* = 8,85, 2H), 7,14 (d, *J* = 8,55, 1H), 3,69 (s, 3H), 3,11 (d ancho, 2H), 2,83 (aparece como d, *J* = 4,58, 3H), 1,87 (m, 1H), 0,91 (d, *J* = 6,71, 6H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 520,40, HPLC Tr = 1,688 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18,

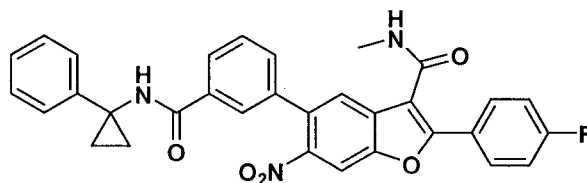
3,5 μ m, 4,6 x 150 mm, Tr = 7,93 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 6,30 min.



5 Ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)-6-nitrobenzofuran-5-il)benzoico

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12
 10 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,98 - 7,51 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, DMSO-*d*₆) δ 13,17 (s, 1H), 8,60 (m, 1H), 8,54 (s, 1H), 8,08–8,05 (m solapando, 2H), 8,02 (d, *J* = 7,63, 1H), 7,95 (s, 1H), 7,74 (s, 1H), 7,67–7,61 (m solapando, 2H), 7,46 (t aparente, *J* = 8,85, 2H), 2,84 (aparece como d, *J* = 4,58,
 15 3H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min,
 20 Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 435,27,

HPLC Tr = 1,588 min.



2-(4-Fluorofenil)-N-metil-6-nitro-5-(3-(1-

5 fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Se preparó 2-(4-Fluorofenil)-N-metil-6-nitro-5-(3-(1-

fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida como se describe en el procedimiento general. La mezcla de reacción se concentró y luego se añadió agua en exceso. Los precipitados blanquecinos del producto se filtraron,

10 se lavaron tres veces con agua y se secaron. RMN de ^1H (500 MHz, $\text{DMSO}-d_6$)

δ 9,31 (s, 1H), 8,60 (m, 1H), 8,55 (s, 1H), 8,05 (m, 2H), 7,99–7,97 (m solapando, 2H), 7,75 (s, 1H), 7,59–7,53 (m solapando, 2H), 7,46 (t, $J = 8,70$, 2H), 7,29 (t, $J = 7,02$, 2H), 7,24 (s, 1H), 7,23 (d, $J = 7,02$, 1H), 7,17 (t, $J = 6,71$, 1H), 2,83 (s, 3H), 1,29 (aparece como d, 4H). Las LC/EM se realizaron usando

15 un instrumento Shimadzu-VP con detección UV a 220 nm y Waters

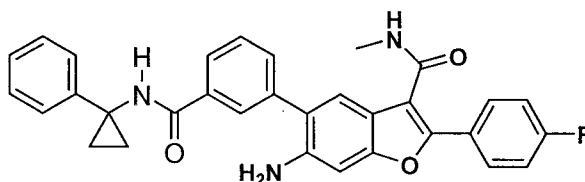
MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al

90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%,

%B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de

detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0

20 x 50 mm; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 550,45, HPLC Tr = 1,738 min.



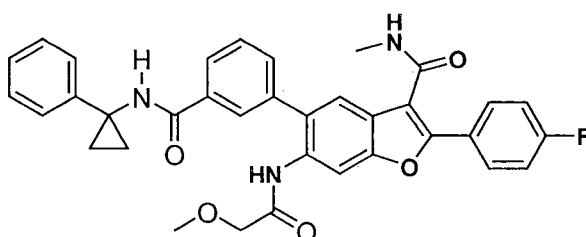
6-Amino-2-(4-fluorofenil)-N-metil-5-(3-(1-

fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Se disolvió 2-(4-fluorofenil)-N-metil-6-nitro-5-(3-(1-

- 5 fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida (83,3 mg, 0,152 mmol) en N₂ a temperatura ambiente en DMF (2 ml) y luego se añadió acetato de etilo (10 ml). La mezcla quedó como una solución marrón clara transparente. A la mezcla se añadió paladio (97 mg, 0,045 mmol, 5%/C), se purgó con H₂ usando un balón y se agitó la mezcla en H₂ durante aproximadamente 8 hr. La mezcla
- 10 se diluyó con EtOAc y se filtró a través de un disco Whatman PTFE 45 µm. El filtrado se evaporó. El residuo se trituró con 3 x 1 ml de Et₂O (la solución de Et₂O se separó usando una pipeta) y se secó el producto sólido naranja claro (64,4 mg, 82%). RMN de ¹H (500 MHz, DMSO-*d*₆) δ 9,26 (s, 1H), 8,32 (c, *J* = 4,17, 1H), 7,94–7,89 (m solapando, 3H), 7,97 (s, 1H), 7,62 (d, *J* = 6,8, 1H), 7,58
- 15 (c, 1H), 7,34 (t, *J* = 8,70, 2H), 7,29 (t, 1H), 7,28 (d, *J* = 7,50, 1H), 7,23 (s, 2H), 7,227 (d, *J* = 8,00, 1H), 7,17 (t, *J* = 7,17, 1H), 6,99 (s, 1H), 5,09 (s, 2H), 2,79 (aparece como d, *J* = 3,97, 3H), 1,29 (aparece como d, 4H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% -
- 20 H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al

0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 520,39, HPLC Tr = 1,497 min.



5

2-(4-Fluorofenil)-6-(2-metoxiacetamido)-N-metil-5-(3-(1-fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

A una mezcla de ácido 2-metoxiacético (10,40 mg, 0,115 mmol) en THF (3 ml) a temperatura ambiente en N₂ se añadió 1,1'-carbonildiimidazol (CDI) (28,1 mg, 0,173 mmol). La mezcla se agitó a 55 °C durante 1 hr. La mezcla se transfirió luego a un matraz que contenía 6-amino-2-(4-fluorofenil)-N-metil-5-(3-(1-fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida (30 mg, 0,058 mmol) a temperatura ambiente en N₂. Se añadió entonces 1,8-diazabicyclo[5.4.0]undec-7-eno (DBU) (0,035 ml, 0,231 mmol) y la mezcla se agitó a 55 °C durante 2 horas 35 min. Se dejó seguidamente la mezcla reposar a temperatura ambiente durante la noche. Se volvió a agitar la mezcla a 55 °C durante 3 hr. La mezcla se enfrió hasta temperatura ambiente, se diluyó con MeOH y se purificó por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al

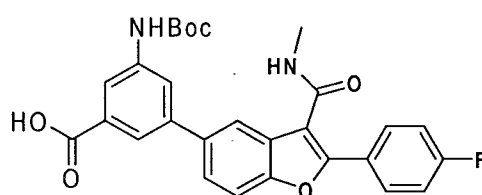
15

90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,28 - 7,84 min. (Detección UV a 220 nm).

5 RMN de ¹H (500 MHz, DMSO-*d*₆) δ 9,29 (s, 1H), 9,04 (s, 1H), 8,49 (c, *J* = 4,58, 1H), 8,31 (s, 1H), 8,03–8,00 (m solapando, 3H), 7,98 (m, 1H), 7,59 (s, 1H), 7,63 (s, 1H), 7,625 (d, *J* = 2,44, 1H), 7,40 (t, *J* = 9,00, 2H), 7,28 (t aparente, *J* = 7,63, 2H,), 7,23 (dd aparente, 2H,), 7,17 (t, *J* = 7,17, 1H,), 3,90 (s, 2H), 3,18 (s, 3H), 2,83 (aparece como d, *J* = 4,58, 3H), 1,28 (s, 4H). Las LC/EM se realizaron

10 usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0

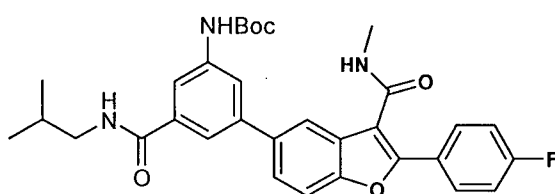
15 x 50 mm; (ES+) *m/z* (M+H)⁺ = 592,49, HPLC Tr = 1,652 min.



Ácido 3-(*terc*-butoxicarbonilamino)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

20 Las LC/EM se realizaron usando un instrumento Shimadzu-VP con

detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC:
 Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B =
 MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100,
 Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min,
 5 Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M – Me₂CCH₂ +
 H)⁺ = 449,35, HPLC Tr = 1,808 min.

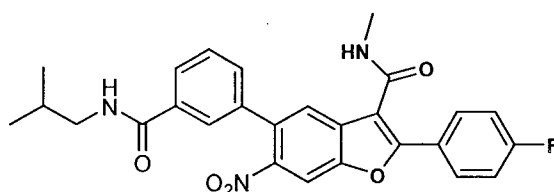


3-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-5-

10 (isobutilcarbamoil)fenilcarbamato de *terc*-butilo

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando
 el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA
 al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial =
 70, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12
 15 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida
 de la fracción: 7,13 - 7,93 min. (Detección UV a 220 nm). RMN de ¹H (500
 MHz, DMSO-*d*₆) δ 9,57 (s, 1H), 8,55 (dt, *J* = 10,38, 5,19, 1H), 8,50 (s ancho,
 1H), 8,01–7,98 (m, 3H), 7,89 (s, 1H), 7,86–7,85 (m, 1H), 7,81 (dd aparente,
 1H), 7,75 (s, 1H), 7,70 (dd, *J* = 8,55, 1,83, 1H), 7,41 (t aparente, *J* = 8,85, 2H),
 20 3,11 (t, *J* = 6,41, 2H), 2,87 (aparece como d, *J* = 4,58, 3H), 1,88 (ddd, *J* =

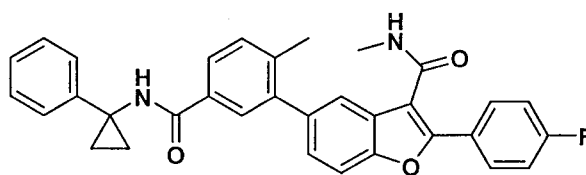
13,50, 6,64, 6,41, 1H), 1,55 (s) y 1,51 (s) (9H), 0,92 (d, $J = 6,50$, mayoritario) y 0,91 (d, $J = 6,50$, minoritario) (6H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 560,40, HPLC Tr = 1,898 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al 0,1%, %B inicial = 70, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 5,77 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 3,70 min.



2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)fenil)-N-metil-6-nitrobenzofuran-3-carboxamida

20 Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando

el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,89 - 8,57 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, DMSO-*d*₆) δ 8,59 (m, 2H), 8,54 (s, 1H), 8,05 (m, 2H), 7,93 (d, *J* = 7,63, 1H), 7,90 (s, 1H), 7,75 (s, 1H), 7,57 (t aparente, *J* = 7,63, 1H), 7,54 (t aparente, 1H), 7,46 (t aparente, *J* = 8,85, 2H), 3,11 (t, *J* = 6,41, 2H), 2,84 (aparece como d, *J* = 4,58, 3H), 1,87 (m, 1H), 0,91 (d, *J* = 6,71, 6H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 490,41, HPLC Tr = 1,693 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al 0,1%, %B inicial = 70, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 8,09 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 6,38 min.

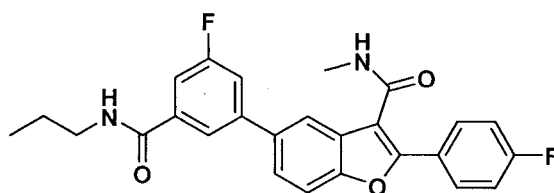


2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-

fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

- 5 Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida
- 10 de la fracción: 8,92 - 9,62 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,97 (dd, *J* = 8,85, 5,49, 2H), 7,79 (m, 2H), 7,65–7,64 (d solapando s, 1H), 7,64 (s, 1H), 7,42 (m, 1H), 7,37 (dd, *J* = 8,24, 1,83, 1H), 7,29–7,26 (m solapando, 6H), 7,16 (m, 1H), 2,95 (s, 3H), 2,34 (s, 3H), 1,36–1,33 (aparece como d, 4H). Las LC/EM se realizaron usando un
- 15 instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0
- 20 x 50 mm; (ES+) *m/z* (M+H)⁺ = 519,40, HPLC Tr = 1,832 min. Las HPLC

analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 µm, 4,6 x 150 mm, Tr = 9,93 min; Columna: XBridge Phenyl 3,5 µm, 4,6 x 150 mm, Tr = 7,64 min.

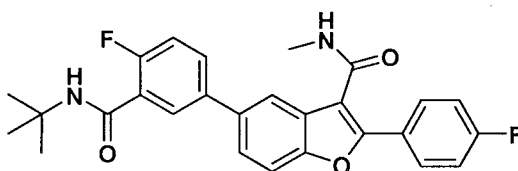


10 5-(3-Fluoro-5-(propilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,32 - 8,96 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 8,00–7,97 (m solapando, 4H), 7,74–7,69 (m solapando, 2H), 7,65–7,62 (m, 1H), 7,58–7,55 (m, 1H), 7,29 (t, J = 8,70, 2H), 3,39 (t, J = 7,00, 2H), 3,00 (s, 3H), 1,69 (m, 2H), 1,02 (t, J = 7,48, 3H). Las LC/EM se realizaron

usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de
5 detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 449,40, HPLC Tr = 1,752 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al
10 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 8,08 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 5,87 min.

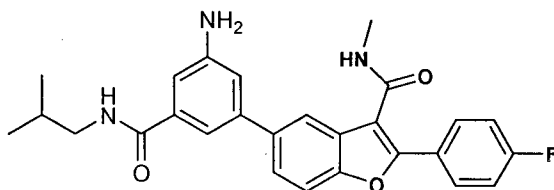
15



5-(3-(*tert*-Butilcarbamoil)-4-fluorofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA
20 al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial =

50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,48 - 9,02 min. (Detección UV a 220 nm). RMN de ^1H (500 MHz, CD_3OD) δ 7,97–7,94 (m solapando, 2H), 7,90 (dd, J = 6,87, 2,59, 1H), 7,88 (s, 1H), 7,78 (ddd, J = 8,47, 4,65, 2,44, 1H), 7,64 (m, 2H), 7,30–7,25 (m solapando, 3H), 2,99 (s, 3H), 1,50 (2, 9H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z $(\text{M}+\text{H})^+$ = 463,36, HPLC Tr = 1,788 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H_2O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H_2O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm , 4,6 x 150 mm, Tr = 9,97 min; Columna: XBridge Phenyl 3,5 μm , 4,6 x 150 mm, Tr = 6,81 min.



5-(3-Amino-5-(isobutylcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Obtenida como la sal clorhidrato a partir de la desprotección de 3-(2-(4-

5 fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)-5-

(isobutylcarbamoyl)fenilcarbamato de *terc*-butilo usando HCl 4 M en 1,4-dioxano

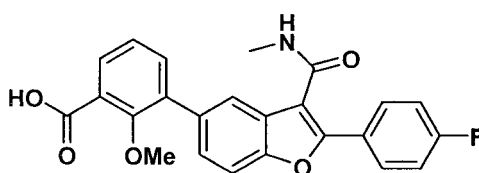
(t.a.). RMN de ^1H (500 MHz, CD_3OD) δ 8,26 (s, 1H), 8,02 (s, 1H), 7,97 (dd, J = 7,63, 5,49, 2H), 7,87 (s, 2H), 7,75 (s, 2H), 7,30 (t, J = 8,39, 2H), 3,28 (d, J = 7,02, 2H), 2,99 (s, 3H), 2,00 (m, 1H), 1,02 (d, J = 6,71, 6H). Las LC/EM se

10 realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0

15 x 50 mm; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 460,42, HPLC Tr = 1,510 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H_2O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H_2O al 5% - TFA al 0,1%, %B inicial = 10, %B final = 100, Tiempo de gradiente = 15 min, Tiempo

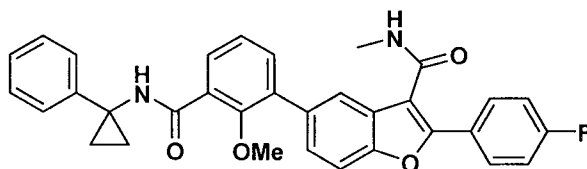
20 de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm , 4,6 x

150 mm, Tr = 8,96 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,23 min.



5 Ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoico

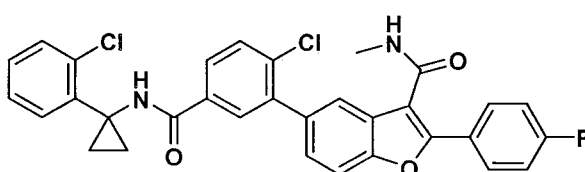
Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,02 - 7,76 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 8,00–7,97 (m solapando, 2H), 7,84 (d, J = 1,53, 1H), 7,81 (dd, J = 7,63, 1,83, 1H), 7,67 (d, J = 8,50, 1H), 7,63–7,60 (m solapando, 2H), 7,32–7,26 (m solapando, 3H), 3,50 (s, 3H), 2,97 (s, 3H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 420,27, HPLC Tr = 1,623 min. Las HPLC



2-(4-Fluorofenil)-5-(2-metoxi-3-(1-fenilciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,65 - 9,45 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,99–7,96 (m solapando, 2H), 7,87 (d, J = 1,83, 1H), 7,69–7,63 (m solapando, 3H), 7,57 (dd, J = 7,48, 1,68, 1H), 7,40 (d, J = 7,63, 1H), 7,39 (s, 1H), 7,34–7,27 (m solapando, 5H), 7,20 (t, J = 7,17, 1H), 3,41 (s, 3H), 2,97 (s, 3H), 1,40–1,37 (aparece como d, 4H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 535,45, HPLC Tr = 1,833 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV

a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5%
 - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al
 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo
 de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x
 5 150 mm, Tr = 9,93 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr =
 7,75 min.

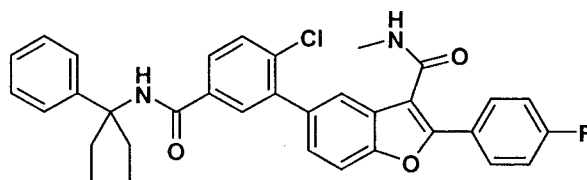


5-(2-Cloro-5-(1-(2-clorofenil)ciclopropilcarbamoyl)fenil)-2-(4-fluorofenil)-N-
 10 metilbenzofuran-3-carboxamida

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando
 el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA
 al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial =
 80, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12
 15 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida
 de la fracción: 5,53 - 6,33 min. (Detección UV a 220 nm). RMN de ¹H (500
 MHz, CD₃OD) δ 7,99–7,96 (m solapando, 2H), 7,84 (d, J = 2,14, 1H), 7,79 (dd,
 J = 7,17, 1,98, 1H), 7,74 (dd, J = 8,39, 2,29, 1H), 7,72 (d, J = 1,53, 1H), 7,65 (d,
 J = 8,55, 1H), 7,58 (d, J = 8,54, 1H), 7,45 (dd, J = 8,55, 1,83, 1H), 7,37 (dd, J =
 20 7,25, 1,75, 1H), 7,30–7,23 (m solapando, 4H), 2,95 (s, 3H), 1,34–1,24 (aparece

como d, 4H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, 5 Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 573,38, HPLC Tr = 1,945 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al 0,1%, %B inicial = 10 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 12,00 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 8,98 min.

15



5-(2-Cloro-5-(3-fenilpentan-3-ilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

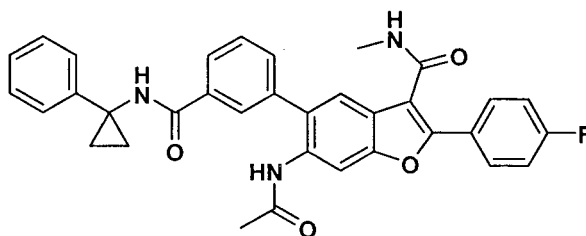
Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 20

80, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,08 - 6,89 min. (Detección UV a 220 nm). RMN de ^1H (500 MHz, CD_3OD) δ 8,00–7,97 (m solapando, 2H), 7,87 (d, $J = 2,14$, 1H), 7,80 (dd, $J = 8,24$, 2,14, 1H), 7,76 (d, $J = 1,53$, 1H), 7,68 (d, $J = 8,54$, 1H), 7,64 (d, $J = 8,00$, 1H), 7,50 (dd, $J = 8,55$, 1,53, 1H), 7,42 (d, $J = 7,32$, 2H), 7,34–7,27 (m solapando, 4H), 7,20 (d, $J = 7,32$, 1H), 2,96 (s, 3H), 2,35 (m, 2H), 2,08 (m, 2H), 0,80 (t, $J = 7,32$, 6H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®.

10 Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z $(\text{M}+\text{H})^+ = 569,47$, HPLC Tr = 1,972 min. Las HPLC analíticas se realizaron

15 usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H_2O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H_2O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm , 4,6 x 150 mm, Tr =

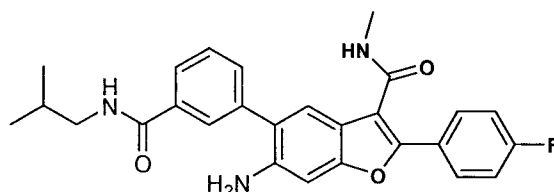
20 13,37 min; Columna: XBridge Phenyl 3,5 μm , 4,6 x 150 mm, Tr = 10,24 min.



6-Acetamido-2-(4-fluorofenil)-N-metil-5-(3-(1-

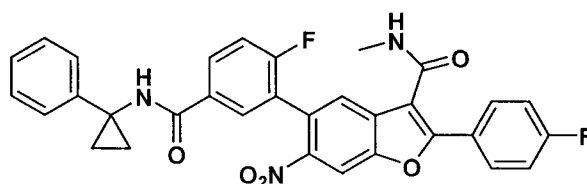
fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Preparada a partir de 6-amino-2-(4-fluorofenil)-N-metil-5-(3-(1-fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida de una forma similar a la descrita. RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ 9,34 (s, 1H), 9,28 (s, 1H), 8,48 (m, 1H), 8,03–8,00 (m solapando, 3H), 7,93 (m, 1H), 7,89 (s, 1H), 7,58–7,56 (m solapando, 3H), 7,40 (t, $J = 8,85$, 2H), 7,30–7,27 (m solapando, 2H), 7,23–7,21 (m solapando, 2H), 7,17 (t, $J = 7,32$, 1H), 2,83 (aparece como d, $J = 4,58$, 3H), 1,92 (s, 3H), 1,29 (aparece como s, 4H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 562,42, HPLC Tr = 1,547 min.



6-Amino-2-(4-fluorofenil)-5-(3-(isobutylcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

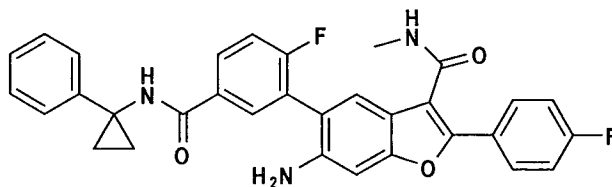
- Obtenida a partir de la reducción de 2-(4-fluorofenil)-5-(3-(isobutylcarbamoil)fenil)-N-metil-6-nitrobenzofuran-3-carboxamida usando H_2 con Pd al 5%/C como catalizador (1:6 DMF/EtOAc, t.a.) de una forma similar a la descrita. RMN de 1H (500 MHz, DMSO- d_6) δ 8,54 (t, $J = 5,95$, 1H), 8,33 (c, $J = 4,58$, 1H), 7,94–7,91 (m solapando, 3H), 7,85 (d, $J = 7,32$, 1H), 7,61–7,55 (m solapando, 2H), 7,34 (t, $J = 8,70$, 2H), 7,23 (s, 1H), 6,99 (s, 1H), 5,05 (s, 2H), 3,11 (d, $J = 7,02$, 2H), 2,80–2,79 (aparece como d, 3H), 1,87 (m, 1H), 0,91 (d, $J = 6,71$, 6H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z $(M+H)^+ = 460,38$, HPLC Tr = 1,407 min.



5-(2-Fluoro-5-(1-phenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metil-6-nitrobenzofuran-3-carboxamida

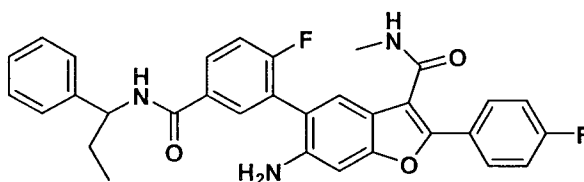
RMN de ^1H (500 MHz, $\text{DMSO}-d_6$) δ 9,33 (s, 1H), 8,64 (s, 2H), 8,12 (dd, J
 5 = 7,32, 2,14, 1H), 8,08–8,05 (m solapando, 3H), 7,83 (s, 1H), 7,47 (t, J = 8,85, 2H), 7,42 (t, J = 9,30, 1H), 7,31–7,28 (m solapando, 2H), 7,25–7,23 (m solapando, 2H), 7,17 (t, J = 7,17, 1H), 2,84 (aparece como d, J = 4,58, 3H), 1,31–1,28 (aparece como d, 4H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters
 10 MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z $(\text{M}+\text{H})^+$ = 568,39, HPLC Tr = 1,768 min. Las HPLC
 15 analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H_2O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H_2O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm , 4,6 x
 20 150 mm, Tr = 9,28 min; Columna: XBridge Phenyl 3,5 μm , 4,6 x 150 mm, Tr =

7,82 min.



6-Amino-5-(2-fluoro-5-(1-phenilciclopropilcarbamoi)fenil)-2-(4-fluorofenil)-N-
5 metilbenzofuran-3-carboxamida

Obtenida a partir de la reducción de 5-(2-fluoro-5-(1-
fenilciclopropilcarbamoi)fenil)-2-(4-fluorofenil)-N-metil-6-nitrobenzofuran-3-
carboxamida usando H_2 con Pd al 5%/C como catalizador (1:5 DMF/EtOAc,
t.a.) de una forma similar a la descrita. Las LC/EM se realizaron usando un
10 instrumento Shimadzu-VP con detección UV a 220 nm y Waters
MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al
90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%,
%B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de
detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0
15 x 50 mm; (ES+) m/z $(M+H)^+$ = 538,41, HPLC Tr = 1,510 min.

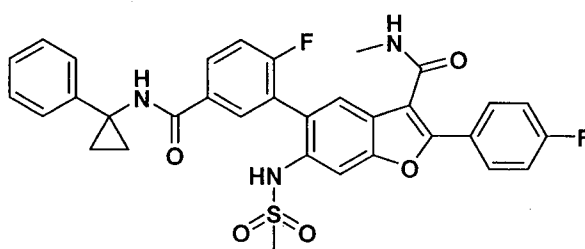


6-Amino-5-(2-fluoro-5-(1-fenilpropilcarbamoi)fenil)-2-(4-fluorofenil)-N-

metilbenzofuran-3-carboxamida

Obtenida como producto secundario a partir de la sobrerreducción de 5-(2-fluoro-5-(1-fenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metil-6-nitrobenzofuran-3-carboxamida en las condiciones usando H_2 con Pd al 5%/C como catalizador (1:5 DMF/EtOAc, t.a.). El producto se obtuvo como una sal TFA después de purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%- H_2O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%- H_2O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,52 - 7,08 min. (Detección UV a 220 nm). RMN de 1H (500 MHz, CD_3OD) δ 7,98 (m, 1H), 7,93–7,91 (m solapando, 3H), 7,51 (s, 1H), 7,40–7,38 (m solapando, 2H), 7,34 (d, J = 7,60, 1H), 7,33 (t, J = 7,78, 2H), 7,27–7,23 (m solapando, 4H), 4,99 (t, J = 7,48, 1H), 2,92 (s, 3H), 1,94 (m, 2H), 0,99 (t, J = 7,32, 3H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z ($M+H$) $^+$ = 540,45, HPLC Tr = 1,587 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV

a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 µm, 4,6 x 150 mm, Tr = 6,56 min; Columna: XBridge Phenyl 3,5 µm, 4,6 x 150 mm, Tr = 5,42 min.

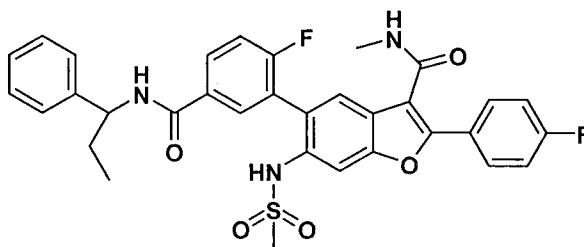


5-(2-Fluoro-5-(1-phenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metil-6-(metilsulfonamido)benzofuran-3-carboxamida

Preparada a partir del acoplamiento entre 6-amino-5-(2-fluoro-5-(1-phenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida y cloruro de metanosulfonilo (*N,N*-diisopropiletilamina, ClCH₂CH₂Cl, t.a.), seguido por la hidrólisis del intermedio *N*-(metilsulfonil)metanosulfonamida (Cs₂CO₃, H₂O/1,4-dioxano 1:5, 90 °C).

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min,

Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,70 - 7,25 min. (Detección UV a 220 nm). RMN de ^1H (500 MHz, CD_3OD) δ 8,00–7,95 (m solapando, 4H), 7,83 (s, 1H), 7,66 (s, 1H), 7,35 (t, J = 9,00, 1H), 7,30–7,27 (m solapando, 6H), 7,18 (m, 1H), 2,94 (s, 3H), 2,88 (s, 3H), 1,37–1,35 (aparece como d, 4H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H_2O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_2O al 10% - TFA al 0,1%, %B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z $(\text{M}+\text{H})^+$ = 616,48, HPLC Tr = 1,563 min. Las HPLC analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5% - H_2O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H_2O al 5% - TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm , 4,6 x 150 mm, Tr = 6,57 min; Columna: XBridge Phenyl 3,5 μm , 4,6 x 150 mm, Tr = 5,80 min.

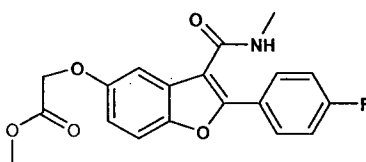


5-(2-Fluoro-5-(1-fenilpropilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metil-6-(metilsulfonamido)benzofuran-3-carboxamida

Preparada de una forma similar a 5-(2-fluoro-5-(1-fenilciclopropilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metil-6-(metilsulfonamido)benzofuran-3-carboxamida.

Purificación por HPLC de fase inversa preparativa Shimadzu-VP usando el procedimiento de separación: Disolvente A = MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 10 min, Tiempo de detección = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,35 - 7,81 min. (Detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 8,00–7,93 (m solapando, 4H), 7,83 (s, 1H), 7,66 (s, 1H), 7,41 (d solapando con s, J = 8,00, 1H), 7,40 (s, 1H), 7,35–7,32 (m solapando, 3H), 7,29 (t, J = 8,10, 2H), 7,25 (t, J = 7,93, 1H), 4,99 (t, J = 7,48, 1H), 2,94 (s, 3H), 2,89 (s, 3H), 1,94 (m, 2H), 1,00 (t, J = 7,17, 3H). Las LC/EM se realizaron usando un instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A = MeOH al 10% - H₂O al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H₂O al 10% - TFA al 0,1%,

%B inicial = 0, %B final = 100, Tiempo de gradiente = 2 min, Tiempo de
detección = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0
x 50 mm; (ES+) m/z (M+H)⁺ = 618,48, HPLC Tr = 1,637 min. Las HPLC
analíticas se realizaron usando un instrumento Shimadzu-VP con detección UV
5 a 220 nm y 254 nm. Procedimiento HPLC analítico: Disolvente A = MeCN al 5%
- H₂O al 95% - TFA al 0,1%, Disolvente B = MeCN al 95% - H₂O al 5% - TFA al
0,1%, %B inicial = 50, %B final = 100, Tiempo de gradiente = 15 min, Tiempo
de detección = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x
150 mm, Tr = 7,76 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr =
10 6,37 min.



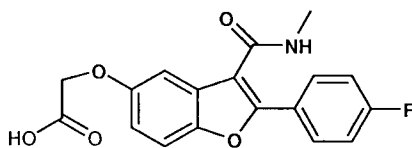
2-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-iloxi)acetato de metilo

A un matraz de fondo redondo de 50 ml se añadió 2-(4-fluorofenil)-5-
15 hidroxil-N-metilbenzofuran-3-carboxamida (285 mg, 1 mmol), carbonato
potásico (207 mg, 1,500 mmol) y bromoacetato de metilo (0,101 ml, 1,1 mmol)
en DMF (3 ml) dando una suspensión amarilla. La mezcla se agitó a
temperatura ambiente en nitrógeno durante la noche. El producto bruto se
diluyó con 100 ml de diclorometano, se lavó con agua, luego salmuera y se
20 secó sobre sulfato de magnesio. El residuo se purificó usando BIOTAGE®

Horizon empleando un gradiente de 0 a 30% de metanol en diclorometano y una columna de gel de sílice 40+M. El producto se trituró entonces con acetato de etilo frío dando un 73% de rendimiento (259 mg) de producto, un sólido amorfo blanco después de secar a vacío.

- 5 Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna PHENOMENEX® 10µm C18, 4,6 x 30mm, con un gradiente de 0-100% de B (B = metanol al 90% calidad HPLC/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ metanol al 10% calidad HPLC), en 2 minutos con un mantenimiento de 1 minuto a una velocidad de 5 ml/minuto.

- Los espectros de RMN se registraron a temperatura ambiente usando un espectrómetro Bruker DRX300. Los desplazamientos químicos se expresan en ppm con respecto al disolvente deuterado usado. Las constantes de acoplamiento se expresan en hertz. La multiplicidad del pico se expresa usando las siguientes abreviaturas: s (singlete), d (doblete), dd (doblete de dobletes), t (triplete), m (multiplete), a (ancho). RMN de ^1H (300 MHz, CD_3OD) δ ppm 2,93 (s, 3 H), 3,79 (s, 3 H), 4,75 (s, 2 H), 7,01 (dd, $J = 8,97, 2,38$ Hz, 1 H), 7,15 (d, $J = 2,38$ Hz, 1 H), 7,22 (t, $J = 8,78$ Hz, 2 H), 7,46 (d, $J = 8,97$ Hz, 1 H), 7,88 (m, 2 H). LCMS m/z 358,27 (M+H), R_t 1,553 min., 97,4% de pureza.



Ácido 2-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-iloxi)acético

A un matraz de fondo redondo de 50 ml se añadió 2-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-iloxi)acetato de metilo (132,3 mg, 0,370 mmol) y

5 2 equivalentes de trimetilsilanolato potásico (95 mg, 0,740 mmol) junto con una solución 1:1 de tetrahidrofurano/diclorometano (10 ml) dando una mezcla heterogénea amarilla. La mezcla se agitó a temperatura ambiente durante la noche. El producto bruto se enfrió entonces hasta 0°C, se diluyó de nuevo con diclorometano y se acidificó con HCl 1 N. El producto se extrajo, se lavó con

10 agua y luego salmuera y se secó sobre sulfato de magnesio. Después de evaporar el disolvente, el producto se trituró con hexano dando un 91% de rendimiento (115 mg), un sólido blanco amorfo después de secar a vacío.

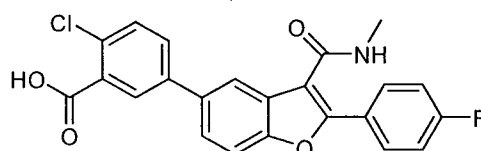
Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de

15 condiciones: Columna PHENOMENEX® 10µm C18, 4,6 x 30mm, con un gradiente de 0-100% de B (B = metanol al 90% calidad HPLC/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ metanol al 10% calidad HPLC), en 2 minutos con un mantenimiento de 1 minuto a una velocidad de 5 ml/minuto. Los

20 espectros de RMN se registraron a temperatura ambiente usando un espectrómetro Bruker DRX300. RMN de ¹H (300 MHz, DMSO-d₆) δ ppm 2,82

(d, $J = 4,39$ Hz, 3 H), 4,72 (s, 2 H), 7,00 (dd, $J = 8,78, 2,56$ Hz, 1 H), 7,08 (d, $J = 2,56$ Hz, 1 H), 7,35 (t, $J = 8,97$ Hz, 2 H), 7,57 (d, $J = 8,78$ Hz, 1 H), 7,92 (dd, $J = 8,78, 5,49$ Hz, 2 H), 8,34 (m, 1 H). LCMS m/z 344,27 ($M+H$), R_t 1,450 min., 96,0% de pureza.

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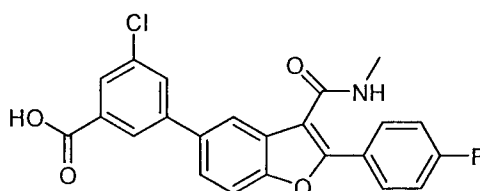


Ácido 2-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

A un tubo herméticamente cerrado de 250 ml se añadió trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo
 10 (3,55 g, 8,5 mmol), dioxano (50 ml), agua (10 ml), tetraquis(trifenilfosfina)paladio(0) (0,196 g, 0,170 mmol), ácido 5-borono-2-clorobenzoico (2,55 g, 12,75 mmol) y carbonato de cesio (4,15 g, 12,75 mmol). El tubo se selló y se calentó en un baño de aceite durante la noche a 85°C. La mezcla de reacción se enfrió entonces, se diluyó con 300 ml de HCl 0,5M frío y
 15 se agitó durante 30 minutos. El sólido resultante se lavó con HCl 0,5 N y luego con agua y se dejó secar a vacío dando un rendimiento cuantitativo de ácido 2-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico que se usó sin purificación posterior. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente
 20 conjunto de condiciones: Columna Waters Sunfire 5 μ m C18, 4,6 x 50mm, con

un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto.

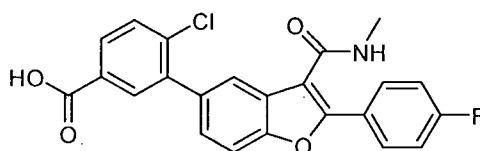
- 5 LCMS m/z 424,77 (M+H), R_t 2,150 min., 90% de pureza.



Ácido 3-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

- A un tubo herméticamente cerrado de 250 ml se añadió
- 10 trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (3,55 g, 8,5 mmol), dioxano (50 ml), agua (10 ml), tetraquis(trifenilfosfina)paladio(0) (0,196 g, 0,170 mmol), ácido 5-borono-3-clorobenzoico (2,55 g, 12,75 mmol) y carbonato de cesio (4,15 g, 12,75 mmol). El tubo se cerró herméticamente y se calentó en un baño de aceite durante la
- 15 noche a 85°C. La mezcla de reacción se enfrió seguidamente, se diluyó con 300 ml de HCl 0,5M frío y se agitó durante 30 minutos. El sólido resultante se lavó con HCl 0,5 N luego con agua y se dejó secar a vacío dando un rendimiento cuantitativo de ácido 3-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico que se usó sin purificación posterior.
- 20 Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC

MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5 µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. LCMS *m/z* 424,09 (M+H), *Rt* 2,658 min., 88% de pureza.



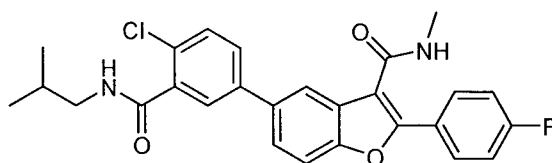
10 Ácido 4-cloro-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

A un tubo herméticamente cerrado de 250 ml se añadió trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (3,55 g, 8,5 mmol), dioxano (50 ml), agua (10 ml), tetraquis(trifenilfosfina)paladio(0) (0,196 g, 0,170 mmol), ácido 3-borono-4-clorobenzoico (2,55 g, 12,75 mmol) y carbonato de cesio (4,15 g, 12,75 mmol). El tubo se cerró herméticamente y se calentó en un baño de aceite durante la noche a 85°C. La mezcla de reacción se enfrió seguidamente, se diluyó con 300 ml de HCl 0,5M frío y se agitó durante 30 minutos. El sólido resultante se lavó con HCl 0,5 N luego con agua y se dejó secar a vacío dando un

20 rendimiento cuantitativo de ácido 4-cloro-5-(2-(4-fluorofenil)-3-

(metilcarbamoil)benzofuran-5-il)benzoico que se usó sin purificación posterior. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5µm de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm empleando agua/metanol/ bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. RMN de ¹H

(500 MHz, DMF- d_7) δ ppm 2,95 (d, J = 4,58 Hz, 3 H), 7,39 - 7,47 (m, 2 H), 7,57 (dd, J = 8,55, 1,83 Hz, 1 H), 7,81 (dd, J = 15,72, 8,39 Hz, 2 H), 7,87 (d, J = 1,83 Hz, 1 H), 8,04 - 8,14 (m, 4 H), 8,40 (d, J = 4,58 Hz, 1 H). LCMS m/z 424,90 (M+H), R_t 2,287 min. HPLC R_t 9,749min. (Sunfire C18) y 10,518min. (XBridge
5 Phenyl C18), 94% de pureza.



5-(4-Cloro-3-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-
carboxamida

- 10 A un matraz de fondo redondo de 250 ml se añadió ácido 2-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil) benzofuran-5-il)benzoico (3,62 g, 8,55 mmol), 2-metilpropan-1-amina (1,274 ml, 12,83 mmol), *N*-etil-*N,N*-diisopropilamina (2,98 ml, 17,10 mmol) y 3 eq. de HATU, hexafluorofosfato(V) de (2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (9,75 g, 25,7 mmol))
15 junto con 114 ml de DMF. La mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción bruta se transfirió a un embudo de separación, se diluyó con 300 ml de diclorometano y se lavó con 100 ml de HCl 1 N, agua y salmuera. Después de secar sobre sulfato de magnesio el residuo bruto se hizo pasar a través de un tapón de gel de sílice y se evaporó hasta un
20 sólido color castaño. El sólido se trituró con éter dietílico y luego acetonitrilo frío

dando un 48% de rendimiento de 5-(4-cloro-3-(isobutilcarbamoil) fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida, como un polvo amarillo claro. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX500. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu

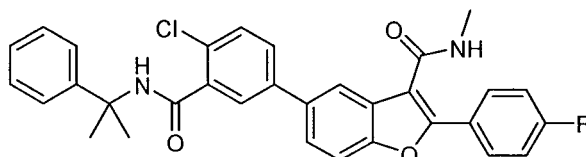
5 /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un

10 mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5µm de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoracético al 0,1%/ agua calidad

15 HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x

20 150mm empleando agua/metanol/ bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% /

bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. RMN de ^1H (500 MHz, acetona- d_6) δ ppm 1,02 (d, $J=6,71$ Hz, 6 H), 1,92 - 2,01 (m, 1 H), 2,99 (d, $J = 4,88$ Hz, 3 H), 3,28 (t, $J = 6,41$ Hz, 2 H), 7,33 (t, $J = 8,70$ Hz, 2 H), 7,56 (d, $J = 8,24$ Hz, 1 H), 7,61 (s ancho, 1 H), 7,66 (s ancho, 1 H), 7,68 - 7,74 (m, 2 H), 7,74 - 7,82 (m, 2 H), 8,01 - 8,06 (m, 1 H), 8,13 (dd, $J=8,70, 5,34$ Hz, 2 H). LCMS m/z 479,06 (M+H), R_t 2,367 min. HPLC R_t 10,263min. (Sunfire C18) y 11,753min. (XBridge Phenyl C18), 93% de pureza.



5-(4-Cloro-3-(2-fenilpropan-2-ilcarbamoi)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

A un vial de $3,54 \text{ cm}^3$ (2 dracmas) se añadió ácido 2-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoi) benzofuran-5-il)benzoico (42,4 mg, 0,1 mmol) en DMF (2 ml) junto con cumilamina (0,029 ml, 0,200 mmol), N,N -diisopropiletilamina (0,035 ml, 0,200 mmol) y HATU (114 mg, 0,300 mmol) dando una solución amarilla. El vial se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se evacuó casi hasta sequedad, se recogió en 2 ml de metanol y se purificó usando una HPLC preparativa Shimadzu empleando metanol/agua/TFA al 0,1% donde el disolvente A era MeOH al 10%

/ H₂O al 90% / ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / MeOH al 90% / ácido trifluoracético al 0,1% con una columna PHENOMENEX® Luna 10µm C18 30x100mm a un gradiente de B del 30-100% y un caudal de 40 ml/minuto durante 10 minutos con 10 minutos de mantenimiento. Los tubos

5 que contiene producto purificado se evaporaron durante la noche en un Savant/Thermo SPEEDVAC® dando un 45% de rendimiento de 5-(4-cloro-3-(2-fenilpropan-2-ilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida como un polvo blanco. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX300. Los datos

10 LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al

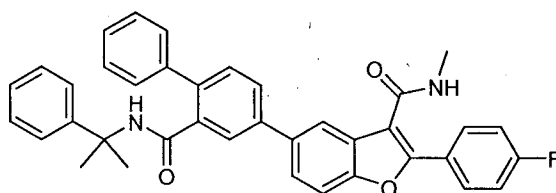
15 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5µm de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad

20 HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1

ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm empleando agua/metanol/bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol/

5 calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. RMN de ^1H (300 MHz, cloroformo- d) δ ppm 1,87 (s, 6 H), 3,02 (d, $J = 4,76$ Hz, 3 H), 6,03 (d, $J = 4,76$ Hz, 1 H), 6,62 (s, 1 H), 7,13

10 - 7,23 (m, 2 H), 7,24 - 7,31 (m, 1 H), 7,33 - 7,42 (m, 2 H), 7,45 (d, $J = 8,42$ Hz, 1 H), 7,48 - 7,63 (m, 5 H), 7,83 - 8,00 (m, 4 H). LCMS m/z 542,90 (M+H), R_t 2,608 min. HPLC R_t 11,069min. (Sunfire C18) y 12,111min. (XBridge Phenyl C18), 97,8% de pureza.



15

2-(4-Fluorofenil)-N-metil-5-(2-(2-fenilpropan-2-ilcarbamoil)bifenil-4-il)
benzofuran-3-carboxamida

A un vial de microondas de 2 ml se añadió dioxano (2 ml), agua (0,200 ml), (S-Phos) diciclohexil (2',6'-dimetoxibifenil-2-il)fosfina, (1,912 mg, 4,66

20 µmol), 5-(4-cloro-3-(2-fenilpropan-2-ilcarbamoil)fenil)-2-(4-fluorofenil)-N-

metilbenzofuran-3-carboxamida (0,0126 g, 0,023 mmol), fosfato potásico tribásico (0,020 g, 0,093 mmol), acetato de paladio(II) (1,046 mg, 4,66 μ mol) y ácido fenilborónico (8,52 mg, 0,070 mmol). El vial se tapó, se desgasificó, se purgó con N₂ y se calentó en el microondas durante 10 minutos a 150°C. El

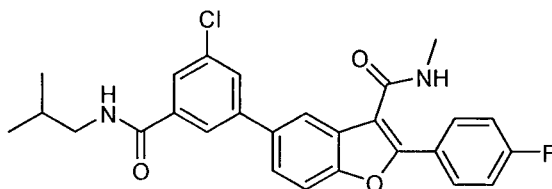
5 producto bruto se recogió en una solución 1:1 de DMF/acetonitrilo y se purificó por una HPLC preparativa Shimadzu empleando acetonitrilo/TFA al 0,1% /agua donde el disolvente A era acetonitrilo al 10% / H₂O al 90%/ ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90%/ ácido trifluoracético al 0,1% con una columna Waters-Atlantis OBD 19 x 100mm 5 μ m

10 a un gradiente de B de 50-100% y un caudal de 25 ml/minuto durante 10 minutos con un mantenimiento de 10 minutos. El producto purificado se evaporó hasta sequedad durante la noche en un Savant Thermo SPEEDVAC® dando un rendimiento de 73% de 2-(4-fluorofenil)-N-metil-5-(2-(2-fenilpropan-2-ilcarbamoil) bifenil-4-il) benzofuran-3-carboxamida. El espectro de RMN se

15 registró a temperatura ambiente usando un espectrómetro Bruker DRX500. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5 μ m C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua

20 calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó

usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5 μ m de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm empleando agua/metanol/ bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. RMN de ^1H (500 MHz, CD₃OD) δ ppm 1,54 (s, 6 H), 3,01 (s, 3 H), 7,15 - 7,20 (m, 1 H), 7,21 - 7,33 (m, 6 H), 7,43 - 7,50 (m, 3 H), 7,51 - 7,55 (m, 3 H), 7,69 - 7,72 (m, 1 H), 7,72 - 7,76 (m, 1 H), 7,80 (d, J = 1,53 Hz, 1 H), 7,84 (dd, J = 7,93, 1,83 Hz, 1 H), 7,96 - 8,02 (m, 3 H), 8,10 (s ancho, 1 H). LCMS m/z 583,03 (M+H), R_t 2,811 min. HPLC R_t 11,683min. (Sunfire C18) y 12,609min. (XBridge Phenyl C18), 99% de pureza.



5-(3-Cloro-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

A un matraz de fondo redondo de 250 ml se añadió ácido 3-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil) benzofuran-5-il)benzoico (3,62 g, 8,55 mmol), 2-metilpropan-1-amina (1,274 ml, 12,83 mmol), *N*-etil-*N,N*-diisopropilamina (2,98 ml, 17,10 mmol) y 3 eq. de HATU (hexafluorofosfato(V) de (2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (9,75 g, 25,7 mmol)) junto con 114 ml de DMF. La mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción bruta se transfirió a un embudo de separación, se diluyó con 300 ml de diclorometano y se lavó con 100 ml de HCl 1 N, agua y salmuera. Después de secar sobre sulfato de magnesio el residuo bruto se hizo pasar a través de un tapón de gel de sílice y se evaporó hasta un sólido color castaño. El sólido se trituró con éter dietílico y luego acetonitrilo frío dando a 52% de rendimiento de 5-(4-cloro-3-(isobutilcarbamoil) fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida, como un polvo amarillo claro. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX500. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente

de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC

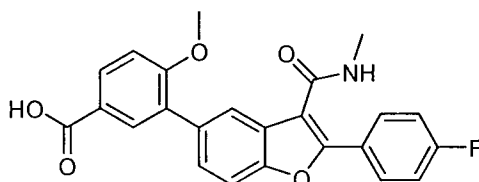
5 se determinó usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5 μ m de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al

10 0,1%/acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm empleando agua/metanol/ bicarbonato amónico 10 mM con un

15 gradiente de B del 10-100% (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. RMN de ^1H (500 MHz, DMSO- d_6) δ ppm 0,94 (d, J = 6,41 Hz, 6 H), 1,72 - 1,97 (m, 1 H),

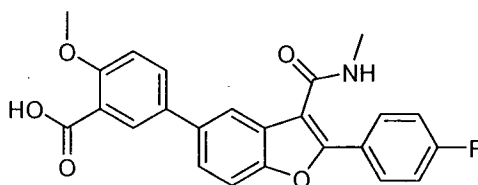
20 2,87 (d, J = 4,58 Hz, 3 H), 3,10 (t, J = 6,26 Hz, 2 H), 7,40 (t, J = 8,85 Hz, 2 H), 7,59 (d, J = 8,55 Hz, 1 H), 7,69 - 7,75 (m, 2 H), 7,76 - 7,82 (m, 2 H), 7,90 (s ancho, 1 H), 7,97 - 8,07 (m, 2 H), 8,55 (s ancho, 2 H). LCMS m/z 479,04 (M+H),

Rt 2,658 min. HPLC *Rt* 10,810min. (Sunfire C18) y 12,154min. (XBridge Phenyl C18), 92% de pureza.



5 Ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metoxibenzoico

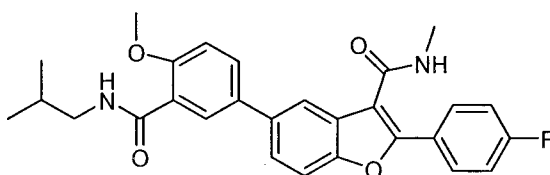
A un tubo herméticamente cerrado de 150 ml se añadió trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (1,252 g, 3 mmol), ácido 3-borono-4-metoxibenzoico (0,882 g, 4,50 mmol), carbonato de cesio (1,466 g, 4,50 mmol), tetraquis(trifenilfosfina)paladio(0) (0,069 g, 0,060 mmol), dioxano (18 ml) y agua (3,60 ml). El vial se cerró herméticamente y se calentó en un baño de aceite durante la noche a 85°C. La mezcla de reacción se filtró entonces a través de CELITE® y se concentró a vacío. Se añadió entonces HCl 0,5N frío y la mezcla heterogénea se agitó durante 30 minutos. El producto resultante, un sólido blanco se filtró, se lavó con agua y se secó durante la noche dando un rendimiento cuantitativo de 2, ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil) benzofuran-5-il)-4-metoxi benzoico que se usó sin purificación posterior. LCMS *m/z* 420,88 (M+H), *Rt* 2,002 min., 88% de pureza.



Ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoico

A un tubo herméticamente cerrado de 150 ml se añadió trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (1,252 g, 3 mmol), ácido 5-borono-2-metoxibenzoico (0,882 g, 4,50 mmol), carbonato de cesio (1,466 g, 4,50 mmol), tetraquis(trifenilfosfina)paladio(0) (0,069 g, 0,060 mmol), dioxano (18 ml) y agua (3,60 ml). El vial se cerró herméticamente y se calentó en un baño de aceite durante la noche a 85°C. La mezcla de reacción se filtró entonces a través de CELITE® y se concentró a vacío. Se añadió HCl 0,5N frío y la mezcla heterogénea se agitó durante 30 minutos. El producto resultante, un sólido blanco se filtró, se lavó con agua y se secó durante la noche dando un rendimiento cuantitativo de ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi benzoico que se usó sin purificación posterior. LCMS m/z 420,92 (M+H), R_t 2,003 min., 87% de pureza.

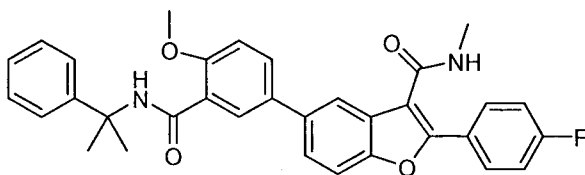
15



2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-4-metoxifenil)-N-metilbenzofuran-3-carboxamida

A un vial que contenía ácido (5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoico (378,5 mg, 0,902 mmol)) se añadió DMF (5 ml), *N*,-etil-*N,N*-diisopropilamina (0,786 ml, 4,51 mmol), 2-metilpropan-1-amina (0,448 ml, 4,51 mmol) y HATU, (hexafluorofosfato(V) de (2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (1029 mg, 2,71 mmol)). El vial se tapó y la solución se agitó durante la noche a temperatura ambiente. El producto bruto se diluyó con acetato de etilo, se lavó con HCl 0,5M y se extrajo. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró. La mezcla de reacción bruta se recogió en acetonitrilo, se filtró y se purificó usando una HPLC preparativa Shimadzu empleando acetonitrilo/agua/TFA donde el disolvente A era acetonitrilo al 10% / H₂O al 90%/ ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90%/ ácido trifluoracético al 0,1% con una columna PHENOMENEX® Luna 10µm C18 30x100mm a un gradiente de 40-100% B y un caudal de 25 ml/minuto durante 10 minutos con un mantenimiento de 10 minutos. El producto purificado se concentró a vacío dando un 38% de rendimiento de 2-(4-fluorofenil)-5-(3-(isobutilcarbamoil)-4-metoxifenil)-*N*-metilbenzofuran-3-carboxamida como un sólido blanco. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX500. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100%

de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua
calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al
0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento
de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó
5 usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters
Sunfire C18 3,5 μ m de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1%
con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/
ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad
HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en
10 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1
ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente
ortogonal y columna usando una LC analítica Shimadzu con una columna
Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm empleando agua/metanol/
bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol
15 calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al
5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol
calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a
una velocidad de 1 ml/minuto. RMN de ^1H (500 MHz, acetona- d_6) δ ppm 1,00
(d, J = 6,41 Hz, 6 H), 1,92 - 1,96 (m, 1 H), 3,01 (d, J = 4,27 Hz, 3 H), 3,30 (t, J =
20 6,26 Hz, 2 H), 4,09 (s, 3 H), 7,23 - 7,39 (m, 3 H), 7,61 (s ancho, 1 H), 7,69 (s, 2
H), 7,84 (dd, J = 8,39, 1,98 Hz, 1 H), 7,99 (s, 1 H), 8,13 (dd, J = 7,93, 5,49 Hz, 3
H), 8,39 (d, J = 2,14 Hz, 1 H). LCMS m/z 475,15 (M+H), R_t 2,452 min. HPLC R_t



2-(4-Fluorofenil)-5-(4-metoxi-3-(2-fenilpropan-2-ilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

A un vial que contenía ácido (5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoico (61 mg, 0,145 mmol)) se añadió DMF (2 ml), *N*,-etil-*N,N*-diisopropilamina (0,050 ml, 0,29 mmol), cumilamina (39,3mg, 0,291 mmol) y finalmente TBTU, tetrafluoroborato de o-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio (140 mg, 0,436 mmol)). El vial se tapó y la solución se agitó durante la noche a temperatura ambiente. El producto bruto se diluyó con acetato de etilo, se lavó con HCl 1M y se extrajo. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró. La mezcla de reacción bruta se recogió en acetonitrilo, se filtró y se purificó usando una HPLC preparativa Shimadzu empleando acetonitrilo/agua/TFA donde el disolvente A era acetonitrilo al 10% / H₂O al 90%/ ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90%/ ácido trifluoracético al 0,1% con una columna PHENOMENEX® Luna 10µm C18 30x100mm a un gradiente de 40-100% B y un caudal de 25 ml/minuto durante 10 minutos con un mantenimiento de 10 minutos. El producto purificado se concentró a vacío dando un 42% de rendimiento de 2-(4-fluorofenil)-5-(4-metoxi-3-(2-fenilpropan-2-ilcarbamoil)fenil)-N-metilbenzofuran-

3-carboxamida como un sólido blanco. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX500. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones:

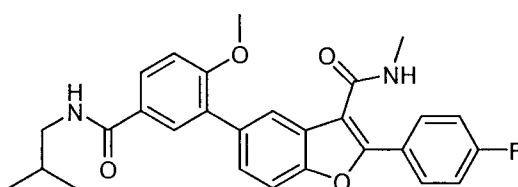
5 Columna Waters Sunfire 5 μ m C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó

10 usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5 μ m de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en

15 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm empleando agua/metanol/ bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol

20 calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a

una velocidad de 1 ml/minuto. RMN de ^1H (500 MHz, CD_3OD) δ ppm 1,69 - 1,88 (m, 6 H), 2,99 (s, 3 H), 4,09 (s, 3 H), 7,20 - 7,32 (m, 4 H), 7,36 (t, $J = 7,63$ Hz, 2 H), 7,52 (d, $J = 8,24$ Hz, 2 H), 7,57 - 7,64 (m, 2 H), 7,79 - 7,89 (m, 2 H), 7,96 (t, $J = 6,10$ Hz, 2 H), 8,12 (s ancho, 1 H). LCMS m/z 537,13 ($\text{M}+\text{H}$), R_t 2,705 min. HPLC R_t 11,563min. (Sunfire C18) y 12,876min. (XBridge Phenyl C18), 93% de pureza.

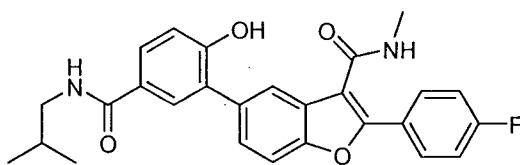


2-(4-Fluorofenil)-5-(5-(isobutylcarbamoyl)-2-metoxifenil)-N-metil benzofuran-3-carboxamida

A un matraz de fondo redondo de 100 ml se añadió ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)-4-metoxibenzoico (1258 mg, 3 mmol), DMF (40 ml), 2-metilpropan-1-amina (447 μl , 4,50 mmol), *N*-etil-*N,N*-diisopropilamina (1,1 ml, 6,00 mmol) y finalmente HATU hexafluorofosfato(V) de (2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (3422 mg, 9,00 mmol)). La mezcla se agitó durante la noche a temperatura ambiente. El producto bruto se diluyó con acetato de etilo, se lavó con HCl 1M y se extrajo. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo bruto se cargó en una columna 40M BIOTAGE® y se purificó usando una BIOTAGE® Horizon con 2200 ml de metanol al 0-6%

en DCM). El producto se concentró a vacío y luego se trituró con acetonitrilo frío dando un 60% de rendimiento de 3, 2-(4-fluorofenil)-5-(5-(isobutylcarbamoil)-2-metoxifenil)-N-metilbenzofuran-3-carboxamida como un sólido amarillo claro. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX500. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5µm de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm empleando agua/metanol/ bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol

calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. RMN de ^1H (500 MHz, CD_3OD) δ ppm 0,89 - 1,07 (m, 6 H), 1,96 (dt, $J=13,43$, 6,71 Hz, 1 H), 2,97 (s, 3 H), 3,22 (d, $J=6,10$ Hz, 2 H), 3,80 - 3,98 (m, 3 H), 7,19 (d, $J=9,46$ Hz, 1 H), 7,24 - 7,33 (m, 2 H), 7,52 - 7,57 (m, 1 H), 7,57 - 7,65 (m, 1 H), 7,80 (s, 1 H), 7,84 - 7,92 (m, 2 H), 7,96 - 8,02 (m, 2 H), 8,46 (s ancho, 1 H). LCMS m/z 475,02 (M+H), R_t 2,290 min. HPLC R_t 14,374min. (Sunfire C18) y 15,689min. (XBridge Phenyl C18), 95% de pureza. RMN de ^1H (500 MHz, CD_3OD) δ ppm 0,89 - 1,07 (m, 6 H), 1,96 (dt, $J=13,43$, 6,71 Hz, 1 H), 2,97 (s, 3 H), 3,22 (d, $J=6,10$ Hz, 2 H), 3,80 - 3,98 (m, 3 H), 7,19 (d, $J=9,46$ Hz, 1 H), 7,24 - 7,33 (m, 2 H), 7,52 - 7,57 (m, 1 H), 7,57 - 7,65 (m, 1 H), 7,80 (s, 1 H), 7,84 - 7,92 (m, 2 H), 7,96 - 8,02 (m, 2 H), 8,46 (s ancho, 1 H). LCMS m/z 475,02 (M+H), R_t 2,290 min. HPLC R_t 14,374min. (Sunfire C18) y 15,689min. (XBridge Phenyl C18), 95% de pureza.



2-(4-Fluorofenil)-5-(2-hidroxi-5-(isobutilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

A un tubo herméticamente cerrado de 250 ml se añadió tolueno (150

ml), 2-(4-fluorofenil)-5-(5-(isobutilcarbamoil)-2-metoxifenil)-N-metilbenzofuran-3-carboxamida (1,187 g, 2,50 mmol) y finalmente, en una corriente estacionaria de N₂ se añadió rápidamente complejo de tribromuro de boro-sulfuro de metilo (8,76 g, 28,0 mmol). El tubo se cerró herméticamente y se calentó hasta 100°C

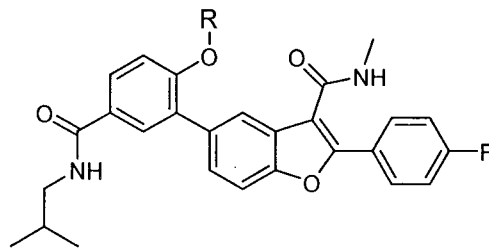
5 en un baño de aceite durante 30 horas. La mezcla de reacción bruta se enfrió hasta temperatura ambiente, se filtró, se lavó con hexano húmedo, luego éter dietílico y se secó durante la noche a vacío dando a 96% de rendimiento de un sólido color castaño. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX500. Los datos LC/EM se obtuvieron en

10 una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad

15 HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5µm de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido

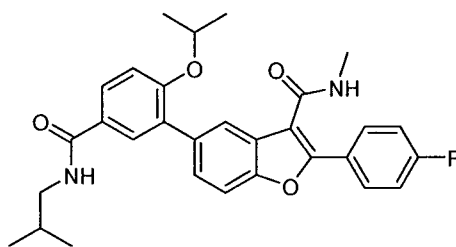
20 trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto.

La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm empleando agua/metanol/bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol
 5 calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. RMN de ^1H (500 MHz, DMF) δ ppm 0,92 (d, J = 6,71 Hz, 6 H), 1,86 - 1,97 (m, 1 H), 2,94 - 2,98 (m, 3 H), 3,17 - 3,23 (m, 2 H),
 10 7,19 (d, J = 8,55 Hz, 1 H), 7,42 (t, J = 9,00 Hz, 2 H), 7,66 - 7,75 (m, 2 H), 7,88 (dd, J = 8,39, 2,29 Hz, 1 H), 8,06 - 8,14 (m, 3 H), 8,37 - 8,46 (m, 2 H). LCMS m/z 461,95 (M+H), R_t 2,033 min. HPLC R_t 8,929min. (Sunfire C18) y 11,454min. (XBridge Phenyl C18), 96% de pureza.



15 Procedimiento General: A un vial de 3,54 cm³ (2 dracmas) se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(isobutilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida (46,0 mg, 0,1 mmol), DMF (2 ml) y 1,5 equivalentes (0,15mmol) de trietilamina o carbonato potásico y 1,5 equivalentes (0,15mmol) de bromuro de alquilo. Los viales se cerraron herméticamente y se agitaron a 22-70°C en

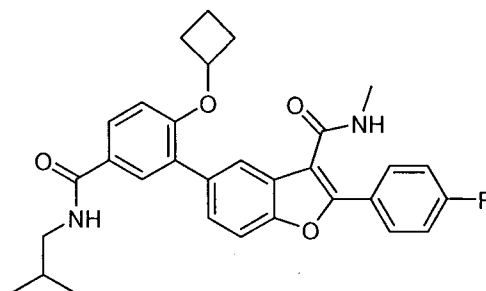
un baño seco. Tras completarse la reacción, se concentraron los productos brutos, se diluyó con 2 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu empleando acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / H₂O al 90%/ ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90%/ ácido trifluoracético al 0,1% con una columna Waters Sunfire 5µm C18 4,6 x 100mm a un gradiente de B al 30-100% y un caudal de 40 ml/minuto durante 8 minutos con un mantenimiento de 10 minutos. Los productos deseados se evaporaron hasta sequedad en un Savant SPEEDVAC® durante la noche obteniendo 25-60% de rendimiento de los éteres deseados como polvos blancos.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-isoproxifenil)-N-metilbenzofuran-3-carboxamida

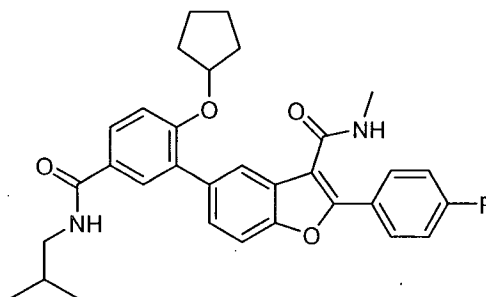
RMN de ¹H (500 MHz, CD₃OD) δ ppm 1,00 (d, *J* = 6,71 Hz, 6 H), 1,32 (d, *J* = 6,10 Hz, 6 H), 1,87 - 2,05 (m, 1 H), 2,98 (s, 3 H), 3,22 (d, *J* = 7,02 Hz, 2 H), 4,64 - 4,79 (m, 1 H), 7,18 (d, *J* = 8,55 Hz, 1 H), 7,24 - 7,36 (m, 2 H), 7,57 - 7,67 (m, 2 H), 7,85 (dd, *J* = 8,55, 2,44 Hz, 1 H), 7,87 (s, 1 H), 7,90 (d, *J* = 2,44 Hz, 1 H), 7,95 - 8,01 (m, 2 H). LCMS *m/z* 503,12 (M+H), *Rt* 2,368 min. HPLC *Rt* 10,789min. (Sunfire C18) y 12,428 min. (XBridge Phenyl C18), 98,7% de

pureza.



5-(2-(Ciclobutiloxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 5 RMN de ^1H (500 MHz, CD_3OD) δ ppm 0,99 (d, $J = 6,41$ Hz, 6 H), 1,71 - 1,81 (m, 1 H), 1,83 - 1,91 (m, 1 H), 1,92 - 2,00 (m, 1 H), 2,08 - 2,20 (m, 2 H), 2,45 - 2,56 (m, 2 H), 2,99 (s, 3 H), 3,22 (d, $J = 6,71$ Hz, 2 H), 4,80 - 4,84 (m, 1 H), 7,01 (d, $J = 8,55$ Hz, 1 H), 7,28 (t, $J = 8,55$ Hz, 2 H), 7,58 - 7,66 (m, 2 H), 7,83 (d, $J = 8,24$ Hz, 1 H), 7,86 - 7,92 (m, 2 H), 7,96 - 8,03 (m, 2 H). LCMS m/z 515,21 ($\text{M}+\text{H}$), R_t 2,613 min. HPLC R_t 11,161min. (Sunfire C18) y 12,693 min. (XBridge Phenyl C18), 97% de pureza.

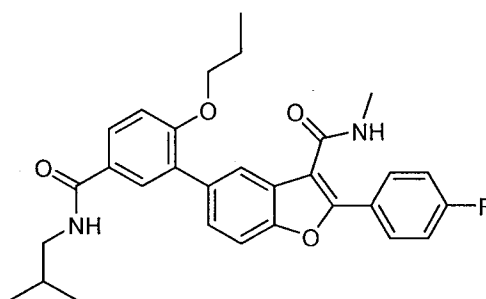


5-(2-(Ciclopentiloxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 15 RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,04 (d, $J = 6,78$ Hz, 6 H), 1,63 -

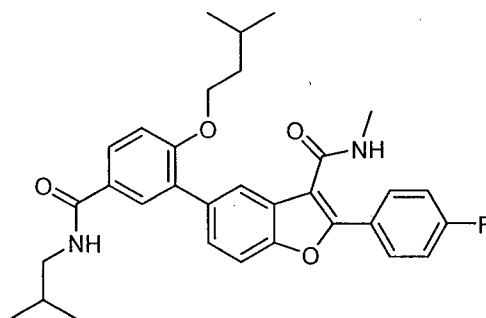
1,82 (m, 4 H), 1,83 - 2,08 (m, 5 H), 3,02 (s, 3 H), 3,27 (d, $J = 7,03$ Hz, 2 H), 5,02 (ddd, $J = 5,21, 2,89, 2,70$ Hz, 1 H), 7,21 (d, $J = 8,78$ Hz, 1 H), 7,28 - 7,36 (m, 2 H), 7,58 - 7,69 (m, 2 H), 7,88 (dd, $J = 8,53, 2,51$ Hz, 1 H), 7,91 (d, $J = 1,25$ Hz, 1 H), 7,95 (d, $J = 2,26$ Hz, 1 H), 7,99 - 8,06 (m, 2 H). LCMS m/z 529,16 (M+H),

5 R_t 2,685 min. HPLC R_t 12,879 min. (XBridge Phenyl C18), 100% de pureza.



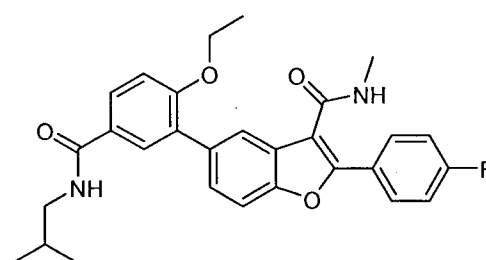
2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-propoxifenil)-N-metilbenzofuran-3-carboxamida

10 RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,04 (m, 9 H), 1,75 - 1,90 (m, 2 H), 1,93 - 2,10 (m, 1 H), 3,02 (s, 3 H), 3,27 (d, $J = 7,03$ Hz, 2 H), 4,11 (t, $J = 6,15$ Hz, 2 H), 7,21 (d, $J = 8,53$ Hz, 1 H), 7,32 (t, $J = 8,78$ Hz, 2 H), 7,59 - 7,72 (m, 2 H), 7,88 - 7,98 (m, 3 H), 7,98 - 8,08 (m, 2 H). LCMS m/z 503,14 (M+H), R_t 2,548 min. HPLC R_t 12,554 min. (XBridge Phenyl C18), 100% de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(isopentiloxi)fenil)-N-
metilbenzofuran-3-carboxamida

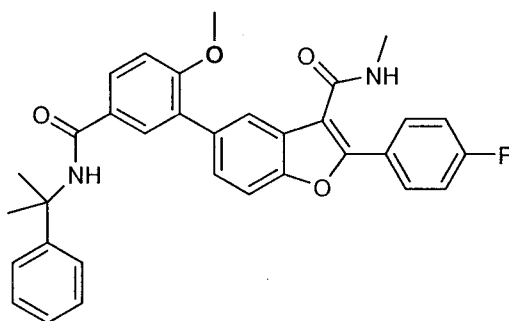
RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,93 - 1,01 (m, 6 H), 1,04 (d, J =
5 6,78 Hz, 6 H), 1,69 (c, J = 6,53 Hz, 2 H), 1,83 (ddd, J = 13,61, 6,71, 6,53 Hz, 1
H), 2,01 (dt, J = 13,74, 6,81 Hz, 1 H), 3,03 (s, 3 H), 3,27 (d, J = 7,03 Hz, 2 H),
4,18 (t, J = 6,27 Hz, 2 H), 7,22 (d, J = 8,78 Hz, 1 H), 7,28 - 7,39 (m, 2 H), 7,56 -
7,72 (m, 2 H), 7,86 - 7,98 (m, 3 H), 7,99 - 8,09 (m, 2 H). LCMS m/z 531,16
(M+H), R_t 2,791 min. HPLC R_t 13,122 min. (XBridge Phenyl C18), 100% de
10 pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-etoxifenil)-N-metilbenzofuran-3-
carboxamida

15 RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,04 (d, J = 6,53 Hz, 6 H), 1,42 (t,

$J = 6,78$ Hz, 3 H), 1,90 - 2,11 (m, 1 H), 3,02 (s, 3 H), 3,27 (d, $J = 7,03$ Hz, 2 H), 4,22 (c, $J = 6,78$ Hz, 2 H), 7,18 - 7,24 (m, 1 H), 7,29 - 7,38 (m, 2 H), 7,64 - 7,67 (m, 2 H), 7,87 - 7,93 (m, 2 H), 7,93 - 7,96 (m, 1 H), 8,00 - 8,08 (m, 2 H). LCMS m/z 489,15 (M+H), R_t 2,432 min. HPLC R_t 10,571 min. (Sunfire C18) y 12,193min. (XBridge Phenyl C18), 93% de pureza.



2-(4-Fluorofenil)-5-(2-metoxi-5-(2-fenilpropan-2-ilcarbamoi)fenil)-N-metilbenzofuran-3-carboxamida

A un matraz de fondo redondo de 50 ml se añadió ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoi)benzofuran-5-il)-4-metoxibenzoico (433,9 mg, 1,035 mmol), DMF (15 ml), 2-fenilpropan-2-amina (210 mg, 1,552 mmol), N-etil-N-isopropilpropan-2-amina (0,360 ml, 2,069 mmol) y finalmente HATU, hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (1180 mg, 3,10 mmol)). La mezcla se agitó durante la noche a temperatura ambiente. La mezcla resultante se diluyó con diclorometano, se lavó con HCl 0,5 M, luego salmuera y se secó sobre $MgSO_4$. La solución se concentró dando un aceite color castaño. El producto bruto se recogió en 10 ml

de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu empleando acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / H₂O al 90%/ ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90%/ ácido trifluoracético al 0,1% con una columna

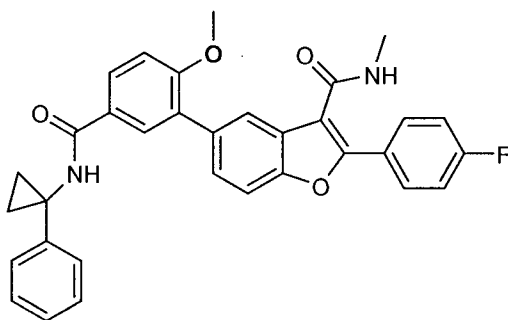
5 PHENOMENEX® Luna 10µm C18 30 x 100mm a un gradiente de B al 40-100% y un caudal de 40 ml/minuto durante 8 minutos con un mantenimiento de 12 minutos dando a 80% de rendimiento de producto como un polvo blanco. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones:

10 Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de B al 0-100% (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó

15 usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters Sunfire C18 3,5µm de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en

20 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna

Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm empleando agua/metanol/
 bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol
 calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al
 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol
 5), en 10 minutos con un mantenimiento de 10 minutos a
 una velocidad de 1 ml/minuto. Todos los espectros de RMN se registraron a
 temperatura ambiente usando un espectrómetro Bruker DRX400. LCMS m/z
 537,18 (M+H), R_t 2,492 min. HPLC R_t 10,694 min. (Sunfire C18), 99,6% de
 pureza y 12,230 min. (XBridge Phenyl C18), 99,6% de pureza. RMN de ^1H (400
 10 MHz, CD_3OD) δ ppm 1,82 (s, 6 H), 3,01 (s, 3 H), 3,94 (s, 3 H), 7,18 - 7,27 (m, 2
 H), 7,28 - 7,40 (m, 4 H), 7,50 (d, $J = 7,53$ Hz, 2 H), 7,57 - 7,67 (m, 2 H), 7,85 (d,
 $J = 1,00$ Hz, 1 H), 7,89 - 7,95 (m, 2 H), 7,98 - 8,09 (m, 2 H).

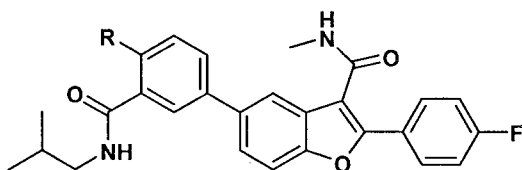


15 2-(4-Fluorofenil)-5-(2-metoxi-5-(1-fenilciclopropilcarbamoi)fenil)-N-
 metilbenzofuran-3-carboxamida

A un matraz de fondo redondo de 50 ml se añadió ácido 3-(2-(4-
 fluorofenil)-3-(metilcarbamoi)benzofuran-5-il)-4-metoxibenzoico (433,9 mg,

1,035 mmol), DMF (15 ml), 1-fenilciclopropanamina, HCl (214 mg, 1,259 mmol), N-etil-N-isopropilpropan-2-amina (0,438 ml, 2,52 mmol) y finalmente HATU, hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (1180 mg, 3,10 mmol)). La mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se diluyó con diclorometano, se lavó con HCl 0,5M, luego salmuera y se secó sobre MgSO₄. La solución se concentró dando un aceite color castaño. El producto bruto se recogió en 10 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu empleando acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / H₂O al 90%/ ácido trifluoracético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90%/ ácido trifluoracético al 0,1% con una columna PHENOMENEX® Luna 10µm C18 30 x 100mm a un gradiente de 40-100% B y un caudal de 40 ml/minuto durante 8 minutos con un mantenimiento de 12 minutos dando a 77% de rendimiento de producto como un polvo blanco. Los datos LC/EM se obtuvieron en una LC analítica Shimadzu /LC MICROMASS® Platform (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna Waters Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90%/ ácido trifluoracético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con un mantenimiento de 1 minuto a una velocidad de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 220nm y 256nm con una columna Waters

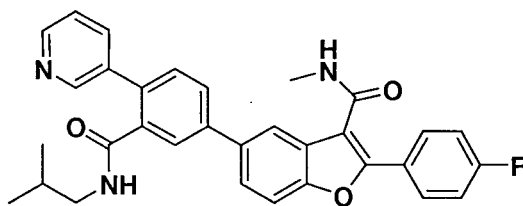
Sunfire C18 3,5 μ m de 4,6 x 150mm empleando agua/acetonitrilo/TFA al 0,1% con un gradiente de B del 10-100% (B = acetonitrilo calidad HPLC al 95%/ácido trifluoracético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoracético al 0,1%/acetonitrilo calidad HPLC al 5%), en 5 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema de disolvente ortogonal y columna usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm empleando agua/metanol/ bicarbonato amónico 10 mM con un gradiente de B del 10-100% (B = metanol 10 calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol 10 calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a una velocidad de 1 ml/minuto. Todos los espectros de RMN se registraron a temperatura ambiente usando un espectrómetro Bruker DRX400. LCMS *m/z* 15 535,16 (M+H), *Rt* 2,373 min. HPLC *Rt* 10,314 min. (Sunfire C18), 95,78% de pureza y 12,230 min. (XBridge Phenyl C18), 99,6% de pureza. RMN de ¹H (400 MHz, CD₃OD) δ ppm 1,40 (dd, *J* = 7,03, 2,01 Hz, 4 H), 3,01 (s, 3 H), 3,94 (s, 3 H), 7,18 - 7,26 (m, 2 H), 7,28 - 7,38 (m, 6 H), 7,56 - 7,62 (m, 1 H), 7,62 - 7,67 (m, 1 H), 7,85 (d, *J* = 1,51 Hz, 1 H), 7,94 - 8,05 (m, 4 H).



Procedimiento general: A un vial de microondas BIOTAGE® (2-5 ml) se
añadió 5-(4-cloro-3-(isobutilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-
3-carboxamida (0,075 mmol, 1 eq.) en 1,4-dioxano seco (1 ml) junto con el ácido
5 borónico deseado (0,150 mmol, 2 eq.), fosfato potásico, tribásico (0,300 mmol,
52,3 mg) en agua (0,2 ml), diciclohexil(2',6'-dimetoxibifenil-3-il)fosfina (S-Phos)
(6,16 mg, 0,015 mmol) y finalmente acetato de paladio (II) (3,37 mg, 0,015
mmol) en 1,4-dioxano (0,5 ml). El vial se purgó con nitrógeno y luego se tapó y
se colocó en un microondas BIOTAGE® durante 10 minutos a 150°C. El
10 disolvente se eliminó en un Thermo/Savant SPEEDVAC® y los productos
brutos se disolvieron en DMF (1,8 ml) y se purificó por HPLC preparativa
empleando un sistema Dionex PrepHPLC equipado con un detector ELS
(Dispersión de Luz Evaporativa). Se usó una columna PHENOMENEX®
Gemini 5µm C18 21,2 x 250mm con acetonitrilo/agua calidad HPLC/acetato
15 amónico 20 mM donde el disolvente A era agua calidad HPLC al 99,9% con
acetato amónico 20 mM y el disolvente B era acetonitrilo al 100% a un
gradiente de B al 30-95% en 23,5 minutos con un mantenimiento de 2,5
minutos a 20 ml/minuto. La pureza HPLC se determinó usando un
espectrómetro de masas Waters ZQ con ESCi con una columna Supelco
20 Ascentis 2,7 µm C18 4,6 x 50mm empleando acetonitrilo/agua calidad

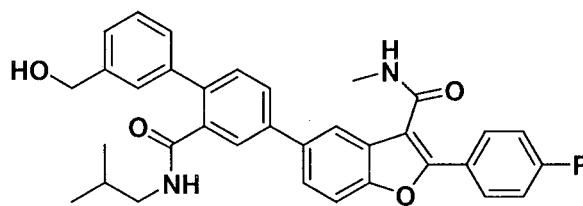
HPLC/acetato amónico al 0,1% donde el disolvente A era acetonitrilo al 5%, agua calidad HPLC al 95% con ácido trifluoroacético al 0,1% y el disolvente B era acetonitrilo al 95%, agua calidad HPLC al 5% con ácido trifluoroacético al 0,1% a un gradiente de B al 10-95% en 8 minutos con un mantenimiento de 1
5 minuto a 2 ml/minuto. Los espectros de RMN se registraron a temperatura ambiente usando un espectrómetro de flujo Varian 400MHz. Los desplazamientos químicos se expresaron en ppm respecto al disolvente DMSO-d₆/CDCl₃ usado.

