Industria y Comercio

SUPERINTENDENCIA

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-11252

54. **TÍTULO** COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

51. **CLASIFICACIÓN INTERNACIONAL**

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

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS

74. **APODERADO** ALVARO CORREA

22. **BOGOTÁ, D.C.,** Febrero 03, 2010.

Radicado Pcl.

TAlo
Fr 08-03-2010

(FORMA P-10)

PETIT

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-011252- -00000-0000
Fecha: 2010-02-03 15:57:54
Tra: 11 PATENTEIYII
Act: 411 PRESENTACION
Dep: 2020 DIR NUEVASCR.
Eve: 378 FASENACIONALI
Folios: 785

ción

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 de América

Lugar de Constitución: Estados Unidos de América

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 6

Teléfono: 6341500 Fax: 3762211

E-Mail: office.bogota@bakernet.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 Usaquén TP 20281

(4) INVENTOR (ES) (72)

Nombre: MARTIN, Scott W.; BERGSTROM, Carl P.; GENTLES, Robert G.; YEUNG, Kap-Sun

Dirección: c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492, US; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492, US; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492, US; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492, US

Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)

(5) PCT (85)

Solicitud Internacional No. PCT/US2008/071831 Fecha 01-08-2008

Publicación Internacional No. WO 2009/029384 Fecha 05-03-2009

(6) Título (54) COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C (Folio 238)

(7) Clasificación Internacional (51) C07D 487/04; A61K 31/55; A61P 31/14

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	09-08-2007	60/954,814
US	02-05-2008	61/049,944
US	28-07-2008	12/180,994

(9) Comprobante de pago No. EN HOJA ANEXA **Fecha** Febrero 02, 2010

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso. Ver documento de Poder General radicado en el Expediente No. 08 129.639
- [X] Documento de cesión del inventor al solicitante o a su causante (ver Declaración)
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

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

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

P2010/000004
BRISTOL-MYERS SQUIBB COMPANY

LISTADO DE RECIBOS A LA SIC

10-3,800

10-7,361

10-7,362

10-3,691

09-80,473

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 -- 3,800
FECHA : ENERO 15 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-011252- -00000-0000

Fecha: 2010-02-03 15:57:54 Dep: 2020 DIR.NULVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 785

10/009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	VR. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	032784387	111704736	14/01/2010	66.910.000.00

1

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554.000,00
		TOTAL : $	554.000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

R[illegible] D DE CAJA APLICADO AL EXPEDIENTE No. _____

S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 7,361
FECHA : FEBRERO 1 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-011252- -00000-0000
Fecha: 2010-02-03 15:57:54 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 785

003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	111710561	28/01/2010	117,410,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS		7,000.00
		TOTAL :	$	7,000.00

SON: SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

2010/003

CERTIFICACION DE EXCEDENTE : 10 - 7,362
FECHA : FEBRERO 1 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-011252- -00000-0000
Fecha: 2010-02-03 15:57:54 Dep. 2020 DIR.NULVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 785

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	111710561	28/01/2010	117,410,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	7,000.00
		TOTAL : $	7,000.00

SON: SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 10 - 3,691
FECHA : ENERO 15 DE 2010

No. 10-011252- -00000-0000

Fecha: 2010-02-03 15:57:54 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTE.IYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 785

2010/00)

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	VR. PAGO
AKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	111704736	14/01/2010	66.710.000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	*** N.CREACION PRORROGA DE TERMINOS C	83.000.00
		TOTAL : $	83.000.00

SON: OCHENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2009/015

8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 80,473
FECHA : OCTUBRE 26 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-011252- -00000-0000

Fecha: 2010-02-03 15:57:54 Dep. 2020 DIR.NULVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 785

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	121953904	26/10/2009	54,821,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	111,000.00
		TOTAL : $	111,000.00

SON: CIENTO ONCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio

SUPERINTENDENCIA

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

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

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

(51) Clasificación Internacional : C07D 487/04; A61K 31/55; A61P 31/14

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

(72) Inventor(es) MARTIN, Scott W.; BERGSTROM, Carl P.; GENTLES, Robert G.; YEUNG, Kap-Sun

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	60/954,814	09-08-2007	US
	61/049,944	02-05-2008	US
	12/180,994	28-07-2008	US

(85) Fecha inicio fase nacional: 09-03-2010

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 01-09-2008
No. de solicitud: PCT/US2008/071881

(87) Publicación internacional
Fecha: 05-03-2009
N° publicación: WO 2009/029334

(54) Titulo: COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

10

Industria y Comercio
SUPERINTENDENCIA

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

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

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional : C07D 487/04; A61K 31/55; A61P 31/14

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

(72) Inventor(es) MARTIN, Scott W.; BERGSTROM, Carl P., GENTLES, Robert G.; YEUNG, Kap-Sun

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) No. Prioridad	32) Fecha	(33) País
	60/954,814	09-08-2007	US
	61/049,944	02-05-2008	US
	12/180,994	28-07-2008	US

(85) Fecha límite inicio fase nacional: 09-03-2010
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 01-09-2008
No. de solicitud PCT/US2008/071881

(87) Publicación internacional:
Fecha: 05-03-2009
No. Publicación: WO 2009/029384

(54) Titulo:
COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

(57) Resumen:

La invención incluye compuestos de fórmula I así como composiciones y procedimientos de uso de los compuestos. Los compuestos tienen actividad contra el virus de la hepatitis C (VHC) y son útiles en el tratamiento de sujetos infectados por el VHC.

CONTINUA AL RESPALDO ...

Industria y Comercio
SUPERINTENDENCIA

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

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

(31) *No.*	32) *Fecha*	(33) *País*
60/954,814	09-08-2007	US
61/049,944	02-05-2008	US
12/180,394	28-07-2008	US

(51) Int Cl: C07D 487/04; A61K 31/55; A61P 31/14

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

(72) Inventor(es) MARTIN, Scott W.; BERGSTROM, Carl P.; GENTLES, Robert G.; YEUNG, Kap-Sun

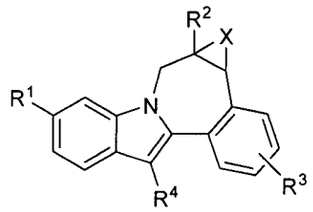
(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(85) Fecha límite inicio fase nacional: 09-03-2010
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 01-08-2008
No. de solicitud PCT/US2008/071881

(87) Publicación internacional
Fecha: 05-03-2009
N° publicación: WO 2009/029384

(54) Título: COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

Reivindicación(es): 1. Un compuesto de fórmula I



I

en la que:

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es furanilo, pirrolilo, tienilo, pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, triazolilo o tetrazolilo, y está sustituido con 0-2 sustituyentes seleccionados de oxo, amino, alquiltio, alquilo y haloalquilo, y 1 sustituyente seleccionado de CO_2R^5, $CON(R^{12})_2$ y COR^{13};

R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, $alquilSO_2$, $cicloalquilSO_2$, $haloalquilSO_2$, $(R^9)(R^{10})NSO_2$ o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, $alquilSO_2$, $cicloalquilSO_2$, $haloalquilSO_2$, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo o piridinilo;

R^9 es hidrógeno o alquilo;

R^{10} es hidrógeno o alquilo; ...

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 March 2009 (05.03.2009)

PCT

(10) International Publication Number
WO 2009/029384 A3

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 31/14* (2006.01)
A61K 31/55 (2006.01)

(21) International Application Number:
PCT/US2008/071881

(22) International Filing Date: 1 August 2008 (01.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/954,814	9 August 2007 (09.08.2007)	US
61/049,944	2 May 2008 (02.05.2008)	US
12/180,994	28 July 2008 (28.07.2008)	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)*: **MARTIN, Scott W.** [US/US]; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492 (US). **BERGSTROM, Carl P.** [US/US]; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492 (US). **GENTLES, Robert G.** [GB/US]; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492 (US). **YEUNG, Kap-Sun** [US/US]; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492 (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, BF, BW, BY, BZ, CA, CH, 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, 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, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
28 May 2009

WO 2009/029384 A3

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

(57) Abstract: The invention encompasses compounds of formula I as well as compositions and methods of using the compounds. The compounds have activity against hepatitis C virus (HCV) and are useful in treating those infected with HCV.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 March 2009 (05.03.2009)

PCT

(10) International Publication Number
WO 2009/029384 A2

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 31/20* (2006.01)
A61K 31/55 (2006.01)

(21) International Application Number:
PCT/US2008/071881

(22) International Filing Date: 1 August 2008 (01.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/954,814	9 August 2007 (09.08.2007)	US
61/049,944	2 May 2008 (02.05.2008)	US
12/180,994	28 July 2008 (28.07.2008)	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)*: **MARTIN, Scott W.** [US/US]; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492 (US). **BERGSTROM, Carl P.** [US/US]; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492 (US). **GENTLES, Robert G.** [GB/US], c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492 (US). **YEUNG, Kap-Sun** [US/US]; c/o Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492 (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, 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, 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, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

WO 2009/029384 A2

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

(57) Abstract: The invention encompasses compounds of formula I as well as compositions and methods of using the compounds. The compounds have activity against hepatitis C virus (HCV) and are useful in treating those infected with HCV.

COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Numbers 61/049,944 filed May 2, 2008 and 60/954,814 filed August 9, 2007.

BACKGROUND OF THE INVENTION

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 individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma (Lauer, G. M.; Walker, B. D. *N. Engl. J. Med.* **2001**, *345*, 41-52).

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 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.

Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have 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.

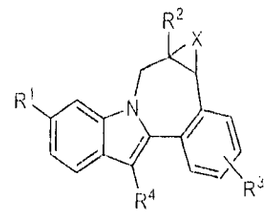
The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural 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., *Journal of Virology* **2002**, 3482-3492; and Defrancesco and Rice, *Clinics in Liver Disease* **2003**, *7*, 211-242.

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* **1998**, *352*, 1426-1432). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy (Zeuzem, S. et al. *N. Engl. J. Med.* **2000**, *343*, 1666-1672). 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.

DESCRIPTION OF THE INVENTION

One aspect of the invention is a compound of formula I



I

where:

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is furanyl, pyrrolyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, or tetrazolyl, and is substituted with 0-2 substituents selected from oxo, amino, alkylthio, alkyl, and haloalkyl, and 1 substituent selected from CO_2R^5, $CON(R^{12})_2$, and COR^{13};

R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)(R^{10})NSO_2$, or $(R^{11})SO_2$;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

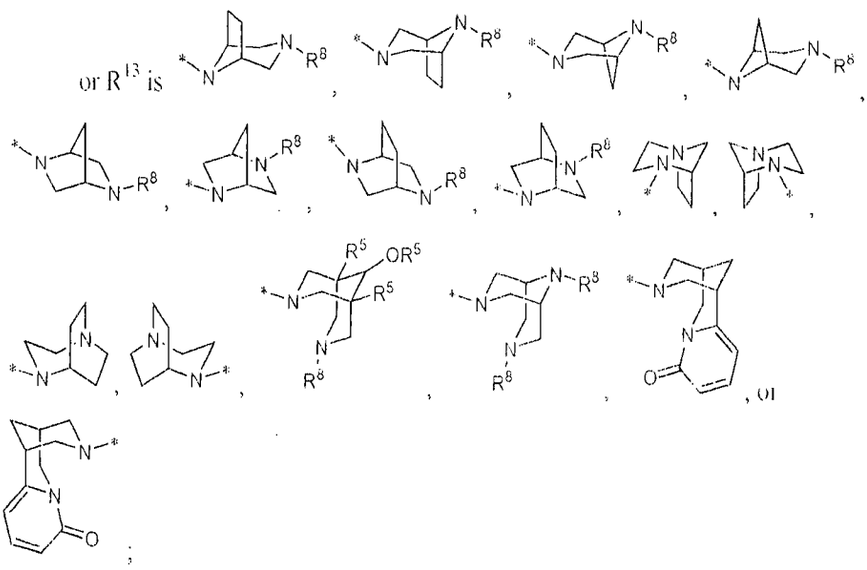
R^9 is hydrogen or alkyl;

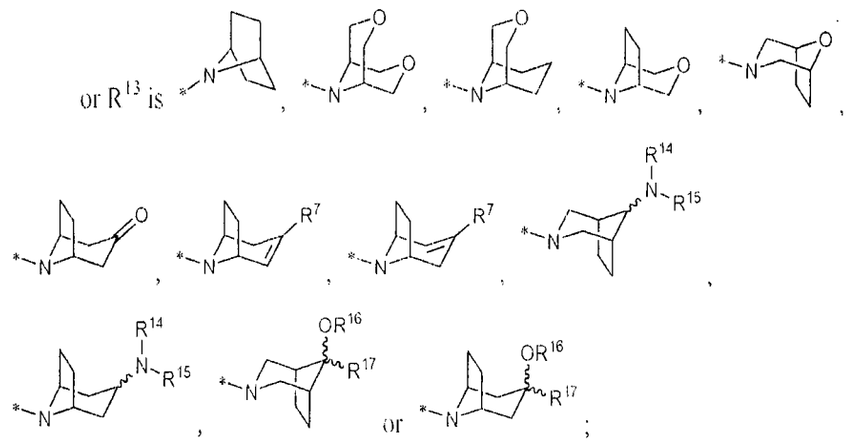
R^{10} is hydrogen or alkyl;

R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-1 alkyl substituents;

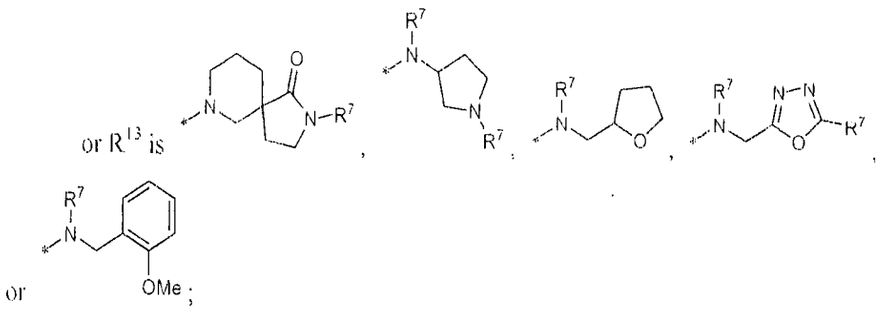
R^{12} is hydrogen, alkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or (R^{11})alkyl;

R^{13} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkoxyalkyl, amino, alkylamino, dialkylamino, R^{11}, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (R^{11})alkyl, or CO_2R^5;

or R^{13} is  ;

or R^{13} is 

or R^{13} is a [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents;

or R^{13} is 

R^{14} is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or benzyl;

R^{15} is is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or benzyl;

or $NR^{14}R^{15}$ taken together is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-(alkyl)piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, or homomorpholinyl;

R^{16} is hydrogen or alkyl;

R^{17} is hydrogen, alkyl, or cycloalkyl; and

X is methylene, a bond, or absent;

or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where:

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is furanyl, pyrrolyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, or tetrazolyl, and is substituted with 0-2 substituents selected from oxo, amino, alkyl, and haloalkyl, and 1 substituent selected from CO_2R^5, $CON(R^{12})_2$, and COR^{13};

R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)(R^{10})NSO_2$, or $(R^{11})SO_2$;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

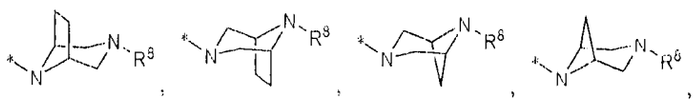
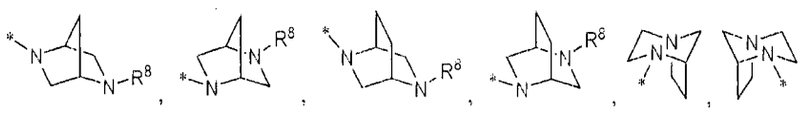
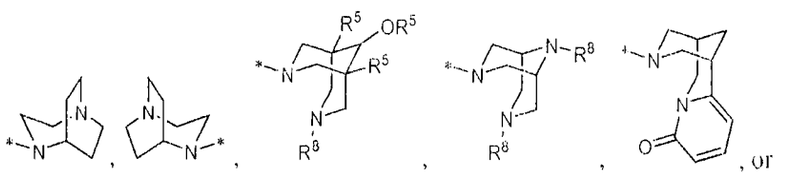
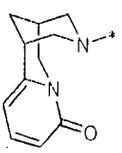
R^9 is hydrogen or alkyl;

R^{10} is hydrogen or alkyl;

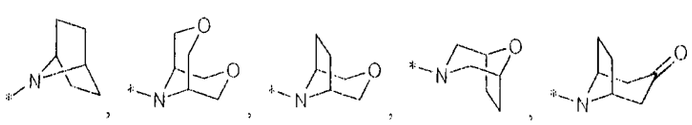
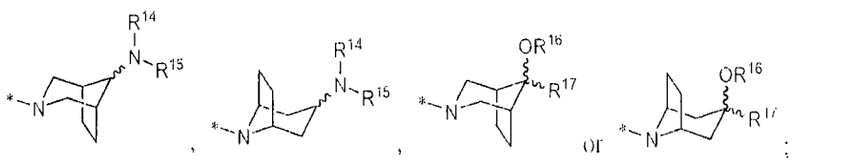
R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-1 alkyl substituents;

R^{12} is hydrogen, alkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or (R^{11})alkyl;

R^{13} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkoxyalkyl, amino, alkylamino, dialkylamino, R^{11}, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (R^{11})alkyl, or CO_2R^5;

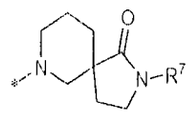
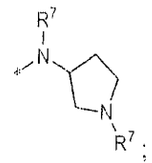
or R^{13} is 



, or

;

or R^{13} is 

or

;

or R^{13} is a [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents;

or R^{13} is  or  ;

R^{14} is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or benzyl;

R^{15} is is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or benzyl;

or $NR^{14}R^{15}$ taken together is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-(alkyl)piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, or homomorpholinyl;

R^{16} is hydrogen or alkyl;

R^{17} is hydrogen, alkyl, or cycloalkyl; and

X is methylene, a bond, or absent;

or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where:

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is furanyl, pyrrolyl, thienyl, pyrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, or tetrazolyl, and is substituted with 0-2

substituents selected from oxo, amino, and alkyl, and 1 substituent selected from CO_2R^5, $CON(R^{12})_2$, and COR^{13};

R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)(R^{10})NSO_2$, or $(R^{11})SO_2$;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

R^9 is hydrogen or alkyl;