10



2-(4-Fluorofenil)-5-(3-(isobutilcarbamoyl)-4-(piridin-3-il)fenil)-N-metilbenzofuran-
3-carboxamida

LCMS m/z 522,19 (M+H), R_t 3,21 min., 100% de pureza.



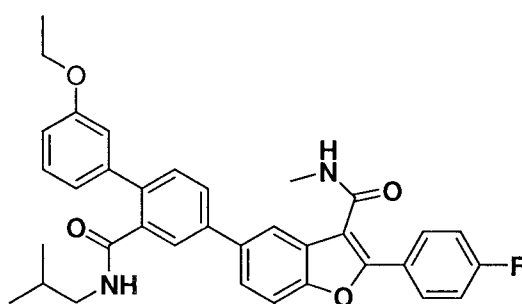
15

2-(4-Fluorofenil)-5-(3'-(hidroximetil)-2-(isobutilcarbamoyl)bifenil-4-il)-N-
metilbenzofuran-3-carboxamida

RMN de ¹H δ ppm 0,76 (d, J = 6,74 Hz, 6 H), 1,68 (m, 1 H), 2,29 (s, 3 H),

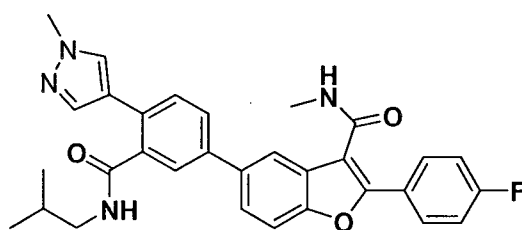
2,81 - 3,00 (m, 4 H), 7,07 - 7,18 (m, 1 H), 7,22 (t, $J = 7,47$ Hz, 1 H), 7,26 - 7,37 (m, 2 H), 7,39 (s, 1 H), 7,48 (d, $J = 7,91$ Hz, 1 H), 7,72 (s ancho, 2 H), 7,80 (d, $J = 8,20$ Hz, 1 H), 7,92 (s, 1 H), 8,01 (dd, $J = 7,47, 5,42$ Hz, 2 H), 8,22 (s, 2 H), 8,46 (s ancho, 1 H). LCMS m/z 551,23 (M+H), R_t 4,23 min., 100% de pureza.

5



5-(3'-Etoxi-2-(isobutilcarbamoil)bifenil-4-il)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

LCMS m/z 565,24 (M+H), R_t 5,28 min., 93,4% de pureza.

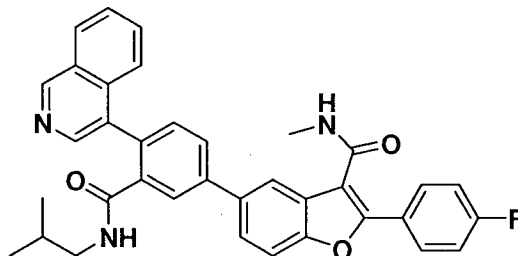


10

2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-4-(1-metil-1H-pirazol-4-il)fenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H δ ppm 0,93 (d, $J = 6,74$ Hz, 6 H), 1,82 - 1,99 (m, 1 H), 2,37 (s, 3 H), 2,89 - 3,00 (m, 2 H), 3,94 (s, 3 H), 7,15 - 7,25 (m, 1 H), 7,25 - 7,33 (m, 1 H), 7,39 (t, $J = 8,20$ Hz, 1 H), 7,62 - 7,82 (m, 5 H), 7,93 (d, $J = 12,89$ Hz, 1 H), 8,02 - 8,12 (m, 1 H), 8,36 - 8,45 (m, 1 H), 8,53 (d, 1 H). LCMS m/z 525,21

(M+H), *Rt* 4,00 min., 100% de pureza.

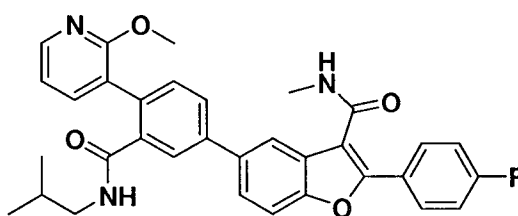


2-(4-fluorofenil)-5-(3-(isobutilcarbamoil)-4-(isoquinolin-4-il)fenil)-*N*-

5

metilbenzofuran-3-carboxamida

RMN de ^1H δ ppm 0,64 (d, $J = 6,44$ Hz, 6 H), 1,38 - 1,48 (m, 1 H), 2,37 (s, 3 H), 2,93 - 3,02 (m, 2 H), 7,14 - 7,24 (m, 2 H), 7,25 - 7,33 (m, 2 H), 7,40 (t, $J = 8,79$ Hz, 1 H), 7,57 (d, $J = 7,32$ Hz, 1 H), 7,75 (s ancho, 2 H), 7,81 - 7,90 (m, 1 H), 7,95 - 8,03 (m, 2 H), 8,08 (s ancho, 2 H), 8,18 - 8,25 (m, 1 H), 8,31 - 8,37 (m, 1 H), 8,48 (s, 1 H), 8,55 (s ancho, 1 H). LCMS m/z 572,22 (M+H), *Rt* 3,49 min., 100% de pureza.



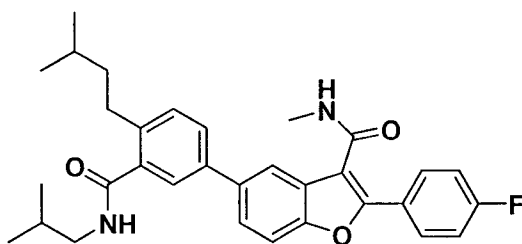
2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-4-(2-metoxipiridin-3-il)fenil)-*N*-

15

metilbenzofuran-3-carboxamida

RMN de ^1H δ ppm 0,88 (d, $J = 6,74$ Hz, 6 H), 1,68 - 1,83 (m, 1 H), 2,37

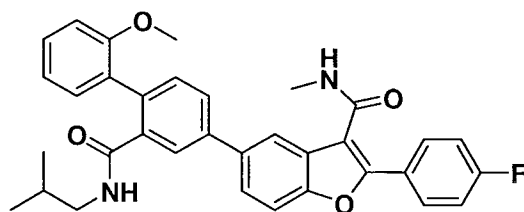
(s, 3 H), 2,96 (d, $J = 4,69$ Hz, 2 H), 3,86 (s, 3 H), 7,04 - 7,13 (m, 1 H), 7,21 (d, $J = 7,32$ Hz, 1 H), 7,28 (d, $J = 7,03$ Hz, 1 H), 7,39 (t, $J = 8,05$ Hz, 1 H), 7,48 (d, $J = 8,49$ Hz, 1 H), 7,67 (d, $J = 7,03$ Hz, 1 H), 7,82 (s, 2 H), 7,88 (s ancho, 2 H), 8,04 (s, 1 H), 8,06 - 8,12 (m, 1 H), 8,18 (d, $J = 4,98$ Hz, 1 H), 8,54 (s ancho, 1 H). LCMS m/z 552,21 (M+H), R_t 4,56 min., 90,5% de pureza.



2-(4-Fluorofenil)-5-(2-(isobutylcarbamoyl)-4'-isopentilbifenil-4-il)-N-metilbenzofuran-3-carboxamida

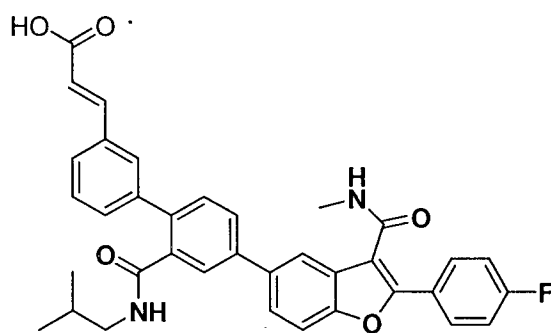
10 RMN de ^1H δ ppm 0,99 (dd, $J = 12,74, 6,59$ Hz, 9 H), 1,23 - 1,37 (m, 3 H), 1,59 - 1,70 (m, 1 H), 1,88 - 2,00 (m, 1 H), 2,37 (s, 3 H), 2,76 - 2,87 (m, 2 H), 2,91 - 2,99 (m, 2 H), 3,10 - 3,20 (m, 2 H), 7,14 - 7,25 (m, 1 H), 7,29 (t, $J = 7,32$ Hz, 1 H), 7,38 (t, $J = 8,05$ Hz, 2 H), 7,64 (s, 1 H), 7,72 (dd, $J = 16,26, 8,05$ Hz, 2 H), 7,93 (s, 1 H), 8,01 - 8,11 (m, 2 H), 8,44 (s ancho, 1 H), 8,52 (s ancho, 1 H).

15 LCMS m/z 515,26 (M+H), R_t 5,63 min., 100% de pureza.



2-(4-Fluorofenil)-5-(2-(isobutilcarbamoil)-2'-metoxibifenil-4-il)-N-metilbenzofuran-3-carboxamida

RMN de ^1H δ ppm 0,85 (d, $J = 6,74$ Hz, 6 H), 1,63 - 1,77 (m, 1 H), 2,37 (s, 3 H), 2,96 (d, $J = 4,39$ Hz, 2 H), 3,77 (s, 3 H), 6,99 - 7,09 (m, 1 H), 7,21 (d, $J = 7,62$ Hz, 1 H), 7,29 (t, $J = 7,62$ Hz, 2 H), 7,34 - 7,46 (m, 3 H), 7,76 - 7,88 (m, 3 H), 7,92 - 7,98 (m, 1 H), 8,02 (s, 1 H), 8,09 (dd, $J = 7,76, 6,00$ Hz, 2 H), 8,54 (s ancho, 1 H). LCMS m/z 551,22 (M+H), R_t 5,07 min., 93,7% de pureza.

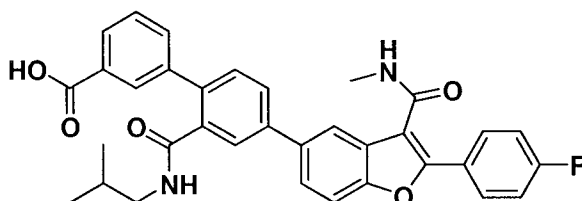


Ácido (E)-3-(4'-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2'-(isobutilcarbamoil) bifenil-3-il)acrílico

RMN de ^1H δ ppm 0,81 (d, $J = 6,44$ Hz, 6 H), 1,65 - 1,77 (m, 1 H), 2,37 (s, 3 H), 2,96 (d, $J = 4,39$ Hz, 2 H), 6,55 (d, $J = 15,82$ Hz, 1 H), 7,14 - 7,25 (m, 2 H), 7,25 - 7,33 (m, 1 H), 7,40 (t, $J = 8,49$ Hz, 2 H), 7,47 - 7,56 (m, 1 H), 7,61 (d,

$J = 8,20$ Hz, 1 H), 7,67 (s ancho, 1 H), 7,73 (s ancho, 1 H), 7,80 (s ancho, 2 H), 7,90 (d, $J = 7,91$ Hz, 1 H), 8,01 (s, 1 H), 8,04 - 8,13 (m, 1 H), 8,36 (s ancho, 1 H), 8,53 (s ancho, 1 H). LCMS m/z 591,23 (M+H), R_t 4,37 min., 100% de pureza.

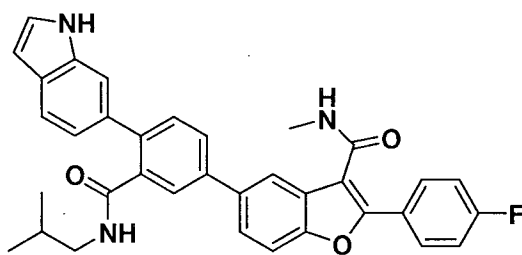
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Ácido 4'-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2'-(isobutilcarbamoil)bifenil-3-carboxílico

- 10 RMN de ^1H δ ppm 0,80 (d, $J = 6,74$ Hz, 6 H), 1,67 - 1,79 (m, 1 H), 2,37 (s, 3 H), 2,96 (d, $J = 4,69$ Hz, 2 H), 7,16 - 7,25 (m, 2 H), 7,26 - 7,32 (m, 1 H), 7,33 - 7,44 (m, 2 H), 7,50 - 7,62 (m, 2 H), 7,66 - 7,73 (m, 1 H), 7,76 - 7,84 (m, 2 H), 7,90 (d, $J = 7,91$ Hz, 1 H), 7,95 - 8,02 (m, 1 H), 8,04 - 8,14 (m, 2 H), 8,32 - 8,37 (m, 1 H), 8,55 (s ancho, 1 H). LCMS m/z 565,22 (M+H), R_t 4,22 min.,
- 15 100% de pureza.

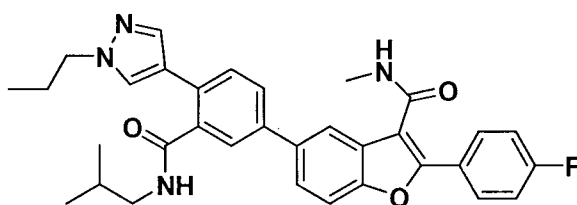
403



5-(4-(1*H*-Indol-6-il)-3-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

LCMS m/z 560,23 ($M+H$), R_t 4,90 min., 97,2% de pureza.

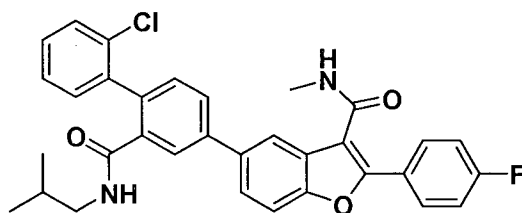
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2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-4-(1-propil-1*H*-pirazol-4-il)fenil)-*N*-metilbenzofuran-3-carboxamida

LCMS m/z 553,25 ($M+H$), R_t 4,49 min., 96% de pureza.

10

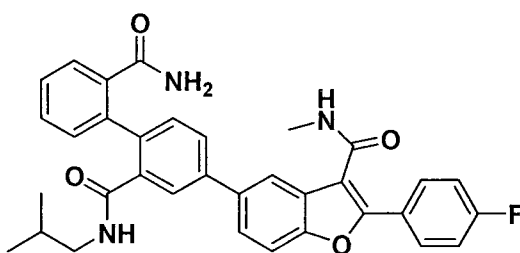


5-(2'-Cloro-2-(isobutilcarbamoil)bifenil-4-il)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

RMN de 1H δ ppm 0,85 (d, J = 6,44 Hz, 6 H), 1,65 - 1,80 (m, 1 H), 2,37

(s, 3 H), 2,93 - 2,97 (m, 2 H), 7,06 (s ancho, 1 H), 7,15 - 7,24 (m, 2 H), 7,25 - 7,35 (m, 2 H), 7,35 - 7,47 (m, 4 H), 7,49 - 7,55 (m, 1 H), 7,79 - 7,86 (m, 1 H), 7,87 - 7,93 (m, 1 H), 7,98 - 8,13 (m, 2 H), 8,21 - 8,27 (m, 1 H), 8,53 (s ancho, 1 H). LCMS m/z 556,19 (M+H), R_t 5,28 min., 100% de pureza.

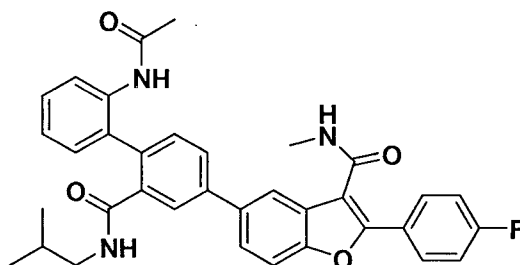
5



4-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-N2-isobutilbifenil-2,2'-dicarboxamida

RMN de ^1H δ ppm 0,69 (d, J = 6,44 Hz, 6 H), 1,42 - 1,54 (m, 1 H), 2,37 (s, 3 H), 2,92 - 2,97 (m, 2 H), 7,13 - 7,23 (m, 2 H), 7,23 - 7,33 (m, 2 H), 7,39 (t, J = 8,64 Hz, 1 H), 7,43 - 7,51 (m, 2 H), 7,61 (d, J = 4,69 Hz, 1 H), 7,75 - 7,82 (m, 2 H), 7,86 (s, 1 H), 7,96 - 8,03 (m, 1 H), 8,08 (d, J = 5,27 Hz, 1 H), 8,13 - 8,18 (m, 1 H), 8,51 (s ancho, 1 H), 8,65 (s ancho, 1 H). LCMS m/z 564,24 (M+H), R_t 4,07 min., 98,9% de pureza.

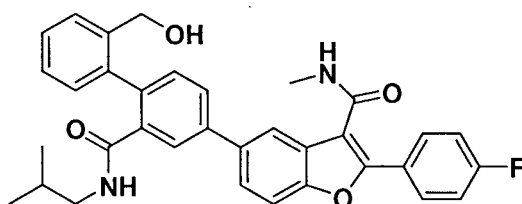
15



5-(2'-Acetamido-2-(isobutilcarbamoil)bifenil-4-il)-2-(4-fluorofenil)-*N*-
metilbenzofuran-3-carboxamida

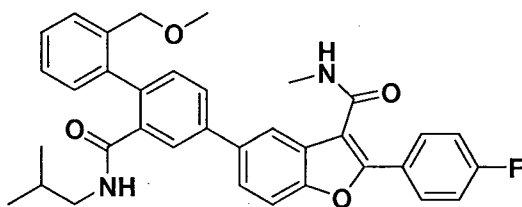
RMN de ^1H δ ppm 0,50 - 0,73 (m, 6 H), 1,33 - 1,50 (m, 1 H), 1,90 (s, 3 H), 2,37 (s, 3 H), 2,92 - 2,97 (m, 2 H), 7,20 (t, $J = 7,91$ Hz, 3 H), 7,25 - 7,44 (m, 6 H), 7,75 - 7,82 (m, 2 H), 7,91 (s, 1 H), 7,96 - 8,03 (m, 1 H), 8,04 - 8,11 (m, 1 H), 8,24 (s ancho, 1 H), 8,52 (s ancho, 1 H), 9,89 - 9,96 (m, 1 H).

LCMS m/z 578,24 (M+H), R_t 4,26 min., 93,5% de pureza.



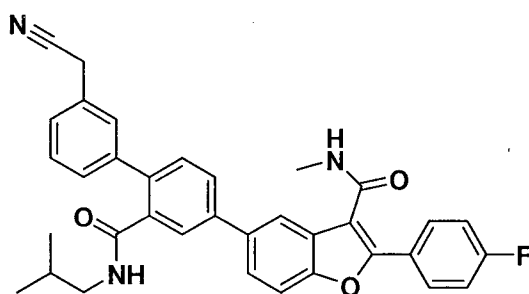
10 2-(4-Fluorofenil)-5-(2'-(hidroximetil)-2-(isobutilcarbamoil)bifenil-4-il)-*N*-
metilbenzofuran-3-carboxamida

RMN de ^1H δ ppm 0,71 (d, $J = 5,27$ Hz, 6 H), 1,45 - 1,57 (m, 1 H), 2,37 (s, 3 H), 2,90 (s ancho, 2 H), 2,96 (d, $J = 4,69$ Hz, 2 H), 7,13 - 7,25 (m, 2 H), 7,25 - 7,35 (m, 1 H), 7,35 - 7,44 (m, 3 H), 7,56 (d, $J = 7,32$ Hz, 1 H), 7,81 (s, 2 H), 7,83 - 7,89 (m, 2 H), 8,01 (s, 1 H), 8,09 (dd, $J = 8,64, 5,42$ Hz, 2 H), 8,52 (s ancho, 1 H). LCMS m/z 551,22 (M+H), R_t 4,58 min., 96% de pureza.



2-(4-Fluorofenil)-5-(2-(isobutilcarbamoil)-2'-(metoximetil)bifenil-4-il)-N-metilbenzofuran-3-carboxamida

RMN de ^1H δ ppm 0,64 - 0,79 (m, 6 H), 1,47 - 1,59 (m, 1 H), 2,37 (s, 3 H), 2,86 - 2,93 (m, 2 H), 2,93 - 2,99 (m, 2 H), 3,25 (s, 3 H), 7,15 - 7,25 (m, 2 H), 7,26 - 7,32 (m, 1 H), 7,33 - 7,44 (m, 4 H), 7,49 - 7,55 (m, 1 H), 7,81 (s, 2 H), 7,87 (s ancho, 2 H), 8,02 (s ancho, 1 H), 8,05 - 8,12 (m, 1 H), 8,53 (s ancho, 1 H). LCMS m/z 565,22 (M+H), R_t 5,30 min., 100% de pureza.

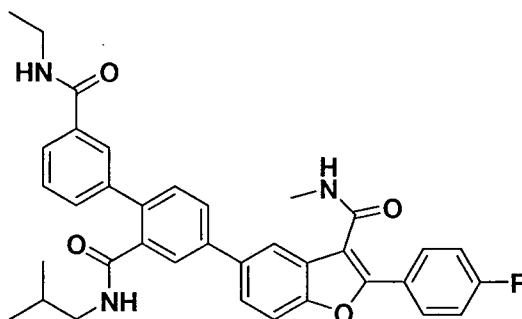


5-(3'-(Cianometil)-2-(isobutilcarbamoil)bifenil-4-il)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H δ ppm 0,83 (d, $J = 6,44$ Hz, 6 H), 1,67 - 1,81 (m, 1 H), 2,37 (s, 3 H), 2,96 (d, $J = 4,39$ Hz, 2 H), 4,08 (s, 2 H), 7,14 - 7,25 (m, 2 H), 7,26 - 7,32 (m, 1 H), 7,35 - 7,44 (m, 2 H), 7,48 (d, $J = 5,27$ Hz, 2 H), 7,56 (d, $J = 7,91$ Hz, 1 H), 7,80 (s ancho, 2 H), 7,90 (d, $J = 7,62$ Hz, 1 H), 8,00 (s, 1 H), 8,04 -

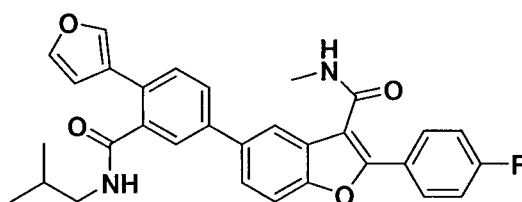
8,13 (m, 2 H), 8,35 (s ancho, 1 H), 8,54 (d, $J = 3,81$ Hz, 1 H).

LCMS m/z 560,23 (M+H), R_t 4,67 min., 91,5% de pureza.



- 5 *N*3'-Etil-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-*N*2-isobutilbifenil-2,3'-dicarboxamida

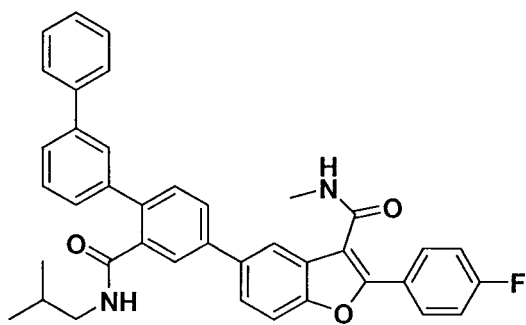
LCMS m/z 592,26 (M+H), R_t 4,28 min., 94,1% de pureza.



- 10 2-(4-Fluorofenil)-5-(4-(furan-3-il)-3-(isobutilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida

- RMN de ^1H δ ppm 0,86 - 1,03 (m, 6 H), 1,80 - 1,94 (m, 1 H), 2,37 (s, 3 H), 2,92 - 3,00 (m, 2 H), 6,79 (s, 1 H), 7,15 - 7,24 (m, 2 H), 7,28 (d, $J = 7,03$ Hz, 2 H), 7,35 - 7,42 (m, 1 H), 7,69 (t, $J = 7,91$ Hz, 2 H), 7,73 - 7,85 (m, 3 H), 7,94 (d, $J = 19,33$ Hz, 1 H), 8,04 - 8,12 (m, 1 H), 8,41 - 8,48 (m, 1 H), 8,53 (d, 1 H).

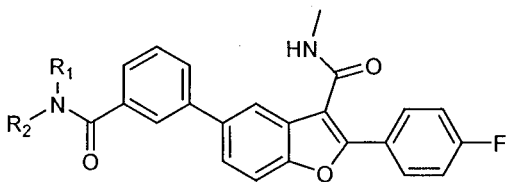
LCMS m/z 511,17 (M+H), R_t 4,69 min., 86,5% de pureza.



3'-Fenil-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-N2-isobutilbifenil-2,3'-dicarboxamida

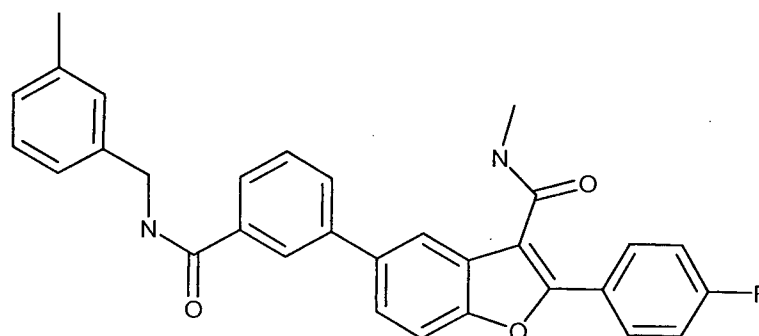
5 RMN de ^1H δ ppm 0,75 (d, $J = 6,74$ Hz, 6 H), 1,59 - 1,72 (m, 1 H), 2,37 (s, 3 H), 2,94 - 2,98 (m, 2 H), 7,15 - 7,24 (m, 3 H), 7,25 - 7,33 (m, 2 H), 7,34 - 7,47 (m, 4 H), 7,49 - 7,58 (m, 2 H), 7,63 - 7,74 (m, 2 H), 7,75 - 7,83 (m, 3 H), 7,89 (s ancho, 1 H), 8,00 (s, 1 H), 8,07 (s ancho, 1 H), 8,54 (s ancho, 1 H).
LCMS m/z 597,27 (M+H), R_t 5,74 min., 80% de pureza.

10



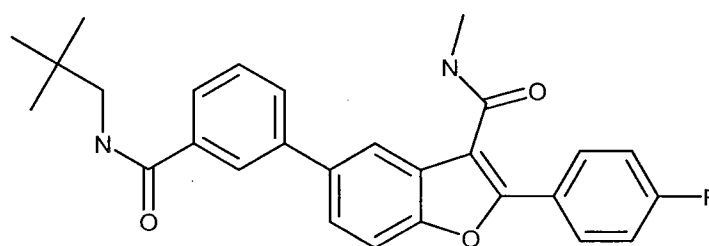
Los procedimientos generales (para formaciones de amida) siguientes pertenecen a los procedimientos experimentales. Algunos de los compuestos se prepararon con diferentes escalas de los ácidos. El ácido (0,075 mmol, 1
15 eq.) se disolvió en DMF secado y seguidamente se añadió HATU (0,090 mmol, 1,2 eq.) y DIPEA (0,225 mmol, 3,0 eq.). La solución se agitó durante 2 minutos

y se añadió en amina (0,090 mmol, 1,2 eq.) a temperatura ambiente. La mezcla se agitó 14 h y se purificó por HPLC prep.



5 2-(4-Fluorofenil)-N-metil-5-(3-(3-metilbencilcarbamoil)fenil)benzofuran-3-carboxamida

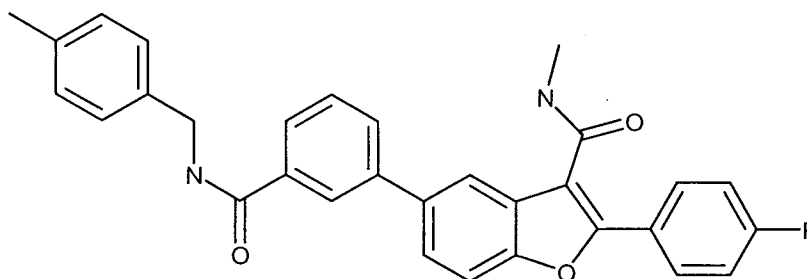
RMN de ^1H (600 MHz, DMSO- d_6 - CDCl_3) δ ppm 9,15 (1 H, t, $J=5,86$ Hz), 8,48 (1 H, d, $J=4,69$ Hz), 8,27 (2 H, d, $J=4,69$ Hz), 8,00 - 8,08 (1 H, m), 7,92 - 7,97 (2 H, m), 7,89 (1 H, d, $J=7,62$ Hz), 7,77 (2 H, s), 7,61 (1 H, t, $J=7,62$ Hz), 7,37 (2 H, t, $J=8,50$ Hz), 7,24 (1 H, t, $J=7,32$ Hz), 7,14 - 7,22 (2 H, m), 7,08 (1 H, d, $J=7,03$ Hz), 4,54 (2 H, d, $J=5,86$ Hz), 2,92 (3 H, d, $J=4,10$ Hz), 2,34 (3 H, s).



15 2-(4-Fluorofenil)-N-metil-5-(3-(neopentilcarbamoil)fenil)benzofuran-3-

carboxamida

RMN de ^1H (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 8,44 - 8,51 (m, 2 H), 8,27 (s, 1 H), 8,20 (s, 1 H), 8,02 - 8,07 (m, 1 H), 7,96 (s, 1 H), 7,88 (t, $J=7,32$ Hz, 2 H), 7,77 (s, 2 H), 7,59 (t, $J=7,62$ Hz, 1 H), 7,37 (t, $J=8,50$ Hz, 2 H), 3,20 (d, $J=6,44$ Hz, 2 H), 2,92 (d, $J=4,69$ Hz, 3 H), 0,98 (s, 9 H).



2-(4-Fluorofenil)-N-metil-5-(3-(4-metilbencilcarbamoi)fenil)benzofuran-3-carboxamida

10 RMN de ^1H (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 9,14 (t, $J=5,86$ Hz, 1 H), 8,48 (d, $J=4,69$ Hz, 1 H), 8,27 (s, 1 H), 8,25 (s, 1 H), 8,01 - 8,06 (m, 1 H), 7,95 (s, 1 H), 7,93 (d, $J=7,62$ Hz, 1 H), 7,89 (d, $J=7,62$ Hz, 1 H), 7,77 (s, 2 H), 7,61 (t, $J=7,62$ Hz, 1 H), 7,37 (t, $J=8,50$ Hz, 2 H), 7,27 (d, $J=7,62$ Hz, 2 H), 7,16 (d, $J=7,62$ Hz, 2 H), 4,52 (d, $J=5,86$ Hz, 2 H), 2,92 (d, $J=4,10$ Hz, 3 H), 2,30 - 2,35 (m, 3 H).

La pureza HPLC se determinó usando un espectrómetro de masas Waters LCT con LC analítica con una fuente MUX de cuatro vías a 220nm empleando acetonitrilo y agua o espectrómetro de masas Waters ZQ con ESCi. A = ACN:Agua 5:95; B = ACN:Agua 95:5; Modificador = NH_4OAc 10 nM. El

tiempo de retención se registró en minutos.

Procedimiento analítico A:

Columna: Waters XTERRA® 2,1x50mm 5 um C18

Tiempo	%B	Caudal
0,00	0	1,0
4,00	100	1,0
5,00	100	1,0

5

Procedimiento analítico B:

Columna: Waters XBridge 2,1x50mm 5 um C18

Tiempo	%B	Caudal
0,00	0	1,0
4,00	100	1,0
5,00	100	1,0
5,05	100	1,0
6,00	0	1,0

Procedimiento analítico C:

10 Columna: Waters XBridge 4,6x50mm 5 um C18

Tiempo	%B	Caudal
0,00	0	2,0
8,00	100	2,0
9,00	100	2,0

Procedimiento analítico D:

Columna: Waters XBridge 4,6x50mm 5 um C18

Tiempo	%B	Caudal
0,00	10	3,00
5,30	95	3,00
6,00	95	3,00
6,20	10	3,00
7,00	10	3,00

5 Procedimiento analítico E:

Waters ZQ con espectrómetro de masas ESCi

Columna: Supelcu Ascentis 4,6x50mm 2,7 um C18

Tiempo	%B	Caudal
0,00	10	1,0
10,00	95	1,0
13,00	95	1,0
13,50	10	1,0
15,00	10	1,0

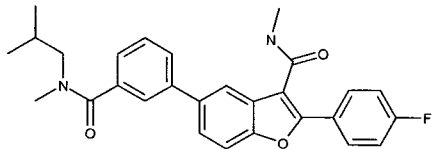
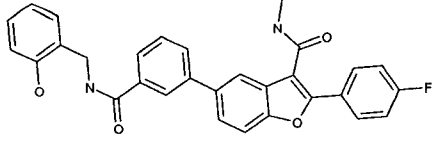
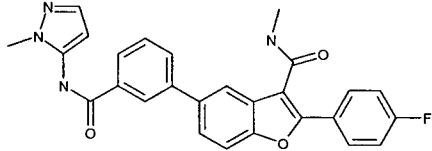
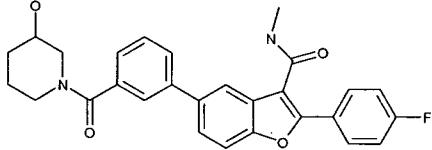
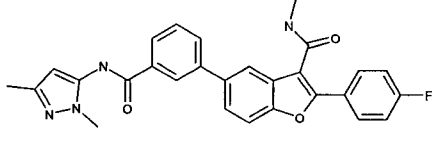
Procedimiento analítico F:

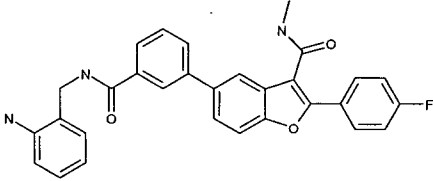
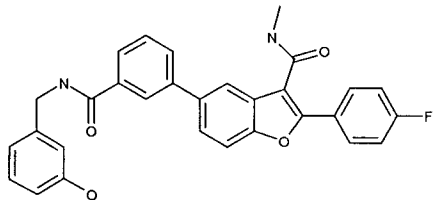
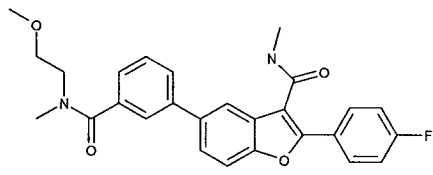
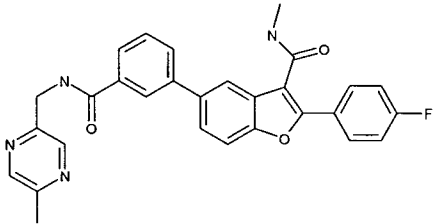
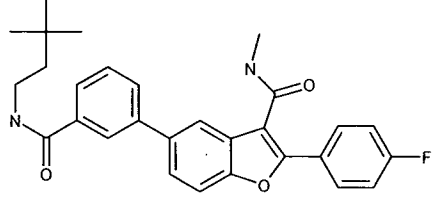
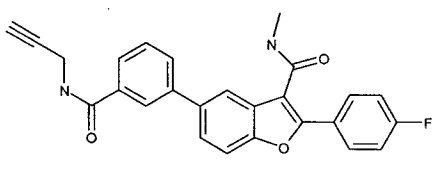
10 Waters ZQ con espectrómetro de masas ESCi

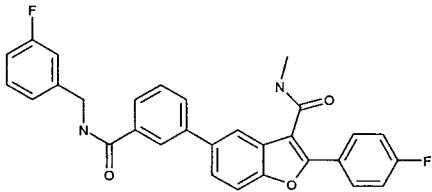
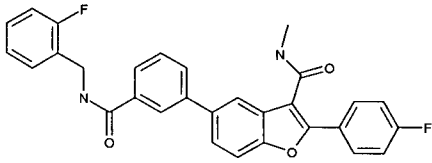
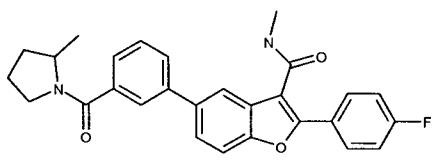
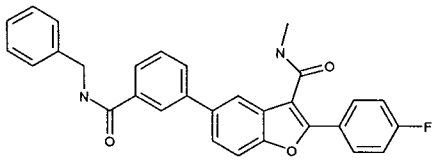
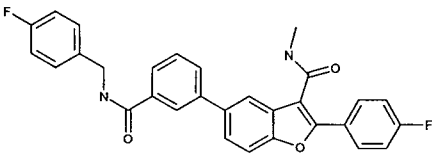
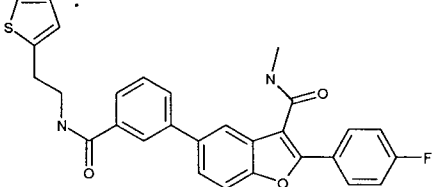
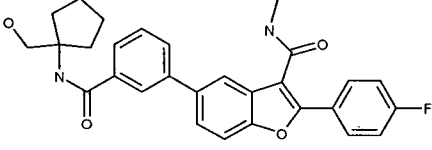
Columna: PHENOMENEX® Gemini 4,6x150mm 3 um C18

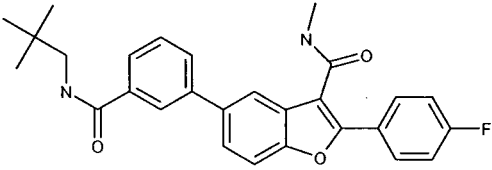
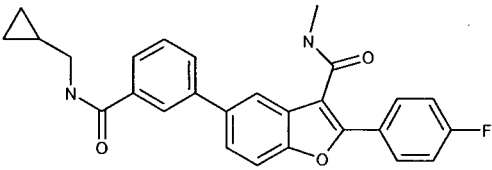
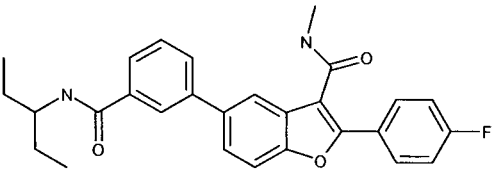
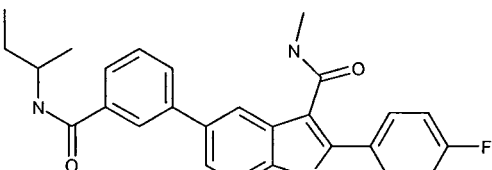
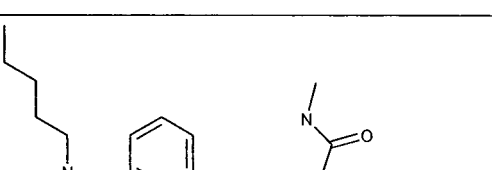
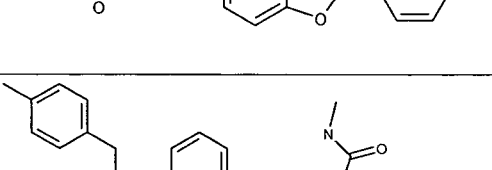
Tiempo	%B	Caudal
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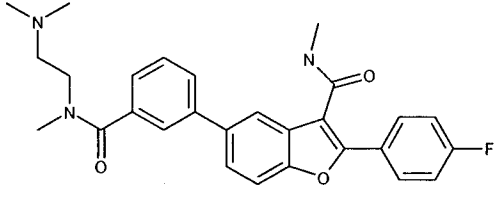
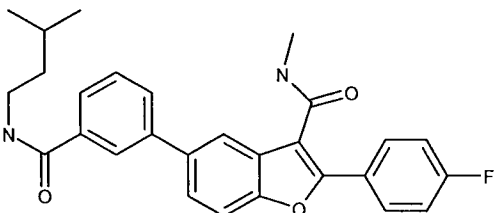
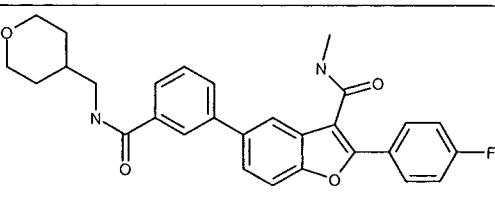
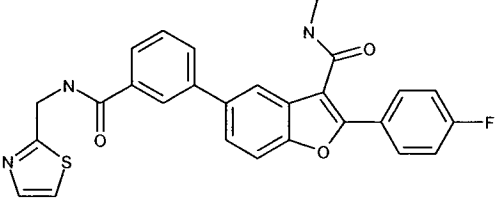
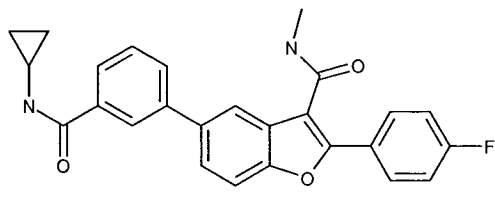
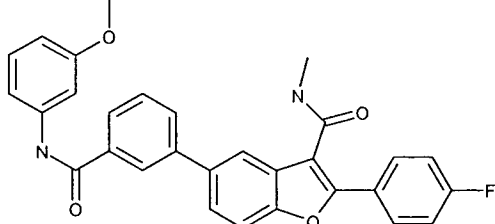
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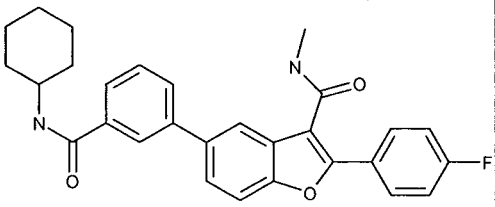
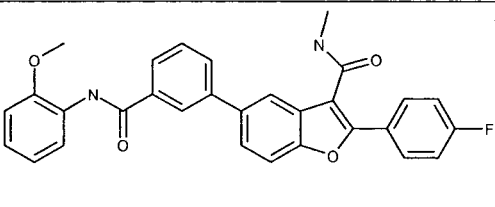
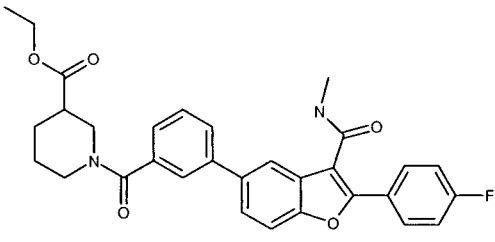
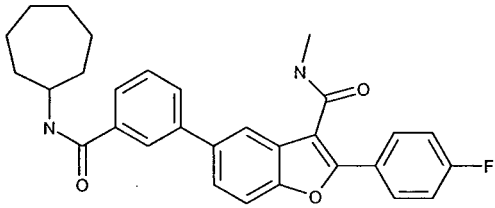
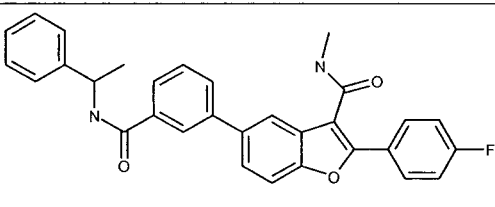
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
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	2,75	100	494,89	Procedimiento A
	2,38	100	468,9	Procedimiento A
	2,22	100	472,91	Procedimiento A
	2,46	100	482,9	Procedimiento A

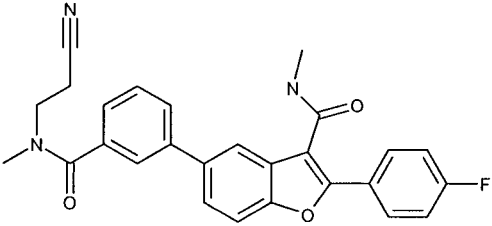
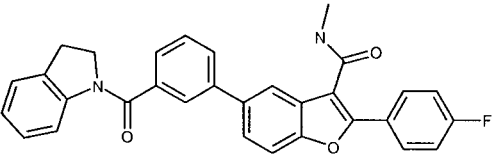
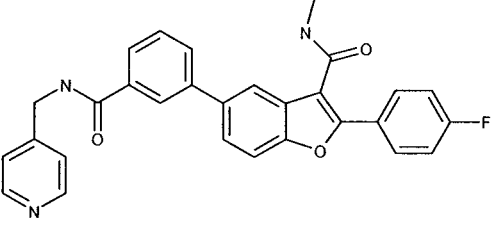
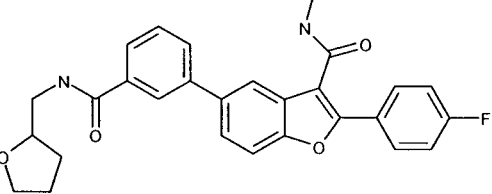
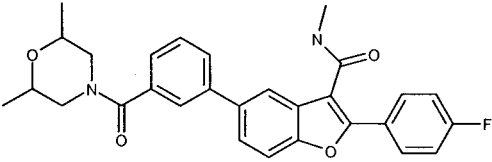
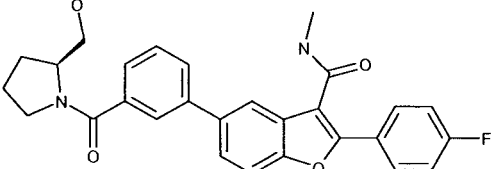
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
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	2,5	98,5972	494,9	Procedimiento A
	2,42	100	460,91	Procedimiento A
	2,34	100	494,9	Procedimiento A
	3,05	100	472,96	Procedimiento A
	2,48	100	426,91	Procedimiento A

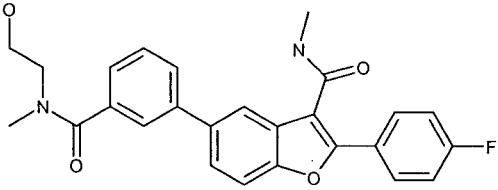
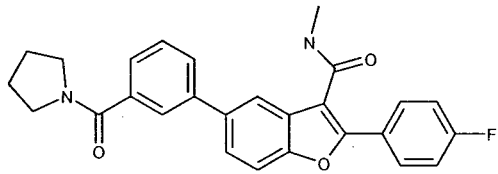
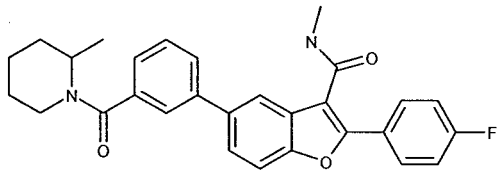
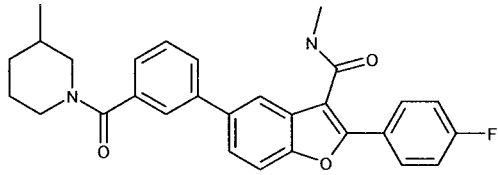
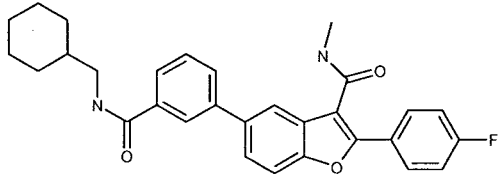
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	2,86	100	513,92	Procedimiento A
	2,89	100	513,91	Procedimiento A
	2,69	100	456,95	Procedimiento A
	2,8	100	495,94	Procedimiento A
	2,84	100	513,93	Procedimiento A
	2,85	100	498,9	Procedimiento A
	2,56	100	486,94	Procedimiento A

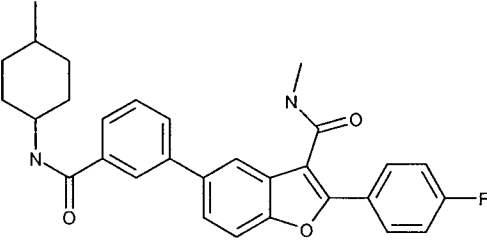
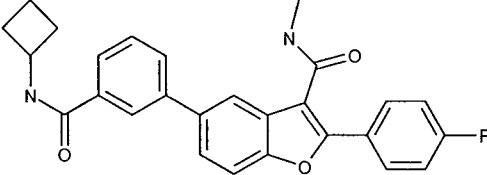
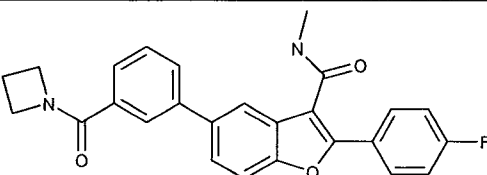
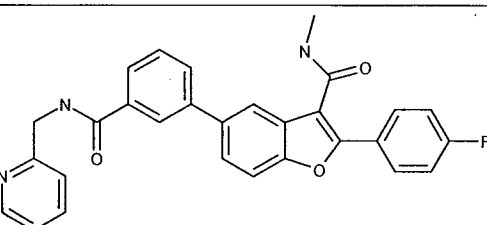
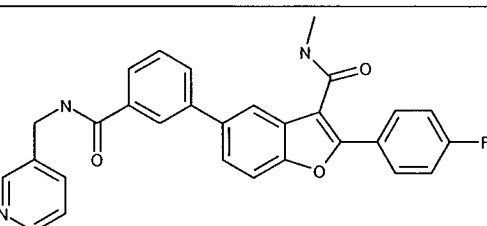
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	2,62	100	459,94	Procedimiento A
	2,85	100	475,95	Procedimiento A
	2,72	100	444,94	Procedimiento A
	2,91	100	475,95	Procedimiento A
	2,97	100	509,93	Procedimiento A

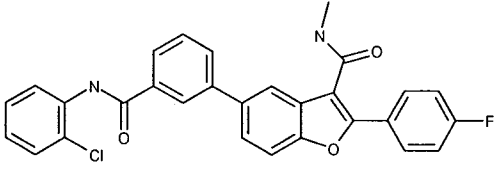
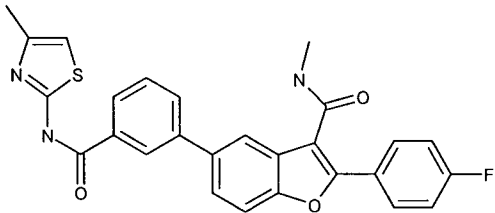
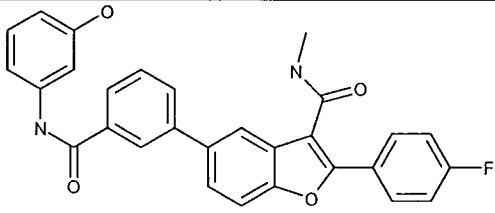
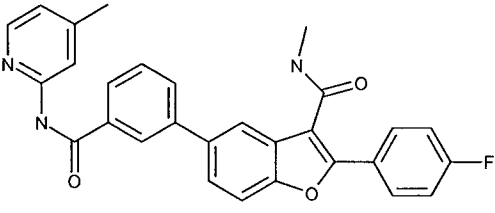
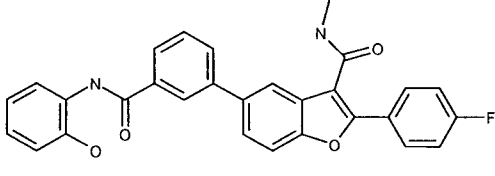
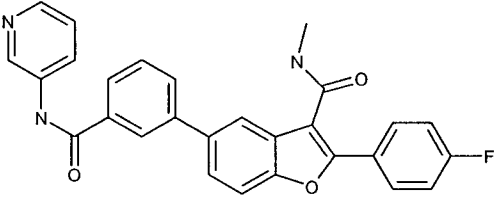
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
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	2,89	100	475,95	Procedimiento A
	2,43	100	486,93	Procedimiento A
	2,44	100	485,85	Procedimiento A
	2,39	100	856,65	Procedimiento B
	2,81	96,6226	494,8	Procedimiento B

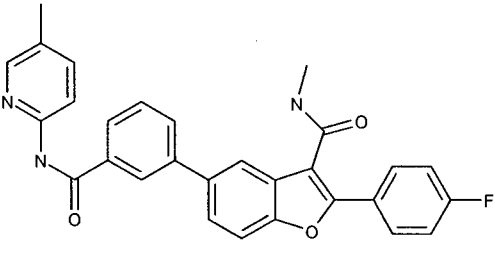
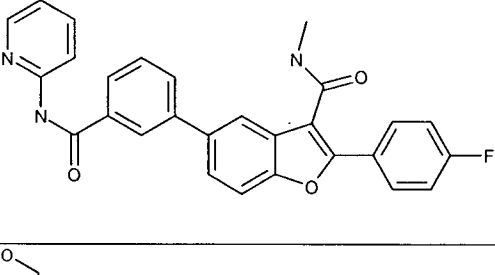
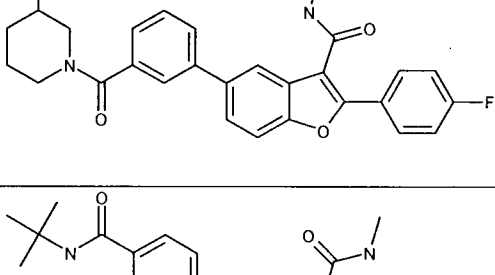
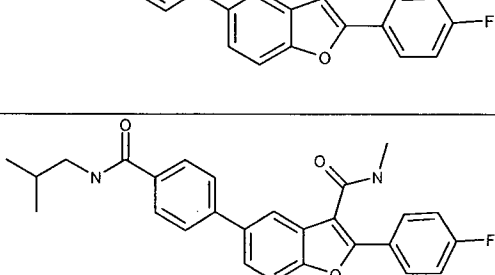
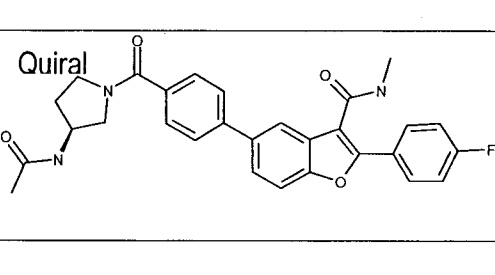
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	2,89	99,0179	988,56	Procedimiento B
	2,7	100	1056,6	Procedimiento B
	2,94	89,8624	968,67	Procedimiento B
	2,75	100	984,61	Procedimiento B

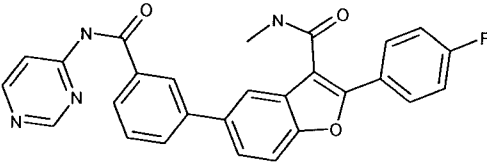
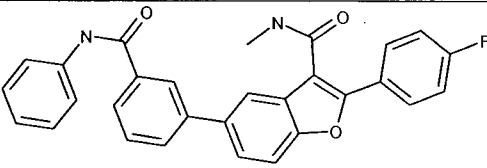
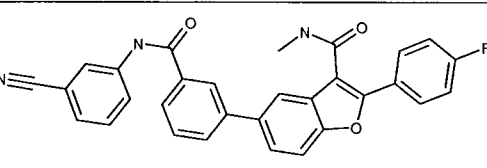
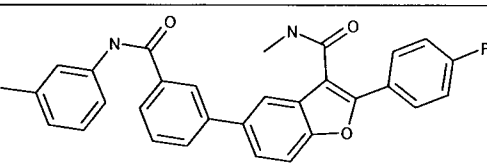
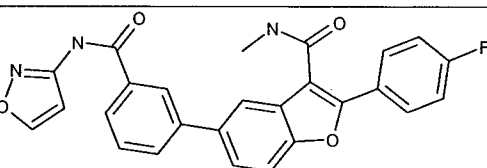
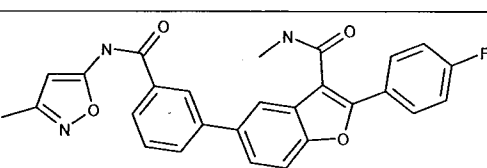
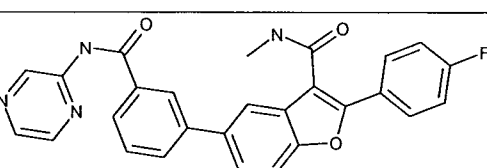
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	2,29	100	455,82	Procedimiento B
	2,92	98,0936	980,59	Procedimiento B
	2,32	98,0376	479,8	Procedimiento B
	2,35	100	472,83	Procedimiento B
	2,56	100	972,64	Procedimiento B
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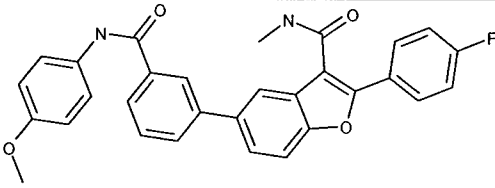
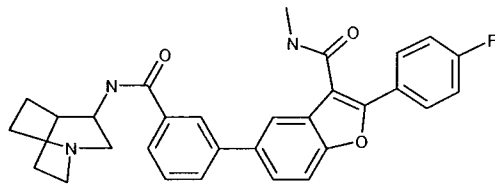
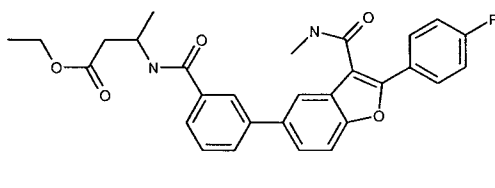
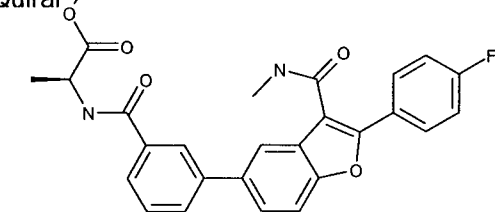
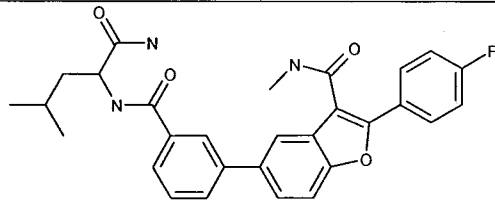
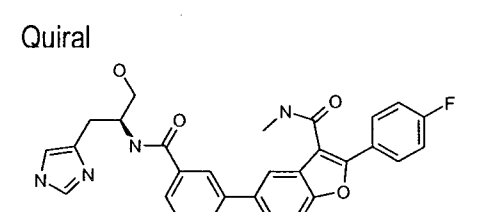
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	2,06	98,6458	892,65	Procedimiento B
	2,43	100	884,66	Procedimiento B
	2,81	100	940,69	Procedimiento B
	2,82	100	940,7	Procedimiento B
	2,93	100	968,72	Procedimiento B

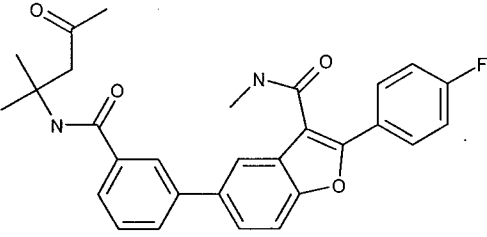
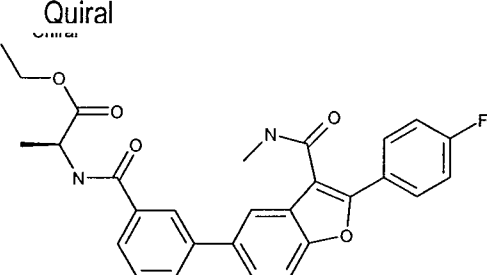
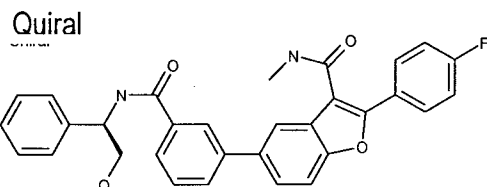
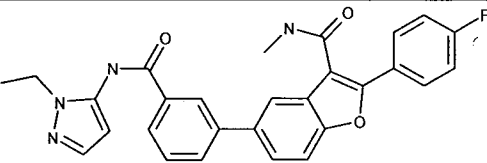
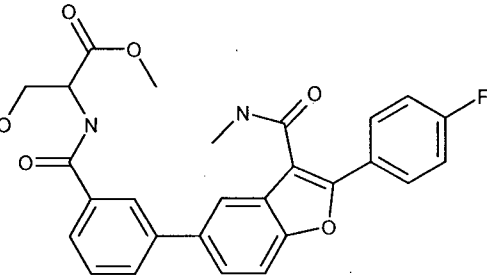
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	2,95	100	968,7	Procedimiento B
	2,6	100	884,67	Procedimiento B
	2,35	100	856,66	Procedimiento B
	2,34	96,8795	958,6	Procedimiento B
	2,26	100	479,81	Procedimiento B

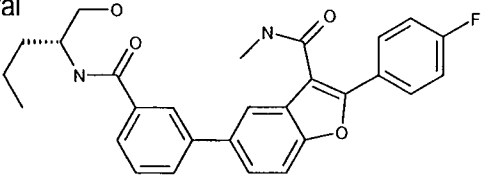
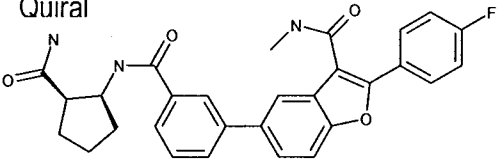
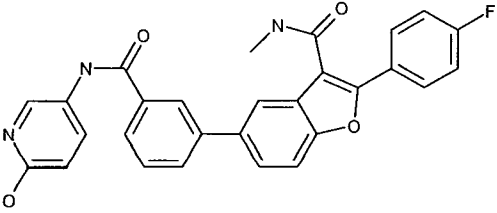
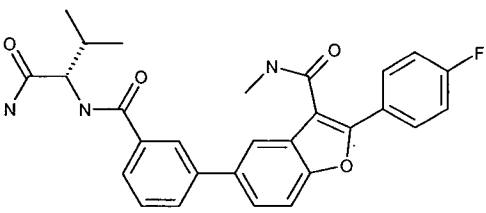
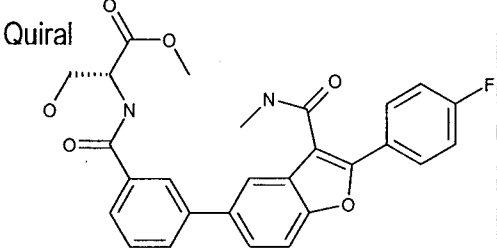
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	2,82	100	806,66	Procedimiento B
	2,75	100	970,55	Procedimiento B
	2,48	100	480,8	Procedimiento B
	2,77	100	479,81	Procedimiento B
	2,7	98,233	480,8	Procedimiento B
	2,57	100	465,64	Procedimiento B

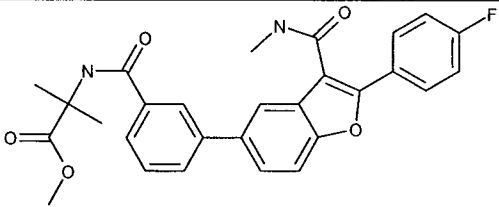
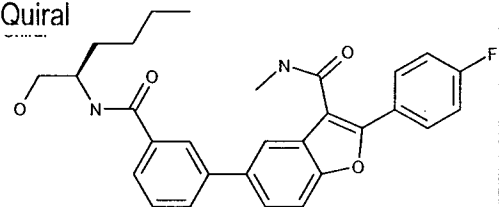
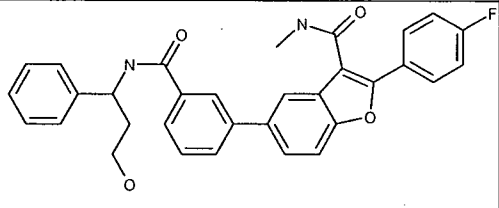
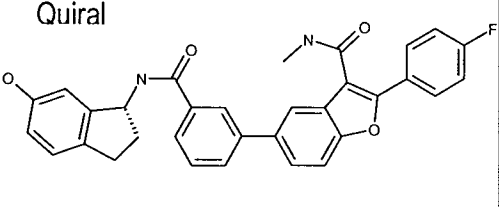
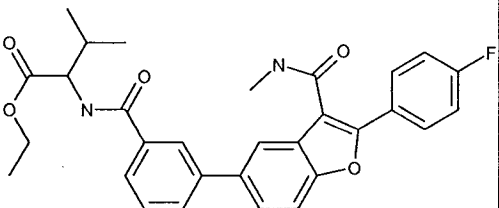
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	2,85	97,8741	958,25	Procedimiento B
	2,64	100	930,26	Procedimiento B
	2,24	100	972,33	Procedimiento B
	5,21	100	444,95	Procedimiento C
	4,95	100	444,96	Procedimiento C
	3,74	100	499,93	Procedimiento C

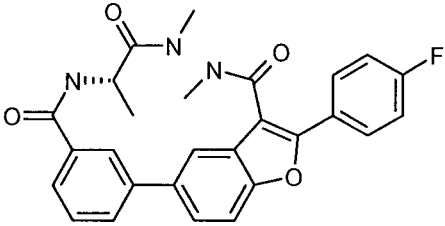
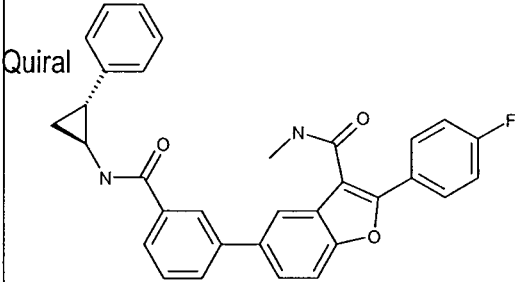
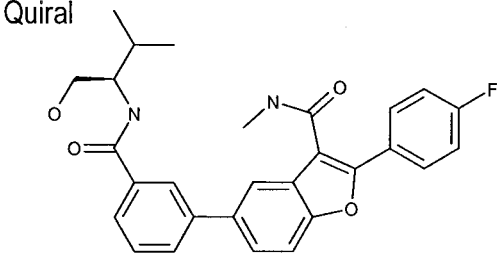
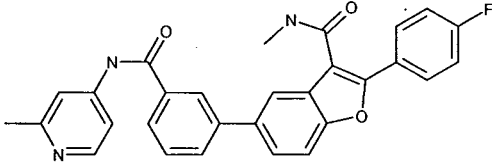
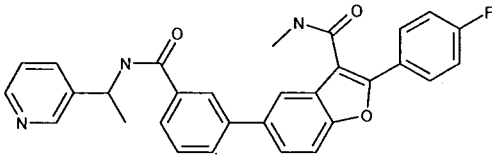
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	4,68	93,1925	466,91	Procedimiento D
	5,72	96,6697	464,93	Procedimiento D
	5,57	96,8314	489,9	Procedimiento D
	5,72	94,0943	478,93	Procedimiento D
	4,93	94,4826	455,9	Procedimiento D
	5,26	88,6355	469,92	Procedimiento D
	4,7	100	466,92	Procedimiento D

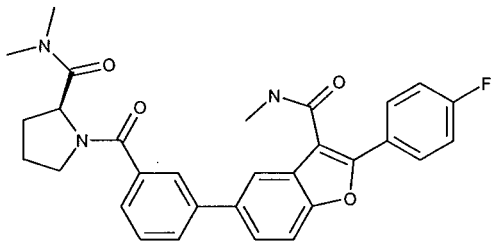
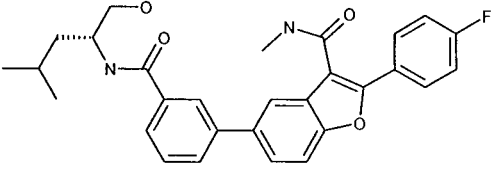
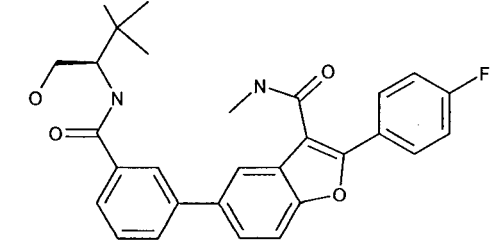
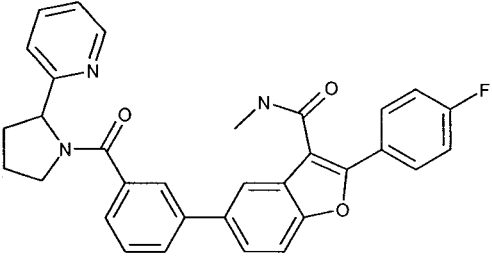
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	5,59	97,7461	494,92	Procedimiento D
	4,06	100	497,98	Procedimiento D
	5,05	97,6492	502,96	Procedimiento D
Quiral 	4,7	100	474,95	Procedimiento D
	4,7	100	501,98	Procedimiento D
Quiral 	3,74	100	512,96	Procedimiento D

Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	5,2	97,5131	486,97	Procedimiento D
Quiral 	5,05	100	488,95	Procedimiento D
Quiral 	4,74	100	508,95	Procedimiento D
	4,79	100	482,96	Procedimiento D
	4,18	100	490,94	Procedimiento D

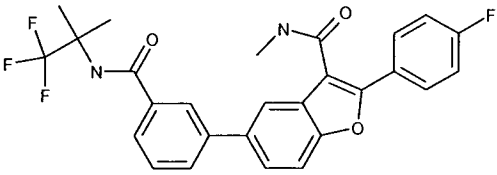
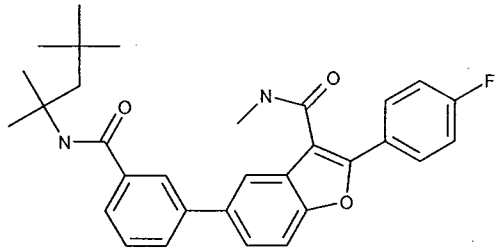
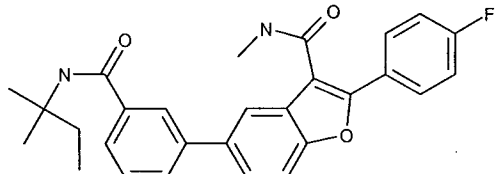
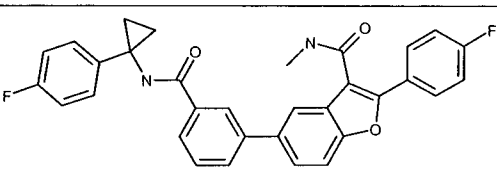
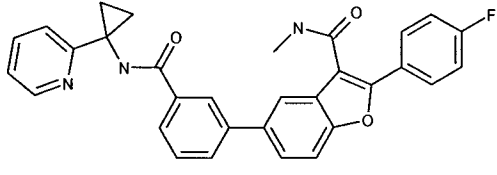
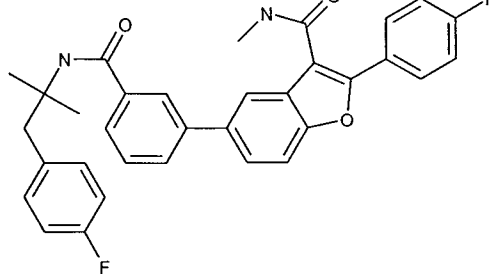
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
Quiral 	4,8	100	474,98	Procedimiento D
Quiral 	4,43	100	499,97	Procedimiento D
	4,04	95,8428	481,93	Procedimiento D
Quiral 	4,5	93,8873	487,97	Procedimiento D
Quiral 	4,26	100	490,94	Procedimiento D

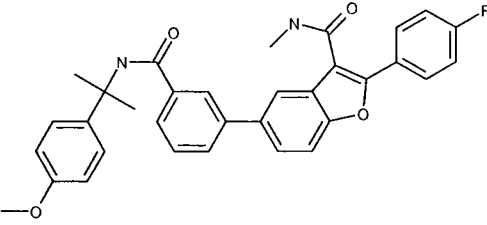
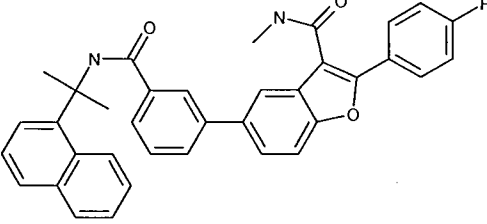
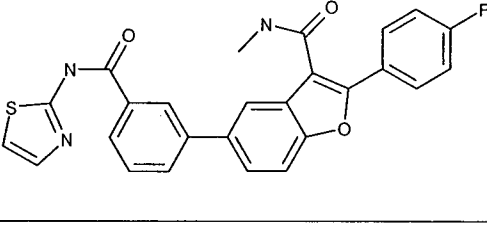
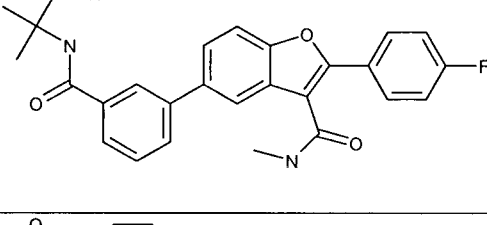
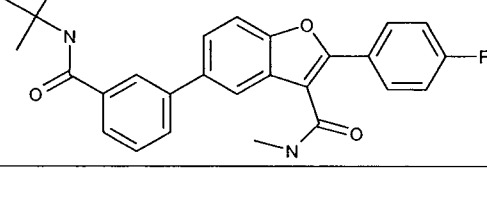
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	4,88	100	488,93	Procedimiento D
Quiral 	5,11	100	488,97	Procedimiento D
	4,81	100	522,93	Procedimiento D
Quiral 	5,06	100	520,93	Procedimiento D
	5,74	100	516,94	Procedimiento D

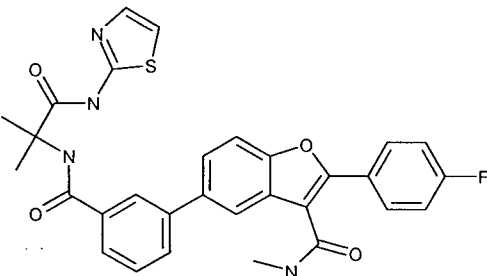
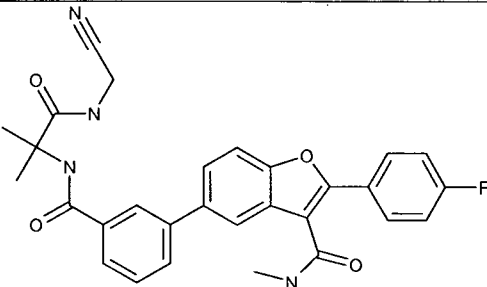
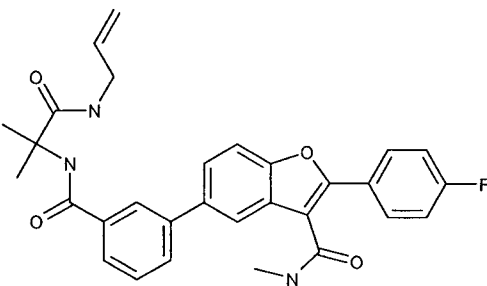
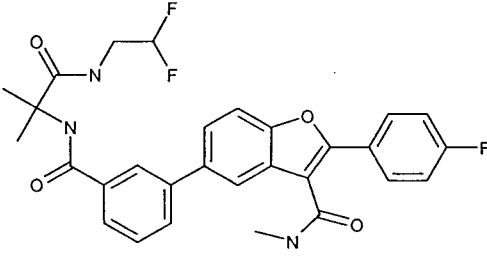
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
Quiral 	4,26	100	473,94	Procedimiento D
Quiral 	5,85	100	504,94	Procedimiento D
Quiral 	4,69	100	474,96	Procedimiento D
	4,74	100	479,92	Procedimiento D
	4,71	100	493,93	Procedimiento D

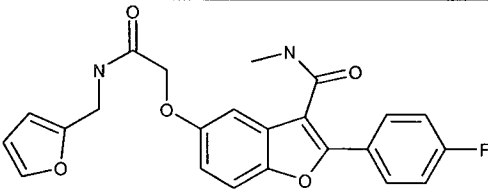
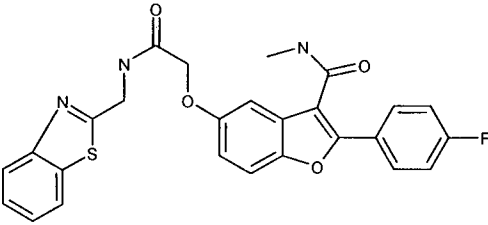
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
Quiral 	4,19	100	513,95	Procedimiento D
Quiral 	5,04	100	488,97	Procedimiento D
Quiral 	4,97	100	488,96	Procedimiento D
Quiral 	4,7	98,2446	519,93	Procedimiento D
Quiral	5,64	100	522,94	Procedimiento D

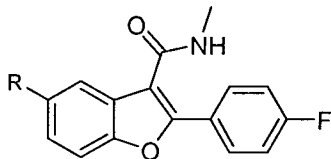
Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
Chiral				
	5,97	100	487	Procedimiento D
	6,1	100	520,96	Procedimiento D
	3,168	100	455,14	Procedimiento E
	2,754	100	461,15	Procedimiento E

Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	3,53	95,5615	499,12	Procedimiento E
	4,061	100	501,23	Procedimiento E
	3,539	98,8021	459,19	Procedimiento E
	3,496	100	523,18	Procedimiento E
	3,008	100	506,17	Procedimiento E
	3,896	98,8111	539,22	Procedimiento E

Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	3,608	100	537,21	Procedimiento E
	3,868	98,488	557,22	Procedimiento E
	3,179	100	472,1	Procedimiento E
	2,536	100	488,16	Procedimiento E
	2,718	100	502,19	Procedimiento E

Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedi- miento HPLC
	3,025	100	557,15	Procedimiento E
	2,664	100	513,16	Procedimiento E
	2,835	100	514,17	Procedimiento E
	2,87	100	538,16	Procedimiento E

Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedimiento HPLC
	8,435	100	423,19	Procedimiento F
	8,778	100	490,13	Procedimiento F

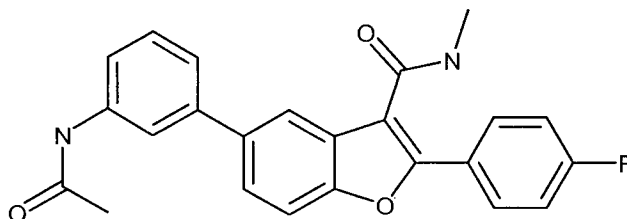


Los siguientes procedimientos generales pertenecen a los procedimientos experimentales. Algunos de los compuestos se prepararon con

5 diferentes escalas. Se disolvió trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (0,100 mmol, 1 eq.) 1,4-dioxano seco (l ml) y se añadió a un vial de microondas BIOTAGE® (0,5-2 ml) que contenía ácido borónico (0,340 mmol, 3,4 eq.). A continuación se añadió Cs₂CO₃ (0,300 mmol, 3 eq.) en forma de sólido y después añadiendo agua (0,25 ml). El vial se purgó

10 con nitrógeno y se añadió Pd(PPh₃)₄. Después se volvió a purgar el vial con nitrógeno y se tapó, se calentó en un reactor de microondas BIOTAGE® a 150°C durante 15 minutos. La mezcla se filtró con un filtro de 0,45 um y se

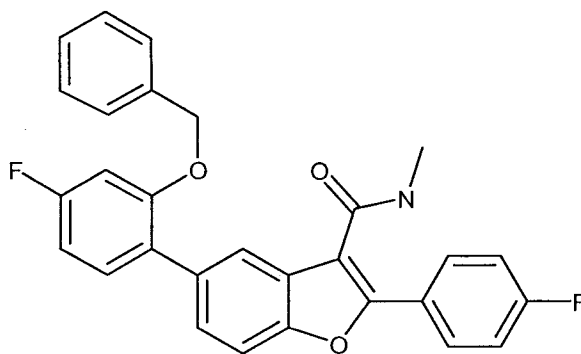
secó con un SppedVac. La muestra se disolvió en DMF (1,6 ml) y se purificó por HPLC prep.



5 5-(3-Acetamidofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 10,03 (s ancho, 1 H), 8,49 (d, $J=4,69$ Hz, 1 H), 8,28 (s, 1 H), 8,03 (dd, $J=8,79$, 5,27 Hz, 2 H), 7,93 (s ancho, 1 H), 7,84 (s, 1 H), 7,75 (d, $J=8,20$ Hz, 1 H), 7,64 (d, $J=6,44$ Hz, 2 H), 7,29 - 7,45 (m, 3 H), 2,92 (s, 3 H), 2,12 (s, 3 H).

10

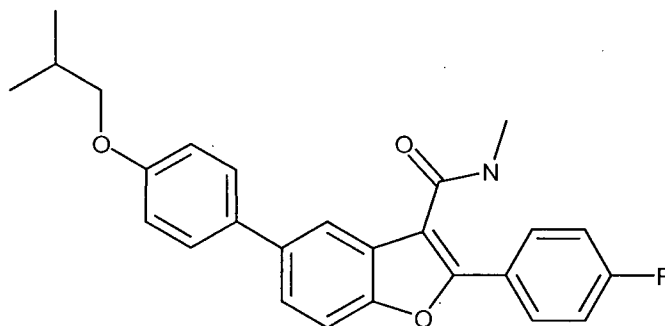


5-(2-(Benciloxi)-4-fluorofenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 8,41 (d, $J=4,69$ Hz, 1 H), 8,28 (s, 1 H), 8,03 (dd, $J=8,79$, 5,27 Hz, 2 H), 7,82 (s, 1 H), 7,67 (d, $J=8,20$ Hz, 1 H), 7,55 (d, $J=7,03$ Hz, 1 H), 7,34 - 7,47 (m, 7 H), 7,13 (d, $J=9,37$ Hz, 1 H),

15

6,83 - 6,94 (m, 1 H), 5,19 (s, 2 H), 2,88 (d, $J=4,10$ Hz, 3 H).



2-(4-Fluorofenil)-5-(4-isobutoxifenil)-N-metilbenzofuran-3-carboxamida

5 RMN de ^1H (600 MHz, $\text{DMSO-d}_6\text{-CDCl}_3$) δ ppm 8,46 (d, $J=4,69$ Hz, 1 H), 8,28 (s, 1 H), 8,04 (dd, $J=8,50, 5,57$ Hz, 1 H), 7,81 (s, 1 H), 7,67 - 7,73 (m, 1 H), 7,60 - 7,67 (m, 2 H), 7,36 (t, $J=8,79$ Hz, 1 H), 7,05 (d, $J=8,79$ Hz, 2 H), 3,83 (d, $J=6,44$ Hz, 2 H), 2,91 (d, $J=4,69$ Hz, 3 H), 2,09 (ddd, $J=13,33, 6,59, 6,44$ Hz, 1 H), 1,05 (d, $J=7,03$ Hz, 6 H).

10 La pureza HPLC se determinó usando un espectrómetro de masas Waters LCT con LC analítica con fuente MUX de cuatro vías a 220nm empleando acetonitrilo y agua o Waters ZQ con espectrómetro de masas ESCi. A = $\text{CH}_3\text{CN:Agua}$ 5:95; B = $\text{CH}_3\text{CN:Agua}$ 95:5; Modificador = NH_4OAc 10 mM . El tiempo de retención se registró en minutos.