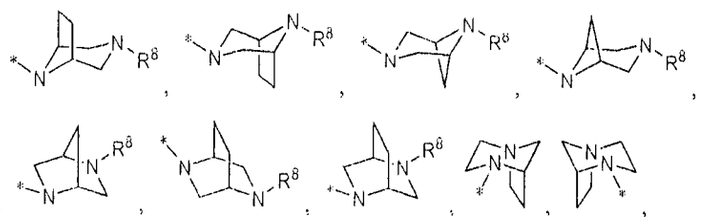
R^{10} is hydrogen or alkyl;

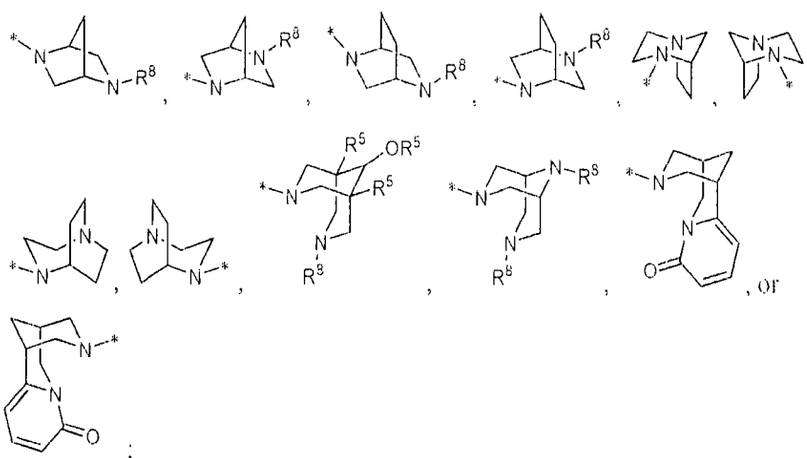
R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl;

R^{12} is hydrogen, alkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or $(R^{11})alkyl$;

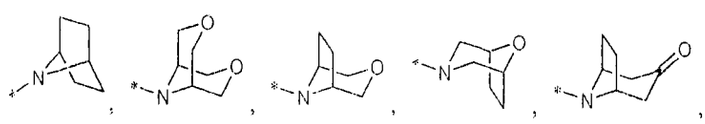
R^{13} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is

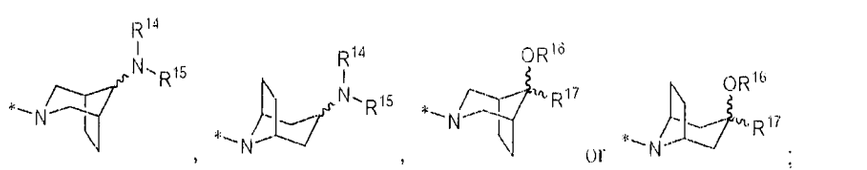
substituted with 0-3 substituents selected from alkyl, amino, alkylamino, dialkylamino, R^{11}, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or (R^{11})alkyl;

or R^{13} is 



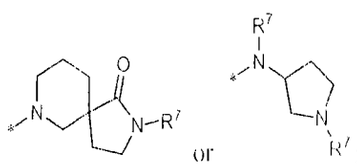
;

or R^{13} is 



;

or R^{13} is a [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents;

or R^{13} is  or ;

R^{14} is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or benzyl;

R^{15} is is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or benzyl;

or $NR^{14}R^{15}$ taken together is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-(alkyl)piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, or homomorpholinyl;

R^{16} is hydrogen or alkyl;

R^{17} is hydrogen, alkyl, or cycloalkyl; and

X is methylene, a bond, or absent;

or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where R^4 is $CONR^6R^7$; R^6 is $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)_2NSO_2$, or $(R^{10})SO_2$; and R^7 is hydrogen.

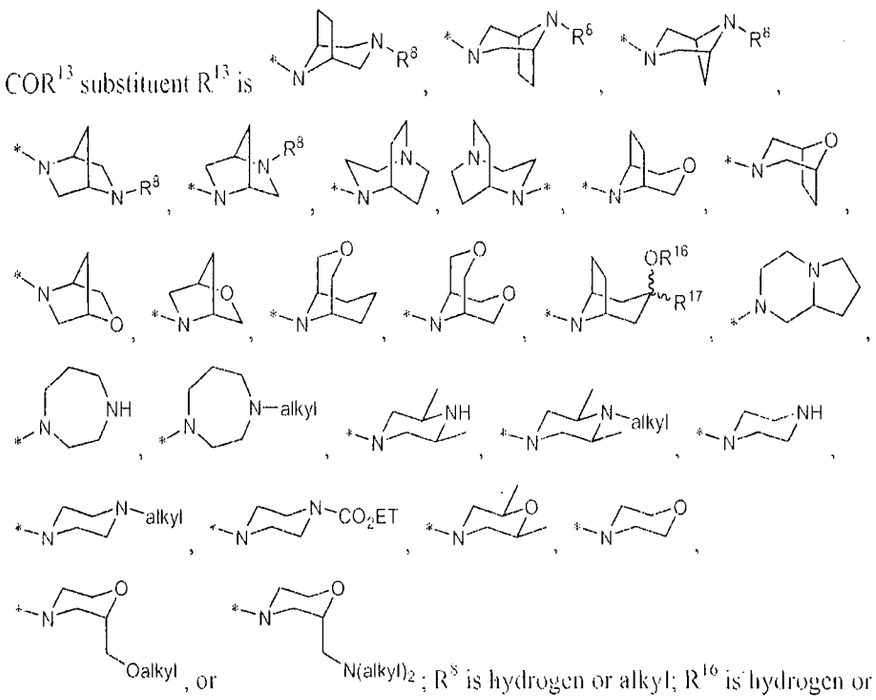
Another aspect of the invention is a compound of formula I where R^3 is hydrogen.

Another aspect of the invention is a compound of formula I where R^3 is methoxy.

Another aspect of the invention is a compound of formula I where R^4 is cyclohexyl.

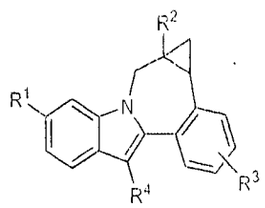
Another aspect of the invention is a compound of formula I where R^6 is $alkylSO_2$, $cycloalkylSO_2$, $(R^9)(R^{10})NSO_2$ or $(R^{11})SO_2$.

Another aspect of the invention is a compound of formula I where R^2 is pyrazolyl substituted with 2 substituents selected from alkyl and haloalkyl and 1

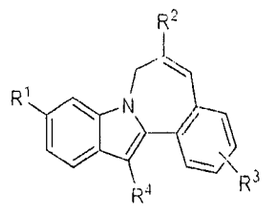
COR^{13} substituent R^{13} is 

; R^8 is hydrogen or alkyl; R^{16} is hydrogen or alkyl; and R^{17} is alkyl.

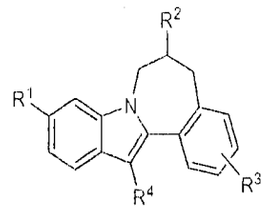
Another aspect of the invention is a compound of formula I where X is methylene.



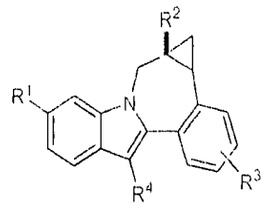
Another aspect of the invention is a compound of formula I where X is a bond.



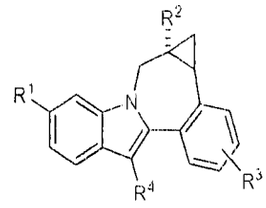
Another aspect of the invention is a compound of formula I where X is absent.



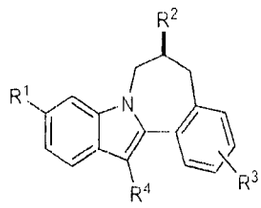
Another aspect of the invention is a compound of formula I according to the following stereochemistry.



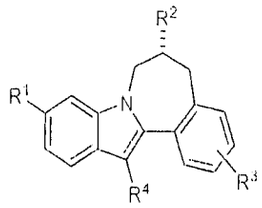
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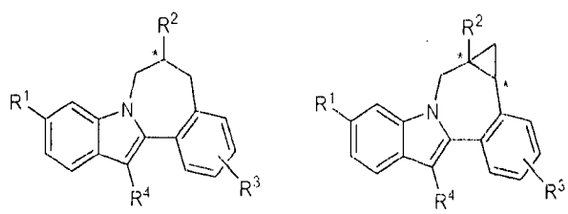
Any scope of any variable, including R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and X can be used independently with the scope of any other instance of a variable.

Unless specified otherwise, these terms have the following meanings. "Alkyl" means a straight or branched alkyl group composed of 1 to 6 carbons. "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. Parenthetic and multiparenthetic 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.

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 according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucouronate, hydrobromide, hydrochloride, hydroiodide,

iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

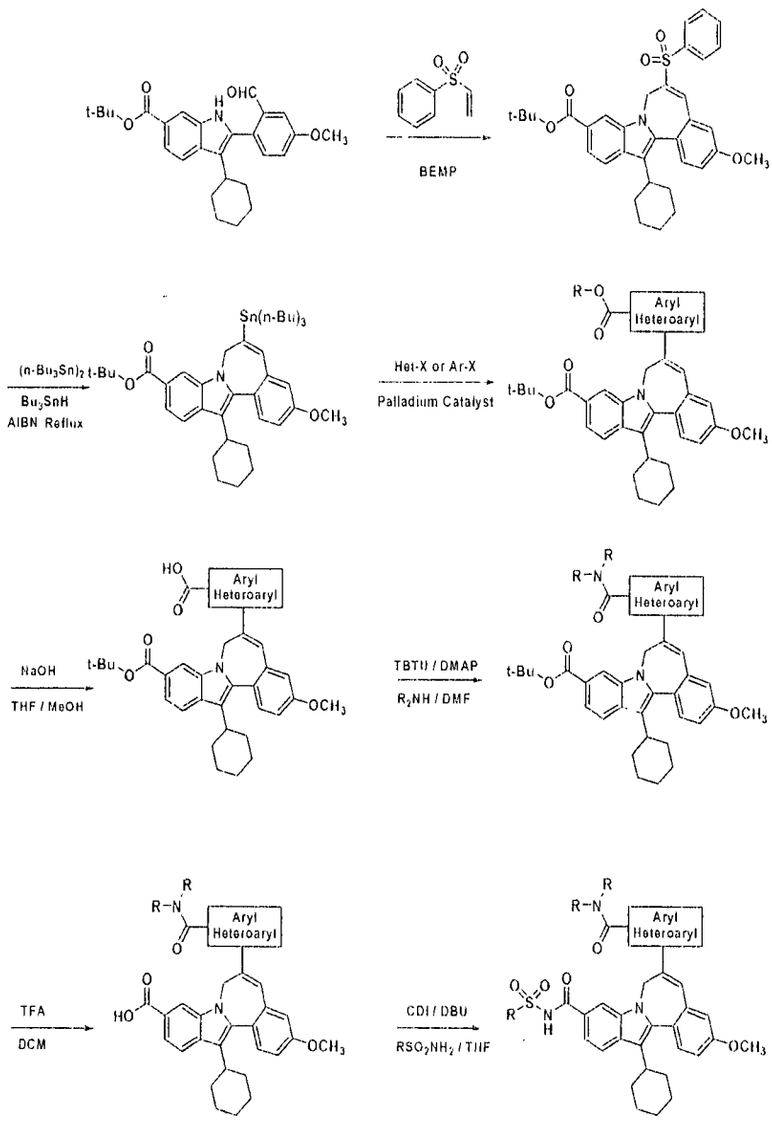
Some of the compounds of the invention possess asymmetric carbon atoms (see, for example, the compound below). The invention includes all stereoisomeric forms, including enantiomers and diastereomers as well as mixtures of stereoisomers such as racemates. Some stereoisomers can be made using methods known in the art. Stereoisomeric mixtures of the compounds and related intermediates can be separated into individual isomers according to methods commonly known in the art.



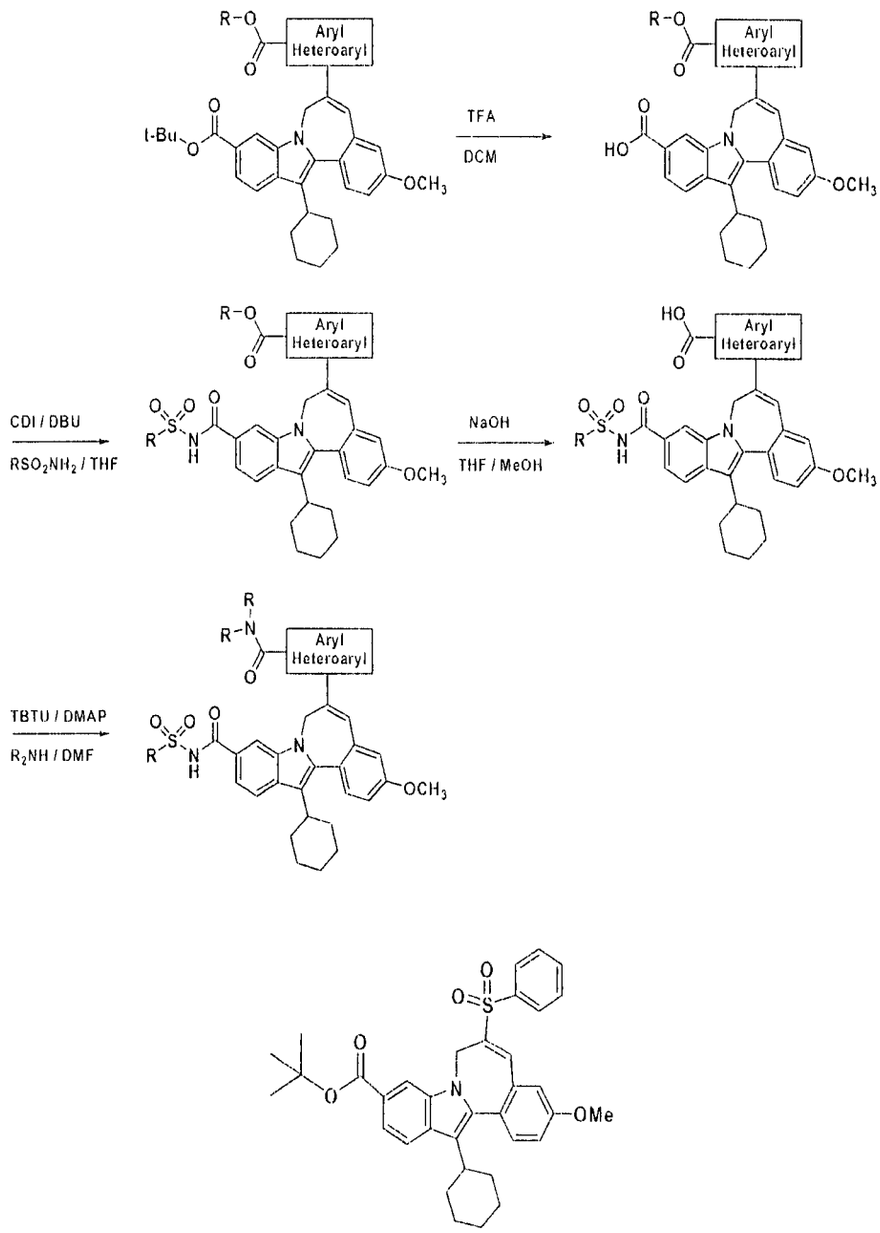
Synthetic Methods

The compounds may be made by methods known in the art including those described below. Some reagents and intermediates are known in the art. Other reagents and intermediates can be made by methods known in the art using 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. Abbreviations used within the schemes generally follow conventions used in the art.

The scheme shown below illustrates methods that can be used for making intermediates and compounds.



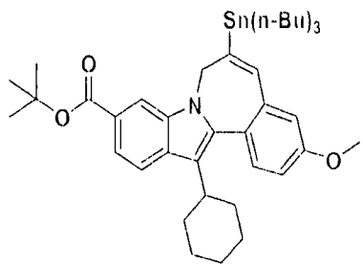
Alternatively, the reaction sequence can be modified as shown below.



7H-Indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(phenylsulfonyl)-, tert-butyl ester.

To a solution of 3-cyclohexyl-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxylate (6.00 g, 13.8 mmol) in dioxane (28.0 mL) and BEMP (7.97 mL, 27.6 mmol) was added phenyl vinyl sulfone (27.6 g, 2.21 mmol). The resulting mixture was stirred in a sealed tube in a microwave at 120 °C for 15 min. The resulting solution was concentrated under reduced pressure. Silica gel chromatography

(CH_2Cl_2) of the concentrate afforded the title compound 6.36g (79%) as a yellow oil. MS m/z 584 (MH^+). 1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 1.18-1.33 (1 H, m), 1.34-1.45 (2 H, m), 1.49-57 (1 H, m), 1.64 (9 H, s.), 1.74-1.82 (2 H, m), 1.90-2.09 (4 H, m), 2.73 (1 H, m,), 3.93 (3 H, s), 4.38 (1 H, broad d), 5.08 (1 H, br. d), 7.09 (1 H, d, *J*=2.75 Hz), 7.12-7.18 (3 H, m), 7.22 (1 H, d, *J*=7.45 Hz), 7.30 (1 H, s), 7.48 (1 H, d, *J*=8.85 Hz), 7.54 (1 H, dd, *J*=8.55, 1.22 Hz), 7.61 (2 H, m), 7.67 (1 H, d, *J*=8.55), 8.01 (1 H, s).