15

Procedimiento analítico A:

Columna: Waters XTERRA® 2,1x50mm 5 μm C18

Tiempo	%B	Caudal
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Tiempo	%B	Caudal
0,00	0	1,0
4,00	100	1,0
5,00	100	1,0

Procedimiento analítico B:

Columna: Waters XBridge 2,1x50mm 5 um C18

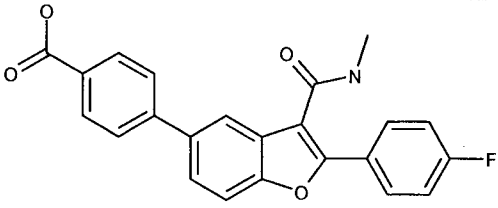
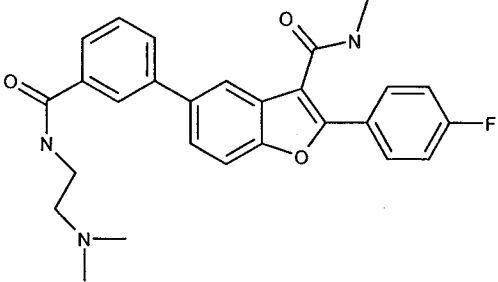
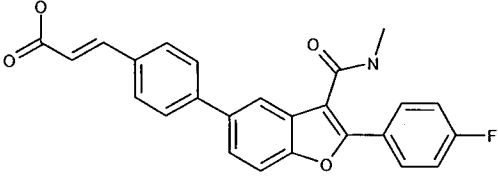
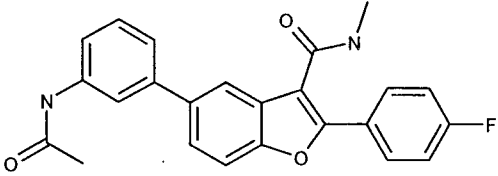
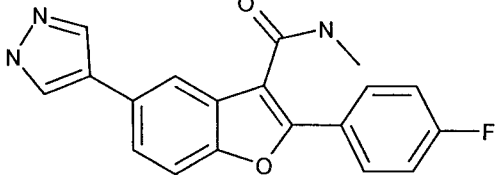
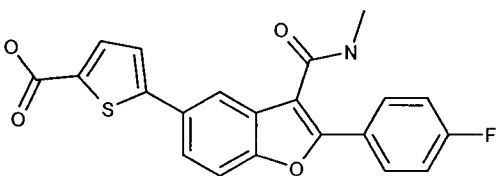
Tiempo	%B	Caudal
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4,00	100	1,0
5,00	100	1,0
5,05	100	1,0
6,00	0	1,0

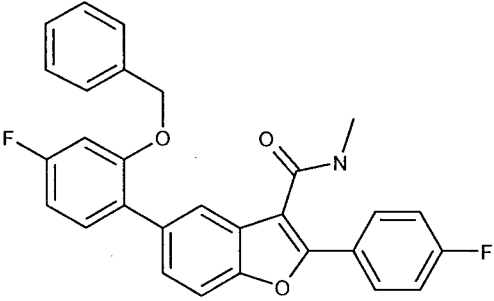
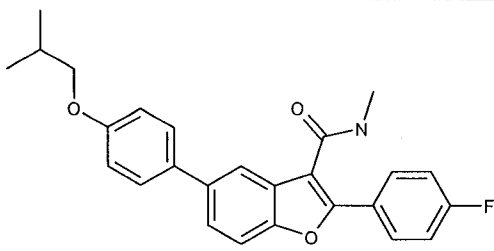
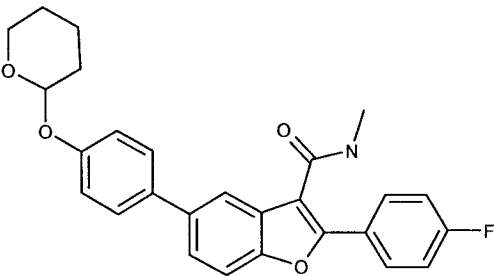
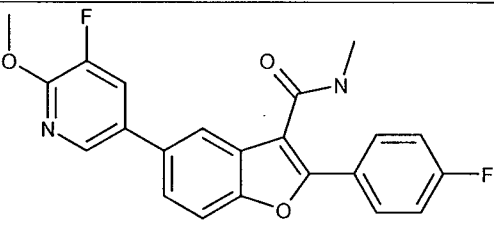
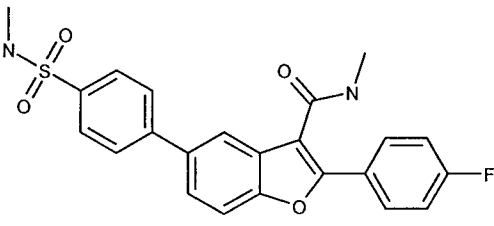
5 Procedimiento analítico F:

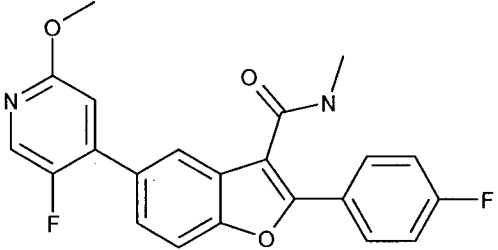
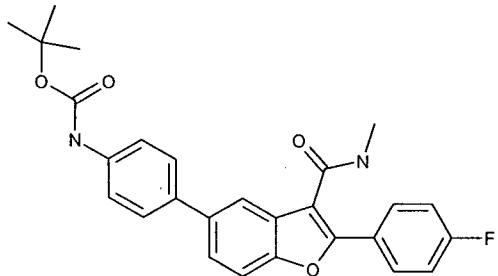
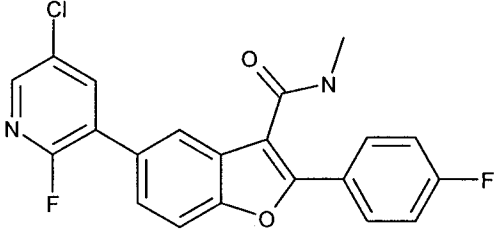
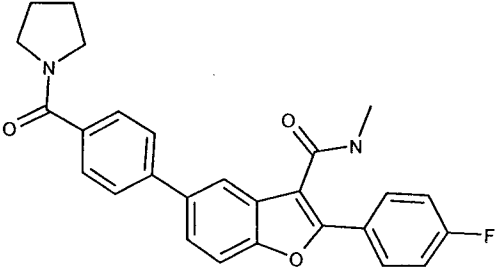
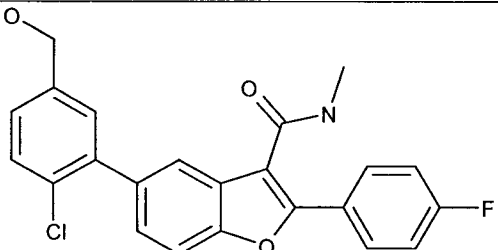
Waters ZQ con espectrómetro de masas ESCi

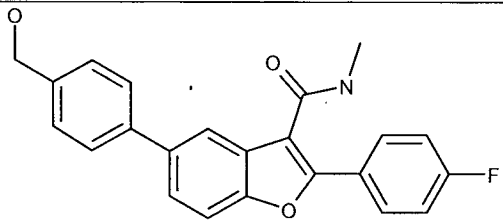
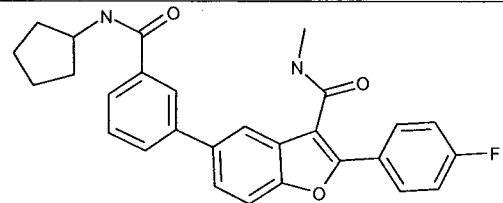
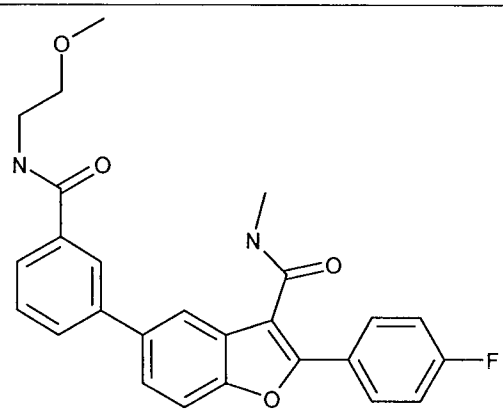
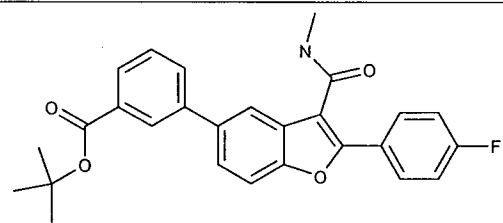
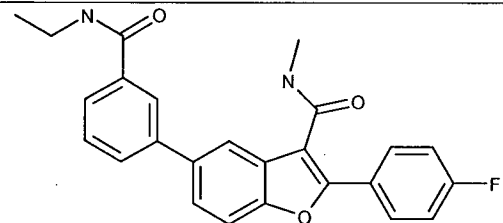
Columna: PHENOMENEX® Gemini 4,6x150mm 3 um C18

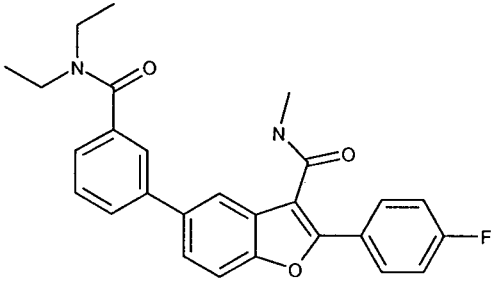
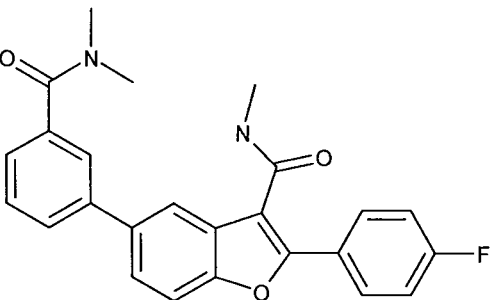
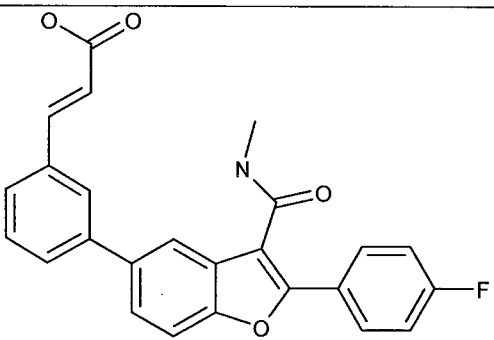
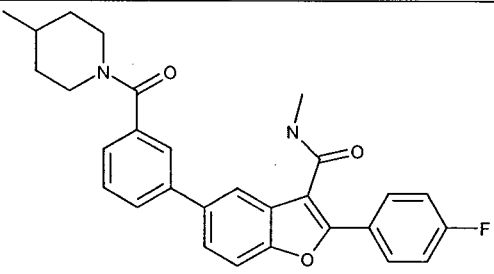
Tiempo	%B	Caudal
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10,00	95	1,0
13,00	95	1,0
13,50	10	1,0
15,00	10	1,0

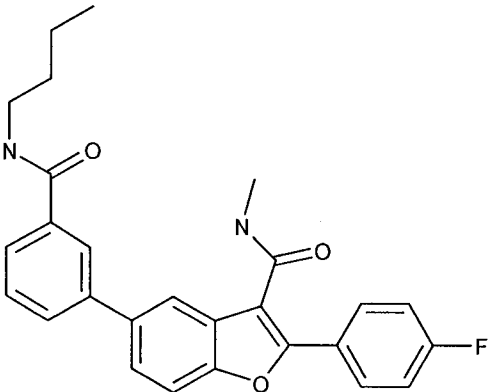
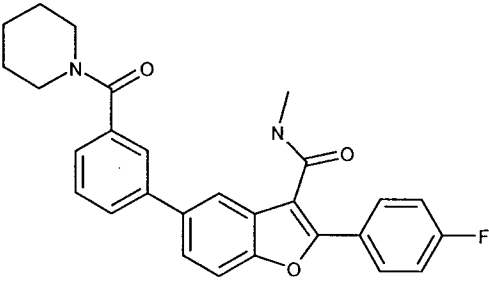
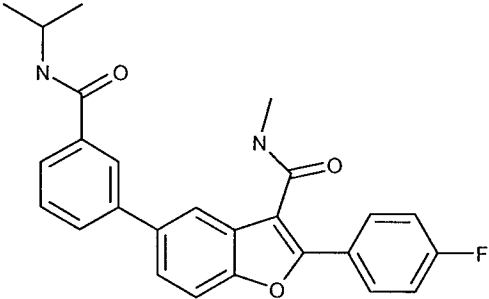
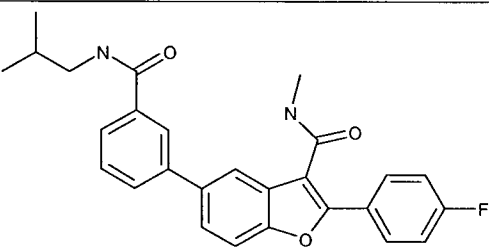
Estructura	Tr HPLC	% de pureza	Ion EM Obs	Procedimiento HPLC
	7,23	100	390,16	Procedimiento F
	3,842	100	460,23	Procedimiento F
	7,666	100	416,18	Procedimiento F
	7,018	100	403,2	Procedimiento F
	5,322	100	336,23	Procedimiento F
	7,091	100	396,13	Procedimiento F

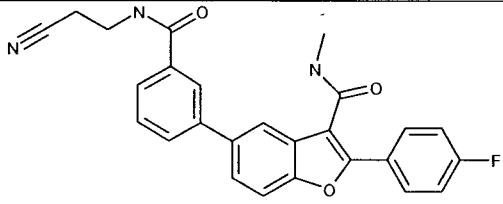
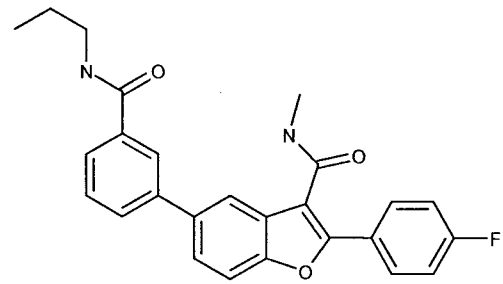
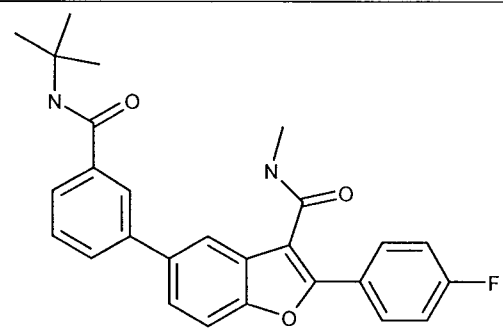
	12,982	100	470,3	Procedimiento F
	13,755	100	418,33	Procedimiento F
	12,669	100	446,26	Procedimiento F
	10,775	100	395,28	Procedimiento F
	8,933	100	439,24	Procedimiento F

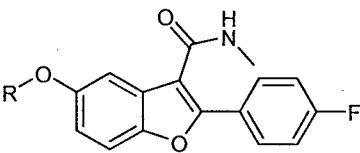
	10,716	100	395,31	Procedimiento F
	11,858	100	461,33	Procedimiento F
	10,916	100	399,21	Procedimiento F
	2,49	100	443,06	Procedimiento B
	2,56	100	410	Procedimiento B

	2,36	100	376,05	Procedimiento B
	2,75	90,0925	457,45	Procedimiento B
	2,36	95,5596	447,39	Procedimiento B
	3,34	100	446,41	Procedimiento B
	2,43	100	417,4	Procedimiento B

	2,67	97,2446	445,4	Procedimiento B
	2,37	100	417,33	Procedimiento B
	2,02	100	416,3	Procedimiento B
	2,92	100	471,37	Procedimiento B

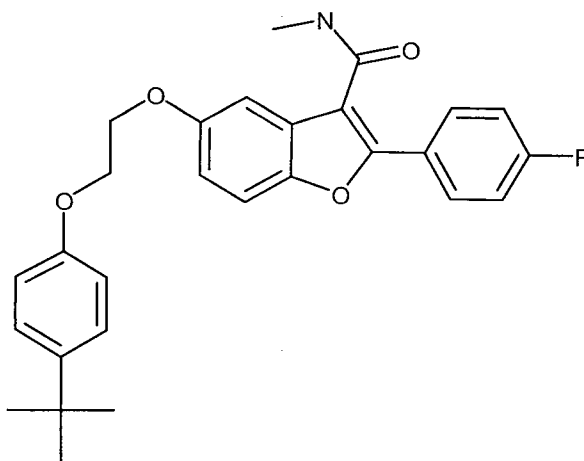
	2,76	100	445,37	Procedimiento B
	2,71	100	457,35	Procedimiento B
	2,52	100	431,35	Procedimiento B
	2,725	94,4043	445,36	Procedimiento B

	2,38	95,3608	442,32	Procedimiento B
	2,56	100	431,34	Procedimiento B
	2,76	97,5284	445,38	Procedimiento B



Los procedimientos generales siguientes pertenecen a los procedimientos experimentales. Se añadió 2-(4-fluorofenil)-5-hidroxi-N-
5 metilbenzofuran-3-carboxamida (0,120 mmol, 1 eq.) en THF (2,3 ml) a viales de microondas BIOTAGE® (5 ml) que contenían ROH (2,28 eq.) y PPh₃ (1,4 eq.). A continuación se añadió DEAD (1,4 eq.) puro. El vial se purgó con nitrógeno, se tapó y se calentó a 140°C durante 20 minutos en un reactor de microondas

BIOTAGE®. La mezcla se secó con SPEEDVAC®, se disolvió en DMF (1,6 ml) y se purificó por HPLC prep.



5 5-(2-(4-*tert*-Butilfenoxi)etoxi)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

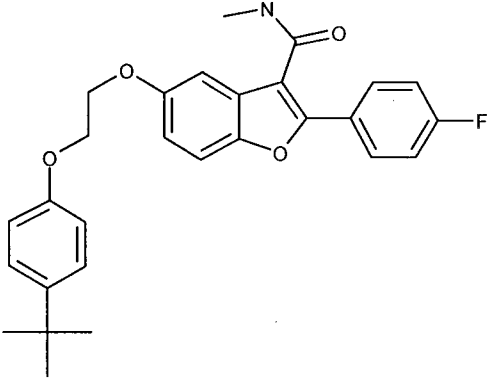
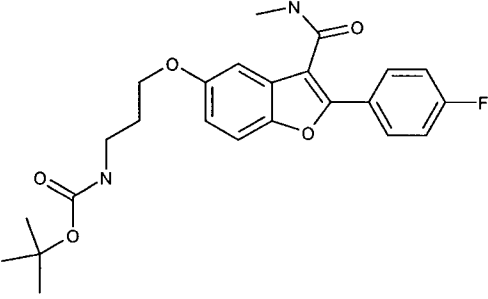
RMN de ^1H (600 MHz, DMSO- d_6 - CDCl_3) δ ppm 8,36 (d, $J=4,69$ Hz, 1 H), 8,27 (s, 1 H), 7,99 (dd, $J=8,50$, 5,57 Hz, 1 H), 7,56 (d, $J=8,79$ Hz, 1 H), 7,28 - 7,39 (m, 3 H), 7,21 (d, $J=2,34$ Hz, 1 H), 7,05 (dd, $J=9,37$, 2,34 Hz, 1 H), 6,94 (d, $J=8,79$ Hz, 3 H), 4,28 - 4,45 (m, 4 H), 2,89 (d, $J=4,69$ Hz, 3 H), 1,30 (s, 9 H).

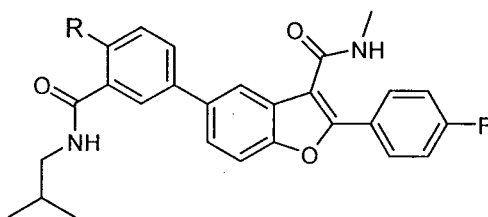
10 La pureza HPLC se determinó usando un Espectrómetro de Masas Waters LCT con LC analítica con fuente MUX de cuatro vías a 220nm empleando acetonitrilo y agua. A = CH_3CN :Agua 5:95; B = CH_3CN :Agua 95:5; Modificador = NH_4OAc 10 mM. El Tiempo de Retención se registró en minutos.

15 Procedimiento analítico B:

Columna: Waters XBridge 2,1x50mm 5 μm C18

Tiempo	%B	Caudal
0,00	0	1,0
4,00	100	1,0
5,00	100	1,0
5,05	100	1,0
6,00	0	1,0

Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedimiento HPLC
	3,63	100	461,8073	Procedimiento B
	2,81	100	442,825	Procedimiento B



Los procedimientos generales siguientes pertenecen a los procedimientos experimentales. Se añadieron 4-[2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il]-2-(isobutilcarbamoyl)fenil-trifluorometanesulfonato (0,076 mmol, 45 mg),

5 diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (S-Phos) (6,24 mg, 0,02 mmol), ácido bórico (0,175 mmol) y fosfato de potasio (0,190 mmol, 40,2 mg) en vial de microondas BIOTAGE® (5 ml), seguido por añadir dioxano (3 ml) y agua (0,3 ml). El vial se purgó con nitrógeno y se añadió Pd(OAc)₂ (0,076 mmol, 1,7 mg). El vial se calentó en un Iniciador de BIOTAGE® a 110°C durante 10 minutos y

10 se secó con un SPEEDVAC®-250 a 40°C durante toda una noche. Se disolvieron las muestras en DMF-MeOH, se filtraron por medio de una placa con filtros, y se purificaron por HPLC prep. HPLC prep.: DIONEX® APS-30000, UV 220nm, Columna: Waters XBridge 19 x 200 mm, 5 um, C18. Disolventes: A = Agua, NH₄OH 20 mM, B = Acetonitrilo).

15

Procedimiento analítico A:

Espectrómetro de masas Waters LCT con fuente MUX de 4 vías.

Condiciones de LC:

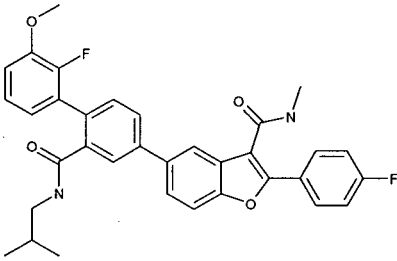
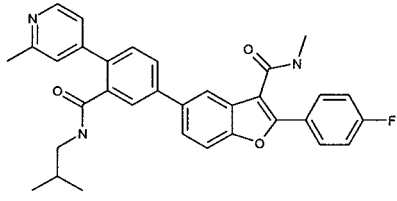
Columna: Ascentis 4,6x50mm 5 um C18

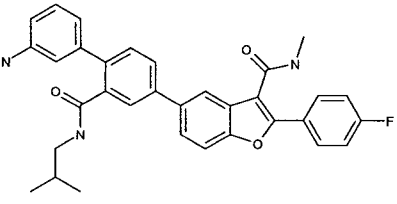
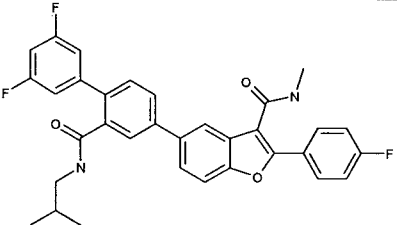
Fase Móvil: A = MeCN:Agua 5:95; B = MeCN:Agua 95:5; Modificador = NH₄OAc 10 mM.

El Tiempo de Retención Tr se registró en minutos.

Tiempo	%B	Caudal
0,00'	0	2,0
8,00'	100	2,0
9,00'	100	2,0

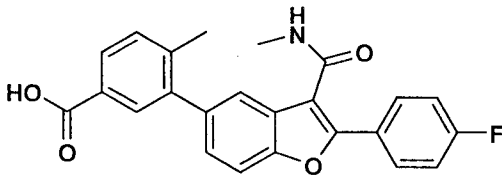
5

Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedimiento HPLC
	5,77	96	569,286	Procedimiento A
	4,86	95	536,2426	Procedimiento A

Estructura	Tr HPLC	% de pureza	Ion EM Obs.	Procedimiento HPLC
	5,20	97	536,26428	Procedimiento A
	5,93	100	557,2553	Procedimiento A

Los siguientes ejemplos/intermedios se prepararon por el acoplamiento de Suzuki del trifluorometanosulfonato de benzofuran-5-ilo correspondiente con

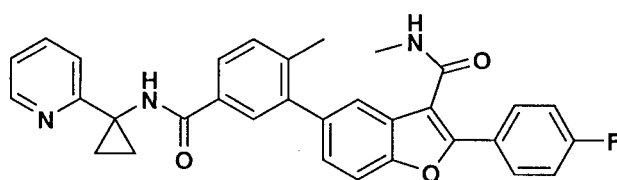
5 ácido 3-borónico (o éster) del ácido benzoico correspondiente, y se acopló el intermedio ácido obtenido con ciclopropilamina como se ha descrito antes.



Ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico

10 Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a

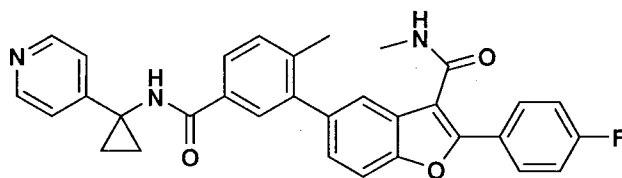
220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7
 5 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 404,04, Tr de HPLC = 1,728 min.



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

- 10 El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa Shimadzu-VP usando primero el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25
 15 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,80 - 9,26 min. (detección UV a 220 nm). Las fracciones deseadas recogidas se evaporaron y el sólido blanco obtenido se purificó de nuevo por el mismo procedimiento salvo con % Inicial de B = 50, % Final de B = 100, Recogida de la fracción: 5,34 - 6,15 min. RMN de ¹H (500 MHz, CD₃OD) δ 8,61 (d, J = 5,80, 1H), 8,44 (t, J = 7,32, 1H), 7,97 (dd, J = 8,85, 5,19, 2H), 7,87 (s, 1H), 7,85 (d, J
 20 1H), 8,44 (t, J = 7,32, 1H), 7,97 (dd, J = 8,85, 5,19, 2H), 7,87 (s, 1H), 7,85 (d, J

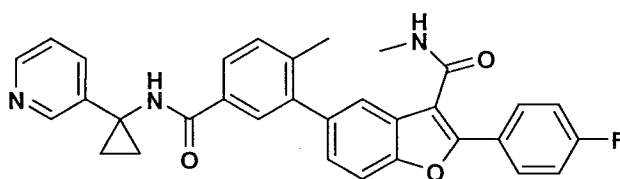
= 6,71, 1H), 7,83-7,81 (m, 2H), 7,67 (d, $J = 8,24$, 1H), 7,64 (d, $J = 0,92$, 1H), 7,47 (d, $J = 8,55$, 1H), 7,38 (dd, $J = 8,39$, 1,68, 1H), 7,29 (t, $J = 8,85$, 2H), 2,95 (s, 3H), 2,36 (s, 3H), 1,82 (m, 2H), 1,75 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 520,41, Tr de HPLC = 1,513 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 8,90 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,43 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl, Tr = 13,20 min.



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(piridin-4-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

- El producto se obtuvo como una sal TFA después de purificación por HPLC
- 5 preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B = MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción:
- 10 5,07 - 5,88 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 8,68 (d, *J* = 7,32, 1H), 7,97 (dd, *J* = 8,85, 5,19, 2H), 7,87 (d, *J* = 2,14, 1H), 7,86 (m solapado con d, 1H), 7,81 (d, *J* = 7,02, 1H), 7,67 (d, *J* = 8,55, 1H), 7,65 (d, *J* = 1,22, 1H), 7,48 (d, *J* = 8,55, 1H), 7,39 (dd, *J* = 8,39, 1,68, 1H), 7,28 (t, *J* = 8,85, 2H), 2,95 (s, 3H), 2,37 (s, 3H), 1,83 (aparece como d, 4H). Las LC/EM se
- 15 realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX®
- 20 Luna, 3,0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 520,15, Tr de HPLC = 1,435 min.

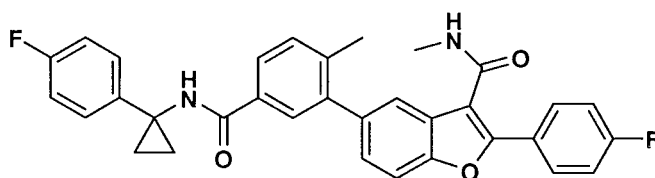
Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 8,03 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm (% Inicial de B = 10, % Final de B = 100), Tr = 14,09 min.



10 2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(piridin-3-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa Shimadzu-VP usando primero el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 5,05 - 5,76 min. (detección UV a 220 nm). Las fracciones deseadas recogidas se evaporaron y el residuo obtenido se purificó de nuevo por el mismo
20 procedimiento salvo con % Inicial de B = 10, % Final de B = 100, Recogida de

la fracción: 8,74 - 9,27 min. RMN de ^1H (500 MHz, CD_3OD) δ 8,76 (d, $J = 2,44$, 1H), 8,71 (dd, $J = 5,80$, 0,92, 1H), 8,50 (ddd, $J = 8,32$, 2,21, 1,37, 1H), 8,04 (dd, $J = 8,39$, 5,65, 1H), 7,96 (dd, $J = 9,00$, 5,34, 2H), 7,83 (d, $J = 1,53$, 1H), 7,82 (m solapado con d, 1H), 7,66 (d, $J = 8,24$, 1H), 7,64 (d, $J = 1,83$, 1H), 7,45 (d, $J = 8,55$, 1H), 7,28 (t, $J = 8,70$, 2H), 2,95 (s, 3H), 2,35 (s, 3H), 1,60 (aparece como td, $J = 4,20$, 2,59, 4H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%- H_2O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%- H_2O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, 10 Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z $(\text{M}+\text{H})^+ = 520,08$, Tr de HPLC = 1,482 min.

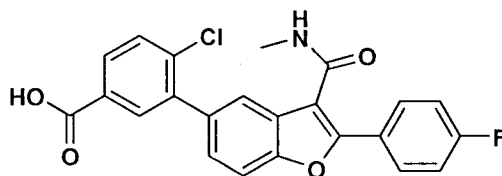


15 2-(4-Fluorofenil)-5-(5-(1-(4-fluorofenil)ciclopropilcarbamoil)-2-metilfenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%- H_2O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%- H_2O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 20

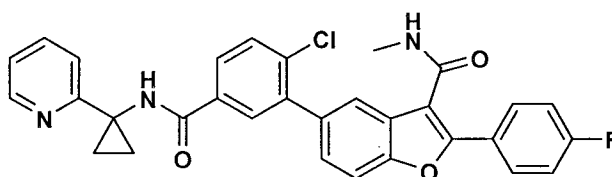
min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 9,08 - 9,63 min. (detección UV a 220 nm). RMN de ^1H (500 MHz, CD_3OD) δ 7,97 (dd, $J = 8,85, 5,19, 2\text{H}$), 7,78 - 7,77 (m solapado, 2H), 7,65 (d, $J = 8,55, 1\text{H}$), 7,63 (d, $J = 1,22, 1\text{H}$), 7,41 (d, $J = 8,55, 1\text{H}$), 7,37 - 7,33 (m solapado, 3H), 7,28 (t, $J = 8,85, 2\text{H}$), 7,01 (t, $J = 8,85, 2\text{H}$), 2,95 (s, 3H), 2,33 (s, 3H), 1,32 (m, 4H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 537,08, Tr de HPLC = 1,840 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm , 4,6 x 150 mm, Tr = 10,20 min; Columna: XBridge Phenyl 3,5 μm , 4,6 x 150 mm (% Inicial de B = 10, % Final de B = 100), Tr = 8,16 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge

Phenyl 3,5 um, 4,6 x 150 mm, Tr = 14,20 min.



Ácido 4-cloro-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

- 5 Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7
- 10 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 424,26, 426,25, Tr de HPLC = 1,763 min.



- 15 5-(2-Cloro-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa Shimadzu-VP usando primero el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente

B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,02 - 6,54 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ

5 8,62 (dd, *J* = 5,80, 0,61, 1H), 8,44 (td, *J* = 7,93, 1,53 1H), 8,04 (d, *J* = 2,44, 1H), 7,96 (dd, *J* = 8,85, 5,19, 2H), 7,93 (dd, *J* = 8,39, 2,29 1H), 7,84 - 7,81 (m solapado, 2H), 7,76 (d, *J* = 1,83, 1H), 7,69 (d, *J* = 2,44, 1H), 7,67 (d, *J* = 2,75, 1H), 7,50 (dd, *J* = 8,55, 1,53, 1H), 7,28 (t, *J* = 8,70, 2H), 2,95 (s, 3H), 1,83 (m, 2H), 1,76 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP

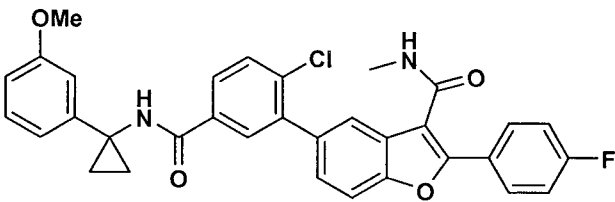
10 con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 540,33, 542,33, Tr

15 de HPLC = 1,568 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min,

20 Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 9,19 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 9,89 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B=

MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl, Tr = 16,19 min.

5



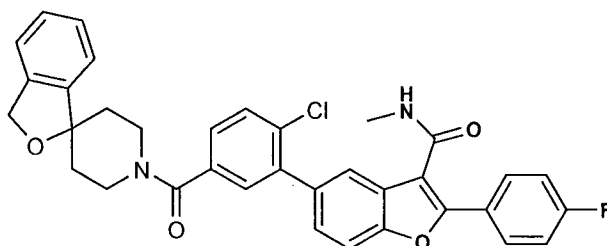
5-(2-Chloro-5-(1-(3-metoxifenil)ciclopropilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando primero el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al

10 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 70, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,61 - 7,41 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,97 (dd, J = 8,70, 5,34, 2H), 7,94 (d, J = 2,14, 1H), 7,85 (dd, J = 8,39, 1,98, 1H), 7,76 (s, 1H), 7,65 (dd, J = 12,51, 8,55, 2H), 7,49 (dd, J = 8,55, 1,53, 1H), 7,28 (t, J = 8,70, 2H), 7,20 (t, J = 7,93, 1H), 6,87 (s, 1H), 6,85 (m solapado con s, 1H), 6,75 (dd, J = 8,70, 1,68, 1H), 3,77 (s, 3H), 2,95 (s, 3H), 1,34 (aparece como d, 4H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters

20 MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al

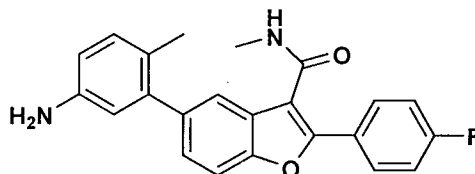
90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
 Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de
 parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x
 50 mm; (ES+) m/z (M+H)⁺ = 569,39, Tr de HPLC = 1,858 min. Las HPLC
 5 analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a
 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al
 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al
 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min,
 Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m,
 10 4,6 x 150 mm, Tr = 10,33 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm,
 Tr = 7,96 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-
 H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-
 NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente
 = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge
 15 Phenyl 3, Tr = 14,80 min.



5-(2-Chloro-5-(3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ilcarbonyl)fenil)-2-(4-
 fluorofenil)-N-metilbenzofuran-3-carboxamida

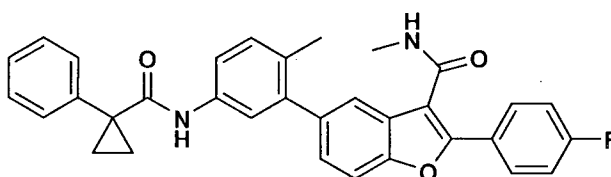
Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando primero el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 70, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de
5 parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,88 - 8,49 min. (detección UV a 220 nm). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA
10 al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 595,39, Tr de HPLC = 1,952 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN
15 al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 11,75 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 8,68 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-
20 H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge

Phenyl 3, Tr = 15,85 min.



5-(5-Amino-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 5 El acoplamiento de Suzuki con 4-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina se realizó usando: diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (S-Phos), Pd(OAc)₂, K₂CO₃, (1:2 de H₂O/1,4-dioxano, 90 °C). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-
- 10 H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 375,22, Tr de HPLC = 1,362 min.



15

2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-

fenilciclopropanocarboxamido)fenil)benzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando

primero el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm

5 S5, Recogida de la fracción: 10,05 - 10,51 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,97 (dd, *J* = 8,85, 5,49, 2H), 7,60 (d, *J* = 8,55, 1H), 7,55 (d, *J* = 1,53, 1H), 7,52 (dd solapado con s, 1H), 7,51 (s, 1H), 7,44 (t, *J* = 7,48, 2H), 7,36 (m, 1H), 7,30 (dd solapado con m, *J* = 1,53, 1H), 7,29 – 7,27 (m solapado, 3H), 7,25 (d, *J* = 2,14, 1H), 7,21 (aparece como d, 1H), 2,95 (s, 3H),

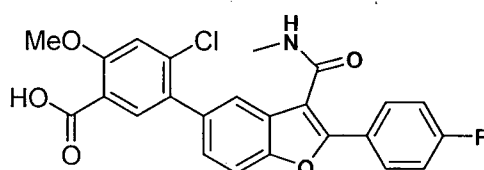
10 2,21 (s, 3H), 1,60 (m, 2H), 1,19 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de

15 parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) *m/z* (M+Na)⁺ = 541,36, Tr de HPLC = 1,952 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al

20 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 12,49 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm,

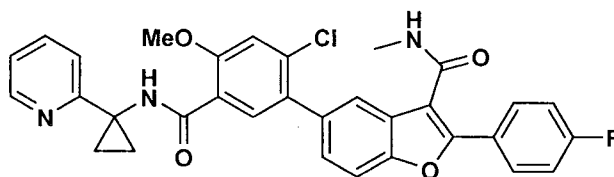
Tr = 9,11 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge

5 Phenyl 3, Tr = 15,98 min.



Ácido 4-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoico

- 10 Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7
- 15 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 453,93, Tr de HPLC = 1,757 min.



5-(2-Cloro-4-metoxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-2-metoxibenzoico

N-metilbenzofuran-3-carboxamida

El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente

5 B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,00 - 6,58 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ

8,61 (d, J = 5,80, 1H), 8,42 (td, J = 8,01, 1,68, 1H), 7,99 (s, 1H), 7,96 (m, J =

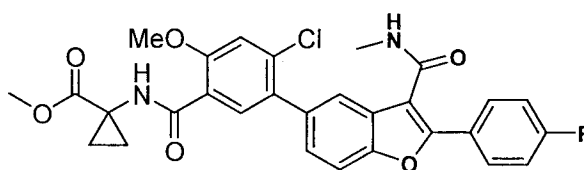
10 8,85, 5,19, 2H), 7,87 (d, J = 8,24, 1H), 7,79 (ddd, J = 7,40, 6,03, 0,92, 1H), 7,69 (d, J = 1,83, 1H), 7,64 (d, J = 8,55, 1H), 7,44 (dd, J = 8,55, 1,83, 1H), 7,40 (s, 1H), 7,27 (t, J = 8,85, 2H), 4,10 (s, 3H), 2,95 (s, 3H), 1,84 (m, 2H), 1,75 (m, 2H).

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH

15 al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 569,90, 570,79, 571,82, Tr de HPLC = 1,592 min. Las HPLC analíticas se realizaron usando instrumento

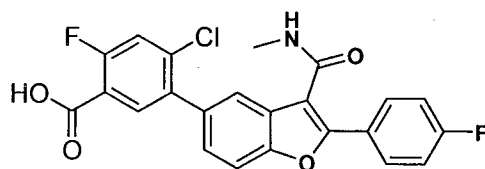
20 Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100,

Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min,
 Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 9,56 min; Columna: XBridge
 Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,97 min. Procedimiento de HPLC analítica:
 Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B=
 5 MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 10, % Final de B =
 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1
 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 16,35 min.



10 1-(4-Cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-
 metoxibenzamido)ciclopropanocarboxilato de metilo

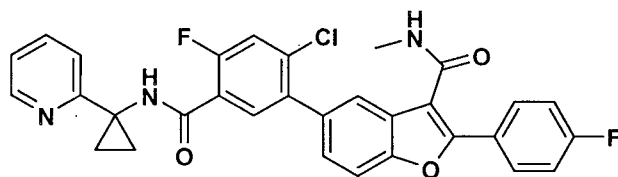
Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a
 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH
 al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-
 15 TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2
 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna:
 PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 551,02, Tr de
 HPLC = 1,753 min.



Ácido 4-cloro-2-fluoro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a
 5 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH
 al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-
 TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2
 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7
 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 441,91, Tr de HPLC = 1,803 min.

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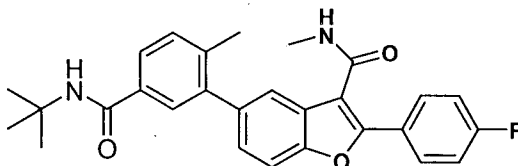


5-(2-Cloro-4-fluoro-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-
 N-metilbenzofuran-3-carboxamida

El producto se obtuvo como una sal TFA después de purificación por HPLC
 15 preparativa de fase inversa Shimadzu-VP usando el procedimiento de
 separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente
 B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B =
 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25

ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 5,63 - 6,40 min. (detección UV a 220 nm). RMN de ^1H (500 MHz, CD_3OD) δ 8,60 (d, $J = 5,49$, 1H), 8,34 (td, $J = 7,93$, 1,83, 1H), 7,97 (m, $J = 8,85$, 5,19, 2H), 7,90 (d, $J = 7,63$, 1H), 7,83 (d, $J = 8,24$, 1H), 7,73 (solapando, 2H), 7,68 (d, $J =$
5 8,54, 1H), 7,56 (d, $J = 10,38$, 1H), 7,47 (dd, $J = 8,55$, 1,83, 1H), 7,29 (t, $J =$ 8,70, 2H), 2,95 (s, 3H), 1,82 (m, 2H), 1,70 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
10 Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z $(\text{M}+\text{H})^+ = 558,04$, Tr de HPLC = 1,558 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm , 4,6 x 150 mm, Tr = 3,10 min; Columna: XBridge Phenyl 3,5 μm , 4,6 x 150 mm, Tr = 3,60 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-
15 H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge

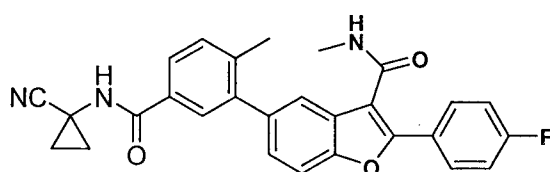
Phenyl 3,5 um, 4,6 x 150 mm, Tr = 13,24 min.



5-(5-(*tert*-Butilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-

- 5 carboxamida. Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm
- 10 S5, Recogida de la fracción: 8,62 - 9,21 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, *J* = 8,85, 5,49, 2H), 7,67 (d solapado con s, 1H), 7,67 (s, 1H), 7,65 (d, *J* = 8,55, 1H), 7,63 (d, *J* = 1,22, 1H), 7,38 (d solapado con dd, 1H), 7,37 (dd, *J* = 1,53, 1H), 7,28 (t, *J* = 8,70, 2H), 2,96 (s, 3H), 2,32 (s, 3H), 1,47 (s, 9H). Las LC/EM se realizaron usando instrumento Shimadzu-VP
- 15 con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) *m/z* (M+H)⁺ = 459,31, Tr de
- 20 HPLC = 1,763 min. Las HPLC analíticas se realizaron usando instrumento

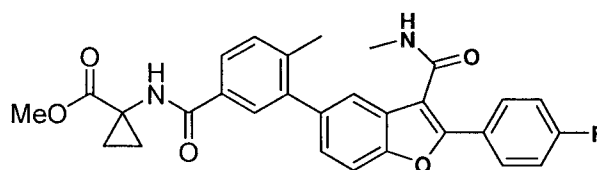
Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, 5 Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 17,08 min; XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 14,81 min.



5-(5-(1-Cianociclopropilcarbamoyl)-2-metilfenil)-2-(4-fluorofenil)-N-
10 metilbenzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 15 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,13 - 7,85 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, J = 8,70, 5,34, 2H), 7,77 (d solapado con s, 1H), 7,76 (s, 1H), 7,66 (d, J = 8,24, 1H), 7,63 (d, J = 1,53, 1H), 7,44 (d, J = 8,24, 1H), 7,37 (dd, J = 8,39, 1,68, 1H), 7,28 (t, J = 8,85, 2H), 2,95 (s, 3H), 2,34 (s, 3H), 1,59 20 (m, 2H), 1,36 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-

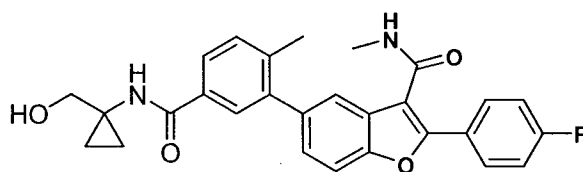
VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, 5 Columna: XTERRA® MS 7 µm, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 468,28, Tr de HPLC = 1,633 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 µm, 4,6 x 150 mm, Tr = 14,21 min; XBridge Phenyl 3,5 µm, 4,6 x 150 mm, Tr = 12,79 min.



15 1-(3-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzamido)ciclopropanocarboxilato de metilo

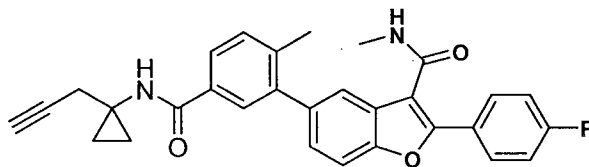
Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 20 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12

min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,26 - 7,97 min. (detección UV a 220 nm). RMN de ^1H (500 MHz, CD_3OD) δ 7,98 (m, J = 8,85, 5,19, 2H), 7,77 (dd, J = 4,27, 2,14, 2H), 7,66 (d, J = 8,55, 1H), 7,63 (d, J = 1,22, 1H), 7,42 (d, J = 8,55, 1H), 7,37 (dd, J = 8,39, 1,68, 1H), 7,28 (t, J = 8,85, 2H), 3,71 (s, 3H), 2,96 (s, 3H), 2,34 (s, 3H), 1,59 (m, 2H), 1,26 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 501,23, Tr de HPLC = 1,657 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm , 4,6 x 150 mm, Tr = 6,81 min; XBridge Phenyl 3,5 μm , 4,6 x 150 mm, Tr = 5,58 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3, Tr = 12,48 min.



2-(4-Fluorofenil)-5-(5-(1-(hidroximetil)ciclopropilcarbamoyl)-2-metilfenil)-N-metilbenzofuran-3-carboxamida

- 5 Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida
- 10 de la fracción: 8,78 - 9,06 min. (detección UV a 220 nm). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min,
- 15 Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 473,33, Tr de HPLC = 1,827 min.



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(prop-2-

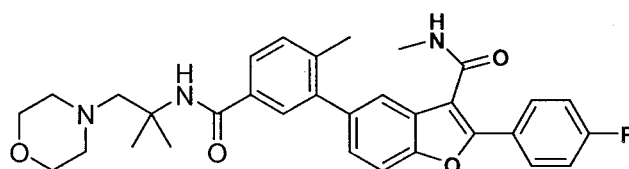
inilcarbamoil)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al

5 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,43 - 7,91 min. (detección UV a 220 nm). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y

10 Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 524,21, Tr de HPLC = 1,642 min.

15



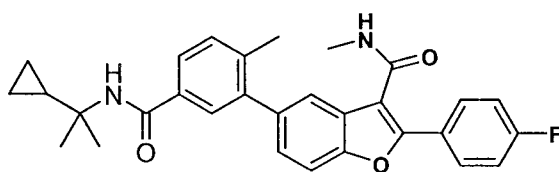
2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(2-metil-1-morfolinopropan-2-

ilcarbamoil)fenil)benzofuran-3-carboxamida

El producto se obtuvo como una sal TFA después de purificación por HPLC

20 preparativa de fase inversa Shimadzu-VP usando el procedimiento de

separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 20, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 5 7,64 - 8,27 min. (detección UV a 220 nm). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de 10 parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 544,38, Tr de HPLC = 1,503 min.

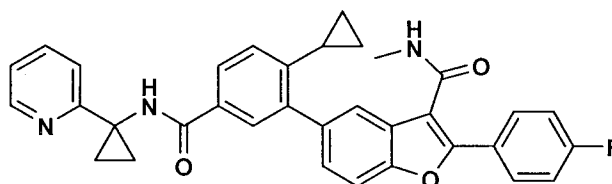


5-(5-(2-Ciclopropilpropan-2-ilcarbamoi)-2-metilfenil)-2-(4-fluorofenil)-N-
15 metilbenzofuran-3-carboxamida

El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 20 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25

ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción:
9,21 - 9,86 min. (detección UV a 220 nm). Las LC/EM se realizaron usando
instrumento Shimadzu-VP con detección UV a 220 nm y Waters
MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al
5 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de
parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x
50 mm; (ES+) m/z (M+H)⁺ = 485,34, Tr de HPLC = 1,842 min.

10



5-(2-Ciclopropil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-
metilbenzofuran-3-carboxamida

El producto se obtuvo como una sal TFA después de purificación por HPLC
preparativa de fase inversa Shimadzu-VP usando el procedimiento de
15 separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente
B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B =
100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25
ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción:
6,26 - 6,59 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ
20 8,54 (d, J = 5,19, 1H), 8,17 (m, 1H), 7,98 (m, J = 8,85, 5,19, 2H), 7,87 - 7,86 (m

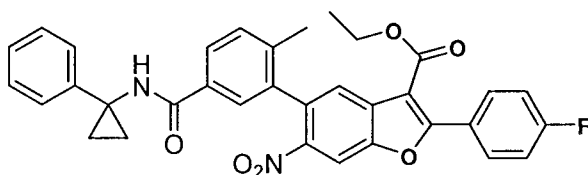
solapado, 2H), 7,77 (d, $J = 1,53$, 1H), 7,69 (d solapado con d, 1H), 7,68 (d, $J = 8,24$, 1H), 7,58 (m, 1H), 7,50 (dd, $J = 8,55$, 1,83, 1H), 7,29 (t, $J = 8,85$, 2H), 7,11 (d, $J = 8,55$, 1H), 2,96 (s, 3H), 1,98 (m, 1H), 1,77 (m, 2H), 1,61 (m, 2H), 0,96 (m, 2H), 0,82 (m, 2H). Las LC/EM se realizaron usando instrumento

5 Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+)

10 m/z (M+H)⁺ = 546,04, Tr de HPLC = 1,603 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada =

15 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 9,71 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 10,26 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo

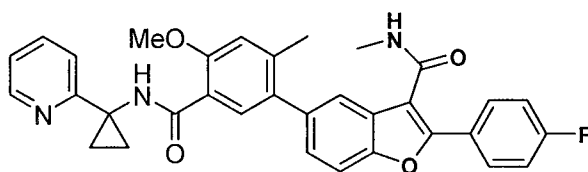
20 de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 13,95 min.



2-(4-Fluorofenil)-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)-6-nitrobenzofuran-3-carboxilato de etilo

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 579,41, Tr de HPLC = 2,032 min.

10



2-(4-Fluorofenil)-5-(4-metoxi-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

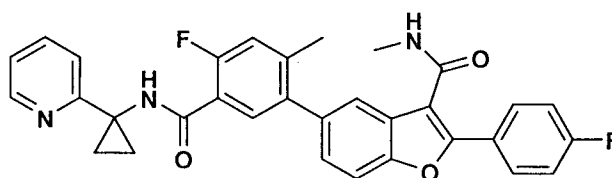
Una mezcla de 5-(2-cloro-4-metoxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (62,7 mg, 0,11 mmol, bruto), diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (52,4 mg, 0,11 mmol), MeBF₃K (20,12 mg, 0,165 mmol), diacetoxipaladio (12,35 mg, 0,055 mmol) y carbonato potásico (76 mg, 0,550 mmol) en una mezcla de H₂O (0,2 ml)/THF (2 ml) se

agitó a 90 °C en N₂ durante 6 horas 30 min. La mezcla se dejó en reposo a ta
durante la noche, y luego se diluyó con MeOH y se filtró a través de un
Whatman 0,45 um PVDF con disco GMF. El filtrado se purificó por HPLC
preparativa de fase inversa Shimadzu-VP usando el procedimiento de
5 separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente
B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 70, % Final de B =
90, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25
ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción:
2,26 - 2,77 min. (detección UV a 220 nm) obteniendo el producto como una sal
10 TFA. RMN de ¹H (500 MHz, CD₃OD) δ 8,60 (d, J = 5,80, 1H), 8,41 (m, 1H),
7,96 (m, J = 9,00, 5,34, 2H), 7,87 (s, 1H), 7,85 (d, J = 9,00, 1H), 7,79 (t, J =
6,56, 1H), 7,64 (d, J = 8,24, 1H), 7,58 (d, J = 1,53, 1H), 7,33 (dd, J = 8,55, 1,83,
1H), 7,17 (s, 1H), 7,28 (t, J = 8,85, 2H), 4,09 (s, 3H), 2,95 (s, 3H), 2,38 (s, 3H),
1,84 (m, 2H), 1,75 (m, 2H). Las LC/EM se realizaron usando instrumento
15 Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®.
Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%,
Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, %
Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min,
Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+)
20 m/z (M+H)⁺ = 550,00, Tr de HPLC = 1,588 min. Las HPLC analíticas se
realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254
nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-

TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 9,12 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,82 min.

- 5 Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 13,46 min.

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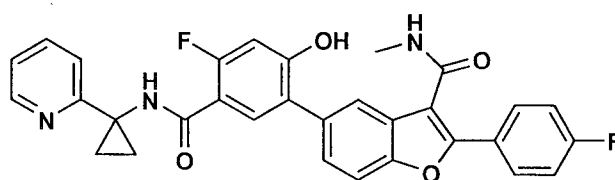
5-(4-Fluoro-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-
N-metilbenzofuran-3-carboxamida

- El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa Shimadzu-VP dos veces usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la
- 20 fracción: 5,58 - 5,94 min. (detección UV a 220 nm). RMN de ¹H (500 MHz,

CD₃OD) δ 8,57 (d, J = 5,49, 1H), 8,26 (td, J = 7,93, 1,53, 1H), 7,97 (m, J = 9,16, 5,19, 2H), 7,79 (d, J = 8,24, 1H), 7,73 (d, J = 7,63, 1H), 7,67 (d, J = 8,55, 1H), 7,65 (m solapando con d, 1H), 7,62 (d, J = 1,83, 1H), 7,35 (dd, J = 8,39, 1,68, 1H), 7,29 (t, J = 8,85, 2H), 7,25 (d, J = 11,90, 1H), 2,95 (s, 3H), 2,35 (s, 3H), 1,80 (m, 2H), 1,66 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®.

Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 538,04, Tr de HPLC = 1,497 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 9,46 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,66 min.

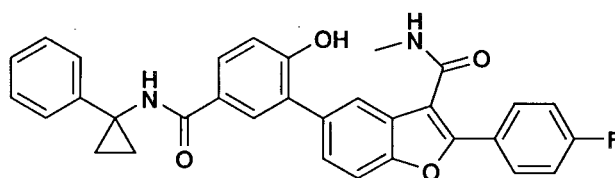
Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 12,95 min.



5-(4-Fluoro-2-hidroxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-
N-metilbenzofuran-3-carboxamida

- 5 Se obtuvo 5-(4-fluoro-2-hidroxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida como un subproducto durante la síntesis de 5-(4-fluoro-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida. El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa
- 10 Shimadzu-VP dos veces usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 4,16 - 4,55 min.
- 15 (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 8,55 (d ancho, *J* = 3,66, 1H), 8,19 (t, *J* = 7,78, 1H), 7,97 (m, *J* = 8,85, 5,19, 2H), 7,86 (d, *J* = 8,54, 1H), 7,82 (s, 1H), 7,74 (d, *J* = 8,24, 1H), 7,61 (t solapando con dd, 1H), 7,58 (dd, 2H), 7,28 (t, *J* = 8,70, 2H), 6,79 (d, *J* = 12,51, 1H), 2,97 (s, 3H), 1,78 (aparece como s, 2H), 1,63 (aparece como s, 2H). Las LC/EM se realizaron
- 20 usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters

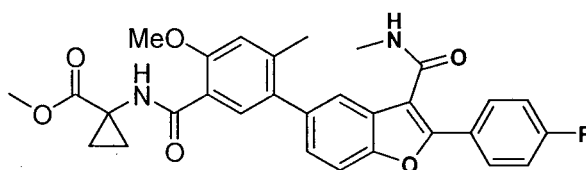
MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 540,07, Tr de HPLC = 1,342 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 µm, 4,6 x 150 mm, Tr = 8,06 min; Columna: XBridge Phenyl 3,5 µm, 4,6 x 150 mm, Tr = 8,56 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 µm, 4,6 x 150 mm, Tr = 13,91 min.



2-(4-Fluorofenil)-5-(2-hidroxi-5-(1-fenilciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

2-(4-Fluorofenil)-5-(2-hidroxi-5-(1-fenilciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida se obtuvo como un subproducto a partir de una reacción similar. Purificación por HPLC preparativa de fase inversa Shimadzu-VP dos veces usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,79 - 8,24 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, J = 9,00, 5,34, 2H), 7,91 (d, J = 2,14, 1H), 7,88 (d, J = 1,53, 1H), 7,76 (dd, J = 8,55, 2,14, 1H), 7,65 - 7,61 (m solapado, 2H), 7,29 - 7,27 (m solapado, 6H), 7,16 (m, 1H), 7,00 (d, J = 8,55, 1H), 2,97 (s, 3H), 1,35 (m, 4H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 521,28, Tr de HPLC = 1,695 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada =

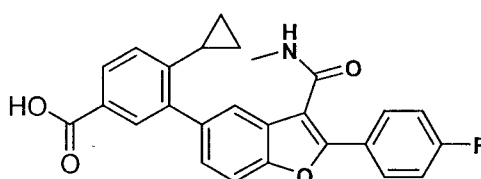
18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 6,84 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 5,71 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl, Tr = 12,68 min.



10 1-(5-(2-(4-Fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)-2-metoxi-4-metilbenzamido)ciclopropanocarboxilato de metilo

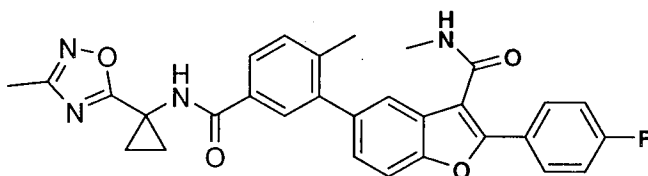
Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,07 - 8,45 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, 2H), 7,85 (s, 1H), 7,63 (d, J = 8,55, 1H), 7,58 (d, J = 1,22, 1H), 7,33 (dd, J = 8,55, 1,83, 1H), 7,27 (t, J = 8,85, 2H), 7,11 (s, 1H), 4,03 (s, 3H), 3,71 (s, 3H), 2,96 (s, 3H), 2,35 (s, 3H), 1,61 (m, 2H), 1,28 (m, 2H). Las

LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, 5 Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 531,23, Tr de HPLC = 1,715 min.



Ácido 4-ciclopropil-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-
10 il)benzoico

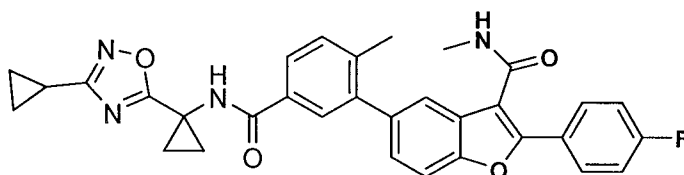
Se preparó ácido 4-ciclopropil-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico se preparó de una forma similar a como se ha descrito usando ciclopropiltrifluoroborato potásico. Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. 15 Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 430,07, Tr de HPLC = 1,802 min.



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(3-metil-1,2,4-oxadiazol-5-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Se agitó a 150°C durante dos horas una mezcla de 1-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzamido)ciclopropanocarboxilato de metilo (25,3 mg, 0,051 mmol), N'-hidroxiacetimidamida (11,23 mg, 0,152 mmol) y K₂CO₃ (41,9 mg, 0,303 mmol) en tolueno (1 ml) en N₂ en un tubo sellado reutilizable. La mezcla se evaporó, se diluyó con MeOH y se purificó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,54 - 8,08 min. (detección UV a 220 nm), dando el producto como un sólido blanco (19,9 mg, 75%). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, J = 9,00, 5,34, 2H), 7,82 (d, J = 2,14, 1H), 7,81 (m solapado, 1H), 7,66 (d, J = 8,55, 1H), 7,65 (d, J = 1,50, 1H), 7,44 (d, J = 8,55, 1H), 7,38 (dd, J = 8,24, 1,83, 1H), 7,28 (m, J = 8,85, 2H), 2,95 (s, 3H), 2,36 (s, 3H), 2,31 (s, 3H), 1,75 (m, 2H), 1,58 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A=

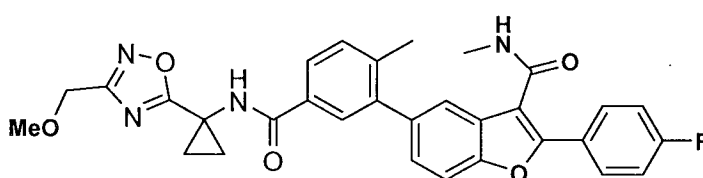
MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 525,12, Tr de HPLC = 1,700 min.



5-(5-(1-(3-Ciclopropil-1,2,4-oxadiazol-5-il)ciclopropilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 10 Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida
- 15 de la fracción: 8,32 - 8,92 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, J = 8,85, 5,49, 2H), 7,81 (d, J = 1,83, 1H), 7,80 (s ancho solapando con d, 1H), 7,66 (d solapado con d, 1H), 7,64 (d, J = 1,53, 1H), 7,44 (d, J = 8,55, 1H), 7,38 (dd, J = 8,39, 1,68, 1H), 7,28 (m, J = 8,85, 2H), 2,95 (s, 3H), 2,35 (s, 3H), 2,02 (m, 1H), 1,72 (m, 2H), 1,54 (m, 2H), 1,04 (m, 2H), 0,95
- 20 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con

detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 551,09, Tr de HPLC = 1,763 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 8,73 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 6,96 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 13,22 min.

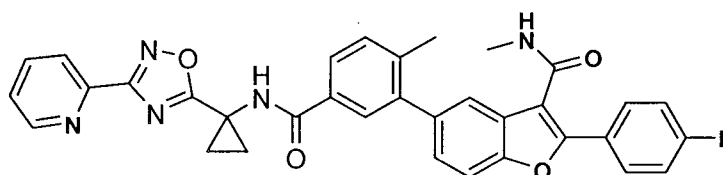


2-(4-Fluorofenil)-5-(5-(1-(3-(metoximetil)-1,2,4-oxadiazol-5-il)ciclopropilcarbamoyl)-2-metilfenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,92 - 8,52 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, *J* = 9,00, 5,34, 2H), 7,82 (d, *J* = 2,14, 1H), 7,81 (t solapado con d, 1H), 7,66 (d solapado con d, 1H), 7,65 (d, *J* = 1,83, 1H), 7,45 (d, *J* = 8,55, 1H), 7,38 (dd, *J* = 8,55, 1,83, 1H), 7,28 (t, *J* = 8,70, 2H), 4,51 (s, 2H), 3,42 (s, 3H), 2,95 (s, 3H), 2,36 (s, 3H), 1,79 (m, 2H), 1,60 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 555,23, Tr de HPLC = 1,700 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm, 4,6 x 150 mm, Tr = 7,11 min; Columna: XBridge Phenyl 3,5 μm,

4,6 x 150 mm, Tr = 5,57 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna:

5 XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 12,51 min.



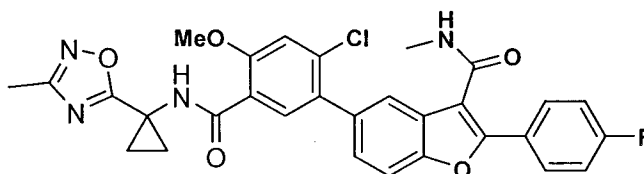
2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(3-(piridin-2-il)-1,2,4-oxadiazol-5-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

- 10 El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25
- 15 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,83 - 8,56 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 8,71 (d, J = 4,88, 1H), 8,19 (d, J = 7,93, 1H), 8,08 (td, J = 7,78, 1,53, 1H), 7,97(m, J = 9,00, 5,34, 2H), 7,85 (s, 1H), 7,84 (m solapando con s, 1H), 7,66 - 7,63 (m solapado, 3H), 7,45 (d, J = 8,55, 1H), 7,38 (dd, J = 8,55, 1,83, 1H), 7,28 (m, J = 8,85, 2H), 2,95 (s, 3H), 2,36 (s, 3H), 1,91 (m, 2H), 1,67 (m, 2H). Las
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ii)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,80 - 8,36 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, J = 9,00, 5,34, 2H), 7,86 (s, 1H), 7,63 (d, J = 8,55, 1H), 7,59 (d, J = 1,83, 1H), 7,33 (dd, J = 8,24, 1,83, 1H), 7,27 (t, J = 8,85, 2H), 7,13 (s, 1H), 4,06 (s, 3H), 2,96 (s, 3H), 2,36 (s, 3H), 2,31 (s, 3H), 1,77 (m, 2H), 1,60 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 555,10, Tr de HPLC = 1,723 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 5,98 min. Procedimiento

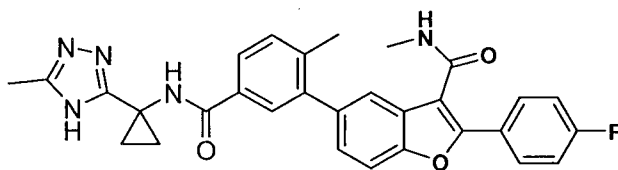
de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 12,98 min.



5-(2-Cloro-4-metoxi-5-(1-(3-metil-1,2,4-oxadiazol-5-il)ciclopropilcarbamoil)fenil)-
2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 10 Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida
- 15 de la fracción: 8,06 - 8,56 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,99-7,96 (m solapando con s, 2H), 7,97 (s, 1H), 7,71 (d, J = 1,53, 1H), 7,64 (d, J = 8,55, 1H), 7,45 (dd, J = 8,55, 1,83, 1H), 7,37 (s, 1H), 7,27 (t, J = 8,85, 2H), 4,06 (s, 3H), 2,96 (s, 3H), 2,32 (s, 3H), 1,78 (m, 2H), 1,61 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a
- 20 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH

al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 575,08, Tr de HPLC = 1,752 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 8,23 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 6,39 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 13,49 min.



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(5-metil-4H-1,2,4-triazol-3-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Se agitó a 150°C durante cuatro horas una mezcla de 5-(5-(1-

cianociclopropilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (33,8 mg, 0,072 mmol), acetohidrazida (16,07 mg, 0,217 mmol) y K_2CO_3 (9,99 mg, 0,072 mmol) en n-BuOH (1 ml) en N_2 en un tubo sellado reutilizable. La mezcla se diluyó con MeOH y se purificó por HPLC preparativa

5 de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 5,93 - 6,53

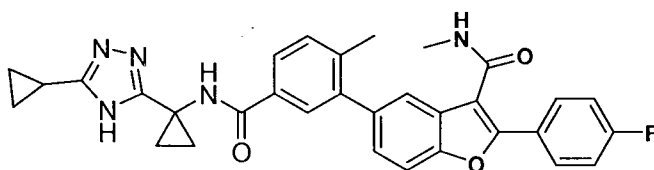
10 min. (detección UV a 220 nm) obteniendo el producto como un solvato en TFA. RMN de ¹H (500 MHz, CD₃OD) δ 7,97 (m, J = 8,85, 5,49, 2H), 7,85 (s, 1H), 7,85 (m solapado con s, J = 1,83, 1H), 7,66 (d, J = 8,55, 1H), 7,64 (d, J = 1,22, 1H), 7,45 (d, J = 7,63, 1H), 7,38 (dd, J = 8,39, 1,68, 1H), 7,29 (t, J = 8,70, 2H), 2,95 (s, 3H), 2,56 (s, 3H), 2,36 (s, 3H), 1,68 (m, 2H), 1,57 (m, 2H). Las LC/EM

15 se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m,

20 C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 524,23, Tr de HPLC = 1,545 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN

al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 11,80 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 12,13 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3, Tr = 11,87 min.

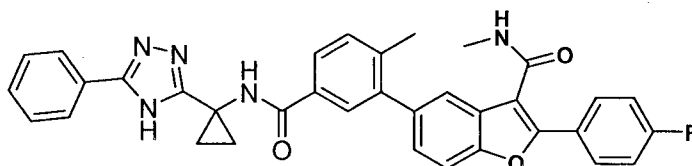
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5-(5-(1-(5-Ciclopropil-4H-1,2,4-triazol-3-il)ciclopropilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,05 - 8,58 min. (detección UV a 220 nm) obteniendo el producto como un solvato en TFA. RMN de ¹H (500 MHz, CD₃OD) δ 7,97 (m, J = 8,85,

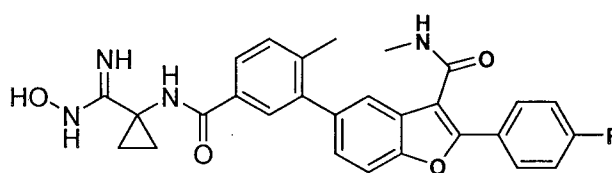
5,19, 2H), 7,85 (s, 1H), 7,84 (dd solapado con s, $J = 1,83$, 1H), 7,67 (d, $J = 8,24$, 1H), 7,64 (d, $J = 1,53$, 1H), 7,45 (d, $J = 7,63$, 1H), 7,38 (dd, $J = 8,39$, 1,68, 1H), 7,29 (t, $J = 8,85$, 2H), 2,95 (s, 3H), 2,36 (s, 3H), 2,15 (m, 1H), 1,66 (m, 2H), 1,55 (m, 2H), 1,23 (m, 2H), 1,11 (m, 2H). Las LC/EM se realizaron usando
5 instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x
10 50 mm; (ES+) m/z (M+H)⁺ = 500,00, Tr de HPLC = 1,598 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min,
15 Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 9,45 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,81 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente
20 = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl, Tr = 15,29 min.



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(5-fenil-4H-1,2,4-triazol-3-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el
 5 procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,48 - 7,03 min. (detección UV a 220 nm) obteniendo el producto
 10 como un solvato en TFA. RMN de ¹H (500 MHz, CD₃OD) δ 7,99 - 7,95 (m solapado, 4H), 7,88 - 7,85 (m solapado, 2H), 7,67 - 7,65 (m solapado, 2H), 7,49 - 7,45 (m solapado, 3H), 7,44 (d, J = 7,93, 1H), 7,39 (dd, J = 8,55, 1,53, 1H), 7,28 (t, J = 8,70, 2H), 2,95 (s, 3H), 2,35 (s, 3H), 1,72 (m, 2H), 1,48 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220
 15 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 585,89, Tr de HPLC = 1,765 min. Las
 20 HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección

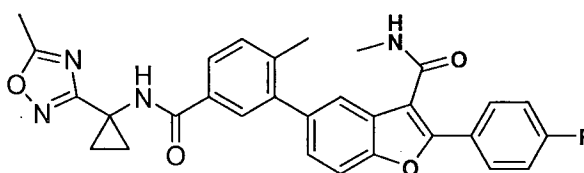
UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 6,85 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 5,81 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl, Tr = 13,04 min.



2-(4-Fluorofenil)-5-(5-(1-(N-hidroxicarbamimidoil)ciclopropilcarbamoil)-2-metilfenil)-N-metilbenzofuran-3-carboxamida

A una mezcla de 5-(5-(1-cianociclopropilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (43,5 mg, 0,093 mmol) en etanol (1,5 ml) a t.a. en N₂ se añadió clorhidrato de hidroxilamina (12,93 mg, 0,186 mmol), seguido por Et₃N (0,039 ml, 0,279 mmol). La mezcla se agitó a reflujo (115 °C) durante aproximadamente 4 horas. La mezcla se enfrió hasta t.a. y se evaporó. El residuo se usó para la etapa siguiente sin purificación posterior.

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 501,13, Tr de HPLC = 1,385 min.



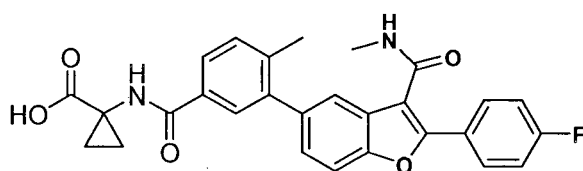
10 2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(5-metil-1,2,4-oxadiazol-3-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

A una mezcla de 2-(4-fluorofenil)-5-(5-(1-(N-hidroxycarbamimidol)ciclopropilcarbamoil)-2-metilfenil)-N-metilbenzofuran-3-carboxamida (46,5 mg, 0,093 mmol, bruto) en piridina (0,5 ml, 6,18 mmol) a t.a. en N₂ se añadió cloruro de acetilo (0,020 ml, 0,279 mmol). La mezcla se agitó a 115 °C durante 2 horas. La mezcla se enfrió hasta t.a., se diluyó con MeOH y se purificó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12

min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,64 - 7,95 min. (detección UV a 220 nm). El residuo obtenido después de la evaporación de las fracciones combinadas se purificó posteriormente por TLC preparativa, MeOH al 10%/CH₂Cl₂, dos placas de 20 cm x 20 cm x 0,5 mm. R_f aproximadamente 0,67 (10% MeOH/CH₂Cl₂). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, J = 9,00, 5,34, 2H), 7,81 (s, 1H), 7,80 ((m solapado con s, J = 2,14, 1H), 7,66 (d, J = 8,55, 1H), 7,65 (d, J = 1,22, 1H), 7,43 (d, J = 8,55, 1H), 7,36 (dd, J = 8,55, 1,83, 1H), 7,28 (m, J = 8,70, 2H), 2,96 (s, 3H), 2,54 (s, 3H), 2,35 (s, 3H), 1,59 (m, 2H), 1,43 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 525,07, Tr de HPLC = 1,682 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm, 4,6 x 150 mm, Tr = 6,67 min; Columna: XBridge Phenyl 3,5 μm, 4,6 x 150 mm, Tr = 5,22 min. Procedimiento de HPLC analítica: Disolvente A=

MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 12,36 min.

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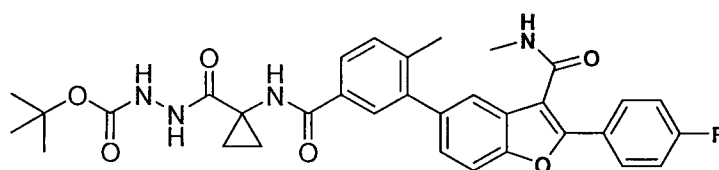


Ácido 1-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzamido)ciclopropanocarboxílico

RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, J = 9,00, 5,34, 2H), 7,78 (s, 1H),
 10 7,77 (m solapando con s, 1H), 7,66 (d, J = 8,55, 1H), 7,64 (d, J = 1,22, 1H),
 7,42 (d, J = 8,55, 1H), 7,38 (dd, J = 8,55, 1,83, 1H), 7,28 (t, J = 8,70, 2H), 2,96
 (s, 3H), 2,34 (s, 3H), 1,60 (m, 2H), 1,25 (m, 2H). Las LC/EM se realizaron
 usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters
 MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al
 15 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
 Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de
 parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x
 50 mm; (ES+) m/z (M+H)⁺ = 487,27, Tr de HPLC = 1,625 min. Las HPLC
 analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a
 20 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al

5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 5,38 min; XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 4,43 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3, Tr = 10,67 min.

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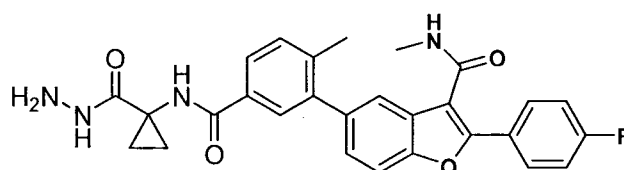
2-(1-(3-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-

metilbenzamido)ciclopropanocarbonil)hidrazinacarboxilato de *tert*-butilo

A una mezcla de ácido 1-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzamido)ciclopropanocarboxílico (41,6 mg, 0,086 mmol), hidrazinacarboxilato de *tert*-butilo (16,95 mg, 0,128 mmol) y tetrafluoroborato de 2-(1H-benzo[d][1,2,3]triazol-1-il)-1,1,3,3-tetrametilisouronio (54,9 mg, 0,171 mmol) en DMF (1 ml) a t.a. en N₂ se añadió N, N-diisopropiletilamina (0,060 ml, 0,342 mmol). La mezcla se agitó a t.a. durante 19 horas. La mezcla se añadió 5 ml H₂O. Los precipitados blancos se filtraron, se lavaron con 3 x 2 ml H₂O y se

secaron (33,1 mg) y se usó sin purificación posterior. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna:

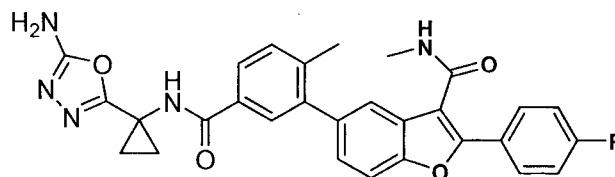
5 PHENOMENEX® Luna, 3,0 x 50 mm, S10; Tr de HPLC = 1,750 min.



2-(4-Fluorofenil)-5-(5-(1-(hidrazinacarbonil)ciclopropilcarbamoil)-2-metilfenil)-N-metilbenzofuran-3-carboxamida

- 10 A 2-(1-(3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzamido)ciclopropanocarbonil)hidrazinacarboxilato de *terc*-butilo (33,1 mg, 0,055 mmol) en un matraz de fondo redondo a t.a. en N₂ se añadió HCl (1 ml, 4,00 mmol, 4 M en 1,4-dioxano). La mezcla se agitó a t.a. durante cuatro horas. La mezcla se evaporó, y la sal clorhidrato bruta se usó sin purificación
- 15 posterior. Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna:
- 20 PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 501,06, Tr de

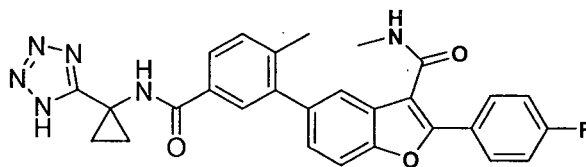
HPLC = 1,483 min.



5-(5-(1-(5-Amino-1,3,4-oxadiazol-2-il)ciclopropilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

A una mezcla de clorhidrato de 2-(4-fluorofenil)-5-(5-(1-(hidrazinacarbonil)ciclopropilcarbamoil)-2-metilfenil)-N-metilbenzofuran-3-carboxamida (29,5 mg, 0,055 mmol, bruto) en 1,4-dioxano (1 ml) a t.a. se añadió una solución de bromuro de cianógeno (58,3 mg, 0,550 mmol) en acetonitrilo (0,5 ml), y luego NaHCO_3 acuoso saturado (0,1 ml). La mezcla se agitó a t.a. durante aproximadamente 5 horas. La mezcla se añadió 0,3 ml de HCl 1N, se diluyó con MeOH y se purificó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%- H_2O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%- H_2O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,53 - 7,18 min. (detección UV a 220 nm) obteniendo el producto como una sal TFA. RMN de ^1H (500 MHz, CD_3OD) δ 7,97 (dd, J = 8,55, 5,19, 2H), 7,80 (s, 1H), 7,80 ((m solapado con s, 1H), 7,66 (d, J = 8,55, 1H), 7,63 (s, 1H), 7,44 (d, J = 8,55, 1H), 7,37 (dd, J = 8,24, 1,22,

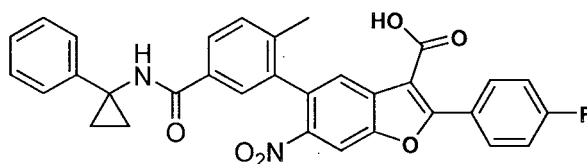
1H), 7,29 (t, $J = 8,70$, 2H), 2,95 (s, 3H), 2,35 (s, 3H), 1,64 (m, 2H), 1,49 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 526,05, Tr de HPLC = 1,577 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 3,23 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 3,39 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 11,04 min.



5-(5-(1-(1*H*-Tetrazol-5-il)ciclopropilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

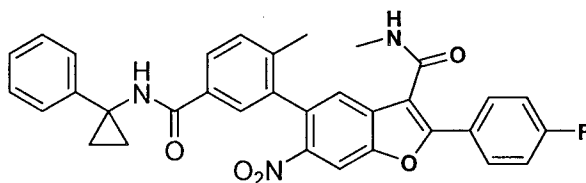
A una mezcla de 5-(5-(1-cianociclopropilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida (25,1 mg, 0,054 mmol) en DMF (1 ml) a t.a. en N₂ se añadió cloruro de amonio (8,62 mg, 0,161 mmol), y luego azida de sodio (6,98 mg, 0,107 mmol). La mezcla se agitó a 120 °C durante aproximadamente 4 horas. La mezcla se enfrió hasta t.a., y se añadió con otros 18 mg de NH₄Cl y luego 14 mg de NaN₃. La mezcla se agitó a 120 °C durante 14,5 horas. La mezcla se enfrió hasta t.a., y se añadió con otros 26 mg de NH₄Cl, seguido por 21 mg de NaN₃. La mezcla se volvió a agitar a 120 °C durante 24 horas. La mezcla se enfrió hasta t.a., y se diluyó con MeOH y se purificó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,82 - 7,27 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,97 (m, *J* = 9,00, 5,34, 2H), 7,85 (d, *J* = 1,22, 1H), 7,84 (dd solapado con d, *J* = 1,83, 1H), 7,67 (d, *J* = 8,24, 1H), 7,65 (d, *J* = 1,22, 1H), 7,45 (d, *J* = 7,63, 1H), 7,39 (dd, *J* = 8,55, 1,83, 1H), 7,29 (t, *J* = 8,85, 2H), 2,95 (s, 3H), 2,36 (s, 3H), 1,70 (m, 2H), 1,58 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters

MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 511,28, Tr de HPLC = 1,595 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 5,10 min; XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 4,23 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3, Tr = 10,58 min.



Ácido 2-(4-fluorofenil)-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)-6-nitrobenzofuran-3-carboxílico

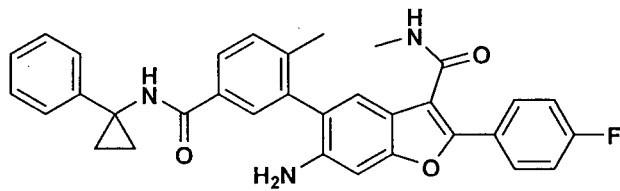
Se preparó por la hidrólisis de 2-(4-fluorofenil)-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)-6-nitrobenzofuran-3-carboxilato de etilo. Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 µm, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 551,34, Tr de HPLC = 1,895 min.



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)-6-nitrobenzofuran-3-carboxamida

Se preparó por el acoplamiento de ácido 2-(4-fluorofenil)-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)-6-nitrobenzofuran-3-carboxílico con clorhidrato de metilamina en las condiciones descritas. Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 µm, C18, 3,0 x

50 mm; (ES+) m/z (M+H)⁺ = 564,36, Tr de HPLC = 1,768 min.



6-Amino-2-(4-fluorofenil)-N-metil-5-(2-metil-5-(1-

5 fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Se obtuvo como una sal TFA a partir de la reducción de 2-(4-fluorofenil)-N-metil-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)-6-nitrobenzofuran-3-carboxamida usando H₂ con Pd al 5%/C como catalizador (DMF/EtOAc 2:5, t.a.) después de purificación por HPLC preparativa de fase inversa Shimadzu-

10 VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,17 - 6,79 min. (detección UV a 220 nm). RMN de 15 ¹H (500 MHz, CD₃OD) δ 7,94 (m, J = 8,85, 5,19, 2H), 7,87 (dd, J = 8,09, 1,98, 1H), 7,74 (d, J = 1,83, 1H), 7,50 (d, J = 7,93, 1H), 7,44 (s, 1H), 7,38 (s, 1H), 7,17 (m, 1H), 7,29 (s, 1H), 7,29 - 7,25 (m solapado, 5H), 2,92 (s, 3H), 2,24 (s, 3H), 1,35 (m, 4H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC:

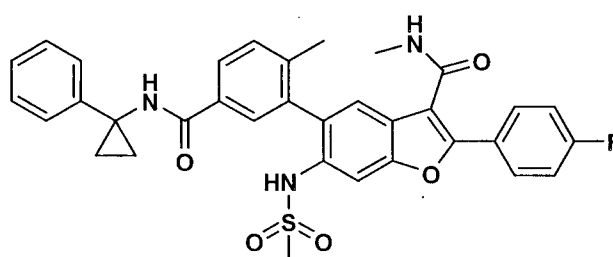
20 Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al

90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 µm, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 534,26, Tr de HPLC = 1,563 min. Las HPLC analíticas se realizaron usando instrumento

5 Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 µm, 4,6 x 150 mm, Tr = 11,58 min; XBridge Phenyl

10 3,5 µm, 4,6 x 150 mm, Tr = 4,96 min (% Inicial de B = 50). Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl, Tr = 15,09 min.