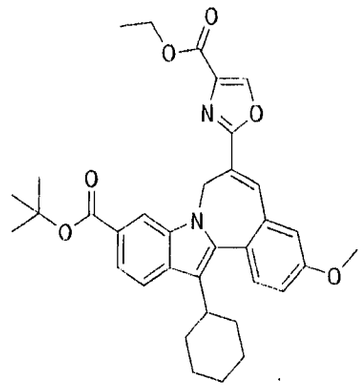


7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(tributylstannyl)-, 1,1-dimethylethyl ester. 1,1-dimethylethyl 13-cyclohexyl-3-(methyloxy)-6-(tributylstannanyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylate. 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(phenylsulfonyl)-, 1,1-dimethylethyl ester (1.00g, 1.71 mMol) was dissolved in 26mL of benzene along with bis(tributyltin) (2.8mL, 5.54 mMol), tributyltin hydride (136uL, 0.513 mMol) and triethylamine (1.05mL, 7.5 mMol). The solution was sparged for approximately for 10 minutes with nitrogen then 2,2'-bisazoisobutyronitrile (AIBN) (96mg, 0.58mMol) added to the reaction. The reaction was heated to reflux under nitrogen for 2hr. The reaction was followed by LC-MS using the following HPLC conditions: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 3 min; Runtime= 10 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Waters Xterra, 3mm x 50mm, S7. To the reaction was added tributyltin hydride (0.45mL, 1.7mMol) and AIBN(95mg, 0.58mMol), the reaction heated to reflux for 2hrs, and analyzed for progress. AIBN (99mg, 0.60mMol) added to the reaction and the reaction heated to reflux under for an additional 6hrs using a

timer. The reaction was analyzed by LC-MS for progress then tributyltin hydride(1.0ml, 3.8mMol) and AIBN (97mg, 0.59mMol) was added and the reaction heated to reflux for 2hrs 20min. The reaction was analyzed by LC-MS and AIBN (97mg, 0.59mMol) added to the reaction. The reaction was heated for 1hr under nitrogen at reflux and the cooled and analyzed by LC-MS. Volatiles were removed *in vacuuo* from the reaction and the reaction was purified by column chromatography using a C_{18} packing of 190g of YMC GEL ODS-A, 120A spherical 75 uM. The reaction residue (6.67g of yellow oil) was dissolved in a minimum of dichloromethane and the solution applied onto the reverse phase column packed in 10% dichloromethane in acetonitrile. Initial elution was done using 10% dichloromethane in acetonitrile followed by elution with 15% dichloromethane in acetonitrile. The chromatography was monitored by TLC using Whatman MKC18F reverse phase 1"x3" 200uM thickness TLC plates eluting using 15% dichloromethane in acetonitrile. Compound observation was accomplished by UV lamp at 254nm and iodine staining of TLC plates. Product fractions were collected and volatiles removed *in vacuuo* to yield 647mg (52%) as a pale yellow foam. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.71 - 0.83 (m, 9 H) 0.85 - 0.96 (m, 3 H) 0.95 - 1.08 (m, 6 H) 1.15 - 1.27 (m, 7 H) 1.27 - 1.49 (m, 11 H) 1.53 (s, 5 H) 1.60 - 1.67 (m, 9 H) 1.68 - 1.82 (m, 2 H) 1.84 - 1.96 (m, 1 H) 1.96 - 2.16 (m, 3 H) 2.74 - 2.91 (m, 1 H) 3.90 (s, 3 H) 4.16 - 4.40 (m, 1 H) 4.82 - 5.03 (m, 1 H) 6.72 - 6.90 (m, 2 H) 6.96 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.43 (d, *J*=8.55 Hz, 1 H) 7.66 (dd, *J*=8.39, 1.37 Hz, 1 H) 7.81 (d, *J*=8.55 Hz, 1 H) 8.04 (s, 1 H) LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 3 min; Runtime= 10 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Waters Xterra, 3mm x 50mm, S7. Retention Time= 4.2min, MS m/z 734(MH^+).

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(tributylstannyl)-, 1,1-dimethylethyl ester. 1,1-dimethylethyl 13-cyclohexyl-3-(methyloxy)-6-(tributylstannanyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylate.

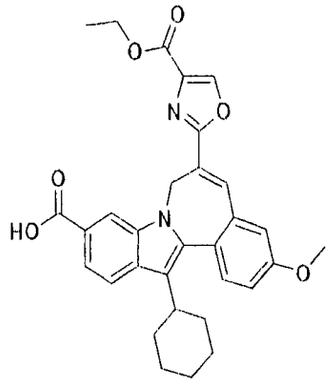
An assembly of a three necked flask fitted with an argon bubbler, reflux condenser and dropping funnel was flame dried and then cooled under a stream of argon. The flask was then charged with benzene (5 mL) and 7H-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(phenylsulfonyl)-, 1,1-dimethylethyl ester 1 (500 mg, 0.857 mmol). The resultant mixture was sonnicated under argon for 5 min (to remove oxygen) and then heated under reflux. A solution of tri-N-butyltin hydride (0.459 ml, 1.713 mmol) and 2,2'-azobis(2-methylpropionitrile (52.0 mg, 0.317 mmol) in degassed benzene (5 mL) was then added to the dropping funnel. Approximately 2.5 mL of this solution was added dropwise over a period of approximately 30 min, and the resultant solution was left to stir under reflux for 1.5 h. The remaining solution was added dropwise, slowly over a period of approximately 30 min, and heating was continued for a further 1.5 h. The mixture was then evaporated under reduced pressure to remove volatiles. The residue was slurried in hexane and applied to a silica gel biotage cartridge and then loaded onto a silica gel column equilibrated in 100% hexanes. The product was then eluted using a step gradient of ethyl acetate-hexane: 0 -100%, then 2-98%, then 5-95%. Homogeneous fractions were combined and evaporated to give yellow oil. This was placed under high vacuum overnight to give the title compound as a viscous yellow colored oil. [373 mg, 57%]. The product was stored under nitrogen in a refrigerator.



tert-butyl 13-cyclohexyl-6-(4-(ethoxycarbonyl)-1,3-oxazol-2-yl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate.

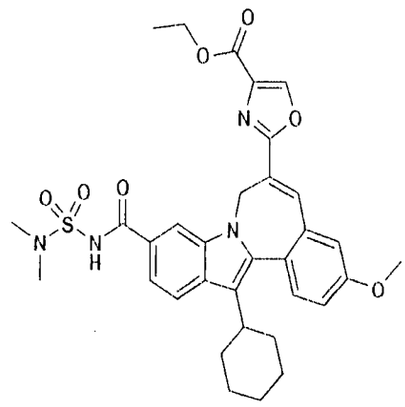
1,1-dimethylethyl 13-cyclohexyl-3-(methyloxy)-6-(tributylstannanyl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylate (266mg, 0.36mMol) was dissolved in 3.4mL of 1,4-dioxane in a 2 dram vial. Ethyl 2-chlorooxazole-4-carboxylate (83.4mg, 0.47mMol) was dissolved in the reaction followed by the addition of bis(triphenylphosphine)palladium(II) chloride (17.7mg, 0.025mMol). The reaction was capped under nitrogen and heated in an oil bath at 100 C for 17hrs, after which the reaction was cooled and the reaction progress was measured by LC-MS. To the reaction mixture was added bis(triphenylphosphine)palladium(II) chloride (10mg, 0.014mMol). The reaction was capped under nitrogen and heated for an additional 5hrs at 100C. The reaction was concentrated *in vacuuo* and the residue adsorbed onto silica gel purified by silica gel chromatography eluting with a gradient of dichloromethane to 2% ethyl acetate in dichloromethane to yield 233mg of a yellow solid product. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.13 - 1.37 (m, 4 H) 1.37 - 1.44 (m, 4 H) 1.46 - 1.55 (m, 1 H) 1.64 (s, 9 H) 1.68 - 1.81 (m, 2 H) 1.83 - 1.98 (m, 3 H) 1.98 - 2.13 (m, 3 H) 2.74 - 2.88 (m, 1 H) 3.91 (s, 3 H) 4.34 - 4.48 (m, 3 H) 5.84 - 6.00 (m, 1 H) 7.00 (d, *J*=2.44 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 (d, *J*=8.85 Hz, 1 H) 7.69 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.74 (s, 1 H) 7.82 (d, *J*=8.24 Hz, 1 H) 8.21 (s, 1 H) 8.30 (s, 1 H); LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 10% methanol, 90% water, 0.1% trifluoroacetic acid %B= 90% methanol, 10% water, 0.1% trifluoroacetic acid; Initial %B= 0; Final % B=100; Gradient= 3 min; Runtime= 5 min; Flow rate= 5 ml/min; Wavelength= 220nm;

Column= Phenomenex Luna 3.0mm x 50mm S10; Retention Time= 3.4 min, MS m/z 583(MH^+).



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-2-oxazolyl]-3-methoxy-.

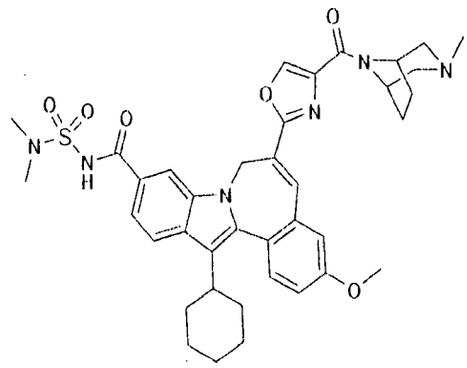
tert-butyl 13-cyclohexyl-6-(4-(ethoxycarbonyl)-1,3-oxazol-2-yl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylate (109mg, 0.19mMol) was dissolved in 2mL of 1,2-dichloroethane and 2mL of trifluoroacetic acid added to the reaction. The reaction was stirred at room temperature for 1.5hrs. Volatiles were removed and the product dried *in vacuuo* to yield 102mg of a yellow solid. ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.11 - 1.37 (m, 4 H) 1.42 (t, *J*=7.02 Hz, 4 H) 1.48 - 1.62 (m, 1 H) 1.77 (d, *J*=10.07 Hz, 2 H) 1.86 - 2.13 (m, 4 H) 2.73 - 2.90 (m, 1 H) 2.98 - 3.39 (m, 6 H) 3.92 (s, 3 H) 4.30 - 4.53 (m, 3 H) 5.87 - 6.03 (m, 1 H) 7.02 (d, *J*=2.44 Hz, 1 H) 7.09 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.75 (s, 1 H) 7.79 (dd, *J*=8.39, 1.37 Hz, 1 H) 7.88 (d, *J*=8.55 Hz, 1 H) 8.24 (s, 1 H) 8.50 (s, 1 H); LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 2 min; Runtime= 3 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Phenomenex Luna 3.0mm x 50mm S10; Retention Time= 1.7min, MS m/z 525(MH^+).



Ethyl 2-(13-cyclohexyl-10-(((dimethylamino)sulfonyl)carbamoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl)-1,3-oxazole-4-carboxylate.

Ethyl 2-(13-cyclohexyl-10-(((dimethylamino)sulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl)-1,3-oxazole-4-carboxylate. 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-2-oxazolyl]-3-methoxy- (115mg, 0.22mMol) was dissolved in 3ml of anhydrous THF and 1,1'-carbonyldiimidazole (61mg, 0.38mMol) added to the reaction. The reaction was stirred under nitrogen for 1hr 20min at room temperature then heated to reflux under nitrogen for 45 minutes. The reaction was cooled and dimethylsulfamide (186mg, 1.49mMol) was added to the reaction followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (39uL,0.26mMol) (DBU). The reaction was heated at 55C for 16hrs under nitrogen. The reaction was partitioned between dichloromethane and 0.1M monosodium phosphate. The dichloromethane extract was washed with 0.1M monosodium phosphate then dried over sodium sulfate. Volatiles were removed *in vacuo* to yield 167mg of crude yellow product. One-half of the crude sample was dissolved in a mixture of acetonitrile and methanol and purified by reverse phase prep HPLC under the following conditions: Shimadzu preparative HPLC using Discovery VP software: %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 50; Final % B=100; Gradient= 12 min; Runtime= 17 min; Flow rate= 25 ml/min; Wavelength= 220nm; Column= Waters Sunfire 19mm x 100mm. Product retention time= 12.25min to 17min (tailing due to solubility). Obtained 25.2mg of amorphous yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.18 - 1.30 (m, 2 H) 1.34 -

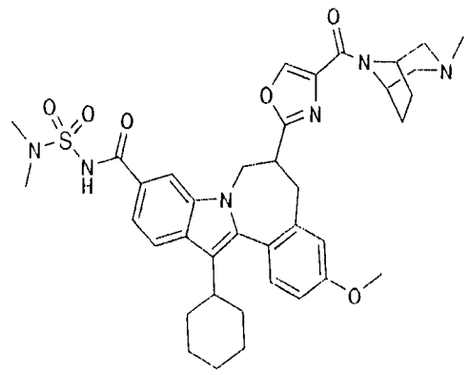
1.46 (m, 5 H) 1.47 - 1.62 (m, 1 H) 1.70 - 1.85 (m, 2 H) 1.86 - 2.21 (m, 4 H) 2.72 - 2.92 (m, 1 H) 3.07 (s, 6 H) 3.92 (s, 3 H) 4.08 - 4.34 (m, 2 H) 4.41 (q, *J*=7.22 Hz, 3 H) 5.75 - 5.99 (m, 1 H) 7.02 (d, *J*=2.75 Hz, 1 H) 7.10 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.45 - 7.65 (m, 2 H) 7.71 (s, 1 H) 7.89 (d, *J*=8.55 Hz, 1 H) 8.20 (s, 1 H) 8.29 (s, 1 H) 9.36 (s, 1 H); LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 2 min; Runtime= 4 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Phenomenex Luna 3.0mm x 50mm S10; Retention Time= 1.9 min, MS m/z 631 (MH^-), m/z 633(MH^+).



13-cyclohexyl-N-((dimethylamino)sulfonyl)-3-methoxy-6-(4-((3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl)-1,3-oxazol-2-yl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

Ethyl 2-(13-cyclohexyl-10-(((dimethylamino)sulfonyl)carbamoyl)-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl)-1,3-oxazole-4-carboxylate (35.7mg, 0.056mMol) was dissolved in 0.6ml of THF in a 2 dram vial. Tetrabutylammonium hydroxide (170ul., 0.17mMol) as a 1M solution in methanol was added to the reaction. The reaction was capped and stirred for 3hrs at room temperature. The reaction was partitioned between 1N hydrochloric acid and dichloromethane. The organic phase was washed with 1N hydrochloric acid and dried over sodium sulfate. The material was concentrated to dryness, dried *in vacuuo* and used without further purification. The hydrolysis product (0.056mMol) was dissolved in 1mL of DMF and TBTU(39mg, 0.12mMol)added. The reaction was stirred at room temperature

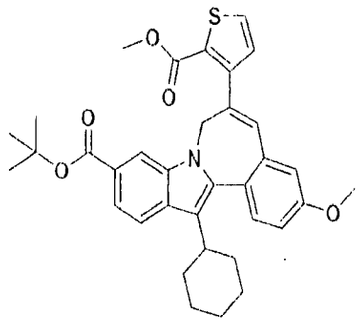
under nitrogen for approximately 50 minutes then add DMAP(37.9mg, 0.31mMol)was added followed by 3-methyl-3,8-diaza-bicyclo[3.2.1]octane dihydrochloride (23mg, 0.11mMol). The reaction was stirred for 4hrs at room temperature under nitrogen atmosphere until complete, then added to 20ml. of water and extracted with dichloromethane, washed organic layer with water and dry over sodium sulfate to yield 50mg of crude product. The product was purified by Prep HPLC under the following conditions: Shimadzu preparative HPLC using Discovery VP software: %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 30; Final % B=100; Gradient= 12 min; Runtime= 20 min; Flow rate= 25 ml/min; Wavelength= 220nm; Column= Waters Sunfire 19mm x 100mm. Product retention time= 6.1min. Product fractions were concentrated *in vacuuo* to yield 30.5mg of the title compound as a trifluoroacetic acid salt. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.09 - 1.30 (m, 1 H) 1.31 - 1.61 (m, 3 H) 1.68 - 1.85 (m, 2 H) 1.87 - 2.20 (m, 5 H) 2.26 - 2.44 (m, 2 H) 2.51 - 2.66 (m, 1 H) 2.77 - 2.90 (m, 1 H) 2.91 - 3.01 (m, 3 H) 3.04 (s, 6 H) 3.12 (d, *J*=11.90 Hz, 1 H) 3.23 (d, *J*=11.60 Hz, 1 H) 3.78 (d, *J*=12.21 Hz, 1 H) 3.94 (s, 3 H) 4.24 (d, *J*=13.12 Hz, 1 H) 4.43 (d, *J*=14.34 Hz, 1 H) 5.01 (d, *J*=5.80 Hz, 1 H) 5.13 - 5.47 (m, 1 H) 5.85 (d, *J*=14.04 Hz, 1 H) 6.02 (s, 1 H) 7.03 (d, *J*=2.75 Hz, 1 H) 7.12 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.25 - 7.32 (m, 1 H) 7.56 (d, *J*=8.55 Hz, 1 H) 7.69 (s, 1 H) 7.88 (d, *J*=8.24 Hz, 1 H) 8.18 (s, 1 H) 8.28 (s, 1 H) 8.52 (s, 1 H) 11.72 (s, 1 H); LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 2 min; Runtime= 3 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Phenomenex Luna 3.0mm x 50mm S10 Retention Time= 1.7 min, MS m/z 711 (MH^+), m/z 713(MH^+).



13-Cyclohexyl-N-((dimethylamino)sulfonyl)-3-methoxy-6-(4-((3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl)-1,3-oxazol-2-yl)-6,7-dihydro-5H-indolo[2,1-a][2]benzazepine-10-carboxamide.

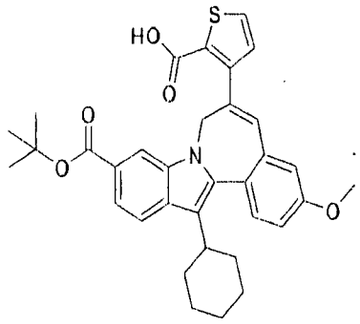
13-Cyclohexyl-*N*-((dimethylamino)sulfonyl)-3-methoxy-6-(4-((3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl)-1,3-oxazol-2-yl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxamide (26.5mg, 0.037mMol) was dissolved in 1mL of THF and 0.3mL of methanol added followed by 10mg of 10% palladium on carbon. The reaction was placed under hydrogen at 1 atmosphere (balloon) and stirred for 18hrs at room temperature. The reaction was filtered through a celite plug and rinsed with acetonitrile. Volatiles were removed from the filtrate *in vacuuo* and the residue was dissolved in acetonitrile and purified by Prep HPLC under the following conditions: Shimadzu preparative HPLC using Discovery VP software: %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 30; Final % B=100; Gradient= 12 min; Runtime= 17 min; Flow rate= 25 ml/min; Wavelength= 220nm; Column= Waters Sunfire 19mm x 100mm. Product retention time= 5.3 minutes. The title compound was isolated as a TFA salt, 17.6mg obtained. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.20 - 1.33 (m, 1.1H) 1.33 - 1.54 (m, 2.1 H) 1.65 (t, *J*=10.99 Hz, 1.1 H) 1.74 - 1.86 (m, 1.9 H) 1.89 - 2.11 (m, 5.6 H) 2.11 - 2.44 (m, 3.0H) 2.71 - 2.86 (m, 3.2 H) 2.87 - 2.98 (m, 2.9 H) 2.98 - 3.10 (m, 7.7 H) 3.08 - 3.45 (m, 6.1 H) 3.72 - 3.83 (m, 0.9 H) 3.82 - 3.93 (m, 3.1 H) 3.92 - 4.00 (m, 0.8 H) 4.05 (dd, *J*=14.80, 5.65 Hz, 0.8 H) 4.55 - 5.12 (m, 2.6 H) 5.60 (d, *J*=12.82 Hz, 0.3 H) 6.64 - 7.12 (m, 2.0 H) 7.29 - 7.62 (m, 1.8 H) 7.77 - 7.97 (m, 1.2 H) 7.97 - 8.43 (m, 1.2 H) 8.55 - 9.33 (m, 0.7 H) 11.70 (s, 0.5 H). LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile,

95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 3 min; Runtime= 5 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Gemini 4.6mm x 50mm S5; Retention Time= 2.2 min, MS m/z 715(MH^+), m/z 713(MH^-).