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2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)-6-(metilsulfonamido)benzofuran-3-carboxamida

A una mezcla de 6-amino-2-(4-fluorofenil)-N-metil-5-(2-metil-5-(1-

fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida (53,3 mg, 0,100 mmol) (bruto) en $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1 ml) a t.a. en N_2 se añadió piridina (0,024 ml, 0,300 mmol). A la mezcla se añadió entonces una solución de cloruro de metanosulfonilo (22,88 mg, 0,200 mmol) en $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0,3 ml), y se agitó

5 durante aproximadamente 22 horas. La mezcla se diluyó con MeOH y se purificó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%- H_2O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%- H_2O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12

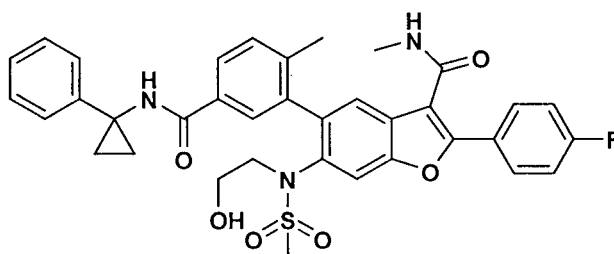
10 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,75 - 7,37 min. (detección UV a 220 nm). RMN de ^1H (500 MHz, CD_3OD) δ 7,98 (m, J = 8,85, 5,19, 2H), 7,85 (dd, J = 8,09, 1,98, 1H), 7,79 (s, 1H), 7,75 (d, J = 1,53, 1H), 7,51 (s, 1H), 7,47 (d, J = 7,93, 1H), 7,17 (m, 1H), 7,30 - 7,26 (m solapado, 5H), 7,29 (s, 1H), 2,93 (s, 3H), 2,88 (s, 3H), 2,23 (s,

15 3H), 1,35 (aparece como d, 4H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%- H_2O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%- H_2O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min,

20 Caudal = 4 ml/min, Columna: XTERRA® MS 7 μm , C18, 3,0 x 50 mm; (ES+) m/z $(\text{M}+\text{H})^+$ = 612,34, Tr de HPLC = 1,583 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254

nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 7,48 min; XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 6,24 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl, Tr = 11,46 min.

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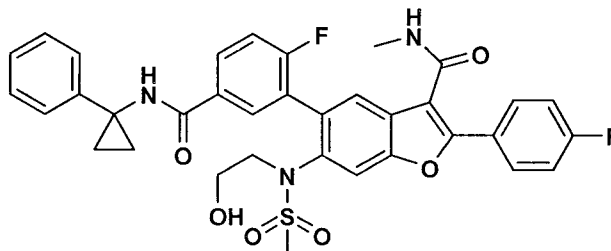


2-(4-Fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metil-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

Se preparó 2-(4-fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metil-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida a partir de la alquilación de 2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-fenilciclopropilcarbamoil)fenil)-6-(metilsulfonamido)benzofuran-3-carboxamida usando (2-bromoetoxi)(*terc*-butil)dimetilsilano (K₂CO₃, DMF 55 °C) seguido por desprotección usando HCl en 1,4-dioxano a t.a. La purificación se realizó por

HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,32 - 6,81 min. (detección UV a 220 nm). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 μ m, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 656,06, Tr de HPLC = 1,563 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 6,05 min; XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 5,38 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5

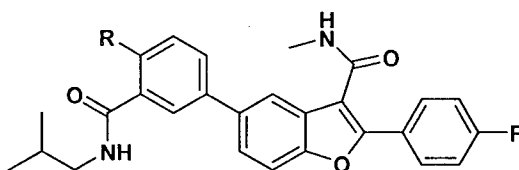
um, 4,6 x 150 mm, Tr = 11,42 min.



5-(2-Fluoro-5-(1-fenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metilbenzofuran-3-carboxamida

La purificación se realizó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 30, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,06 - 8,30 min. (detección UV a 220 nm). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: XTERRA® MS 7 um, C18, 3,0 x 50 mm; (ES+) m/z (M+H)⁺ = 660,50, Tr de HPLC = 1,530 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN

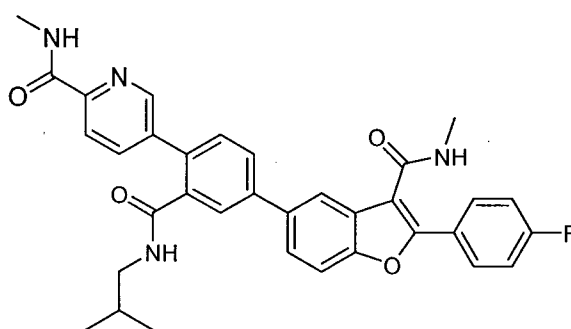
al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 5,68 min; XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 5,18 min.



Procedimiento general: A un vial de microondas BIOTAGE® (2-5 ml) se añadió bien 5-(4-cloro-3-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (0,075 mmol, 1 eq.) o trifluorometanosulfonato de 4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-(isobutilcarbamoil)fenilo (0,075 mmol, 1 eq.) en 1,4-dioxano seco (1 ml) junto con el ácido borónico deseado (0,150 mmol, 2 eq.), fosfato potásico, tribásico (0,300 mmol, 52,3 mg) en agua (0,2 ml), dicitclohexil(2',6'-dimetoxibifenil-3-il)fosfina (S-Phos) (6,16 mg, 0,015 mmol), y finalmente acetato de paladio (II) (3,37 mg, 0,015 mmol) en 1,4-dioxano (0,5 ml). El vial se purgó con nitrógeno, luego se tapó y se colocó en el microondas BIOTAGE® durante 10 minutos a 150 °C. El disolvente se eliminó en un Thermo/Savant SPEEDVAC® y los productos brutos se disolvieron en DMF (1,8 ml) y se purificó por HPLC preparativa usando una HPLC Prep Shimadzu que emplea acetonitrilo/agua/TFA al 0,1% donde el disolvente A era

acetonitrilo al 10% / H₂O al 90%/ ácido trifluoroacético al 0,1% y el disolvente B era H₂O al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 30x100mm a un gradiente de 30-100% de B y un caudal de 40 ml/minutos durante 8 minutos con un mantenimiento de 10 minutos. Los tubos con el producto deseado se evaporaron durante la noche en un Thermo/Savant SPEEDVAC®. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ TFA al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / TFA al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ TFA al 0,1% con un gradiente de 20-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 20-100% de B (B = metanol

calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. Tr representa el tiempo de retención de la LC en 5 minutos. Todos los espectros de RMN se registraron a temperatura ambiente usando disolventes de RMN deuterados.

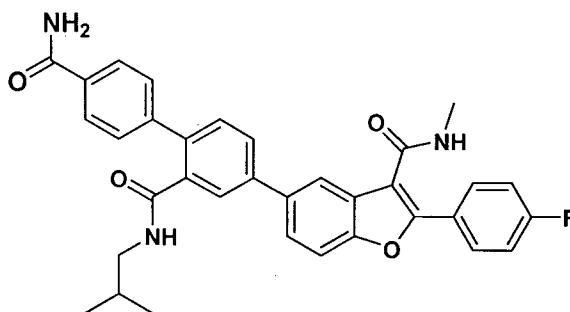


5-(4-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-(isobutilcarbamoil)fenil)-N-metilpicolinamida

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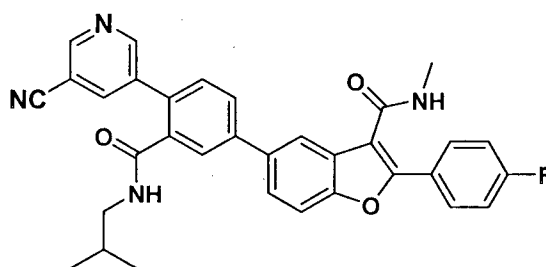
RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,75 (d, $J=7$ Hz, 6 H), 1,63 - 1,71 (m, 1 H), 2,93 (d, $J=5$ Hz, 6 H), 3,00 (t, $J=6$ Hz, 2 H), 7,23 (t, $J=9$ Hz, 2 H), 7,37 (t, $J=6$ Hz, 1 H), 7,44 - 7,51 (m, 1 H), 7,53 (d, $J=8$ Hz, 1 H), 7,60 - 7,66 (m, 1 H), 7,67 - 7,73 (m, 1 H), 7,80 - 7,88 (m, 2 H), 7,98 (dd, $J=8$, 2 Hz, 1 H), 8,05 (s, 1 H), 8,08 - 8,18 (m, 3 H), 8,30 (d, $J=5$ Hz, 1 H), 8,66 (d, $J=2$ Hz, 1 H). Tr de LCEM 2,125 min., m/z 579,32 ($M+H$), Tr de HPLC 8,594 min. (Sunfire C18), 98,7 % de pureza y 11,276 min. (Gemini C18), 100 % de pureza.

15



4-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-N2-isobutilbifenil-2,4'-
dicarboxamida

RMN de ^1H (400 MHz, DMF- d_7) δ ppm 0,81 (d, $J=6,78$ Hz, 6 H), 1,71 - 1,82 (m,
5 1 H), 3,00 (d, $J=4,77$ Hz, 3 H), 3,06 (t, $J=6,40$ Hz, 2 H), 7,42 - 7,48 (m, 2 H),
7,57 (d, $J=8,28$ Hz, 1 H), 7,62 (m, 2 H), 7,78 (d, $J=8,28$ Hz, 1 H), 7,84 (m, 2 H),
7,94 (d, $J=8,03$ Hz, 1 H), 8,00 (d, $J=8,28$ Hz, 2 H), 8,06 - 8,08 (m, 1 H), 8,10 -
8,14 (m, 2 H), 8,20 (t, $J=5,77$ Hz, 1 H), 8,40 (d, $J=4,52$ Hz, 1 H). Tr de LCEM
2,020 min, m/z 564,25 (M+H). Tr de HPLC 8,224 min. (Sunfire C18), 98,2 % de
10 pureza y 11,098 min. (Gemini C18), 98,3 % de pureza.



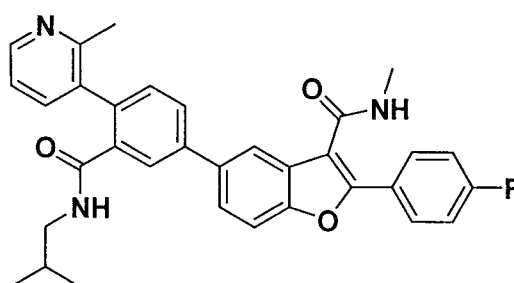
5-(4-(5-Cianopiridin-3-il)-3-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-
metilbenzofuran-3-carboxamida

15 RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,82 (d, $J=6,78$ Hz, 6 H), 1,74 - 1,80 (m,

1 H), 2,93 (d, $J=4,52$ Hz, 3 H), 3,01 - 3,11 (m, 2 H), 7,18 - 7,30 (m, 2 H), 7,42 - 7,51 (m, 1 H), 7,55 (d, $J=7,78$ Hz, 1 H), 7,56 - 7,61 (m, 1 H), 7,62 - 7,67 (m, 1 H), 7,68 - 7,75 (m, 1 H), 7,83 - 7,92 (m, 2 H), 8,04 - 8,15 (m, 3 H), 8,20 (t, $J=2,13$ Hz, 1 H), 8,85 (dd, $J=13,93, 2,13$ Hz, 2 H). Tr de LCEM 2,278 min, m/z 547,23 (M+H). Tr de HPLC 9,246 min. (Sunfire C18), 96,0 % de pureza y 11,343 min. (Gemini C18), 98,6 % de pureza.

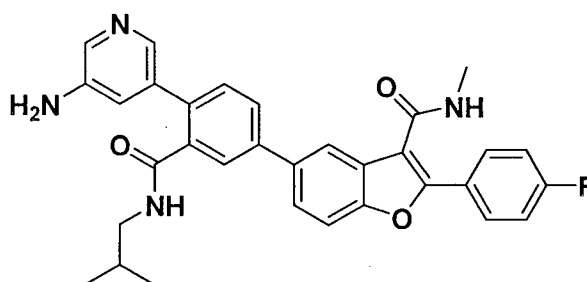
Una técnica alternativa al acoplamiento. A un vial de microondas de pequeño tamaño se añadió 5-(4-cloro-3-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (47,9 mg, 0,1 mmol), BuOH (2 ml), ácido/éster borónico (0,150 mmol), dicitclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (19,07 mg, 0,040 mmol), fosfato potásico, tribásico (85 mg, 0,400 mmol) y finalmente Tris(dibencilidenacetona) dipaladio(0) (18,31 mg, 0,020 mmol). El vial se tapó y se sometió a calentamiento en microondas (130 °C) durante 12 minutos. Se eliminó el butanol en una corriente de nitrógeno y los productos brutos se disolvieron en DMF (1,8 ml) y se purificaron por HPLC preparativa que emplea un sistema de HPLC Prep DIONEX® equipado con un ELS detector (Dispersión de Luz Evaporativa). Se usó una columna Waters XBridge 19x200mm 5 um C18 con acetonitrilo/agua calidad HPLC/acetato amónico 10mM donde el disolvente A era agua calidad HPLC con acetato amónico 10mM y el disolvente B era acetonitrilo al 100% a un gradiente de 30-95% de B en 30 minutos con un caudal de 25 ml/minuto. La LCEM se realizó usando un espectrómetro de masas Waters ZQ con ESCi con una columna SUPELCO®

Ascentis Express 3 μ m C18 4,5 x 50mm que emplea acetonitrilo/agua calidad HPLC/acetato amónico 10mM donde el disolvente A era acetonitrilo al 5%, agua calidad HPLC al 95% con acetato amónico 10mM y el disolvente B era acetonitrilo al 95%, agua calidad HPLC al 5% con acetato amónico 10mM a un
5 gradiente de 0-100% de B en 8 minutos con un mantenimiento de 1 minuto a 2 ml/minuto.



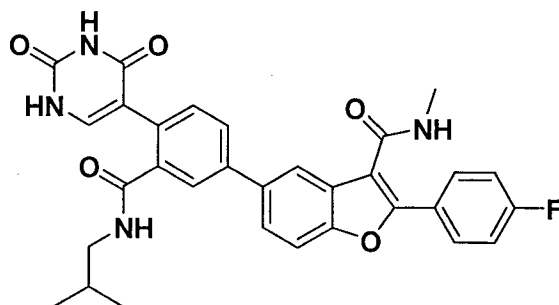
2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-4-(2-metilpiridin-3-il)fenil)-N-
10 metilbenzofuran-3-carboxamida

LCEM m/z 535,90 (M+H), Tr 4,89 min., 100 % de pureza.



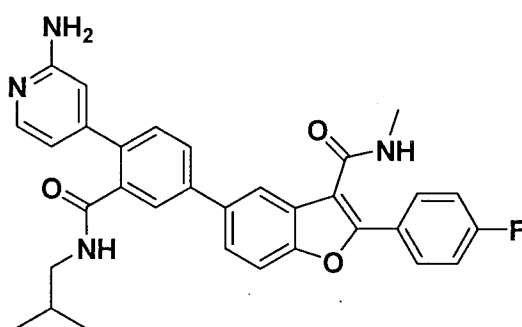
5-(4-(5-Aminopiridin-3-il)-3-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-
15 metilbenzofuran-3-carboxamida

LCEM m/z 536,96 (M+H), Tr 4,37 min., 100 % de pureza.



5 5-(4-(2,4-Dioxo-1,2,3,4-tetrahydropirimidin-5-il)-3-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

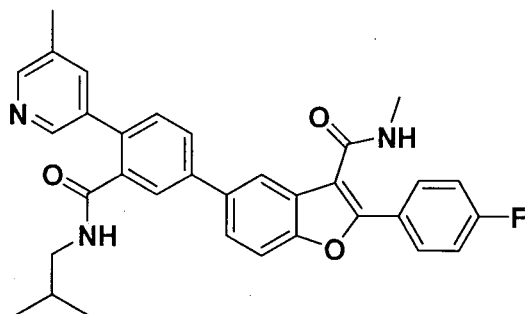
LCEM m/z 554,94 (M+H), Tr 3,88 min., 100 % de pureza.



10 5-(4-(2-Aminopiridin-4-il)-3-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

LCEM m/z 536,97 (M+H), Tr 4,55 min., 100 % de pureza.

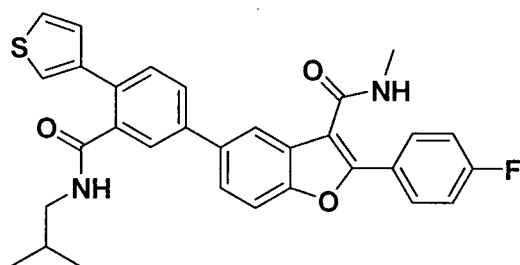
527



2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-4-(5-metilpiridin-3-il)fenil)-*N*-metilbenzofuran-3-carboxamida

LCEM m/z 535,95 (M+H), Tr 4,99 min., 100 % de pureza.

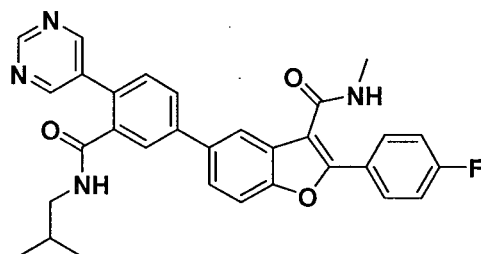
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2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-4-(tiofen-3-il)fenil)-*N*-metilbenzofuran-3-carboxamida

LCEM m/z 526,96 (M+H), Tr 5,83 min., 74 % de pureza.

10

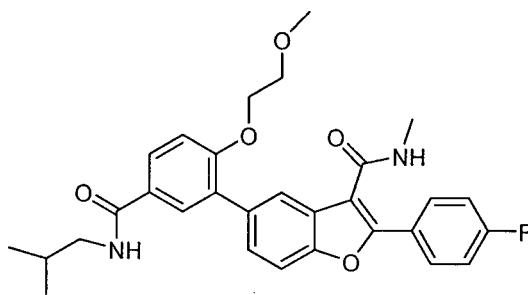


2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-4-(pirimidin-5-il)fenil)-*N*-

metilbenzofuran-3-carboxamida

Purificación usando una HPLC preparativa Shimadzu que emplea CH_3CN /agua/TFA donde el disolvente A era acetonitrilo al 10% / H_2O al 90%/ ácido trifluoroacético al 0,1% y el disolvente B era H_2O al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5u C18 30x100mm a un gradiente de 30-100% de B y un caudal de 40 ml/minutos durante 10 minutos con un mantenimiento de 10 minutos. Los datos de LC/EM de la purificación posterior se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5 μm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ TFA al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / TFA al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5 μm 4,6 x 150mm que emplea agua/acetonitrilo/ TFA al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna

PHENOMENEX® Gemini C18 3µm 4,6 x 150mm que emplea agua/metanol/
 bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol
 calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al
 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol
 5 calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un
 caudal de 1 ml/minuto. RMN de ^1H (400 MHz, DMSO- d_6) δ ppm 0,76 (d, $J=6,78$
 Hz, 6 H), 1,61 - 1,74 (m, 1 H), 2,87 (d, $J=4,52$ Hz, 3 H), 2,96 (t, $J=6,27$ Hz, 2 H),
 7,39 (t, $J=8,91$ Hz, 2 H), 7,64 (d, $J=8,03$ Hz, 1 H), 7,77 - 7,87 (m, 3 H), 7,91 -
 8,07 (m, 4 H), 8,47 - 8,60 (m, 2 H), 8,81 (s, 2 H), 9,16 (s, 1 H). LCEM m/z
 10 523,22 (M+H), Tr 2,052 min. Tr de HPLC 8,908 min. (Sunfire C18), 96,0 % de
 pureza y 11,353 min. (Gemini C18), 98,6 % de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(2-metoxietoxi)fenil)-N-
 15 metilbenzofuran-3-carboxamida

A un vial de microondas pequeño se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-
 (isobutilcarbamoil) fenil)-N-metilbenzofuran-3-carboxamida (33 mg, 0,072
 mmol), tetrahidrofurano (2 ml), trifenilfosfina (37,6 mg, 0,143 mmol), 2-
 metoxietanol (0,011 ml, 0,139 mmol), y azodicarboxilato de di-*terc*-butilo (33,0

mg, 0,143 mmol). El vial se cerró y se calentó hasta 100 °C durante 10 minutos. Después de volver a la temperatura ambiente, se eliminó el tetrahidrofurano en una corriente de nitrógeno. El producto bruto se recogió en 2 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que empleaba

5 acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 30 x 100mm a un gradiente de 40-100% de B y un caudal de 40 ml/minutos durante 8 minutos con un mantenimiento de 10 minutos. El

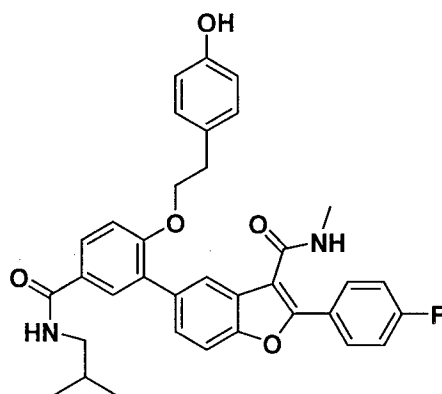
10 material deseado se concentró hasta sequedad. El sólido blanco resultante (41% de rendimiento) se colocó en alto vacío antes del análisis final. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de

15 B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters

20 Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/TFA al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al

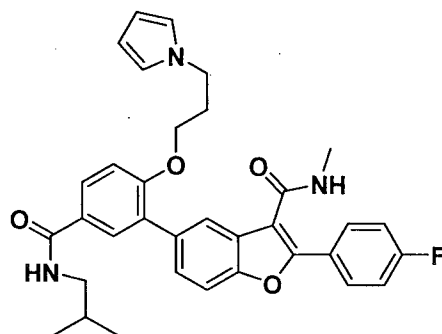
95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX400. Los desplazamientos químicos se expresaron en ppm relativas al disolvente deuterado usado. Las constantes de acoplamiento se expresaron en hertz. La multiplicidad de los picos se expresó usando las siguientes abreviaturas: s (singlete), d (doblete), dd (doblete de dobletes), t (triplete), m (multiplete), a (ancho). RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,04 (d, $J = 6,53$ Hz, 6 H), 1,35 - 1,40 (m, 3 H), 1,96 - 2,08 (m, 1 H), 2,97 - 3,10 (m, 3 H), 3,24 - 3,32 (m, 2 H), 3,73 - 3,82 (m, 2 H), 4,25 - 4,34 (m, 2 H), 7,24 (d, $J = 8,53$ Hz, 1 H), 7,29 - 7,38 (m, 2 H), 7,63 - 7,72 (m, 2 H), 7,91 (dd, $J = 8,53, 2,26$ Hz, 1 H), 7,94 - 7,99 (m, 2 H), 8,00 - 8,09 (m, 2 H), 8,48 (s ancho, 1 H). LCEM m/z 519,25 ($\text{M}+\text{H}$), Tr 2,292 min. HPLC (Sunfire C18) Tr 10,054 min, 96% de pureza y (XBridge phenyl C18) Tr 11,846 min., 97 % de pureza.

A continuación se presentan otros ejemplos de compuestos unidos por éter. Los compuestos se sintetizaron del mismo modo que antes. El disolvente (tetrahidrofurano) se eliminó en una corriente de nitrógeno y los productos brutos se disolvieron en DMF (1,8 ml) y se purificó por HPLC preparativa que
5 emplea un sistema de HPLC Prep DIONEX® equipado con un detector ELS (Dispersión de Luz Evaporativa). Se usó una columna SUPELCO® Ascentis 5µm C18 21,2 x 250mm con acetonitrilo/agua calidad HPLC/acetato amónico 10mM donde el disolvente A era 99,9% de agua calidad HPLC con acetato amónico 10mM y el disolvente B era 100% de acetonitrilo a un gradiente de 30-
10 95% de B en 20 minutos con un mantenimiento de 2,5 minutos a 20ml/minuto. La LCEM se realizó usando un espectrómetro de masas Waters ZQ con ESCi con una columna SUPELCO® Ascentis Express 3 µm C18 4,5 x 50mm que emplea acetonitrilo/agua calidad HPLC/acetato amónico 10mM donde el disolvente A era acetonitrilo al 5%, agua calidad HPLC al 95% con acetato
15 amónico 10mM y el disolvente B era acetonitrilo al 95%, agua calidad HPLC al 5% con acetato amónico 10mM a un gradiente de 0-100% de B en 8 minutos con un mantenimiento de 1 minuto a 2ml/minuto. Los espectros de RMN se registraron a temperatura ambiente usando un espectrómetro de flujo Varian 600MHz. Los desplazamientos químicos se expresaron en ppm relativas al
20 disolvente usado DMSO-d₆ al 75%/ CDCl₃ al 25% (v/v).



2-(4-Fluorofenil)-5-(2-(4-hidroxifenetoxi)-5-(isobutilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida

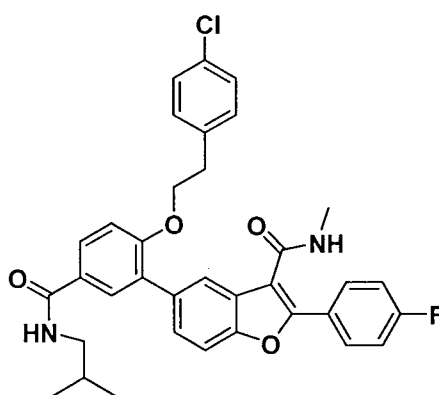
- RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,88 (d, $J=7,03$ Hz, 6 H), 1,85
 5 (ddd, $J=13,33$, 6,59, 6,44 Hz, 1 H), 2,77 - 2,94 (m, 5 H), 3,08 (t, $J=6,15$ Hz, 2 H), 4,20 (t, $J=6,44$ Hz, 2 H), 6,59 - 6,68 (m, 2 H), 6,98 (d, $J=8,20$ Hz, 2 H), 7,13 (d, $J=8,79$ Hz, 1 H), 7,32 (t, $J=8,79$ Hz, 1 H), 7,41 (d, $J=8,79$ Hz, 1 H), 7,59 (d, $J=8,20$ Hz, 1 H), 7,75 (s, 1 H), 7,81 - 7,91 (m, 2 H), 8,00 (dd, $J=8,20$, 5,27 Hz, 1 H), 8,33 (t, $J=5,57$ Hz, 1 H), 8,39 (d, $J=4,10$ Hz, 1 H). LCEM m/z 581,48 ($\text{M}+\text{H}$),
 10 Tr 5,30 min., 90 % de pureza.



5-(2-(3-(1*H*-Pirrol-1-il)propoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-

metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,89 (d, $J=6,44$ Hz, 6 H), 1,80 - 1,91 (m, 1 H), 2,07 (m, 2 H), 2,79 (d, $J=4,10$ Hz, 3 H), 3,09 (t, $J=6,44$ Hz, 2 H), 3,90 - 4,01 (m, 4 H), 5,94 (s, 2 H), 6,61 (s, 2 H), 7,08 (d, $J=8,79$ Hz, 1 H), 7,32 (t, $J=8,50$ Hz, 2 H), 7,58 (d, $J=8,20$ Hz, 1 H), 7,70 (d, $J=8,79$ Hz, 1 H), 7,79 - 7,87 (m, 2 H), 7,92 (s, 1 H), 7,97 (dd, $J=8,50, 5,57$ Hz, 2 H), 8,32 - 8,42 (m, 2 H). LCEM m/z 568,47 (M+H), Tr 5,98 min., 100 % de pureza.

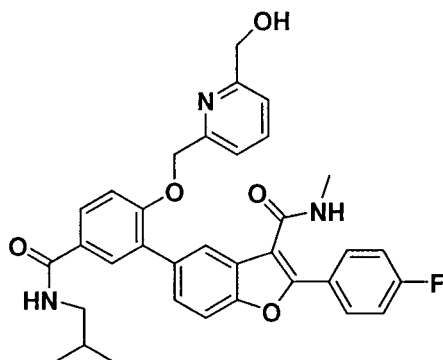


10 2-(4-Fluorofenil)-5-(2-(4-clorofenetoxi)-5-(isobutilcarbamoil)fenil)-N-

metilbenzofuran-3-carboxamida

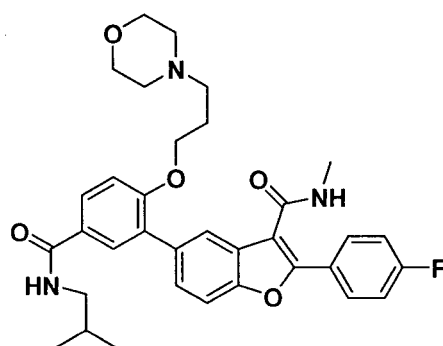
RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,88 (d, $J=7,03$ Hz, 6 H), 1,80 - 1,90 (m, 1 H), 2,84 (d, $J=4,69$ Hz, 3 H), 2,96 (t, $J=6,15$ Hz, 2 H), 3,08 (t, $J=6,15$ Hz, 2 H), 4,26 (t, $J=6,44$ Hz, 2 H), 7,14 (d, $J=8,79$ Hz, 1 H), 7,19 (d, $J=8,20$ Hz, 2 H), 7,23 - 7,27 (m, 2 H), 7,29 - 7,39 (m, 3 H), 7,58 (d, $J=8,79$ Hz, 1 H), 7,73 (s, 1 H), 7,83 - 7,89 (m, 2 H), 8,00 (dd, $J=8,50, 5,57$ Hz, 2 H), 8,33 (t, $J=5,27$ Hz, 1 H), 8,38 (d, $J=4,10$ Hz, 1 H). LCEM m/z 599,47 (M+H), Tr 6,52 min., 92 % de

pureza.



5 2-(4-Fluorofenil)-5-(2-((6-(hidroximetil)piridin-2-il)metoxi)-5-(isobutilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida

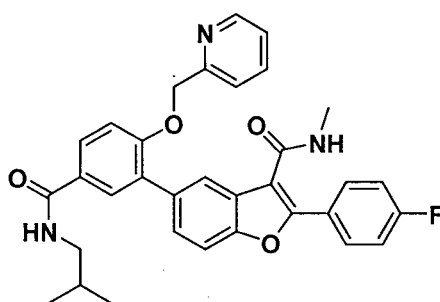
RMN de ^1H (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0,89 (d, $J=6,44$ Hz, 6 H), 1,79 - 1,91 (m, 1 H), 2,82 (d, $J=4,10$ Hz, 3 H), 3,09 (t, $J=6,44$ Hz, 2 H), 4,56 (s, 2 H), 5,23 (s, 2 H), 7,24 (t, $J=9,37$ Hz, 2 H), 7,32 (t, $J=8,79$ Hz, 2 H), 7,37 (d, $J=8,20$ Hz, 1 H), 7,60 - 7,65 (m, 1 H), 7,66 - 7,70 (m, 1 H), 7,75 (t, $J=7,62$ Hz, 1 H), 7,84 - 7,90 (m, 2 H), 7,93 (s, 1 H), 7,96 - 8,03 (m, 2 H), 8,36 (t, $J=5,57$ Hz, 1 H), 8,40 (d, 1 H). LCEM m/z 582,48 (M+H), Tr 4,57 min., 93 % de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(2-morfolinoetoxi)fenil)-*N*-
metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,89 (d, $J=6,44$ Hz, 6 H, 1,79 -
1,91 (m, 1 H), 2,38 (s ancho, 4 H), 2,64 (t, $J=5,57$ Hz, 2 H), 2,84 (d, $J=4,10$ Hz,
5 3 H), 3,08 (t, $J=6,15$ Hz, 2 H), 3,52 (t, $J=4,39$ Hz, 4 H), 4,17 (t, $J=5,57$ Hz, 2 H),
7,16 (d, $J=8,79$ Hz, 1 H), 7,32 (t, $J=8,79$ Hz, 2 H), 7,56 - 7,61 (m, 1 H), 7,61 -
7,66 (m, 1 H), 7,75 (s, 1 H), 7,83 - 7,91 (m, 2 H), 7,98 (dd, $J=8,20, 5,86$ Hz, 2
H), 8,35 (t, $J=5,27$ Hz, 1 H), 8,38 (d, 1 H). LCEM m/z 574,35 (M+H), Tr 3,95
min., 100 % de pureza.

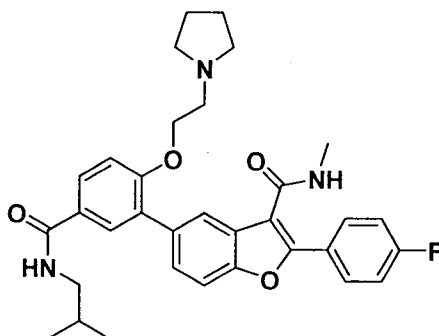
10



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(piridin-2-ilmetoxi)fenil)-*N*-
metilbenzofuran-3-carboxamida

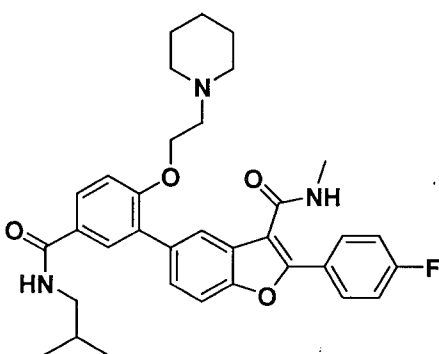
RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,89 (d, $J=7,03$ Hz, 6 H), 1,82 -
15 1,91 (m, 1 H), 2,79 - 2,86 (m, 3 H), 3,09 (t, $J=6,44$ Hz, 2 H), 5,27 (s, 2 H), 7,22 -
7,30 (m, 2 H), 7,33 (t, $J=8,50$ Hz, 2 H), 7,40 (d, $J=7,62$ Hz, 1 H), 7,62 (d, $J=8,79$
Hz, 1 H), 7,66 - 7,71 (m, 1 H), 7,76 (t, $J=7,62$ Hz, 1 H), 7,84 - 7,91 (m, 2 H),
7,94 (s, 1 H), 7,99 (dd, $J=8,50, 5,57$ Hz, 2 H), 8,35 - 8,44 (m, 2 H), 8,53 (d,

$J=4,69$ Hz, 1 H). LCEM m/z 552,29 (M+H), Tr 4,29 min., 100 % de pureza.



2-(4-Fluorofenil)-5-(5-(isobutylcarbamoyl)-2-(2-(pirrolidin-1-il)etoxi)fenil)-N-metilbenzofuran-3-carboxamida

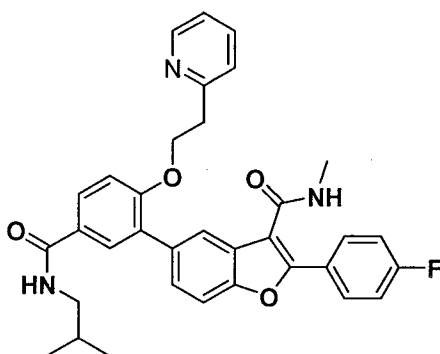
5 RMN de ^1H (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0,89 (d, $J=6,44$ Hz, 6 H), 1,64 (s ancho, 4 H), 1,80 - 1,91 (m, 1 H), 2,47 (s ancho, 4 H), 2,75 - 2,82 (m, 2 H), 2,84 (d, $J=4,10$ Hz, 3 H), 3,08 (t, $J=6,44$ Hz, 2 H), 4,16 (t, $J=5,27$ Hz, 2 H), 7,16 (d, 1 H), 7,32 (t, $J=8,79$ Hz, 2 H), 7,56 - 7,61 (m, 1 H), 7,61 - 7,66 (m, 1 H), 7,78 (s, 1 H), 7,86 (d, $J=8,20$ Hz, 1 H), 7,89 (s, 1 H), 7,98 (dd, $J=8,20, 5,27$ Hz, 2 H), 8,31 - 8,43 (m, 2 H). LCEM m/z 558,37 (M+H), Tr 3,52 min., 100 % de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(2-(piperidin-1-il)etoxi)fenil)-*N*-
metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,89 (d, $J=6,44$ Hz, 6 H), 1,32 -
1,38 (m, 2 H), 1,38 - 1,43 (m, 2 H), 1,44 - 1,52 (m, 2 H), 1,79 - 1,93 (m, 1 H),
5 2,32 - 2,45 (m, 4 H), 2,57 - 2,68 (m, 2 H), 2,84 (d, $J=4,10$ Hz, 3 H), 3,08 (t,
 $J=6,15$ Hz, 2 H), 4,10 - 4,20 (m, 2 H), 7,16 (d, $J=8,79$ Hz, 1 H), 7,32 (t, $J=8,79$
Hz, 2 H), 7,61 (c, $J=8,79$ Hz, 2 H), 7,76 (s, 1 H), 7,86 (d, $J=8,20$ Hz, 1 H), 7,89
(s, 1 H), 7,98 (dd, $J=8,20$, 5,86 Hz, 2 H), 8,31 - 8,44 (m, 2 H). LCEM m/z 572,37
($\text{M}+\text{H}$), Tr 3,89 min., 95,4 % de pureza.

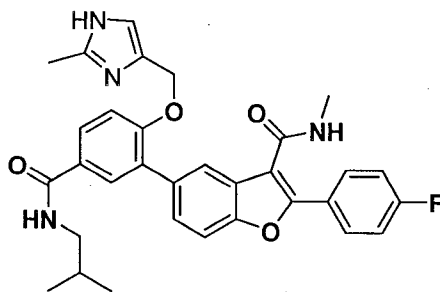
10



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(2-(piridin-2-il)etoxi)fenil)-*N*-
metilbenzofuran-3-carboxamida

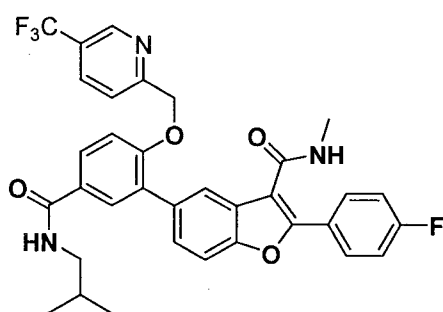
RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,88 (d, $J=6,44$ Hz, 6 H), 1,79 -
15 1,91 (m, 1 H), 2,84 (d, $J=4,69$ Hz, 3 H), 3,08 (t, $J=6,15$ Hz, 2 H), 3,21 (t, $J=6,15$
Hz, 2 H), 4,47 (t, $J=6,15$ Hz, 2 H), 7,20 (dd, $J=19,92$, 8,20 Hz, 2 H), 7,29 - 7,41
(m, 4 H), 7,50 (d, $J=8,79$ Hz, 1 H), 7,67 (s, 1 H), 7,79 - 7,91 (m, 3 H), 8,00 (dd,
 $J=8,50$, 5,57 Hz, 2 H), 8,34 (t, $J=5,57$ Hz, 1 H), 8,45 (d, $J=4,10$ Hz, 1 H), 8,51

(d, $J=4,69$ Hz, 1 H). LCEM m/z 566,34 (M+H), Tr 4,32 min., 100 % de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-((2-metil-1H-imidazol-4-il)metoxi)fenil)-N-metilbenzofuran-3-carboxamida

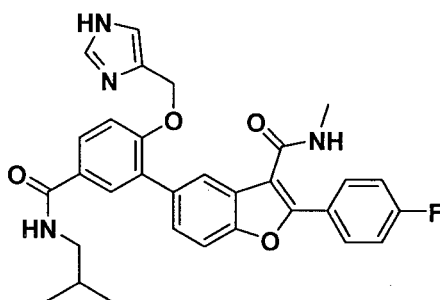
5 RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,89 (d, $J=6,44$ Hz, 6 H), 1,85 (dd, $J=12,01$, 6,74 Hz, 1 H), 2,14 - 2,38 (m, 3 H), 2,81 - 2,88 (m, 3 H), 3,04 - 3,12 (m, 2 H), 5,00 (s, 1 H), 6,91 - 7,03 (m, 1 H), 7,32 (t, $J=9,08$ Hz, 2 H), 7,50 - 7,68 (m, 2 H), 7,70 (d, $J=6,44$ Hz, 1 H), 7,79 (d, $J=4,10$ Hz, 2 H), 7,86 (d, $J=11,72$ Hz, 1 H), 7,94 (s, 1 H), 7,96 - 8,04 (m, 1 H), 8,34 (t, $J=5,57$ Hz, 1 H), 8,40 (d, $J=4,69$ Hz, 1 H). LCEM m/z 555,34 (M+H), Tr 3,57 min., 93,3 % de pureza.



15 2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-((5-(trifluorometil)piridin-2-il)metoxi)

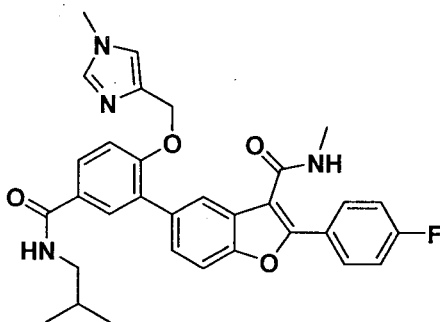
fenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0,90 (d, $J=7,03$ Hz, 6 H), 1,82 -
 1,92 (m, 1 H), 2,79 (d, $J=4,69$ Hz, 3 H), 3,09 (t, $J=6,15$ Hz, 2 H), 5,39 (s, 2 H),
 7,27 (d, $J=8,79$ Hz, 1 H), 7,34 (t, $J=8,50$ Hz, 2 H), 7,62 (t, $J=8,50$ Hz, 2 H), 7,71
 5 (d, $J=8,20$ Hz, 1 H), 7,89 (d, $J=8,20$ Hz, 1 H), 7,92 (s, 1 H), 7,95 - 8,02 (m, 3 H),
 8,16 (d, $J=8,20$ Hz, 1 H), 8,39 (t, $J=5,57$ Hz, 1 H), 8,44 (d, $J=4,69$ Hz, 1 H), 8,90
 (s, 1 H). LCEM m/z 620,32 (M+H), Tr 5,09 min., 97,9 % de pureza.



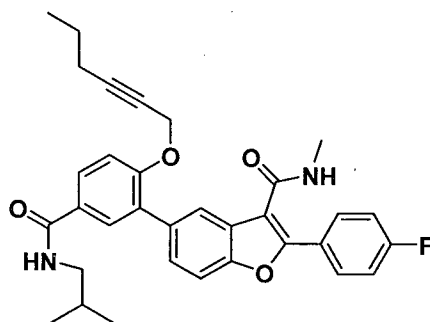
10 5-(2-((1*H*-imidazol-4-il)metoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-
 metilbenzofuran-3-carboxamida

LCEM m/z 541,29 (M+H), Tr 3,51 min., 100 % de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-((1-metil-1*H*-imidazol-4-il)metoxi)fenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0,88 (d, $J=6,44$ Hz, 6 H), 1,83 (dt, $J=13,48$, 6,74 Hz, 1 H), 2,84 (d, $J=4,69$ Hz, 3 H), 3,06 (t, $J=6,44$ Hz, 2 H),
 5 3,63 (s, 3 H), 3,88 (s, 2 H), 7,00 (s, 1 H), 7,32 (t, $J=8,79$ Hz, 2 H), 7,55 (d, $J=8,20$ Hz, 1 H), 7,63 - 7,70 (m, 3 H), 7,74 (d, $J=14,65$ Hz, 2 H), 7,94 (s, 1 H), 7,99 (dd, $J=8,20$, 5,27 Hz, 2 H), 8,23 (s, 1 H), 8,39 (d, $J=4,10$ Hz, 1 H). LCEM m/z 555,35 (M+H), Tr 4,11 min., 100 % de pureza.

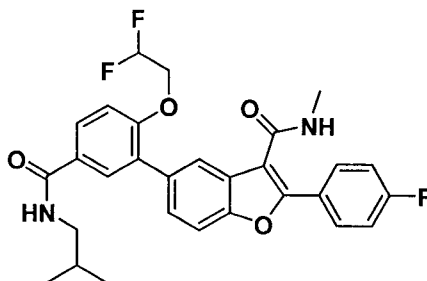


10

2-(4-Fluorofenil)-5-(2-(hex-2-iniloxi)-5-(isobutilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, DMSO- d_6 /CDCl $_3$) δ ppm 0,83 - 0,97 (m, 9 H), 1,36 - 1,48 (m, 2 H), 1,82 - 1,90 (m, 1 H), 2,16 (t, $J=6,74$ Hz, 2 H), 2,84 (d, $J=4,69$ Hz, 3 H),
 15 3,09 (t, $J=6,44$ Hz, 2 H), 4,82 (s ancho, 2 H), 7,23 (d, $J=8,20$ Hz, 1 H), 7,29 - 7,33 (m, 2 H), 7,51 (d, $J=8,79$ Hz, 1 H), 7,65 (d, $J=8,20$ Hz, 1 H), 7,72 (s, 1 H), 7,84 - 7,91 (m, 2 H), 7,99 (dd, $J=8,20$, 5,27 Hz, 2 H), 8,36 (t, $J=5,57$ Hz, 1 H), 8,40 (d, $J=4,10$ Hz, 1 H). LCEM m/z 541,35 (M+H), Tr 5,20 min., 95,3 % de

pureza.



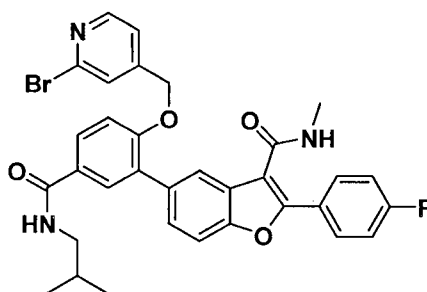
5-(2-(2,2-Difluoroetoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-

5

metilbenzofuran-3-carboxamida

RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,89 (d, $J=6,44$ Hz, 6 H), 1,86 (dt, $J=13,48, 6,74$ Hz, 1 H), 2,84 (d, $J=4,10$ Hz, 3 H), 3,09 (t, $J=6,44$ Hz, 2 H), 4,39 (td, $J=14,35, 2,93$ Hz, 2 H), 6,15 - 6,40 (m, 1 H), 7,23 (d, $J=8,79$ Hz, 1 H), 7,32 (t, $J=8,79$ Hz, 2 H), 7,56 (d, $J=8,79$ Hz, 1 H), 7,66 (d, $J=8,20$ Hz, 1 H), 7,79 (s, 1 H), 7,89 (d, $J=8,79$ Hz, 1 H), 7,93 (s, 1 H), 7,99 (dd, $J=8,20, 5,27$ Hz, 2 H), 8,35 - 8,44 (m, 2 H). LCEM m/z 525,27 ($\text{M}+\text{H}$), Tr 4,44 min., 97,4 % de pureza.

10

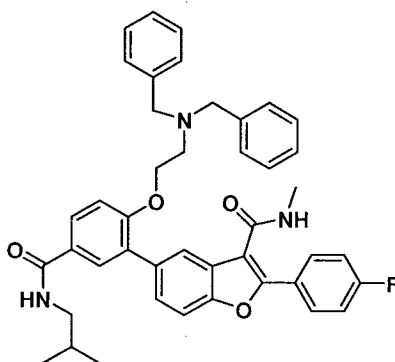


5-(2-((2-Bromopiridin-4-il)metoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-

15

metilbenzofuran-3-carboxamida

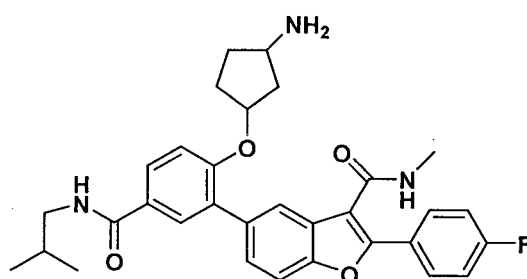
RMN de ^1H (600 MHz, $\text{DMSO-d}_6/\text{CDCl}_3$) δ ppm 0,89 (d, $J=6,44$ Hz, 6 H), 1,81 - 1,91 (m, 1 H), 2,82 (d, $J=4,69$ Hz, 3 H), 3,09 (t, $J=6,15$ Hz, 2 H), 5,27 (s, 2 H), 7,21 (d, $J=8,79$ Hz, 1 H), 7,33 (t, $J=8,50$ Hz, 2 H), 7,37 (d, $J=4,69$ Hz, 1 H), 7,54 (s, 1 H), 7,61 (d, $J=8,79$ Hz, 1 H), 7,70 (d, $J=8,79$ Hz, 1 H), 7,83 (s, 1 H), 7,89 (d, $J=8,79$ Hz, 1 H), 7,94 (s, 1 H), 7,99 (dd, $J=8,20, 5,27$ Hz, 2 H), 8,32 (d, $J=5,27$ Hz, 1 H), 8,38 (d, $J=4,69$ Hz, 2 H). LCEM m/z 630,26 (M+H), Tr 4,71 min., 98,4 % de pureza.



10 5-(2-(2-(Dibencilamino)etoxi)-5-(isobutylcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Los datos de LC/EM de la purificación posterior se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5 μm C18, 4,6 x 15 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%),

en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-
5 100% de B (B = metanol calidad HPLC al 95% / bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX400.
10 RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,96 (d, $J = 6,53$ Hz, 6 H), 1,83 - 2,07 (m, 1 H), 2,81 (t, $J = 5,40$ Hz, 2 H), 2,90 (s, 3 H), 3,19 (d, $J = 7,03$ Hz, 2 H), 3,53 (s, 4 H), 4,10 (t, $J = 5,40$ Hz, 2 H), 6,99 (d, $J = 8,53$ Hz, 1 H), 7,14 (dd, $J = 5,52$, 3,01 Hz, 2 H), 7,17 - 7,23 (m, 8 H), 7,23 - 7,29 (m, 2 H), 7,41 - 7,47 (m, 1 H), 7,48 - 7,55 (m, 1 H), 7,75 - 7,82 (m, 2 H), 7,84 (d, $J = 2,26$ Hz, 1 H), 7,92 (dd, $J = 8,66$, 5,40 Hz, 2 H). LCEM m/z 684,40 ($\text{M}+\text{H}$), Tr = 1,897min. Tr de HPLC
15 14,159 min. (XBridge phenyl C18), 100 % de pureza.



5-(2-(3-Aminociclopentiloxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-

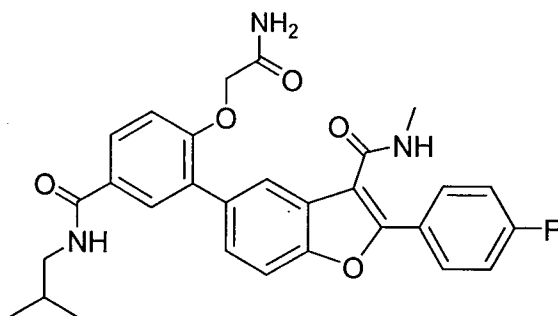
metilbenzofuran-3-carboxamida

Los datos de LC/EM de la purificación posterior se obtuvieron en una LC analítica Shimadzu / Plataforma de LC MICROMASS® (ESI+/-) a 220nm usando el siguiente conjunto de condiciones: Columna Luna 10µm C18, 3,0 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 95%/ acetato amónico 10mM/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / acetato amónico 10mM/ acetonitrilo calidad HPLC al 5%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 5 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna a Gemini C18 3,0µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX400. RMN de ¹H (400 MHz, THF-d₈) δ ppm 0,93 (d, J = 6,78 Hz, 6 H), 1,77 - 1,97 (m, 3 H), 2,04 - 2,19 (m, 2 H), 2,19 - 2,32 (m, 2 H), 2,90 (d, J = 4,52 Hz, 3 H), 3,17 (t, J = 6,40 Hz, 2 H), 3,69 - 3,82 (m, 2 H), 7,04 (d, J = 8,53 Hz, 1 H), 7,21 (t, J = 8,78 Hz, 2 H), 7,41 - 7,50 (m, 1 H), 7,50 - 7,56 (m, 1 H), 7,60 - 7,72 (m, 2 H), 7,81 (dd, J = 8,66, 2,13 Hz, 1 H), 7,85 (d, J = 1,25 Hz, 1 H), 7,90 (d, J = 2,01 Hz, 1 H), 7,99 - 8,10 (m, 2 H), 8,42 (s ancho, 2 H). Tr de LCEM 1,937min., m/z 542,34 (M-H) y

m/z 544,29 (M+H). Tr de HPLC 6,870 min. (Sunfire C18), 99,1 % de pureza y 11,133 min. (Gemini C18), 98,9 % de pureza.

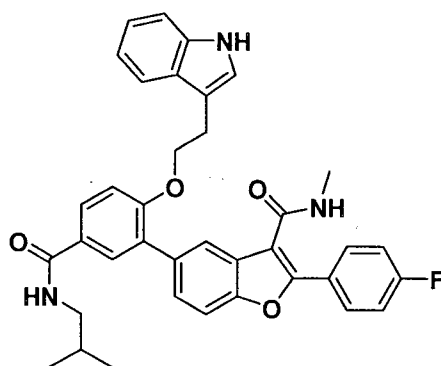
Se llevó a cabo una síntesis alternativa de estos análogos unidos por éter usando estructuras plantilla de fenol en DMF con bromuros de alquilo y DBU. A un vial de 3,54 ml se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(isobutilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida (46,0 mg, 0,1 mmol), DMF (2 ml), 4,0 equivalentes de DBU, 1,8-diazabicyclo[5,4,0]undec-7-eno (0,4mmol) y 3,0 equivalentes (0,3 mmol) de bromuro de alquilo. Los viales se cerraron y agitaron a 75 °C en un baño seco. Tras completarse la reacción, los productos brutos se concentraron, se diluyeron con 2ml de acetonitrilo y se purificaron usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 4,6 x 100mm a un gradiente de 30-100% de B y un caudal de 40 ml/minutos durante 8 minutos con un mantenimiento de 10 minutos. Los productos deseados se evaporaron hasta sequedad en un Savant SPEEDVAC® durante la noche obteniendo 25-60% de rendimiento de los éteres deseados como polvos. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX400. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters

Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/TFA al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto.



5-(2-(2-Amino-2-oxoetoxy)-5-(isobutylcarbamoyl)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

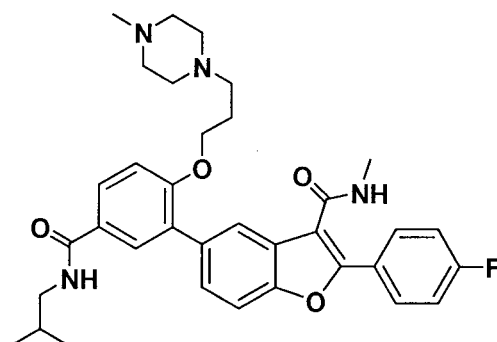
RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,86 - 1,02 (m, 6 H), 1,81 - 1,99 (m, 1 H),
 5 2,91 (d, $J = 4,77$ Hz, 3 H), 3,06 - 3,29 (m, 2 H), 4,46 (s, 2 H), 6,43 (s ancho, 1 H), 6,69 (s ancho, 1 H), 7,08 (d, $J = 8,78$ Hz, 1 H), 7,16 - 7,27 (m, 2 H), 7,53 (s ancho, 1 H), 7,56 - 7,62 (m, 2 H), 7,86 (dd, $J = 8,53, 2,26$ Hz, 1 H), 7,93 (d, $J = 2,26$ Hz, 1 H), 7,97 (s, 1 H), 8,09 - 8,19 (m, 2 H). LCEM m/z 518,36 (M+H), Tr 1,880 min. HPLC (Sunfire C18) Tr 8,209min, 100% de pureza y (XBridge
 10 phenyl C18) Tr 11,254 min., 99,8 % de pureza.



5-(2-(2-(1*H*-Indol-3-il)etoxy)-5-(isobutylcarbamoyl)fenil)-2-(4-fluorofenil)-*N*-

metilbenzofuran-3-carboxamida

RMN de ^1H (500 MHz, CD_3OD) δ ppm 0,92 - 1,04 (m, 6 H), 1,87 - 2,03 (m, 1 H), 2,95 (s, 3 H), 3,15 - 3,24 (m, 4 H), 4,37 (t, $J = 6,71$ Hz, 2 H), 6,94 (t, $J = 7,48$ Hz, 1 H), 6,98 (s, 1 H), 7,07 (t, $J = 7,63$ Hz, 1 H), 7,18 (d, $J = 8,55$ Hz, 1 H),
 5 7,24 - 7,36 (m, 3 H), 7,44 - 7,50 (m, 2 H), 7,51 - 7,56 (m, 1 H), 7,84 (td, $J = 4,27, 2,44$ Hz, 2 H), 7,88 (d, $J = 2,14$ Hz, 1 H), 7,94 - 8,03 (m, 2 H). LCEM m/z 604,31 (M+H), Tr 2,621 min. Tr de HPLC 11,054 min. (Sunfire C18), 98,1 % de pureza y 12,561 min. (XBridge phenyl C18), 97,8 % de pureza.



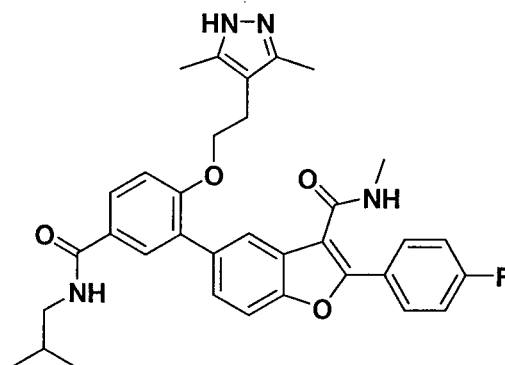
10

5-(2-(2-(1H-Indol-3-il)etoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-

metilbenzofuran-3-carboxamida

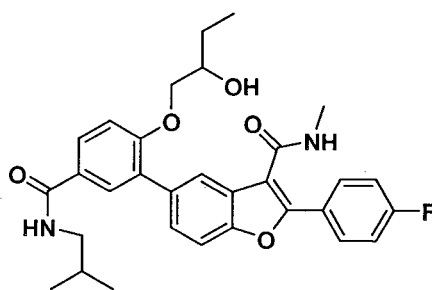
RMN de ^1H (500 MHz, CD_3OD) δ ppm 0,87 - 1,03 (m, 6 H), 1,83 - 2,00 (m, 1 H), 2,17 (dd, $J = 9,77, 5,49$ Hz, 2 H), 2,81 - 2,90 (s, 3 H), 2,90 - 3,00 (s, 3 H), 3,12 -
 15 3,25 (m, 4 H), 3,42 (s ancho, 8 H), 4,21 (t, $J = 5,65$ Hz, 2 H), 7,17 (d, $J = 8,85$ Hz, 1 H), 7,22 - 7,33 (m, 2 H), 7,53 (dd, $J = 8,55, 1,83$ Hz, 1 H), 7,65 (d, $J = 8,24$ Hz, 1 H), 7,86 (td, $J = 8,47, 2,29$ Hz, 3 H), 7,89 - 7,96 (m, 2 H). LCEM m/z 601,36 (M+H), Tr 1,375 min. Tr de HPLC 6,010 min. (Sunfire C18), 99,3% de

pureza y 11,793 min. (XBridge phenyl C18), 98,4% de pureza.



5-*(2-(2-(3,5-Dimetil-1H-pirazol-4-il)etoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida*

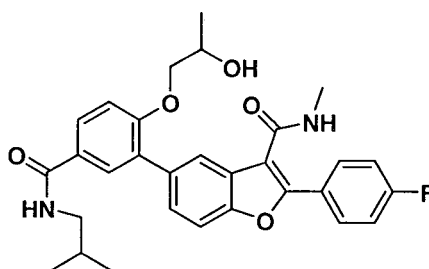
RMN de ^1H (500 MHz, CD_3OD) δ ppm 0,89 - 1,01 (m, 6 H), 1,86 - 1,98 (m, 1 H), 2,02 (s, 6 H), 2,90 (t, $J=5,95$ Hz, 2 H), 2,95 (s, 3 H), 3,14 - 3,22 (m, 2 H), 4,24 (t, $J=5,95$ Hz, 2 H), 7,18 (d, $J=8,55$ Hz, 1 H), 7,24 - 7,33 (m, 2 H), 7,37 (dd, $J=8,39$, 1,68 Hz, 1 H), 7,59 (d, $J=8,55$ Hz, 1 H), 7,68 (d, $J=1,83$ Hz, 1 H), 7,80 (d, $J=2,44$ Hz, 1 H), 7,85 (dd, $J=8,70$, 2,29 Hz, 1 H), 7,93 - 8,02 (m, 2 H). LCEM m/z 583,32 ($\text{M}+\text{H}$), Tr 1,698 min. Tr de HPLC 7,270 min. (Sunfire C18), 92,6 % de pureza y 11,994 min. (XBridge phenyl C18), 92,0 % de pureza.



2-(4-Fluorofenil)-5-(2-(2-hidroxibutoxi)-5-(isobutilcarbamoil)fenil)-*N*-
metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,93 - 1,15 (m, 9 H), 1,45 - 1,61 (m, 1 H),
1,61 - 1,77 (m, 1 H), 2,01 (dt, $J=13,55$, 6,78 Hz, 1 H), 3,03 (s, 3 H), 3,27 (d,
5 $J=7,03$ Hz, 2 H), 3,81 - 3,90 (m, 1 H), 4,10 (d, $J=5,02$ Hz, 2 H), 7,24 (d, $J=8,78$
Hz, 1 H), 7,28 - 7,38 (m, 2 H), 7,62 - 7,72 (m, 2 H), 7,91 (dd, $J=8,53$, 2,26 Hz, 1
H), 7,96 (d, $J=2,01$ Hz, 2 H), 8,00 - 8,08 (m, 2 H). LCEM m/z 533,30 ($\text{M}+\text{H}$), Tr
2,238 min. Tr de HPLC 11,383 min. (Sunfire C18), 95,4 % de pureza y 11,896
min. (XBridge phenyl C18), 98,5% de pureza.

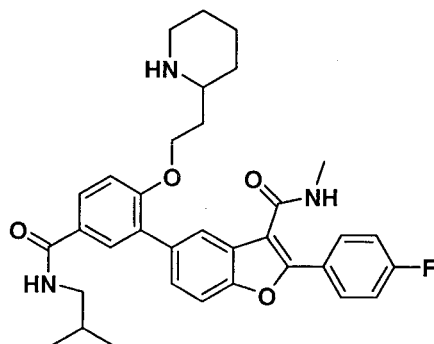
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2-(4-Fluorofenil)-5-(2-(2-hidroxipropoxi)-5-(isobutilcarbamoil)fenil)-*N*-
metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,04 (d, $J=6,53$ Hz, 6 H), 1,27 (d, $J=6,27$
15 Hz, 3 H), 1,93 - 2,08 (m, 1 H), 3,03 (s, 3 H), 3,27 (d, $J=7,03$ Hz, 2 H), 3,97 -
4,15 (m, 3 H), 7,23 (d, $J=8,53$ Hz, 1 H), 7,32 (t, $J=8,91$ Hz, 2 H), 7,67 (d, $J=1,00$
Hz, 2 H), 7,86 - 7,93 (m, 1 H), 7,96 (d, $J=2,26$ Hz, 2 H), 8,03 (dd, $J=9,04$, 5,27
Hz, 2 H). LCEM m/z 519,28 ($\text{M}+\text{H}$), Tr 2,100 min. Tr de HPLC 9,279 min.
(Sunfire C18), 98,4 % de pureza y 11,674 min. (XBridge phenyl C18), 98,8% de

pureza.

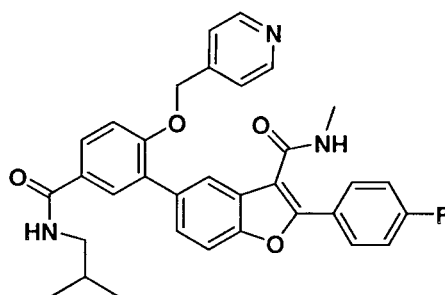


2-(4-Fluorofenil)-5-(5-(isobutylcarbamoyl)-2-(2-(piperidin-2-yl)etoxy)fenil)-N-

5

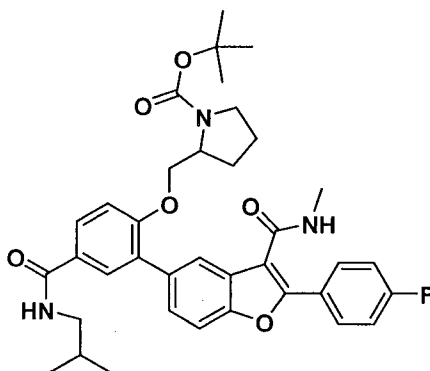
metilbenzofuran-3-carboxamida

RMN de ^1H (500 MHz, CD_3OD) δ ppm 0,92 - 1,04 (m, 6 H), 1,32 - 1,48 (m, 2 H), 1,59 (d, $J=14,34$ Hz, 1 H), 1,78 (s ancho, 2 H), 1,88 - 2,06 (m, 3 H), 2,11 - 2,25 (m, 1 H), 2,85 (m, 1 H), 2,96 (s, 3 H), 3,11 - 3,27 (m, 4 H), 4,17 - 4,37 (m, 2 H), 7,23 (d, $J=8,85$ Hz, 1 H), 7,26 - 7,36 (m, 2 H), 7,55 (dd, $J=8,55$, 1,83 Hz, 1 H), 7,70 (d, $J=8,55$ Hz, 1 H), 7,83 - 8,01 (m, 5 H). LCEM m/z 572,33 ($\text{M}+\text{H}$), Tr 1,663 min. Tr de HPLC 7,638 min. (Sunfire C18), 98,8 % de pureza y 12,003 min. (XBridge phenyl C18), 97,3 % de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(piridin-4-ilmetoxi)fenil)-*N*-
metilbenzofuran-3-carboxamida

RMN de ^1H (500 MHz, CD_3OD) δ ppm 0,98 (d, $J=6,71$ Hz, 6 H), 1,83 - 2,07 (m, 1 H), 2,92 (s, 3 H), 3,22 (d, $J=7,02$ Hz, 2 H), 5,54 (s, 2 H), 7,19 - 7,39 (m, 3 H),
5 7,62 (dd, $J=8,55, 1,53$ Hz, 1 H), 7,65 - 7,72 (m, 1 H), 7,88 - 7,99 (m, 5 H), 8,01 (d, $J=6,41$ Hz, 2 H), 8,79 (d, $J=6,71$ Hz, 2 H). LCEM m/z 552,28 (M+H), Tr 1,600 min. Tr de HPLC 6,831 min. (Sunfire C18), 99,5 % de pureza y 11,871 min. (XBridge phenyl C18), 99,3% de pureza.

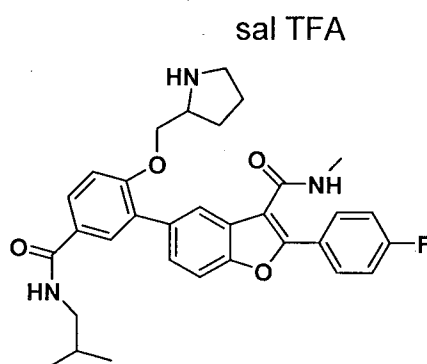


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2-((2-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-
(isobutilcarbamoil)fenoxi)metil)pirrolidin-1-carboxilato de *terc*-butilo

RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,04 (d, $J=6,53$ Hz, 6 H), 1,48 (s, 9 H),
1,65 - 1,84 (m, 2 H), 1,91 - 2,12 (m, 3 H), 3,02 (s, 3 H), 3,06 - 3,21 (m, 1 H),
15 3,27 (d, $J=7,28$ Hz, 2 H), 3,29 - 3,34 (m, 1 H), 4,09 (s ancho, 1 H), 4,18 - 4,30 (m, 2 H), 7,26 (d, $J=7,53$ Hz, 1 H), 7,29 - 7,37 (m, 2 H), 7,58 (s ancho, 1 H), 7,68 (d, $J=8,53$ Hz, 1 H), 7,82 - 7,96 (m, 3 H), 7,99 - 8,08 (m, 2 H). LCEM m/z

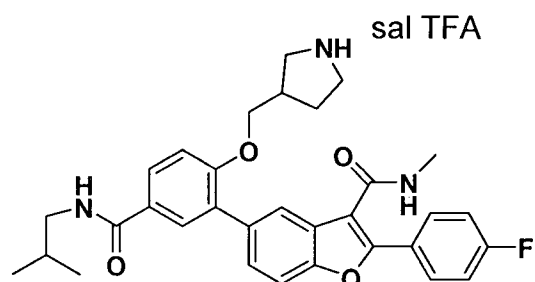
666,32 (M+Na), Tr 2,716 min. Tr de HPLC 11,711 min. (Sunfire C18), 98,4 % de pureza y 12,663 min. (XBridge phenyl C18), 98,8 % de pureza.



5 2-(4-Fluorofenil)-5-(5-(isobutylcarbamoyl)-2-(pirrolidin-2-ilmetoxi)fenil)-N-metilbenzofuran-3-carboxamida, TFA.

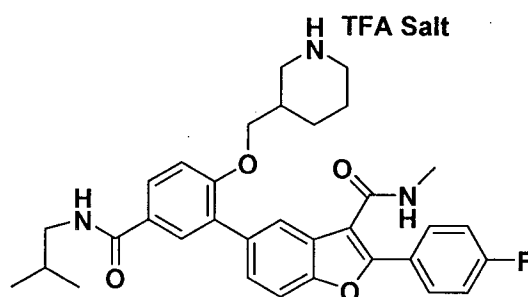
A un matraz de fondo redondo de 10 ml se añadió dicloroetano (1 ml), 2-((2-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)-4-(isobutylcarbamoyl)fenoxi)metil)pirrolidin-1-carboxilato de *terc*-butilo (10,2 mg, 15,8 μ mol) y TFA, ácido trifluoroacético, (800 μ l). La solución se agitó durante 30 minutos a temperatura ambiente, luego se evaporó en el evaporador rotatorio. El producto se diluyó con dicloroetano y evaporó una vez más dando un sólido blanco (99% de rendimiento). RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,04 (d, $J=6,53$ Hz, 6 H), 1,93 - 2,12 (m, 4 H), 2,24 - 2,37 (m, 1 H), 3,00 (s, 3 H), 3,13 - 3,22 (m, 1 H), 3,25 - 3,30 (m, 2 H), 3,30 - 3,36 (m, 1 H), 4,10 (dd, $J=7,15$, 2,89 Hz, 1 H), 4,29 (dd, $J=10,67$, 7,15 Hz, 1 H), 4,51 (dd, $J=10,54$, 3,26 Hz, 1 H), 7,28 (d, $J=8,53$ Hz, 1 H), 7,35 (t, $J=8,78$ Hz, 2 H), 7,60 (dd, $J=8,53$, 1,51 Hz, 1 H), 7,73 (d, $J=8,53$ Hz, 1 H), 7,92 - 8,08 (m, 5 H). LCEM m/z 544,22 (M+H),

Tr 1,577 min. Tr de HPLC 6,775 min. (Sunfire C18), 99,7 % de pureza y 11,724 min. (XBridge phenyl C18), 100 % de pureza.



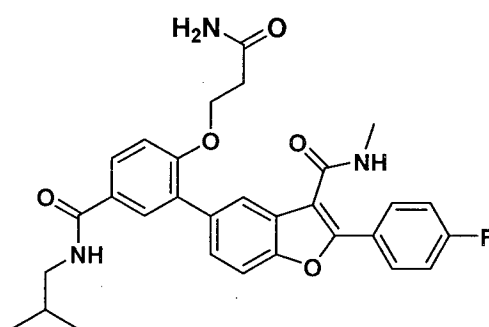
5 2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(pirrolidin-3-ilmetoxi)fenil)-N-metilbenzofuran-3-carboxamida, TFA

RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,93 (d, $J=6,78$ Hz, 6 H), 1,77 - 1,98 (m, 2 H), 2,10 (dd, $J=13,05$, 6,78 Hz, 1 H), 2,76 - 2,86 (m, 1 H), 2,88 - 2,98 (m, 3 H), 3,18 (t, $J=6,40$ Hz, 5 H), 3,55 (s ancho, 1 H), 4,02 - 4,26 (m, 2 H), 7,08 (d, $J=8,53$ Hz, 1 H), 7,23 (t, $J=8,78$ Hz, 2 H), 7,48 (dd, $J=8,53$, 1,76 Hz, 1 H), 7,59 (d, $J=8,53$ Hz, 1 H), 7,70 (t, $J=5,77$ Hz, 1 H), 7,80 - 7,89 (m, 2 H), 7,94 (dd, $J=9,79$, 1,76 Hz, 2 H), 7,99 (dd, $J=8,91$, 5,40 Hz, 2 H). Tr de HPLC 6,130 min. (Sunfire C18), 98,9 % de pureza y 10,184 min. (XBridge phenyl C18), 98,6 % de pureza. LCEM m/z 544,18 ($M+H$), Tr 1,557min.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(piperidin-3-ilmetoxi)fenil)-*N*-metilbenzofuran-3-carboxamida, TFA

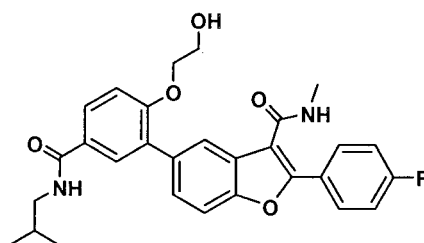
RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,93 (d, $J=6,78$ Hz, 6 H), 1,40 - 1,57 (m, 1 H), 1,75 - 2,00 (m, 4 H), 2,33 (s ancho, 1 H), 2,80 - 3,00 (m, 5 H), 3,18 (t, $J=6,40$ Hz, 2 H), 3,32 (d, $J=12,05$ Hz, 1 H), 3,45 (d, $J=10,79$ Hz, 1 H), 3,90 - 4,12 (m, 2 H), 7,03 (d, $J=8,53$ Hz, 1 H), 7,22 (t, $J=8,78$ Hz, 2 H), 7,47 (dd, $J=8,53, 1,51$ Hz, 1 H), 7,58 (d, $J=8,53$ Hz, 1 H), 7,71 (t, $J=5,65$ Hz, 1 H), 7,75 - 7,86 (m, 2 H), 7,92 (s, 2 H), 8,01 (dd, $J=8,78, 5,52$ Hz, 2 H). LCEM m/z 558,20 (M+H), Tr 1,595 min. Tr de HPLC 6,443 min. (Sunfire C18), 99,2 % de pureza y 10,418 min. (XBridge phenyl C18), 99,2 % de pureza.



5-(2-(3-Amino-3-oxopropoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,88 - 0,97 (m, 6 H), 1,77 (dt, $J=6,71$, 3,29 Hz, 1 H), 1,89 (dt, $J=13,36$, 6,74 Hz, 1 H), 2,65 (s ancho, 1 H), 2,96 (s, 3 H), 3,10 - 3,21 (m, 3 H), 3,60 - 3,65 (m, 1 H), 6,90 (d, $J=8,28$ Hz, 1 H), 7,16 - 7,25 (m, 2 H), 7,48 - 7,56 (m, 1 H), 7,66 - 7,73 (m, 2 H), 7,73 - 7,80 (m, 2 H), 7,84 (t, $J=5,40$ Hz, 1 H), 7,89 (s ancho, 1 H), 7,92 - 8,03 (m, 3 H). Tr de LCEM 1,835min., m/z 532,26 (M+H). Tr de HPLC 7,465 min. (Sunfire C18), 100 % de pureza y 10,929 min. (XBridge phenyl C18), 92,9 % de pureza.



2-(4-Fluorofenil)-5-(2-(2-hidroxi-5-(isobutilcarbamoil)fenil)-N-

metilbenzofuran-3-carboxamida

A un vial pequeño de tapa a rosca se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(isobutilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida (92 mg, 0,2 mmol) en DMF (4 ml), (2-Bromoetoxi)-*terc*-butildimetilsilano (0,129 ml, 0,600 mmol), y DBU (0,121 ml, 0,800 mmol). El vial se tapó y se agitó a 80 °C durante la noche. El DMF se eliminó en una corriente de nitrógeno dando un aceite color castaño que se recogió en 6 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/acetato amónico 10mM

donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10mM con una columna PHENOMENEX® Luna 10µm C18 30x100mm a un gradiente de 40-100% de B y un caudal de 30 ml/minutos durante 8 minutos

5 con un mantenimiento de 10 minutos. El disolvente se eliminó en el rotovap dando 44 mg del alcohol protegido con TBS como un aceite incoloro transparente. LCEM *m/z* 619,47 (M+H), Tr 3,123 min., 96% de pureza. Al alcohol protegido con TBS se añadieron entonces 2,5 ml de tetrahidrofurano junto con 2 eq. de solución 1 M de HCl (0,14 mmol, 140 µl). La mezcla se agitó

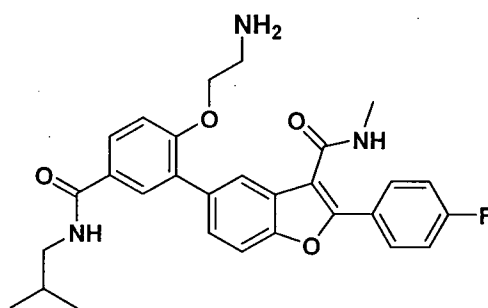
10 durante 1 hora a temperatura ambiente. La mezcla de reacción se transfirió a un embudo de separación, se diluyó con acetato de etilo, se lavó con bicarbonato sódico, salmuera y se secó sobre sulfato de magnesio. El disolvente orgánico se evaporó y el producto se colocó a vacío. El producto bruto se diluyó con 2ml de acetonitrilo y se purificó usando una HPLC

15 preparativa Shimadzu que emplea acetonitrilo/agua/acetato amónico donde el disolvente A era acetonitrilo al 5% / H₂O al 95% / acetato amónico 10mM y el disolvente B era H₂O al 5% / acetonitrilo al 95% / acetato amónico 10mM con una columna XBridge C18 5µm OBD 19 x 100mm a un gradiente de 30-100% de B y un caudal de 20 ml/minutos durante 7 minutos con un mantenimiento de

20 13 minutos. Se obtuvieron, después de evaporar el disolvente 18,3 mg de un sólido blanco (17% de rendimiento, 2 etapas). RMN de ¹H (400 MHz, THF-d₈) δ ppm 0,93 (d, *J* = 6,78 Hz, 6 H), 1,80 - 1,98 (m, 1 H), 2,91 (d, *J* = 4,77 Hz, 3 H),

3,13 - 3,23 (m, 2 H), 3,79 (t, $J = 4,89$ Hz, 2 H), 4,10 (t, $J = 4,89$ Hz, 2 H), 7,08 (d, $J = 8,53$ Hz, 1 H), 7,21 (t, $J = 8,78$ Hz, 2 H), 7,52 (s ancho, 1 H), 7,52 - 7,54 (m, 2 H), 7,59 (s ancho, 1 H), 7,84 (dd, $J = 8,53, 2,26$ Hz, 1 H), 7,92 (d, $J = 2,26$ Hz, 1 H), 8,02 (s, 1 H), 8,09 - 8,20 (m, 2 H). LCEM m/z 505,36 (M+H), Tr 2,013min. Tr de HPLC 8,901 min. (Sunfire C18), 92,5 % de pureza y 11,479 min. (XBridge phenyl C18), 92,0 % de pureza. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5 μ m C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5 μ m 4,6 x 150mm que emplea agua/acetonitrilo/TFA al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm que emplea agua/metanol/ bicarbonato

amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 5 ml/minuto.



5-(2-(2-Aminoetoxy)-5-(isobutilcarbamoi)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 10 A un vial de 3,54 ml se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(isobutilcarbamoi)fenil)-N-metilbenzofuran-3-carboxamida (92,0 mg, 0,20 mmol) en 3 ml de DMF junto con 2-(2-bromoetil) isoindolin-1,3-diona (152 mg, 0,600 mmol) y DBU (0,120 ml, 0,800 mmol). El vial se tapó y se agitó a 75 °C durante la noche. La mezcla de reacción bruta se evacuó entonces casi hasta
- 15 sequedad, se recogió en 6 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido

trifluoroacético al 0,1% con una columna Waters Sunfire 5 μ m C18 30x100mm a un gradiente de 40-100% de B y un caudal de 40 ml/minutos durante 10 minutos con un mantenimiento de 10 minutos dando 5-(2-(2-(1,3-dioxoisindolin-2-il)etoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida como un sólido blanco (30 mg, 23% de rendimiento). RMN de ^1H (400 MHz, DMF- d_7) δ ppm 0,93 (d, $J=6,78$ Hz, 6 H), 1,86 - 1,99 (m, 1 H), 2,97 (d, $J=4,77$ Hz, 3 H), 3,14 - 3,26 (m, 2 H), 4,06 (t, $J=5,90$ Hz, 2 H), 4,47 (t, $J=5,90$ Hz, 2 H), 7,33 (d, $J=9,29$ Hz, 1 H), 7,36 - 7,49 (m, 4 H), 7,74 - 7,86 (m, 5 H), 7,97 - 8,02 (m, 2 H), 8,11 - 8,17 (m, 2 H), 8,20 (d, $J=4,27$ Hz, 1 H), 8,42 (s, 1 H). LCEM m/z 634,25 (M+H), Tr 2,408 min. Tr de HPLC 9,339 min. (Sunfire C18), 100 % de pureza y 11,696 min. (Gemini C18), 98,9 % de pureza. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5 μ m C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5 μ m 4,6 x 150mm que emplea agua/acetonitrilo/TFA al 0,1% con un gradiente de 30-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad

HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1% / acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica

5 Shimadzu con una columna Waters XBridge phenyl C18 3 μ m 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 30-100% de B (B = metanol calidad HPLC al 95% / bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un

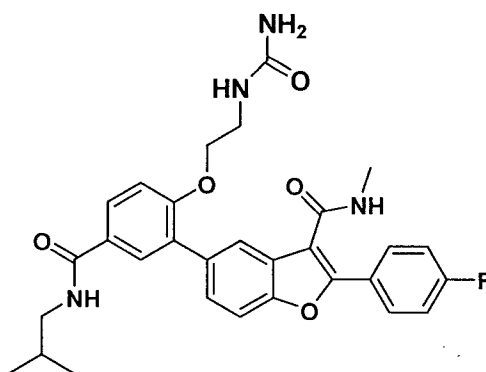
10 mantenimiento de 10 minutos a un caudal de 1 ml/minuto. A un matraz de fondo redondo de 100 ml provisto de un condensador de reflujo se añadió 5-(2-(2-(1,3-dioxoisindolin-2-il)etoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (26,4 mg, 0,042 mmol) en metanol y solución de hidrazina anhidra (1,308 μ l, 0,042 mmol) (Aldrich, 215155-50G). El matraz

15 se colocó en un baño de aceite previamente equilibrado y se llevó a reflujo durante 2 horas. El producto bruto se concentró en el rotovap para eliminar el metanol, se diluyó con diclorometano, se lavó con una solución de hidróxido sódico 0,5M y se extrajo. El disolvente se eliminó y el producto bruto se purificó usando la HPLC preparativa Shimadzu que emplea acetonitrilo/agua/TFA al

20 0,1% citada antes con un gradiente de 20-100% de B dando (13 mg, 58%) de un sólido blanco. RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,94 (d, $J=6,78$ Hz, 6 H), 1,91 (dt, $J=13,55, 6,78$ Hz, 1 H), 2,91 (s, 3 H), 3,18 (d, $J=7,28$ Hz, 2 H), 3,33

(t, $J=5,02$ Hz, 2 H), 4,30 (t, $J=5,14$ Hz, 2 H), 7,21 (d, $J=8,78$ Hz, 1 H), 7,26 (t, $J=8,78$ Hz, 2 H), 7,50 - 7,59 (m, 1 H), 7,60 - 7,68 (m, 1 H), 7,81 - 8,00 (m, 5 H). LCEM m/z 504,31 (M+H), Tr 1,538 min. Tr de HPLC 6,435 min. (Sunfire C18), 97,1 % de pureza y 11,376 min. (XBridge phenyl C18), 100 % de pureza.