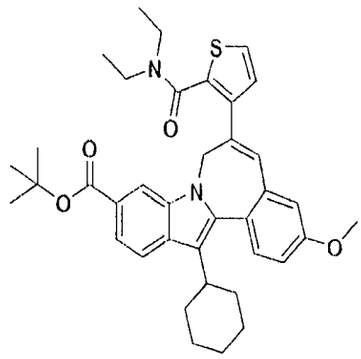
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[2-(methoxycarbonyl)-3-thienyl]-, 1,1-dimethylethyl ester. 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(tributylstannyl)-, 1,1-dimethylethyl ester (140mg, 0.19mMol) was dissolved in 2ml. of 1,4-dioxane along with methyl 3-bromothiophene-2-carboxylate (79mg, 0.36mMol) in a 2 dram vial. To the reaction was added bis(triphenylphosphine)palladium dichloride (9.2mg, 0.013mMol). The reaction was capped under a nitrogen atmosphere and heated to 100C for 4.5hrs. The reaction was cooled and filtered through a 0.45uM nylon syringe filter and the volatiles removed *in vacuuo* to yield 226mg of a yellow oil. The title compound was purified by silica gel chromatography eluting with 30% hexanes in dichloromethane to yield 73mg (66%) of product. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.92 (t, *J*=7.32 Hz, 2 H) 1.24 - 1.44 (m, 6 H) 1.57 (s, 9 H) 1.58 - 1.71 (m, 2 H) 1.77 (d, *J*=8.85 Hz, 2 H) 1.85 - 1.99 (m, 1 H) 2.00 - 2.17 (m, 3 H) 2.83 - 2.93 (m, 1 H) 3.82 (s, 3 H) 3.88 (s, 3 H) 4.71 (s, 1 H) 5.10 (s, 1 H) 6.80 (s, 1 H) 6.83 (d, *J*=4.88 Hz, 1 H) 6.90 (d, *J*=2.75 Hz, 1 H) 7.01 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.40 (d, *J*=5.19 Hz, 1 H) 7.51 (d, *J*=8.85 Hz, 1 H) 7.63 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.82 (d, *J*=8.55 Hz, 1 H) 7.88 (s, 1 H); LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 10% methanol, 90% water, 0.1% trifluoroacetic acid %B= 90% methanol, 10% water, 0.1% trifluoroacetic acid; Initial %B= 0; Final % B=100; Gradient= 2 min; Runtime= 5 min; Flow rate= 5 ml/min; Wavelength=

220nm; Column= Phenomenex Luna 3.0mm x 50mm S10; Retention Time= 2.95 min, MS m/z 584(MH^+).



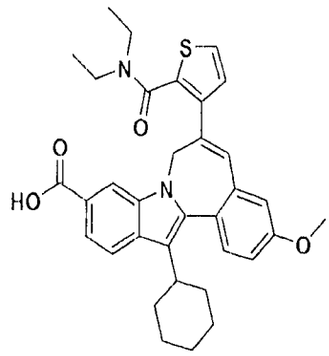
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 6-(2-carboxy-3-thienyl)-13-cyclohexyl-3-methoxy-, 10-(1,1-dimethylethyl) ester.

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[2-(methoxycarbonyl)-3-thienyl]-, 1,1-dimethylethyl ester (65mg, 0.11mMol) was dissolved in 1mL of THF in a 2 dram vial. To this solution was added 1.0M tetrabutylammonium hydroxide (0.33mL, 0.33mMol) in methanol. The reaction was capped and stirred at room temperature for 3hrs then monitored by HPLC. Additional 1.0M tetrabutylammonium hydroxide (0.10mL, 0.1mMol) in methanol was added to the reaction and the reaction stirred capped at room temperature for an additional 21hrs. The reaction was partitioned between dichloromethane and 0.1M citric acid. The aqueous phase was extracted with dichloromethane and the organic extracts were combined and dried over sodium sulfate. Volatiles were removed *in vacuuo* to yield 72mg of crude product. LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 3 min; Runtime= 5 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Phenomenex Luna 3.0mm x 50mm S10; Retention Time= 2.50min, MS m/z 570(MH^+).

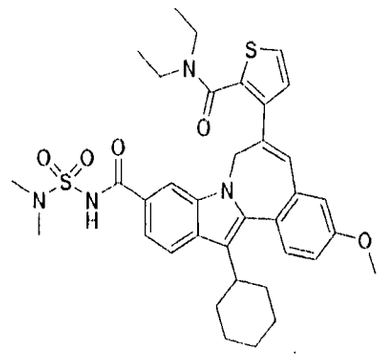


7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[2-[(diethylamino)carbonyl]-3-thienyl]-3-methoxy-, 1,1-dimethylethyl ester.

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 6-(2-carboxy-3-thienyl)-13-cyclohexyl-3-methoxy-, 10-(1,1-dimethylethyl) ester (36mg, 0.063mMol) was dissolved in 0.7mL of anhydrous DMF and TBTU (36.5mg, 0.114mMol) added to the reaction. The reaction was capped under nitrogen and stirred at room temperature for 1.5hrs. DMAP (29mg, 0.24mMol) was then dissolved in the reaction then diethyl amine (26uL, 0.25mMol) added. The reaction was capped under a nitrogen atmosphere and stirred for 21hrs at room temperature. The reaction was added to 15mL of water and the aqueous suspension extracted with dichloromethane. The organic phase was washed sequentially with 0.1M citric acid, water and dried over sodium sulfate, filtered and volatiles removed *in vacuuo* to yield a amber oil. LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 10% methanol, 90% water, 0.1% trifluoroacetic acid %B= 90% methanol, 10% water, 0.1% trifluoroacetic acid; Initial %B= 50; Final % B=100; Gradient= 5 min; Runtime= 6 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Phenomenex Luna 3.0mm x 50mm S10; Retention Time= 4.64 min, MS m/z 625(MH$^+$), 647(M+Na).



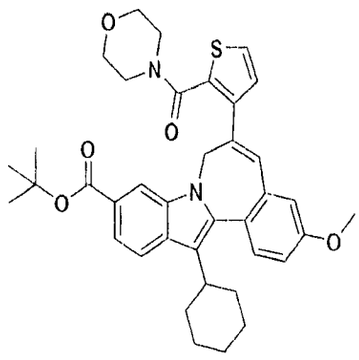
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[2-[(diethylamino)carbonyl]-3-thienyl]-3-methoxy-. 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[2-[(diethylamino)carbonyl]-3-thienyl]-3-methoxy-, 1,1-dimethylethyl ester (39mg, 0.06mMol) was dissolved in 1mL of 1,2-dichloroethane and 1mL of trifluoroacetic acid was added. The reaction was stirred at room temperature for 2hrs then volatiles were removed *in vacuuo*. The reaction product was repeatedly dissolved in benzene and volatiles removed in vacuuo to aid in the removal of residual TFA. Weight of product was 39mg as an amorphous solid. LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 3 min; Runtime= 5 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Phenomenex Luna 3.0mm x 50mm S10; Retention Time= 2.31, MS m/z 569(MH+).



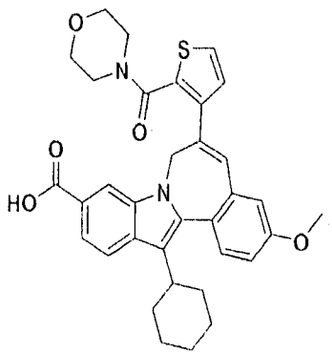
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[2-[(diethylamino)carbonyl]-3-thienyl]-N-[(dimethylamino)sulfonyl]-3-methoxy-. 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[2-

[(diethylamino)carbonyl]-3-thienyl]-3-methoxy- (36.7mg, 0.064mmol) was dissolved in THF (1ml) and carbonyldiimidazole (19mg, 0.117mmol) added to the reaction. The reaction was stirred under a nitrogen atmosphere at room temperature for 1.5 hours. The reaction was then heated to 60C for 1.5 hours, then cooled and dimethylsulfamide (55mg, 0.444mmol) was added to the reaction followed by DBU (13.3uL, 0.089mmol). The reaction was capped under a nitrogen atmosphere and heated at 65C to 70C overnight. The reaction was cooled then partitioned between dichloromethane and 1N aqueous hydrochloric acid. The aqueous phase was back extracted with dichloromethane and the organic layers combined and washed sequentially with 1N aqueous hydrochloric acid, aqueous 0.1M NaH2PO4. The dichloromethane phase was dried over sodium sulfate, filtered and volatiles removed in vacuuo to yield 47mg of brown film. The sample was dissolved in acetonitrile / DMF (1:1) and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 50 solvent A / 50% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Solvent was removed from the product fraction in vacuuo to yield 18.1mg of an amorphous yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.53 (br.s, 3 H) 0.96 (br.s, 3 H) 1.04 - 1.44 (m, 4 H) 1.51 (d, *J*=10.07 Hz, 1 H) 1.78 (d, *J*=9.46 Hz, 2 H) 1.88 - 2.13 (m, 4 H) 2.40 - 2.52 (m, 1 H) 2.80 - 2.97 (m, 3 H) 3.05 (s, 6 H) 3.57 (br.s, 1 H) 3.89 (s, 3 H) 4.49 (d, *J*=14.65 Hz, 1 H) 5.20 (d, *J*=14.04 Hz, 1 H) 6.93 (d, *J*=2.75 Hz, 1 H) 6.98 (s, 1 H) 7.02 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.11 (d, *J*=5.19 Hz, 1 H) 7.38 (d, *J*=4.88 Hz, 1 H) 7.41 - 7.52 (m, 2 H) 7.86 (d, *J*=8.55 Hz, 1 H) 8.01 (s, 1 H) 9.18 (s, 1 H); LC-MS retention time 2.19 min; 673 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 5% acetonitrile / 95% H2O / 10 mM ammonium acetate and solvent B was 5% H2O / 95% acetonitrile / 10 mM

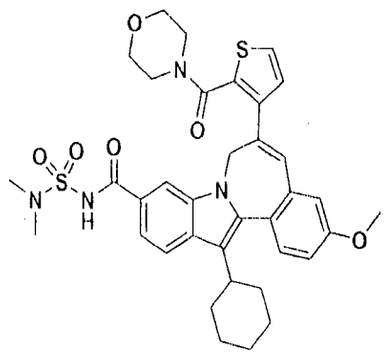
ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.



tert-Butyl 13-cyclohexyl-3-methoxy-6-(2-(4-morpholinylcarbonyl)-3-thienyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylate. In a 2 dram vial, 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 6-(2-carboxy-3-thienyl)-13-cyclohexyl-3-methoxy-, 10-(1,1-dimethylethyl) ester (33.7mg, 0.059 mmol) and O-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (34.2 mg, 0.106 mmol) was dissolved in DMF (0.7 ml) to give a clear yellow solution. The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 1hr 20min. DMAP (28.9 mg, 0.237 mmol) was dissolved in the reaction then morpholine (10.5 µl, 0.121 mmol) was added. The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 2 days. Pour reaction into 15mL of water. A pale yellow precipitate forms. Extract into dichloromethane. Wash dichloromethane solution with 0.1M aqueous citric acid, back extract aqueous using dichloromethane. Combine dichloromethane phases wash 1x with water and dry over sodium sulfate. Remove volatiles *in vacuuo* to yield 45mg of the title product as a yellow oil. LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 10% methanol, 90% water, 0.1% trifluoroacetic acid %B= 90% methanol, 10% water, 0.1% trifluoroacetic acid; Initial %B= 50; Final % B=100; Gradient= 6 min; Runtime= 6 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Phenomenex Luna 3.0mm x 50mm S10; Retention Time= 4.38 min, MS m/z 639(MH^+).



13-Cyclohexyl-3-methoxy-6-(2-(4-morpholinylcarbonyl)-3-thienyl)-7H indolo[2,1-a][2]benzazepine-10-carboxylic acid. In a 2 dram vial, dissolve tert-Butyl 13-cyclohexyl-3-methoxy-6-(2-(4-morpholinylcarbonyl)-3-thienyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (37.7 mg, 0.059 mmol) in 1,2-Dichloroethane (1 mL) add TFA (1 mL, 12.98 mmol). The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 1.5hrs. Transfer reaction contents to a 25mL pear flask using benzene to rinse. Remove volatiles *in vacuo*. Dissolve product in benzene and rotovap to aid in trace TFA removal. Obtained 41mg of title compound as a yellow brown film. A LC-MS was obtained to confirm product and the product used in the next step without further purification. LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 3 min; Runtime= 5 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Waters Xterra, 3mm x 50mm, S7. Retention Time= 1.73 min, MS m/z 583(MH^+), m/z 581($M-H)^-$.

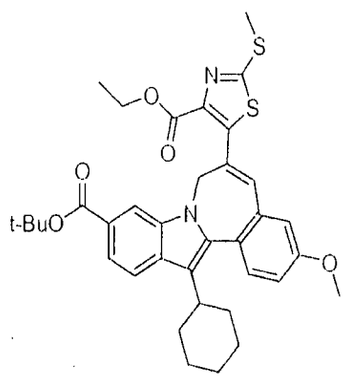


13-Cyclohexyl-N-(dimethylsulfamoyl)-3-methoxy-6-(2-(4-morpholinylcarbonyl)-3-thienyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

In a 2 dram vial, dissolve 13-Cyclohexyl-3-methoxy-6-(2-(4-morpholinylcarbonyl)-3-thienyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid (38 mg, 0.065 mmol) in 1mL of anhydrous THF, add CDI (19.03 mg, 0.117 mmol) to the reaction. The reaction was capped under a nitrogen atmosphere and stirred at room temperature for approximately 1 hour. The reaction was heated capped under nitrogen at 65C for 1 hour, then cooled to room temperature and N,N-Dimethylsulfamide (44.3 mg, 0.357 mmol) then DBU (13.8 µL, 0.092 mmol) added to the reaction. The reaction was capped and heated under nitrogen over night at 65°C. Analysis of an aliquot by LC-MS indicated that the reaction was incomplete. To the reaction was added more dimethylsulfamide(19mg, 0.153mmol) and DBU (13.8uL, 0.092mmol). The reaction was capped under a nitrogen atmosphere and heated at 69C for 3.25hrs. Analysis of the reaction by LC-MS indicated that the reaction was complete. The reaction was partitioned between dichloromethane and 1N aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane. The organic layers were combined and washed sequentially with 1N aqueous hydrochloric acid then 0.1M sodium dihydrogen phosphate (NaH_2PO_4) and dried over sodium sulfate. Volatiles were removed *in vacuuo* to give a yellow oil/film. The crude title compound was dried *in vacuuo* overnight at room temperature. Weight of crude product is 43mg as a yellow/brown solid. Dissolve in a mixture of acetonitrile and DMF and purify by reverse phase HPLC under the following conditions: Shimadzu Preparative HPLC running Discovery VP software, %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 50; Final % B=100; Gradient= 15 min; Runtime= 25 min; Flow rate= 25 ml/min; Wavelength= 220nm; Column= Waters Sunfire 19mm x 100mm. Product collection time= 9.72min. to 10.49min. Volatiles were removed *in vacuuo* from the product fraction to yield 14.2mg of the title compound as a yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.17 - 1.30 (m, 1 H) 1.32 - 1.50 (m, 2 H) 1.55 (d, *J*=11.29 Hz, 1 H) 1.78 (d, *J*=10.99 Hz, 2 H) 1.90 - 2.16 (m, 4 H) 2.42 - 2.58 (m, 1 H) 2.60 - 2.86 (m, 4 H) 2.85 - 2.94 (m, 2 H) 2.95 - 3.04 (m, 2 H) 3.06 (s, 6 H) 3.10 - 3.30 (m, 1 H) 3.91 (s, 3 H) 4.56 (d, *J*=14.65 Hz, 1 H) 5.09 (d, *J*=14.65 Hz, 1 H) 6.87 (s, 1 H) 6.93 (d, *J*=2.75 Hz, 1 H) 7.05 (dd, *J*=8.70, 2.59 Hz, 1

H) 7.08 (d, *J*=4.88 Hz, 1 H) 7.45 (d, *J*=4.88 Hz, 1 H) 7.47 - 7.54 (m, 2 H) 7.83 (s, 1 H) 7.91 (d, *J*=8.55 Hz, 1 H) 9.59 (s, 1 H). LC-MS: Shimadzu Analytical HPLC using Discovery VP software: %A= 5% acetonitrile, 95% water, 10mmol Ammonium Acetate %B= 95% acetonitrile, 5% water, 10mmol Ammonium Acetate; Initial %B= 0; Final % B=100; Gradient= 3 min; Runtime= 4 min; Flow rate= 5 ml/min; Wavelength= 220nm; Column= Waters Xterra, 3mm x 50mm, S7. Retention Time= 2.05min min, MS m/z 689 (MH^+), m/z 687 $(M-H)^-$.

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-2-(methylthio)-5-thiazolyl]-3-methoxy-, 1,1-dimethylethyl ester



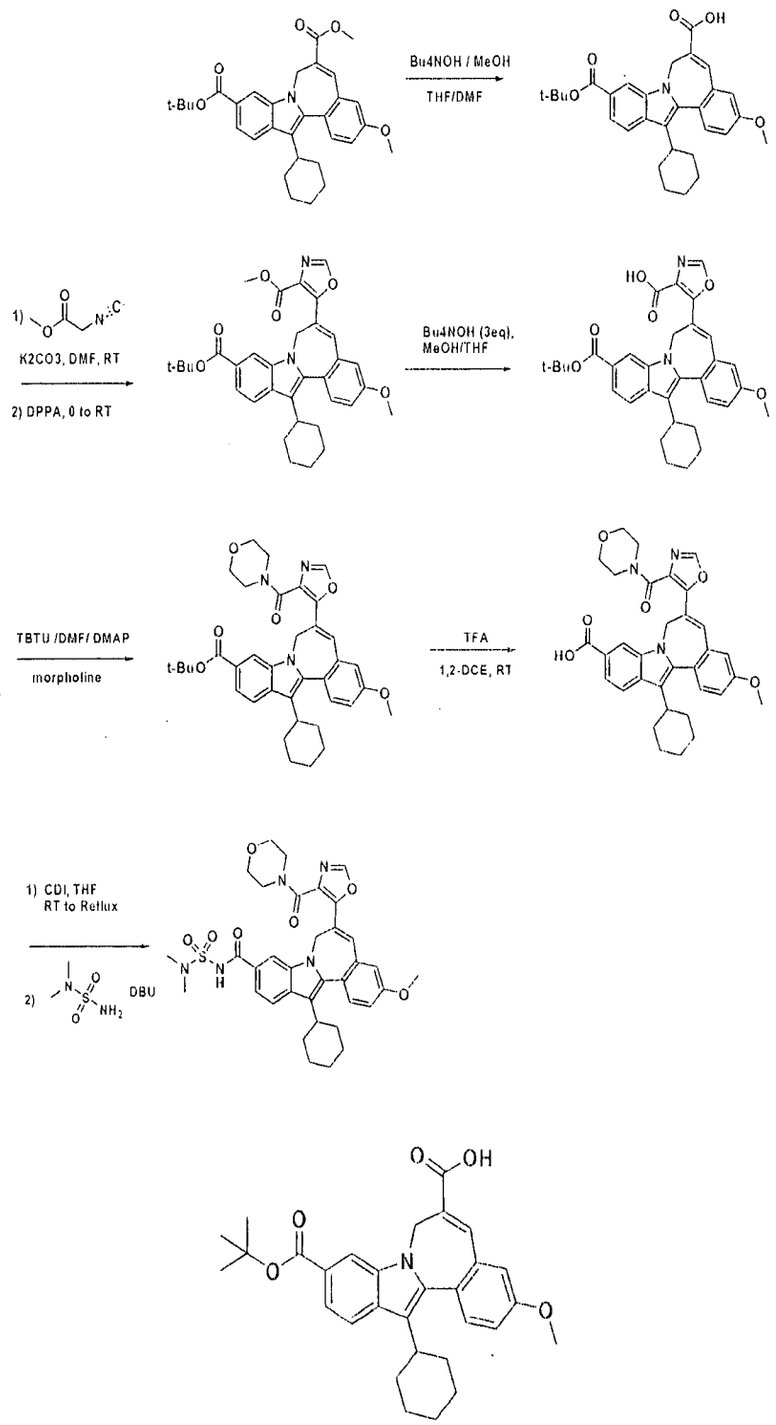
7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(tributylstannyl)-, 1,1-dimethylethyl ester (203 mg, 0.277 mmol) was dissolved in 1,4-dioxane (2.7 ml)) in a 2-5mL tapered microwave vessel with magnetic stir bar. To the reaction was added ethyl 5-bromo-2-(methylthio)thiazole-4-carboxylate (171 mg, 0.606 mmol), and bis(triphenylphosphine)palladium(II) chloride (14.9 mg, 0.021 mmol). The reaction was capped under a nitrogen atmosphere and heated to 100C for 17.5hrs. HPLC analysis of the reaction indicated only approximately 45% conversion of starting material. Additional catalyst bis(triphenylphosphine)palladium(II) chloride (5.7mg) was added to the reaction and the reaction was heated under a nitrogen atmosphere at 110C for 23hrs. Volatiles were removed from the reaction mixture in vacuuo and the crude reaction mixture was dissolved in a 8ml of a DMF/acetonitrile mixture and purified as four 2ml. injections using reverse phase HPLC. The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector.

The sample was dissolved in acetonitrile and DMF purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 40% solvent A / 60% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 30 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product = 26.6min. Volatiles from the product fractions were removed *in vacuuo* using a speed vac at a medium heating setting.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.16 - 1.26 (m, 1 H) 1.30 (t, *J*=7.02 Hz, 3 H) 1.33 - 1.56 (m, 3 H) 1.60 (s, 10 H) 1.63 - 1.83 (m, 5 H) 1.94 (br.s, 1 H) 1.98 - 2.16 (m, 3 H) 2.71 (s, 3 H) 2.82 - 2.92 (m, 1 H) 3.90 (s, 3 H) 4.28 (q, *J*=7.02 Hz, 2 H) 4.53 (d, *J*=14.95 Hz, 1 H) 5.52 (d, *J*=14.65 Hz, 1 H) 6.98 (d, *J*=2.75 Hz, 1 H) 7.03 (dd, *J*=8.85, 2.75 Hz, 1 H) 7.49 - 7.54 (m, 2 H) 7.65 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.81 (d, *J*=8.55 Hz, 1 H) 8.13 (d, *J*=1.22 Hz, 1 H).

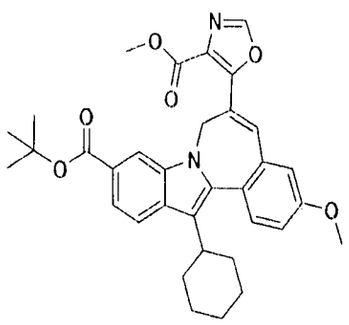
LC-MS retention time 3.08 min; 645m/z (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min , a gradient 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 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.

The scheme shown below is illustrative of methods that can be used to make intermediates and compounds.

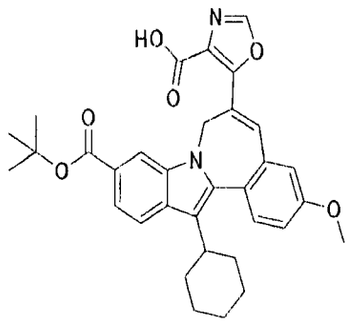


10-(tert-butoxycarbonyl)-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid. Dissolve 10-(1,1-dimethylethyl) 6-methyl 13-cyclohexyl-3-(methyloxy)-7*H*-indolo[2,1-*a*][2]benzazepine-6,10-dicarboxylate (5.53 g, 11.02 mmol) in THF (70ml) with heating, add DMF (20 ml) to maintain solubility,

allow to cool to room temperature then add tetrabutylammonium hydroxide (33.1 ml, 33.1 mmol) 1.0M in methanol. Stir reaction at room temperature for 2hrs then add 0.1N aqueous 0.1N hydrochloric acid to the reaction followed by 01M aqueous NaH2PO4. Separate phases, wash organic layer sequentially with 1.0N aqueous hydrochloric acid, 0.1M aqueous NaH2PO4. Back extract aqueous 1x using ethyl acetate. Combine ethyl acetate fractions and wash sequentially with 0.1M aqueous NaH2PO4 and brine. Dry over magnesium sulfate, filter and remove solvents *in vacuuo* to yield a bright yellow solid. Dry product *in vacuuo* at room temperature to give 5.21g (97%). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.12 - 1.28 (m, 2 H) 1.28 - 1.45 (m, 2 H) 1.46 - 1.60 (m, 2 H) 1.63 (s, 9 H) 1.66 - 1.96 (m, 4 H) 1.96 - 2.16 (m, 3 H) 2.76 - 2.84 (m, 1 H) 3.91 (s, 3 H) 4.18 (br.s., 1 H) 5.66 (br.s, 1 H) 7.00 (d, *J*=2.44 Hz, 1 H) 7.10 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 (d, *J*=8.54 Hz, 1 H) 7.65 - 7.71 (m, 1 H) 7.82 (d, *J*=8.24 Hz, 1 H) 7.93 (s, 1 H) 8.22 (s, 1 H). LC-MS retention time 1.47 min; 486 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.

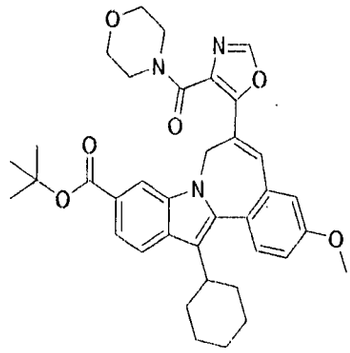


tert-Butyl 13-cyclohexyl-3-methoxy-6-(4-(methoxycarbonyl)-1,3-oxazol-5-yl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylate. 10-(*tert*-butoxycarbonyl)-13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepine-6-carboxylic acid (1.00 g, 2.051 mmol) was dissolve in DMF (10 ml) and potassium carbonate (0.624 g, 4.51 mmol)was added to the reaction followed by methyl isocyanoacetate (0.24 ml, 2.64 mmol). The reaction was stirred under a nitrogen atmosphere at room temperature for approximately 5 minutes then cooled to 0C. Diphenylphosphoryl azide (0.5 ml, 2.320 mmol) was slowly added to the reaction over 10 minutes. The reaction was stirred at 0C under a nitrogen atmosphere and allowed to slowly warm to room temperature overnight. Dilute reaction. with 100ml of benzene:ethyl acetate (1:1) and wash with water. Back extract aqueous layer using ethyl acetate. Combine organic extracts and wash successively with 0.1M aqueous citric acid, saturated aqueous sodium bicarbonate and then brine and dry over magnesium sulfate. Filter and remove volatiles *in vacuuo*. Chromatograph on 43.4g of silica gel slurry packed in 5% ethyl acetate /dichloromethane. Elute with 5% ethyl acetate / dichloromethane. Combination of pure product fractions and removal of volatiles in *vacuuo* yeilded 215mg of an amorphous yellow solid. Combination of less pure fractions yielded an additional 189mg of product with purity greater than 92%. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.11 - 1.29 (m, 2 H) 1.30 - 1.48 (m, 3 H) 1.57 (s, 2 H) 1.61 (s, 10 H) 1.69 - 1.80 (m, 2 H) 1.86 - 1.98 (m, 1 H) 1.99 - 2.13 (m, 4 H) 2.76 - 2.90 (m, 1 H) 3.92 (s, 3 H) 3.98 (s, 3 H) 4.47 (d, *J*=12.82 Hz, 1 H) 5.84 (d, *J*=14.65 Hz, 1 H) 7.02 (d, *J*=2.44 Hz, 1 H) 7.07 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 (d, *J*=8.55 Hz, 1 H) 7.65 - 7.71 (m, 1 H) 7.82 (d, *J*=8.24 Hz, 1 H) 7.87 (s, 1 H) 8.08 (s, 1 H) 8.16 (s, 1 H). LC-MS retention time 2.75 min; m/z (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 0 min, and an analysis time of 3min 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-(10-(tert-Butoxycarbonyl)-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl)-1,3-oxazole-4-carboxylic acid. *tert*-Butyl 13-cyclohexyl-3-methoxy-6-(4-(methoxycarbonyl)-1,3-oxazol-5-yl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylate (205 mg, 0.360 mmol) was dissolved in THF (3.0ml) and tetrabutylammonium hydroxide (1.1 mL, 1.100 mmol) (1.0M in methanol) was added to the reaction. The reaction was capped and stirred at room temperature for 2hrs. A 0.1M aqueous solution of NaH2PO4 was added to the reaction followed by 0.1N aqueous hydrochloric acid. The product was extracted into ethyl acetate and the organic phase washed sequentially with 0.1N aqueous hydrochloric acid, 0.1M aqueous NaH2PO4, brine and dried over magnesium sulfate. The product solution was filtered, solvent removed and product dried *in vacuuo* to yield 191mg of a yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.77 - 0.94 (m, 1 H) 1.12 - 1.31 (m, 3 H) 1.30 - 1.59 (m, 5 H) 1.62 (s, 9 H) 1.76 (d, *J*=11.29 Hz, 2 H) 1.87 - 2.18 (m, 4 H) 2.76 - 2.90 (m, 1 H) 3.91 (s, 3 H) 4.45 (d, *J*=14.04 Hz, 1 H) 6.03 (d, *J*=12.21 Hz, 1 H) 7.03 (d, *J*=2.44 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 (d, *J*=8.85 Hz, 1 H) 7.68 (d, *J*=8.24 Hz, 1 H) 7.82 (d, *J*=8.55 Hz, 1 H) 7.91 (s, 1 H) 8.21 (d, *J*=5.80 Hz, 2 H). LC-MS retention time 1.86 min; m/z 553 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 5% acetonitrile / 95% H2O / 10 mM ammonium acetate and solvent B

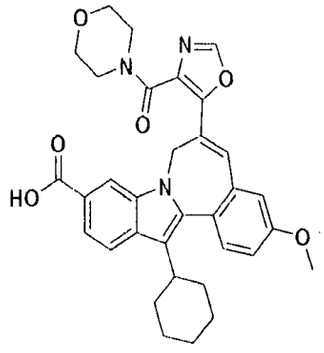
was 5% H2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.



tert-Butyl 13-cyclohexyl-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylate.

5-(10-(*tert*-Butoxycarbonyl)-13-cyclohexyl-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl)-1,3-oxazole-4-carboxylic acid (185mg, 0.334 mmol) was dissolved in DMF (3.2 ml), and O-benzotriazol-1-yl-N,N,N',N'-tetra-methyluronium tetrafluoroborate (193 mg, 0.600 mmol) was added. The reaction was stirred capped at room temperature for 25 minutes and DMAP (163 mg, 1.334 mmol) was dissolved in the reaction then morpholine (0.058 ml, 0.667 mmol) was added. The reaction was capped and stirred at room temperature overnight. The reaction was poured into 30ml of water and extracted with dichloromethane. The organic layer was washed sequentially with 0.1M aqueous citric acid, 0.1M aqueous NaH2PO4, then dried over anhydrous sodium sulfate. The sample was filtered, volatiles removed and the sample dried in vacuuo to obtain 227mg of an amorphous orange solid . 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.16 - 1.50 (m, 7 H) 1.53 - 1.61 (m, 6 H) 1.62 (s, 10 H) 1.76 (d, *J*=10.38 Hz, 2 H) 1.83 - 2.15 (m, 5 H) 3.40 - 3.84 (m, 7 H) 3.83 - 3.95 (m, 5 H) 4.40 (d, *J*=11.60 Hz, 1 H) 5.64 (d, *J*=12.21 Hz, 1 H) 6.97 (d, *J*=2.75 Hz, 1 H) 7.05 (dd, *J*=8.39, 2.59 Hz, 1 H) 7.50 (d, *J*=8.55 Hz, 1 H) 7.53 (s, 1 H) 7.65 (d, *J*=8.24 Hz, 1 H) 7.77 - 7.86 (m, 2 H) 7.97 - 8.04 (m, 1 H) 8.10 (s, 1 H). LC-MS retention time 2.64 min m/z 624 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM.

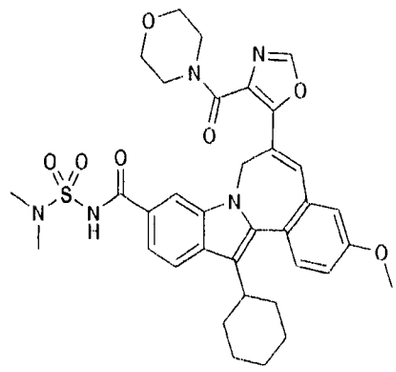
The elution conditions employed a flow rate of 5 ml/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 2 min, and an analysis time of 5 min where solvent A was 5% acetonitrile / 95% H2O / 10 mM ammonium acetate and solvent B was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



13-Cyclohexyl-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid.

Dissolve *tert*-Butyl 13-cyclohexyl-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylate (203mg, 0.325 mmol) in 1,2-dichloroethane (3 ml) add TFA (3 ml, 38.9 mmol), The reaction was capped under a nitrogen atmosphere at 25 °C for 2 hrs. Reaction volatiles were removed in vacuuo and the residue dissolved in 80mL of ethyl acetate with heating. The solution was washed with 1N aqueous hydrochloric acid (2x40mL), brine and dried over magnesium sulfate. The product solution was filtered, volatiles removed and the sample dried *in vacuuo* at room temperature overnight to give 179mg (97%) of a yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.74 - 1.03 (m, 4 H) 1.06 - 1.31 (m, 6 H) 1.32 - 1.50 (m, 3 H) 1.56 (d, *J*=9.16 Hz, 2 H) 1.77 (d, *J*=8.85 Hz, 2 H) 1.86 - 2.18 (m, 5 H) 2.83 - 2.91 (m, 1 H) 3.60 (s, 3 H) 3.64 - 3.89 (m, 4 H) 3.88 - 3.93 (m, 4 H) 3.95 - 4.08 (m, 1 H) 4.43 (d, *J*=15.56 Hz, 1 H) 5.64 (d, *J*=14.95 Hz, 1 H) 6.99 (d, *J*=2.75 Hz, 1 H) 7.07 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.48 - 7.56 (m, 2 H) 7.85 - 7.94 (m, 2 H) 8.15 (s, 1 H). LC-MS retention time1.65 min; 568 m/z (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph

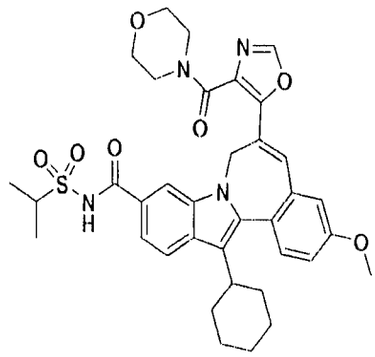
equipped with a Waters Xterra MS 7u C18 3 0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 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.