5

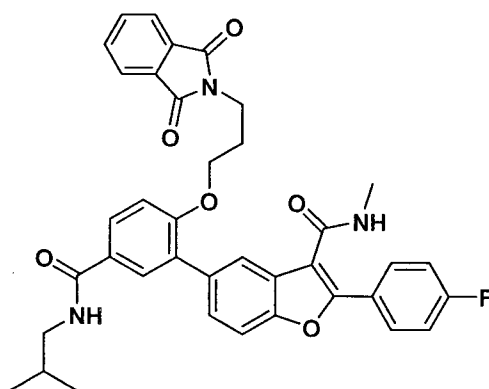


2-(4-Fluorofenil)-5-(5-(isobutylcarbamoyl)-2-(2-ureidoetoxy)fenil)-N-metilbenzofuran-3-carboxamida

A un vial de 3,54 ml se añadió 5-(2-(2-aminoetoxy)-5-(isobutylcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (22,7 mg, 0,045 mmol) en etanol (2 ml) junto con agua (0,667 ml) y cianato potásico (5,34 μ l, 0,135 mmol). El vial se selló y la mezcla se calentó hasta 80°C con agitación durante 24 horas. Se añadieron 3 equivalentes más de cianato potásico a la mezcla de reacción y el vial se volvió a tapar y calentar durante 3 días. La mezcla de reacción bruta se evaporó, se diluyó con acetonitrilo, se filtró y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido

trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90% / ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 30x100mm a un gradiente de 30-100% de B y un caudal de 40 ml/minutos durante 8 minutos con un mantenimiento de 6 minutos. El disolvente se evaporó dando 10 mg (40%) de un sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90% / TFA al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / TFA al 0,1% / acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ TFA al 0,1% con un gradiente de 20-100% de B (B = acetonitrilo calidad HPLC al 95% / ácido trifluoroacético al 0,1% / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1% / acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 20-100% de B (B = metanol calidad HPLC al 95% / bicarbonato amónico 10 mM

/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF-d_8) δ ppm 0,94 (d, $J=6,53$ Hz, 6 H), 1,82 - 1,98 (m, 1 H), 2,88 (d, $J=4,77$ Hz, 3 H), 3,14 - 3,23 (m, 2 H), 3,47 (c, $J=4,94$ Hz, 2 H), 4,03 (t, $J=4,52$ Hz, 2 H), 5,55 (s ancho, 1 H), 6,18 (s ancho, 1 H), 7,03 (d, $J=8,53$ Hz, 1 H), 7,21 - 7,32 (m, 2 H), 7,46 - 7,51 (m, 1 H), 7,51 - 7,56 (m, 1 H), 7,56 - 7,62 (m, 1 H), 7,80 (dd, $J=8,53, 2,26$ Hz, 1 H), 7,84 (d, $J=4,52$ Hz, 1 H), 7,91 - 8,02 (m, 3 H), 8,22 (d, $J=1,25$ Hz, 1 H). Tr de LCEM 1,988 min., m/z 547,24 (M+H). Tr de HPLC 8,126 min. (Sunfire C18), 99,7 % de pureza y 11,214 min. (Gemini C18), 99,5 % de pureza.

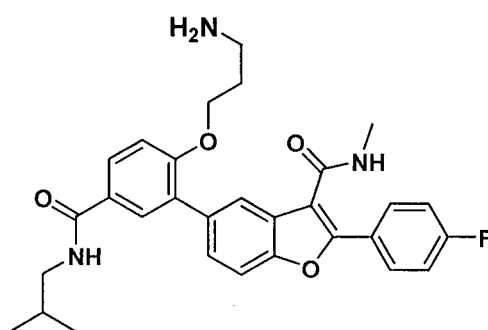


5-(2-(3-(1,3-Dioxoisindolin-2-il)propoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, THF-d_8) δ ppm 0,93 (d, $J=6,78$ Hz, 6 H), 1,81 - 1,97 (m, 1 H), 2,09 (m, 2 H), 2,90 (d, $J=4,77$ Hz, 3 H), 3,12 - 3,26 (m, 2 H), 3,79 (t,

$J=6,65$ Hz, 2 H), 4,11 (t, $J=5,90$ Hz, 2 H), 7,03 (d, $J=8,78$ Hz, 1 H), 7,16 - 7,28 (m, 2 H), 7,45 (d, $J=4,27$ Hz, 1 H), 7,48 - 7,51 (m, 1 H), 7,51 - 7,56 (m, 1 H), 7,59 (dd, $J=8,78$, 1,76 Hz, 1 H), 7,65 - 7,74 (m, 4 H), 7,79 - 7,90 (m, 3 H), 8,08 - 8,24 (m, 2 H). LCEM m/z 648,19 (M+H), Tr 2,458 min. Tr de HPLC 10,158 min.

5 (Sunfire C18), 99,4 % de pureza y 12,111 min. (Gemini C18), 99,7 % de pureza.

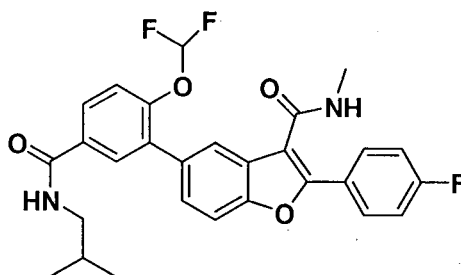


5-(2-(2-Aminoetoxy)-5-(isobutylcarbamoyl)fenil)-2-(4-fluorofenil)-N-

10 metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,93 (d, $J=6,53$ Hz, 6 H), 1,82 - 1,93 (m, 1 H), 2,15 (m, 2 H), 2,91 (d, $J=4,52$ Hz, 3 H), 3,08 - 3,24 (m, 4 H), 4,17 (t, $J=5,65$ Hz, 2 H), 7,06 (d, $J=8,53$ Hz, 1 H), 7,18 - 7,28 (m, 2 H), 7,47 (dd, $J=8,53$, 1,76 Hz, 1 H), 7,53 - 7,66 (m, 2 H), 7,82 (dd, $J=8,53$, 2,26 Hz, 2 H), 7,90 (d, $J=2,26$ Hz, 1 H), 7,95 (d, $J=1,51$ Hz, 1 H), 7,97 - 8,05 (m, 2 H), 8,28 (s ancho, 2 H). Tr de LCEM 1,537 min., m/z 518,16 (M+H). Tr de HPLC 10,734 min. (Sunfire C18), 99,2 % de pureza y 10,881 min. (Gemini C18), 99,3 % de pureza. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu /

Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/TFA al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto.



5-(2-(Difluorometoxi)-5-(isobutilcarbamoi)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

A un vial de microondas pequeño se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(isobutilcarbamoi) fenil)-*N*-metilbenzofuran-3-carboxamida (23,02 mg, 0,05 mmol), acetonitrilo (400 µl), agua (400 µl), y 2-cloro-2,2-difluoro-1-feniletanona (47,6 mg, 0,250 mmol). El vial se selló y la mezcla de reacción se sometió a calentamiento en microondas (BIOTAGE® Initiator) a 110 °C durante 8 minutos. La mezcla de reacción bruta se diluyó de nuevo con acetonitrilo, se filtró y purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 30x100mm a un gradiente de 30-100% de B y un caudal de 40 ml/minutos durante 10 minutos con un mantenimiento de 10 minutos. El disolvente se evaporó dando producto (35%) como un sólido blanco. RMN de ¹H (500 MHz, THF-d₈) δ ppm 0,86 - 1,01 (m, 6 H), 1,89 (dt, *J* = 13,50, 6,83 Hz, 1 H), 2,90 (d, *J* = 4,58 Hz, 3 H), 3,12 - 3,28 (m, 2 H), 6,61 - 7,04 (m, 1 H), 7,18 - 7,27 (m, 2 H), 7,31 (d, *J* = 8,54 Hz, 1 H), 7,49 (dd, *J* = 8,55, 1,83 Hz, 1 H), 7,53

(d, $J = 4,27$ Hz, 1 H), 7,59 (d, $J = 8,55$ Hz, 1 H), 7,78 (t, $J = 5,49$ Hz, 1 H), 7,82 (d, $J = 1,22$ Hz, 1 H), 7,91 (dd, $J = 8,55, 2,44$ Hz, 1 H), 7,98 (d, $J = 2,14$ Hz, 1 H), 8,09 - 8,17 (m, 2 H). LCEM m/z 511,21 (M+H), Tr 2,393 min. Tr de HPLC 12,213 min. (Sunfire C18), 99,3 % de pureza y 15,427 min. (XBridge C18), 99,8 % de pureza. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5 μ m C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5 μ m 4,6 x 150mm que emplea agua/acetonitrilo/TFA al 0,1% con un gradiente de 30-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters Phenyl XBridge C18 3,5 μ m 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 30-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM

/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto.

5 3-Bromo-*N*-isobutil-5-isopropoxibenzamida

A un vial grande de tapa a rosca se añadió ácido 3-bromo-5-hidroxibenzoico (1 g, 4,61 mmol), piridina (10 ml), *N*1-((etilimino)metilen)-*N*3,*N*3-dimetilpropano-1,3-diamina, HCl (0,972 g, 5,07 mmol) (EDAC) junto con 2-metilpropan-1-amina (0,504 ml, 5,07 mmol). El vial se tapó y la mezcla se agitó durante la noche. La
10 mezcla de reacción se acidificó con 10 ml de una solución enfriada en hielo de HCl. La mezcla se diluyó con diclorometano, se extrajo, se lavó con salmuera y se secó sobre sulfato de magnesio. La mezcla de reacción se filtró entonces y se añadió a un cartucho de gel de sílice de 240 g Thomson. El producto se eluyó con metanol al 0-12% (3000 ml) en diclorometano dando 3-bromo-5-
15 hidroxí-*N*-isobutilbenzamida (95%) como un sólido amarillo. Tr de LCEM 1,632 min., *m/z* 273,99 (*M*+*H*), 93% de pureza. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad
20 HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4

ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/TFA al 0,1% con un gradiente de 30-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. A un tubo sellado se añadió 3-bromo-5-hidroxi-*N*-isobutilbenzamida (380,4 mg, 1,398 mmol), DMF (15 ml), 2-yodopropano (0,210 ml, 2,097 mmol) y carbonato potásico (290 mg, 2,097 mmol). El tubo se selló y se calentó hasta 90 °C durante la noche. La mezcla de reacción se enfrió, se transfirió a un embudo de separación, se diluyó con acetato de etilo y se extrajo. La solución orgánica se lavó con HCl 1M, salmuera, se secó sobre sulfato de magnesio, se filtró y se evaporó hasta sequedad. El aceite naranja resultante se recogió en diclorometano y se purificó usando el BIOTAGE® Horizon con una columna de gel de sílice de 110g Thomson que emplea 0-5% de metanol y 2000 ml de disolvente, dando un rendimiento casi cuantitativo de 3-bromo-*N*-isobutil-5-isopropoxibenzamida como un sólido amarillo claro. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad

HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea
5 agua/acetonitrilo/TFA al 0,1% con un gradiente de 30-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ¹H (400 MHz, CDCl₃) δ ppm 0,87
10 - 1,04 (m, 6 H), 1,23 - 1,37 (m, 6 H), 1,79 - 2,00 (m, 1 H), 3,25 (t, J=6,40 Hz, 2 H), 4,57 (dt, J=12,05, 6,02 Hz, 1 H), 6,29 (s ancho, 1 H), 7,08 - 7,19 (m, 1 H), 7,21 - 7,26 (m, 1 H), 7,38 (s, 1 H). Tr de LCEM 2,413 min., m/z 315,01 (M+H), 95% de pureza.

15 3-Bromo-N-isobutil-4-(trifluorometoxi)benzamida

A un vial grande de tapa a rosca se añadió ácido 3-bromo-4-(trifluorometoxi)benzoico previamente sintetizado (100 mg, 0,351 mmol), piridina (5 ml), 2-metilpropan-1-amina (0,038 ml, 0,386 mmol), N1-((etilimino)metilen)-N3,N3-dimetilpropano-1,3-diamina, HCl (EDAC) (74,0 mg,
20 0,386 mmol) y HATU, hexafluorofosfato de 2-(7-aza-1H-benzotriazole-1-il)-1,1,3,3-tetrametiluronio (400 mg, 1,053 mmol). El vial se tapó y se agitó durante la noche a temperatura ambiente. La mezcla de reacción bruta se diluyó con

metanol y se purificó usando una HPLC preparativa Shimadzu que emplea metanol/agua/TFA al 0,1% donde el disolvente A era metanol al 10% / agua al 90% / ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / metanol al 90% / ácido trifluoroacético al 0,1% con una columna PHENOMENEX® Luna

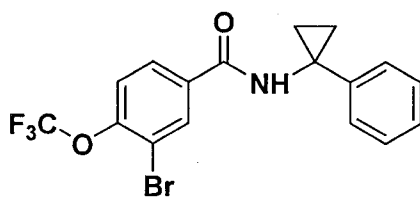
5 10µm C18 30x100mm a un gradiente de 30-100% de B y un caudal de 40 ml/minutos durante 9 minutos con un mantenimiento de 11 minutos 75 mg (62%) de un sólido amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x

10 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y

15 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/TFA al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10

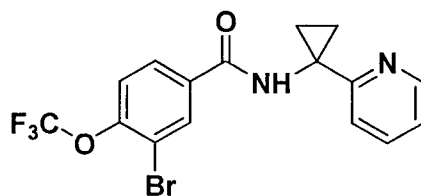
20 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3µm 4,6 x 150mm

que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,98 - 1,11 (m, 6 H), 1,91 - 2,09 (m, 1 H), 3,22 - 3,30 (m, 2 H), 7,57 (dd, $J=8,53, 1,51$ Hz, 1 H), 7,96 (dd, $J=8,53, 2,26$ Hz, 1 H), 8,25 (d, $J=2,01$ Hz, 1 H), 8,68 (s ancho, 1 H). Tr de HPLC 17,141 min. (Sunfire C18), 99,5 % de pureza y 15,912 min. (Gemini C18), 100 % de pureza. Tr de LCEM 2,367 min., m/z 341,99 (M+H).



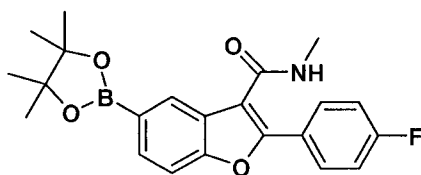
3-Bromo-*N*-(1-fenilciclopropil)-4-(trifluorometoxi)benzamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,40 (d, $J = 4,52$ Hz, 4 H), 7,16 - 7,30 (m, 1 H), 7,32 - 7,41 (m, 4 H), 7,58 (dd, $J = 8,66, 1,38$ Hz, 1 H), 7,99 (dd, $J = 8,66, 2,13$ Hz, 1 H), 8,28 (d, $J = 2,01$ Hz, 1 H), 9,42 (s ancho, 1 H). Tr de LCEM 2,56 min., m/z 401,97 (M+H). Tr de HPLC 15,171 min. (Sunfire C18), 98,8 % de pureza y 16,066 min. (Gemini C18), 100 % de pureza.



3-Bromo-*N*-(1-(piridin-2-il)ciclopropil)-4-(trifluorometoxi)benzamida

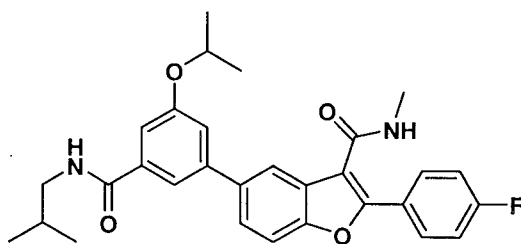
RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,70 - 1,80 (m, 2 H), 1,80 - 1,91 (m, 2 H),
 7,57 (dd, $J=8,78$, 1,25 Hz, 1 H), 7,76 - 7,88 (m, 2 H), 8,03 (dd, $J=8,53$, 2,26 Hz,
 5 1 H), 8,33 (d, $J=2,01$ Hz, 1 H), 8,43 (t, $J=8,03$ Hz, 1 H), 8,63 (d, $J=5,52$ Hz, 1
 H). Tr de LCEM 1,420 min, m/z 402,95 ($\text{M}+\text{H}$). Tr de HPLC 5,611 min. (Sunfire
 C18), 93,8 % de pureza y 11,206 min. (Gemini C18), 98,4 % de pureza.



10 2-(4-Fluorofenil)-*N*-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-
 il)benzofuran-3-carboxamida

A un tubo sellado se añadió trifluorometanosulfonato de 2-(4-fluorofenil)-3-
 (metilcarbamoil)benzofuran-5-ilo (2,000 g, 4,79 mmol), dioxano (20 ml),
 trietilamina (1,993 ml, 14,38 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-
 15 dioxaborolano) (4,87 g, 19,17 mmol) y finalmente $\text{PdCl}_2(\text{dppf})$ (0,235 g, 0,144
 mmol). El vial se purgó con N_2 , se selló y se calentó durante la noche en un
 baño de aceite a 80 °C. La mezcla de reacción se enfrió, se diluyó con
 diclorometano y se lavó con una solución de HCl 0,1M y luego salmuera. La

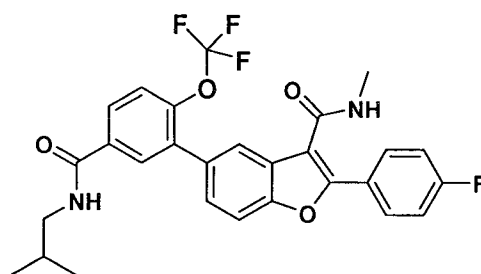
mezcla marrón se aspiró a través de un tapón de sulfato de magnesio/CELITE® 1:1 dando un sólido marrón oscuro después de evaporar el disolvente. El producto bruto se recogió en 50ml de diclorometano y se añadió a la parte superior de un cartucho preequilibrado de gel de sílice de 240g Thomson. El producto se eluyó con metanol al 0-2% en diclorometano dando un 80% de rendimiento de 2-(4-fluorofenil)-*N*-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzofuran-3-carboxamida como un sólido color castaño. RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,34 (s, 12 H), 2,92 - 2,95 (m, 3 H), 7,20 (t, $J=8,91$ Hz, 2 H), 7,50 (d, $J=8,28$ Hz, 2 H), 7,74 (dd, $J=8,28$, 1,00 Hz, 1 H), 8,08 - 8,13 (m, 2 H), 8,14 (s, 1 H). LCEM m/z 396,18 (M+H), Tr 2,455 min., 90% de pureza.



2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-5-isoproxifenil)-*N*-metilbenzofuran-3-carboxamida

A un vial de microondas de tamaño medio se añadió 1 (465 mg, 1,0 mmol), dioxano (15 ml), agua (1,500 ml), 3-bromo-*N*-isobutil-5-isopropoxibenzamida (377 mg, 1,200 mmol), diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (82 mg, 0,200 mmol), fosfato potásico, tribásico (849 mg, 4,00 mmol) y finalmente acetato de

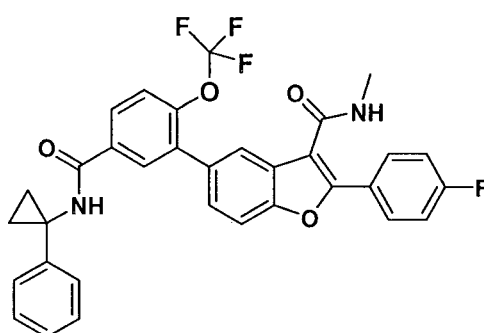
paladio(II) (44,9 mg, 0,200 mmol). El vial se tapó y se sometió a calentamiento en microondas (150 °C) en un BIOTAGE® Initiator durante 13 minutos. La mezcla de reacción se diluyó con 150 ml de diclorometano, se lavó con una solución 1M d HCl, luego agua y finalmente salmuera. La solución se filtró a
5 través de una almohadilla de CELITE®/sulfato de magnesio 1:1 y luego se evaporó dando un aceite marrón. El producto bruto se recogió en diclorometano y se añadió a la parte superior de un cartucho de gel de sílice previamente equilibrado de 100g BIOTAGE®. El producto se eluyó con una mezcla disolvente de metanol al 0-3% metanol en diclorometano dando
10 producto como un sólido color castaño claro (51%). RMN de ^1H (400 MHz, THF-d_8) δ ppm 0,95 (d, $J=6,53$ Hz, 6 H), 1,35 (d, $J=6,02$ Hz, 6 H), 1,83 - 1,98 (m, 1 H), 2,90 - 2,98 (m, 3 H), 3,14 - 3,29 (m, 2 H), 4,66 - 4,82 (m, 1 H), 7,18 - 7,25 (m, 2 H), 7,26 - 7,29 (m, 1 H), 7,38 - 7,42 (m, 1 H), 7,48 (m, 1 H), 7,58 - 7,65 (m, 2 H), 7,65 - 7,72 (m, 2 H), 7,96 (d, $J=1,00$ Hz, 1 H), 8,08 - 8,16 (m, 2
15 H). Tr de LCEM 2,588 min., m/z 503,25 ($M+H$), 98% de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(trifluorometoxi)fenil)-N-metilbenzofuran-3-carboxamida

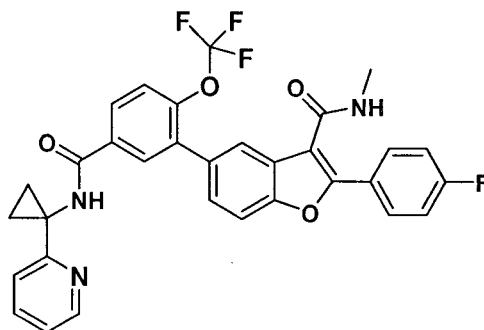
Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ TFA al 0,1%/ agua
5 calidad HPLC al 10%), (A = agua calidad HPLC al 90% / TFA al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5mm 4,6 x 150mm que emplea agua/acetonitrilo/ TFA al 0,1% con un
10 gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente
15 ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Phenyl XBridge C18 3,5mm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM /
20 metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ¹H (400 MHz, THF-d₈) δ ppm 0,94 (dd, J=6,78, 2,26 Hz, 6 H), 1,82 - 1,97 (m, 1 H), 2,90 (d, J=4,77 Hz, 3 H), 3,12 -

- 3,24 (m, 2 H), 7,17 - 7,29 (m, 2 H), 7,47 (dd, $J=8,53$, 1,76 Hz, 2 H), 7,61 (d, $J=8,53$ Hz, 1 H), 7,71 - 7,81 (m, 2 H), 7,83 (d, $J=1,26$ Hz, 1 H), 7,92 - 7,98 (m, 1 H), 7,99 - 8,05 (m, 1 H), 8,07 - 8,15 (m, 2 H). Tr de LCEM 2,565min., m/z 529,13 (M+H). Tr de HPLC 11,166 min. (Sunfire C18), 99,5 % de pureza y
- 5 11,813 min. (Phenyl XBridge C18), 86,7 % de pureza.



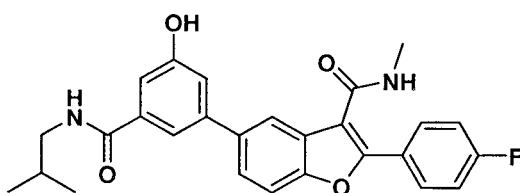
2-(4-Fluorofenil)-*N*-metil-5-(5-(1-fenilciclopropilcarbamoil)-2-(trifluorometoxi)fenil)benzofuran-3-carboxamida

- 10 RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,20 - 1,39 (m, 4 H), 2,89 (d, $J=4,52$ Hz, 3 H), 7,06 - 7,15 (m, 1 H), 7,17 - 7,27 (m, 4 H), 7,29 - 7,35 (m, 2 H), 7,44 (s ancho, 1 H), 7,47 (m, 2 H), 7,61 (d, $J=8,53$ Hz, 1 H), 7,83 (d, $J=1,26$ Hz, 1 H), 7,98 (dd, $J=8,66$, 2,38 Hz, 1 H), 8,05 (d, $J=2,01$ Hz, 1 H), 8,08 - 8,15 (m, 2 H), 8,50 (s ancho, 1 H). Tr de LCEM 2,796 min., m/z 589,23 (M+H). Tr de HPLC
- 15 11,419 min. (Sunfire C18), 98,9 % de pureza y 12,424 min. (Phenyl XBridge C18), 100 % de pureza.



2-(4-Fluorofenil)-*N*-metil-5-(5-(1-(piridin-2-il)ciclopropilcarbamoil)-2-(trifluoro metoxi)fenil)benzofuran-3-carboxamida

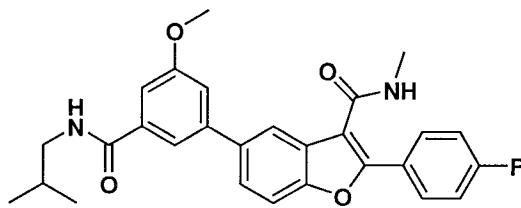
- RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,21 - 1,33 (m, 2 H), 1,62 - 1,70 (m, 2 H),
 5 2,89 (d, $J=4,77$ Hz, 3 H), 7,01 (m, 1 H), 7,18 - 7,28 (m, 2 H), 7,40 (d, $J=8,03$ Hz,
 1 H), 7,43 (s ancho, 1 H), 7,46 - 7,58 (m, 3 H), 7,62 (d, $J=8,53$ Hz, 1 H), 7,86 (d,
 $J=1,26$ Hz, 1 H), 8,04 (dd, $J=8,66$, 2,38 Hz, 1 H), 8,07 - 8,17 (m, 3 H), 8,36 -
 8,42 (m, 1 H), 8,57 (s ancho, 1 H). Tr de LCEM 1,768 min., m/z 590,13 (M+H).
 Tr de HPLC 7,645 min. (Sunfire C18), 99,0 % de pureza y 12,041 min. (Phenyl
 10 XBridge C18), 99,9 % de pureza.



2-(4-Fluorofenil)-5-(3-hidroxi-5-(isobutilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida

- 15 A un matraz de fondo redondo de 250 ml se añadió 2-(4-fluorofenil)-5-(3-(isobutilcarbamoil)-5-isopropoxifenil)-*N*-metilbenzofuran-3-carboxamida (1,3409

g, 2,67 mmol) en diclorometano (20 ml). El matraz se selló con un septo, se colocó en N₂ y se agitó durante 5 minutos. Se añadió entonces a esta mezcla tricloroborano 1M (frío) (8,00 ml, 8,00 mmol) en diclorometano. La solución se agitó a temperatura ambiente durante 6 horas. La mezcla de reacción se enfrió hasta 0 °C y se añadió metanol para inactivar la reacción. Se dejó el matraz calentar hasta temperatura ambiente y se eliminaron los volátiles dando un rendimiento cuantitativo de un sólido color castaño. RMN de ¹H (400 MHz, CD₃OD) δ ppm 1,06 (d, *J* = 6,78 Hz, 6 H), 1,97 - 2,12 (m, 1 H), 3,01 - 3,12 (m, 3 H), 3,29 (t, *J* = 6,53 Hz, 2 H), 7,27 - 7,40 (m, 4 H), 7,64 (s, 1 H), 7,72 (s, 2 H), 7,98 (s, 1 H), 8,03 (dd, *J* = 8,66, 5,40 Hz, 2 H), 8,56 (s ancho, 1 H). Tr de LCEM 2,157 min., *m/z* 461,03 (M+H), 97,6% de pureza.



2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-5-metoxifenil)-N-metilbenzofuran-3-carboxamida

Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido

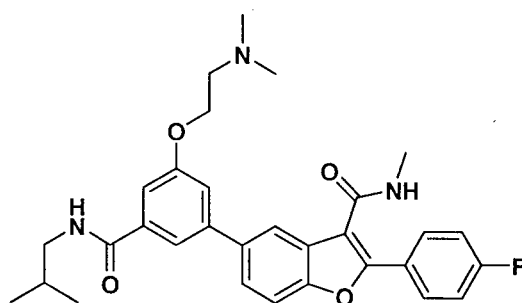
trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea

5 agua/acetonitrilo/TFA al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con

10 un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters Phenyl XBridge C18 3,5µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato

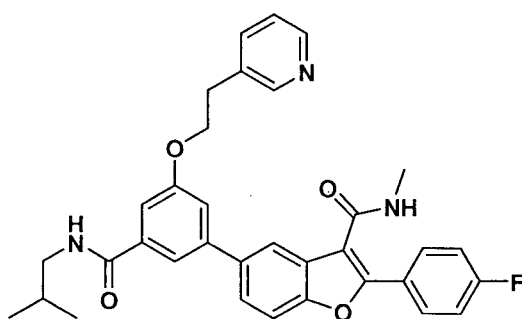
15 amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,87 - 1,03 (m, 6 H), 1,83 - 1,99 (m, 1 H), 2,93 (d, $J=4,77$ Hz, 3 H), 3,16 - 3,25 (m, 2 H), 3,88 (s, 3 H), 7,18 - 7,26 (m, 2 H), 7,29 - 7,32 (m, 1 H), 7,42 (dd, $J=2,38, 1,38$ Hz, 1 H), 7,50 (s ancho, 1 H), 7,57 - 7,66 (m, 2 H),

20 7,71 (s ancho, 2 H), 7,97 (d, $J=1,25$ Hz, 1 H), 8,08 - 8,16 (m, 2 H). LCEM m/z 475,22 (M+H), Tr 2,373 min.. Tr de HPLC 10,268 min. (Sunfire C18), 96,7 % de pureza y 12,104 min. (XBridge phenyl C18), 99,2 % de pureza.



5-(3-(2-(Dimetilamino)etoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 5 RMN de ^1H (400 MHz, THF-d_8) δ ppm 0,95 (d, $J = 6,78$ Hz, 6 H), 1,87 - 1,98 (m, 1 H), 2,89 (s, 6 H), 2,93 (d, $J = 4,52$ Hz, 3 H), 3,21 (t, $J = 6,40$ Hz, 2 H), 3,47 - 3,54 (m, 2 H), 4,54 - 4,64 (m, 2 H), 7,22 (t, $J = 8,66$ Hz, 2 H), 7,42 (s, 1 H), 7,51 (s ancho, 1 H), 7,58 (d, $J = 5,27$ Hz, 1 H), 7,61 (s, 1 H), 7,62 - 7,69 (m, 1 H), 7,80 (s, 1 H), 7,83 (s ancho, 1 H), 7,98 (s, 1 H), 8,12 (dd, $J = 8,91, 5,40$ Hz, 2 H). Tr de LCEM 1,543 min., m/z 532,28 ($\text{M}+\text{H}$). Tr de HPLC 6,816 min. (Sunfire C18), 96,0 % de pureza y 12,073 min. (Phenyl XBridge C18), 98,2 % de pureza.

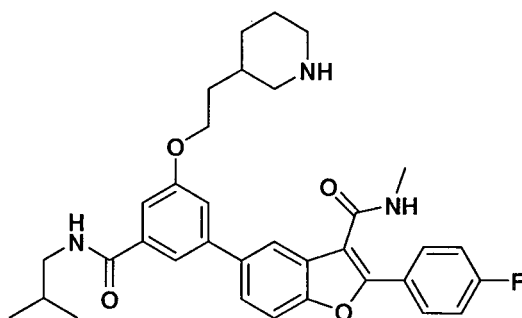


- 15 2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-5-(2-(piridin-3-il)etoxi)fenil)-N-metilbenzofuran-3-carboxamida

metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,94 (d, $J = 6,53$ Hz, 6 H), 1,83 - 1,98 (m, 1 H), 2,92 (d, $J = 4,27$ Hz, 3 H), 3,13 - 3,30 (m, 4 H), 4,32 - 4,47 (m, 2 H), 7,22 (t, $J = 8,66$ Hz, 2 H), 7,32 (s, 1 H), 7,41 - 7,53 (m, 3 H), 7,55 - 7,67 (m, 2 H), 7,72 (s ancho, 2 H), 7,91 - 8,01 (m, 2 H), 8,11 (dd, $J = 8,03, 5,52$ Hz, 2 H), 8,55 (s ancho, 1 H), 8,72 (s ancho, 1 H). Tr de LCEM 1,632 min., m/z 566,26 (M+H). Tr de HPLC 7,216 min. (Sunfire C18), 98,1 % de pureza y 12,073 min. (Phenyl XBridge C18), 99,0 % de pureza.

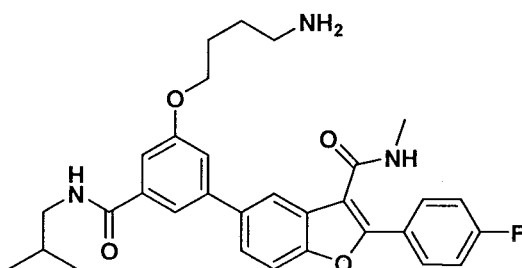
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2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-5-(2-(piperidin-3-il)etoxi)fenil)-*N*-metilbenzofuran-3-carboxamida

Los datos de LC/EM se obtuvieron en una LC analítica Waters Acquity SDS / Plataforma de LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Acquity UPLC BEH 1,7 μ m C18, 2,1 x 50mm, con un gradiente de 2-98% de B (B = acetonitrilo calidad HPLC al 100%/ 0,05% TFA), (A = agua calidad HPLC al 100% / 0,05% TFA), en 2,2 minutos a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC

analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ TFA al 0,1% con un gradiente de 20-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,99 (d, $J=6,78$ Hz, 6 H), 1,36 (dd, $J=12,30$, 3,01 Hz, 1 H), 1,69 - 1,89 (m, 3 H), 1,91 - 2,16 (m, 4 H), 2,77 (t, $J=12,17$ Hz, 1 H), 2,87 - 2,95 (m, 1 H), 3,23 (d, $J=7,03$ Hz, 2 H), 3,29 - 3,40 (m, 4 H), 3,43 - 3,52 (m, 1 H), 4,19 (t, $J=6,02$ Hz, 2 H), 7,24 (t, $J=8,78$ Hz, 2 H), 7,36 (dd, $J=10,54$, 1,51 Hz, 2 H), 7,58 - 7,68 (m, 2 H), 7,70 (s, 1 H), 7,87 - 7,98 (m, 3 H). LCEM m/z 572,16 (M+H). Tr de HPLC 6,518 min. (Sunfire C18), 98% de pureza.

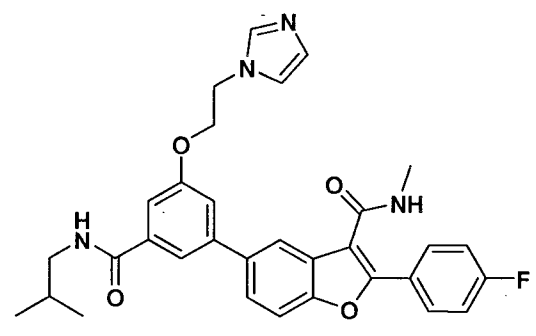


5-(3-(4-Aminobutoxi)-5-(isobutylcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,99 (d, $J=6,78$ Hz, 6 H), 1,86 - 2,04 (m, 5 H), 2,95 - 3,00 (m, 3 H), 3,06 (t, $J=7,15$ Hz, 2 H), 3,21 - 3,27 (m, 2 H), 4,19 (t,

$J=5,40$ Hz, 2 H), 7,23 - 7,31 (m, 2 H), 7,38 (dd, $J=3,76$, 1,25 Hz, 2 H), 7,64 - 7,70 (m, 2 H), 7,71 (s, 1 H), 7,91 - 7,99 (m, 3 H), 8,60 (s ancho, 1 H). LCEM m/z 532,00 (M+H). Tr de HPLC 6,386 min. (Sunfire C18), 100 % de pureza.

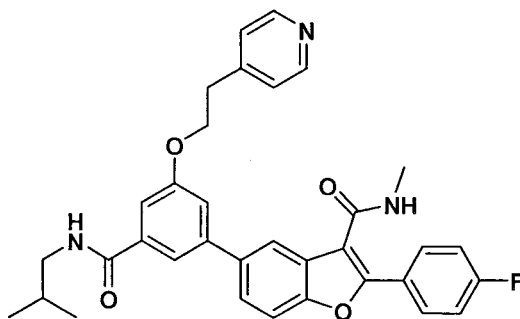
5



5-(3-(2-(1*H*-imidazol-1-il)etoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,06 (d, $J=6,78$ Hz, 6 H), 2,03 (d, $J=6,78$ Hz, 1 H), 3,05 (s, 3 H), 3,31 (d, $J=7,03$ Hz, 2 H), 4,62 (t, $J=4,77$ Hz, 2 H), 4,79 (s ancho, 2 H), 7,35 (t, $J=8,78$ Hz, 2 H), 7,49 (d, $J=2,76$ Hz, 2 H), 7,68 (s, 1 H), 7,73 - 7,77 (m, 2 H), 7,83 (s, 1 H), 7,88 (s, 1 H), 7,98 - 8,07 (m, 3 H), 9,17 (s, 1 H). LCEM m/z 555,00 (M+H). Tr de HPLC 6,295 min. (Sunfire C18), 95,2% de pureza.

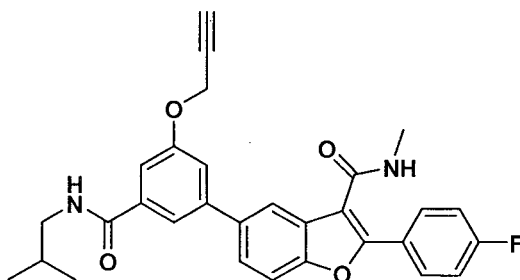
587



2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-5-(2-(piridin-4-il)etoxi)fenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,05 (d, $J=6,53$ Hz, 6 H), 1,95 - 2,09 (m, 1 H), 3,04 (s, 3 H), 3,24 - 3,33 (m, 2 H), 3,54 (t, $J=5,90$ Hz, 2 H), 4,60 (t, $J=5,77$ Hz, 2 H), 7,27 - 7,38 (m, 2 H), 7,41 - 7,49 (m, 2 H), 7,71 - 7,75 (m, 2 H), 7,78 (t, $J=1,51$ Hz, 1 H), 7,96 - 8,05 (m, 3 H), 8,12 (d, $J=6,53$ Hz, 2 H), 8,80 (d, $J=6,78$ Hz, 2 H). LCEM m/z 566,00 ($\text{M}+\text{H}$). Tr de HPLC 6,4921 min. (Sunfire C18), 98,6% de pureza.

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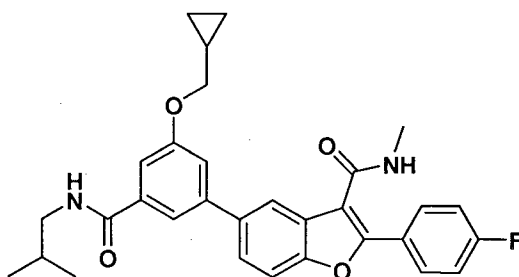


2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-5-(prop-2-iniloxi)fenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,07 (d, $J=6,78$ Hz, 6 H), 1,94 - 2,18 (m, 1 H), 3,00 - 3,13 (m, 4 H), 3,30 (d, $J=7,03$ Hz, 2 H), 4,94 - 4,98 (m, 2 H), 7,27 -

7,42 (m, 2 H), 7,47 - 7,59 (m, 2 H), 7,68 - 7,79 (m, 2 H), 7,82 (t, $J=1,51$ Hz, 1 H), 7,98 - 8,11 (m, 3 H). LCEM m/z 499,00 ($M+H$). Tr de HPLC 9,984min. (Sunfire C18), 99,4% de pureza.

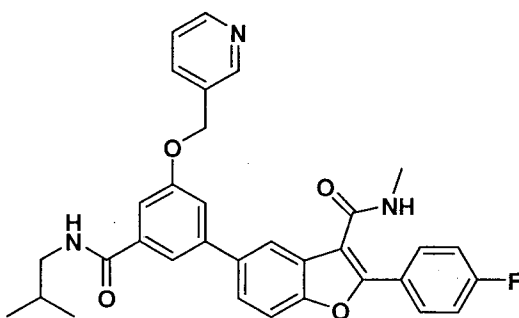
5



5-(3-(Ciclopropilmetoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

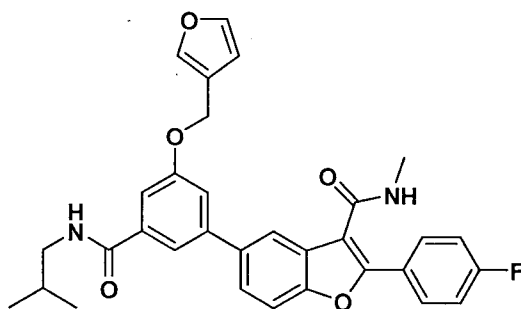
RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,48 (d, $J=14,81$ Hz, 2 H), 0,72 (d, $J=7,78$ Hz, 2 H), 1,06 (d, $J=6,53$ Hz, 6 H), 1,51 - 1,59 (m, 1 H), 1,98 - 2,10 (m, 1 H), 3,05 (s, 3 H), 3,30 (d, $J=7,03$ Hz, 2 H), 4,04 (d, $J=6,78$ Hz, 2 H), 7,33 (t, $J=8,66$ Hz, 2 H), 7,43 (s, 2 H), 7,49 (s ancho, 1 H), 7,75 (d, $J=9,04$ Hz, 3 H), 7,97 - 8,09 (m, 3 H). LCEM m/z 515,17 ($M+H$). Tr de HPLC 10,878 min. (Sunfire C18), 91,4% de pureza.

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2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-5-(piridin-3-ilmetoxi)fenil)-*N*-
metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,06 (d, $J=6,78$ Hz, 6 H), 2,03 (dt, $J=13,55, 6,78$ Hz, 1 H), 3,04 (s, 3 H), 3,30 (d, $J=7,03$ Hz, 2 H), 5,52 (s, 2 H),
5 7,33 (t, $J=8,78$ Hz, 2 H), 7,59 (dd, $J=6,40, 1,38$ Hz, 2 H), 7,69 - 7,80 (m, 2 H),
7,84 (s, 1 H), 7,96 - 8,09 (m, 4 H), 8,64 (d, $J=8,28$ Hz, 1 H), 8,83 (d, $J=4,52$ Hz,
1 H), 9,02 (s, 1 H). LCEM m/z 552,05 ($\text{M}+\text{H}$). Tr de HPLC 6,401 min. (Sunfire
C18), 100% de pureza.

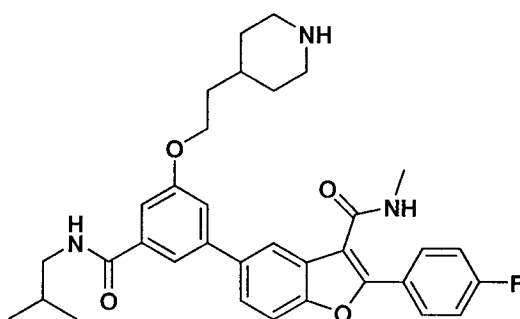


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2-(4-Fluorofenil)-5-(3-(furan-3-ilmetoxi)-5-(isobutilcarbamoil)fenil)-*N*-
metilbenzofuran-3-carboxamida

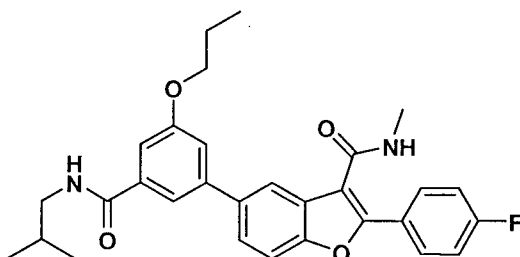
RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,06 (d, $J=6,53$ Hz, 6 H), 1,96 - 2,14 (m,
1 H), 3,06 (s, 3 H), 3,30 (d, $J=7,03$ Hz, 2 H), 5,19 (s, 2 H), 6,64 (s, 1 H), 7,33 (t,
15 $J=8,78$ Hz, 2 H), 7,51 (s, 2 H), 7,59 (s ancho, 1 H), 7,70 - 7,82 (m, 4 H), 8,01 (d,
 $J=11,54$ Hz, 3 H). LCEM m/z 541,00 ($\text{M}+\text{H}$). Tr de HPLC 10,426 min. (Sunfire
C18), 90,0% de pureza.

590



2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-5-(2-(piperidin-4-il)etoxi)fenil)-*N*-metilbenzofuran-3-carboxamida

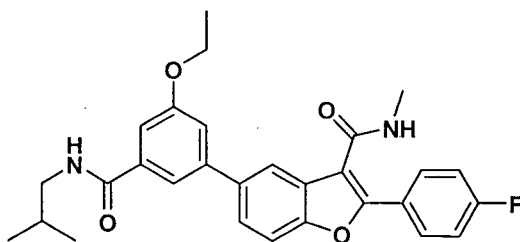
RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,06 (d, $J=6,53$ Hz, 6 H), 1,96 - 2,14 (m, 1 H), 3,06 (s, 3 H), 3,30 (d, $J=7,03$ Hz, 2 H), 5,19 (s, 2 H), 6,64 (s, 1 H), 7,33 (t, $J=8,78$ Hz, 2 H), 7,51 (s, 2 H), 7,59 (s ancho, 1 H), 7,70 - 7,82 (m, 4 H), 8,01 (d, $J=11,54$ Hz, 3 H). LCEM m/z 572,17 ($\text{M}+\text{H}$). Tr de HPLC 6,571min. (Sunfire C18), 95,8 % de pureza.



2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-5-propoxifenil)-*N*-metilbenzofuran-3-carboxamida

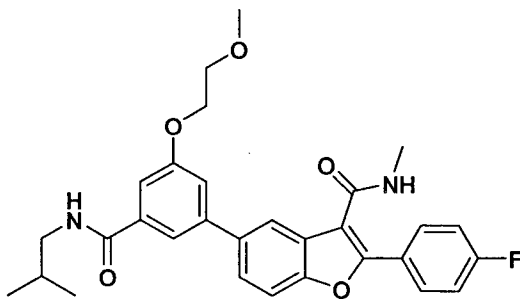
RMN de ^1H (400 MHz, $\text{THF}-d_8$) δ ppm 0,87 - 0,98 (m, 6 H), 1,07 (t, $J=7,40$ Hz, 3 H), 1,79 - 1,96 (m, 3 H), 2,93 (d, $J=4,52$ Hz, 3 H), 3,21 (t, $J=6,40$ Hz, 2 H), 4,05 (t, $J=6,53$ Hz, 2 H), 7,22 (t, $J=8,66$ Hz, 2 H), 7,30 (s ancho, 1 H), 7,39 - 7,56 (m,

2 H), 7,56 - 7,79 (m, 4 H), 7,97 (s, 1 H), 8,12 (dd, $J=8,53, 5,52$ Hz, 2 H). LCEM m/z 503,15 (M+H). Tr de HPLC 11,141 min. (Sunfire C18), 98,9 % de pureza.



5 2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-5-etocefenil)-N-metilbenzofuran-3-carboxamida

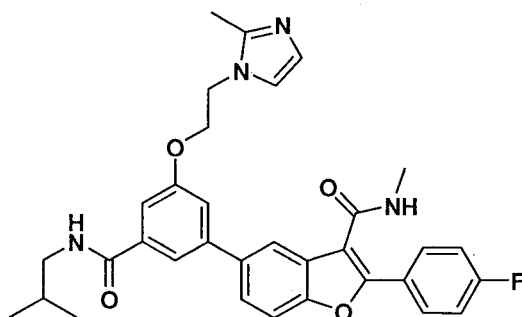
RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,06 (d, $J=6,78$ Hz, 6 H), 1,47 - 1,62 (m, 3 H), 1,92 - 2,15 (m, 1 H), 3,05 (s, 3 H), 3,30 (d, $J=7,03$ Hz, 2 H), 4,26 (c, $J=6,94$ Hz, 2 H), 7,33 (t, $J=8,78$ Hz, 2 H), 7,43 (s, 2 H), 7,70 - 7,83 (m, 3 H),
10 7,97 - 8,09 (m, 3 H). LCEM m/z 489,00 (M+H). Tr de HPLC 10,464 min. (Sunfire C18), 93,7% de pureza.



15 2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-5-(2-metoxietoxi)fenil)-N-metilbenzofuran-3-carboxamida

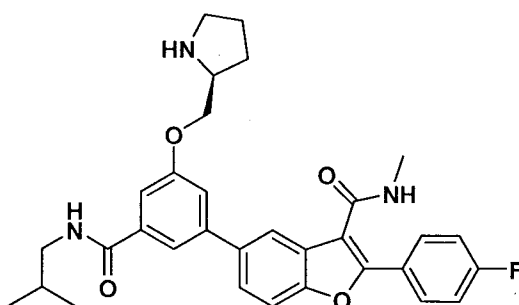
RMN de ^1H (400 MHz, THF-d_8) δ ppm 0,86 - 1,05 (m, 6 H), 1,82 - 2,02 (m, 1 H),

2,86 - 3,04 (m, 3 H), 3,21 (t, $J=6,40$ Hz, 2 H), 3,34 - 3,45 (m, 3 H), 3,72 (t, $J=4,77$ Hz, 2 H), 4,21 (t, $J=4,77$ Hz, 2 H), 7,22 (t, $J=8,78$ Hz, 2 H), 7,33 (s, 1 H), 7,42 (s, 1 H), 7,49 (s ancho, 1 H), 7,55 - 7,83 (m, 4 H), 7,97 (s, 1 H), 8,12 (dd, $J=8,78, 5,52$ Hz, 2 H). LCEM m/z 519,10 (M+H). Tr de HPLC 9,676min. (Sunfire C18), 100% de pureza.



2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-5-(2-(2-metil-1H-imidazol-1-il)etoxi)fenil)-N-metilbenzofuran-3-carboxamida

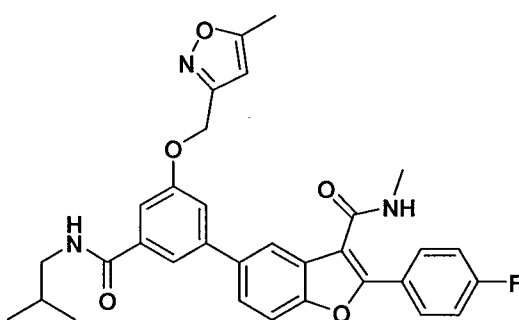
- 10 RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,99 (d, $J=6,53$ Hz, 6 H), 1,90 - 2,03 (m, 1 H), 2,78 (s, 3 H), 2,94 - 3,02 (m, 3 H), 3,23 (d, $J=7,03$ Hz, 2 H), 4,53 (t, $J=4,89$ Hz, 2 H), 4,65 (t, $J=4,89$ Hz, 2 H), 7,22 - 7,32 (m, 2 H), 7,38 (d, $J=1,51$ Hz, 2 H), 7,46 (d, $J=2,01$ Hz, 1 H), 7,63 - 7,69 (m, 3 H), 7,75 (t, $J=1,51$ Hz, 1 H), 7,91 - 8,00 (m, 3 H). LCEM m/z 569,12 (M+H). Tr de HPLC 6,340 min. (Sunfire C18), 100% de pureza.



(S)-2-(4-Fluorofenil)-5-(3-(isobutylcarbamoil)-5-(pirrolidin-2-ilmetoxi)fenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, CD_3OD) δ ppm 1,06 (d, $J=6,78$ Hz, 6 H), 1,98 - 2,12 (m, 2 H), 2,16 - 2,32 (m, 2 H), 2,34 - 2,48 (m, 1 H), 3,04 (s, 3 H), 3,31 (d, $J=7,03$ Hz, 2 H), 3,44 - 3,55 (m, 2 H), 4,12 - 4,22 (m, 1 H), 4,34 (dd, $J=10,54, 8,28$ Hz, 1 H), 4,51 - 4,62 (m, 1 H), 7,27 - 7,42 (m, 2 H), 7,49 - 7,59 (m, 2 H), 7,71 - 7,82 (m, 2 H), 7,85 (s, 1 H), 7,97 - 8,10 (m, 3 H). LCEM m/z 544,12 ($\text{M}+\text{H}$). Tr de HPLC 6,326 min. (Sunfire C18), 95,8 % de pureza.

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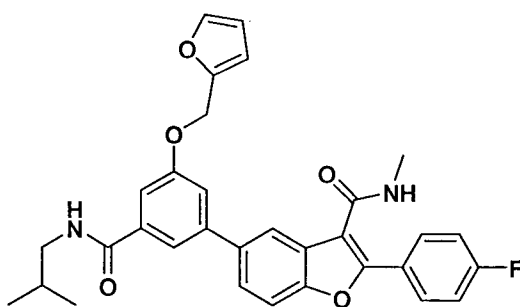
2-(4-Fluorofenil)-5-(3-(isobutylcarbamoil)-5-((5-metilisoxazol-3-il)metoxi)fenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, THF-d_8) δ ppm 0,92 - 0,99 (m, 6 H), 1,83 - 1,99 (m, 1 H), 2,40 (s, 3 H), 2,90 - 2,98 (m, 3 H), 3,17 - 3,27 (m, 2 H), 5,18 - 5,25 (m, 1 H),

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6,17 - 6,25 (m, 1 H), 7,17 - 7,27 (m, 2 H), 7,41 - 7,46 (m, 1 H), 7,47 - 7,54 (m, 2 H), 7,57 - 7,68 (m, 3 H), 7,68 - 7,74 (m, 1 H), 7,76 (d, $J=1,51$ Hz, 1 H), 7,98 (d, $J=1,26$ Hz, 1 H), 8,07 - 8,19 (m, 2 H). LCEM m/z 556,00 (M+H). Tr de HPLC 10,106 min. (Sunfire C18), 90,0% de pureza.

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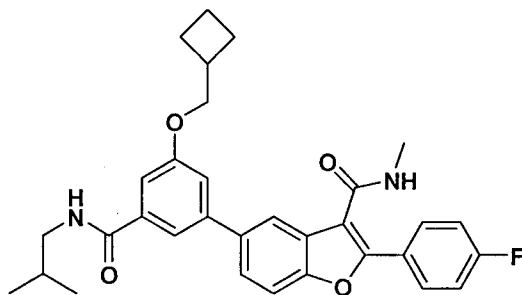


2-(4-Fluorofenil)-5-(3-(isobutylcarbamoyl)-5-((5-metilisoxazol-3-il)metoxi)fenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (500 MHz, THF- d_8) δ ppm 0,98 (d, $J=6,71$ Hz, 6 H), 1,88 - 2,01 (m, 1 H), 2,92 - 3,00 (m, 3 H), 3,20 - 3,27 (m, 2 H), 5,17 (s, 2 H), 6,42 (dd, $J=3,05$, 1,83 Hz, 1 H), 6,53 (d, $J=3,36$ Hz, 1 H), 7,21 - 7,30 (m, 3 H), 7,43 (d, $J=1,53$ Hz, 1 H), 7,55 (d, $J=12,51$ Hz, 1 H), 7,59 - 7,66 (m, 3 H), 7,67 - 7,71 (m, 1 H), 7,78 (s, 1 H), 8,02 (s, 1 H), 8,13 - 8,18 (m, 2 H). LCEM m/z 541,17 (M+H). Tr de HPLC 10,401 min. (Sunfire C18), 90,0% de pureza.

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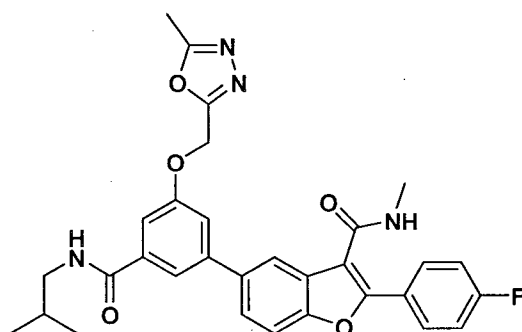
595



5-(3-(Ciclobutilmetoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H (500 MHz, THF- d_8) δ ppm 0,95 (d, $J=6,71$ Hz, 6 H), 1,86 - 2,02 (m, 6 H), 2,10 - 2,21 (m, 2 H), 2,87 - 2,97 (m, 3 H), 3,20 (d, $J=6,71$ Hz, 2 H), 4,07 (d, $J=6,71$ Hz, 2 H), 7,23 (t, $J=8,85$ Hz, 2 H), 7,32 (s, 1 H), 7,43 (s, 1 H), 7,57 - 7,63 (m, 2 H), 7,63 - 7,68 (m, 1 H), 7,73 (s, 1 H), 7,79 - 7,86 (m, 1 H), 7,99 (s, 1 H), 8,09 - 8,16 (m, 2 H). LCEM m/z 529,00 (M+H). Tr de HPLC 11,771 min. (Sunfire C18), 94,2% de pureza.

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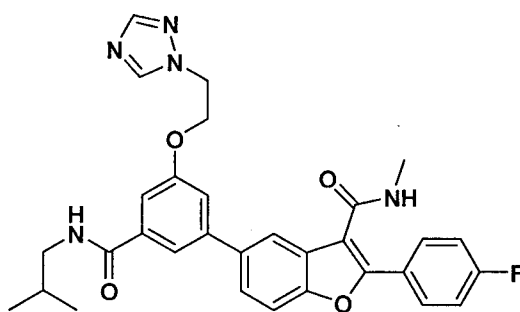


2-(4-Fluorofenil)-5-(3-(isobutilcarbamoil)-5-((5-metil-1,3,4-oxadiazol-2-il)metoxi)fenil)-*N*-metilbenzofuran-3-carboxamida

RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,90 - 1,02 (m, 6 H), 1,84 - 2,00 (m, 1 H),

2,50 (s, 3 H), 2,94 (d, $J=4,77$ Hz, 3 H), 3,17 - 3,27 (m, 2 H), 5,39 (s, 2 H), 7,18 - 7,29 (m, 2 H), 7,46 - 7,56 (m, 3 H), 7,58 - 7,68 (m, 2 H), 7,71 (s ancho, 1 H), 7,79 (s, 1 H), 8,00 (d, $J=1,51$ Hz, 1 H), 8,08 - 8,21 (m, 2 H). LCEM m/z 557,11 (M+H). Tr de HPLC 8,964 min. (Sunfire C18), 92,0% de pureza.

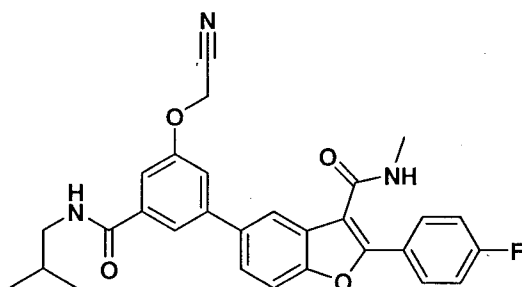
5



5-(3-(2-(1H-1,2,4-Triazol-1-il)etoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

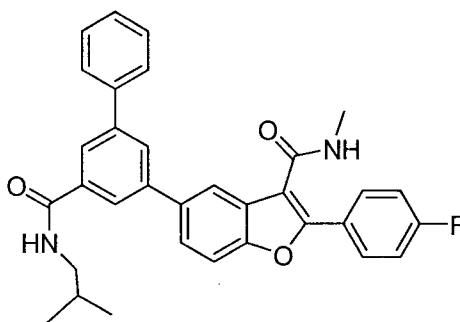
RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,87 - 1,01 (m, 6 H), 1,83 - 1,98 (m, 1 H),
 10 2,93 (d, $J=4,52$ Hz, 3 H), 3,13 - 3,26 (m, 2 H), 4,49 (t, $J=5,14$ Hz, 2 H), 4,61 (t, $J=5,02$ Hz, 2 H), 7,19 - 7,27 (m, 2 H), 7,28 - 7,33 (m, 1 H), 7,39 - 7,42 (m, 1 H), 7,43 - 7,52 (m, 1 H), 7,57 - 7,66 (m, 2 H), 7,71 - 7,77 (m, 1 H), 7,81 (s, 1 H), 7,96 (d, $J=1,00$ Hz, 1 H), 8,06 - 8,17 (m, 3 H), 8,30 (s, 1 H). LCEM m/z 556,11 (M+H). Tr de HPLC 7,969 min. (Sunfire C18), 92,0% de pureza.

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5-(3-(Cianometoxi)-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

RMN de ^1H (500 MHz, THF-d_8) δ ppm 0,96 (d, $J=6,71$ Hz, 6 H), 1,85 - 1,98 (m, 1 H), 2,85 - 2,98 (m, 3 H), 3,16 - 3,27 (m, 2 H), 5,11 (s, 2 H), 7,18 - 7,29 (m, 2 H), 7,42 - 7,49 (m, 1 H), 7,54 (s, 1 H), 7,60 - 7,71 (m, 2 H), 7,79 - 7,88 (m, 2 H), 8,00 (s, 1 H), 8,08 - 8,19 (m, 2 H). LCEM m/z 500,00 ($\text{M}+\text{H}$). Tr de HPLC 9,584 min. (Sunfire C18), 95,9% de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)bifenil-3-il)-N-metilbenzofuran-3-carboxamida

A un vial de microondas BIOTAGE® se añadió 1,4-dioxano (2,0 ml), agua (200 μl), diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (16,42 mg, 0,040 mmol), 5-(3-cloro-5-(isobutilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-

carboxamida (96 mg, 0,2 mmol), fosfato potásico tribásico (170 mg, 0,800 mmol), acetato de paladio(II) (8,98 mg, 0,040 mmol) y ácido fenilborónico (73,2 mg, 0,600 mmol). El vial se tapó, se desgasificó, se purgó con N₂ y se calentó en el microondas durante 15 minutos a 150 °C. El disolvente se eliminó en un

5 Thermo/Savant SPEEDVAC® y el producto bruto se disolvió en DMF (1,8 ml) y se purificó por HPLC preparativa usando una HPLC Prep Shimadzu que emplea acetonitrilo/agua/TFA al 0,1% donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna

10 Waters Sunfire 5µm C18 30x100mm a un gradiente de 30-100% de B y un caudal de 40 ml/minutos durante 8 minutos con un mantenimiento de 10 minutos. Los tubos con el producto deseado se evaporaron durante la noche en un Savant/Thermo SPEEDVAC®. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando

15 el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ TFA al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / TFA al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó

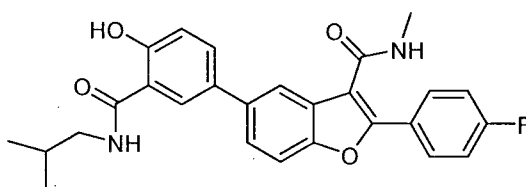
20 usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ TFA al 0,1% con un gradiente de 20-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido

trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente

5 ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge phenyl C18 3µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 20-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en

10 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, CD_3OD) δ ppm 0,99 (d, $J=6,78$ Hz, 6 H), 1,92 - 2,05 (m, 1 H), 2,91 - 3,03 (m, 3 H), 3,21 - 3,27 (m, 2 H), 7,25 (t, $J=8,78$ Hz, 2 H), 7,36 - 7,42 (m, 1 H), 7,49 (t, $J=7,53$ Hz, 2 H), 7,65 - 7,70 (m, 1 H), 7,75 (d, $J=8,28$ Hz, 3 H), 7,91 - 7,98 (m, 2 H), 8,00 (d, $J=1,51$ Hz, 1 H), 8,03 - 8,10 (m, 3 H). LCEM

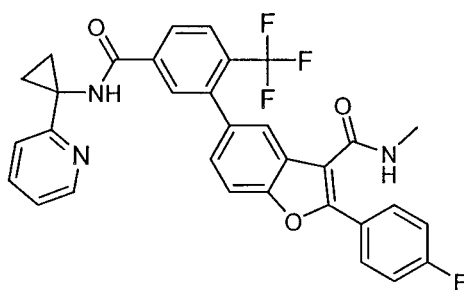
15 m/z 521,33 (M+H), Tr 2,715 min. HPLC (Sunfire C18) Tr 11,531 min, 95% de pureza y (XBridge phenyl C18) Tr 12,868 min., 92 % de pureza.



2-(4-Fluorofenil)-5-(4-hidroxi-3-(isobutilcarbamoil)fenil)-N-metilbenzofuran-3-
20 carboxamida

A un tubo sellado de 350 ml se añadió 2-(4-fluorofenil)-5-(3-(isobutilcarbamoil)-4-metoxifenil)-*N*-metilbenzofuran-3-carboxamida (1,14 g, 2,4 mmol), dicloroetano (250 ml) y complejo de tribromuro de boro-sulfuro de metilo (6,0 g, 19,2 mmol). El recipiente se selló y la mezcla se calentó con agitación a 90 °C durante la noche. La mezcla de reacción se enfrió hasta 0 °C y se añadieron 100 ml de metanol frío y la mezcla se agitó durante 30 minutos y luego se evaporó casi hasta sequedad. La adición de metanol seguido por evaporación se repitió dando un sólido color castaño (78%). Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ TFA al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / TFA al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ TFA al 0,1% con un gradiente de 40-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica

Shimadzu con una columna Gemini C18 3µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 50-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (500 MHz, THF- d_8) δ ppm 0,97 (d, $J=6,71$ Hz, 6 H), 1,83 - 2,07 (m, 1 H), 2,92 (d, $J=4,88$ Hz, 3 H), 3,24 (t, $J=6,41$ Hz, 2 H), 6,96 (d, $J=8,55$ Hz, 1 H), 7,23 (t, $J=8,70$ Hz, 2 H), 7,50 - 7,55 (m, 1 H), 7,55 - 7,59 (m, 2 H), 7,67 (dd, $J=8,55$, 2,14 Hz, 1 H), 7,89 (s, 1 H), 7,99 (d, $J=2,14$ Hz, 1 H), 8,09 (dd, $J=8,70$, 5,34 Hz, 2 H), 8,35 (s ancho, 1 H). LCEM m/z 461,18 (M+H), Tr 2,613 min. HPLC (Sunfire C18) Tr 10,033 min., 100% de pureza y (Gemini C18) Tr 9,748 min., 100 % de pureza.

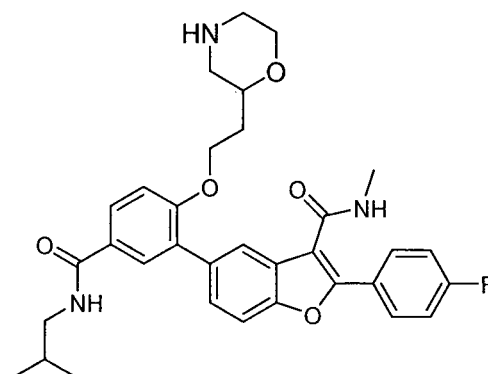


2-(4-Fluorofenil)-*N*-metil-5-(5-(1-(piridin-2-il)ciclopropilcarbamoi)-2-(trifluorometil)fenil)benzofuran-3-carboxamida

A un vial de microondas BIOTAGE® se añadió 2-(4-fluorofenil)-*N*-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzofuran-3-carboxamida (39,5 mg, 0,1 mmol), dioxano (2 ml), agua (0,200 ml), 3-cloro-*N*-(1-(piridin-2-il)ciclopropil)-

4-(trifluorometil)benzamida (37,5 mg, 0,110 mmol) (preparada a partir del acoplamiento de ácido 3-cloro-4-(trifluorometil)benzoico con diclorhidrato de 1-(piridin-2-il)ciclopropanamina usando HATU y N,N-diisopropiletilamina en DMF a t.a.), dicitclohexil(2',6'-dimetoxibifenil-2-il)fosfina (S-Phos, 8,21 mg, 0,020 mmol), fosfato potásico tribásico, (85 mg, 0,400 mmol) y finalmente acetato de paladio(II) (4,49 mg, 0,020 mmol). El vial se tapó y se sometió a calentamiento en microondas (100 °C) durante 10 minutos. Después de enfriar la mezcla de reacción, se eliminó el disolvente y el producto bruto se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 19 x 150mm a un gradiente de 20-100% de B y un caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 5 minutos. El disolvente se eliminó proporcionando 11,2 mg (20% de rendimiento) de la piridilcarboxamida deseada como un sólido amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / metanol calidad HPLC al 10%), en 4 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza

HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5 μ m 4,6 x 150mm que emplea agua/acetonitrilo/ ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua
5 calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna a Gemini C18 3,0 μ m 4,6 x 150mm que
10 emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400
15 MHz, THF- d_8) δ ppm 1,22 - 1,33 (m, 2 H), 1,63 - 1,69 (m, 2 H), 2,87 (d, $J=4,77$ Hz, 3 H), 7,03 (dd, $J=7,40$, 4,89 Hz, 1 H), 7,23 (t, $J=8,66$ Hz, 2 H), 7,33 (d, $J=8,28$ Hz, 1 H), 7,40 (d, $J=7,53$ Hz, 2 H), 7,52 - 7,63 (m, 2 H), 7,73 (d, $J=1,25$ Hz, 1 H), 7,90 (d, $J=8,03$ Hz, 1 H), 7,97 (s, 1 H), 8,05 - 8,16 (m, 3 H), 8,40 (d, $J=4,77$ Hz, 1 H), 8,69 (s, 1 H). LCEM Tr = 2,193min., m/z 574,3 (M+H). Tr de
20 HPLC = 7,435 min. (Sunfire C18), 97,5 % de pureza y 11,823 min. (Gemini C18), 100 % de pureza.



2-(4-Fluorofenil)-5-(5-(isobutilcarbamoil)-2-(2-(morfolin-2-il)etoxi)fenil)-*N*-
metilbenzofuran-3-carboxamida, TFA

A un vial de 3,54 ml se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-
5 (isobutilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida (46,0 mg, 0,1 mmol),
DMF (2 ml), 4,0 equivalentes (60 μ l, 0,400mmol) de DBU, 1,8-
diazabicciclo[5,4,0]undec-7-eno (0,4mmol) y 4,0 equivalentes de 2-(2-
bromoetil)morfolin-4-carboxilato de *terc*-butilo (236 mg, 0,400 mmol). El vial se
tapó y la mezcla de reacción se calentó durante 18 horas a 85 °C. El producto
10 bruto se purificó usando una HPLC preparativa Shimadzu que emplea
acetonitrilo/agua/ácido trifluoroacético donde el disolvente A era acetonitrilo al
10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al
10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna
Waters Sunfire 5 μ m C18 19 x 150 mm a un gradiente de 20-100% de B y un
15 caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 10
minutos. La mezcla disolvente se eliminó en el rotovap y el sólido blanco
resultante (19,2 mg) se recogió en 2 ml de dicloroetano que contenía 200 μ l de

ácido trifluoroacético. La mezcla ácida se agitó durante 60 minutos. Los volátiles se eliminaron entonces, se repitió de nuevo el procedimiento dando 20 mg (29% de rendimiento, 2 etapas) de 2-(4-fluorofenil)-5-(5-(isobutilcarbamoil)-2-(2-(morfolin-2-il)etoxi)fenil)-N-metilbenzofuran-3-carboxamida, TFA como un sólido blanco. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX400. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato

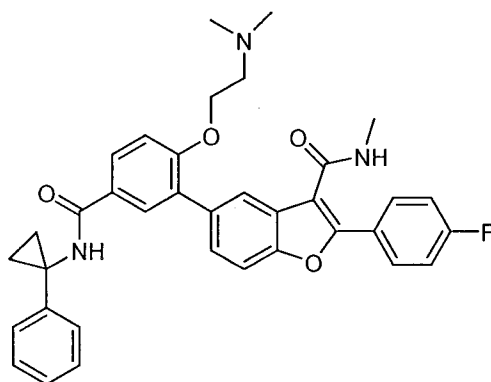
amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,93 (d, $J=6,53$ Hz, 6 H), 1,87 (m, 3 H), 2,90 (d, $J=4,77$ Hz, 3 H), 3,08 - 3,12 (m, 2 H), 3,16 - 3,20 (m, 2 H), 3,31 (d, $J=9,54$ Hz, 2 H), 3,95 - 4,11 (m, 3 H), 4,23 - 4,31 (m, 1 H), 4,35 (s ancho, 1 H), 7,08 (d, $J=8,78$ Hz, 1 H), 7,25 (t, $J=8,66$ Hz, 2 H), 7,45 (dd, $J=8,53$, 1,76 Hz, 1 H), 7,54 (t, $J=5,65$ Hz, 1 H), 7,62 (d, $J=8,53$ Hz, 1 H), 7,84 (dd, $J=8,53$, 2,26 Hz, 1 H), 7,88 (d, $J=2,01$ Hz, 1 H), 7,91 (d, $J=4,02$ Hz, 1 H), 7,98 - 8,07 (m, 3 H). LCEM m/z 574,5 (M+H), Tr = 2,390 min. HPLC (Sunfire C18) Tr = 6,870 min., 99,3% de pureza y (XBridge phenyl C18) Tr = 10,973 min., 99,2% de pureza.

15 2-(2-Bromoetil)morfolin-4-carboxilato de *terc*-butilo

A un matraz de fondo redondo de 25 ml se añadió 2-(morfolin-2-il)etanol (100 mg, 0,762 mmol), DCM (1 ml) y trietilamina (0,106 ml, 0,762 mmol). Se añadió entonces, gota a gota mediante una jeringa dicarbonato de di-*terc*-butilo (0,177 ml, 0,762 mmol) en DCM (1 ml). La mezcla se agitó a temperatura ambiente en nitrógeno durante 3 horas. Se eliminaron los volátiles y se tomó la RMN del aceite incoloro (176 mg, 100% de rendimiento, 96% de pureza). RMN de ^1H (500 MHz, DMSO- d_6) δ ppm 1,39 (s, 9 H), 1,47 - 1,61 (m, 2 H), 2,83 (s ancho, 1

H), 3,28 - 3,42 (m, 3 H), 3,46 (c, $J=6,10$ Hz, 2 H), 3,68 (d, $J=11,29$ Hz, 1 H), 3,76 (d, $J=10,38$ Hz, 2 H), 4,45 (t, $J=5,04$ Hz, 1 H).

A un matraz de fondo redondo de 25 ml a 0 °C se añadió 2-(2-hidroxietil)morfolina-4-carboxilato de *terc*-butilo (0,176 g, 0,762 mmol), DCM (4 ml), 1*H*-imidazol (0,104 g, 1,524 mmol), perbromometano (0,379 g, 1,143 mmol) y trifenilfosfina (0,190 g, 0,723 mmol). La mezcla se agitó durante la noche lentamente alcanzando a la temperatura ambiente. La solución amarilla se diluyó de nuevo con 50 ml de DCM, se lavó con agua, salmuera, se secó sobre sulfato sódico y se filtró. El producto bruto se hizo pasar a través de un tapón de gel de sílice y se eliminó el disolvente dando 213 mg de un aceite amarillo claro. RMN de ^1H (400 MHz, DMSO- d_6) δ ppm 1,40 (s, 9 H), 1,94 (c, $J=6,86$ Hz, 1 H), 2,56 - 2,66 (m, 1 H), 2,76 - 2,91 (m, 1 H), 3,35 - 3,47 (m, 4 H), 3,50 - 3,61 (m, 1 H), 3,68 (s ancho, 1 H), 3,74 - 3,86 (m, 2 H).

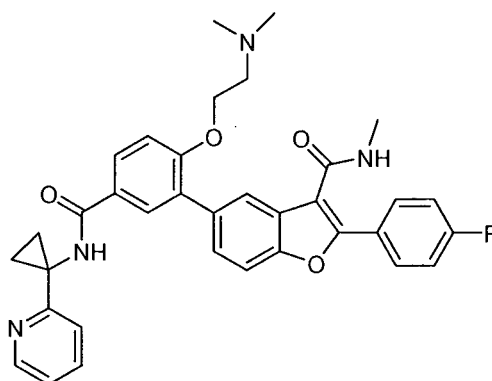


5-(2-(2-(Dimetilamino)etoxi)-5-(1-fenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida, TFA

A un vial de microondas pequeño se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(1-fenilciclopropilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida (11,3 mg, 0,022 mmol) (obtenida de la desmetilación del precursor metoxi usando complejo de tribromuro de boro-sulfuro de metilo (1,2-dicloroetano, 90 °C)),
5 dioxano (2 ml), trifenilfosfina (105 mg, 0,400 mmol), 2-(dimetilamino)etanol (0,025 ml, 0,250 mmol) y azodicarboxilato de di-*tert*-butilo (69,1 mg, 0,300 mmol). El vial se selló y la mezcla de reacción se sometió a calentamiento en microondas (140 °C) durante 20 minutos en un BIOTAGE® Initiator. El disolvente se eliminó en una corriente de nitrógeno, el producto bruto se
10 recogió en 2ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Sunfire 5µm C18 19 x 150mm a un
15 gradiente de 20-100% de B y un caudal de 20 ml/minutos durante 20 minutos con un mantenimiento de 5 minutos. El disolvente se eliminó dando 14,5 mg (90% de rendimiento) de 5-(2-(2-(dimetilamino)etoxi)-5-(1-fenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida, sal TFA como un sólido blanco. Los datos de LC/EM se
20 obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad

HPLC al 90%/ TFA al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / TFA al 0,1%/ metanol calidad HPLC al 10%), en 4 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una
5 columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10
10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna a Gemini C18 3,0µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad
15 HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. El espectro de RMN se registró a temperatura ambiente usando un espectrómetro Bruker DRX400. Los desplazamientos químicos se expresaron en ppm relativas al disolvente
20 deuterado usado. Las constantes de acoplamiento se expresaron en hertz. La multiplicidad de los picos se expresó usando las siguientes abreviaturas: s (singlete), d (doblete), dd (doblete de dobletes), t (triplete), m (multiplete), a

(ancho). RMN de ^1H (400 MHz, THF-d_8) δ ppm 1,22 - 1,27 (m, 2 H), 1,28 - 1,33 (m, 2 H), 2,70 (s, 6 H), 2,90 (d, $J=4,52$ Hz, 3 H), 3,41 - 3,46 (m, 2 H), 4,47 - 4,53 (m, 2 H), 7,06 - 7,12 (m, 1 H), 7,14 - 7,27 (m, 5 H), 7,28 - 7,35 (m, 2 H), 7,47 (dd, $J=8,53, 1,76$ Hz, 1 H), 7,54 - 7,61 (m, 2 H), 7,89 (dd, $J=8,53, 2,26$ Hz, 1 H), 7,94 (dd, $J=4,02, 2,01$ Hz, 2 H), 8,03 - 8,10 (m, 2 H), 8,28 (s, 1 H). LCEM m/z 592,4 (M+H), Tr = 2,065 min. Tr de HPLC = 7,025 min. (Sunfire C18), 95,2 % de pureza y 11,979 min. (Gemini C18), 95,7 % de pureza.

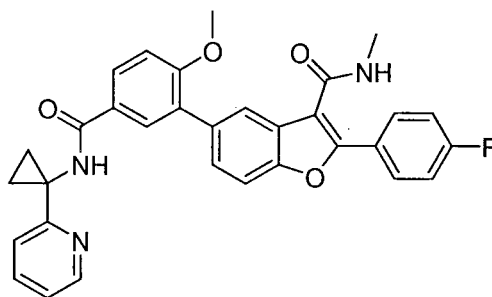


10 5-(2-(2-(Dimetilamino)etoxi)-5-(1-(piridin-2-il)ciclopropilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida, TFA

Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Sunfire 5 μm C18, 4,6 x 50mm, con un gradiente de 0-
15 100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / metanol calidad HPLC al 10%), en 4 minutos con un

mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetoneitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetoneitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3,0µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,32 - 1,37 (m, 2 H), 1,59 - 1,65 (m, 2 H), 2,77 (s, 6 H), 2,90 (d, $J=4,77$ Hz, 3 H), 3,47 - 3,54 (m, 2 H), 4,48 - 4,55 (m, 2 H), 7,17 (d, $J=8,53$ Hz, 1 H), 7,20 - 7,27 (m, 2 H), 7,31 (dd, $J=6,90, 5,65$ Hz, 1 H), 7,49 - 7,59 (m, 2 H), 7,61 - 7,70 (m, 2 H), 7,86 (td, $J=7,78, 1,51$ Hz, 1 H), 7,94 (dd, $J=8,53, 2,26$ Hz, 1 H), 7,97 (d, $J=1,00$ Hz, 1 H), 7,99 - 8,09 (m, 3 H), 8,54 (d, $J=4,27$ Hz, 1 H), 9,07 (s, 1 H). LCEM Tr = 2,412 min., m/z 593,4 (M+H). Tr de HPLC = 5,185 min. (Sunfire C18), 96,4 % de pureza y 11,558 min. (Gemini

C18), 98,2 % de pureza.

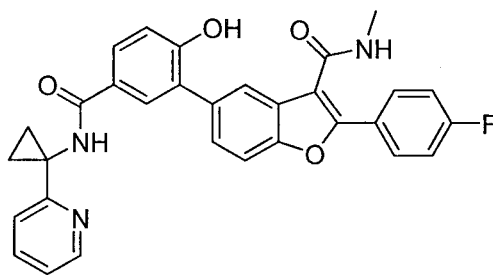


2-(4-Fluorofenil)-5-(2-metoxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-*N*-
5 metilbenzofuran-3-carboxamida

Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 10 μM C18, 3,0 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / metanol calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 5 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5μm 4,6 x 150mm que emplea agua/acetonitrilo/ ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó

entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3,0 μ m 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, DMSO- d_6) δ ppm 1,31 - 1,40 (m, 2 H), 1,56 - 1,65 (m, 2 H), 2,82 (d, $J=4,52$ Hz, 3 H), 3,85 (s, 3 H), 7,24 (d, $J=8,53$ Hz, 1 H), 7,30 (dd, $J=6,78$, 5,52 Hz, 1 H), 7,39 (t, $J=8,91$ Hz, 2 H), 7,46 (d, $J=8,03$ Hz, 1 H), 7,52 (dd, $J=8,53$, 1,76 Hz, 1 H), 7,68 - 7,75 (m, 2 H), 7,86 (s, 1 H), 7,93 - 8,02 (m, 4 H), 8,45 (d, $J=4,52$ Hz, 1 H), 8,49 (d, $J=4,27$ Hz, 1 H), 9,23 (s, 1 H). LCEM Tr = 2,557 min., m/z 536,10 (M+H). Tr de HPLC = 6,683 min. (Sunfire C18), 96,3 % de pureza y 11,493 min. (Gemini C18), 99,5 % de pureza.