13-Cyclohexyl-N-(dimethylsulfamoyl)-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

In a 2 dram vial, 13-Cyclohexyl-3-methoxy-6-(4-(4-morpholinylcarbonyl) 1,3-oxazol-5-yl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (40 mg, 0.070 mmol) in THF (1 ml) and CDI (23.8mg, 0.147 mmol) was added to the reaction. The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 1hr. The reaction was then heated at 60C for 1hr, cooled and N,N-Dimethylsulfamide (46.5 mg, 0.375 mmol) was added to the reaction followed by DBU (0.014 ml, 0.092 mmol). The reaction was capped under a nitrogen atmosphere and heated overnight(16hrs) at 60C. The reaction was monitored by HPLC and additional N,N-Dimethylsulfamide (22.9 mg, 0.184 mmol) and DBU (0.015 ml, 0.099 mmol) was added and the reaction heated to 70C under a nitrogen atmosphere for 5hrs. The reaction mixture was partitioned between 1N aqueous hydrochloric acid and dichloromethane. The organic phase was washed sequentially with 1N

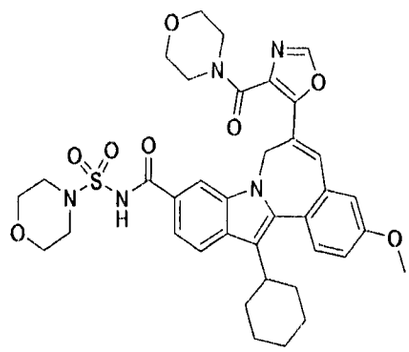
aqueous hydrochloric acid and 0.1M aqueous NaH2PO4 and dried over sodium sulfate. Solvent was removed *in vacuuo* to yield 46mg of crude product. The title compound was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software and interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 12 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.05 - 1.28 (m, 1.2 H) 1.29 - 1.62 (m, 3.7 H) 1.64 - 1.84 (m, 4.0 H) 1.84 - 2.20 (m, 4.6 H) 2.47 (d, *J*=14.04 Hz, 0.1 H) 2.78 - 2.88 (m, 1.1 H) 3.04 (s, 5.9 H) 3.10 (s, 0.9 H) 3.35 - 3.89 (m, 9.0 H) 3.91 (s, 3.0 H) 4.09 (s, 0.4 H) 4.18 (d, *J*=1.83 Hz, 0.9 H) 4.41 (d, *J*=15.56 Hz, 0.9 H) 4.55 (d, *J*=16.48 Hz, 0.1 H) 5.59 (d, *J*=14.95 Hz, 0.9 H) 6.62 (d, *J*=14.34 Hz, 0.1 H) 6.97 (d, *J*=2.44 Hz, 1.0 H) 7.07 (dd, *J*=8.70, 2.59 Hz, 1.0 H) 7.27 - 7.36 (m, 0.3 H) 7.46 - 7.54 (m, 1.9 H) 7.59 (d, *J*=8.55 Hz, 0.9 H) 7.75 (d, *J*=7.93 Hz, 0.1 H) 7.82 (s, 1.0 H) 7.87 (d, *J*=8.54 Hz, 0.9 H) 8.15 (s, 0.1 H) 8.28 - 8.35 (m, 0.2 H) 8.44 (s, 0.9 H) 8.94 (d, *J*=9.16 Hz, 0.1 H) 9.43 (s, 0.9 H) 9.88 (s, 0.1 H) 12.11 (s, 0.1 H). LC-MS retention time 1.40min; 672 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.



13-cyclohexyl-N-(isopropylsulfonyl)-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

13-Cyclohexyl-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (40.8mg, 0.072 mmol) was dissolved in THF(1ml) and CDI (26 mg, 0.160 mmol) added to the reaction. The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 50min then heated in an oil bath at 60C for 1.5hrs. The reaction was cooled and propane-2-sulfonamide (46 mg, 0.373 mmol) was added to the reaction followed by DBU (0.022 ml, 0.144 mmol). The reaction was capped under a nitrogen atmosphere and heated at 65C overnight (16hr). The reaction was partitioned between dichloromethane and 1.0N aqueous hydrochloric acid. The organic layer was washed sequentially with 1N aqueous hydrochloric acid, 0.1M aqueous NaH2PO4. The organic layer was dried over sodium sulfate and solvent removed in vacuuo to yield 50mg of an amorphous yellow solid. The title was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 12 minutes with a run time of 15 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Removal of solvents and drying

in vacuuo yielded 28.3mg of a yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.15 - 1.28 (m, 1.2 H) 1.29 - 1.60 (m, 10.9 H) 1.59 - 1.85 (m, 6.7 H) 1.86 - 2.15 (m, 4.7 H) 2.78 - 2.87 (m, 1.0 H) 3.37 - 3.50 (m, 1.4 H) 3.51 - 3.89 (m, 7.3 H) 3.91 (s, 3.3 H) 4.02 - 4.12 (m, 1.5 H) 4.15 - 4.26 (m, 0.9 H) 4.42 (d, *J*=13.73 Hz, 0.9 H) 4.54 (d, *J*=15.26 Hz, 0.1 H) 5.54 (d, *J*=14.65 Hz, 0.9 H) 6.57(d, *J*=14.04Hz, 0.1H) 6.97 (d, *J*=2.44 Hz, 0.9 H) 7.07 (dd, *J*=8.55, 2.44 Hz, 1.0 H) 7.28 - 7.35 (m, 0.3 H) 7.48 - 7.54 (m, 2.0 H) 7.62 - 7.67 (m, 1.0 H) 7.75 (d, *J*=7.93 Hz, 0.1 H) 7.82 (s, 1.0 H) 7.87 (d, *J*=8.55 Hz, 1.0 H) 8.21 (s, 0.9 H) 8.31 (s, 0.2 H) 8.48 (s, 1.0 H) 8.94 (d, *J*=9.15 Hz, 0.1 H) 9.46 (s, 0.9 H) 9.86 (s, 0.1 H). LC-MS retention time 1.26 min; 671 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.

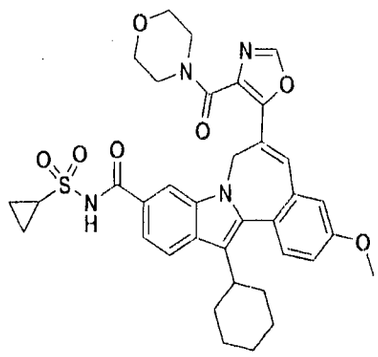


13-cyclohexyl-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-N-(4-morpholinylsulfonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

13-Cyclohexyl-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (40.8mg, 0.072 mmol) was dissolved in THF(1ml) and CDI (26 mg, 0.160 mmol) added to the reaction. The

reaction was capped under a nitrogen atmosphere and stirred at room temperature for 50min then heated in an oil bath at 60C for 1.5hrs. The reaction was cooled and propane-2-sulfonamide (46 mg, 0.373 mmol) was added to the reaction followed by DBU (0.022 ml, 0.144 mmol). The reaction was capped under a nitrogen atmosphere and heated at 65C overnight (16hr). The reaction was partitioned between dichloromethane and 1.0N aqueous hydrochloric acid. The organic layer was washed sequentially with 1N aqueous hydrochloric acid, 0.1M aqueous NaH2PO4. The organic layer was dried over sodium sulfate and solvent removed in vacuuo to yield 50mg of an amorphous yellow solid. The title was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 12 minutes with a run time of 15 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Removal of solvents and drying *in vacuuo* yielded 28.3mg of a yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.15 - 1.28 (m, 1.3 H) 1.30 - 1.46 (m, 2.4 H) 1.48 - 1.61 (m, *J*=16.48 Hz, 1.2 H) 1.77 (d, *J*=9.77 Hz, 2.3 H) 1.87 - 2.15 (m, 4.8 H) 2.22 - 2.52 (m, 4.6 H) 2.78 - 2.90 (m, 1.1 H) 3.37 - 3.72 (m, 8.9 H) 3.76 (s, 6.2 H) 3.80 - 3.89 (m, 3.2 H) 3.91 (s, 3.6 H) 4.08 (s, 0.3 H) 4.13 - 4.23 (m, 1.0 H) 4.42 (d, *J*=13.73 Hz, 0.9 H) 4.65 (d, *J*=14.95 Hz, 0.1 H) 5.55 (d, *J*=14.04 Hz, 1.0 H) 6.97 (d, *J*=2.44 Hz, 1.0 H) 7.07 (dd, *J*=8.70, 2.59 Hz, 1.0 H) 7.27 - 7.33 (m, 0.2 H) 7.38 (s, 0.1 H) 7.46 - 7.55 (m, 2.0 H) 7.60 (d, *J*=9.77 Hz, 1.0 H) 7.78 (d, *J*=8.24 Hz, 0.1 H) 7.83 (s, 1.0 H) 7.87 (d, *J*=8.55 Hz, 1 H) 8.07 (s, 0.1 H) 8.10 (d, *J*=4.27 Hz, 0.1 H) 8.31 (d, *J*=8.54 Hz, 0.1 H) 8.42 (s, 0.9 H) 8.94 (d, *J*=9.16 Hz, 0.1 H) 9.55 (s, 0.9 H) 9.60 (s, 0.1 H). LC-MS retention time 1.63 min;714 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.

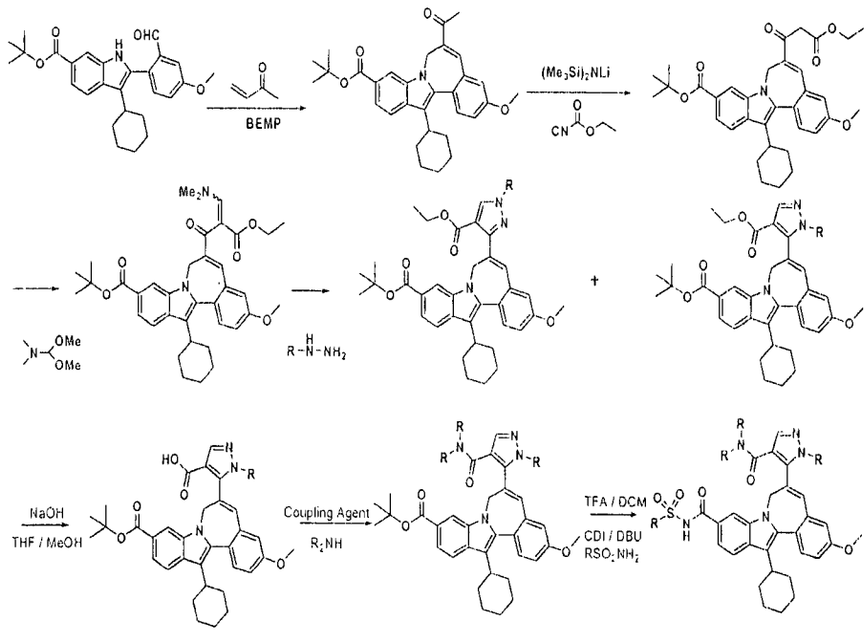


13-cyclohexyl-N-(cyclopropylsulfonyl)-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

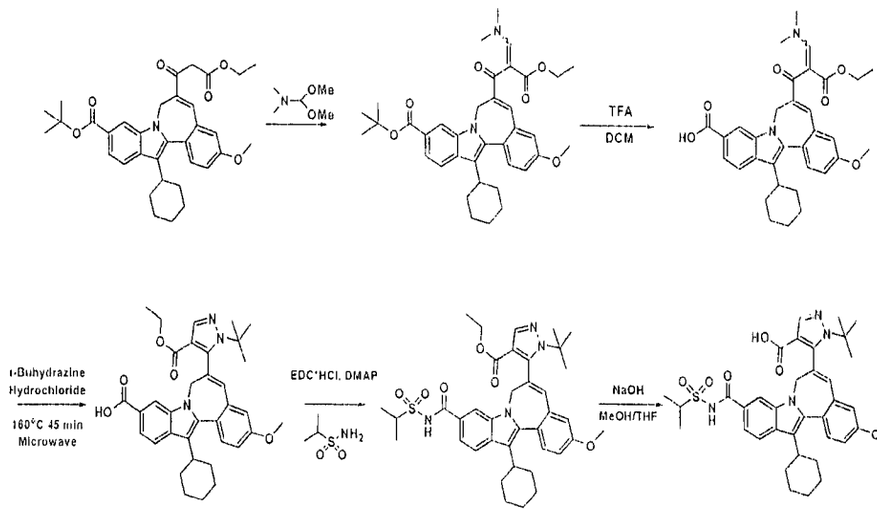
13-Cyclohexyl-3-methoxy-6-(4-(4-morpholinylcarbonyl)-1,3-oxazol-5-yl)-7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid (40mg, 0.070 mmol) was dissolved in THF(1ml) and CDI (26 mg, 0.160 mmol) added to the reaction. The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 1hr 50min then heated in an oil bath at 65C for 1hr 10min. The reaction was cooled and cyclopropanesulfonamide (48 mg, 0.396 mmol) then DBU (0.022 ml, 0.146 mmol) was added to the reaction. The reaction was capped under a nitrogen atmosphere and heated at 68C overnight (18hr). The reaction was partitioned between dichloromethane and 1.0N aqueous hydrochloric acid. The organic layer was washed sequentially with 1N aqueous hydrochloric acid, 0.1M aqueous NaH2PO4. The organic layer was dried over sodium sulfate and solvent removed in vacuuo to yield 62mg of an amorphous yellow solid. The title was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored

using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Removal of solvents and drying *in vacuuo* yielded 30.8mg of the title compound as a yellow amorphous solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.99 - 1.28 (m, 4.0 H) 1.29 - 1.45 (m, 3.9 H) 1.47 - 1.68 (m, 7.9 H) 1.75 (m, 2.3 H) 1.84 - 2.17 (m, 4.5 H) 2.77 - 2.88 (m, 1.0 H) 3.14 - 3.23 (m, 1.2 H) 3.33 - 3.89 (m, 8.3 H) 3.91 (s, 3.3 H) 4.09 (s, 0.5 H) 4.17 (s, 0.9 H) 4.42 (d, *J*=14.34 Hz, 0.9 H) 5.54 (d, *J*=15.56 Hz, 0.9 H) 6.60 (d, 0.1 H) 6.97 (d, *J*=2.44 Hz, 1.0 H) 7.07 (dd, *J*=8.55, 2.75 Hz, 1.0 H) 7.27 - 7.35 (m, 0.3 H) 7.49 (s, 1.0 H) 7.52 (d, *J*=8.85 Hz, 1.0 H) 7.64 (dd, *J*=8.55, 1.53 Hz, 1.0 H) 7.75 (d, *J*=7.94 Hz, 0.2 H) 7.82 (s, 1.0 H) 7.87 (d, *J*=8.55 Hz, 1.0 H) 8.21 (s, 0.1 H) 8.31 - 8.36 (m, 0.3 H) 8.43 (d, *J*=1.53 Hz, 1.0 H) 8.95 (d, *J*=9.16 Hz, 0.2 H) 9.61 (s, 1.0 H) 9.82 (s, 0.1 H). LC-MS retention time 1.59 min; 669 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.

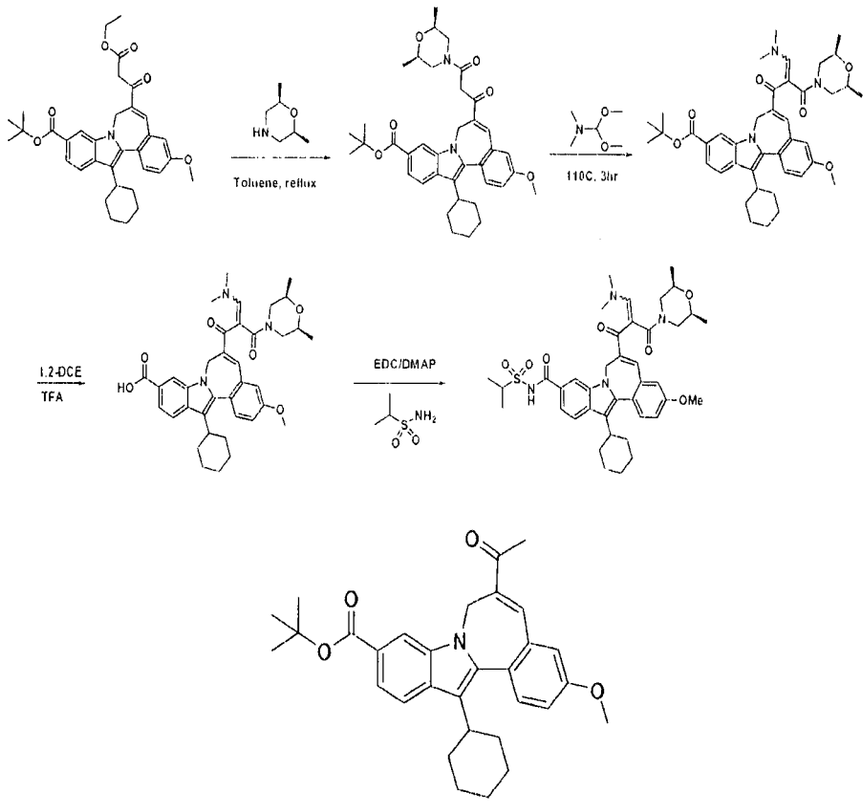
The scheme depiced below is illustrative of methods that can be used to make intermediates and compounds.



An additional variation in the methodology that can be employed for the synthesis of intermediates and compounds is shown in the following scheme.



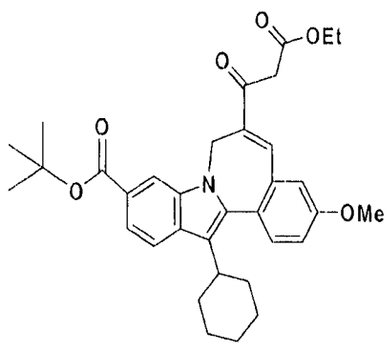
A further variation of the methodology that can be used for the synthesis of further intermediates and compouns is depicted the the scheme shown below.



tert-Butyl 6-acetyl-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate.

To a suspension of tert-butyl 3-cyclohexyl-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxylate (2 g, 4.61 mmol) in dioxane (9.2 mL) add 2-tert-butylimino-2-diethylamino-1,3-di- methylperhydrodiazaphosphorine (2.00 mL, 6.92 mmol) then but-3-en-2-one (0.756 mL, 9.23 mmol) in a 20ml microwave vessel. Cap the heterogenous reaction under nitrogen and heat in the microwave at 120C for 40 minutes. This reaction was repeated two more times on the above scale and one last time with tert-butyl 3-cyclohexyl-2-(2-formyl-4-methoxyphenyl)-1H-indole-6-carboxylate (2.51g, 5.79mmol) dissolved in dioxane (11.5ml), add BEMP (2.5ml, 8.64 mmol) followed by but-3-en-2-one (0.95ml, 11.46 mmol). Each reaction segment was worked up while the next sequence was running in the microwave. Work up consisted of partitioning the reaction between ethyl acetate and 1N aqueous hydrochloric acid in a 250ml separatory funnel. The aqueous phase was back extracted once with ethyl acetate and the organic phases combined and washed sequentially with 1N aqueous hydrochloric acid, 0.1M NaH2PO4, and brine. The

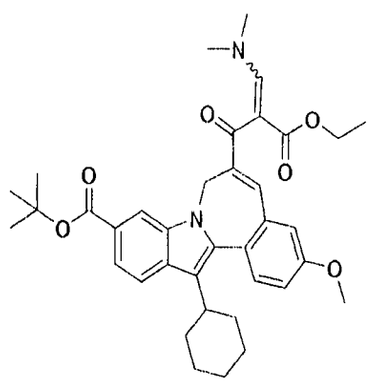
solution was then combined with a previous workup in a 1L erlenmeyer flask containing magnesium sulfate. Filter and remove volatiles, dry *in vacuuo* at room temperature overnight to obtain 10.67g of a yellow-orange foam. Adsorb the crude product onto 25g of silica gel using dichloromethane, removing volatiles *in vacuuo*. Chromatograph on 299g of silica gel slurry packed in 20% ethyl acetate in hexanes and eluting with 20% ethyl acetate in hexanes. Pure product fractions from the chromatography were combined and solvents removed *in vacuuo*. The residue was dissolved in benzene and removed *in vacuuo* to aid in the removal of trace ethyl acetate. The title compound as a yellow foam/ amorphous solid was dried *in vacuuo* overnight at room temperature to yield 6.83g (71.7%). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.12 - 1.29 (m, 1 H) 1.30 - 1.61 (m, 4 H) 1.64 (s, 10 H) 1.67 - 2.00 (m, 4 H) 1.98 - 2.19 (m, 3 H) 2.43 (s, 3 H) 2.75 - 2.87 (m, 1 H) 3.85 - 4.01 (m, 4 H) 5.86 (s, 1 H) 7.00 (d, *J*=2.75 Hz, 1 H) 7.11 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.35 (s, 1.8 H, benzene) 7.69 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.82 (d, *J*=8.24 Hz, 1 H) 8.24 (s, 1 H). LC-MS retention time 3.28 min; m/z (MH+). 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 30% solvent A / 70% solvent B to 0% solvent A / 100% solvent B, a gradient time of 5min, a hold time of 1 min, and an analysis time of 6 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.



7H-Indolo[2,1-a][2]benzazepine-6-propanoic acid, 13-cyclohexyl-10-[(1,1-dimethylethoxy)carbonyl]-3-methoxy-beta-oxo-, ethyl ester.

To a solution of 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 6-acetyl-13-cyclohexyl-3-methoxy-, 1,1-dimethylethyl ester (2.50 g, 5.15 mmol) in THF (15.0 mL) was added a 1M solution of LHMDS (5.41 mL, 5.41 mmol) in THF at -78 °C and stirred for 15 min. Ethyl cyanoformate (0.510 mL, 5.15 mmol) was added at -78 °C to the resulting solution and stirring continued for 30 min. Saturated aqueous NH_4Cl (50 mL) was added and the aqueous layer was extracted with $CHCl_3$ (2 x 50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel chromatography (2:1 methylene chloride:hexanes) of the concentrate afforded the title compound (1.75 g, 61%) as a yellow oil. MS m/z 558 (MH^+). A previous reaction which was run in an analogous fashion to the above reaction and in which starting material 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 6-acetyl-13-cyclohexyl-3-methoxy-, 1,1-dimethylethyl ester was still present was separated under the following conditions: This procedure describes the separation of tert-butyl 13-cyclohexyl-6-(3-ethoxy-3-oxopropanoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (desired product) from the starting material ketone, tert-butyl 6-acetyl-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate. Total weight of materials was estimated to be 2.6g. 3.9g of an the sample mixture as an orange oil was dissolved in dichloromethane and adsorbed on 10g of silica gel. The volatiles were removed *in vacuuo* using a rotoary evaporator. The sample adsorbed onto silica gel was applied to a column of 294g of silica gel which was slurry packed in 30% diethyl ether in hexanes. A bed of sand was placed on top of the adsorbed sample to aid in solvent addition. The approximate size of the silica gel column packing was 75mm diameter x 175mm in height. The product was eluted using a gradient of 30% diethyl ether in hexanes to 35% diethyl ether in hexanes to 40% diethyl ether in hexanes. Elute with approximately 1L of 30%Et2O/hexanes, then 1L of 35%Et2O/hexanes, and finally using 40%Et2O/hexanes. The volumes of fractions collected were approximately 125ml to 150ml. The product fractions were combined and volatiles removed and the title keto-ester dried *in vacuuo* to yield 1.63g of a yellow-orange amorphous solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.12 (t, *J*=7.02 Hz, 2.5 H) 1.15 - 1.28 (m, 1.6 H) 1.32 (q, *J*=7.12 Hz, 1.0 H) 1.35 - 1.43 (m, 1.5 H) 1.59 (s, 1.5

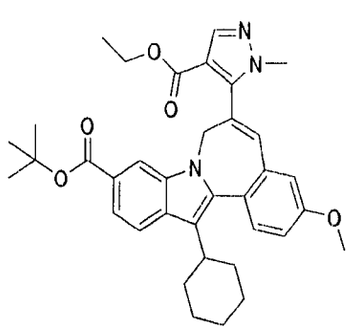
H) 1.61 - 1.69 (m, 9.4 H) 1.72 - 1.82 (m, 2.0 H) 1.94 (s, 1.2 H) 2.04 (s, 2.9 H) 2.76 - 2.85 (m, 1.0 H) 3.64 - 3.79 (m, 0.8 H) 3.88 (s, 0.7 H) 3.90 (s, 0.7 H) 3.92 (s, 2.6 H) 3.94 - 4.06 (m, 0.7 H) 4.12 (q, *J*=7.22 Hz, 1.9 H) 4.21 - 4.33 (m, 0.7 H) 4.39 (q, *J*=7.12 Hz, 0.2 H) 5.67 (s, 0.2 H) 5.71 - 5.90 (m, 0.7 H) 6.95 - 7.02 (m, 1.0 H) 7.06 (dd, *J*=8.55, 2.75 Hz, 0.2 H) 7.12 (dd, *J*=8.70, 2.59 Hz, 0.82 H) 7.46 - 7.57 (m, 1.2 H) 7.64 (s, 0.8 H) 7.69 (d, *J*=8.55 Hz, 0.9 H) 7.76 - 7.85 (m, 0.9 H) 8.14 (s, 0.2 H) 8.22 (s, 0.8 H) 12.40 (s, 0.1 H). LC-MS retention time 2.78 min; 556 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.

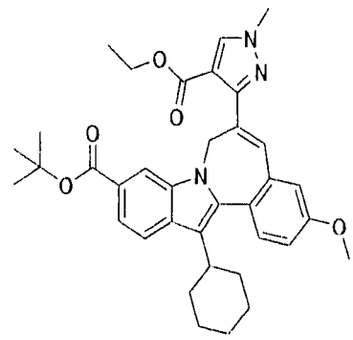


tert-Butyl 13-cyclohexyl-6-((2E,Z)-3-(dimethylamino)-2-(ethoxycarbonyl)-2-propenoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate.

tert-Butyl 13-cyclohexyl-6-(3-ethoxy-3-oxopropanoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (1.63 g, 2.92 mmol) was dissolved in N,N-dimethylformamide dimethyl acetal (7.0 mL, 52.7 mmol) in a 50ml round bottom flask. The reaction was maintained under a nitrogen atmosphere and heated in oil bath under refluxing conditions (110°C) for 2.75hrs. The reaction was then cooled reaction under a nitrogen atmosphere and the volatiles were evaporated *in*

vacuuo to give an orange colored foam. TLC analysis (SiO2 plate, elution- 50% diethyl ether in hexanes) confirmed that the reaction had gone to completion. This material was dried *in vacuuo* at room temperature overnight to yield 1.87g of the enamine intermediate as an orange amber foam which was used in the next step without any further purification. LC-MS of intermediate enamine: LC-MS retention time 2.81 min; 613 m/z (MH+). 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.





7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester and 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]-3-methoxy-, 1,1-dimethylethyl ester.

The intermediate enamine, tert-butyl 13-cyclohexyl-6-((2E,Z)-3-(dimethylamino)-2-(ethoxycarbonyl)-2-propenoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate, (1.83 g, 2.99 mmol) was dissolved in absolute ethanol (10 mL). Within a few minutes of dissolution in ethanol the reaction became heterogeneous with a fine yellow/orange precipitate forming. Methylhydrazine (0.173 mL, 3.29 mmol) was added to the reaction and the reaction was placed under a

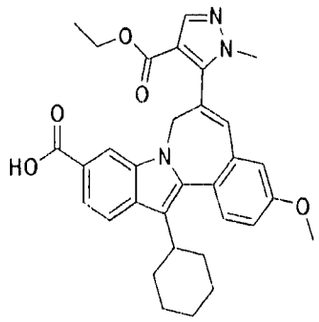
nitrogen atmosphere with a condenser. The reaction was heated to 80C and remained heterogeneous at 80C. An additional 5ml of absolute ethanol was added and the reaction stirred at 80C for 15minutes. The reaction was still heterogeneous and 1,4-dioxane (5ml) was added and the reaction slowly became homogeneous. The reaction was heated for 2 hours then cooled and the volatiles removed *in vacuuo* to obtain an orange amber foam. The residue was dissolved in benzene and then volatiles removed in vacuuo and the sample was dried at room temperature overnight *in vacuuo* to yield 1.79g of a yellow amorphous solid/foam. LC-MS analysis indicated two possible isomeric products. 102mg of the crude product was purified by reverse phase prep HPLC. The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (4ml) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 25% solvent A / 75% solvent B to 0% solvent A / 100% solvent B, a gradient time of 10 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. First eluting product is 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester with retention time of 11.7minutes with the minor component product being 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]-3-methoxy-, 1,1-dimethylethyl ester with a retention of 14.5 minutes.

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.13 - 1.27 (m, 1 H) 1.30 (t, *J*=7.02 Hz, 3 H) 1.34 - 1.55 (m, 3 H) 1.58 (s, 9 H) 1.61 - 1.84 (m, 3 H) 1.85 - 2.00 (m, 1 H) 1.99 - 2.18 (m, 3 H) 2.86 (t, *J*=11.75 Hz, 1 H) 3.28 (s, 3 H) 3.90 (s, 3 H) 4.27 (d, *J*=4.27 Hz, 2 H) 4.71 (s, 1 H) 4.97 (s, 1 H) 6.77 (s, 1 H) 6.93 (d, *J*=2.44 Hz, 1 H) 7.07 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.65 (d, *J*=8.55 Hz, 1 H) 7.79 - 7.88 (m, 2 H) 7.97 (s, 1 H).

LC-MS retention time 3.92min; 596 m/z (MH+). 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 70% solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 5min, a hold time of 1 min, and an analysis time of 6 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.

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]-3-methoxy-, 1,1-dimethylethyl ester. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.13 - 1.26 (m, 1 H) 1.30 (t, *J*=7.17 Hz, 3 H) 1.33 - 1.60 (m, 3 H) 1.61 (s, 9 H) 1.64 - 1.83 (m, 3 H) 1.91 (s, 2 H) 1.98 - 2.16 (m, 3 H) 2.82 - 2.91 (m, 1 H) 3.90 (s, 3 H) 3.94 (s, 3 H) 4.20 - 4.30 (m, 2 H) 4.41 (d, *J*=14.04 Hz, 1 H) 5.76 (d, *J*=14.04 Hz, 1 H) 6.96 - 7.03 (m, 2 H) 7.49 - 7.54 (m, 1 H) 7.64 (dd, *J*=8.39, 1.37 Hz, 1 H) 7.79 (d, *J*=8.55 Hz, 1 H) 7.84 (s, 1 H) 7.90 (s, 1 H) 8.26 (s, 1 H). LC-MS retention time 4.26min; 596 m/z (MH+). 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 70% solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 5min, a hold time of 1 min, and an analysis time of 6 min where solvent A was 5% acetonitrile / 95% H2O / 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. The remainder of the sample (1.615g) was adsorbed onto 4g of silica gel using dichloromethane and chromatographed on 50g of silica gel slurry packed using 2% ethyl acetate in dichloromethane and eluting with 2% ethyl acetate in dichloromethane. The first component to elute is the minor product, 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]-3-methoxy-, 1,1-dimethylethyl ester, 179mg isolated. The second component, 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-

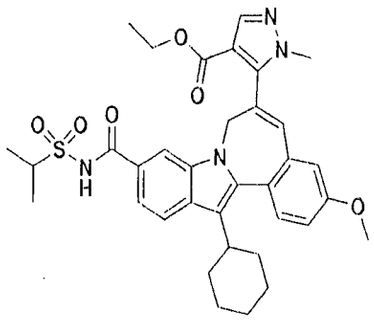
cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester was the major component to elute and yielded 966mg.



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-.

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester (53 mg, 0.089 mmol) was dissolved in 1,2-dichloroethane (2 mL), under a nitrogen atmosphere. Tifluoroacetic acid was then added (2 ml, 26.0 mmol), and the reaction was stirred at room temperature for 2.5 hours. The volatiles were then removed in vacuuo and the residue dissolved in benzene and the resultant solution was evaporated under reduced pressure to remove residual TFA. This process was repeated once. This gave the title compound as a yellow solid, (46.2mg). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.12 - 1.26 (m, 1 H) 1.31 (t, *J*=7.02 Hz, 3 H) 1.40 (s, 2 H) 1.51 - 1.89 (m, 3 H) 1.87 - 2.23 (m, 4 H) 2.87 (t, *J*=11.29 Hz, 1 H) 3.29 (s, 3 H) 3.91 (s, 3 H) 4.27 (br.s, 2 H) 4.73 (br.s, 1 H) 4.97 (br.s, 1 H) 6.78 (s, 1 H) 6.94 (d, *J*=2.14 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.54 (d, *J*=8.85 Hz, 1 H) 7.77 (d, *J*=8.24 Hz, 1 H) 7.86 - 7.95 (m, 2 H) 7.98 (s, 1 H) 8.36 (br.s, 2 H). LC-MS retention time 1.84 min; 538 m/z (MH-). 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 70% solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 5min, a hold time of 0 min, and an analysis time of 5 min where solvent A was 5% acetonitrile / 95% H2O / 10 mM ammonium acetate and solvent B was 5% H_2O /

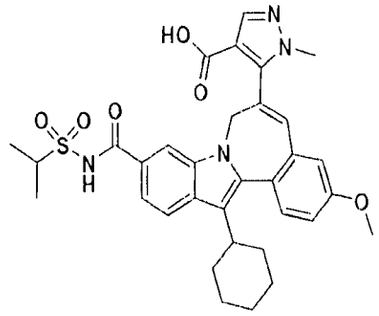
95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.



1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester.

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy- (981mg, 1.818 mmol) was dissolved in THF (18 mL). Carbonyldiimidazole (649 mg, 4.00 mmol) was added to the reaction. The reaction was placed under a nitrogen atmosphere and stirred at room temperature for 45minutes then heated to reflux for 1 hour. The reaction was cooled under a nitrogen atmosphere and propane-2-sulfonamide (1164 mg, 9.45 mmol) was added to the reaction followed by DBU (0.548 mL, 3.64 mmol). The reaction was then immersed in oil bath at 80°C under nitrogen atmosphere and heated overnight at 70-80°C. The reaction was then diluted with ethyl acetate and the organic layer washed sequentially with 1.0 N aqueous hydrochloric acid, 0.1M aqueous NaH_2PO_4 and brine. The organic layer was dried over $MgSO_4$, filtered and volatiles removed *in vacuuo* to yield a yellow foam which was dried *in vacuuo* at room temperature overnight to yield 1.170g of a yellow amorphous solid. Proton NMR analysis revealed the presence of propane-2-sulfonamide (1.41ppm, d, 500MHz, CDCl3) in the sample. The crude sample was dissolved in approximately 200ml of dichloromethane and washed 2 x with 125ml of water, then sequentially with 1N aqueous hydrochloric acid, 2 x with 0.1M NaH2PO4 then again with 1N aqueous hydrochloric acid. The dichloromethane solution was dried over sodium sulfate, filtered and volatiles removed and the product dried *in vacuuo* at room

temperature overnight to yield 1.046g (89%) of the title compound as a yellow amorphous solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.80 - 0.90 (m, 1 H) 1.20 - 1.27 (m, 4 H) 1.30 (t, *J*=7.02 Hz, 4 H) 1.32 - 1.43 (m, 3 H) 1.46 (d, *J*=7.02 Hz, 6 H) 1.53 - 1.64 (m, 3 H) 1.79 (d, *J*=9.77 Hz, 3 H) 1.85 - 2.13 (m, 5 H) 2.81 - 2.91 (m, 1 H) 3.90 (s, 3 H) 4.00 - 4.10 (m, 1 H) 4.24 (s, 2 H) 4.71 (d, *J*=12.21 Hz, 1 H) 4.99 (d, *J*=16.48 Hz, 1 H) 6.77 (s, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.38 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.52 (d, *J*=8.85 Hz, 1 H) 7.76 (d, *J*=1.22 Hz, 1 H) 7.86 - 7.92 (m, 2 H) 8.26 (br.s, 1 H). LC-MS retention time 1.79 min; 643 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.



1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-.

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester (1.044 g, 1.619 mmol) was dissolved in THF (11 ml) with heating. DMF was then added (5 mL) and the mixture was gently heated to ensure dissolution. The mixture was then cooled to room temperature and

tetrabutylammonium hydroxide (6.5 ml, 6.50 mmol) (1.0M in methanol) was added. The resultant mixture was then stirred at room temperature under nitrogen for 2.5hrs and progress was monidered by LC-MS. Results showed predominately methyl and ethyl esters. The mixture was then stirred for an additional 3hrs, after which a further 2.0mL (2mmol) of tetrabutylammonium hydroxide(1.0M in methanol) was added and the reaction was stirred at room temperature under nitrogen for a further 2 days. Subsequent analysis shows reaction had proceeded to approximately 22% conversion to the desired acid product. Volatiles (methanol, ethanol, THF) were removed from the reaction *in vacuuo* (30°C) using a rotary evaporator. To the reaction was added 200uL of 10N aqueous sodium hydroxide and 4 ml of THF. The reaction was mixed by placing on rotary evaporator, gently heated (25°C, 3hrs) then add approximately 6ml of DMF and heat at 35C for3hrs and using house vacuum to remove volatiles generated from hydrolysis. Analysis of the reaction by LC-MS indicated approximately 83% conversion to acid product. The reaction was stirred overnight at room temperature and subsequent analysis showed no additional conversion to product. An additional 4.0ml of 1.0M tetrabutylammonium hydroxide in methanol was added to the reaction. The reaction was placed on a rotary evaporator and volatiles removed *in vacuuo* and the reaction continued to heat at 40-45C for approximately 6 hours. The reaction was then worked up by adding 1N aqueous hydrochloric acid (100ml) into the reaction and then the mixture was rinsed into a 500ml sepratory funnel using ethyl acetate bring the organic volume to approx. 200ml. Partition the reaction between ethyl acetate and 1.0N aqueous hydrochloric acid. The organic layer was wash 3x (~300ml each) with 1.0N aqueous hydrochloric acid, then brine and dried over MgSO4, filtered and the volatiles removed *in vacuuo* to yield 1.03g of a yellow film foam. The sample was dried in vacuuo at room temperature to 0.92g (92%) of the title compound. LC-MS retention time 1.48 min; 615 m/z (MH-). 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 5% acetonitrile / 95% H2O / 10 mM ammonium acetate and solvent B was 5% H2O / 95% acetonitrile

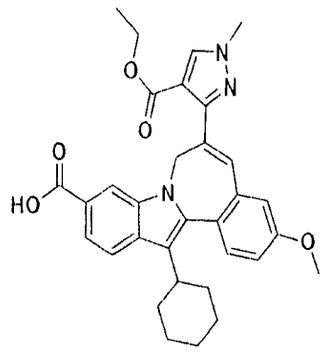
/ 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.