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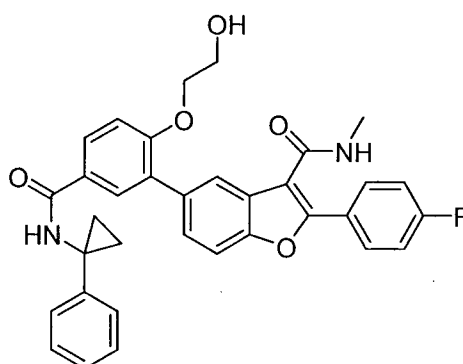


2-(4-Fluorofenil)-5-(2-hidroxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

A un matraz de fondo redondo de 100 ml equipado con un condensador de

reflujo se añadió 2-(4-fluorofenil)-5-(2-metoxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida (400 mg, 0,747 mmol), DCE (42 ml) y complejo de tribromuro de boro-sulfuro de metilo (1868 mg, 5,97 mmol). La solución se colocó en nitrógeno y se agitó durante la noche a 90 °C. La mezcla de reacción se enfrió hasta temperatura ambiente, se inactivó con metanol y se evaporó casi hasta sequedad. La mezcla se recogió en 10 ml de metanol y se purificó usando una HPLC preparativa Shimadzu que emplea metanol/agua/ácido trifluoroacético al 0,1% donde el disolvente A era metanol al 10% / agua al 90% / ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / metanol al 90% / ácido trifluoroacético al 0,1% con una columna PHENOMENEX® Luna 10µm C18 30x100mm a un gradiente de 40-100% de B y un caudal de 40 ml/minutos durante 10 minutos con un mantenimiento de 5 minutos. El disolvente se evaporó dando 234 mg (60% de rendimiento) de 2-(4-fluorofenil)-5-(2-hidroxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida como un sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / metanol calidad HPLC al 10%), en 4 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. RMN de ¹H (400 MHz,

THF- d_8) δ ppm 1,25 - 1,31 (m, 2 H), 1,59 - 1,66 (m, 2 H), 2,90 (d, $J=4,52$ Hz, 3 H), 6,91 (d, $J=8,53$ Hz, 1 H), 7,08 (dd, $J=6,90, 5,40$ Hz, 1 H), 7,17 - 7,24 (m, 2 H), 7,45 - 7,65 (m, 5 H), 7,79 (dd, $J=8,41, 2,13$ Hz, 1 H), 7,88 (d, $J=1,25$ Hz, 1 H), 7,93 (d, $J=2,01$ Hz, 1 H), 8,08 - 8,17 (m, 2 H), 8,39 - 8,45 (m, 1 H), 8,49 (s ancho, 1 H). LCEM Tr = 1,495 min., m/z 522,33 (M+H), 94% de pureza.

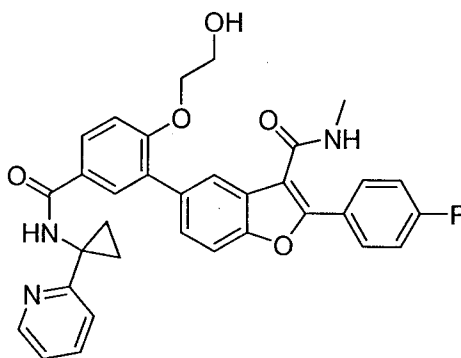


2-(4-Fluorofenil)-5-(2-(2-hidroxietoxi)-5-(1-fenilciclopropilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida

- 10 A un vial pequeño con tapa a rosca se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(1-fenilciclopropilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida (19,5 mg, 0,037 mmol) en DMF (1,3 ml), (2-bromoetoxi)(*terc*-butil)dimetilsilano (0,024 ml, 0,112 mmol) y DBU (1,8-diazabicyclo [5,4,0]undec-7-eno, 0,023 ml, 0,150 mmol). El vial se tapó y se agitó a 80 °C durante 18 horas. El DMF se eliminó
- 15 en una corriente de nitrógeno dando 5-(2-(2-(*terc*-butildimetilsililoxi) etoxi)-5-(1-fenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida como un aceite color castaño. A la mezcla se añadieron entonces 1,3 ml de tetrahidrofurano junto con 2 eq. de HCl 1 M (0,075 ml, 0,075 mmol).

La solución se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción se transfirió a un embudo de separación, se diluyó con acetato de etilo, se lavó secuencialmente con bicarbonato sódico, salmuera y se secó sobre sulfato de magnesio. La mezcla producto se filtró y se evaporó el disolvente. El producto bruto se recogió en 1,8 ml de acetonitrilo y 200 µl de DMF y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Sunfire C18 19 x 150mm a un gradiente de 20-100% de B y un caudal de 20 ml/minutos durante 20 minutos con un mantenimiento de 5 minutos. Se obtuvieron 15,2 mg de 2-(4-fluorofenil)-5-(2-(2-hidroxietoxi)-5-(1-fenilciclopropilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida (70% de rendimiento, 2 etapas) después de evaporar el disolvente. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / metanol calidad HPLC al 10%), en 4 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que

emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un
5 mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna a Gemini C18 3,0 μ m 4,6 x 150mm que emplea agua/metanol / bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM
10 / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,20 - 1,27 (m, 2 H), 1,28 - 1,36 (m, 2 H), 2,87 - 2,96 (m, 3 H), 3,75 - 3,83 (m, 3 H), 4,10 (t, $J=4,89$ Hz, 2 H), 7,04 - 7,13 (m, 2 H), 7,16 -
15 7,25 (m, 4 H), 7,29 - 7,35 (m, 2 H), 7,43 (d, $J=4,27$ Hz, 1 H), 7,51 - 7,59 (m, 2 H), 7,87 (dd, $J=8,53, 2,26$ Hz, 1 H), 7,94 (d, $J=2,26$ Hz, 1 H), 8,02 (s, 1 H), 8,11 - 8,18 (m, 2 H), 8,25 (s, 1 H). LCEM Tr = 2,671min., m/z 565,3 (M+H). Tr de HPLC = 9,454 min. (Sunfire C18), 95,0 % de pureza y 11,611 min. (Gemini C18), 99,7 % de pureza.



2-(4-Fluorofenil)-5-(2-(2-hidroxiethoxi)-5-(1-(piridin-2-il)-
ciclopropilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida

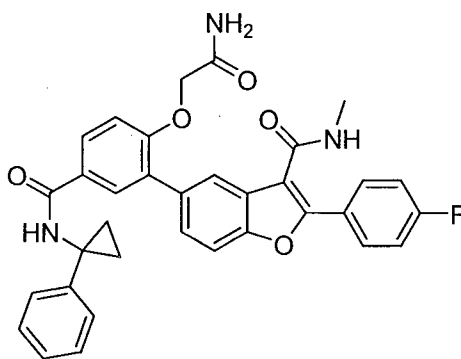
Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma

5 LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4

10 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5mm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua

15 calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC

analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,23 - 1,29 (m, 2 H), 1,62 - 1,68 (m, 2 H), 2,91 (d, $J=4,77$ Hz, 3 H), 3,80 (t, $J=4,77$ Hz, 2 H), 4,13 (t, $J=4,89$ Hz, 2 H), 6,99 (m, 1 H), 7,14 (d, $J=8,53$ Hz, 1 H), 7,17 - 7,25 (m, 2 H), 7,37 - 7,47 (m, 2 H), 7,49 - 7,61 (m, 3 H), 7,93 (dd, $J=8,53, 2,26$ Hz, 1 H), 8,00 (d, $J=2,26$ Hz, 1 H), 8,03 - 8,06 (m, 1 H), 8,11 - 8,18 (m, 2 H), 8,33 (s, 1 H), 8,35 - 8,41 (m, 1 H). LCEM m/z 566,4 (M+H), Tr = 2,038 min. HPLC (Sunfire C18) Tr = 5,916min., 100% de pureza y (XBridge phenyl C18) Tr = 10,474min., 100% de pureza.



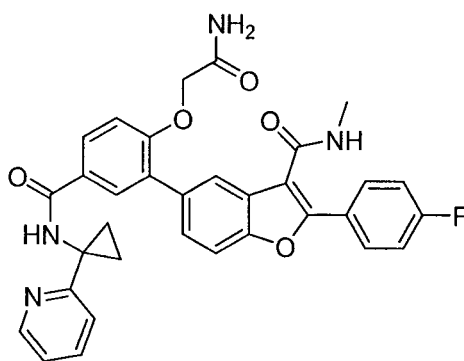
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5-(2-(2-Amino-2-oxoetoxi)-5-(1-fenilciclopropilcarbamoi)fenil)-2-(4-fluorofenil)-
N-metilbenzofuran-3-carboxamida

A un vial pequeño con tapa a rosca se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(1-

fenilciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida (15,6 mg, 0,030 mmol) en DMF (2 ml), 2-bromoacetamida (41,4 mg, 0,300 mmol), y DBU (1,8-diazabicyclo [5,4,0]undec-7-eno, 0,060 ml, 0,400 mmol). El vial se tapó y se agitó a 75 °C durante la noche. La mezcla de reacción bruta se enfrió, se evaporó, se recogió en 2 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna XTERRA® C18 19 x 100mm a un gradiente de 25-100% de B y un caudal de 25 ml/minutos durante 12 minutos con un mantenimiento de 8 minutos. El disolvente se evaporó durante la noche dando 9,9 mg (54,9% de rendimiento) de carboxamida como un sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90% / ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / acetonitrilo calidad HPLC al 10%), en 4 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B =

acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna a Gemini C18 3,0 μ m 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,21 - 1,26 (m, 2 H), 1,26 - 1,33 (m, 2 H), 2,87 - 2,92 (m, 3 H), 4,47 (s, 2 H), 7,05 - 7,13 (m, 2 H), 7,15 - 7,25 (m, 4 H), 7,27 - 7,34 (m, 2 H), 7,45 - 7,51 (m, 1 H), 7,52 - 7,61 (m, 2 H), 7,84 - 7,92 (m, 2 H), 7,93 - 8,00 (m, 2 H), 8,09 - 8,20 (m, 3 H), 8,29 (s, 1 H). LCEM Tr = 2,522min., m/z 578,3(M+H). Tr de HPLC = 8,693 min. (Sunfire C18), 91,0 % de pureza y 11,423 min. (Gemini C18), 92 % de pureza.



5-(2-(2-Amino-2-oxoetoxy)-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

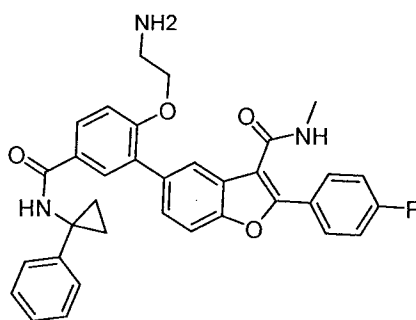
Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma

5 LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90% / ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / acetonitrilo calidad HPLC al 10%), en 4

10 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua

15 calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC

analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3,0µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,25 - 1,37 (m, 2 H), 1,57 - 1,67 (m, 2 H), 2,88 - 2,96 (m, 3 H), 4,49 (s, 2 H), 6,51 (s ancho, 1 H), 6,79 (s ancho, 1 H), 7,10 (d, $J=8,78$ Hz, 1 H), 7,17 - 7,27 (m, 3 H), 7,52 - 7,66 (m, 4 H), 7,72 - 7,82 (m, 1 H), 7,94 (dd, $J=8,53, 2,26$ Hz, 1 H), 7,99 (s, 1 H), 8,03 (d, $J=2,26$ Hz, 1 H), 8,08 - 8,18 (m, 2 H), 8,50 (d, $J=4,27$ Hz, 1 H), 8,91 (s ancho, 1 H). LCEM Tr = 2,578min., m/z 580,3 ($M + 2\text{H}$). Tr de HPLC = 9,368 min. (Sunfire C18), 96,0 % de pureza y 10,756 min. (Gemini C18), 97,9 % de pureza.



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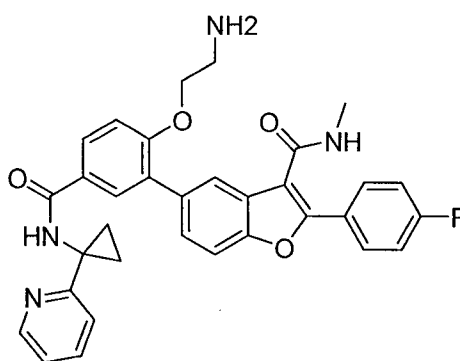
5-(2-(2-Aminoetoxy)-5-(1-fenilciclopropilcarbamoyl)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida, TFA

A un vial de 3,54 ml se añadió 2-(4-fluorofenil)-5-(2-hidroxi-5-(1-

fenilciclopropilcarbamoil) fenil)-*N*-metilbenzofuran-3-carboxamida (40,2 mg, 0,078 mmol) en 3 ml de DMF junto con 3 equivalentes de 2-(2-bromoetil)isoindolin-1,3-diona (58,8 mg, 0,232 mmol) y 4 equivalentes de DBU (1,8-diaza biciclo [5,4,0]undec-7-eno, 0,046 ml, 0,308 mmol). El vial se tapó y se agitó a 75 °C durante la noche. La mezcla de reacción bruta se evaporó, se recogió en 2 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético al 0,1% donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna XTERRA® C18 19 x 100mm a un gradiente de 25-100% de B y un caudal de 25 ml/minutos durante 12 minutos con un mantenimiento de 8 minutos. El disolvente se evaporó proporcionando 10,7 mg del intermedio ftalimida como un sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / metanol calidad HPLC al 10%), en 4 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. LCEM *m/z* 694,4 (M+H), Tr = 3,128 min., 93,7% de pureza. A un vial pequeño con tapa a rosca se añadió el intermedio ftalimida, 5-(2-(2-(1,3-dioxoisoindolin-2-il)etoxi)-5-(1-fenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-

metilbenzofuran-3-carboxamida (10,7 mg, 0,015 mmol) en 2ml de metanol e hidrazina anhidra (0,780 µl, 0,025 mmol). El vial se colocó en un baño de aceite previamente equilibrado ajustado a 75°C y la solución se llevó a reflujo durante 90 minutos. El producto se enfrió hasta temperatura ambiente y se evaporó el disolvente. El aceite resultante se diluyó con 10ml de DCM, se lavó con 1ml de NaOH 0,5M y se extrajo. El disolvente se evaporó y el producto bruto se recogió en 1,8 ml de acetonitrilo y 200 µl de DMF y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Sunfire C18 19 x 150mm a un gradiente de 20-100% de B y un caudal de 20 ml/minutos durante 20 minutos con un mantenimiento de 5 minutos. El disolvente se evaporó dando 7,0 mg (14% de rendimiento, 2 etapas) de 5-(2-(2-aminoetoxi)-5-(1-fenilciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida, TFA como un sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Sunfire 5µm C18, 4,6 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / metanol calidad HPLC al 10%), en 4 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La

pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5 μ m 4,6 x 150mm que emplea agua/acetonitrilo/ ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua
5 calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna a Gemini C18 3,0 μ m 4,6 x 150mm que
10 emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400
15 MHz, THF- d_8) δ ppm 1,21 - 1,27 (m, 2 H), 1,28 - 1,35 (m, 2 H), 2,89 (d, $J=4,77$ Hz, 3 H), 3,39 (t, $J=4,77$ Hz, 2 H), 4,38 (t, $J=5,02$ Hz, 2 H), 7,05 - 7,13 (m, 1 H), 7,16 - 7,28 (m, 5 H), 7,29 - 7,35 (m, 2 H), 7,49 - 7,60 (m, 2 H), 7,62 (s ancho, 1 H), 7,87 (dd, $J=8,53, 2,26$ Hz, 1 H), 7,96 - 8,05 (m, 3 H), 8,07 (d, $J=1,00$ Hz, 1 H), 8,30 (s, 1 H). LCEM Tr = 2,023 min., m/z 564,3 (M+H). Tr de HPLC = 6,931
20 min. (Sunfire C18), 100 % de pureza y 11,423 min. (Gemini C18), 98,9 % de pureza.



5-(2-(2-Aminoetoxi)-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-
N-metilbenzofuran-3-carboxamida, 2 TFA

Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma

5 LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4

10 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua

15 calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC

analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,23 - 1,33 (m, 2 H), 1,60 - 1,67 (m, 2 H), 2,89 (d, $J=4,77$ Hz, 3 H), 3,41 (t, $J=5,14$ Hz, 2 H), 4,40 (t, $J=5,14$ Hz, 2 H), 6,58 (s ancho, 2 H), 7,01 - 7,11 (m, 1 H), 7,16 - 7,29 (m, 3 H), 7,46 (d, $J=8,03$ Hz, 1 H), 7,52 - 7,70 (m, 4 H), 7,93 (dd, $J=8,53, 2,26$ Hz, 1 H), 7,98 - 8,05 (m, 3 H), 8,07 (s, 1 H), 8,41 (d, $J=4,77$ Hz, 1 H), 8,56 (s, 1 H). LCEM m/z 565,4 (M+H), Tr = 1,628 min. HPLC (Sunfire C18) Tr = 5,048 min., 99,9% de pureza y (XBridge phenyl C18) Tr = 10,531 min., 100% de pureza.

15 5-Bromo-2,4-dimetoxi-*N*-(1-(piridin-2-il)ciclopropil)benzamida

A un matraz de fondo redondo de 250 ml se añadió cloroformo (60 ml) junto con ácido 2,4-dimetoxibenzoico (2,0 g, 10,98 mmol). La solución se enfrió hasta 0 °C y se añadió bromo (0,566 ml, 10,98 mmol) gota a gota durante 5 minutos. La solución se dejó calentar hasta temperatura ambiente y se agitó durante la noche. El sólido resultante se filtró, se lavó con cloroformo frío y se secó a vacío dando 2,49g (8,6mmol, 78% de rendimiento) de ácido 5-bromo-2,4-dimetoxibenzoico como un sólido amarillo. Los datos de LC/EM se obtuvieron

- en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 30mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A =
- 5 agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 2 minutos con un mantenimiento de 1 minuto a un caudal de 1,0 ml/minuto. RMN de ^1H (400 MHz, DMSO- d_6) δ ppm 3,88 (s, 3 H), 3,95 (s, 3 H), 6,78 (s, 1 H), 7,86 (s, 1 H). LCEM Tr = 1,453min., m/z 262,99 (M+H), 93% de pureza.
- 10 A un vial de 3,54 ml se añadió ácido 5-bromo-2,4-dimetoxibenzoico (1,044 g, 4mmol), DMF (48,2 ml), *N,N*-diisopropiletilamina (2,79 ml, 16,00 mmol), 1-(piridin-2-il)ciclopropanamina, 2 HCl (0,911 g, 4,40 mmol), y finalmente HATU hexafluorofosfato (V) de (2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetramethylisouronio 6,08 g, 16,00 mmol). El vial se tapó y se agitó durante 16
- 15 horas a temperatura ambiente. La mezcla de reacción bruta se diluyó con 10ml de DCM, se lavó con 5ml de HCl 1M, se extrajo, se lavó con 20ml de salmuera y se secó sobre sulfato de magnesio. La solución se hizo pasar a través de un tapón de gel de sílice y se evaporó hasta sequedad. La trituración con 20 ml de éter etílico dio 1,6 gramos de 5-bromo-2,4-dimetoxi-*N*-(1-(piridin-2-
- 20 il)ciclopropil)benzamida como un sólido color castaño (76% de rendimiento). RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,22 - 1,32 (m, 2 H), 1,59 - 1,67 (m, 2 H), 3,94 (s, 3 H), 4,02 (s, 3 H), 6,72 (s, 1 H), 7,09 (m, 1 H), 7,47 (d, $J=8,03$ Hz, 1

H), 7,62 (td, $J=7,72$, 1,88 Hz, 1 H), 8,20 (s, 1 H), 8,39 - 8,52 (m, 2 H). LCEM Tr = 2,162 min., m/z 379,2 (M+2H), 96 % de pureza.

Ácido 5-bromo-2-metoxi-4-metilbenzoico

- 5 Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5 μ m C18, 4,6 x 30mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ metanol calidad HPLC al 10%), en 2 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. Sólido amarillo, 63,5% de rendimiento. LCEM Tr = 1,545 min., m/z 246,99 (M+H), 90 % de pureza. RMN de ^1H (400 MHz, DMSO- d_6) δ ppm 2,21 - 2,44 (m, 3 H), 3,82 (s, 3 H), 7,17 (s, 1 H), 7,78 (s, 1 H), 12,72 (s ancho, 1 H).
- 10
- 15

5-Bromo-2-metoxi-4-metil-*N*-(1-(piridin-2-il)ciclopropil)benzamida

- Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3 μ m C18, 2,0 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4
- 20

minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. Sólido color cataño, 68% de rendimiento, 100% de pureza. RMN de ^1H (400 MHz, DMSO- d_6) δ ppm 1,34 - 1,42 (m, 2 H), 1,58 - 1,66 (m, 2 H), 2,39 (s, 3 H), 3,96 (s, 3 H), 7,05 (s, 1 H), 7,40 (dd, $J=6,90, 5,90$ Hz, 1 H), 7,76 (d, $J=8,03$ Hz, 1 H), 7,97 (td, $J=7,78, 1,76$ Hz, 1 H), 8,10 (s, 1 H), 8,60 (d, $J=5,27$ Hz, 1 H), 8,88 (s, 1 H). LCEM Tr = 3,525 min., m/z 362,88 (M+H), 98 % de pureza.

4-Hidroxi-2-metoxibenzoato de metilo

A un matraz Erlenmeyer de 250 ml se añadió 4-amino-2-metoxibenzoato de metilo (7,5 g, 41,4 mmol) y una solución de ácido sulfúrico al 25% (40 ml, 188 mmol). La solución se enfrió hasta 0°C y se añadió gota a gota una solución saturada de nitrito sódico (4,29 g, 62,2 mmol). La mezcla naranja se agitó durante 15 minutos. La solución de diazonio resultante se vertió luego muy lentamente en un matraz de 1 litro que contenía 500 ml de ácido sulfúrico al 3%. La solución se agitó durante 5 minutos y luego se traspasó a un embudo de adición. La mezcla de reacción se diluyó con 150ml de DCM, se extrajo, se secó sobre sulfato de magnesio y se concentró hasta un sólido rojo. El sólido resultante se trituró con hexano dando 5,71 g del fenol deseado como un polvo rojo (73% de rendimiento). Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5 μm C18, 4,6 x 30mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/

ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ metanol calidad HPLC al 10%), en 2 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. RMN de ^1H (400 MHz, DMSO- d_6) δ ppm 3,67 - 3,72 (m, 3 H), 3,74 (s, 3 H), 6,39 (dd, $J=8,66, 2,13$ Hz, 1 H), 6,45 (d, $J=2,13$ Hz, 1 H), 7,59 (d, $J=8,66$ Hz, 1 H). LCEM Tr = 1,070 min., m/z 183,09 (M+H), 96% de pureza.

4-(2-Amino-2-oxoetoxi)-5-bromo-2-metoxibenzoato de metilo

A un tubo sellado se añadió 2-bromoacetamida (2,272 g, 16,47 mmol), DMF (50 ml), carbonato de cesio (7,15 g, 21,96 mmol) y 4-hidroxi-2-metoxibenzoato de metilo (1,00 g, 5,49 mmol). El tubo se selló y se calentó durante 16 horas a 85 °C. La mezcla de reacción se diluyó con DCM, se lavó secuencialmente con 10ml de HCl 1M, agua y salmuera. La solución se secó sobre sulfato sódico, se filtró y se eliminó el disolvente dando 1,2 gramos de 4-(2-amino-2-oxoetoxi)-2-metoxibenzoato de metilo (78% de rendimiento) como un polvo amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5 μm C18, 4,6 x 30mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ metanol calidad HPLC al 10%), en 2 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ

ppm 3,71 - 3,76 (m, 3 H), 3,80 - 3,84 (m, 3 H), 4,45 (s, 2 H), 6,56 (dd, $J=8,66$, 2,38 Hz, 1 H), 6,65 (d, $J=2,26$ Hz, 1 H), 6,77 (s ancho, 1 H), 6,92 (s ancho, 1 H), 7,75 (d, $J=8,78$ Hz, 1 H). LCEM Tr = 1,385 min., m/z 240,2 (M+H), 92% de pureza.

- 5 A un matraz de fondo redondo de 250 ml se añadió 4-(2-amino-2-oxoetoxi)-2-metoxibenzoato de metilo (1,2 g, 5,14 mmol) y cloroformo (40 ml). La mezcla se colocó en una atmósfera de nitrógeno y se enfrió hasta 0°C. Se añadió gota a gota bromo (0,263 ml, 5,14 mmol) (en 3ml de cloroformo) y la solución se dejó calentar hasta temperatura ambiente durante la noche. El sólido naranja se
- 10 enfrió con un baño de hielo, se filtró, se lavó secuencialmente con cloroformo frío, luego éter dietílico. El producto se secó a vacío dando 1,7 gramos (91% de rendimiento) de 4-(2-amino-2-oxoetoxi)-5-bromo-2-metoxibenzoato de metilo como un sólido naranja. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente
- 15 conjunto de condiciones: columna Waters Sunfire 5 μ m C18, 4,6 x 30mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ metanol calidad HPLC al 10%), en 2 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. RMN de
- 20 ^1H (400 MHz, THF- d_8) δ ppm 3,76 (s, 3 H), 3,88 (s, 3 H), 4,63 (s, 2 H), 6,76 (s, 1 H), 7,10 (s ancho, 2 H), 7,96 (s, 1 H). LCEM Tr = 1,793 min., m/z 319,1 (M+H), 90% de pureza.

5-(2,4-Dimetoxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

A un vial de microondas se añadió 5-bromo-2,4-dimetoxi-*N*-(1-(piridin-2-il)ciclopropil)benzamida (41,5 mg, 0,110 mmol), 2-(4-fluorofenil)-*N*-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzofuran-3-carboxamida (39,5 mg, 0,1 mmol), dioxano (2,00 ml), agua (0,200 ml), dicitclohexil(2',6'-dimetoxibifenil-2-il)fosfina (S-Phos, 8,21 mg, 0,020 mmol), fostato potásico tribásico (85 mg, 0,400 mmol) y acetato de paladio(II) (4,49 mg, 0,020 mmol). El disolvente se eliminó y la mezcla de reacción bruta se recogió en 2 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 3,5µm C18 4,6x150mm a un gradiente de 20-100% de B y un caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 10 minutos. El disolvente se evaporó dando 18,1mg (30,4% de rendimiento) de la piridilcarboxamida deseada como un sólido amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: Columna PHENOMENEX® Luna 10µm C18, 3,0 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua

calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ metanol calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 5 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3,0 µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF-d_8) δ ppm 1,26 - 1,37 (m, 2 H), 1,60 - 1,67 (m, 2 H), 2,89 (d, $J=4,77$ Hz, 3 H), 3,87 (s, 3 H), 4,07 (s, 3 H), 6,78 (s, 1 H), 7,10 - 7,23 (m, 3 H), 7,39 - 7,44 (m, 1 H), 7,46 - 7,52 (m, 2 H), 7,57 (d, $J=7,78$ Hz, 1 H), 7,68 (td, $J=7,72$, 1,63 Hz, 1 H), 7,74 (d, $J=1,25$ Hz, 1 H), 8,09 (s, 1 H), 8,11 - 8,19 (m, 2 H), 8,47 (d, $J=4,52$ Hz, 1 H), 8,59 (s, 1 H). LCEM m/z 566,2 (M+H), Tr = 2,608 min. HPLC (Sunfire C18) Tr = 6,816min,

93,9% de pureza y (Gemini C18) Tr = 11,676min., 95,8% de pureza.

2-(4-Fluorofenil)-5-(4-metoxi-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-
N-metilbenzofuran-3-carboxamida

- 5 Síntesis alternativa. A un tubo sellado se añadió 5-bromo-2-metoxi-4-metil-*N*-(1-(piridin-2-il)ciclopropil) benzamida (1,9024 g, 5,27 mmol), dioxano (70 ml), 2-(4-fluorofenil)-*N*-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzofuran-3-carboxamida (2,529 g, 6,40 mmol), carbonato de cesio (2,57 g, 7,90 mmol), agua (14,00 ml) y finalmente tetraquis(trifenilfosfina)paladio(0) (0,304 g, 0,263
- 10 mmol). El recipiente se selló y se calentó durante 16 horas a 85 °C en un baño de aceite. La mezcla se enfrió hasta temperatura ambiente, se diluyó con 20 ml de DCM y se hizo pasar a través de un tapón de CELITE®. La solución oscura resultante se concentró hasta un aceite gris. A este residuo se añadieron 20 ml de HCl 0,5N, seguido por 20 ml de agua. El matraz se enfrió en un baño de
- 15 hielo durante 30 minutos y los sólidos resultantes se recogieron por filtración y se lavaron con 10 ml de agua y se secaron a vacío. El producto bruto se recogió en acetato de etilo/ hexano 1:1 y se hizo pasar a través de un tapón de gel de sílice. El disolvente se eliminó dando 1,65 gramos del producto como un sólido color castaño claro.

20

4-(2-Amino-2-oxoetoxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoato de metilo

A un tubo sellado se añadió 4-(2-amino-2-oxoetoxi)-5-bromo-2-metoxibenzoato de metilo (318 mg, 1,0 mmol), dioxano (30 ml), agua (6,00 ml), 2-(4-fluorofenil)-N-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzofuran-3-carboxamida (593 mg, 1,500 mmol), carbonato de cesio (489 mg, 1,500 mmol) y tetraquis(trifenilfosfina)paladio(0) (23,11 mg, 0,020 mmol). El recipiente se selló y la mezcla se calentó durante la noche a 85 °C. La mezcla de reacción se enfrió, se diluyó con 200ml de DCM, se lavó secuencialmente con 50 ml de HCl 1M y luego salmuera. El producto se extrajo y la solución amarilla resultante se evaporó hasta sequedad. Las fases acuosas se reunieron, se enfriaron durante 5 minutos en un baño de hielo y los sólidos que se formaron se filtraron y secaron a vacío. Los sólidos se reunieron entonces y trituraron secuencialmente con éter dietílico y luego acetonitrilo enfriado en hielo (10 ml de cada uno) dando 171,6 mg (30% de rendimiento) de 4-(2-amino-2-oxoetoxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoato de metilo como un sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a

254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters Phenyl XBridge C18 3,5µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, CD_3OD) δ ppm 3,04 (s, 3 H), 3,92 (s, 3 H), 4,03 (s, 3 H), 4,71 (s, 2 H), 6,85 (s, 1 H), 7,33 (t, $J=8,78$ Hz, 2 H), 7,57 - 7,64 (m, 1 H), 7,66 - 7,73 (m, 1 H), 7,87 (s, 1 H), 7,96 (s, 1 H), 8,00 - 8,08 (m, 2 H). LCEM m/z 507,3 (M+H), Tr = 2,635 min. Tr de HPLC = 8,193 min. (Sunfire C18), 100 % de pureza y Tr = 10,678 min. (Phenyl XBridge C18), 100 % de pureza.

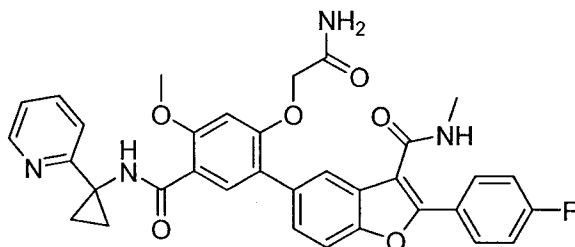
20 Ácido 4-(2-amino-2-oxoetoxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoico

A un matraz de fondo redondo de 50 ml se añadió 4-(2-amino-2-oxoetoxi)-5-(2-

(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoato de metilo (171,6 mg, 0,295 mmol) en una mezcla 1:1 de metanol (7ml) y THF (7 ml). A esta solución se añadieron entonces 4 equivalentes de hidróxido sódico acuoso 1M (1,2 ml, 1,2 mmol). La mezcla de reacción se agitó durante la noche a temperatura ambiente. Se eliminó el disolvente y el producto bruto se diluyó con 50ml de DCM/acetato de etilo 1:1, se lavó secuencialmente con 10ml de HCl 1M y luego salmuera. La solución producto se secó sobre sulfato sódico, se filtró y se evaporó hasta sequedad. Las fases acuosas se reunieron, se enfriaron en un baño de hielo y el producto que se formó en las caras del matraz se filtró y secó a vacío. Se reunieron los sólidos, se recogieron en 10 ml de DMF y se purificaron usando una HPLC preparativa Shimadzu que emplea metanol/agua/ ácido trifluoroacético donde el disolvente A era metanol al 10% / agua al 90% / ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / metanol al 90% / ácido trifluoroacético al 0,1% con una columna PHENOMENEX® Luna 10µm C18 30x100mm a un gradiente de 40-100% de B y un caudal de 40 ml/minutos durante 12 minutos con un mantenimiento de 10 minutos. Se eliminó el disolvente dando 87mg (60% de rendimiento) de ácido 4-(2-amino-2-oxoetoxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoico como un polvo blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 30mm, con un gradiente de 0-100% de B (B = metanol calidad

HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ metanol calidad HPLC al 10%), en 2 minutos con 1 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, DMF- d_7) δ ppm 2,97 (d, $J=4,52$ Hz, 3 H), 4,02 (s, 3 H), 4,79 (s, 2 H), 6,97 (s, 1 H), 7,31 (s ancho, 1 H), 7,38 - 7,46 (m, 2 H), 7,51 (s ancho, 1 H), 7,67 - 7,77 (m, 2 H), 7,92 (s, 1 H), 7,95 (s, 1 H), 8,09 - 8,16 (m, 2 H), 8,35 (d, 1 H). LCEM m/z 493,00 (M+H), Tr = 1,618 min. HPLC (Sunfire C18) Tr = 7,108 min, 100% de pureza y (XBridge phenyl C18) Tr = 6,383 min., 99,3%

de pureza.



5-(2-(2-Amino-2-oxoetoxy)-4-metoxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-

5 2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

A un matraz de 25 ml se añadió ácido 4-(2-amino-2-oxoetoxy)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxibenzoico (48,8 mg, 0,099 mmol), DMF (2 ml), *N*-etil-*N*-diisopropilpropan-2-amina (0,069 ml, 0,396 mmol), 1-(piridin-2-il)ciclopropanamina (19,94 mg, 0,149 mmol) y finalmente
10 HATU (hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio, 151 mg, 0,396 mmol). El matraz se selló con un septo, se colocó en N₂ y se agitó a temperatura ambiente durante la noche. El producto bruto se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al
15 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 19 x 150mm a un gradiente de 20-100% de B y un caudal de 25 ml/minutos durante 22 minutos con un mantenimiento de 8 minutos. El disolvente se eliminó dando 53,0 mg (87% de rendimiento) de 5-(2-

(2-amino-2-oxoetoxi)-4-metoxi-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida como un polvo amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones:

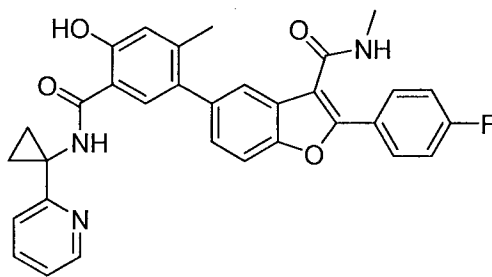
5 columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se

10 determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al

15 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/bicarbonato amónico 10 mM con un

20 gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con

un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, DMF- d_7) δ ppm 1,46 - 1,53 (m, 2 H), 1,69 - 1,76 (m, 2 H), 2,96 (d, $J=4,77$ Hz, 3 H), 4,16 (s, 3 H), 4,82 (s, 2 H), 7,04 (s, 1 H), 7,34 (s ancho, 1 H), 7,36 - 7,48 (m, 3 H), 7,52 (s ancho, 1 H), 7,66 - 7,78 (m, 3 H), 7,92 - 8,01 (m, 2 H), 8,03 (d, $J=2,76$ Hz, 1 H), 8,08 - 8,14 (m, 2 H), 8,36 (d, $J=4,77$ Hz, 1 H), 8,57 - 8,62 (m, 1 H), 8,94 (s, 1 H). LCEM m/z 609,5 ($M+H$), Tr = 2,030 min. HPLC (Sunfire C18) Tr = 5,800 min, 99,4% de pureza y (XBridge phenyl C18) Tr = 9,546 min., 99,7% de pureza.

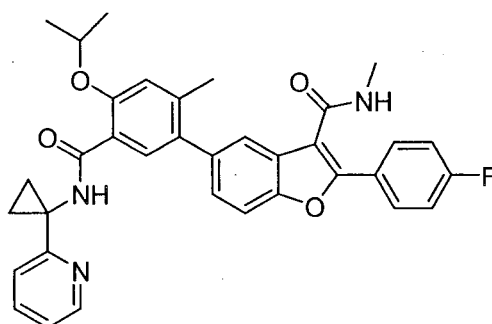


2-(4-Fluorofenil)-5-(4-hidroxi-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoi)fenil)-
N-metilbenzofuran-3-carboxamida

A un matraz de fondo redondo de 250 ml se añadió 2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoi)fenil)-N-metilbenzofuran-3-carboxamida (1,0008 g, 1,821 mmol) y DCM (18 ml). La solución se colocó en una atmósfera de nitrógeno y se enfrió hasta 0 °C. A la mezcla color castaño se añadió gota a gota tricloroborano 1M (9,10 ml, 9,10 mmol). Se dejó calentar la mezcla lentamente hasta temperatura ambiente durante la noche. La mezcla de reacción se enfrió hasta 0 °C y se añadieron 100 ml de metanol frío y la mezcla

se agitó durante 30 minutos y luego se evaporó casi hasta sequedad. Se repitió la adición de metanol seguido por evaporación dando un sólido color castaño (82% de rendimiento). Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 95%/ acetato amónico 10mM/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / acetato amónico 10mM/ acetonitrilo calidad HPLC al 5%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. RMN de ¹H (400 MHz, THF-d₈) δ ppm 1,26 - 1,37 (m, 2 H), 1,57 - 1,66 (m, 2 H), 2,28 (s, 3 H), 3,02 (d, *J*=4,02 Hz, 3 H), 6,77 (s, 1 H), 7,18 (t, *J*=8,78 Hz, 3 H), 7,32 (d, *J*=8,28 Hz, 1 H), 7,51 (d, *J*=8,53 Hz, 1 H), 7,69 - 7,79 (m, 1 H), 7,83 - 7,97 (m, 3 H), 8,08 (s, 1 H), 8,22 - 8,39 (m, 4 H), 8,66 (s ancho, 1 H). LCEM *m/z* 536,5 (M+H), 534,4 (M - H), Tr = 3,446 min., 90% de pureza.

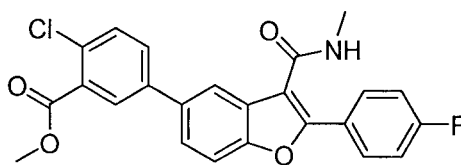
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2-(4-Fluorofenil)-5-(4-isopropoxi-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida, TFA

A un vial de microondas se añadió 2-(4-fluorofenil)-5-(4-hidroxi-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida (16,6 mg, 0,031 mmol), dioxano (2 ml), trifenilfosfina (32,5 mg, 0,124 mmol), diazen-1,2-dicarboxilato de (*E*)-di-*tert*-butilo (21,41 mg, 0,093 mmol) y propan-2-ol (5,92 µl, 0,077 mmol). El vial se selló y sometió a calentamiento en microondas (140°C) durante 20 minutos. El producto bruto se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 19 x 150mm a un gradiente de 20-100% de B y un caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 5 minutos. El disolvente se eliminó dando 6 mg (25% de rendimiento) de 2-(4-fluorofenil)-5-(4-isopropoxi-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-*N*-metilbenzofuran-3-carboxamida como un polvo incoloro. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y

256nm con una columna Waters Sunfire C18 3,5 μ m 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5 μ m 4,6 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, THF- d_8) δ ppm 1,24 - 1,31 (m, 2 H), 1,46 (d, $J=6,02$ Hz, 6 H), 1,64 - 1,69 (m, 2 H), 2,29 (s, 3 H), 2,89 (d, $J=4,52$ Hz, 3 H), 4,83 - 4,95 (m, 1 H), 6,98 - 7,04 (m, 1 H), 7,07 (s, 1 H), 7,16 - 7,24 (m, 2 H), 7,26 (dd, $J=8,28$, 1,76 Hz, 1 H), 7,47 (d, $J=8,03$ Hz, 2 H), 7,52 - 7,59 (m, 2 H), 7,62 (d, $J=1,26$ Hz, 1 H), 7,95 (s, 1 H), 8,11 - 8,19 (m, 2 H), 8,36 - 8,43 (m, 1 H), 8,61 (s, 1 H). LCEM m/z 578,4 (M+H), Tr = 2,746 min. HPLC (Sunfire C18) Tr = 7,695 min, 98,38% de pureza y (XBridge phenyl C18) Tr = 12,003 min., 95,9 % de pureza.

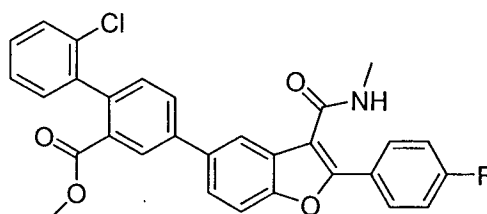


2-Cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoato de metilo

A un tubo sellado de 150 ml se añadió trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (0,5 g, 1,198 mmol), dioxano (7,18 ml), agua (1,437 ml), tetraquis (trifenilfosfina)paladio(0) (0,028 g, 0,024 mmol), ácido 4-cloro-3-(metoxycarbonil)fenilborónico (0,385 g, 1,797 mmol), y carbonato de cesio (0,586 g, 1,797 mmol). El tubo se selló y se calentó en un baño de aceite durante la noche a 85 °C. La mezcla de reacción se enfrió; el producto bruto se diluyó con 100 ml de acetato de etilo, lavó secuencialmente con 50 ml de agua y luego salmuera. La solución producto se secó sobre sulfato de magnesio y se filtró. El disolvente se evaporó dando un sólido amarillo bruto. El sólido se trituroó con éter dietílico (30 ml x2) y hexano (30 ml x1) luego se secó a vacío dando 394 mg de un sólido color marfil (53% de rendimiento). Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. RMN

de ^1H (400 MHz, THF- d_8) δ ppm 2,92 (d, $J=4,77$ Hz, 3 H), 3,91 (s, 3 H), 7,18 - 7,27 (m, 2 H), 7,52 - 7,55 (m, 1 H), 7,57 (d, $J=8,53$ Hz, 1 H), 7,63 (d, $J=1,25$ Hz, 2 H), 7,82 (dd, $J=8,41, 2,38$ Hz, 1 H), 7,96 - 8,00 (m, 1 H), 8,09 - 8,17 (m, 3 H). LCEM m/z 438,3 (M+H), Tr = 3,518 min., 90 % de pureza.

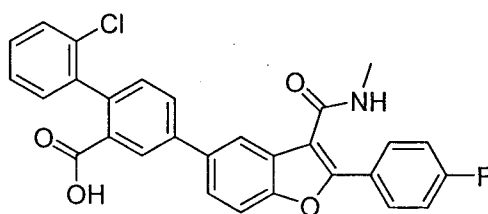
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2'-Cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)bifenil-2-carboxilato de metilo

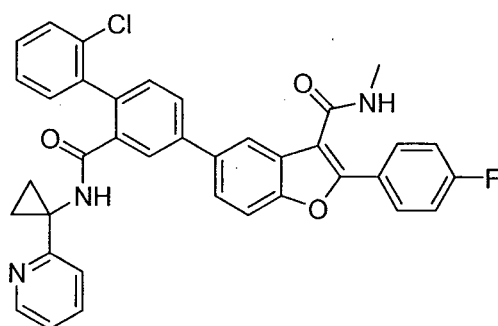
A un vial de microondas se añadió dioxano (6 ml), agua (0,600 ml),
 10 diciclohexil(2',6'-dimetoxi bifenil-2-il)fosfina (S-Phos, 16,42 mg, 0,040 mmol), 2-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoato de metilo (87,6 mg, 0,2 mmol), fostato potásico tribásico (0,170 g, 0,800 mmol), acetato de paladio(II) (8,98 mg, 0,040 mmol) y ácido 2-clorofenilborónico (0,094 g, 0,600 mmol). El vial se tapó, se desgasificó, se llenó con N_2 y se calentó en el
 15 microondas durante 10 minutos a 130 °C. El disolvente se eliminó y la mezcla de reacción bruta se recogió en 4 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al
 20 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5 μm C18

19x150mm a un gradiente de 20-100% de B y un caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 10 minutos. El disolvente se eliminó dando 43,8 mg (80% de rendimiento) de 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)bifenil-2-carboxilato de metilo como un sólido amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. RMN de ¹H (400 MHz, THF-d₈) δ ppm 2,92 - 2,97 (m, 3 H), 3,60 - 3,62 (m, 3 H), 7,19 - 7,26 (m, 2 H), 7,27 - 7,34 (m, 3 H), 7,37 (d, J=8,03 Hz, 1 H), 7,41 - 7,45 (m, 1 H), 7,46 - 7,52 (m, 1 H), 7,62 - 7,67 (m, 1 H), 7,68 - 7,73 (m, 1 H), 7,92 (dd, J=7,91, 2,13 Hz, 1 H), 8,05 (d, J=1,25 Hz, 1 H), 8,12 - 8,19 (m, 2 H), 8,29 (d, J=2,01 Hz, 1 H). LCEM *m/z* 514,2 (M+H), Tr =3,908 min., 93% de pureza.



Ácido 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)bifenil-2-carboxílico

A un matraz de fondo redondo de 25 ml se añadió 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)bifenil-2-carboxilato de metilo (43,8 mg, 0,079 mmol), metanol (1 ml), THF (1 ml) y 8 equivalentes de una solución 1M de hidróxido sódico (0,63 ml, 0,63 mmol). La mezcla se agitó a temperatura ambiente durante 48 horas. El producto bruto se diluyó con 20 ml de acetato de etilo, se acidificó con HCl 0,5M, se extrajo, se lavó con salmuera, se secó sobre sulfato sódico, se filtró y se evaporó hasta sequedad dando 47,2 mg (96% de rendimiento) de ácido 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-5-metilbifenil-2-carboxílico como un sólido amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. LCEM m/z 500,2 (M+H), Tr = 3,426 min., 90% de pureza.

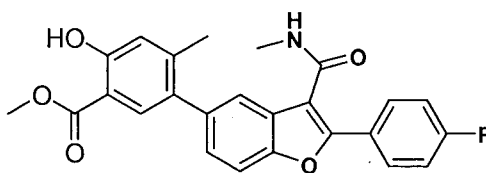


5-(2'-Cloro-2-(1-(piridin-2-il)ciclopropilcarbamoil)bifenil-4-il)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

A un matraz de 25 ml añadió ácido 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)bifenil-2-carboxílico (39,6 mg, 0,079 mmol), DMF (2 ml), *N*-etil-*N,N*-isopropilpropan-2-amina (0,055 ml, 0,317 mmol), 1-(piridin-2-il) ciclopropanamina (15,94 mg, 0,119 mmol) y finalmente HATU (hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo [4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio, (120 mg, 0,317 mmol). El matraz se selló y la mezcla se agitó durante la noche a temperatura ambiente. El producto bruto se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 19 x 150mm a un gradiente de 20-100% de B y un caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 10 minutos. Se eliminó el disolvente dando 40,7 mg (70% de rendimiento) de 5-(2'-cloro-2-(1-(piridin-2-il)ciclopropilcarbamoil)bifenil-4-il)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-

carboxamida como un sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ¹H (400 MHz, THF-d₈) δ ppm 0,90 - 1,10 (m, 2 H), 1,42 -

1,53 (m, 2 H), 2,94 (d, $J=4,52$ Hz, 3 H), 7,11 (dd, $J=6,90, 5,40$ Hz, 1 H), 7,18 - 7,27 (m, 2 H), 7,30 - 7,43 (m, 5 H), 7,44 - 7,49 (m, 1 H), 7,52 - 7,58 (m, 1 H), 7,59 - 7,67 (m, 2 H), 7,73 (dd, $J=8,53, 1,76$ Hz, 1 H), 7,81 (dd, $J=7,78, 2,01$ Hz, 1 H), 7,95 - 8,01 (m, 2 H), 8,06 (d, $J=1,51$ Hz, 1 H), 8,09 - 8,17 (m, 2 H), 8,41 (d, $J=4,02$ Hz, 1 H). LCEM m/z 617,3 (M+H), Tr = 2,765 min. HPLC (Sunfire C18) Tr = 7,823 min, 100% de pureza y (XBridge phenyl C18) Tr = 11,871min., 99,8% de pureza.



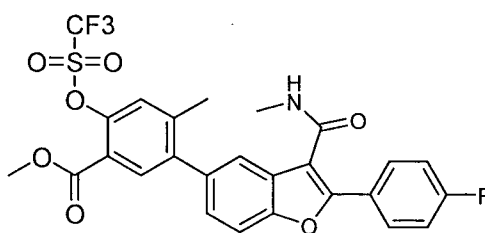
10 5-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-hidroxi-4-metilbenzoato de metilo

A un matraz de fondo redondo de 100 ml se añadió 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoato de metilo (350,5 mg, 0,783 mmol) en DCM (8 ml). A esta solución se añadió, en nitrógeno, una solución de tricloruro de boro 1M (3,92 ml, 3,92 mmol) y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se enfrió en un baño de hielo y se añadieron lentamente 10 ml de metanol. El disolvente se eliminó a vacío. El matraz se enfrió de nuevo, se añadieron 25 ml de metanol enfriado en hielo y el sólido resultante se filtró dando 264,5 mg (78% de rendimiento) de 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-hidroxi-

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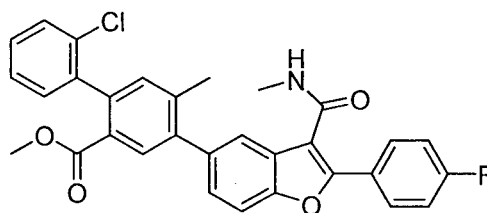
4-metilbenzoato de metilo como un sólido color marfil. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. RMN de ^1H (400 MHz, DMF- d_7) δ ppm 2,30 (s, 3 H), 2,95 (d, $J=4,77$ Hz, 3 H), 3,98 (s, 3 H), 7,02 (s, 1 H), 7,38 - 7,48 (m, 3 H), 7,68 - 7,73 (m, 2 H), 7,76 (d, $J=8,53$ Hz, 1 H), 8,08 - 8,15 (m, 2 H), 8,33 (s ancho, 1 H). LCEM Tr = 3,636, m/z 434,3 (M+H), 100% de pureza.



15 5-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metil-2-(trifluorometilsulfonilo)benzoato de metilo

A un matraz de fondo redondo de 25 ml se añadió 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-hidroxi-4-metilbenzoato de metilo (260 mg, 0,600 mmol), DCM (6 ml), trietilamina (0,166 ml, 1,200 mmol) y 1,1,1-trifluoro-

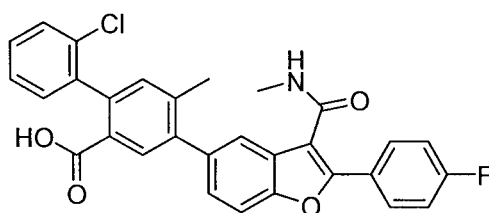
N-fenil-*N*-(trifluorometilsulfonil)metanosulfonamida (321 mg, 0,900 mmol). La solución se agitó durante la noche a temperatura ambiente. Se añadió entonces a la mezcla de reacción DMF (6 ml) junto con trietilamina (0,166 ml, 1,200 mmol) y 1,1,1-trifluoro-*N*-fenil-*N*-(trifluorometilsulfonil)metanosulfonamida (321 mg, 0,900 mmol). La mezcla se calentó hasta 65 °C durante cuarenta y ocho horas. La mezcla producto bruta se llevó de nuevo hasta temperatura ambiente, se diluyó con 100 ml de DCM, lavó secuencialmente con 50 ml de HCl 0,1M frío, agua y salmuera. El disolvente se evaporó y el producto bruto resultante se trituró con 10 ml de éter dietílico (x2) dando 180,7 mg (44,7% de rendimiento) de un sólido color marfil. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. RMN de ¹H (500 MHz, DMSO-d₆) δ ppm 2,37 (s, 3 H), 2,82 (d, *J*=4,58 Hz, 3 H), 3,88 (s, 3 H), 7,36 - 7,47 (m, 3 H), 7,56 - 7,65 (m, 2 H), 7,78 (d, *J*=8,54 Hz, 1 H), 7,91 (s, 1 H), 7,95 - 8,05 (m, 2 H), 8,47 (d, 1 H). LCEM *m/z* 566,3 (M+H), Tr = 3,913 min., 90% de pureza.



2'-Cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-5-metilbifenil-2-carboxilato de metilo

A un tubo pequeño sellado se añadió 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metil-2-(trifluorometilsulfonilo)benzoato de metilo (67,3 mg, 0,1 mmol), dioxano (3 ml), agua (0,600 ml), ácido 2-clorofenilborónico (18,76 mg, 0,120 mmol), carbonato de cesio (32,6 mg, 0,100 mmol) y tetraquis(trifenilfosfina)paladio(0) (2,311 mg, 2,000 μ mol). El tubo se selló y se calentó durante la noche a 80 °C. La reacción se enfrió hasta temperatura ambiente, se filtró a través de un tapón de CELITE® y se concentró casi hasta sequedad en una corriente de nitrógeno. La mezcla de reacción bruta se recogió en 6 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 3,5 μ m C18 19 x 150mm a un gradiente de 30-100% de B y un caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 10 minutos. El disolvente se eliminó dando 48 mg (89% de rendimiento) de 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-5-metilbifenil-2-carboxilato de metilo como un

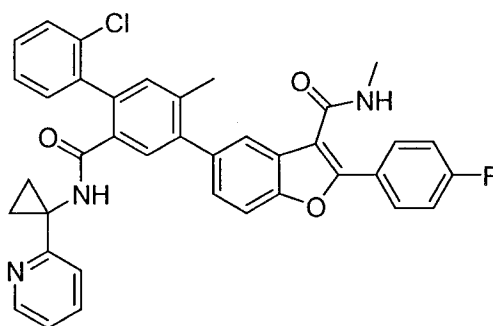
sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1% / agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1% / acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. RMN de ¹H (500 MHz, THF-d₈) δ ppm 2,35 (s, 3 H), 2,91 (d, J=4,58 Hz, 3 H), 3,57 (s, 3 H), 7,21 - 7,26 (m, 3 H), 7,27 - 7,30 (m, 1 H), 7,30 - 7,34 (m, 2 H), 7,38 (dd, J=8,39, 1,68 Hz, 1 H), 7,41 - 7,44 (m, 1 H), 7,50 (d, J=4,27 Hz, 1 H), 7,63 (d, J=8,24 Hz, 1 H), 7,75 (d, J=1,53 Hz, 1 H), 7,92 (s, 1 H), 8,13 - 8,19 (m, 2 H). LCEM *m/z* 528,4 (M+H), Tr = 4,036 min., 98,3% de pureza.



15 Ácido 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-5-metilbifenil-2-carboxílico

A un matraz de fondo redondo de 25 ml se añadió 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-5-metilbifenil-2-carboxilato de metilo (48 mg, 0,091 mmol), THF (2,2 ml), metanol (2,2 ml) e hidróxido sódico acuoso 1M
20 (0,728 ml, 0,728 mmol). El matraz se selló y se agitó a temperatura ambiente

durante 48 horas. Se eliminaron los volátiles y el producto bruto se diluyó con 30 ml de acetato de etilo, lavó secuencialmente con 10 ml de HCl 1M, salmuera, se secó sobre sulfato sódico, se filtró y se evaporó hasta sequedad. El producto resultante se trituró con 10 ml de éter dietílico dando 47,2 mg (96% de rendimiento) de ácido 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-5-metilbifenil-2-carboxílico como un sólido amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. RMN de ¹H (400 MHz, DMF-d₇) δ ppm 2,42 (s, 3 H), 2,97 (d, J=4,52 Hz, 3 H), 7,30 (s, 1 H), 7,39 - 7,48 (m, 5 H), 7,50 - 7,57 (m, 2 H), 7,78 - 7,85 (m, 2 H), 7,99 (s, 1 H), 8,10 - 8,17 (m, 2 H), 8,35 - 8,43 (m, 1 H). LCEM *m/z* 514,3 (M+H), Tr = 3,950 min., 95,4% de pureza.

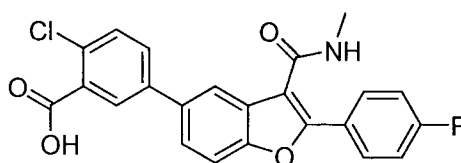


5-(2'-Cloro-5-metil-2-(1-(piridin-2-il)ciclopropilcarbamoil)bifenil-4-il)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida, TFA

A un matraz de 25 ml se añadió ácido 2'-cloro-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-5-metilbifenil-2-carboxílico (47,2 mg, 0,087 mmol), DMF (2 ml), *N*-etil-*N,N*-diisopropilpropan-2-amina (0,061 ml, 0,349 mmol), 1-(piridin-2-il)ciclopropanamina (17,56 mg, 0,131 mmol) y finalmente HATU (hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio, 133 mg, 0,349 mmol). El matraz se selló con un septo, se colocó en N₂ y se agitó a temperatura ambiente durante 5 horas. El producto bruto se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 19 x 150mm a un gradiente de 30-100% de B y un caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 10 minutos. El disolvente se evaporó dando 66,1 mg (92% de rendimiento) de 5-(2'-cloro-5-metil-2-(1-(piridin-2-il)ciclopropilcarbamoil)bifenil-4-il)-2-(4-

fluorofenil)-N-metilbenzofuran-3-carboxamida como un sólido blanco. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/bicarbonato amónico 10 mM con un gradiente de 10-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ¹H (400 MHz, THF-d₈) δ ppm 0,85

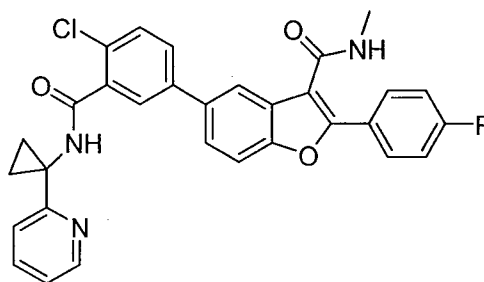
- 0,96 (m, 1 H), 0,99 - 1,09 (m, 1 H), 1,38 - 1,53 (m, 2 H), 2,33 (s, 3 H), 2,90 (d, $J=4,52$ Hz, 3 H), 7,07 - 7,14 (m, 1 H), 7,20 - 7,28 (m, 3 H), 7,30 - 7,36 (m, 3 H), 7,37 - 7,42 (m, 2 H), 7,44 - 7,49 (m, 1 H), 7,56 (d, $J=4,52$ Hz, 1 H), 7,58 - 7,65 (m, 3 H), 7,77 (d, $J=1,51$ Hz, 1 H), 7,89 (s, 1 H), 8,10 - 8,18 (m, 2 H), 8,37 - 8,42 (m, 1 H). LCEM m/z 631,39 (M+H), Tr = 2,925 min. HPLC (Sunfire C18) Tr = 8,118 min, 99,9% de pureza y (XBridge phenyl C18) Tr = 11,519min., 100% de pureza.



10 2-Cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico ácido

Procedimiento alternativo: A un tubo sellado de 150 ml se añadió trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (1,0 g, 2,4 mmol), dioxano (14,4 ml), agua (2,9 ml), tetraquis(trifenilfosfina)paladio(0) (0,055 g, 0,048 mmol), ácido 5-borono-2-clorobenzoico (0,720 g, 3,59 mmol) y carbonato de cesio (1,171 g, 3,59 mmol). El tubo se selló y se calentó en un baño de aceite durante la noche a 85 °C. La mezcla de reacción se enfrió, se diluyó con 150 ml de acetato de etilo, lavó secuencialmente con 20 ml de HCl 0,5M y luego salmuera. La solución producto se filtró a través de un tapón de CELITE® y luego se evaporó hasta sequedad. El sólido resultante se recogió en 10 ml de DMF y acetonitrilo 1:1 y

se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna
5 Waters Sunfire 3,5µm C18 4,6x150mm a un gradiente de 50-100% de B y un caudal de 40 ml/minutos durante 20 minutos con un mantenimiento de 5 minutos. Se evaporó el disolvente dando 319,5 mg (32 % de rendimiento) de ácido 2-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico como un polvo blanco. Los datos de LC/EM se obtuvieron en una LC analítica
10 Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: PHENOMENEX® Columna Luna 10µm C18, 3,0 x 50mm, con un gradiente de 0-100% de B (B = metanol calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ metanol calidad HPLC al 10%),
15 en 4 minutos con un mantenimiento de 1 minuto a un caudal de 5 ml/minuto. RMN de ¹H (400 MHz, DMSO-d₆) δ ppm 2,83 - 2,91 (m, 3 H), 7,35 - 7,45 (m, 2 H), 7,65 (d, J=8,53 Hz, 1 H), 7,69 - 7,75 (m, 1 H), 7,76 - 7,82 (m, 1 H), 7,85 - 7,93 (m, 2 H), 7,98 - 8,05 (m, 2 H), 8,08 (d, J=2,26 Hz, 1 H), 8,43 - 8,53 (m, 1 H), 13,50 (s ancho, 1 H). LCEM *m/z* 424,0 (M+H), Tr = 3,105min., 100% de
20 pureza.



5-(4-Cloro-3-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida

A un matraz de fondo redondo de 250 ml se añadió ácido 2-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (0,299 g, 0,705 mmol), 1-(piridin-2-il)ciclopropanamina (0,142 g, 1,058 mmol), DMF (8,50 ml), *N*-etil-*N,N*-diisopropilpropan-2-amina (0,493 ml, 2,82 mmol) y HATU (hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio, 1,073 g, 2,82 mmol). El matraz se selló, se colocó en N₂ y se agitó durante la noche a temperatura ambiente. La mezcla de reacción se diluyó con 50 ml de acetato de etilo, se lavó con 5 ml de HCl 1M, se extrajo, se secó sobre sulfato de magnesio, se filtró y se evaporó hasta un aceite rojo. La mezcla de reacción bruta se evacuó entonces casi hasta sequedad, se recogió en 8 ml de metanol y DMF 1:1 y se purificó usando una HPLC preparativa Shimadzu que emplea metanol/agua/ ácido trifluoroacético donde el disolvente A era metanol al 10% / agua al 90% / ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / metanol al 90% / ácido trifluoroacético al 0,1% con una columna PHENOMENEX® Luna 10µm C18 30x100mm a un gradiente de 50-100% de B y un caudal de 40 ml/minutos durante 8 minutos con un

mantenimiento de 7 minutos. Se evaporó el disolvente dando 261,3 mg (66,4% de rendimiento) de 5-(4-cloro-3-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-*N*-metilbenzofuran-3-carboxamida como un sólido amarillo claro. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma

5 LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna Waters Sunfire 5µm C18, 4,6 x 50mm con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 3 minutos con 1

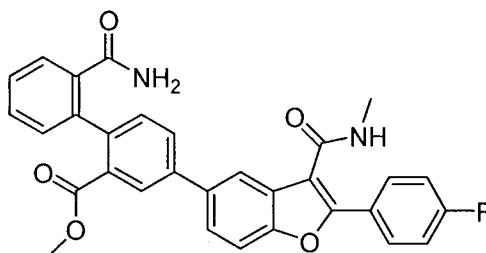
10 minuto de mantenimiento a un caudal de 4 ml/minuto. La pureza HPLC se determinó usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 20-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua

15 calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna PHENOMENEX® Gemini C18 3,0µm 4,6

20 x 150mm que emplea agua/metanol/ bicarbonato amónico 10 mM con un gradiente de 20-100% de B (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% /

bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 1,33 - 1,40 (m, 2 H), 1,56 - 1,64 (m, 2 H), 2,83 - 2,91 (m, 3 H), 7,27 (dd, $J=6,78$, 5,27 Hz, 1 H), 7,35 - 7,45 (m, 2 H), 7,63 (d, $J=8,28$ Hz, 1 H), 7,69 - 7,96 (m, 7 H), 7,97 - 8,06 (m, 2 H), 8,50 (d, $J=4,52$ Hz, 2 H), 9,34 (s, 1 H). LCEM m/z 540,39 (M+H), Tr = 1,643min., 94,2% de pureza. HPLC (Sunfire C18) Tr = 6,388min, 94% de pureza y (Gemini C18) Tr = 11,238min., 99,6% de pureza.

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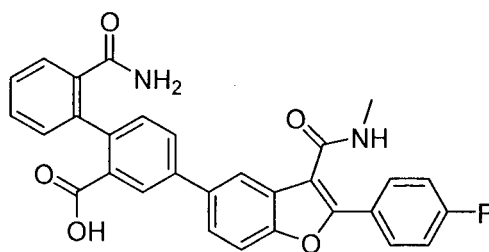


2'-Carbamoyl-4-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)bifenil-2-carboxilato de metilo

15

A un vial de microondas se añadió dioxano (9 ml), agua (0,900 ml), ácido 2-carbamoylfenilborónico (148 mg, 0,900 mmol), 2-cloro-5-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)benzoato de metilo (131 mg, 0,3 mmol), fostato potásico tribásico (255 mg, 1,200 mmol), dicitclohexil (2',6'-dimetoxibifenil-2-il)fosfina (S-Phos, 24,63 mg, 0,060 mmol) y acetato de paladio(II) (13,47 mg, 0,060 mmol). El vial se tapó, se desgasificó, se llenó con N_2 y se calentó en el microondas durante 13 minutos a 130 °C. La mezcla de reacción se filtró y el

disolvente se eliminó en una corriente de nitrógeno. El producto bruto se recogió entonces en 4 ml de acetonitrilo y se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5µm C18 19x150mm a un gradiente de 20-100% de B y un caudal de 25 ml/minutos durante 20 minutos con un mantenimiento de 10 minutos. El disolvente se eliminó dando 58,3 mg (36% de rendimiento) de 2'-carbamoil-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)bifenil-2-carboxilato de metilo como un sólido amarillo. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. RMN de ¹H (400 MHz, THF-d₈) δ ppm 2,93 (d, J=4,52 Hz, 3 H), 3,62 (s, 3 H), 6,35 (s ancho, 2 H), 7,09 - 7,15 (m, 1 H), 7,22 (t, J=8,91 Hz, 2 H), 7,31 - 7,43 (m, 3 H), 7,52 (d, J=4,27 Hz, 1 H), 7,58 - 7,71 (m, 3 H), 7,81 (dd, J=8,03, 2,01 Hz, 1 H), 8,01 (d, J=1,25 Hz, 1 H), 8,09 - 8,20 (m, 3 H). LCEM *m/z* 523,3 (M+H), Tr = 3,051 min., 96% de pureza.

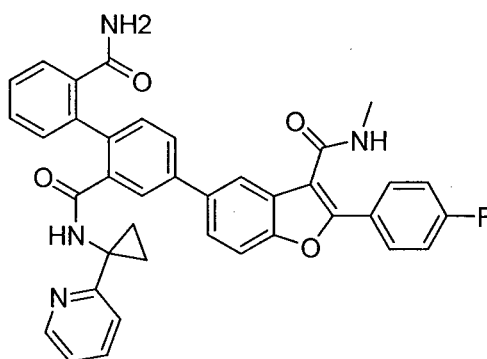


Ácido 2'-carbamoyl-4-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)bifenil-
2-carboxílico

- 5 A un matraz de fondo redondo de 25 ml se añadió 2'-carbamoyl-4-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)bifenil-2-carboxilato de metilo (58,3 mg, 0,107 mmol), metanol (1 ml), THF (1 ml) y 8 equivalentes de una solución 1M de hidróxido sódico (0,856 ml, 0,856 mmol). La mezcla se diluyó con 20 ml de acetato de etilo, se acidificó con HCl 0,5M y el producto bruto se
- 10 extrajo, se lavó con salmuera y se secó sobre sulfato sódico. La solución producto se filtró y se evaporó hasta sequedad dando 52 mg (98% de rendimiento) de ácido 2'-carbamoyl-4-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)bifenil-2-carboxílico como un sólido amarillo.
- Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma
- 15 LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4

minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto.

LCEM m/z 509,3 (M+H), Tr = 2,695 min., 90% de pureza.



5 4-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-N2-(1-(piridin-2-il)ciclopropil) bifenil-2,2'-dicarboxamida, TFA

A un matraz de fondo redondo de 25 ml se añadió ácido 2'-carbamoil-4-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)bifenil-2-carboxílico (52mg, 0,104 mmol), DMF (2 ml), *N*-etil-*N,N*-isopropilpropan-2-amina (0,075 ml, 0,429 mmol),
 10 1-(piridin-2-il)ciclopropanamina (21,57 mg, 0,161 mmol) y finalmente HATU (hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio, 163 mg, 0,429 mmol). El matraz se selló y la mezcla se agitó a temperatura ambiente durante la noche. El producto bruto se purificó usando una HPLC preparativa Shimadzu que emplea acetonitrilo/agua/ ácido
 15 trifluoroacético donde el disolvente A era acetonitrilo al 10% / 90% de agua/ ácido trifluoroacético al 0,1% y el disolvente B era agua al 10% / acetonitrilo al 90%/ ácido trifluoroacético al 0,1% con una columna Waters Sunfire 5 μ m C18 19 x 150mm a un gradiente de 20-100% de B y un caudal de 25 ml/minutos

durante 20 minutos con un mantenimiento de 10 minutos. El disolvente se evaporó dando 2 rotámetros como se ha mostrado antes. Los datos de LC/EM se obtuvieron en una LC analítica Shimadzu / Plataforma LC MICROMASS® (ESI+) a 220nm usando el siguiente conjunto de condiciones: columna

5 PHENOMENEX® Luna 3µm C18, 2 x 50mm, con un gradiente de 0-100% de B (B = acetonitrilo calidad HPLC al 90%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 10%), (A = agua calidad HPLC al 90% / ácido trifluoroacético al 0,1%/ acetonitrilo calidad HPLC al 10%), en 4 minutos con un mantenimiento de 1 minuto a un caudal de 0,8 ml/minuto. La pureza HPLC se determinó

10 usando una LC analítica Shimadzu a 254nm y 256nm con una columna Waters Sunfire C18 3,5µm 4,6 x 150mm que emplea agua/acetonitrilo/ácido trifluoroacético al 0,1% con un gradiente de 10-100% de B (B = acetonitrilo calidad HPLC al 95%/ ácido trifluoroacético al 0,1%/ agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / ácido trifluoroacético al 0,1%/ acetonitrilo

15 calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10 minutos a un caudal de 1 ml/minuto. La pureza HPLC se confirmó entonces con un sistema y columna de disolvente ortogonal usando una LC analítica Shimadzu con una columna Waters XBridge Phenyl C18 3,5µm 4,6 x 150mm que emplea agua/metanol/bicarbonato amónico 10 mM con un gradiente de 10-100% de B

20 (B = metanol calidad HPLC al 95%/ bicarbonato amónico 10 mM / agua calidad HPLC al 5%), (A = agua calidad HPLC al 95% / bicarbonato amónico 10 mM / metanol calidad HPLC al 5%), en 10 minutos con un mantenimiento de 10

minutos a un caudal de 1 ml/minuto.

- Isómero A: RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,53 - 0,79 (m, 2 H), 1,36 (d, $J=4,27$ Hz, 2 H), 2,95 (d, $J=4,52$ Hz, 3 H), 6,79 (s ancho, 1 H), 6,88 - 7,00 (m, 2 H), 7,16 - 7,26 (m, 4 H), 7,39 (td, $J=7,72$, 1,88 Hz, 1 H), 7,46 - 7,53 (m, 3 H),
5 7,57 - 7,61 (m, 1 H), 7,61 - 7,65 (m, 2 H), 7,69 (ddd, $J=10,23$, 8,22, 1,88 Hz, 2 H), 7,91 (d, $J=2,01$ Hz, 1 H), 8,04 (d, $J=1,51$ Hz, 1 H), 8,13 - 8,19 (m, 2 H), 8,25 - 8,31 (m, 1 H), 9,01 (s, 1 H). LCEM m/z 625,4 (M+H), Tr = 2,310 min. HPLC (Sunfire C18) Tr = 6,796 min, 100% de pureza y (XBridge phenyl C18) Tr = 10,793 min., 100% de pureza.
- 10 Isómero B: RMN de ^1H (400 MHz, THF- d_8) δ ppm 0,64 - 0,92 (m, 2 H), 1,39 (d, $J=4,02$ Hz, 2 H), 2,93 (d, $J=4,77$ Hz, 3 H), 6,76 (s ancho, 1 H), 6,88 (dd, $J=6,90$, 5,14 Hz, 1 H), 6,96 (d, $J=8,03$ Hz, 1 H), 7,11 - 7,18 (m, 1 H), 7,20 - 7,30 (m, 3 H), 7,31 - 7,43 (m, 3 H), 7,50 (s ancho, 1 H), 7,59 (dd, $J=7,15$, 1,88 Hz, 1 H), 7,62 - 7,67 (m, 1 H), 7,68 - 7,76 (m, 2 H), 7,82 (dd, $J=7,78$, 2,01 Hz, 1 H), 7,92
15 (d, $J=1,76$ Hz, 1 H), 8,07 (d, $J=1,76$ Hz, 1 H), 8,09 - 8,17 (m, 2 H), 8,26 (d, $J=4,27$ Hz, 1 H), 8,98 (s, 1 H). LCEM m/z 625,4 (M+H), Tr = 2,275 min. HPLC (Sunfire C18) Tr = 6,688 min, 100% de pureza y (XBridge phenyl C18) Tr = 10,821 min., 100% de pureza.

20 4-Fluoro-2-(4-fluorofenil)-5-hidroxibenzofuran-3-carboxilato de etilo

A una mezcla de 2-(4-fluorofenil)-5-hidroxibenzofuran-3-carboxilato de etilo (500 mg, 1,665 mmol) en acetonitrilo (10 ml) a t.a. en N_2 se añadió

tetrafluoroborato de 1-(clorometil)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octano (708 mg, 1,998 mmol). La mezcla se agitó a t.a. (la mezcla viró a color amarillo brillante) durante 20 horas. La mezcla se evaporó. El residuo se añadió con 10 ml de H₂O. Se decantó la fase acuosa y el residuo se lavó de nuevo con 2 x 5 ml de H₂O. La mezcla se disolvió en MeOH (aproximadamente 10 ml) y se filtró el insoluble. El filtrado se purificó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 60, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,44 - 7,24 min. (detección UV a 220 nm). Las fracciones deseadas se reunieron y evaporaron dando un sólido amarillo. El sólido amarillo se purificó de nuevo por cromatografía ultrarrápida BIOTAGE® Horizon (EtOAc al 0 a 70%/Hexano, columna de gel de sílice, 3 x 80 g) dando un sólido amarillo claro (108,9 mg). RMN de ¹H (500 MHz, CD₃OD) δ 7,95 (m, 2H), 7,26 (t solapando con dd, 2H), 7,25 (dd, 1H), 7,03 (t, J = 8,39, 1H), 4,39 (c, J = 7,17, 2H), 1,36 (t, J = 7,17, 3H). RMN de ¹⁹F (470,45 MHz, CD₃OD) δ 112,36, 142,29. La posición del átomo de F en C4 se confirmó por correlación de enlace a través de ¹H-¹H entre H6 y H7, ¹H-¹³C HMBC y acoplamiento F-C4 en RMN de ¹³C (125,75 MHz, CD₃OD) (δ 144,8 ppm, d, J = 247, C4). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC:

Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 319,14, Tr de HPLC = 1,718 min. Las fracciones minoritarias recogidas a aproximadamente 7,69 - 8,20 min. se confirmaron por correlación de enlace a través de ¹H-¹H, ¹H-¹³C HMBC y acoplamiento F-C6 en RMN de ¹³C (125,75 MHz, CD₃OD) (δ 152,5 ppm, d, J = 242 Hz, C6) que eran el isómero del átomo F en C6 (C4 : C6 aproximadamente 3:1 basado en el área % del HPLC preparativa de la traza UV); RMN de ¹H (500 MHz, CD₃OD) δ 8,04 (dd, J = 8,55, 5,49, 2H), 7,59 (d, J = 8,85, 1H), 7,38 (d, J = 10,07, 1H), 7,25 (t, J = 8,70, 2H), 4,40 (c, J = 7,17, 2H), 1,41 (t, J = 7,17, 3H). RMN de ¹⁹F (470,45 MHz, CD₃OD) δ 112,29, 138,52. Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 319,14, Tr de HPLC = 1,798 min.

20 Ácido 4-fluoro-2-(4-fluorofenil)-5-hidroxibenzofuran-3-carboxílico

A una mezcla de 4-fluoro-2-(4-fluorofenil)-5-hidroxibenzofuran-3-carboxilato de etilo (108,9 mg, 0,342 mmol) en una mezcla de MeOH (2 ml)/THF (2 ml) a t.a.

en N₂ se añadió hidróxido sódico (1,0 ml, 1,0 mmol) (1 M ac.). La mezcla se agitó a 100 °C durante 1,5 horas. La mezcla se enfrió hasta t.a., se añadió con 1,5 ml de HCl 1N, y luego se añadieron 10 ml de H₂O. Los precipitados blandos se filtraron y lavaron con 3 x 2 ml de H₂O y secaron (73 mg). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (m, 2H), 7,25 (t solapando con dd, 2H), 7,24 (dd, 1H), 7,02 (t, J = 8,39, 1H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 291,01, Tr de HPLC = 1,478 min.

4-Fluoro-2-(4-fluorofenil)-5-hidroxi-N-metilbenzofuran-3-carboxamida

A una mezcla de ácido 4-fluoro-2-(4-fluorofenil)-5-hidroxibenzofuran-3-carboxílico (73 mg, 0,252 mmol), metilamina, HCl (25,5 mg, 0,377 mmol), HOBT hidrato (65,5 mg, 0,428 mmol) y clorhidrato de EDC (87 mg, 0,453 mmol) a t.a. en N₂ se añadió N,N-diisopropiletilamina (0,220 ml, 1,258 mmol). La mezcla se agitó a t.a. durante 16 horas. Después de concentrar, la mezcla se añadió con 5 ml de HCl 1N, y luego 14 ml de H₂O. El sólido blanco se filtró y lavó con 3 x 5 ml H₂O y se secó (64 mg). RMN de ¹H (500 MHz, CD₃OD) δ 7,89 (dd, J = 8,09, 5,34, 2H), 7,25 (t solapando con dd, 2H), 7,23 (dd, 1H), 6,99 (t, J

= 8,55, 1H), 2,96 (s, 3H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, %
5 Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 304,06, Tr de HPLC = 1,262 min.

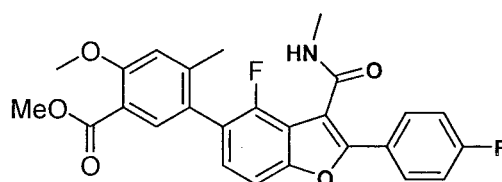
Trifluorometanosulfonato de 4-fluoro-2-(4-fluorofenil)-3-

10

(metilcarbamoil)benzofuran-5-ilo

A una suspensión blanca de 4-fluoro-2-(4-fluorofenil)-5-hidroxi-N-metilbenzofuran-3-carboxamida (64 mg, 0,211 mmol) en CH₂Cl₂ (2 ml) a t.a. en N₂ se añadió trietilamina (0,059 ml, 0,422 mmol). La mezcla se enfrió hasta 0 °C, y luego se añadió 1,1,1-trifluoro-N-fenil-N-
15 (trifluorometilsulfonil)metanosulfonamida (113 mg, 0,317 mmol). La mezcla se agitó entonces a t.a. (la suspensión blanca viró a color amarillo claro después de agitar durante aproximadamente 10 min) durante 2 horas 35 min. La mezcla se dejó en reposo a ta durante la noche y luego se evaporó. El residuo se enfrió en un baño de hielo-agua, se añadió con 2 ml de H₂O. Los sólidos se
20 filtraron y se lavaron 3 x 2 ml de H₂O y se secó (94 mg). RMN de ¹H (500 MHz, CD₃OD) δ 7,95 (m, 2H), 7,59 (dd, J = 9,00, 1,00, 1H), 7,50 (dd, J = 9,00, 7,50, 1H), 7,30 (t, J = 8,55, 2H), 2,99 (s, 3H). Las LC/EM se realizaron usando

instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de
 5 parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 436,04, Tr de HPLC = 1,678 min.



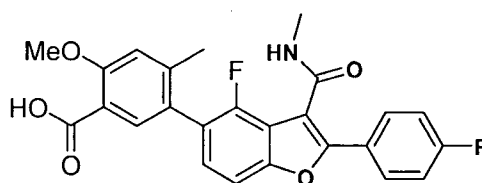
5-(4-Fluoro-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-

10

metilbenzoato de metilo

Una mezcla del trifluorometanosulfonato de 4-fluoro-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo preparado antes (se suponen 0,211 mmol), 2-metoxi-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoato de metilo (0,078 g, 0,253 mmol), (Ph₃P)₄Pd (0,024 g, 0,021 mmol) y carbonato de cesio
 15 (0,103 g, 0,317 mmol) en una mezcla de H₂O (0,2 ml)/1,4-dioxano (1 ml) se agitó a 95 °C durante 2 horas 30 min. La mezcla se dejó en reposo a ta durante la noche. La mezcla se diluyó con 3,5 ml 1,4-dioxano, se filtró a través de un disco Whatman PVDF 0,45 um (con lavados de 3 x 1 ml). Se concentró el filtrado. La mezcla se añadió con 3,5 ml de HCl 1N, y luego 6 ml de H₂O (el
 20 sólido amarillo se depositó en la pared del matraz). Se decantó la fase acuosa

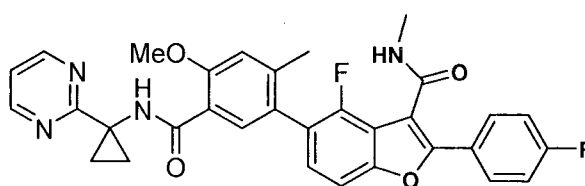
y el residuo se lavó con 3 x 2 ml de H₂O y se secó. Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
 5 Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 466,27, Tr de HPLC = 1,708 min.



10 Ácido 5-(4-fluoro-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoico

Al 5-(4-fluoro-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoato de metilo preparado antes (se suponen 0,211 mmol) en una mezcla de MeOH (2 ml)/THF (2 ml) a t.a. en N₂ se añadió hidróxido sódico
 15 (0,84 ml, 0,84 mmol). La mezcla se agitó a t.a. durante 24 horas. La mezcla se añadió con 2 ml de HCl 1N, y se concentró hasta que se formaron sólidos blancos. La mezcla se añadió con 5 ml H₂O, se filtraron los sólidos y se lavaron con 3 x 2 ml H₂O y secaron (75,1 mg). RMN de ¹H (500 MHz, CD₃OD) δ 7,95 (m, 2H), 7,73 (s, 1H), 7,51 (d, J = 8,24, 1H), 7,30-7,25 (t solapando con m, 3H),
 20 7,13 (s, 1H), 3,99 (s, 3H), 2,96 (s, 3H), 2,28 (s, 3H). Las LC/EM se realizaron

usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de
 5 parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 452,23, Tr de HPLC = 1,582.

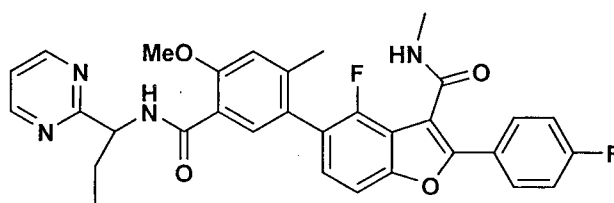


4-Fluoro-2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-
 10 il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

A una mezcla de ácido 5-(4-fluoro-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoico (30 mg, 0,066 mmol), 1-(pirimidin-2-il)ciclopropanamina, TFA (33,1 mg, aproximadamente 75% puro, se suponen 0,133 mmol,) y tetrafluoroborato de 2-(1H-benzo[d][1,2,3]triazol-1-
 15 il)-1,1,3,3-tetrametilisouronio (64,0 mg, 0,199 mmol) en DMF (1 ml) a t.a. en N₂ se añadió N,N-diisopropiletilamina (0,058 ml, 0,332 mmol). La mezcla se agitó a t.a. durante 20 horas. La mezcla se diluyó con MeOH y se purificó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente
 20 B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B =

100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, detección UV a 220 nm, Recogida de la fracción: 7,25-7,73 min. El residuo, después de evaporar las fracciones combinadas, se purificó posteriormente por TLC preparativa (dos de
5 placas 500 μ m x 20 x 20 cm, MeOH al 5%/CH₂Cl₂) dando 4-fluoro-2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida como un sólido blanco. TLC analítica R_f = 0,32 (5% MeOH/CH₂Cl₂). RMN de ¹H (500 MHz, CD₃OD) δ 8,65 (d, J = 4,88, 2H), 7,95 (m, 2H), 7,89 (s, 1H), 7,50 (d, J = 8,55, 1H), 7,28 (t, J = 8,70, 2H), 7,28-
10 7,25 (m solapando con t, 1H), 7,23 (t, J = 4,88, 1H), 7,17 (s, 1H), 4,09 (s, 3H), 2,95 (s, 3H), 2,30 (s, 3H), 1,79 (m, 2H), 1,51 (m, 2H). RMN de ¹⁹F (470,45 MHz, CD₃OD) δ 112,81, 123,16. Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%,
15 Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 569,38, Tr de HPLC = 1,660 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254
20 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada =

18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 6,29 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 5,18 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,39 min.



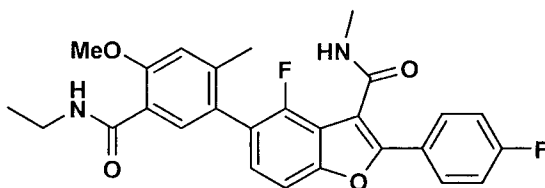
10 4-Fluoro-2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-il)propilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

4-Fluoro-2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-il)propilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida se formó como un subproducto minoritario durante la síntesis de 4-fluoro-2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida descrita antes y se aisló durante la purificación por HPLC preparativa de fase inversa (Recogida de la fracción: 7,82 - 8,48 min). RMN de ¹H (500 MHz, DMSO-d₆) δ 9,08 (d, J = 7,32, 1H), 8,87 (d, J = 4,88, 2H), 8,70 (c, J = 4,58, 1H), 7,94 (m, 2H), 7,78 (s, 1H), 7,62 (d, J = 8,24, 1H), 7,46 (t, J = 4,88, 1H), 7,42 (t, J = 9,00, 2H), 7,30 (dd, J = 8,39, 7,17, 1H), 7,24 (s, 1H), 5,16 (m,

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20

1H), 4,08 (s, 3H), 2,80 (d, $J = 4,58$, 3H), 2,24 (s, 3H), 1,97 (m, 2H), 0,82 (t, $J = 7,32$, 3H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 571,35, Tr de HPLC = 1,743 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 7,33 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 5,69 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 10,23 min.



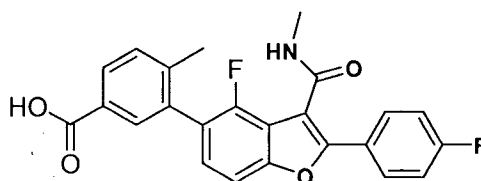
5-(5-(Etilcarbamoil)-4-metoxi-2-metilfenil)-4-fluoro-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

5-(5-(Etilcarbamoil)-4-metoxi-2-metilfenil)-4-fluoro-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida se formó como un subproducto minoritario durante la síntesis de 4-fluoro-2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida como se ha descrito antes, y se aisló durante la purificación por TLC preparativa (la banda derecha superior la banda del producto mayoritario). RMN de ^1H (500 MHz, CD_3OD) δ 7,95 (m, 2H), 7,81 (s, 1H), 7,51 (d, $J = 8,55$, 1H), 7,30-7,25 (t solapando con dd, 3H), (7,13 (s, 1H), 4,04 (s, 3H), 3,46 (c, $J = 7,17$, 2H), 2,95 (s, 3H), 2,28 (s, 3H), 1,25 (t, $J = 7,17$, 3H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%- H_2O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%- H_2O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z ($\text{M}+\text{H}$) $^+$ = 479,30, Tr de HPLC = 1,670 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%- H_2O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%- H_2O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire

C18, 3,5 μ m, 4,6 x 150 mm, Tr = 6,94 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 5,31 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de
5 gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,20 min.

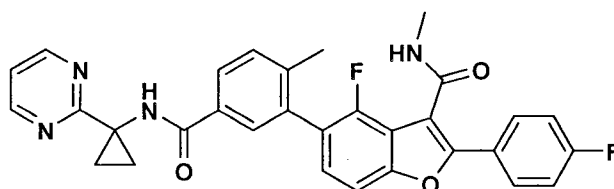
2,4-Dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoato de dimetilo
Una mezcla de 5-yodo-2,4-dimetilbenzoato de metilo (1 g, 3,45 mmol),
10 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (1,050 g, 4,14 mmol), acetato potásico (1,015 g, 10,34 mmol) y PdCl₂(dppf)(Cl₂CH₂) ([1,1'-bis(difenilfosfino)ferroceno]dicloropaladio(II), diclorometano) (0,284 g, 0,345 mmol) en DMF (25 ml) en N₂ se agitó a 100 °C durante 20 horas. La mezcla se enfrió hasta t.a., se añadió con 30 ml de H₂O. El sólido oscuro se filtró y se lavó
15 con 3 x 5 ml de H₂O y se secó. El sólido se purificó por cromatografía ultrarrápida BIOTAGE® Horizon (EtOAc al 0 a 70%/Hexano) dando el producto como un sólido blanco (442,7 mg). RMN de ¹H (500 MHz, CD₃OD) δ 8,26 (s, 1H), 7,11 (s, 1H), 3,88 (s, 3H), 2,56 (s, 3H), 2,53 (s, 3H), 1,37 (s, 12H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220
20 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min,

Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 291,14, Tr de HPLC = 1,933 min.



- 5 Ácido 3-(4-fluoro-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 422,19, Tr de HPLC = 1,653 min.



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- 4-Fluoro-2-(4-fluorofenil)-N-metil-5-(2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

La purificación se realizó por HPLC preparativa de fase inversa Shimadzu-VP

usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm

5 S5, Recogida de la fracción: 6,80-7,18 min. (detección UV a 220 nm). El material obtenido se purificó posteriormente por TLC preparativa (placa de 500 um x 20 x 20 cm, MeOH al 5%/CH₂Cl₂). Tr de la TLC analítica = 0,35 (5% MeOH/CH₂Cl₂). RMN de ¹H (500 MHz, CD₃OD) δ 8,64 (d, J = 4,88, 2H), 7,96 (m, 2H), 7,90 (dd, J = 7,93, 1,83, 1H), 7,84 (d, J = 1,83, 1H), 7,54 (d, J = 8,54,

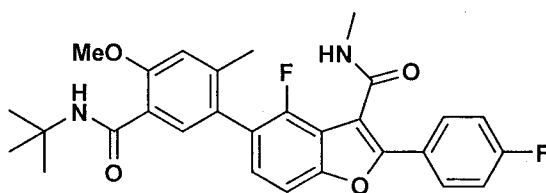
10 1H), 7,46 (d, J = 7,93, 1H), 7,34-7,27 (m solapando con t, 3H), 7,22 (t, J = 4,88, 1H), 2,96 (s, 3H), 2,29 (s, 3H), 1,77 (m, 2H), 1,46 (m, 2H). RMN de ¹⁹F (470,45 MHz, CD₃OD) δ 112,72, 123,10. Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®.

Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%,

15 Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 539,32, Tr de HPLC = 1,585 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254

20 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada =

18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 5,64 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 4,66 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 8,43 min.



10 5-(5-(*tert*-Butilcarbamoil)-4-metoxi-2-metilfenil)-4-fluoro-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

La purificación se realizó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,68 - 9,29 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,88 (dd, *J* = 8,55, 5,19, 2H), 7,72 (s, 1H), 7,43 (d, *J* = 8,55, 1H), 7,23–7,17 (m solapado, 3H), 7,06 (s, 1H), 3,98 (s, 3H), 2,89 (s, 3H), 2,20 (s, 3H), 1,41 (s, 9H). Las LC/EM se realizaron usando instrumento

Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®.

Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%,

Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, %

Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min,

5 Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+)

m/z (M+H)⁺ = 507,33, Tr de HPLC = 1,837 min. Las HPLC analíticas se

realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254

nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-

TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de

10 B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada =

18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 µm, 4,6 x 150 mm, Tr =

10,19 min; Columna: XBridge Phenyl 3,5 µm, 4,6 x 150 mm, Tr = 7,50 min.

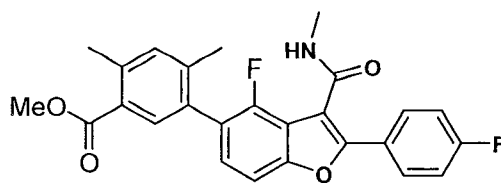
Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-

NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM,

15 % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo

de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 µm, 4,6 x

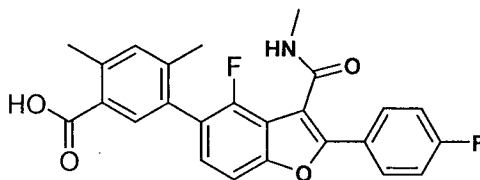
150 mm, Tr = 11,25 min.



20 5-(4-Fluoro-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2,4-

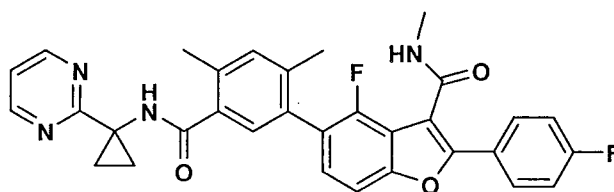
dimetilbenzoato de metilo

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 450,11, Tr de HPLC = 1,852 min.



Ácido 5-(4-fluoro-2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2,4-dimetilbenzoico

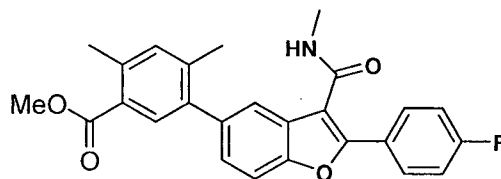
RMN de ¹H (500 MHz, CD₃OD) δ 7,95 (m, 2H), 7,80 (s, 1H), 7,51 (d, J = 8,55, 1H), 7,30-7,25 (s y m solapado 4H), 2,96 (s, 3H), 2,63 (s, 3H), 2,23 (s, 3H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 436,09, Tr de HPLC = 1,735 min.



5-(2,4-Dimetil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)-4-fluoro-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

- 5 La purificación se realizó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Sunfire Prep C18 19 x 100
- 10 5µm, Recogida de la fracción: 6,93 - 7,43 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, DMSO-d₆, los picos fueron generalmente anchos) δ 8,93 (s, 1H), 8,71 (ancho s, 1H), 8,68 (m, 2H), 7,93 (m, 2H), 7,65 (m, 1H), 7,44 (m, 2H), 7,33 (m, 2H), 7,27 (m, 1H), 7,25 (m, 1H), 2,81 (s, 3H), 2,45 (s, 3H), 2,17 (s, 3H), 1,57 (s, 2H), 1,33 (s, 2H). ¹⁹F NMR (470,45 MHz, DMSO-d₆) δ 110,88, 121,61.
- 15 Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna:
- 20 PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 553,22, Tr de

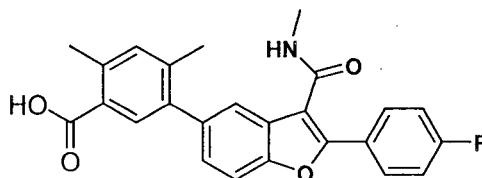
HPLC = 1,645 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, 5 Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um, 4,6 x 150 mm, Tr = 6,26 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 5,23 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, 10 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm, Tr = 9,00 min.



15 5-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2,4-dimetilbenzoato de metilo

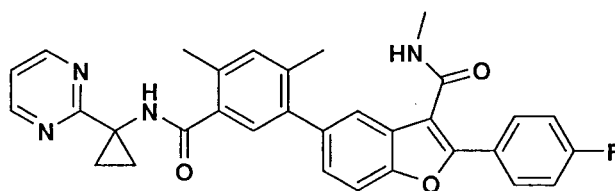
Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 20 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna:

PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 432,10, Tr de HPLC = 1,928 min.



5 Ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2,4-dimetilbenzoico

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 418,10, Tr de HPLC = 1,810 min.



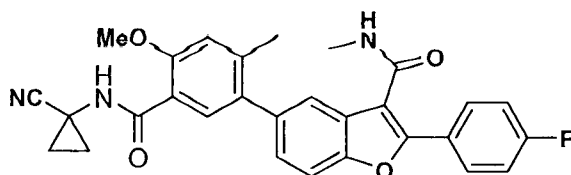
15 5-(2,4-Dimetil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

La purificación se realizó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al

90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de
parada = 12 min, Caudal = 25 ml/min, Columna: Sunfire Prep C18 19 x 100
5um, Recogida de la fracción: 7,75 - 8,16 min. (detección UV a 220 nm). RMN
5 de ¹H (500 MHz, CD₃OD) δ 8,67 (d, J = 4,88, 2H), 7,97 (m, 2H), 7,65 (s
solapado con d, 1H), 7,64 (d, J = 8,50, 1H), 7,50 (s, 1H), 7,38 (dd, J = 8,55,
1,83, 1H), 7,28 (t, J = 8,85, 2H), 7,24 (t, J = 4,88, 1H), 7,22 (s, 1H), 2,95 (s, 3H),
2,52 (s, 3H), 2,30 (s, 3H), 1,76 (m, 2H), 1,46 (m, 2H). Las LC/EM se realizaron
usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters
10 MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al
90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de
parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50
mm, S10; (ES+) m/z (M+H)⁺ = 535,23, Tr de HPLC = 1,722 min. Las HPLC
15 analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a
220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al
5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al
0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min,
Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 um,
20 4,6 x 150 mm, Tr = 7,24 min; Columna: XBridge Phenyl 3,5 um, 4,6 x 150 mm,
Tr = 5,62 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-
H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-

NH_4HCO_3 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μm , 4,6 x 150 mm, Tr = 9,24 min.

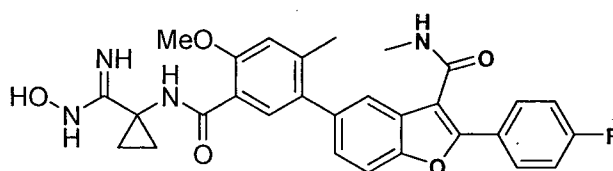
5



5-(5-(1-Cianociclopropilcarbamoil)-4-metoxi-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

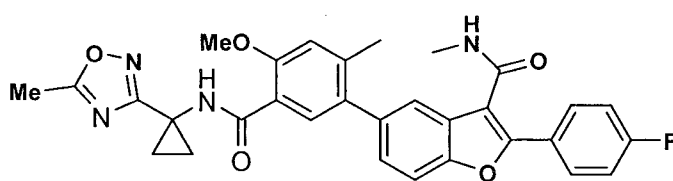
Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 498,21, Tr de HPLC = 1,647 min.

15



2-(4-Fluorofenil)-5-(5-(1-(N-hidroxicarbamimidoil)ciclopropilcarbamoil)-4-metoxi-2-metilfenil)-N-metilbenzofuran-3-carboxamida

La purificación se realizó por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 30, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de
 5 parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 6,82 - 7,62 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 7,96 (dd, *J* = 8,24, 5,80, 2H), 7,88 (s, 1H), 7,63 (d, *J* = 8,24, 1H), 7,57 (s, 1H), 7,32 (d, *J* = 8,54, 1H), 7,28 (t, *J* = 8,70, 2H), 7,13 (s, 1H), 4,05 (s, 3H), 2,96 (s, 3H), 2,36 (s, 3H), 1,67 (m, 2H), 1,50 (m, 2H). Las
 10 LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX®
 15 Luna, 3,0 x 50 mm, S10; (ES+) *m/z* (*M*+*H*)⁺ = 531,22, Tr de HPLC = 1,457 min.



2-(4-Fluorofenil)-5-(4-metoxi-2-metil-5-(1-(5-metil-1,2,4-oxadiazol-3-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

20 Se preparó 2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(5-metil-1,2,4-oxadiazol-3-

il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida a partir de 2-(4-fluorofenil)-5-(5-(1-(N-hidroxicarbamimidoil)ciclopropilcarbamoil)-4-metoxi-2-metilfenil)-N-metilbenzofuran-3-carboxamida en condiciones similares a las descritas pero usando como disolvente PhMe. La mezcla bruta se purificó por

5 TLC preparativa (placas de 20 x 20 cm x 500 μ m, MeOH al 5%/CH₂Cl₂) dando el producto, que se purificó posteriormente por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de

10 gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 7,95 - 8,47 min. (detección UV a 220 nm). Tr de la TLC analítica = 0,38 (5 % MeOH/CH₂Cl₂). RMN de ¹H (500 MHz, CD₃OD) δ 7,97 (dd, J = 7,93, 5,49, 2H), 7,87 (s, 1H), 7,62 (d, J = 8,24, 1H), 7,58 (s, 1H), 7,33 (d, J = 8,55, 1H), 7,27 (t, J = 8,39, 2H),

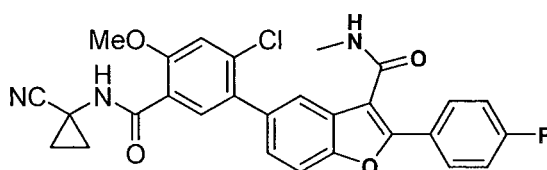
15 7,11 (s, 1H), 4,05 (s, 3H), 2,96 (s, 3H), 2,54 (s, 3H), 2,36 (s, 3H), 1,60 (m, 2H), 1,45 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo

20 de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 555,34, Tr de HPLC = 1,735 min. Las HPLC analíticas se realizaron usando instrumento

Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min,

5 Columna: Sunfire C18, 3,5 µm, 4,6 x 150 mm, Tr = 7,75 min; Columna: XBridge Phenyl 3,5 µm, 4,6 x 150 mm, Tr = 5,93 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1

10 ml/min, Columna: XBridge Phenyl 3,5 µm, 4,6 x 150 mm, Tr = 11,98 min.

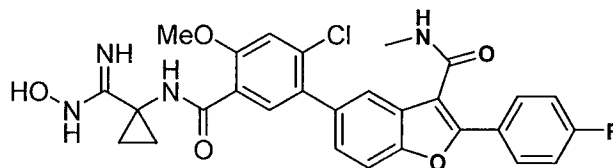


5-(2-Cloro-5-(1-cianociclopropilcarbamoyl)-4-metoxifenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

15 Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna:

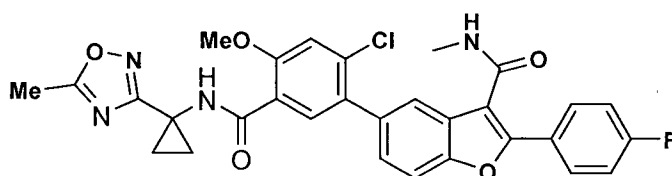
20 PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 518,20, 520,18,

Tr de HPLC = 1,692 min.



- 5 5-(2-Cloro-5-(1-(N-hidroxicarbamimidoil)ciclopropilcarbamoil)-4-metoxifenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 551,21, Tr de HPLC = 1,478 min.

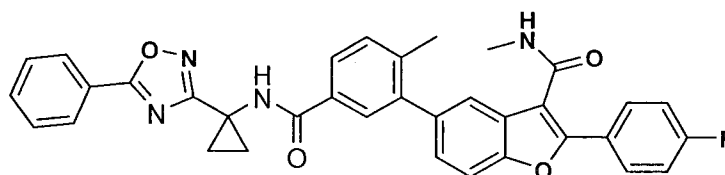


- 15 5-(2-Cloro-4-metoxi-5-(1-(5-metil-1,2,4-oxadiazol-3-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

La mezcla se purificó primero por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O

al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
Inicial de B = 60, % Final de B = 100, Tiempo de gradiente = 5 min, Tiempo de
parada = 6 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 50 mm S5,
Recogida de la fracción: 3,85 - 4,21 min. (detección UV a 220 nm). El residuo
5 obtenido después de la evaporación de las fracciones deseadas se purificó
posteriormente por TLC preparativa (5% MeOH/CH₂Cl₂, placas 20 cm x 20 cm
x 0,5 mm). RMN de ¹H (500 MHz, CD₃OD) δ 7,98 (dd solapado con s, J = 5,19,
2H), 7,97 (s, 1H), 7,71 (d, J = 1,22, 1H), 7,65 (d, J = 8,55, 1H), 7,45 (dd, J =
8,55, 1,83, 1H), 7,36 (s, 1H), 7,28 (t, J = 8,85, 2H), 4,05 (s, 3H), 2,96 (s, 3H),
10 2,54 (s, 3H), 1,61 (m, 2H), 1,46 (m, 2H). Las LC/EM se realizaron usando
instrumento Shimadzu-VP con detección UV a 220 nm y Waters
MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al
90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, %
Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de
15 parada = 3 min, Caudal = 4 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50
mm, S10; (ES+). m/z (M+H)⁺ = 575,10, Tr de HPLC = 1,817 min. Las HPLC
analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a
220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al
5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al
20 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min,
Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μm,
4,6 x 150 mm, Tr = 7,92 min; Columna: XBridge Phenyl 3,5 μm, 4,6 x 150 mm,

Tr = 6,21 min.



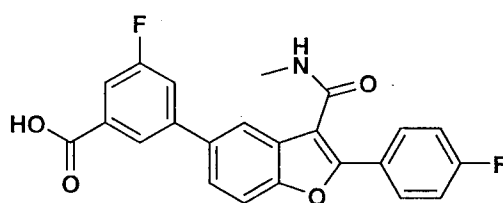
2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(5-fenil-1,2,4-oxadiazol-3-

5 il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

La mezcla se purificó primero por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de
10 parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 9,11 - 9,39 min. (detección UV a 220 nm) para aislar el producto deseado. El residuo, después de evaporar las fracciones deseadas, se purificó posteriormente por TLC preparativa (5% MeOH/CH₂Cl₂, placa de 20 cm x 20 cm x 0,5 mm). Tr de la TLC analítica = 0,52 (5%
15 MeOH/CH₂Cl₂). RMN de ¹H (500 MHz, CD₃OD) δ 8,11 (d, J = 7,02, 2H), 7,99 (m, 2H), 7,84 (s, 1H), 7,83 (m solapando con s, 1H), 7,68–7,64 (m solapado, 3 H), 7,60–7,57 (m solapado, 2 H), 7,45 (d, J = 8,55, 1H), 7,40 (d, J = 8,24, 1,83, 1H), 7,28 (m, 2H), 2,96 (s, 3H), 2,36 (s, 3H), 1,72 (m, 2H), 1,50 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220
20 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al

10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 4 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 587,20, Tr de HPLC = 1,950 min.

5

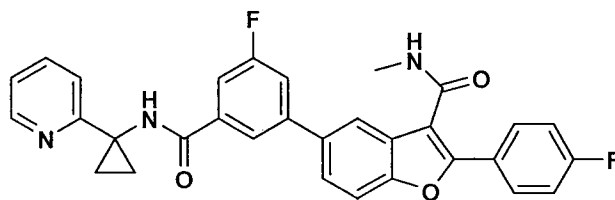


Ácido 3-fluoro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH

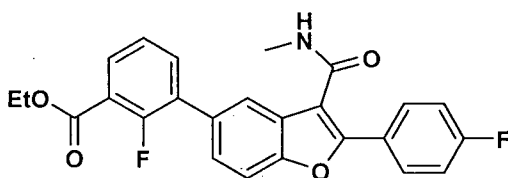
10 al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 408,15, Tr de HPLC = 1,757 min.

15



5-(3-Fluoro-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

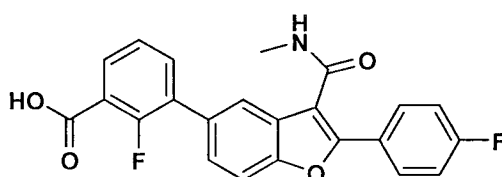
El producto precipitó de la mezcla de reacción durante el acoplamiento de ácido 3-fluoro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico (escala 0,068 mmol) con diclorhidrato de 1-(piridin-2-il)ciclopropanamina (TBTU, iPr₂NET, DMF, t.a.). La mezcla se diluyó con 4 ml de H₂O, se filtró el sólido blanquecino y se lavó 3 x 2 ml de H₂O. El sólido se lavó después con 3 x 1 ml de MeOH y se secó. RMN de ¹H (500 MHz, DMSO-d₆) δ 9,50 (s, 1H), 8,52 (d, *J* = 4,58, 1H), 8,47 (d, *J* = 3,97, 1H), 8,17 (s, 1H), 8,03-8,00 (m solapado, 3H), 7,83 (m solapado, 3H), 7,73 (d, 1H), 7,70 (dt solapando con d, 1H), 7,43-7,40 (m solapado, 3H), 7,17 (dd, *J* = 6,87, 5,34, 1H), 2,88 (d, *J* = 4,27, 3H), 1,59 (m, 2H), 1,32 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) *m/z* (M+H)⁺ = 524,25, Tr de HPLC = 1,512 min.



2-Fluoro-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoato de etilo

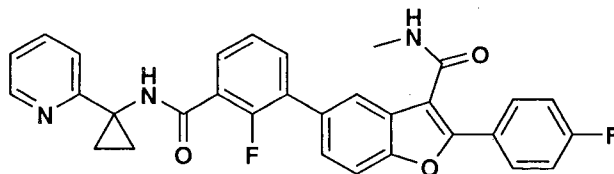
Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a

220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: 5 PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 436,01, Tr de HPLC = 1,820 min.



Ácido 2-fluoro-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)benzoico

10 Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: 15 PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 408,01, Tr de HPLC = 1,623 min.



5-(2-Fluoro-3-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida

El producto se obtuvo como una sal TFA después de purificación por HPLC preparativa de fase inversa Shimadzu-VP usando el procedimiento de separación: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 10 min, Tiempo de parada = 12 min, Caudal = 25 ml/min, Columna: Waters-Sunfire 19 x 100 mm S5, Recogida de la fracción: 8,11 - 8,43 min. (detección UV a 220 nm). RMN de ¹H (500 MHz, CD₃OD) δ 8,64 (d, J = 5,19, 1H), 8,42 (t, J = 7,78, 1H), 7,97 (dd, J = 8,24, 5,49, 2H), 7,91 (d, J = 8,24, 1H), 7,88 (s, 1H), 7,80 (c, J = 6,61, 2H), 7,76 (t, J = 7,17, 1H), 7,71 (d, J = 8,55, 1H), 7,60 (d, J = 8,24, 1H), 7,43 (t, J = 7,78, 1H), 7,29 (t, J = 8,55, 2H), 2,97 (s, 3H), 1,84 (m, 2H), 1,74 (m, 2H). Las LC/EM se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90%-TFA al 0,1%, Disolvente B= MeOH al 90%-H₂O al 10%-TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente = 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 524,08, Tr de HPLC = 1,417 min. Las HPLC analíticas se realizaron usando instrumento Shimadzu-VP con detección UV a 220 nm y 254 nm. Procedimiento de HPLC analítica: Disolvente A= MeCN al 5%-H₂O al 95%-TFA al 0,1%, Disolvente B= MeCN al 95%-H₂O al 5%-TFA al

0,1%, % Inicial de B = 10, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: Sunfire C18, 3,5 μ m, 4,6 x 150 mm, Tr = 8,57 min; Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 9,09 min. Procedimiento de HPLC analítica: Disolvente A= MeOH al 5%-
5 H₂O al 95%-NH₄HCO₃ 10 mM, Disolvente B= MeOH al 95%-H₂O al 5%-NH₄HCO₃ 10 mM, % Inicial de B = 50, % Final de B = 100, Tiempo de gradiente = 15 min, Tiempo de parada = 18 min, Caudal = 1 ml/min, Columna: XBridge Phenyl 3,5 μ m, 4,6 x 150 mm, Tr = 12,08 min.

10

3-(4-Fluorofenil)-3-oxopropanoato de etilo

A una suspensión de carbonato de dietilo (7,69 g, 65,14 mmol, 1,8 eq) y NaH (lavado en hexano) (90,47 mmol, 2,5 eq) en THF seco (30 ml) se añadió gota a gota a 60°C p-fluoroacetofenona (36,19 mmol). La reacción se mantuvo a reflujo suave ajustando la temperatura y velocidad de adición (exotérmica).
15 Después de completarse la adición, la reacción se calentó a reflujo durante 4 horas y luego se enfrió hasta temperatura ambiente. La mezcla de reacción se vertió cuidadosamente en ácido acético frío (6,0 ml) y agua (20 ml). El producto se extrajeron con éter y las fases de éter reunidas se lavaron con bicarbonato acuoso saturado, salmuera y se secaron. Se evaporó el éter y el producto bruto
20 se purificó by cromatografía en columna sobre gel de sílice (60-120) usando EtOAc al 2%/hexano como eluyente. Rendimiento: 7,3 g (96 %). RMN de ¹H (400MHz, CDCl₃): δ 1,27 (t, 3H, J = 7,12 Hz), 3,96 (s, 2H), 4,24 (c, 2H, J = 7,12

Hz), 7,17 (t, 2H, $J = 7,59$ Hz), 7,98 (m, 2H). LCEM : (ES+) $m/z = 211(M+H)$.

2-(4-Fluorofenil)-5-hidroxibenzofuran-3-carboxilato de etilo

A una solución agitada de cloruro de cinc (8,39 g, 1,14 mmol, 1 eq) en tolueno
5 a temperatura ambiente se añadió 3-(4-fluorofenil)-3-oxopropanoato de etilo (13
g, 2,74 mmol, 1 eq) y se agitó a 70 °C durante 15 min. Se añadió benzoquinona
(6,66 g, 0,72 mmol, 1 eq) en varias porciones a la mezcla de reacción y se
agitó a la misma temperatura durante 15-20 min. Se acopló un aparato de
Dean-stark y la mezcla de reacción se calentó a 140 °C durante 12 h y se enfrió
10 hasta temperatura ambiente. La finalización de la reacción se valoró por TLC.
Se añadió a la masa de reacción EtOAc y se filtró a través de papel de filtro,
para separar el material inorgánico. Se añadió salmuera a la mezcla de
reacción (filtrado) y se extrajo, se secó sobre sulfato sódico y se concentró
dando le material bruto. Se purificó de nuevo por cromatografía en columna
15 usando el sistema EtOAc al 10 %/Hexano. Rendimiento : 8,0 g (43 %). RMN de
 ^1H (400MHz, CDCl_3): δ 1,38-1,42 (t, 3H, $J = 7,14$ Hz), 4,37-4,42 (c, 2H, $J = 7,13$
Hz), 5,2 (s ancho, 1H), 6,87-6,9 (c, 1H, $J = 3,81$ Hz), 7,14-7,18 (c, 2H, $J = 5,82$
Hz), 7,36-7,39 (d, 1H, $J = 8,80$ Hz), 7,50-7,51 (d, 1H, $J = 2,56$ Hz), 8,00-8,03
(m, 2H). LCEM : (ES+) $m/z = 301(M+H)$.

20

Ácido 2-(4-fluorofenil)-5-hidroxibenzofuran-3-carboxílico

A una mezcla de 2-(4-fluorofenil)-5-hidroxibenzofuran-3-carboxilato (1 g, 3,5

mmol, 1 eq) en una mezcla 1:1 de MeOH/THF a temperatura ambiente se añadieron 5 equivalentes de NaOH y se calentó hasta 60 °C durante 3 h. La mezcla se enfrió hasta temperatura ambiente y hasta 0 °C en un baño de hielo-agua, se acidificó lentamente con HCl 1,5 N y luego se concentró. La mezcla con precipitados blancos se diluyó con agua y se filtró dando el sólido. Se lavó de nuevo con agua y se secó a vacío. Rendimiento : 0,9 g (94,6 %). RMN de ^1H (400MHz, DMSO- d_6): δ 6,82-6,85 (m, 1H), 7,35-7,40 (m, 3H), 7,46-7,49 (d, 1H, $J = 8,84$ Hz), 8,02-8,05 (m, 2H), 9,4 (s, 1H), 13,05 (s, 1H). LCEM : (ES-) $m/z = 271,1$

10

2-(4-Fluorofenil)-5-hidroxi-N-metilbenzofuran-3-carboxamida

A una mezcla de ácido 2-(4-fluorofenil)-5-hidroxibenzofuran-3-carboxílico (1 g, 3,7mmol, 1 eq), metilamina en THF (solución 2 M) (0,689 g, 21,5 mmol, 1 eq), HOBT (0,83 g, 6,2 mmol, 1,7 eq), EDC.HCl (1,24 g, 6,6 mmol, 1,8 eq) en DMF a temperatura ambiente en nitrógeno se añadió diisopropil etilamina (2,32 g, 18,5 mmol, 3,0 eq). La mezcla transparente se agitó a temperatura ambiente durante 12 h. La LCEM indicó el producto deseado. La se concentró fría en un baño de hielo-agua, luego se diluyó con agua. El sólido blanco se filtró y lavó con agua y secó a vacío. Rendimiento : 0,85 g (90 %), RMN de ^1H (400MHz, DMSO- d_6): δ 2,81-2,82 (d, 3H, $J = 4,5\text{Hz}$), 6,80-6,83 (m, 1H), 6,94-6,95 (d, 1H, $J = 2,3$ Hz), 7,34-7,38 (t, 2H, $J = 8,7$ Hz), 7,44-7,47 (d, 1H, $J = 8,8$ Hz), 7,90-7,93 (m, 2H), 8,39-8,40 (d, 1H, $J = 4,4$ Hz), 9,3 (s, 1H). LCEM : (ES+) $m/z =$

20

286,1(M+H).

Trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo

A una mezcla de 2-(4-fluorofenil)-5-hidroxi-N-metilbenzofuran-3-carboxamida (5
5 g, 17,5 mmol, 1 eq) en diclorometano (50 ml) a temperatura ambiente en N₂ se
añadió trietilamina (2,6 g, 26 mmol, 1,5 eq). La mezcla se enfrió hasta 0 °C y
luego se añadió 1,1,1-trifluoro-N-fenil-N(trifluorometilsulfonil) metano
sulfonamida (7,5 g, 21 mmol, 1,2 eq). La mezcla se agitó entonces a
temperatura ambiente durante 12 h. La mezcla de reacción se concentró, se
10 diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó luego dos
veces con agua, se secó sobre sulfato sódico y se concentró dando el
producto. El producto se purificó luego por cromatografía en columna usando
gel de sílice 230-400 y EtOAc al 50 %/Hexano. Rendimiento : 6,2 g (85 %).
RMN de ¹H (400MHz, DMSO-d₆): δ 2,83-2,84 (d, 3H, J = 4,6 Hz), 7,40-7,44 (t,
15 2H, J = 8,9 Hz), 7,51-7,53 (m, 1H), 7,75-7,76 (d, 1H, J = 2,52 Hz), 7,88-7,90 (d,
1H, J = 8,96 Hz), 7,94-7,98 (m, 2H), 8,51-8,52 (d, 1H, J = 4,6 Hz). LCEM :
(ES+) m/z = 418(M+H).

3-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoato

20 A una mezcla de trifluorometanosulfonato de 2-(4-fluorofenil)-3-
(metilcarbamoil)benzofuran-5-ilo (3,5 g, 8,4 mmol, 1 eq), ácido borónico (1,95 g,
10,1 mmol, 1,2 eq), en 1,4-dioxano/H₂O (5:1) se añadió carbonato de cesio

(8,21 g, 26 mmol, 3 eq) y el nitrógeno gas se hizo pasar a través de la mezcla durante 10 minutos. Seguidamente se añadió a la mezcla de reacción tetraquistrifenilfosfina paladio (0,97 g, 0,8 mmol, 0,1 eq) y se hizo pasar de nuevo nitrógeno gas a través de la mezcla durante 10 min. La mezcla de
5 reacción anterior se calentó en un microondas durante una hora a 90°C. De nuevo se añadieron 50 ml de agua a la mezcla de reacción y se extrajo con EtOAc. La fase orgánica se lavó de nuevo dos veces con agua y se secó sobre sulfato sódico y concentró dando el producto. El producto obtenido se purificó luego por cromatografía en columna usando EtOAc al 40 % /Hexano como
10 eluyente. Rendimiento: 1,5 g (40 %) RMN de ^1H (400MHz, DMSO- d_6): δ 2,32 (s, 3H), 2,81-2,82 (d, 3H, $J = 4,56$ Hz), 3,85 (s, 3H), 7,39-7,43 (t, 2H, $J = 8,9$ Hz), 7,39-7,43 (m, 1H), 7,49-7,51 (d, 1H, $J = 8,16$ Hz), 7,56 (s, 1H), 7,75-7,77 (d, 1H, $J = 8,6$), 7,83 (s, 1H), 7,89-7,91 (d, 1H, $J = 7,82$ Hz), 7,98-8,02 (m, 2H), 8,48-8,49 (d, 1H, $J = 4,6$ Hz).LC-MS : (ES+) $m/z = 418$ (M+H).

15

Ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico
A una mezcla de 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoato de metilo (1 g, 2,4 mmol, 1 eq) en una mezcla 1:1 de MeOH/THF a temperatura ambiente se añadieron 5 equivalentes de NaOH y se calentó
20 hasta 60 °C durante 5 h. La mezcla se enfrió hasta temperatura ambiente y luego en un baño de hielo-agua, se inactivó lentamente con HCl 1,5 N y luego se concentró. La mezcla con precipitados blancos se diluyó con agua y se filtró

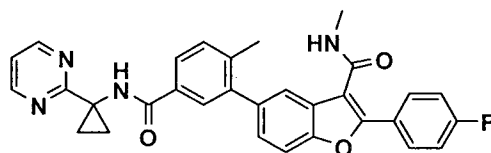
dando el sólido. Este se lavó con agua y se secó a vacío. Rendimiento: 0,850 g (90 %). Este ácido también se preparó acoplando trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo con ácido 4-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoico (Cs_2CO_3 , $(\text{Ph}_3)_4\text{Pd}$, $\text{H}_2\text{O}/1,4\text{-dioxano}$ 5 (1:5), 90 °C) de una forma similar a la descrita. RMN de ^1H (400MHz, DMSO-d_6): δ 2,32 (s, 3H), 2,82-2,83 (d, 3H, $J = 4,6$ Hz), 7,36-7,48 (m, 6H), 7,56-7,57 (d, 1H, $J = 1,44$ Hz), 7,75-7,77 (d, 1H, $J = 8,48$ Hz), 7,81-8,03 (m, 2H), 8,46-8,48 (d, 1H, $J = 4,7$ Hz), 12,92 (s, 1H). LCEM : (ES+) $m/z = 404,0$ (M+H).

10

1-(Pirimidin-2-il)ciclopropanamina

Se recogió 2-ciano pirimidina (5 g, 47,6 mmol, 1 eq) en una atmósfera de THF seco en argon, luego se añadió lentamente isopropóxido de titanio (17 ml, 57,1 mmol, 1,2 eq) a temperatura ambiente y la mezcla de reacción se agitó durante 15 minutos. Se añadió lentamente mediante una jeringa bromuro de etil 15 magnesio (solución 1M) en THF (107 ml, 809 mmol, 2,5 eq) a temperatura ambiente, (durante la adición de EtMgBr la masa de reacción se vuelve negra). A continuación se agitó la masa de reacción durante 1 hora. Se añadió lentamente a través de una jeringa a 0°C $\text{BF}_3 \cdot \text{EtO}$ (16,7 ml, 119,0 mmol, 2,5 eq). Se dejó que la mezcla alcanzara temperatura ambiente y se agitó durante 20 otra hora. Se añadieron 50 ml de agua a la mezcla de reacción y se filtró a través de CELITE® y se lavó el lecho con agua y acetato de etilo. La masa de reacción se basificó con solución al 10% de NaOH (pH = 9) luego se extrajo

con DCM y se lavó con solución de salmuera. El producto requerido se purificó por cromatografía en columna sobre gel de sílice (230-400) usando DCM/metanol como eluyente. Rendimiento : 2,1 g (30 %). RMN de ^1H (400MHz, DMSO- d_6): δ 1,49-1,52 (m, 2H), 1,59-1,62 (m, 2H), 7,47-7,49 (t, 1H, J = 4,80), 8,83-8,84 (d, 2H, J = 4,80).



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

- 10 A una mezcla de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico (0,1 g, 0,25 mmol, 1 eq), 1-(pirimidin-2-il)ciclopropanamina (0,041 g, 0,3 mmol, 1,2 eq) (60 % de pureza), HOBT (0,057 g, 0,42 mmol, 1,7 eq), EDC.HCl (0,086 g, 0,44 mmol, 1,8 eq) en DCM a temperatura ambiente en nitrógeno se añadió diisopropiletilamina (0,16 g, 1,3 mmol). La mezcla
- 15 transparente se agitó a temperatura ambiente durante 12 h. La mezcla se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó de nuevo con agua, se secó sobre sulfato sódico y se concentró. El producto obtenido se purificó de nuevo por cromatografía en columna (alúmina neutra) usando metanol al 0,5 %/DCM y finalmente se purificó por HPLC preparativa.
- 20 Rendimiento : 0,15 g (14 %). RMN de ^1H (400MHz, DMSO- d_6): δ 1,33-1,36 (m,

2H), 1,59-1,61 (m, 2H), 2,31(s, 3H), 2,82-2,83 (d, 3H, $J = 4,8$ Hz), 7,26-7,29 (t, 1H, $J = 4,8$ Hz), 7,39-7,45 (m, 4H), 7,59 (s, 1H), 7,76-7,78 (d, 1H, $J = 8,4$ Hz), 7,86-7,87 (d, 2H, $J = 4,4$ Hz), 7,98-8,02 (m, 2H), 8,47-8,50 (m, 1H), 8,67-8,68 (d, 2H, $J = 4,8$ Hz), 9,20 (s, 1H). LCEM : (ES+) $m/z = 521,2$ (M+H). Columna :
5 Ascentis Express C18 (5X2,1mm-2,7 μ m). Fase móvil A : MeCN al 2% -H₂O al 98%-NH₄COOH 10mM. Fase móvil B : MeCN al 98% – H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min.

Tiempo	%A	%B
0,0	100,0	0
1,5	0,0	100,0
3,2	0,0	100,0
3,6	100,0	0,0

Tr min : 1,908, longitud de onda: 220nm.

10 Procedimiento HPLC:

Columna : ZORBAX® C18 (4,6X150mm-5,0 μ m)

A : Tampón : acetato amónico 20mM

B : Metanol

Caudal : 1ml/min

Tiempo	B%
0	10

Tiempo	B%
12	100
15	100

Longitud de onda : 254 nm, Tr min :19,7

Longitud de onda : 220 nm, Tr min :19,7

Procedimiento HPLC:

5 Sunfire C18 (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : ACN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15.	100

10 Longitud de onda : 254 nm, Tr min :17,2

Longitud de onda : 220 nm, Tr min :17,2

Procedimiento HPLC:

XBridge phenyl (4,6X150)mm, 3,5 micrómetros

15 Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :15,764

5 Longitud de onda : 220 nm, Tr min :15,764

Ácido 3-fluoro-5-yodo-4-metilbenzoico

Se disolvió ácido 3-fluoro-4-metilbenzoico (1 g, 6,48 mmol, 1 eq) en ácido trifluorometanosulfónico (10 ml) y la reacción se enfrió hasta 0 °C. A la solución anterior se añadió *N*-yodosuccinimida (1,46 g, 6,48 mmol, 1 eq) en una porción y la reacción se agitó a temperatura ambiente durante 14 h. Seguidamente, la solución anterior se vertió en 50 ml de hielo-agua, se filtró el sólido obtenido. El sólido se disolvió en acetato de etilo, se lavó con solución de tiosulfato sódico y salmuera, se concentró la fase orgánica dando el producto deseado como sólido marrón claro. Rendimiento : 1,5 g (83 %). RMN de ¹H (400MHz, CDCl₃): δ 2,35 (s, 3H), 7,68 (d, 1H, *J* = 8 Hz), 8,14 (s, 1H). 13,50 (ancho, 1H).

3-Fluoro-5-yodo-4-metilbenzoato de metilo

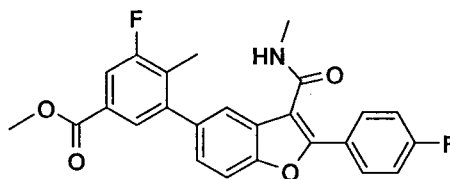
Se disolvió ácido 3-fluoro-5-yodo-4-metilbenzoico (1,3 g, 4,6 mmol, 1 eq) en metanol y se trató con ácido sulfúrico concentrado (0,49 ml, 9,2 mmol, 2 eq). La solución anterior se agitó a 50 °C durante 15 h. Seguidamente se eliminó el disolvente y se añadió al residuo resultante éter dietílico y se lavó la fase orgánica con solución al 10% de bicarbonato sódico y agua. Finalmente, la fase orgánica se concentró y se purificó por cromatografía ultrarrápida en columna sobre gel de sílice usando gel de sílice 240-400 y usando EtOAc al 10 % en hexano como eluyente. Rendimiento : 1 g (77 %). RMN de ^1H (400MHz CDCl_3). δ 2,39 (s, 3H), 3,90 (s, 3H), 7,64 (d, 1H, $J = 8$ Hz), 8,25 (s, 1H).

10

3-Fluoro-4-metil-5-(3,3,4,4-tetramethylborolan-1-il)benzoato de metilo

Una mezcla de 3-fluoro-5-yodo-4-metilbenzoato de metilo (0,85 g, 2,89 mmol, 1 eq), acetato potásico (1,41 g, 14,45 mmol, 5 eq), bispinacolatodiboro (1,1 g, 4,33 mmol, 1,5 eq) y 1,1-bis (difenilfosfino)ferroceno)-dicloropaladio (II) (0,047 g, 0,057 mmol, 0,02 eq) se disolvió en DMF y la reacción se agitó a 90 °C durante 18 h. Seguidamente se eliminó el disolvente, se añadió agua y se extrajo con diclorometano, se lavó la fase orgánica con HCl 2 M, cloruro de litio al 10 % y salmuera. La fase orgánica se concentró y se añadió hexano. El sólido obtenido se filtró y se secó dando el producto deseado como un sólido blanco. Rendimiento : 0,35 g, (41 %). RMN de ^1H (400MHz CDCl_3): δ 1,35(s, 12H), 2,49 (s, 3H), 3,90 (s, 3H), 7,69-7,71 (d, 1H, $J = 8$ Hz), 8,18 (s, 1H).

20



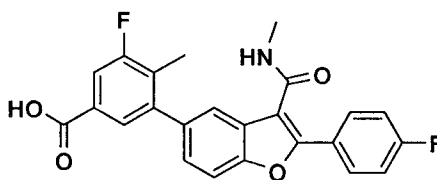
3-Fluoro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoato
de metilo

A una mezcla de trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (0,5 g, 1,2 mmol, 1 eq), éster borónico (0,42 g, 1,4 mmol, 1,2 eq) en 1,4-dioxano/H₂O (5:1) se añadió carbonato de cesio (1,17 g, 3,6 mmol, 3 eq) y se hizo pasar nitrógeno gas a través de la solución durante 10 minutos. A continuación se añadió tetraquistrifenilfosfina paladio (0,14 g, 0,12 mmol, 0,1 eq) a la mezcla de reacción y se hizo pasar nitrógeno gas a través de la solución de nuevo durante 15 min. La mezcla de reacción anterior se calentó en microondas durante una hora a 90 °C. Se añadieron aproximadamente 100 ml de agua a la mezcla de reacción y se extrajo con EtOAc. La fase orgánica se lavó luego dos veces con agua, se secó y se concentró dando el producto. El producto obtenido se purificó luego por cromatografía en columna usando EtOAc al 40 %/Hexano como eluyente. Rendimiento : 0,5 g (40 %). RMN de ¹H (400MHz, DMSO-d₆): δ 2,23 (d, 3H, J = 1,9 Hz), 2,82-2,83 (d, 3H, J = 4,6 Hz), 3,8 (s, 3H), 7,39-7,43 (t, 2H, J = 8,4 Hz), 7,39-7,43 (1H, m), 7,61 (s, 1H), 7,70-7,72 (d, 2H, J = 7,2 Hz), 7,78-7,80 (d, 1H, J = 8,4 Hz), 7,99-8,03 (m, 2H), 8,49-8,51 (d, 1H, J = 4,7 Hz). LCEM : (ES+) m/z = 436 (M+H). PHENOMENEX® Luna C18 (4,6X3,0mm-5,0µm). Fase móvil A :

10% CH₃OH -H₂O al 90%-NH₄OAc 10 mM. Fase móvil B : 90% CH₃OH -H₂O al 10%-NH₄OAc 10 mM. Caudal : 5 ml/Min.

Tiempo	%B
0,0	0,0
2,0	100,0
3,0	0,0

Tr min : 2,135, longitud de onda: 220nm



Ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico

A una mezcla de 3-fluoro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoato de metilo (0,3 g, 0,68 mmol, 1 eq) en una mezcla 1:1 de MeOH/THF a temperatura ambiente se añadieron 5 equivalentes de NaOH y se calentó hasta 60 °C durante 5 h. La mezcla se enfrió hasta temperatura ambiente y luego se enfrió en un baño de hielo-agua. Se acidificó lentamente con HCl 1,5N y luego se concentró. La mezcla con precipitados blancos se diluyó con agua y se filtró dando el sólido. Se lavó de nuevo con agua y se secó a vacío. Rendimiento : 0,2 g (60 %). RMN de ¹H (400MHz, DMSO-d₆): δ 2,22 (s, 3H), 2,82-2,84 (d, 3H, J = 4,6 Hz), 7,39-7,43 (m, 3H), 7,61 (s, 1H), 7,66-7,70 (d, 1H, J = 8,6 Hz), 7,66-7,70 (m, 1H), 7,78-7,80 (d, 1H, J = 8,5 Hz),

8,01-8,03 (m, 2H), 8,49-8,51 (d, 1H, $J = 4,76$ Hz), 13,2 (s, 1H). LCEM : (ES-) $m/z = 420,0$ (M-H). CHROMOLITH® SpeedROD C18 (4,6X3,0mm-5,0 μ m). Fase móvil A : 10% CH₃OH -H₂O al 90%-TFA al 0,1%. Fase móvil B : 90% CH₃OH -H₂O al 10%-TFA al 0,1%. Caudal : 5 ml/Min.

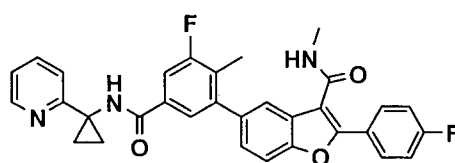
Tiempo	%B
0,0	0,0
2,0	100,0
3,0	0,0

5 Tr min : 2,040, longitud de onda: 220 nm.

1-(Piridin-2-il)ciclopropanamina

Se recogió 2-ciano piridina (5 g, 48,0 mmol, 1 eq) en THF seco en atmósfera de argon. A esta mezcla se añadió lentamente isopropóxido de titanio (17 ml, 57,6 mmol, 1,2 eq) a temperatura ambiente. La masa de reacción se agitó durante 15 minutos. Se añadió bromuro de etil magnesio (solución 1 M) en THF (107 ml, 809 mmol, 2,5 eq) mediante jeringa lentamente a temperatura ambiente, (durante la adición de EtMgBr, la masa de reacción se volvió negra). A continuación se agitó la masa de reacción durante una hora y se añadió lentamente a 0°C BF₃.Et₂O (16,7 ml, 120,0 mmol, 2,5 eq). Después de completar el proceso de adición, se dejó que la masa de reacción llegara a temperatura ambiente y continuó la agitación durante una hora más. Finalmente se añadieron 50 ml de agua y la masa de reacción se filtró a través

de CELITE®. El lecho se lavó luego con agua y acetato de etilo. El filtrado se basificó con solución al 10% de NaOH (pH = 9) luego se extrajo con DCM y se lavó con solución de salmuera, se purificó el producto requerido por cromatografía en columna sobre gel de sílice (60-120) usando DCM/metanol como eluyente. Rendimiento : 1,3 g (23 %). RMN de ^1H (400MHz, CDCl_3): δ 1,12-1,14 (m, 2H), 1,27-1,29 (m, 2H), 2,12 (ancho s, 2H), 7,03-7,07 (t, 1H), 7,33-7,35 (d, 1H), 7,60-7,62 (t, 1H), 8,48-8,49 (d, 1H).



10 5-(3-Fluoro-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoi)fenil)-2-(4-fluorofenil)-
N-metilbenzofuran-3-carboxamida

A una mezcla de ácido 3-fluoro-5-(2-(4-fluorofenil)-3-(metilcarbamoi)benzofuran-5-il)-4-metilbenzoico (0,2 g, 0,47 mmol, 1 eq), 1-(piridin-2-il)ciclopropanamina (0,075 g, 5,5mmol, 1,2 eq) (60 % de pureza),
15 HOBT (0,81 g, 0,015 mmol, 1,7 eq), EDC.HCl (0,16 g, 0,083 mmol, 1,8 eq) en DCM a temperatura ambiente y en nitrógeno se añadió diisopropiletilamina (0,30 g, 2,3 mmol, 5,0 eq). La mezcla transparente se agitó a temperatura ambiente durante 12 h. La mezcla se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó luego con agua, se secó sobre sulfato
20 sódico y se concentró. El producto obtenido se purificó luego por cromatografía

en columna (alúmina neutra) usando metanol al 0,5 %/DCM y luego se realizó la purificación usando HPLC preparativa. Rendimiento : 0,1 g (50 %). RMN de ¹H (400MHz, CDCl₃): δ 1,39-1,42 (m, 2H), 1,67-1,70(m, 2H), 2,21-2,22 (d, 3H, J = 2,24 Hz), 2,9-3,0 (d, 3H, J = 4,88 Hz), 5,98-5,99 (s, 1H), 7,06-7,09 (dd, 1H, J = 5,2, 7,2 Hz), 7,18-7,36 (m, 5H), 7,53-7,62 (m, 4H), 7,76 (d, 1H, J = 1,36 Hz), 7,94-7,97 (m, 2H), 8,4 (s, 1H). LCEM : (ES+) m/z = 538,2 (M+H). Procedimiento LCEM : Columna : Atlantis dC18 (50X4,6mm-5µm). A: NH₄OAc 10 mM. B : acetonitrilo. Caudal : 1 ml/Min.

Tiempo	%B
0,0-3,0	30-95
3,0-4,0	95
4,0-4,5	95-30
4,5-6,0	30

Tr mín : 3,665, longitud de onda: 220nm

10

Información del procedimiento HPLC:
Sunfire C18 (4,6X150)mm, 3,5 micrómetros
Tampón : 0,05% TFA en agua pH 2,5
Fase móvil A : Tampón : MeCN (95:5)
15 Fase móvil B : MeCN :Tampón (95:5)
Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :10,441

Longitud de onda : 220 nm, Tr min :10,441

Pureza : 96%

5 XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN : Buffer (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

10 Longitud de onda : 254 nm, Tr min :9,592

Longitud de onda : 220 nm, Tr min :9,592

Pureza : 95,9 %

3,5-Dihidroxi-4-metilbenzoato de metilo

Se disolvieron ácido 3,5-dihidroxi-4-metilbenzoico (5,0 g, 29,79 mmol, 1,0 eq) y PTSA (1,13 g, 5,94 mmol, 0,2 eq) en 50 ml de metanol y la mezcla se calentó hasta reflujo durante 6 h. Se evaporó el metanol. El sólido resultante se lavó con solución al 10% de bicarbonato sódico. La solución acuosa se extrajo tres veces con acetato de etilo. La fase orgánica reunida se secó sobre sulfato sódico y se evaporó a vacío. Rendimiento : 5,25 g (96 %). RMN de ¹H (400MHz, DMSO-d₆): δ 1,98 (s, 3H), 3,78 (s, 3H), 6,93(s, 2H), 9,53(s, 2H). LCEM : (ES+) m/z = 183 (M+H) Procedimiento: Columna : PHENOMENEX® Luna C18 (4,6x30) mm, 5 micrómetro. Fase móvil A : MeOH al 10% – H₂O al 90% – NH₄OAc 10 mM. Fase móvil B : MeOH al 90% –H₂O al 10% – NH₄OAc 10 mM. Caudal : 5 ml/min

Tiempo (min.)	%A	%B
0,0	100,0	0,0
2,0	0,0	100,0
3,0	0,0	0,0

Tr min : 0,956

15 Longitud de onda : 220 nm

3-(Benciloxi)-5-hidroxi-4-metilbenzoato de metilo

Se disolvió 3,5-dihidroxi-4-metilbenzoato de metilo (3,5 g, 19,22 mmol, 1,0 eq) en 300 ml de DMF. A esta solución se añadió solución de carbonato potásico (2,52 g, 18,26 mmol, 0,95 eq). A esta suspensión agitada se añadió, gota a gota durante un período de 3 horas, bromuro de bencilo (3,12 g, 18,26 mmol, 0,95 eq) (se diluyó con 50ml de DMF). La solución se agitó durante la noche a temperatura ambiente. Seguidamente se evaporó el DMF a presión reducida. El residuo se lavó con agua y el producto se extrajo tres veces con DCM. Las fases de DCM reunidas se secaron sulfato sódico y se evaporaron a vacío. El producto requerido se purificó por cromatografía en columna sobre gel de sílice (240-400) usando acetato de etilo al 10%/hexano como eluyente. Rendimiento : 1,6 g (30 %). RMN de ^1H (400MHz, DMSO- d_6): δ 2,07 (s, 3H), 3,81 (s, 3H), 5,14 (s, 2H), 7,08 (s, 1H), 7,14 (s, 1H), 7,33-7,35 (d, 1H, $J = 7,04$ Hz), 7,39-7,42 (t, 2H, $J = 7,40$ Hz), 7,46-7,48 (d, 2H, $J = 7,48$ Hz), 9,78 (s, 1H).

15 3-(Benciloxi)-4-metil-5-(trifluorometilsulfoniloxi)benzoato de metilo

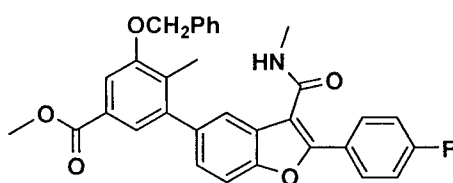
Se disolvió 3-(benciloxi)-5-hidroxi-4-metilbenzoato de metilo (3,0 g, 11,02 mmol, 1,0 eq) en DCM seguido por *N*-fenil bis (trifluorometilsulfonimida) (5,9 g, 16,53 mmol, 1,5 eq). A esta solución agitada se añadió gota a gota solución de TEA (3,34 g, 33,06 mmol, 3,0 eq). La solución resultante se agitó durante la noche a temperatura ambiente. A esta masa de reacción se añadió agua y se separó la fase de DCM. La fase acuosa se extrajo dos veces con DCM. La fase de DCM reunida se secó sobre sulfato sódico y se evaporó. El aceite resultante se

purificó por cromatografía en columna sobre gel de sílice (60-120) usando acetato de etilo al 5%/hexano como eluyente. Rendimiento : 4,0 g (80 %). RMN de ^1H (400MHz, DMSO) : δ 2,26 (s, 3H), 3,90 (s, 3H), 5,77 (s, 2H), 7,36-7,39 (d, 1H, $J = 8,20$ Hz), 7,43-7,45 (t, 2H, $J = 7,60$ Hz), 7,51 (s, 3H), 7,70 (s, 1H).

5

3-(Benciloxi)-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoato de metilo

A una solución de 3-(benciloxi)-4-metil-5(trifluorometilsulfoniloxi)benzoato de metilo (1,2 g, 2,96 mmol, 1,0 eq) en 1,4-dioxano se añadió $\text{PdCl}_2(\text{dppf})$ en
10 complejo de DCM (242 mg, 0,296 mmol, 0,1 eq) seguido por bis(pinacolato)diboro (1,5 g, 5,93 mmol, 2,0 eq). A esta solución agitada se añadió TEA (1,5 g, 14,83 mmol, y 5,0 eq). La mezcla de reacción se calentó lentamente hasta 110 °C y se mantuvo durante dos días en un tubo sellado. Se evaporó el 1,4-dioxano a presión reducida. Al residuo se añadió agua y la fase
15 acuosa se extrajo tres veces con DCM. La fase de DCM reunida se secó sobre sulfato sódico y se evaporó a vacío. El bruto se purificó por cromatografía en columna sobre gel de sílice (60-120) usando acetato de etilo al 1%/hexano como eluyente. Rendimiento : 0,8 g (70 %). RMN de ^1H (400MHz, CDCl_3): δ 1,39 (s, 12H), 2,53 (s, 3H), 3,91 (s, 3H), 5,17 (s, 2H), 7,33-7,35 (d, 1H, $J = 7,36$
20 Hz), 7,39-7,42 (t, 2H, $J = 7,50$ Hz), 7,48-7,50 (d, 2H, $J = 7,40$ Hz), 7,67-7,68 (d, 1H, $J = 1,20$ Hz), 8,00-8,01 (d, 1H, $J = 1,40$ Hz).



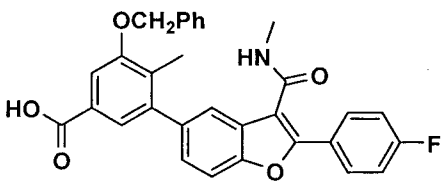
3-(Benciloxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-
metilbenzoato de metilo

A una mezcla de trifluorometanosulfonato de 2-(4-fluorofenil)-3-
5 (metilcarbamoil)benzofuran-5-ilo (0,5 g, 1,2mmol, 1 eq), éster borónico (0,55 g, 1,4 mmol, 1,2 eq) en 1,4-dioxano/H₂O (5:1) se añadió carbonato de cesio (1,37 g, 4,2 mmol, 3eq) y el nitrógeno gas se hizo pasar a través de la solución durante 10 minutos. A continuación, se añadió a la mezcla de reacción tetraquistrifenilfosfinapaladio (0,12 g, 0,16 mmol, 0,1 eq) y se hizo pasar
10 nitrógeno gas de nuevo durante 15 min. La mezcla de reacción anterior se calentó en microondas durante una hora a 90°C. Se añadieron aproximadamente 100 ml de agua a la mezcla de reacción y se extrajo con EtOAc. La fase orgánica se lavó de nuevo dos veces con agua y se secó sobre sulfato sódico y se concentró dando el producto. El producto obtenido se
15 purificó de nuevo por cromatografía en columna usando gel de sílice 60-120 y sistema de EtOAc al 40 %/Hexano. Rendimiento : 0,3 g (48 %). RMN de ¹H (400MHz, DMSO-d₆): δ 2,20 (s, 3H), 2,82-2,83 (d, 3H, J = 4,6 Hz), 3,8 (s, 3H), 5,3 (s, 2H), 7,39-7,46 (m, 6H), 7,52-7,56 (m, 4H), 7,62 (s, 1H), 7,76-7,78 (d, 1H, J = 8,44 Hz), 7,99-8,03 (m, 2H), 8,49-8,50 (d, 1H, J = 4,52 Hz). LCEM : (ES+)
20 m/z = 524,0 (M+H). CHROMOLITH® SpeedROD C18 (4,6X3,0mm-5,0µm).

Fase móvil A : 10% CH₃OH -H₂O al 90%-TFA al 0,1%. Fase móvil B : 90% CH₃OH -H₂O al 10%-TFA al 0,1%. Caudal : 5 ml/Min.

Tiempo	%B
0,0	0,0
2,0	100,0
3,0	0,0

Tr min : 2,303, longitud de onda : 220 nm



5

Ácido 3-(benciloxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico

A una mezcla de 3-(benciloxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoato de metilo (0,3 g, 0,57mmol, 1 eq) en una mezcla 1:1 de MeOH/THF a temperatura ambiente se añadieron 5 equivalentes de NaOH y la mezcla resultante se calentó hasta 60 °C durante 5h. La mezcla se enfrió hasta temperatura ambiente y luego se enfrió en baño de hielo-agua. La mezcla de reacción se acidificó con HCl 1,5 N y luego se concentró. La mezcla con precipitados blancos se diluyó con agua y se filtró dando el sólido. Se lavó con agua y se secó a vacío. Rendimiento : 0,2 g (70 %). RMN de ¹H (400MHz, DMSO-d₆): δ 2,19 (s, 3H), 2,82-2,83 (d, 3H, J = 4,56 Hz), 5,27 (s, 2H), 7,34-

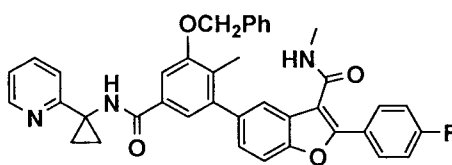
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7,46 (m, 6H), 7,50-7,55 (m, 4H), 7,60 (s, 1H), 7,75-7,77 (d, 1H, $J = 8,44$ Hz), 7,99-8,03 (m, 2H), 8,49-8,50 (d, 1H), 13,0 (s, 1H). LCEM : (ES+) $m/z = 510$ (M+H). Ascentis Express C18 (5,0X2,1-2,7 μ m). Fase móvil A : MeCN al 2% - H₂O al 98%-NH₄COOH 10mM. Fase móvil B : MeCN al 98% -2% H₂O-
5 NH₄COOH 10mM. Caudal : 5 ml/Min.

Tiempo	%A	%B
0,0	100,0	0,0
1,5	0,0	100,0
3,2	0,0	100,0
3,6	100,0	0,0

Tr min : 1,963, longitud de onda : 220 nm

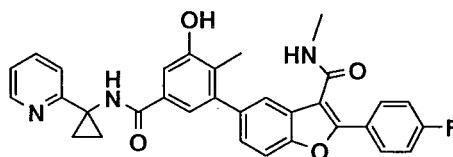


5-(3-(Benciloxi)-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoyl)fenil)-2-(4-
10 fluorofenil)-N-metilbenzofuran-3-carboxamida

A una mezcla de ácido 3-(benciloxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoyl)benzofuran-5-il)-4-metilbenzoico (0,2 g, 0,40 mmol, 1 eq), 1-(piridin-2-il)ciclopropanamina (0,064 g, 0,47 mmol, 1,2 eq) (60 % de pureza), HOBT (0,68 g, 0,012 mmol, 1,7 eq), EDC.HCl (0,064 g, 0,72 mmol, 1,8 eq) en
15 DCM a temperatura ambiente en nitrógeno se añadió diisopropiletilamina (0,26

g, 2,0 mmol, 5,0 eq). La mezcla transparente se agitó a temperatura ambiente durante 12 h. La mezcla se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó luego con agua, se secó sobre sulfato sódico y se concentró. El producto obtenido se purificó luego por cromatografía en columna (alúmina neutra) usando metanol al 0,5 %/DCM y HPLC preparativa. Rendimiento : 0,17 g (70 %). RMN de ^1H (400MHz, DMSO- d_6): δ 1,26-1,27 (m, 2H), 1,54-1,56 (m, 2H), 2,18 (s, 3H), 2,81-2,82 (s, 3H), 5,26 (s, 2H) 7,13-7,15 (c, 1H, $J = 4,4$ Hz), 7,30-7,43 (m, 6H), 7,58 (d, 4H), 7,65-7,69 (t, 2H, $J = 3,9$ Hz), 7,74-7,79 (d, 1H, $J = 8,0$ Hz), 7,97-8,01 (m, 2H), 8,43-8,48 (dd, 2H, $J = 4,89$ Hz), 9,186 (s, 1H). LCEM : (ES+) $m/z = 626$ (M+H) Ascentis Express C18 (5,0X2,1-2,7 μm). Fase móvil A : MeCN al 2% -H₂O al 98%-NH₄COOH 10mM. Fase móvil B : MeCN al 98% -2% H₂O-NH₄COOH 10mM. Caudal : 5 ml/Min.

Tiempo	%A	%B
0,0	100,0	0,0
1,5	0,0	100,0
3,2	0,0	100,0
3,6	100,0	0,0



15 2-(4-Fluorofenil)-5-(3-hidroxi-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-

N-etilbenzofuran-3-carboxamida

A una solución de ácido 3-(benciloxi)-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico (0,17 g, 0,27 mmol, 1 eq) en DCM se añadió BCl₃ en DCM (0,32 g, 2,7 mmol, 10 eq). La mezcla
5 transparente se agitó a temperatura ambiente durante la noche. La LCEM mostró el producto deseado. La mezcla se inactivó con NaHCO₃ al 10% y se extrajo con EtOAc. La fase orgánica se lavó luego con agua, se secó sobre sulfato sódico y se concentró. El producto obtenido se purificó luego por cromatografía en columna (alúmina neutra) usando metanol al 0,5 % /DCM y se
10 purificó luego por HPLC preparativa. Rendimiento : 0,048 g (33 %). RMN de ¹H (400MHz, DMSO-d₆): δ 1,22-1,24 (m, 2H), 1,51-1,53 (m, 2H), 2,09 (s, 3H), 2,82-2,83 (s, 3H, J = 4,4 Hz), 7,12-7,15 (c, 1H), 7,30-7,32 (d, J = 8 Hz, 1H), 7,37-7,43 (m, 5H), 7,58 (s, 1H), 7,65-7,69 (t, 1H, J = 8 Hz), 7,74-7,76 (d, 1H, J = 8,8 Hz), 7,97-8,01 (m, 2H), 8,43-8,48 (dd, 2H, J = 16, 4,8 Hz), 9,18 (s, 1H), 9,77
15 (s, 1H). LCEM : (ES+) m/z = 536,2 (M+H). Columna : Ascentis Express C18 (5X2,1mm-2,7µm). Fase móvil A : MeCN al 2% -H₂O al 98%-NH₄COOH 10mM. Fase móvil B : MeCN al 98% – H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min.

Tiempo	%A	%B
0,0	100,0	0
1,5	0,0	100,0

Tiempo	%A	%B
3,2	0,0	100,0
3,6	100,0	0,0

Tr min : 1,862, longitud de onda: 220nm

Información del procedimiento HPLC:

Sunfire C18 (4,6X150)mm, 3,5 micrómetros

5 Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN : Buffer (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :9,255

10 Longitud de onda : 220 nm, Tr min :9,255

Pureza : 95,2%

XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

15 Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :9,046

Longitud de onda : 220 nm, Tr min :9,046

5 Pureza : 95,8%

2-Fluoro-3-yodo-4-metilbenzonitrilo

Una solución de 2,2,6,6-tetrametil-4-piperidina (TMP) (550 mg, 3,93 mmol, 2,1 eq) en THF (5 ml) se enfrió hasta -78 °C en atmósfera de nitrógeno. Se añadió
10 lentamente n-butil litio (1,6 M en hexano, 1,52 ml, 3,96 mmol, 2,1 eq) manteniendo la temperatura por debajo de -70 °C. Después de la adición, la mezcla de reacción se calentó hasta -50 °C y se agitó durante una hora. La solución transparente se enturbió indicando la formación de sal. La mezcla de
reacción se enfrió hasta -80 °C, y se añadió lentamente una solución de 2-
15 fluoro-4-metilbenzonitrilo (250 mg, 1,85 mmol, 1,0 eq) en THF (1 ml) manteniendo la temperatura por debajo de -70 °C. La mezcla se calentó entonces hasta -50 °C y se agitó durante 30 minutos. La mezcla se volvió a enfriar hasta -78 °C y se añadió lentamente una solución saturada de yodo

(516 mg, 2,03 mmol, 1,1 eq) en THF (1 ml) manteniendo la temperatura por debajo de -70 °C. Después de la adición, la mezcla se calentó hasta temperatura ambiente. La mezcla de reacción se vertió en una solución saturada de Na₂S₂O₃ (10 ml) y se agitó durante 30 minutos. La fase orgánica se separó, y la fase acuosa se extrajo con acetato de etilo. Las fases orgánicas se reunieron, se lavaron con salmuera y se secaron sobre sulfato sódico. Los volátiles se evaporaron a presión reducida. El producto bruto se purificó en una cromatografía en columna sobre gel de sílice (60-120) usando acetato de etilo al 0,5 %/hexano como eluyente. Rendimiento : 187 mg (38 %). RMN de ¹H (400MHz, CDCl₃): δ 2,55 (s, 3H), 7,13-7,15 (d, 1H, J = 7,92 Hz), 7,48-7,50 (t, 1H, J = 4,80 Hz).

Ácido 2-fluoro-3-yodo-4-metilbenzoico

Una mezcla de 2-fluoro-3-yodo-4-metilbenzonitrilo (450 mg, 1,71 mmol, 1,0 eq) en dioxano 2 ml y ácido sulfúrico al 60% (2 ml) se calentó a 115 °C en un baño de aceite durante 12 h. Después de enfriar la mezcla hasta temperatura ambiente, ésta se vertió en 10 g de hielo. El sólido color cartón se filtró, se lavó con agua seguido por acetato de etilo. El sólido recogido se secó proporcionando ácido 2-fluoro-3-yodo-4-metilbenzoico como un sólido cristalino color castaño. El filtrado se transfirió a un embudo de separación. Se separó la fase de acetato de etilo, se lavó con salmuera, se secó sobre sulfato sódico y se concentró proporcionando más ácido 2-fluoro-3-yodo-4-metilbenzoico.

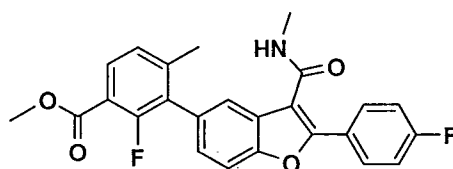
Rendimiento : 450 mg (93 %). RMN de ^1H (400MHz, DMSO- d_6): δ 2,48 (s, 3H), 7,27-7,29 (d, 1H, J = 8,00 Hz), 7,74-7,78 (t, 1H, J = 7,82 Hz), 13,2 (a, 1H).

2-Fluoro-3-yodo-4-metilbenzoato de metilo

- 5 A la solución de ácido 2-fluoro-3-yodo-4-metilbenzoico (450 mg, 1,6 mmol, 1,0 eq) en metanol (5 ml), se añadió una cantidad catalítica de HCl concentrado (0,1 ml). La solución resultante se calentó hasta reflujo a 80 °C durante la noche. Se evaporó el metanol. A este residuo se añadió agua y la fase acuosa se extrajo tres veces con acetato de etilo. Los extractos reunidos de acetato de
- 10 etilo se secaron sobre sulfato sódico, se filtraron y evaporaron proporcionando 2-fluoro-3-yodo-4-metilbenzoato de metilo. Rendimiento: 450 mg (95 %). RMN de ^1H (400MHz, DMSO): δ 2,49 (s, 3H), 3,85 (s, 3H), 7,30-7,32 (d, 1H, J = 7,84 Hz), 7,76-7,80 (t, 1H, J = 7,82 Hz). LCEM : (ES+) m/z = 295 (M+H).

- 15 2-Fluoro-4-metil-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoato de metilo
- A la solución de 2-fluoro-3-yodo-4-metilbenzoato de metilo (1,1 g, 3,74 mmol, 1,0 eq) en DMSO se añadió [1,1'-bis(difenilfosfino)ferroceno]-dicloropaladio (305 mg, 0,37 mmol, 0,1 eq) seguido por bis(pinacolato)diboro (1,9 g, 7,48 mmol, 2,0 eq). A esta solución se añadió acetato potásico (1,83 g, 18,7 mmol,
- 20 5,0 eq) y se hizo pasar nitrógeno gas a su través durante 10 minutos. La solución resultante se irradió con microondas a 80 °C durante 40 minutos. La mezcla de reacción se inactivó con solución de salmuera. La fase acuosa se

extrajo tres veces con acetato de etilo. La fase orgánica reunida se secó sobre sulfato sódico y la fase de acetato de etilo transparente se evaporó a vacío. El bruto se purificó por cromatografía en columna sobre gel de sílice (60-120) usando acetato de etilo al 1%/hexano como eluyente. Rendimiento : 400 mg
 5 (36 %). RMN de ^1H (400MHz, CDCl_3): δ 1,38 (s, 12H), 2,46 (s, 3H), 3,89 (s, 3H), 6,98-7,00 (d, 1H, $J = 7,84$ Hz), 7,81-7,85 (t, 1H, $J = 7,82$ Hz). LCEM : (ES+) $m/z = 295$ (M+H).



10 2-Fluoro-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoato
 de metilo

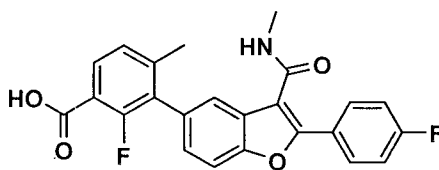
A una mezcla de trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (0,4 g, 0,96 mmol, 1 eq), éster borónico (0,366 g, 1,24 mmol, 1,3 eq), en 1,4-dioxano/ H_2O (5:1) se añadió carbonato de cesio
 15 (0,938 g, 2,87 mmol, 3 eq) y el nitrógeno gas se hizo pasar a su través durante 10 min. A continuación se añadió a la mezcla de reacción tetraquistrifenilfosfina paladio (0,111 g, 0,095 mmol, 0,1 eq) y se hizo pasar de nuevo nitrógeno gas a través de la mezcla durante 15 minutos. La mezcla de reacción anterior se calentó en microondas durante una hora a 90°C . Se añadieron
 20 aproximadamente 100 ml de agua a la mezcla de reacción y se extrajo con

EtOAc. La fase orgánica se lavó de nuevo dos veces con agua y se secó sobre sulfato sódico, se concentró dando el producto. El producto obtenido se purificó luego por cromatografía en columna usando gel de sílice 60-120 y EtOAc al 25 %/Hexano como eluyente. Rendimiento : 0,320 g (76 %). RMN de ^1H (400MHz, DMSO- d_6) : δ 2,19 (s, 3H), 2,81-2,82 (d, 3H, $J = 4,64$ Hz), 3,85 (s, 3H), 7,31-7,34 (d, 2H, $J = 8,28$ Hz), 7,39-7,44 (t, 2H, $J = 8,90$ Hz), 7,54 (s, 1H), 7,79-7,85 (m, 2H), 7,97-8,01 (m, 2H), 8,45-8,46 (d, 1H, $J = 4,32$ Hz). LCEM : (ES+) $m/z = 436$ (M+H). Procedimiento: Columna : CHROMOLITH® SpeedRod C18 (4,6x30)mm, 5 micrómetro. Fase móvil A : MeOH al 10% – H_2O al 90% – TFA al 0,1%. Fase móvil B : MeOH al 90% – H_2O al 10% – TFA al 0,1%. Caudal : 5 ml/min.

Tiempo (min.)	%A	%B
0,0	100,0	0,0
2,0	0,0	100,0
3,0	0,0	0,0

Tr min : 2,034

Longitud de onda : 220 nm



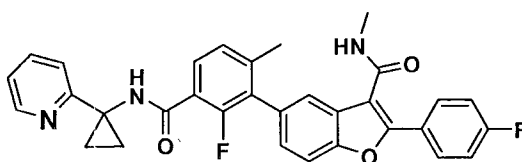
Ácido 2-fluoro-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-
metilbenzoico

A una mezcla de 3-fluoro-5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-
4-metilbenzoato de metilo (0,320 g, 1 eq) en una mezcla 1:1 de MeOH/THF, se
5 añadió solución 1 M de NaOH (0,088 g, 2,20 mmol, 3,0 eq) y se calentó hasta
90 °C durante 3h. La mezcla se enfrió hasta temperatura ambiente y luego en
un baño de hielo-agua. Se acidificó con HCl 1,5 N y luego se evaporaron los
volátiles. La mezcla con precipitado blanco se diluyó con agua y se filtró dando
el producto. Se lavó luego con agua y se secó a vacío. Rendimiento : 0,220 g
10 (71 %). RMN de ¹H (400MHz, DMSO-d₆) : δ 2,17 (s, 3H), 2,81-2,82 (d, 3H, J =
4,60 Hz), 7,28-7,33 (m, 2H, J = 4,33 Hz), 7,39-7,44 (m, 2H, J = 8,88 Hz), 7,53
(d, 1H, J = 1,24 Hz), 7,78-7,83 (m, 2H, J = 5,93 Hz), 7,97-8,01 (m, 2H), 8,45-
8,47 (d, 1H, J = 4,60 Hz), 13,13 (s, 1H). LCEM : (ES+) m/z = 422,0 (M+H).
Procedimiento: Columna : CHROMOLITH® SpeedRod C18 (4,6x30)mm, 5
15 micrómetro. Fase móvil A : MeOH al 10% – H₂O al 90% – TFA al 0,1%. Fase
móvil B : MeOH al 90% –H₂O al 10% – TFA al 0,1%. Caudal : 5 ml/min.

Tiempo (min.)	%A	%B
0,0	100,0	0,0
2,0	0,0	100,0
3,0	0,0	0,0

Tr min : 1,961

Longitud de onda : 220 nm



5-(2-Fluoro-6-metil-3-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-

5

N-metilbenzofuran-3-carboxamida

A la solución de ácido 2-fluoro-3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico (0,1 g, 0,273 mmol, 1,0 eq) en DMF (5,0 ml), se añadieron 1-(piridin-2-il)ciclopropanamina (0,038 g, 0,285 mmol, 1,2 eq), TBTU (0,130 g, 0,403 mmol, 1,7 eq) y DIPEA (0,154 g, 1,187 mmol, 5,0 eq). La mezcla se agitó a temperatura ambiente durante 12 h en atmósfera de nitrógeno. Se concentró en DMF y se añadió a este residuo agua y se extrajo con acetato de etilo. La fase orgánica reunida se secó sobre sulfato sódico y se evaporó el acetato de etilo. El bruto se purificó por TLC preparativa eluída con hexano/EtOAc (5:5). El producto se purificó luego por recristalización con DCM y hexano. Rendimiento : 0,045 g (39 %). RMN de ^1H (400MHz, DMSO- d_6): δ 1,23-1,25 (m, 2H), 1,51-1,54 (m, 2H), 2,18 (s, 3H), 2,81-2,82 (d, 3H, $J = 4,0$ Hz), 7,13-7,15 (t, 1H, $J = 3,78$ Hz), 7,27-7,29 (d, 1H, $J = 8,00$ Hz), 7,33-7,35 (d, 1H, $J = 4,26$ Hz), 7,39-7,44 (m, 3H, $J = 5,26$ Hz), 7,56-7,60 (t, 2H, $J = 7,56$ Hz), 7,68-7,72 (m, 1H), 7,80-7,82 (d, 1H, $J = 8,44$ Hz), 7,96-8,00 (m, 2H), 8,43-8,49 (m, 2H), 9,12 (s, 1H). LCEM : (ES+) m/z = 538,0 (M+H). Procedimiento: Columna :

20

CHROMOLITH® SpeedRod C18 (4,6x30) mm, 5 micrómetro. Fase móvil A : MeOH al 10% – H₂O al 90% – TFA al 0,1%. Fase móvil B : MeOH al 90% –H₂O al 10% – TFA al 0,1%. Caudal : 5 ml/min.

Tiempo (min.)	%A	%B
0,0	100,0	0,0
2,0	0,0	100,0
3,0	0,0	0,0

Tr min : 1,813

5 Longitud de onda : 220 nm

Procedimiento HPLC:

Columna : Sunfire C18 (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

10 Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min : 10,566 (Pureza : 98,287%)

Longitud de onda : 220 nm, Tr min :10,041 (Pureza : 97,3%)

Columna : XBridge Phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

5 Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min : 10,041 (Pureza : 98,3%)

Longitud de onda : 220 nm, Tr min : 10,041 (Pureza : 97,3%)

10

2-Metiloxazol-4-carbonitrilo

Se suspendieron clorhidrato de acetimidato de etilo (25 g, 340 mmol, 1 eq) y aminoacetonitrilo (38,5 g, 410 mmol, 1,2 eq) en diclorometano (300 ml) a temperatura ambiente. Se añadió trietilamina (148,4 ml, 380 mmol, 1,1 eq) gota a gota durante 1 h. Después de completarse la adición, la mezcla de reacción se enfrió hasta 0 °C, se añadió agua (125 ml), se separó la fase orgánica y la fase acuosa se extrajo con 50 ml de diclorometano. La mezcla de diclorometano reunida se concentró hasta 50 ml. Se añadió éter dietílico (500

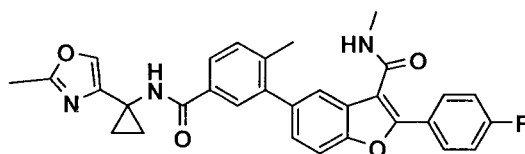
15

ml) a esta solución que se enfrió entonces hasta 0°C. A la solución anterior se añadió formiato de etilo (13,93 g, 190 mmol, 0,55 eq) seguido por la adición de *tert*-butóxido potásico (20,6 g, 172 mmol, 0,51 eq). La reacción se dejó agitando a temperatura ambiente durante 90 minutos y a 50 °C durante 90 minutos. Se añadió clorotrimetilsilano (56,5g, 520 mmol, 1,5 eq) en condiciones de reflujo y la reacción se agitó a 50 °C durante 5 h. Se añadió posteriormente agua y el producto se extrajo con diclorometano y la fase orgánica se lavó con agua y se purificó por cromatografía en columna proporcionando producto como aceite incoloro. Rendimiento : 6 g (16 %) rendimiento global. RMN de ¹H (400MHz, DMSO-d₆): δ 2,5 (s, 3H), 8,07 (s, 1H).