An alterantive procedure for the preparation of the title compound is described below.

Dissolve 1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester (1.044 g, 1.619 mmol) in a pre-mixed solution of THF(20 mL), MeOH (20 mL) and sodium hydroxide (20 mL, 20.00 mmol). The reaction was homogenous and was stirred at room temperature under a nitrogen atmosphere for 26hrs then concentrated in vacuuo using a rotary evaporator with a bath temperature at 20C. The reaction was poured into 1N aqueous hydrochloric acid and extract using ethyl acetate. The combined organic layers were washed sequentially with 1N aqueous hydrochloric acid and brine, then dried over magnesium sulfate, filtered and solvent removed *in vacuuo*. The crude product dried *in vacuuo* at room temperature to yield 1.68g of an orange amorphous solid. The crude product was dissolved in chloroform (approximately 50mL) with heating and hexanes were added until some material starts to precipitate but re-dissolves on swirling (approximately 10-12ml of hexanes). The mixture was allowed to slowly cool to room temperature and then allowed to stand at room temperature for a few hours. The very fine particulate yellow precipitate was filtered using a Buchner funnel and dried in vacuuo at room temperature to yield 819mg (45%) of purified product as a bright yellow amorphous solid. The title compound 4.6mg was dissolved in CDCl3 (2ml) with the addition of approximately 5 drops of CD3OD to aid in dissolution for 1H NMR acquisition. 1H NMR (500 MHz, CHLOROFORM-D / CD3OD) δ ppm 1.11 - 1.39 (m, 3 H) 1.41 (d, *J*=7.02 Hz, 6 H) 1.47 - 1.65 (m, 1 H) 1.75 (d, *J*=8.85 Hz, 2 H) 1.82 - 2.27 (m, 13 H) 2.77 - 2.90 (m, 1 H) 3.28 (s, 3 H) 3.88 (s, 3 H) 3.97 - 4.06 (m, 1 H) 4.66 (s, 1 H) 5.01 (s, 1 H) 6.76 (s, 1 H) 6.92 (d, *J*=2.75 Hz, 1 H) 7.04 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.47 - 7.54 (m, 2 H) 7.81 (d, *J*=1.22 Hz, 1 H) 7.86 (d, *J*=8.54 Hz, 1 H) 7.91 (s, 1 H)

LC-MS retention time 1.39 min; 615 m/z (MH-). 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

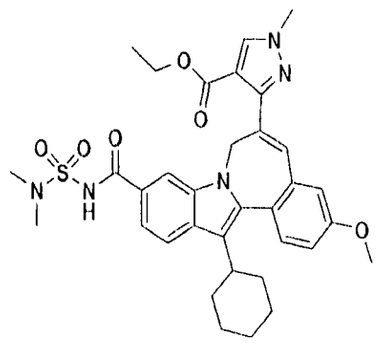
length of 220nM. The elution conditions employed a flow rate of 5 ml/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% acetonitrile / 95% H2O / 10 mM ammonium acetate 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]-3-methoxy-.

Dissolve 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]-3-methoxy-, 1,1-dimethylethyl ester (176 mg, 0.295 mmol) in 1,2-dichloroethane (3 mL), place reaction under a nitrogen atmosphere, then add trifluoroacetic acid (3 ml, 38.9 mmol). Stir the reaction at room temperature under a nitrogen atmosphere for 2hr 20min then remove volatiles *in vacuuo*. Dissolve product in a mixture of benzene and dichloromethane then remove volatiles *in vacuuo*. Repeat dissolution in benzene and dichloromethane and remove volatiles to aid in removal of trace trifluoroacetic acid. The title compound was dried *in vacuuo* at room temperature to yield 164mg of a yellow amorphous solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.01 - 1.29 (m, 3 H) 1.32 (t, *J*=7.17 Hz, 3 H) 1.35 - 1.53 (m, 2 H) 1.52 - 1.85 (m, 3 H) 1.86 - 2.20 (m, 4 H) 2.79 - 2.95 (m, 1 H) 3.91 (s, 3 H) 3.97 (s, 3 H) 4.27 (q, *J*=7.22 Hz, 2 H) 4.41 (d, *J*=14.34 Hz, 1 H) 5.84 (d, *J*=14.34 Hz, 1 H) 6.97 - 7.08 (m, 2 H) 7.54 (d, *J*=8.24 Hz, 1 H) 7.76 (d, *J*=8.55 Hz, 1 H) 7.85 (d, *J*=8.54 Hz, 1 H) 7.91 (s, 1 H) 7.95 (s, 1 H) 8.50 (s, 1 H). LC-MS retention time 2.08 min; 538 m/z (MH-). LC data was

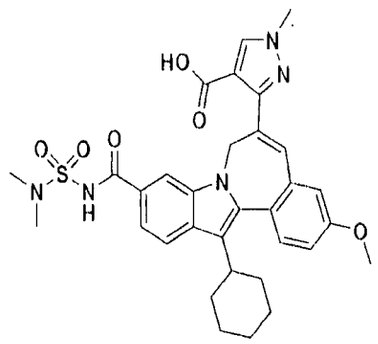
recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min , a gradient of 70% solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 5min, a hold time of 1 min, and an analysis time of 6 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.



1H-pyrazole-4-carboxylic acid, 3-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester.

Dissolve 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]-3-methoxy- (60mg, 0.111 mmol) in THF (1.0 mL), then add carbonyl diimidazole (42 mg, 0.259 mmol) to the reaction. The reaction was stirred under a nitrogen atmosphere for 1 hour at room temperature. The reaction was then heated at 70C for 1 hour then cooled and N,N-dimethylsulfamide (70 mg, 0.564 mmol) was added to the reaction followed by DBU (0.034 mL, 0.222 mmol). The reaction was again capped under a nitrogen atmosphere and heated at 70C for 16.5 hours. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid, 0.1M aqueous NaH2PO4 and again with 1.0N aqueous hydrochloric acid, and finally with brine. The organic phase was dried over magnesium sulfate, filtered, solvent removed and the product dried *in vacuuo* at room temperature to yield 70mg of an amorphous yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.76 - 0.95 (m, 2 H)

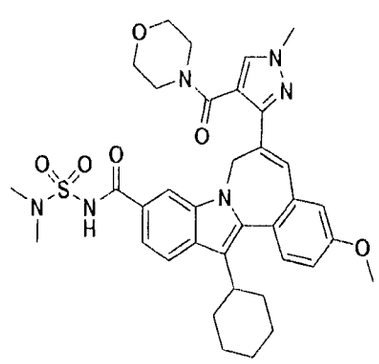
1.12 - 1.26 (m, 5 H) 1.32 (t, *J*=7.17 Hz, 3 H) 1.38 (s, 2 H) 1.51 - 1.61 (m, 4 H) 1.67 - 1.81 (m, 3 H) 1.87 - 2.01 (m, 2 H) 2.01 - 2.11 (m, 3 H) 2.82 - 2.92 (m, 1 H) 3.06 (s, 6 H) 3.91 (s, 3 H) 3.96 (s, 3 H) 4.26 (d, *J*=7.02 Hz, 2 H) 4.42 (d, *J*=14.34 Hz, 1 H) 5.75 (d, *J*=14.04 Hz, 1 H) 6.99 - 7.05 (m, 2 H) 7.38 (d, *J*=8.24 Hz, 1 H) 7.52 (d, *J*=8.24 Hz, 1 H) 7.85 (d, *J*=8.55 Hz, 1 H) 7.89 - 7.96 (m, 2 H) 8.18 (s, 1 H) 8.36 (br.s, 1 H). LC-MS retention time 2.34 min; 644 m/z (MH-). 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 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.



1H-pyrazole-4-carboxylic acid, 3-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-.

1*H*-pyrazole-4-carboxylic acid, 3-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl-, ethyl ester (66mg, 0.102 mmol) was dissolved in THF (1 mL) and a 1.0M solution of tetrabutylammonium hydroxide (0.41 mL, 0.410 mmol) in methanol was added to the reaction. The reaction was stirred at room temperature under a nitrogen atmosphere for 4hrs then analyzed by LC-MS. The reaction was concentrated in vacuuo on a rotary evaporator then 1ml of THF was

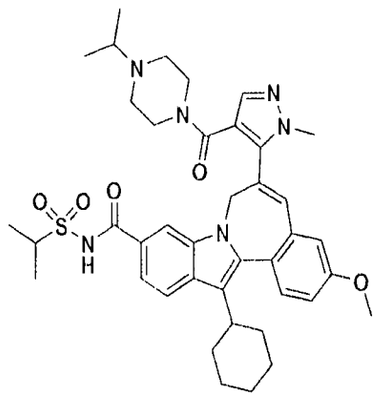
added to the reaction and the reaction once again capped under a nitrogen atmosphere. The reaction was placed in a water bath at 40C and allowed to stir overnight. Sometime overnight the heating element on the water bath failed and the reaction was observed to at room temperature the next morning. LC-MS analysis of the reaction indicated the reaction was complete. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid, then again with 1.0N aqueous hydrochloric acid and finally with brine. The organic layer was dried over magnesium sulfate, filtered and solvent removed *in vacuuo*. The title compound was dried *in vacuuo* to yield 63mg of an amorphous yellow solid. H1 NMR (500 MHz, CHLOROFORM-D) δ ppm 0.81 - 0.97 (m, 3 H) 1.18 - 1.30 (m, 4 H) 1.30 - 1.65 (m, 6 H) 1.66 - 1.83 (m, 3 H) 1.84 - 2.10 (m, 6 H) 2.84 - 2.92 (m, 3 H) 3.04 (s, 6 H) 3.88 (s, 3 H) 3.97 (s, 3 H) 4.43 (d, *J*=14.34 Hz, 1 H) 5.68 (d, *J*=13.73 Hz, 1 H) 6.99 (d, *J*=2.75 Hz, 1 H) 7.02 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.35 (d, *J*=8.24 Hz, 1 H) 7.52 (d, *J*=8.55 Hz, 1 H) 7.77 (s, 1 H) 7.83 (d, *J*=8.24 Hz, 1 H) 7.98 (s, 1 H) 8.15 (s, 1 H) 8.71 (s, 1 H). LC-MS retention time1.58 min; 616 m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-3-yl]-.

1*H*-pyrazole-4-carboxylic acid, 3-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (57mg, 0.092 mmol) was dissolved in DMF (1.0ml) and TBTU (55.8 mg, 0.174 mmol) added to the reaction. The reaction was capped under a nitrogen atmosphere and stir at room temperature for 1 hour then DMAP (47 mg, 0.385 mmol) was added to the reaction followed by morpholine (16 µl , 0.184 mmol). The reaction was capped under a nitrogen atmosphere and stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid, 0.1M aqueous NaH2PO4 and brine. The organic phase was dried over magnesium sulfate, filtered and solvent removed *in vacuuo*. The title compound was dried overnight *in vacuuo* at room temperature to yield 63mg of a yellow amorphous solid. The title compound was further purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (total volume 2ml) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 60% solvent A / 40% solvent B to 0% solvent A / 100% solvent B, a gradient time of 12 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. The sample was run as two 1ml injections. The run time of the second Prep HPLC run was truncated to 15 minutes base on data from the first run. The product fractions (retention time= 8.75min.) were combined and solvent removed *in vacuuo*. The compound was dried at room temperature *in vacuuo* to yield 38mg of the title compound as a yellow amorphous solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.23 (q, *J*=12.21 Hz, 1 H) 1.30 - 1.56 (m, 3 H) 1.77 (d, *J*=10.38 Hz, 2 H) 1.90 - 2.14 (m, 4 H) 2.54 - 2.81 (m, 4 H) 2.82 - 2.95 (m, 2 H) 2.95 - 3.05 (m, 2 H) 3.07 (s, 6 H) 3.09 - 3.39 (m, 5 H) 3.90 (s, 3 H) 3.97 (s, 3 H) 4.45 (d, *J*=14.65 Hz, 1 H) 5.45 (d, *J*=14.65 Hz, 1 H) 6.95 (d, *J*=2.75 Hz, 1 H) 6.97 (s,

1 H) 7.04 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.46 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.52 (d, *J*=8.55 Hz, 1 H) 7.55 (s, 1 H) 7.89 (d, *J*=8.55 Hz, 1 H) 7.94 (d, *J*=1.22 Hz, 1 H) 9.13 (br.s, 1 H). LC-MS retention time 1.82 min; 685 m/z (MH-). 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 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.



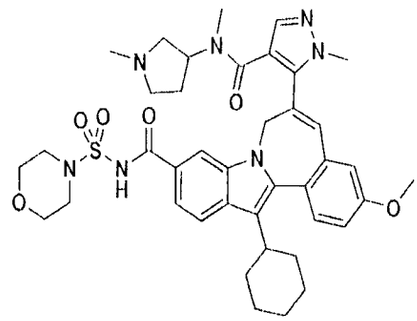
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[4-(1-methylethyl)-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-.

1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (0.92g, 1.5mmol) was dissolved in DMF (25ml) and HATU (1141mg, 3.0mmol) was added followed by diisopropylethylamine (1306uL, 7.5mmol). A 1mL solution of the reaction solution containing 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- / HATU / DIEA was transferred a 16x100mm wheaton vial containing 1-isopropylpiperazine (36.9mg, 0.288mmol). The reaction was capped and shaken at room temperature overnight. The reaction

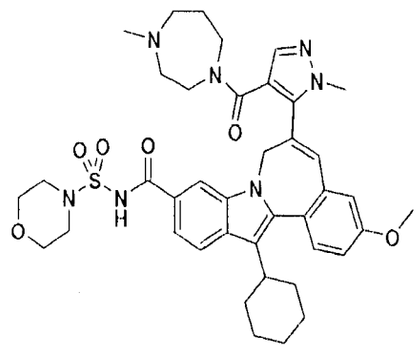
was transferred into a 96well plate and the reaction vial rinsed with DMF (800uL) to bring the final reaction volume to 1.800mL. The reaction mixture was purified by reverse phase HPLC under the following conditions. The Prep HPLC was controlled by Dionex Chromeleon 6.70 sp1 LC software using Varian a prostar binary pump with 50 mL/min pump head and detection using a Sedex 75 ELS detector for fraction collection. A Dionex UVD340U UV spectrometer was used to observe the UV trace of the HPLC run. A Waters Sunfire C18 19mm x 25mm 10u was employed for the isolation using a solvent system of A= water and 20mM ammonium acetate, B= acetonitrile. The following gradient was used: 80%A and 20%B hold for 3 minutes followed by a 19 minute gradient to 5%A and 95%B with a final hold at 5%A and 95%B of 5 minutes. The flow rate for purification was 20ml/ min. The fractions of interest were collected and concentrated to dryness using a Zymark Turbo Vap Evaporator. NMR analysis was performed on the peaks of interest (analytical retention time 5.69 minutes and 6.30minutes). The title compound was determined to be the peak with analytical retention time of 6.30 minutes by NMR analysis (rotomers). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.17 (s, 0.5 H) 0.91 (t, *J*=6.87 Hz, 3.3 H) 1.10 (t, *J*=14.95 Hz, 1.2 H) 1.17 - 1.32 (m, 2.6 H) 1.33 - 1.59 (m, 13.1 H) 1.68 - 1.83 (m, 3.5 H) 1.88 - 2.18 (m, 8.7H) 2.20 - 2.67 (m, 7.8 H) 2.76 - 3.05 (m, 3.3 H) 3.23 (d, *J*=10.99 Hz, 1.3 H) 3.29 - 3.53 (m, 1.6 H) 3.63 - 3.86 (m, 2.7 H) 3.88 - 3.98 (m, 6.0 H) 4.02 - 4.10 (m, 1.0 H) 4.61 (d, *J*=14.65 Hz, 1.3 H) 4.89 (d, *J*=14.95 Hz, 0.9 H) 6.76 - 6.86 (m, 0.8 H) 6.91 - 7.00 (m, 1.9 H) 7.06 - 7.13 (m, 1.3 H) 7.51 - 7.57 (m, 1.4 H) 7.57 - 7.66 (m, 1.6 H) 7.66 - 7.75 (m, 1.9 H) 7.89 (d, *J*=8.55 Hz, 1.5 H). LCMS analysis using MassLynx 4.0 SP4 LC-MS software, a CTC-Leap HTS-PAL autosampler, with an Agilent 1100 binary pump, Agilent 1100 photodiode array UV detector, Polymer Lab 2100 ELS detector (Temp=45C, nebulizer temp 35C) and a Waters ZQ With ESCi mass spectrometer. The analysis was performed using a Phenomenex Gemini 4.6x 150mm C18 3u column with a mobile phase solvent system of A= water and 20mM ammonium acetate, B= acetonitrile with a flow rate of 1.0ml/min and a gradient starting at 70%A and 30%B and a final composition 5%A and 95%B, gradient time of 11minutes and a hold time of 2 minutes to give an analysis runtime of 13 minutes.

Retention time = 6.63 minutes, m/z= 725 (MH+).

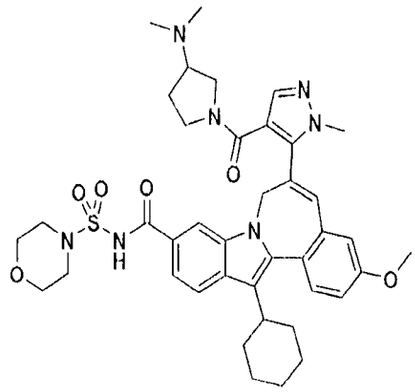
The following compounds were synthesized by an analogous method as described above for 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxamide, 13-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1*H*-pyrazol-3-yl]- and 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-*N*-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[4-(1-methylethyl)-1-piperazinyl]carbonyl]-1*H*-pyrazol-5-yl]-. Analytical LCMS data on the following examples were acquired using the following columns and conditions. Method 1: Gradient: 3 minutes; Flow rate: 5 mL/min; Stop time: Gradient time + 1 minute; Eluent A: 5% CH_3CN / 95% H_2O with 10 mM NH_4OAc; Eluent B: 95% CH_3CN / 5% H_2O with 10 mM NH_4OAc; Initial %B= 30; Final % B=100; Column: Waters Xterra, 3mm x 50mm, S7. Method 2: Gradient: 3 minutes; Flow rate: 5 mL/min; Stop time: Gradient time + 1 minute; Eluent A= 10% methanol, 90% water, 0.1% trifluoroacetic acid; %B= 90% methanol, 10% water, 0.1% trifluoroacetic