1-(2-Metiloxazol-4-il)ciclopropanamina

Se disolvió 2-metiloxazol-4-carbonitrilo (5 g, 46,1 mmol, 1 eq) en THF seco a temperatura ambiente, y se añadió al mismo isopropóxido de titanio (IV) (16 ml, 655 mmol, 1,2 eq) gota a gota durante un período de 15 minutos. La mezcla resultante se agitó durante 10 minutos y se añadió lentamente gota a gota bromuro de etil magnesio (85 ml, 17 volúmenes) a temperatura ambiente y la reacción se agitó durante 1 h. A continuación se añadió lentamente BF₃.eterato (16,7 ml, 115 mmol, 2,5 eq) a temperatura ambiente y la solución anterior se agitó a temperatura ambiente durante 3 h. Finalmente se añadió agua y el pH se llevó a 10 usando solución al 10 % de hidróxido sódico. La mezcla de reacción se extrajo con diclorometano, se concentró y se purificó por

cromatografía combiflash. Rendimiento : 1,5 g (20 %). RMN de ^1H (400MHz, DMSO- d_6): δ 0,93 (m, 2H), 1,00 (m, 2H), 1,98 (s ancho, 2H), 2,39 (s, 3H), 7,33 (s, 1H). LCEM : (ES+) m/z = 138,9 (M+H).



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(1-metil-1H-pirazol-3-il)
ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

A una mezcla de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico (0,15 g, 0,37 mmol, 1 eq), 1-(2-metiloxazol-4-il)ciclopropanamina
10 (0,066 g, 0,47, 1,2 eq), HOBt (0,092 g, 0,68 mmol, 1,7 eq), EDC.HCl (0,14 g, 0,73 mmol, 1,8 eq) en DCM a temperatura ambiente en nitrógeno se añadió diisopropiletilamina (0,26 g, 2,2 mmol, 5,0 eq). La mezcla transparente se agitó a temperatura ambiente durante 12 h. La mezcla se concentró, se diluyó con
15 agua y se extrajo con EtOAc. La fase orgánica se lavó luego con agua, se secó sobre sulfato sódico y se concentró. El producto obtenido se purificó luego por cromatografía en columna (alúmina neutra) usando metanol al 0,5 %/DCM como eluyente seguido por HPLC preparativa. Rendimiento : 0,02 g (20 %).
RMN de ^1H (400MHz, DMSO- d_6): δ 1,10-1,13 (m, 2H), 1,21-1,24 (m, 2H), 2,29 (s, 3H), 2,33 (s, 3H), 2,81-2,82 (d, 3H, J = 4,6 Hz), 7,38-7,43 (m, 4H), 7,57 (s,
20 1H), 7,61 (s, 1H), 7,75-7,71 (d, 1H, J = 8,4 Hz), 7,80-7,81 (s y m, 2H), 7,97-8,01

(m, 2H), 8,47-8,48 (d, 1H, $J = 4,76$ Hz), 9,1 (s, 1H). LCEM : (ES+) $m/z = 524,2$ (M+H). Procedimiento LCEM : CHROMOLITH® SpeedROD C18 (4,6X3,0mm-5,0 μ m). Fase móvil A : MeCN al 2% -H₂O al 98%-NH₄COOH 10mM. Fase móvil B : MeCN al 98% – H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min.

Tiempo	%B
0,0	0,0
2,0	100,0
3,0	100,0

5 Tr min : 2,018, longitud de onda : 220 nm

Procedimiento HPLC:

Sunfire C18 (4,6X150) mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

10 Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :10,757

Longitud de onda : 220 nm, Tr min :10,757

Pureza: 96,7%

XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

5 Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN : Buffer (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :9,993

Longitud de onda : 220 nm, Tr min :9,993

10 Pureza: 96,7%

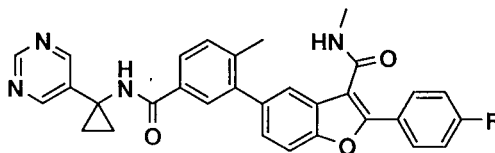
1-(Pirimidin-5-il)ciclopropanamina

Se recogió 5-ciano pirimidina (5 g, 47,6 mmol, 1 eq) en THF seco en atmósfera de argon, luego se añadió lentamente a temperatura ambiente isopropóxido de titanio (17 ml, 57,1 mmol, 1,2 eq) y la masa resultante se agitó durante 15 minutos. A la solución agitada anterior se añadió bromuro de etil magnesio (solución 1 M en THF, 107 ml, 809,3 mmol, 2,5 eq) lentamente mediante jeringa a temperatura ambiente. (Durante la adición del EtMgBr, la masa de

reacción se volvió negra). A continuación se agitó durante 1 hora la masa de reacción, se añadió lentamente $\text{BF}_3 \cdot \text{EtO}$ (16,7 ml, 119,0 mmol, 2,5 eq) a través de jeringa a 0 °C. Luego se dejó que la reacción alcanzara temperatura ambiente y se continuó agitando durante otra hora. Finalmente, la reacción se

5 inactivó añadiendo 50 ml de agua y la masa de reacción se hizo pasar a través de CELITE® y se lavó el lecho con agua y acetato de etilo. El filtrado se basificó con solución de NaOH al 10 % (pH = 9) y luego se extrajo con DCM y se lavó con solución de salmuera. El producto requerido se purificó por

10 cromatografía en columna sobre gel de sílice (60-120) usando DCM/metanol como eluyente. Rendimiento: 0,1 g (5 %) RMN de ^1H (400MHz, DMSO-d_6) : 1,04-1,08 (c, 2H, $J = 3,96$ Hz), 1,18-1,25 (c, 2H, $J = 3,96$ Hz), 8,26 (d, 2H), 9,05 (s, 1H). LCEM : (ES+) $m/z = 136$ (M+H).



15 2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(pirimidin-5-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

A una mezcla de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico (0,1 g, 0,25 mmol, 1 eq), 1-(pirimidin-5-il)ciclopropanamina (0,041 g, 0,3 mmol, 1,2 eq) (60 % de pureza), HOBT (0,057 g, 0,42 mmol, 1,7

20 eq), EDC.HCl (0,086 g, 0,44 mmol, 1,8 eq) en DCM a temperatura ambiente en

nitrógeno se añadió diisopropiletilamina (0,162 g, 1,2 mmol, 5,0 eq). La mezcla transparente se agitó a temperatura ambiente durante la noche. La mezcla se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó luego con agua, se secó sobre sulfato sódico y se concentró. El producto
5 obtenido se purificó luego por cromatografía en columna (alúmina neutra) usando metanol al 0,5%/DCM y finalmente se purificó por HPLC preparativa. Rendimiento : 0,02 g (20 %). RMN de ¹H (400MHz, DMSO-d₆) : δ 1,34-1,35 (m, 2H), 1,41-1,42 (m, 2H), 2,29 (s, 3H), 2,81-2,82 (d, 3H, J = 4,56 Hz), 7,38-7,45 (m, 4H), 7,58 (d, 1H, J = 0,96 Hz), 7,75 (d, 1H, J = 8,4 Hz), 7,81 (s, 1H), 7,83
10 (m, 1H), 7,98-8,01 (m, 2H), 8,46-8,47 (d, 1H, J = 4,6 Hz), 8,64 (s, 2H), 9,01 (s, 1H), 9,31 (s, 1H). LCEM : (ES+) m/z = 521,2(M+H). Procedimiento LCEM : Columna : Ascentis Express C18 (5X2,1mm-2,7µm). Fase móvil A : 2% ACN - H₂O al 98%-NH₄COOH 10mM. Fase móvil B : 98% ACN - H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min.

Tiempo	%A	%B
0,0	100,0	0
1,5	0,0	100,0
3,2	0,0	100,0
3,6	100,0	0,0

15 Tr min : 1,825, longitud de onda: 220 nm

Procedimiento HPLC:

Sunfire C18 (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

5 Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :10,061

Longitud de onda : 220 nm, Tr min :10,061

Pureza : 92,3 %

10 XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min.

Tiempo	B%
0	10
12	100

Tiempo	B%
15	100

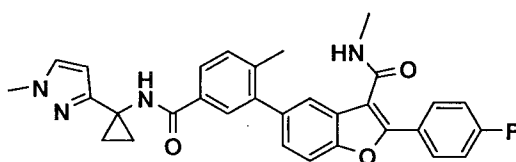
Longitud de onda : 254 nm, Tr min :9,542

Longitud de onda : 220 nm, Tr min :9,542

Pureza : 92,5 %

5 1-(1-Metil-1H-pirazol-3-il)ciclopropanamina

Se añadió bromuro de etil magnesio (2,5 mol, 1 M en éter) a -78 °C a una solución de 1-metil-1H-pirazol-3-carbonitrilo (0,5 g, 1 mmol) y $\text{Ti}(\text{O}i\text{-Pr})_4$ (1,1 mmol) en Et_2O (5 ml). La solución amarilla se agitó durante 10 minutos. Después se calentó la solución hasta temperatura ambiente (1 h), se añadió $\text{BF}_3 \cdot \text{OEt}_2$ (2 mmol). Después la mezcla se agitó durante 1 h, se añadieron HCl 1 N y éter. Se añadió NaOH (10 %) a las dos fases transparentes resultantes y la mezcla se extrajo con éter. Las fases de éter reunidas se secaron (Na_2SO_4), se filtraron y concentraron a presión reducida. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (Et_2O). RMN de ^1H (400MHz, CDCl_3): δ 0,94-1,05 (m, 4H), 2,32 (s, 2H), 3,83 (s, 3H), 5,92 (d, 1H), 7,23-7,24 (d, 1H). LCEM : (ES+) m/z observado 137,7.



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(1-metil-1H-pirazol-3-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

A una mezcla de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico (0,15 g, 0,37 mmol, 1 eq), 1-(1-metil-1H-pirazol-3-il)ciclopropanamina (0,061 g, 0,44 mmol, 1,2 eq), HOBT (0,057 g, 0,42 mmol, 1,7 eq), EDC.HCl (0,086 g, 0,44 mmol, 1,8 eq) en DCM a temperatura ambiente en nitrógeno se añadió diisopropiletilamina (0,16 g, 1,2mmol, 5,0 eq). La mezcla transparente se agitó a temperatura ambiente durante 12 h. La mezcla se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó luego con agua, se secó sobre sulfato sódico y se concentró. El producto obtenido se purificó luego por cromatografía en columna (alúmina neutra) usando metanol al 0,5%/DCM y finalmente por HPLC preparativa. Rendimiento : 0,06 g (40 %) RMN de ¹H (400MHz, DMSO-d₆): δ 1,12-1,16 (m, 2H), 1,20-1,23 (m, 2H), 2,29 (s, 3H), 2,82-2,83 (d, 3H, J = 4,64 Hz), 3,37 (s, 3H), 5,9-6,0 (d, 1H, J = 2,12 Hz), 7,39-7,48 (m, 5H), 7,58 (d, 1H, J = 1,68 Hz), 7,75-7,77 (d, 1H, J = 9,7 Hz), 7,81-7,83 (t, 2H, J = 2,87 Hz), 7,98-8,46 (m, 2H), 8,47-8,48 (d, 1H, J = 4,52 Hz), 9,14 (s, 1H). LCEM : (ES+) m/z = 523,2 (M+H). Procedimiento LCEM : Columna : Ascentis Express C18 (5X2,1mm-2,7µm). Fase móvil A : MeCN al 2% -H₂O al 98%-NH₄COOH 10mM. Fase móvil B : MeCN al 98% - H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min.

Tiempo	%A	%B
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Tiempo	%A	%B
0,0	100,0	0,0
1,0	70,0	30,0
2,5	0,0	100,0
4,0	0,0	100,0

Tr min : 1,882, longitud de onda : 220 nm

Información del procedimiento HPLC:

Sunfire C18 (4,6X150)mm, 3,5 micrómetros

5 Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
25	100
30	100

Longitud de onda : 254 nm, Tr min :16,999

10 Longitud de onda : 220 nm, Tr min :16,999

Pureza: 96%

XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

5 Longitud de onda : 254 nm, Tr min :15,556

Longitud de onda : 220 nm, Tr min :15,556

Pureza: 97 %

2-Metoxi-4-metilbenzoato de metilo

- 10 Se disolvió ácido metil 2-metoxi-4-metilbenzoico (1,5 g, 9,0 mmol, 1 eq) en DMF, se añadió yoduro de metilo (0,86 ml, 13,5 mmol, 1,5 eq) seguido por la adición de carbonato potásico (3,11 g, 22,5 mmol, 2,5 eq). La mezcla anterior se agitó a temperatura ambiente durante 12 h. Finalmente, la mezcla de reacción se hizo pasar a través de CELITE®. El filtrado se evaporó y se añadió
- 15 agua y el producto se extrajo con acetato de etilo. La fase orgánica se lavó con agua y se concentró. Rendimiento : 1,6 g (98 %). RMN de ¹H (400MHz, CDCl₃): δ 2,31 (s, 3H), 3,86 (s, 3H), 3,89 (s, 3H), 6,77 (s, 1H), 6,79 (d, 1H), 7,14 (d, 1H).

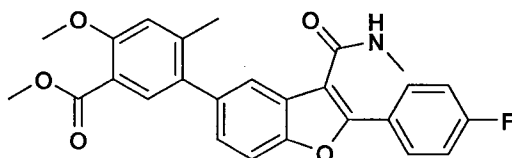
5-Yodo-2-metoxi-4-metilbenzoato de metilo

Se disolvió 2-metoxi-4-metilbenzoato de metilo (1,5 g, 8,32 mmol, 1 eq) en metanol. A esta solución se añadió gota a gota monoclóruo de yodo (6,75 g, 41,6 mmol, 5 eq) en metanol a temperatura ambiente. La mezcla de reacción
5 se calentó a 50 °C durante 15 h. Finalmente, se concentró el metanol, se diluyó con agua y se extrajo con acetato de etilo. La fase orgánica se lavó con HCl 0,1 N (50 ml), agua (100 ml) y solución de salmuera (100 ml). El producto se purificó por cromatografía en columna usando gel de sílice 60-120 y usando acetato de etilo al 5%/hexano como eluyente. Rendimiento : 1,7 g (80 %), RMN
10 de ^1H (400MHz, CDCl_3): δ 2,44 (s, 3H), 3,86 (s, 3H), 3,88 (s, 3H), 6,86 (s, 1H), 8,20 (s, 1H). LCEM : (ES+) m/z = 307,0 (M+H).

2-Metoxi-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoato de metilo

Se disolvieron en DMF 5-yodo-2-metoxi-4-metilbenzoato de metilo (1,5 g, 4,9
15 mmol, 1 eq), Bispinacolatodiboro (1,49 g, 5,8 mmol, 1,2 eq), acetato potásico (1,44 g, 14,7 mmol, 3 eq) y Pd(dppf)Cl_2 (0,4 g, 0,49 mmol, 0,1 eq). Se hizo pasar nitrógeno gas a través de la mezcla durante 10 minutos y la mezcla se agitó a 90 °C durante 14 horas. Luego se hizo pasar la solución a través de CELITE®. El filtrado se evaporó y se diluyó con agua y se extrajo con acetato
20 de etilo y se purificó por cromatografía en columna usando gel de sílice 60-120 y usando acetato de etilo al 20%/hexano como eluyente. Rendimiento : 1,2 g (80 %), RMN de ^1H (400MHz, CDCl_3): δ 1,33 (s, 12H), 2,56 (s, 3H), 3,86 (s, 3H),

3,91 (s, 3H), 6,75 (s, 1H), 8,21 (s, 1H). LCEM : (ES+) m/z = 307,2 (M+H).

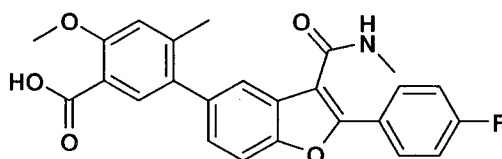


5-(2-(4-Fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoato

5

de metilo

Se disolvieron 2-metoxi-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoato de metilo (1,2 g, 3,92 mmol, 1 eq), trifluorometanosulfonato de 2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-ilo (1,6 g, 3,92 mmol, 1 eq), carbonato de cesio (3,8 g, 11,7 mmol, 3 eq) y tetraquis trifenilfosfinapaladio
 10 (0,13 g, 0,11 mmol, 0,03 eq) en 1,4-dioxano/agua y la solución anterior se agitó a 90 °C durante 10 h. A continuación la mezcla de reacción se diluyó con agua y el producto se extrajo con acetato de etilo y se purificó por cromatografía combiflash usando acetato de etilo al 40 %/hexano como eluyente. Rendimiento : 0,95 g (55 %). RMN de ^1H (400MHz, DMSO- d_6): δ 2,3 (s, 3H),
 15 2,82 (d, J = 4,6 Hz, 3H), 3,78 (s, 3H), 3,88 (s, 3H), 7,15 (s, 1H), 7,51 (s, 1H), 7,64 (m, 2H), 7,65 (m, 2H), 7,74 (d, 1H, J = 8,48 Hz), 8,00-8,01 (m, 2H), 8,48 (d, 1H). LCEM : (ES+) m/z = 448 (M+H).



Ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoico

Se disolvieron 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoato de metilo (0,9 g, 2 mmol, 1 eq) e hidróxido sódico (0,4 g, 10 mmol, 5 eq) en metanol/agua (20/5 ml) y la reacción se agitó a 50 °C durante 10 h. A continuación, la mezcla de reacción se concentró y se diluyó con agua y el pH de la solución se llevó hasta 3 usando HCl concentrado. El sólido obtenido se filtró y se secó durante la noche. Rendimiento : 0,72 g (82 %). RMN de ¹H (400MHz, DMSO-d₆): δ 2,29 (s, 3H), 2,87 (d, 3H), 3,87 (s, 3H), 7,09 (s, 1H), 7,40-7,60 (m, 3H), 7,57 (m, 2H), 7,65 (d, 1H, J = 8,74 Hz), 7,98-8,01 (m, 2H), 8,46 (c, 1H, J = 4,40 Hz), 12,5 (s ancho, 1H). LCEM : (ES+) m/z = 434 (M+H) Procedimiento : Fase móvil A : agua; Fase móvil B : acetona al 0,1% en agua; Caudal : 2 ml/Min.

Tiempo	%B
0-20	100

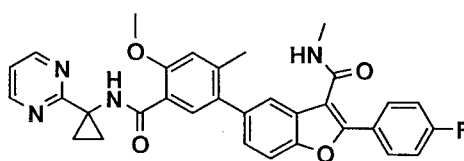
Tr min : 1,741

15 Longitud de onda : 220 nm

Se llevó a cabo otra LCEM usando instrumento Shimadzu-VP con detección UV a 220 nm y Waters MICROMASS®. Procedimiento HPLC: Disolvente A= MeOH al 10%-H₂O al 90% TFA al 0,1%, Disolvente B= MeOH al 90% - H₂O al 10% TFA al 0,1%, % Inicial de B = 0, % Final de B = 100, Tiempo de gradiente

= 2 min, Tiempo de parada = 3 min, Caudal = 5 ml/min, Columna: PHENOMENEX® Luna, 3,0 x 50 mm, S10; (ES+) m/z (M+H)⁺ = 434,10, Tr de HPLC = 1,653 min.

5



2-(4-Fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoi)fenil)-N-metilbenzofuran-3-carboxamida

A una mezcla de ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoi)benzofuran-5-il)-2-metoxi-4-metilbenzoico (0,2 g, 0,46 mmol, 1 eq), 1-(pirimidin-2-il)ciclopropanamina (0,074 g, 0,55 mmol, 1,2 eq), HOBT (0,105 g, 0,77 mmol, 1,7 eq), EDC.HCl (0,0,158 g, 0,82 mmol, 1,8 eq), en DCM a temperatura ambiente y en atmósfera de nitrógeno se añadió diisopropiletilamina (0,297 g, 2,2 mmol, 5,0 eq). La mezcla transparente se agitó a temperatura ambiente durante 12 h. La mezcla se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó adicionalmente con agua, se secó sobre sulfato sódico y se concentró. El producto obtenido se purificó luego por cromatografía en columna (alúmina neutra) usando metanol al 0,5%/DCM y HPLC preparativa. Rendimiento : 0,055 g (45%), RMN de ¹H (400MHz, DMSO-d₆): δ 1,43-1,44 (m, 2H), 1,59-1,62 (m, 2H), 2,31 (s, 3H), 2,81-2,82 (d, 3H, J = 4,56 Hz), 4,01 (s, 3H), 7,17 (s, 1H), 7,26-7,29 (t, 1H, J = 4,8 Hz), 7,33-7,36 (dd,

1H, $J = 8,4, 4 \text{ Hz}$), 7,38-7,43 (t, 2H, $J = 8,8 \text{ Hz}$), 7,50-7,51 (d, 1H, $J = 1,6 \text{ Hz}$), 7,72-7,76 (m, 2H), 7,97-8,01 (m, 2H), 8,48-8,49 (d, 1H, $J = 4,4 \text{ Hz}$), 8,7 (d, 2H, $J = 4,8 \text{ Hz}$), 8,87 (s, 1H). LCEM : (ES+) $m/z = 551,2 \text{ (M+H)}$. Columna : Ascentis Express C18 (5X2,1mm-2,7 μ m). Fase móvil A : MeCN al 2% -H₂O al 98%-
5 NH₄COOH 10mM. Fase móvil B : MeCN al 98% – H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min

Tiempo	%A	%B
0,0	100,0	0,0
1,0	70,0	30,0
2,5	0,0	100,0
4,0	0,0	100,0

Tr min : 1,946, longitud de onda: 220nm

Procedimiento HPLC:

10 Sunfire C18 (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10

754

Tiempo	B%
25	100
30	100

Longitud de onda : 254 nm, Tr min :18,209

Longitud de onda : 220 nm, Tr min :18,209

Pureza: 99,4%

5 XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

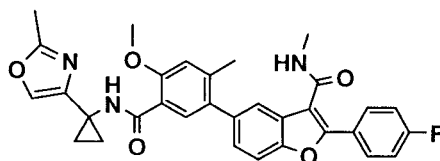
Caudal : 1ml/min

Tiempo	B%
0	10
25	100
30	100

10 Longitud de onda : 254 nm, Tr min :16,549

Longitud de onda : 220 nm, Tr min :16,549

Pureza: 99,5 %



2-(4-Fluorofenil)-5-(4-metoxi-2-metil-5-(1-(2-metiloxazol-4-

il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

Se disolvieron ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-
 5 metoxi-4-metilbenzoico (0,15 g, 0,34 mmol, 1 eq), 1-(2-metiloxazol-4-
 il)ciclopropanamina (0,047 g, 0,34 mmol, 1 eq), EDCI.HCl (0,076 g, 0,4 mmol,
 1,2 eq), HOBT (0,054 g, 0,4 mmol, 2 eq) y TEA (0,14 ml, 1,02 mmol, 3 eq) en
 diclorometano y la reacción se agitó a temperatura ambiente durante 14 h. La
 reacción se diluyó con agua y el producto se extrajo con diclorometano y se
 10 purificó por HPLC preparativa proporcionando el producto deseado.
 Rendimiento: 47 mg (25 %) RMN de ^1H (400MHz, DMSO- d_6): δ 1,12-1,15 (m,
 2H), 1,21-1,24 (m, 2H), 2,29 (s, 3H), 2,34 (s, 3H), 2,81-2,82 (d, 3H, $J = 4,60$
 Hz), 3,95 (s, 3H), 7,12 (s, 1H), 7,31-7,32 (m, 1H), 7,34-7,40 (t, 2H, $J = 3,21$ Hz),
 7,56 (s, 1H), 7,61 (s, 1H), 7,71 (s, 1H), 7,73 (s, 1H), 7,97-8,01 (m, 2H), 8,46-
 15 8,48 (m, 1H), 8,67 (s, 1H). LCEM : (ES+) $m/z = 554,2$ (M+H). Columna :
 Ascentis Express C18 (5X2,1mm-2,7 μm). Fase móvil A : 2% ACN - H_2O al 98%-
 NH_4COOH 10mM. Fase móvil B : 98% ACN - H_2O al 2%- NH_4COOH 10mM.
 Caudal : 1 ml/Min

Tiempo	%A	%B
0,0	100,0	0

Tiempo	%A	%B
1,0	70,0	30,0
2,5	0,0	100,0
4,0	0,0	100,0

Tr min : 1,964, longitud de onda : 220 nm

Procedimiento HPLC:

Sunfire C18 (4,6X150)mm, 3,5 micrómetros

5 Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :11,403

10 Longitud de onda : 220 nm, Tr min :11,402

Pureza: 98,8 %

XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

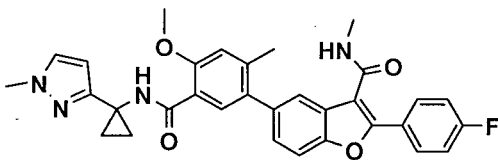
Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :10,588

5 Longitud de onda : 220 nm, Tr min :10,588

Pureza : 98,96 %



2-(4-Fluorofenil)-5-(4-metoxi-2-metil-5-(1-(1-metil-1H-pirazol-3-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

10

A una mezcla de ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoico (0,15 g, 0,35 mmol, 1 eq), 1-(1-metil-1H-pirazol-3-il)ciclopropanamina (0,058 g, 0,42 mmol, 1,2 eq), HOBt (0,08 g, 0,069 mmol, 1,7 eq), EDC.HCl (0,073 g, 0,014mmol, 1,8 eq), en DCM a temperatura ambiente en nitrógeno se añadió diisopropiletilamina (0,297 g, 2,2 mmol, 5,0 eq). La mezcla transparente se agitó a temperatura ambiente durante 12 h. La

15

mezcla se concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó luego con agua, se secó sobre sulfato sódico y se concentró. El producto obtenido se purificó luego por cromatografía en columna (alúmina neutra) usando metanol al 0,5%/DCM y la purificación final se realizó por HPLC preparativa. Rendimiento : 0,06 g (45 %) RMN de ¹H (400MHz, DMSO-d₆) : δ 1,18-1,20 (m, 4H), 2,29 (s, 3H), 2,81-2,82 (d, 3H, J = 4,64 Hz), 3,73 (s, 3H), 3,96 (s, 3H), 6,06-6,07 (d, 1H, J = 2,4 Hz), 7,12 (s, 1H), 7,32-7,34 (dd, 1H, J = 8,4, 1,6 Hz), 7,38.-7,42 (t, 2H, J = 8,8 Hz), 7,48.-7,49 (d, 2H, J = 2,34 Hz), 7,59 (s, 1H), 7,71-7,73 (d, 1H, J = 8,4 Hz), 7,97-7,97-8,01 (m, 2H), 8,47-8,48 (d, 1H, J = 4,8 Hz), 8,69 (s, 1H). LCEM : (ES+) m/z = 553,2 (M+H). Columna : Ascentis Express C18 (5X2,1mm-2,7µm). Fase móvil A : MeCN al 2% -H₂O al 98%-NH₄COOH 10mM. Fase móvil B : MeCN al 98% – H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min.

Tiempo	%A	%B
0,0	100,0	0
1,5	0,0	100,0
3,2	0,0	100,0

Tr min : 1,937, longitud de onda : 220 nm

15

Procedimiento HPLC:
Sunfire C18 (4,6X150)mm, 3,5 micrómetros
Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :11,289

5 Longitud de onda : 220 nm, Tr min :11,289

Pureza: 99,3 %

XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

10 Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

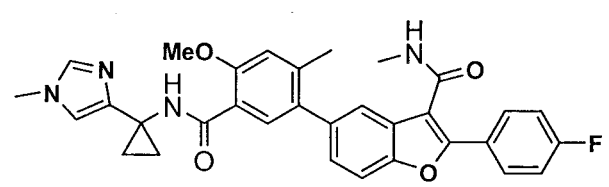
Longitud de onda : 254 nm, Tr min :10,548

Longitud de onda : 220 nm, Tr min :10,548

Pureza: 99,5 %

1-(1-Metil-1H-imidazol-4-il) ciclopropanamina

Se disolvió en THF 1-metil-1H-imidazol-4-carbonitrilo (0,5 g, 4,6 mmol, 1 eq), y
5 se añadió isopropóxido de titanio (1,6 g, 5,6 mmol, 2,5 eq) gota a gota durante
15 minutos. La mezcla se agitó durante 15 minutos a temperatura ambiente, y
luego se añadió a temperatura ambiente durante 15 minutos bromuro de etil
magnesio (1,6 g, 11,5 mmol, 2,5 eq). La mezcla de reacción se agitó durante 1
hora, se añadió BF₃ eterato (0,8 g, 5,6 mmol, 2,2 eq) y la mezcla se agitó a
10 temperatura ambiente durante 1 h. Se añadió solución de NaOH 1 N a la
mezcla para llevar el pH hasta 9-10. La masa de reacción se filtró a través de
CELITE® y el filtrado se lavó con DCM. La mezcla orgánica se concentró y el
residuo se purificó por cromatografía ultrarrápida sobre gel de sílice usando
cloroformo al 10 %/ metanol. Rendimiento: 0,6 g RMN de ¹H (400MHz, CDCl₃):
15 δ 0,97 (t, J = 3,4 Hz, 2H), 1,00 (t, J = 3,4 Hz, 2H), 3,63 (s, 3H), 7,28 (s, 1H), 7,31
(s, 1H). LCEM : (ES+) m/z = 138,2 (M+H).



2-(4-Fluorofenil)-5-(4-metoxi-2-metil-5-(1-(1-metil-1H-imidazol-4-
20 il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

Se disolvieron ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoico (0,2 g, 1 eq), 1-(1-metil-1H-imidazol-4-il)ciclopropanamina (0,07 g, 1,1 eq), EDCI.HCl (0,13 g, 1,5 eq), HOBT (0,094 g, 1,5 eq) y TEA (0,19 ml, 3 eq) en diclorometano y la solución anterior se agitó a 5 temperatura ambiente durante 18 h. A continuación se añadió agua y se separó la fase orgánica. La fase orgánica se lavó con agua y el producto bruto se purificó por HPLC Prep. Rendimiento : 24,69 mg (10 %) RMN de ¹H (400MHz, CDCl₃): δ 1,39 (s, 4H), 2,30 (s, 3H), 2,99-3,01 (d, J = 4,6 Hz, 3H), 3,81 (s, 3H), 4,04 (s, 3H), 5,90 (s, 1H), 6,87 (s, 1H), 7,16-7,25 (m, 3H), 7,24 (s, 1H), 7,51 (d, 10 J = 8,4 Hz, 1H), 7,65 (s, 1H), 7,98-7,99 (m, 3H), 8,29 (s, 1H), 8,95 (s, 1H). LCEM : (ES+) m/z = 553,2 (M+H). Procedimiento: Columna : Ascentis Express C18 (5X2,1mm-2,7µm). Fase móvil A : 2% ACN -H₂O al 98%-NH₄COOH 10mM. Fase móvil B : 98% ACN – H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min.

Tiempo	%A	%B
0,0	100,0	0
1,5	0,0	100,0
3,2	0,0	100,0

15 Tr min : 1,854

Longitud de onda : 220 nm

HPLC Columna:

Sunfire C18 (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : MeCN :Tampón (95:5)

5 Caudal : 1ml/min

Tiempo	B%
0	10
25	100
30	100

Longitud de onda : 254 nm, Tr min :11,685

Longitud de onda : 220 nm, Tr min : 11,685

Pureza : 99,1%

10 HPLC Columna:

XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Buffer: MeCN (95:5)

Fase móvil B : 0,05% TFA en MeCN : Buffer (95:5)

15 Caudal : 1ml/min

Tiempo	B%
0	10

Tiempo	B%
25	100
30	100

Longitud de onda : 254 nm, Tr min :13,396

Longitud de onda : 220 nm, Tr min : 13,396

Pureza : 96,5%

5 Procedimiento de HPLC preparativa:

Columna : Symmetry C18 (19X250X10μ)

Fase móvil: TFA al 0,1% (A), MeCN (B)

Gradiente:

Tiempo	Caudal	A	B
0	15ml/min	95	5
10	15ml/min	55	45

TR: 10,5 min

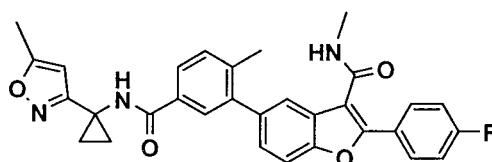
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1-(5-Metilisoxazol-3-il)ciclopropanamina

Se disolvió 5-metilisoxazol-3-carbonitrilo (1,0 g, 1 mmol) en THF. Se añadió gota a gota Ti (Oi-Pr) 4 (1,2 mmol) durante un período de 5-10 min y la mezcla de reacción se agitó a t.a durante 15 min. Se concentró hasta 0 °C y se añadió EtMgBr (2,5 mmol) gota a gota durante un período de 10-15min. Se agitó a 0 °C durante 15 minutos y luego se agitó a ta durante 1 hora. La mezcla se enfrió

de nuevo hasta 0 °C y se añadió BF_3OEt_2 (2 mmol) gota a gota durante un período de 5-10 min a 0 °C. Después se agitó la mezcla durante 10 min a 0 °C y 1 hora a ta, se añadió NaOH 1 N a 0 °C. Se añadió DCM a la mezcla de reacción que se agitó seguidamente durante 5-10 minutos. Esta solución
 5 alcalina se filtró a través de CELITE® y se lavó con DCM. La fase orgánica se concentró y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice usando cloroformo al 10 %/ metanol. Rendimiento: 0,6g RMN de ^1H (400MHz, CDCl_3): δ 0,96-1,05 (m, 4H), 2,36 (s, 3H), 5,59 (s, 1H). LCEM : (ES+) m/z observado 138,7.

10



2-(4-Fluorofenil)-N-metil-5-(2-metil-5-(1-(5-metilisoxazol-3-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida

A una mezcla de ácido 3-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-4-metilbenzoico (0,15 g, 0,37 mmol, 1 eq), amina (0,06 g, 0,43 mmol, 1,2 eq),
 15 HOBT (0,084 g, 0,62 mmol, 1,7 eq), EDC.HCl (0,127 g, 0,087 mmol, 1,8 eq) en DCM a temperatura ambiente en nitrógeno se añadió diisopropiletilamina (0,239 g, 1,8 mmol, 5,0 eq). La mezcla transparente se agitó a temperatura ambiente durante 12 h. La LCEM mostró el producto deseado. La mezcla se
 20 concentró, se diluyó con agua y se extrajo con EtOAc. La fase orgánica se lavó

luego con agua, se secó sobre sulfato sódico, se filtró y luego se concentró. El producto obtenido se purificó luego por cromatografía en columna (alúmina neutra) usando metanol al 0,5%/DCM y HPLC preparativa. Rendimiento : 0,03 g (20 %). RMN de ¹H (400MHz, DMSO-d₆): δ 1,24-1,29 (m, 4H), 2,29 (s, 3H), 2,32 (s, 3H), 2,81-2,82 (d, 3H, J = 4,6 Hz), 6,05 (s, 1H), 7,38-7,44 (m, 4H), 7,57 (d, 1H, J = 1. 6 Hz), 7,75-7,82 (m, 3H), 7,97-8,0 (m, 2H), 8,46-8,47 (m, 1H), 9,24 (s, 1H). LCEM : (ES+) m/z = 524,2 (M+H). Procedimiento LCEM : Columna : Ascentis Express C18 (5X2,1mm-2,7µm). Fase móvil A : 2% ACN -H₂O al 98%-NH₄COOH 10mM. Fase móvil B : 98% ACN – H₂O al 2%-NH₄COOH 10mM. Caudal : 1 ml/Min

Tiempo	%A	%B
0,0	100,0	0
1,5	0,0	100,0
3,2	0,0	100,0

Tr min : 1,966, longitud de onda : 220nm

Procedimiento HPLC:

Columna : Atlantis T3 (4,6X150mm-5,0µm)

15 A : Tampón : acetato amónico 20mM en agua

B : MeCN

Caudal : 1ml/min

Tiempo	B%
20	0
35	5
35	30
100	35
100	40

Longitud de onda : 254 nm, Tr min :15,155

Longitud de onda : 220 nm, Tr min :15,155

Procedimiento HPLC:

5 Sunfire C18 (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : MeCN (95:5)

Fase móvil B : ACN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

10 Longitud de onda : 254 nm, Tr min :18,678

Longitud de onda : 220 nm, Tr min :18,678

Pureza: 99,4%

XBridge phenyl (4,6X150)mm, 3,5 micrómetros

Tampón : 0,05% TFA en agua pH 2,5

Fase móvil A : Tampón : ACN (95:5)

5 Fase móvil B : ACN :Tampón (95:5)

Caudal : 1ml/min

Tiempo	B%
0	10
12	100
15	100

Longitud de onda : 254 nm, Tr min :17,135

Longitud de onda : 220 nm, Tr min :17,135

Pureza: 99,5%

10

5-Metiltiazol-2-carbaldehído

A una solución de BuLi (5 mmol) en éter a -78 °C se añadió gota a gota una solución de 5-metiltiazol (5 mol) en éter a -78 °C durante 1,5 horas. Se añadió de una vez una solución de DMF (5 mmol) en éter y se dejó la reacción calentarse hasta temperatura ambiente y se agitó durante la noche. Se añadió a la mezcla hielo seguido por la adición lenta de HCl 4 N. La mezcla se extrajo con éter. La fase acuosa se llevó hasta pH 7,5 con NaHCO₃ sólido y se extrajo con éter. Los extractos de éter reunidos se secaron, filtraron y concentraron

15

dando un residuo bruto, que se purificó por cromatografía ultrarrápida sobre gel de sílice usando EtOAc al 10%/ Hexano. Rendimiento: 6 g RMN de ^1H (400MHz, CDCl_3): δ 2,56 (s, 3 H), 7,79 (s, 1H), 9,90 (s, 1H). LCEM : (ES+) m/z = 128 (M+H).

5

Oxima de 5-metiltiazol-2-carbaldehído

A una solución de 5-metiltiazol-2-carbaldehído (4,8 mmol) en DCM se añadió piridina (4,8 mmol) y $\text{HONH}_2\cdot\text{HCl}$ (4,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 12 horas, luego se diluyó con DCM y se extrajo con agua. El extracto orgánico se secó, se filtró y se concentró obteniendo la oxima. Rendimiento: 6 g; LCEM : (ES+) m/z = 143 (M+H).

10

5-Metiltiazol-2-carbonitrilo

Se disolvió oxima de 5-metiltiazol-2-carbaldehído (4,2 mmol) en DCM y se añadió con CDI (4,3 mmol) en varias porciones. La mezcla de reacción se agitó a ta durante la noche, y luego se añadió con agua. La mezcla se extrajo con DCM, y la fase orgánica se secó y concentró dando el residuo bruto, que se purificó por cromatografía ultrarrápida sobre gel de sílice usando EtOAc al 10 % / Hexano. Rendimiento : 3,2 g;RMN de ^1H (400MHz, CDCl_3): δ 2,59 (s, 3 H), 7,71 (s, 1H).

15

20

1-(5-Metiltiazol-2-il)ciclopropanamina

Se disolvió 5-metiltiazol-2-carbonitrilo (1,0 g, 1 mmol) en THF. Se añadió gota a gota $\text{Ti}(\text{O}i\text{-Pr})_4$ (1,2 mmol) a la mezcla durante un período de 5-10 min y la mezcla de reacción se agitó a ta durante 15 min. Se enfrió entonces hasta 0 °C y se añadió gota a gota EtMgBr (2,5 mmol) durante un período de 10-15 min.

5 La mezcla de reacción se agitó de nuevo a 0 °C durante 15 minutos y luego se agitó a temperatura ambiente durante 1 h. Se añadió entonces gota a gota $\text{BF}_3 \cdot \text{OEt}_2$ (2,5 mmol) durante un período de 5-10 minutos a la mezcla que se enfrió de nuevo hasta 0 °C. Después se agitó la mezcla durante 10 min a 0 °C y

10 1 h a temperatura ambiente, se añadió NaOH 1 N a la mezcla enfriada hasta 0 °C. Se añadió DCM a la mezcla de reacción y se agitó durante 5-10 min. Esta solución alcalina se filtró a través de CELITE® y se lavó con DCM. La fase orgánica se concentró y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice usando cloroformo al 10 % / metanol. Rendimiento : 0,6 g; RMN de ^1H (400MHz, CDCl_3): δ 1,20 (m, 2H) 1,31 (m, 2H), 2,40 (s, 3H), 7,26

15 (s, 1H). LCEM : (ES+) m/z observado 154,7.

2-(4-Fluorofenil)-5-(4-metoxi-2-metil-5-(1-(5-metiltiazol-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida

Se disolvieron ácido 5-(2-(4-fluorofenil)-3-(metilcarbamoil)benzofuran-5-il)-2-metoxi-4-metilbenzoico (0,2 g, 1 eq), 1-(5-metiltiazol-2-il)ciclopropanamina

20 (0,07 g, 1 eq), $\text{EDCI} \cdot \text{HCl}$ (0,13 g, 1,5 eq), HOBT (0,094 g, 1,5 eq) y TEA (0,19 ml, 3 eq) en diclorometano y la solución anterior se agitó a temperatura

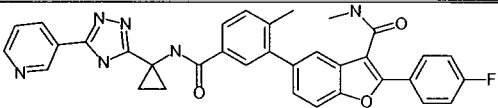
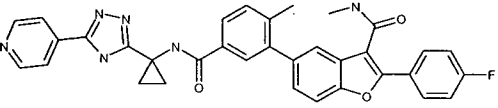
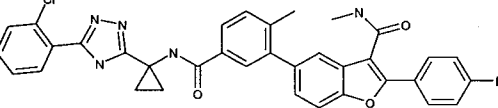
ambiente durante 18 h. A continuación se añadió agua a la mezcla y la fase orgánica se separó. La fase orgánica se lavó con agua y el producto se purificó por HPLC prep. Rendimiento : 65 mg (25 %) RMN de ^1H (400MHz, CDCl_3): δ 1,43-1,46 (m, 2H), 1,74-1,77 (m, 2H), 2,32 (s, 3H), 2,37 (s, 3H), 3,01-3,03 (d, J = 5,2 Hz, 3H), 4,04 (s, 3H), 5,89 (m, 1H), 6,91 (s, 1H), 7,16 (t, 2H), 7,27 (m, 2H), 7,51 (d, J = 4 Hz, 1H), 7,66 (s, 1H), 8,00 (m, 2H), 8,13 (s, 1H), 8,7 (s, 1H). LCEM : (ES+) m/z = 570,2 (M+H).

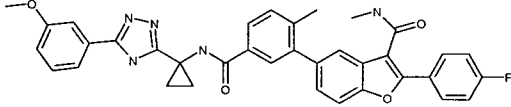
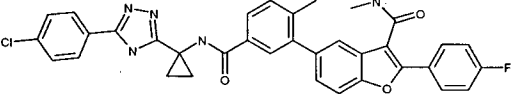
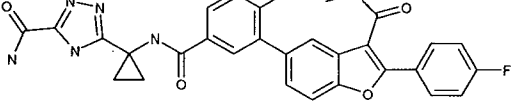
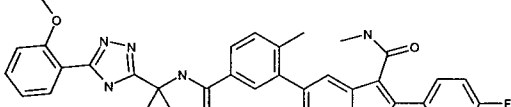
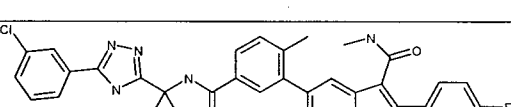
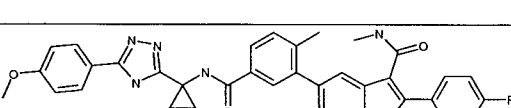
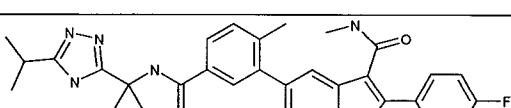
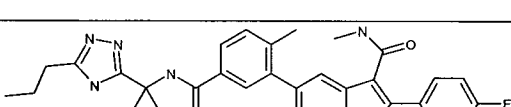
Procedimiento general: Se disolvieron 5-(5-(1-cianociclopropilcarbamoil)-2-metilfenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida (448 mg) en butan-1-ol (22,50 ml) y se distribuyó uniformemente en 15 hidrazidas previamente pesadas en viales de microondas (de 1,5 ml) y seguido por la adición de K_2CO_3 (8,85 mg) como sólido. El vial se sometió a cromatografía ultrarrápida con argon y se tapón, luego se calentó a 165 °C durante 30 minutos en un reactor de microondas BIOTAGE®. Las muestras se secaron por SPEEDVAC®, se disolvieron en DMF (1,8 ml) y se purificaron por HPLC preparativa. Procedimiento de purificación: Cw313a (19x100mm): Disolvente A= MeCN:Agua 5:95; Disolvente B= MeCN:agua 95:5; Modificador = NH_4OAc 10 mM; 0' (25 ml/min) = 30% de B, 0,5' (12,5 ml/min) = 30% de B, 2' (12,5 ml/min) = 30% de B, 2,5' = 30% de B, 22' = 95% de B, 36' = 95% de B. La pureza HPLC se determinó usando un espectrómetro de masas Waters ZQ con ESCi. Disolvente A= MeCN:agua 5:95; Disolvente B= MeCN:agua 95:5; Modificador = NH_4OAc 10 mM. El tiempo de retención se registró en minutos.

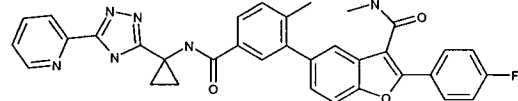
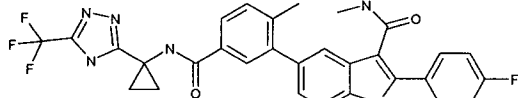
Procedimiento analítico A:

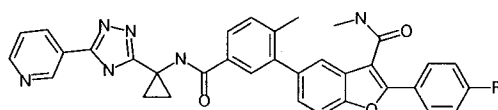
Waters XBridge 4,6x50mm 5 um C18v

Tiempo	B%	Caudal (ml/min)
0,00'	5	2,00
8,00'	95	2,00
9,00'	95	2,00
9,01'	5	2,00
10,00	5	2,00

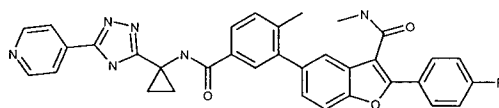
Estructura	Tr de HPLC	% de pureza	Ion EM Obs.	Procedi miento HPLC
	4,73	89,3	587,33	A
	4,76	90,6	587,33	A
	5,44	88,5	620,37	A

Estructura	Tr de HPLC	% de pureza	Ion EM Obs.	Procedimiento HPLC
	5,4	93,4	616,33	A
	5,37	100	620,187	A
	3,85	98,3	553,181	A
	5	100	616,218	A
	5,84	88,8	620,29	A
	4,86	100	616,166	A
	4,28	100	552,208	A
	4,32	100	552,207	A

Estructura	Tr de HPLC	% de pureza	Ion EM Obs.	Procedimiento HPLC
	4,37	95	587,153	A
	4,94	94,9	578,118	A

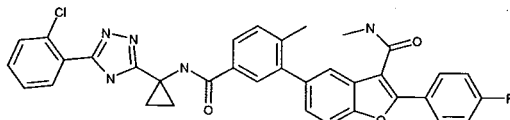


RMN de ^1H (600 MHz, $\text{<DMSO-d}_6\text{-CDCl}_3\text{>}$) δ ppm 1,41 (s ancho, 2 H) 1,62 (s ancho, 2 H) 2,28 - 2,47 (m, 3 H) 2,89 (d, $J=4,69$ Hz, 3 H) 7,29 - 7,51 (m, 5 H) 7,66 (s, 1 H) 7,75 (d, $J=8,79$ Hz, 1 H) 7,86 - 7,99 (m, 2 H) 8,05 (dd, $J=8,20, 5,86$ Hz, 2 H) 8,44 (d, $J=4,10$ Hz, 1 H) 8,61 (s ancho, 1 H) 9,17 (s, 1 H) 9,32 (s ancho, 2 H).

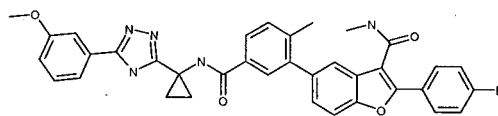


10 RMN de ^1H (600 MHz, CDCl_3) δ ppm 1,42 (s ancho, 2 H) 1,61 (s ancho, 2 H) 2,22 - 2,44 (m, 3 H) 2,56 - 2,63 (m, 3 H) 7,32 - 7,55 (m, 4 H) 7,66 (s, 1 H) 7,76 (d, $J=8,79$ Hz, 1 H) 7,89 - 8,03 (m, 2 H) 8,04 (dd, $J=8,50, 5,57$ Hz, 2 H) 8,44 (d, $J=4,10$ Hz, 1 H) 8,66 (d, $J=4,10$ Hz, 2 H) 9,33 (s ancho, 1 H) 14,09

(s ancho, 1 H).



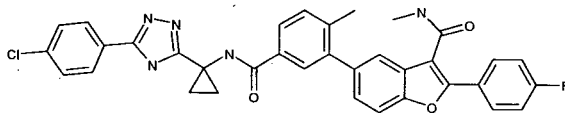
RMN de ^1H (600 MHz, $\text{<DMSO-d}_6\text{_CDCl}_3\text{>}$) δ ppm 1,42 (s ancho, 2 H) 1,60 (s ancho, 2 H) 2,37 (s, 3 H) 2,89 (d, $J=4,10$ Hz, 3 H) 7,31 - 7,51 (m, 4 H) 7,51 - 7,59 (m, 1 H) 7,66 (s, 1 H) 7,75 (d, $J=8,20$ Hz, 1 H) 7,80 - 7,94 (m, 2 H) 8,05 (dd, $J=8,20, 5,86$ Hz, 2 H) 8,27 (s, 1 H) 8,44 (d, $J=4,10$ Hz, 1 H) 9,31 (s ancho, 1 H) 13,93 (s ancho, 1 H).



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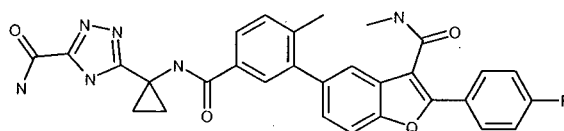
RMN de ^1H (600 MHz, $\text{<DMSO-d}_6\text{_CDCl}_3\text{>}$) δ ppm 1,40 (s ancho, 2 H) 1,60 (s ancho, 2 H) 2,36 (s, 3 H) 2,89 (d, $J=4,69$ Hz, 3 H) 3,86 (s, 3 H) 7,23 - 7,49 (m, 5 H) 7,53 (s ancho, 1 H) 7,55 - 7,62 (m, 1 H) 7,65 (s, 1 H) 7,75 (d, $J=8,20$ Hz, 1 H) 7,90 (d, $J=8,20$ Hz, 1 H) 8,05 (dd, $J=8,20, 5,86$ Hz, 1 H) 8,27 (s, 1 H) 8,44 (d, $J=4,69$ Hz, 1 H) 9,31 (s ancho, 1 H) 13,77 (s ancho, 1 H).

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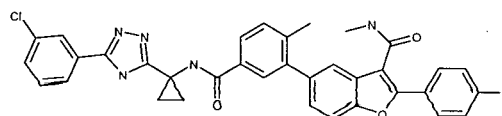


RMN de ^1H (600 MHz, $\text{<DMSO-d}_6\text{_CDCl}_3\text{>}$) δ ppm 1,40 (s ancho, 2 H) 1,60 (s ancho, 2 H) 2,37 (s, 3 H) 2,89 (d, $J=4,69$ Hz, 3 H) 7,32 - 7,54 (m, 4 H) 7,65 (s, 1

H) 7,75 (d, $J=8,79$ Hz, 1 H) 7,85 - 7,96 (m, 1 H) 7,96 - 8,11 (m, 3 H) 8,27 (s, 1 H) 8,43 (s ancho, 1 H) 9,31 (s, 1 H) 13,84 (s ancho, 1 H).



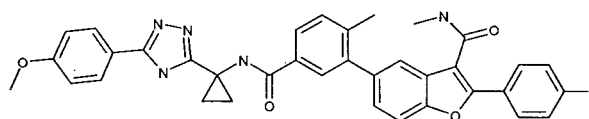
5 RMN de ^1H (600 MHz, $\text{<DMSO-d}_6\text{_CDCl}_3\text{>}$) δ ppm 1,39 (s ancho, 2 H) 1,57 (s ancho, 2 H) 2,36 (s, 3 H) 2,89 (d, $J=4,69$ Hz, 3 H) 7,36 - 7,60 (m, 3 H) 7,75 (d, $J=8,20$ Hz, 1 H) 7,85 - 7,96 (m, 1 H) 8,04 (dd, $J=8,20, 5,27$ Hz, 2 H) 8,27 (s, 1 H) 8,43 (d, $J=4,69$ Hz, 1 H) 9,27 (s ancho, 1 H) 14,10 (s ancho, 1 H).



10

RMN de ^1H (600 MHz, $\text{<DMSO-d}_6\text{_CDCl}_3\text{>}$) δ ppm 1,41 (s ancho, 2 H) 1,61 (s ancho, 2 H) 2,37 (s, 3 H) 2,89 (d, $J=4,69$ Hz, 3 H) 7,28 - 7,58 (m, 4 H) 7,65 (s, 1 H) 7,75 (d, $J=8,79$ Hz, 1 H) 7,86 - 8,02 (m, 1 H) 8,02 - 8,18 (m, 3 H) 8,27 (s, 1 H) 8,44 (d, $J=4,10$ Hz, 1 H) 9,31 (s ancho, 1 H) 13,90 (s ancho, 1 H).

15



RMN de ^1H (600 MHz, $\text{<DMSO-d}_6\text{_CDCl}_3\text{>}$) δ ppm 1,39 (s ancho, 2 H) 1,59 (s ancho, 2 H) 2,36 (s ancho, 3 H) 2,89 (d, $J=4,10$ Hz, 3 H) 3,85 (s, 3 H) 6,99 (m,

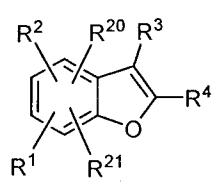
2H) 7,29 - 7,54 (m, 4 H) 7,65 (s, 1 H) 7,75 (d, $J=8,20$ Hz, 1 H) 7,82 - 7,99 (m, 3 H) 7,99 - 8,14 (m, 2 H) 8,27 (s, 1 H) 8,43 (s ancho, 1 H) 9,29 (s, 1 H) 13,63 (s ancho, 1 H).

- 5 Para un experto en la técnica será evidente que la presente revelación no queda limitada a los ejemplos ilustrativos anteriores, y que se puede ilustrar en otras formas específicas sin apartarse de sus atributos esenciales. Por tanto, se desea que los ejemplos sean considerados en todos los sentidos como ilustrativos y no restrictivos, haciéndose referencia a las reivindicaciones
- 10 adjuntas, y no a los ejemplos anteriores y, por tanto, se pretende que queden comprendidos en las mismas todos los cambios que estén dentro del significado e intervalo de equivalencia de las reivindicaciones.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

- 5 1. Un compuesto de la fórmula I



I

R¹ es R⁵R⁶N; alcoxi; (alcoxicarbonilamino)alcoxi; (alquilfenil)alcoxi; (carboxi)alquenilo; (alcoxicarbonil)alquenilo; (benciloxycarbonil)alquenilo; ((N-
10 dimetilbencil)aminocarbonil)alquenilo; o fenilo donde dicho fenilo está sustituido con 1-2 sustituyentes que se seleccionan a partir del grupo constituido por halo, ciano, alquilo, haloalquilo, hidroxialquilo, alcoxialquilo, (carboxi)alquilo, alcoxi, hidroxialquilo, alcoxialquilo, benciloxi, tetrahidropiraniloxi, carboxi, alcoxicarbonilo, alquilsulfonilo, (carboxi)alquenilo, (alcoxicarbonil)alquenilo,
15 alquilcarboxamido, alcoxicarboxamido, alquilsulfamido, (alquilsulfamido)alquilo, Ar⁵, SO₂NR¹⁵R¹⁶, y CONR⁷R⁸; y donde dicho fenilo también está sustituido con 0-2 sustituyentes que se seleccionan a partir del grupo constituido por halo; nitro; alquilo; cicloalquilo; haloalquilo; aminoalquilo; hidroxialquilo; alcoxialquilo; hidroxi; alcoxi; OR¹⁷; cicloalcoxi; amino; alquilamino; dialquilamino;
20 alquilcarboxamido; alcoxicarboxamido; alcoxialquilcarboxamido; furanilo, tienilo,

o pirazolilo sustituido con 0-2 sustituyentes alquilo; piridinilo sustituido con 0-2 sustituyentes halo, ciano, alquilo, hidroxilo, alcoxi, amino, o alquilaminocarbonilo; pirimidinilo; pirimidindionilo; aminopirimidinilo; indolilo; isoquinolinilo; y fenilo sustituido con 0-2 sustituyentes que se seleccionan a partir del grupo
 5 constituido por halo, alquilo, cianoalquilo, hidroxialquilo, alcoxialquilo, hidroxilo, alcoxi, amino, carboxi, alcóxicarbonilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, alquilcarboxamido, carboxialqueno, y fenilo;

R^2 es hidrógeno, halo, nitro, amino, fenilo, o R^5R^6N ;

R^3 es ciano, alcóxicarbonilo, (cicloalquil)oxycarbonilo,
 10 (alquilsulfonil)aminocarbonilo, $CONR^{11}R^{12}$, $(R^{11})(R^{12})NCONH$, triazolilo, tiazolilo, o tetrazolilo;

R^4 es fenilo sustituido con 0-2 sustituyentes halo;

R^5 es hidrógeno, alquilo, o alquilsulfonilo;

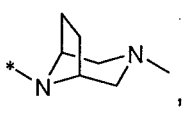
R^6 es hidrógeno, alquilo, hidroxialquilo, alcoxialquilo, o alquilsulfonilo;

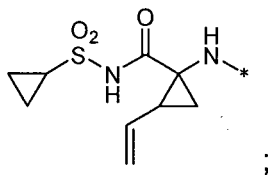
15 R^7 es hidrógeno, alquilo, alqueno, alquino, cianoalquilo, haloalquilo, hidroxialquilo, dihidroxialquilo, alcoxialquilo, oxoalquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo, (cicloalquil)alquilo, cicloalquilo, (alquil)cicloalquilo, (hidroxialquil)cicloalquilo, (tetrahidrofuranil)alquilo, (tetrahidropiranyl)alquilo, (carboxi)alquilo, (alcóxicarbonil)alquilo,
 20 (alquenoiloxycarbonil)alquilo, (alcóxicarbonil)hidroxialquilo, $(CONR^{13}R^{14})$ alquilo, $(CONR^{13}R^{14})($ hidroxialquil)alquilo, $(CONR^{13}R^{14})$ cicloalquilo, (alquilcarbonil)aminoalquilo, (fenil)alquilo, (piridinil)alquilo, alquilsulfonilo,

fenilsulfonilo, Ar^2 , Ar^3 , $\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagup \quad \diagdown \\ * \quad \text{C} \\ \diagdown \quad \diagup \\ \text{R}^{19} \end{array}$, $\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagup \quad \diagdown \\ * \quad \text{C} \\ \diagdown \quad \diagup \\ \text{Ar}^1 \end{array}$, $\begin{array}{c} \text{R}^9 \quad \text{R}^{10} \\ \diagup \quad \diagdown \\ * \quad \text{C} \\ \diagdown \quad \diagup \\ \text{CH}_2 \text{Ar}^1 \end{array}$, O, $\begin{array}{c} \text{Ar}^1 \\ | \\ \text{Cyclopropyl} \end{array}$;

R^8 es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;

- o $\text{R}^7\text{R}^8\text{N}$ tomado conjuntamente es azetidino, pirrolidino, piperidino, piperazino, morfolino, dihidroindolilo, o isoindolino, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, hidroxialquilo, alcoxialquilo, hidroxilo, alcoxi, carboxi, alcóxicarbonilo, dialquilcarboxamido, alquilcarbonilamino, alcóxicarbonilamino, piridinilo, y fenilo donde dicho fenilo está sustituido con 0-2 sustituyentes halo o alquilo;

- o donde $\text{R}^7\text{R}^8\text{N}$ tomado conjuntamente es ,
 10 (quinuclidinil)amino, (quinuclidinil)(alquil)amino, (metilpirrolidinil)(alquil)amino,
 ((imidazolil)alquil)(hidroxialquil)amino, (alquiltiazolil)amino,
 ((carboxamido)ciclopentanil)amino, ((halofenil)ciclopentanil)amino,
 3H-espiro(isobenzofuranil)piperidinilo, (hidroxiindanil)amino, o



- 15 R^9 es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;
 R^{10} es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;
 o R^9 y R^{10} tomados conjuntamente son etileno, propileno, butileno, pentileno, o hexileno;
 R^{11} es hidrógeno, alquilo, o cicloalquilo;

R^{12} es hidrógeno, alquilo, o cicloalquilo;

o R^{11} y R^{12} tomados conjuntamente con el nitrógeno al que están unidos son azetidino, pirrolidino, piperidino, piperazino, o morfolino;

R^{13} es hidrógeno, alquilo, cianoalquilo, haloalquilo, alqueno, alquino, o
5 tiazolo;

R^{14} es hidrógeno o alquilo;

R^{15} es hidrógeno, alquilo, hidroxialquilo, cicloalquilo, o bencilo;

R^{16} es hidrógeno o alquilo;

o R^{15} y R^{16} tomados conjuntamente con el nitrógeno al que están unidos
10 son azetidino, pirrolidino, piperidino, piperazino, o morfolino;

R^{17} es haloalquilo, cianoalquilo, (cicloalquil)alquilo, hidroxialquilo, alcoxialquilo, aminoalquilo, (R^{18})alquilo, (Ar^4)alquilo, alquino, o aminocicloalquilo;

R^{18} es $CONH_2$, H_2NCONH , dibencilamino, ftalimido, amino, alquilamino,
15 dialquilamino, azetidino, pirrolidino, piperidino, piperazino, o morfolino
donde azetidino, pirrolidino, piperidino, piperazino, o morfolino están
sustituidos con 0-3 sustituyentes alquilo o alcóxicarbonilo;

R^{19} es ciano, hidroxialquilo, morfolinilalquilo, carboxi, alcóxicarbonilo,
cicloalquilsulfoxamido, ((alquil)pirazolil)amino, ((alquil)isoxazolil)amino,
20 (tiadiazolil)amino, (triazinil)amino, o alquilaminocarbonilo;

R^{20} es hidrógeno, halo, alquilo, o alcoxi;

R^{21} es hidrógeno, halo, alquilo, o alcoxi;

Ar¹ es fenilo, naftalenilo, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, oxadiazolilo, triazolilo, tetrazolilo, pirazinilo, pirimidinilo, o benzotiazolilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, cicloalquilo, haloalquilo, alcoxialquilo, hidroxilo, alcoxi, amino, alquilamino, dialquilamino, aminocarbonilo, piridinilo, fenilo, halofenilo, alquilfenilo, y alcoxifenilo;

Ar² es fenilo, bifenilo, o piridinilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, ciano, hidroxilo, alcoxi, y carboxi;

10 Ar³ es pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, triazolilo, oxadiazolilo, oxadiazolilo, pirimidinilo, o pirazinilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de hidroxilo, alquilo, hidroxialquilo, y CONR¹³R¹⁴;

15 Ar⁴ es furanilo, tienilo, pirrolilo, pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piridinilo, indolilo, o fenilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, haloalquilo, hidroxilo, y alcoxi; y

Ar⁵ es pirazolilo, imidazolilo, u oxadiazolilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, carboxi, alcoxicarbonilo, bencilo, y fenilo;

o una sal farmacéuticamente aceptable del mismo.

2. Un compuesto de la reivindicación 1 donde R^{20} y R^{21} son hidrógeno.

3. Un compuesto de la reivindicación 2 donde

5 R^1 es R^5R^6N ; (carboxi)alquenilo; (alcoxicarbonil)alquenilo; (benciloxicarbonil)alquenilo; o fenilo donde dicho fenilo está sustituido con 1-2 sustituyentes que se seleccionan a partir del grupo constituido por ciano, alquilo, alcoxi, hidroxialquilo, alcoxialquilo, hidroxialquilo, alcoxialquilo, haloalquilo, benciloxi, carboxi, alcoxicarbonilo, alquilsulfonilo, 10 (carboxi)alquenilo, (alcoxicarbonil)alquenilo, alquilcarboxamido, alcoxicarboxamido, alquilsulfamido, (alquilsulfamido)alquilo, tetrahidropiranioloxi, Ar^5 , $SO_2NR^{15}R^{16}$, y $CONR^7R^8$; y donde dicho fenilo también está sustituido con 0-1 sustituyentes que se seleccionan a partir del grupo constituido por halo; alquilo; hidroxialquilo; alcoxialquilo; hidroxilo; alcoxi; OR^{17} ; cicloalcoxi; amino; 15 alquilamino; dialquilamino; alquilcarboxamido; alcoxialquilcarboxamido; furanilo; indolilo; isoquinolinilo; piridinilo sustituido con 0-2 sustituyentes halo, alquilo, hidroxilo, o alcoxi; pirazolilo sustituido con 0-2 sustituyentes alquilo; y fenilo sustituido con 0-2 sustituyentes halo, alquilo, cianoalquilo, hidroxialquilo, alcoxialquilo, hidroxilo, alcoxi, carboxi, alcoxicarbonilo, aminocarbonilo, 20 alquilaminocarbonilo, dialquilaminocarbonilo, alquilcarboxamido, carboxialquenilo, o fenilo;

R^2 es hidrógeno, nitro, o R^5R^6N ;

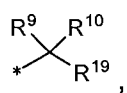
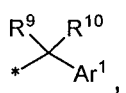
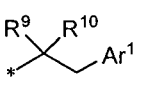
R^3 es ciano, alcóxicarbonilo, (cicloalquil)oxícarbonilo, (alquilsulfonil)aminocarbonilo, $\text{CONR}^{11}\text{R}^{12}$, $(\text{R}^{11})(\text{R}^{12})\text{NCONH}$, triazolilo, tiazolilo, o tetrazolilo;

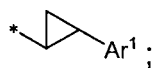
R^4 es fenilo sustituido con 0-2 sustituyentes halo;

5 R^5 es hidrógeno, alquilo, o alquilsulfonilo;

R^6 es hidrógeno, alquilo, hidroxialquilo, alcóxialquilo, o alquilsulfonilo;

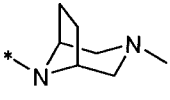
R^7 es hidrógeno, alquilo, alquenilo, alquinilo, cianoalquilo, haloalquilo, hidroxialquilo, alcóxialquilo, oxoalquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo, (cicloalquil)alquilo, cicloalquilo, (alquil)cicloalquilo, 10 (hidroxialquil)cicloalquilo, (tetrahidrofuranil)alquilo, (tetrahidropiranyl)alquilo, (carboxi)alquilo, (alcóxicarbonil)alquilo, (alcóxicarbonil)hidroxialquilo, ($\text{CONR}^{13}\text{R}^{14}$)alquilo, (alquilcarbonil)aminoalquilo, (fenil)alquilo, (piridinil)alquilo,

alquilsulfonilo, fenilsulfonilo, Ar^2 , Ar^3 , , , , o



15 R^8 es hidrógeno, alquilo, hidroxialquilo, o alcóxialquilo;

o $\text{R}^7\text{R}^8\text{N}$ tomado conjuntamente es azetidínico, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, o dihidroindolilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, hidroxialquilo, alcóxialquilo, hidroxí, alcóxí, carboxí, alcóxicarbonilo, dimetilcarboxamido, alquilcarbonilamino, 20 alcóxicarbonilamino, piridinilo, y fenilo donde fenilo está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo y alquilo;

o donde R^7R^8N tomado conjuntamente es ,
 (quinuclidinil)(alquil)amino, (metilpirrolidinil)(alquil)amino, (alquiltiazolil)amino,
 ((carboxamido)ciclopentanil)amino, ((halofenil)ciclopentanil)amino, o
 (hidroxiindanil)amino;

5 R^9 es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;

R^{10} es hidrógeno, alquilo, hidroxialquilo, o alcoxialquilo;

o R^9 y R^{10} tomados conjuntamente son etileno, propileno, butileno, o
 pentileno;

R^{11} es hidrógeno, alquilo, o cicloalquilo;

10 R^{12} es hidrógeno, alquilo, o cicloalquilo;

o R^{11} y R^{12} tomados conjuntamente con el nitrógeno al que están unidos
 son azetidino, pirrolidinilo, piperidinilo, piperazinilo, o morfolinilo;

R^{13} es hidrógeno, alquilo, cianoalquilo, alqueno, o alquino;

R^{14} es hidrógeno o alquilo;

15 R^{15} es hidrógeno o alquilo;

R^{16} es hidrógeno o alquilo;

R^{17} es haloalquilo, hidroxialquilo, alcoxialquilo, alquino, (R^{18}) alquilo o
 (Ar^4) alquilo;

R^{18} es $CONH_2$, dibencilamino, amino, alquilamino, dialquilamino,
 20 azetidino, pirrolidinilo, piperidinilo, piperazinilo, o morfolinilo donde azetidino,
 pirrolidinilo, piperidinilo, piperazinilo, o morfolinilo están sustituidos con 0-3

sustituyentes que se seleccionan a partir de alquilo y alcóxicarbonilo;

R^{19} es ciano, ((alquil)pirazolil)amino, ((alquil)isoxazolil)amino (tiadiazolil)amino, o (triazinil)amino;

5 Ar^1 es fenilo, naftalenilo, piridinilo, tienilo, tiazolilo, o pirazinilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, halo, hidroxilo, alcoxilo, amino, alquilamino, y dialquilamino;

Ar^2 es fenilo, bifenilo, o piridinilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, ciano, hidroxilo, y alcoxilo;

10 Ar^3 es pirazolilo, isoxazolilo, tiazolilo, pirimidinilo, o pirazinilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo e hidroxialquilo;

Ar^4 es pirrolilo, imidazolilo, piridinilo, indolilo, o fenilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, hidroxilo, y alcoxilo; y

15 Ar^5 es pirrozolilo, imidazolilo, u oxadiazolilo y está sustituido con 0-2 sustituyentes que se seleccionan a partir de alquilo, carboxi, alcóxicarbonilo, bencilo, y fenilo;

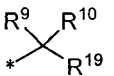
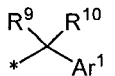
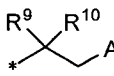
o una sal farmacéuticamente aceptable del mismo.

20 4. Un compuesto de la reivindicación 2 donde

R^1 es alcoxilo; (alcóxicarbonilamino)alcoxilo; (alquilfenil)alcoxilo; (carboxi)alquenilo; ((N-dimetilbencil)aminocarbonil)alquenilo; o fenilo donde

- dicho fenilo está sustituido con 1-2 sustituyentes que se seleccionan a partir del grupo constituido por halo, ciano, alquilo, haloalquilo, hidroxialquilo, (carboxi)alquilo, alcoxi, hidroxialquiloxi, tetrahidropiraniloxi, carboxi, alcoxycarbonilo, (carboxi)alquenilo, alquilcarboxamido, alcoxycarboxamido, (alquilsulfamido)alquilo, Ar^5 , $SO_2NR^{15}R^{16}$, y $CONR^7R^8$; y donde dicho fenilo también está sustituido con 0-2 sustituyentes que se seleccionan a partir del grupo constituido por halo; nitro; alquilo; cicloalquilo; haloalquilo; aminoalquilo; hidroxil; alcoxi; OR^{17} ; cicloalcoxi; amino; alcoxycarboxamido; furanilo, tienilo, o pirazolilo sustituido con 0-2 sustituyentes alquilo; piridinilo sustituido con 0-2 sustituyentes halo, ciano, alquilo, hidroxil, alcoxi, amino, o alquilaminocarbonilo; pirimidinilo; pirimidindionilo; aminopirimidinilo; indolilo; isoquinolinilo; y fenilo sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, cianoalquilo, hidroxialquilo, alcoxialquilo, alcoxi, amino, carboxi, aminocarbonilo, alquilaminocarbonilo, alquilcarboxamido, y carboxialquenilo;
- 15 R^2 es hidrógeno, halo, nitro, amino, fenilo, o R^5R^6N ;
 R^3 es $CONR^{11}R^{12}$;
 R^4 es fenilo sustituido con 0-2 sustituyentes halo;
 R^5 es hidrógeno o alquilsulfonilo;
 R^6 es hidrógeno, alquilo, hidroxialquilo, o alquilsulfonilo;
- 20 R^7 es hidrógeno, alquilo, alquinilo, cianoalquilo, haloalquilo, hidroxialquilo, dihidroxialquilo, alcoxialquilo, oxoalquilo, (dialquilamino)alquilo, (cicloalquil)alquilo, cicloalquilo, (alquil)cicloalquilo, (hidroxialquil)cicloalquilo,

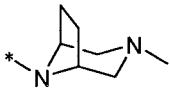
(tetrahidrofuranil)alquilo, (tetrahidropiranil)alquilo, (carboxi)alquilo,
 (alcoxicarbonil)alquilo, (alqueniloxicarbonil)alquilo, (alcoxicarbonil)hidroxialquilo,
 (CONR¹³R¹⁴)alquilo, (CONR¹³R¹⁴)(hidroxialquil)alquilo,
 (CONR¹³R¹⁴)cicloalquilo, (alquilcarbonil)aminoalquilo, (fenil)alquilo,

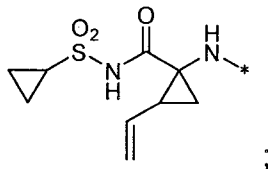
5 alquilsulfonilo, fenilsulfonilo, Ar², Ar³, , , , o



R⁸ es hidrógeno, alquilo, o alcoxialquilo;

o R⁷R⁸N tomado conjuntamente es azetidino, pirrolidino, piperidino,
 piperazino, morfolino, dihidroindolilo, o isoindolinilo, y está sustituido con 0-2
 10 sustituyentes que se seleccionan a partir de alquilo, hidroxialquilo, alcoxialquilo,
 hidroxilo, alcoxicarbonilo, dialquilcarboxamido, alquilcarbonilamino, piridinilo, y
 fenilo donde dicho fenilo está sustituido con 0-2 sustituyentes halo o alquilo;

o donde R⁷R⁸N tomado conjuntamente es ,
 (quinuclidinil)amino, (quinuclidinil)(alquil)amino, (metilpirrolidinil)(alquil)amino,
 15 ((imidazolil)alquil)(hidroxialquil)amino, (alquiltiazolil)amino,
 ((carboxamido)ciclopentanil)amino, ((halofenil)ciclopentanil)amino,
 3H-espiro(isobenzofuranil)piperidinilo, (hidroxiindanil)amino, o



R^9 es hidrógeno, alquilo, o hidroxialquilo;

R^{10} es hidrógeno o alquilo;

o R^9 y R^{10} tomados conjuntamente son etileno o propileno;

R^{11} es alquilo;

5 R^{12} es hidrógeno;

R^{13} es hidrógeno, alquilo, cianoalquilo, haloalquilo, alquenilo, o tiazolilo;

R^{14} es hidrógeno o alquilo;

R^{15} es alquilo, hidroxialquilo, cicloalquilo, o bencilo;

R^{16} es hidrógeno;

10 o R^{15} y R^{16} tomados conjuntamente con el nitrógeno al que están unidos son azetidínico, pirrolidinilo, piperidinilo, piperazinilo, o morfolinilo;

R^{17} es haloalquilo, cianoalquilo, (cicloalquil)alquilo, hidroxialquilo, alcóxialquilo, aminoalquilo, (R^{18})alquilo, (Ar^4)alquilo, alquinilo, o aminocicloalquilo;

15 R^{18} es $CONH_2$, H_2NCONH , dibencilamino, ftalimido, amino, dialquilamino, pirrolidinilo, piperidinilo, piperazinilo, o morfolinilo donde azetidínico, pirrolidinilo, piperidinilo, piperazinilo, o morfolinilo están sustituidos con 0-3 sustituyentes alquilo o alcóxicarbonilo;

R^{19} es ciano, hidroxialquilo, morfolinilalquilo, carboxi, alcóxicarbonilo, 20 cicloalquilsulfoxamido, ((alquil)pirazolil)amino, ((alquil)isoxazolil)amino, (tiadiazolil)amino, (triazinil)amino, o alquinilaminocarbonilo;

Ar^1 es fenilo, naftalenilo, piridinilo, furanilo, pirazolilo, isoxazolilo,

imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, triazolilo, tetrazolilo, pirazinilo, pirimidinilo, o benzotiazolilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, cicloalquilo, haloalquilo, alcoxialquilo, hidroxilo, alcoxi, amino, aminocarbonilo, piridinilo, fenilo, halofenilo, alquilfenilo, y
5 alcoxifenilo;

Ar^2 es fenilo, bifenilo, o piridinilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, ciano, hidroxilo, alcoxi, y carboxi;

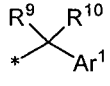
Ar^3 es pirazolilo, isoxazolilo, tiazolilo, triazolilo, pirimidinilo, o pirazinilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de hidroxilo,
10 alquilo, y $CONR^{13}R^{14}$;

Ar^4 es furanilo, pirrolilo, pirazolilo, isoxazolilo, imidazolilo, oxadiazolilo, triazolilo, piridinilo, indolilo, o fenilo, y está sustituido con 0-2 sustituyentes que se seleccionan a partir de halo, alquilo, haloalquilo, e hidroxilo; y

Ar^5 es pirrolozilo, imidazolilo, u oxadiazolilo, y está sustituido con 0-2
15 sustituyentes que se seleccionan a partir de alquilo, alcóxicarbonilo, bencilo, y fenilo;

o una sal farmacéuticamente aceptable del mismo.

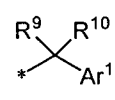
5. Un compuesto de la reivindicación 2 donde R^1 es fenilo sustituido
20 con 1 sustituyente $CONR^7R^8$ y también sustituido con 0-2 sustituyentes halo, alquilo, o alcoxi; R^2 es hidrógeno, halo, o R^5R^6N ; R^3 es $CONR^{11}R^{12}$; R^4 es

monofluorofenilo; R^5 es alquilsulfonilo; R^6 es hidroxialquilo; R^7 es ; R^8 es hidrógeno; R^9 es alquilo; R^{10} es alquilo o R^9 y R^{10} tomados conjuntamente son etileno o propileno; R^{11} es alquilo; R^{12} es hidrógeno; y Ar^1 es fenilo, piridinilo, pirimidinilo, isoxazolilo, oxazolilo, u oxadiazolilo, y está sustituido con
 5 0-1 sustituyentes halo o alquilo; o una sal farmacéuticamente aceptable del mismo.

6. Un compuesto de la reivindicación 1 donde R^1 es fenilo sustituido con 1-2 sustituyentes que se seleccionan a partir del grupo constituido por halo, ciano, alquilo, haloalquilo, hidroxialquilo, (carboxi)alquilo, alcoxi, hidroxialquiloxi, tetrahidropiraniloxi, carboxi, alcoxicarbonilo, (carboxi)alquenilo, alquilcarboxamido, alcoxicarboxamido, (alquilsulfamido)alquilo, Ar^5 , $SO_2NR^{15}R^{16}$, y $CONR^7R^8$; y donde dicho fenilo también está sustituido con 0-2 sustituyentes que se seleccionan a partir del grupo constituido por halo; nitro; alquilo; cicloalquilo; haloalquilo; aminoalquilo; hidroxilo; alcoxi; OR^{17} ; cicloalcoxi; amino; alcoxicarboxamido; furanilo, tienilo, o pirazolilo sustituido con 0-2 sustituyentes alquilo; piridinilo sustituido con 0-2 sustituyentes halo, ciano, alquilo, hidroxilo, alcoxi, amino, o alquilaminocarbonilo; pirimidinilo; pirimidindionilo; aminopirimidinilo; indolilo; isoquinolinilo; y fenilo sustituido con
 15
 20 0-2 sustituyentes que se seleccionan a partir de halo, cianoalquilo, hidroxialquilo, alcoxialquilo, alcoxi, amino, carboxi, aminocarbonilo,

alquilaminocarbonilo, alquilcarboxamido, y carboxialquenilo.

7. Un compuesto de la reivindicación 1 donde R¹ es fenilo sustituido con 1 sustituyente CONR⁷R⁸ y también sustituido con 0-2 sustituyentes halo, alquilo, o alcoxi.

8. Un compuesto de la reivindicación 7 donde R⁷ es  y al menos uno de R⁹ y R¹⁰ no es hidrógeno.

9. Un compuesto de la reivindicación 1 que se selecciona a partir del grupo constituido por

- 2-(4-fluorofenil)-N-metil-5-(2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida;
- 4-fluoro-2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida;
- 4-fluoro-2-(4-fluorofenil)-N-metil-5-(2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida;
- 2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(pirimidin-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida;
- 2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(3-metil-1,2,4-oxadiazol-5-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida;

2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(5-metil-1,2,4-oxadiazol-3-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida;

2-(4-fluorofenil)-N-metil-5-(2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)benzofuran-3-carboxamida;

5 5-(3-fluoro-2-metil-5-(1-(piridin-2-il)ciclopropilcarbamoil)fenil)-2-(4-fluorofenil)-N-metilbenzofuran-3-carboxamida;

2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(5-metiltiazol-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida;

2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(5-metilisoxazol-3-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida;

2-(4-fluorofenil)-5-(4-metoxi-2-metil-5-(1-(5-metiloxazol-2-il)ciclopropilcarbamoil)fenil)-N-metilbenzofuran-3-carboxamida;

2-(4-fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metil-5-(3-(2-fenilpropan-2-ilcarbamoil)fenil)benzofuran-3-carboxamida

15 2-(4-fluorofenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metil-5-(3-(1-fenilciclopropilcarbamoil)fenil)benzofuran-3-carboxamida; y

2-(4-fluorofenil)-5-(3-(1-(4-fluorofenil)ciclopropilcarbamoil)fenil)-6-(N-(2-hidroxietil)metilsulfonamido)-N-metilbenzofuran-3-carboxamida;

o una sal farmacéuticamente aceptable del mismo.

20

10. Una composición que comprende un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un



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PATENTE DE INVENCION ☐

MODELO DE UTILIDAD ☐

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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 INVENCION 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 ☐



Bogotá D.C.,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL-MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	11 041979
	Solicitud internacional	PCT/US2009/56166
	Fecha inicio fase nacional	11/04/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

08239

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 considerará abandonada y perderá su prelación.

Continúa 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)

20 MAYO 2011

El anterior requerimiento fue notificado por fijación en lista de fecha _____
adpa11

Al contestar favor indique el número de
radicación que se encuentra a continuación

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10 PBX: 5870000
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Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia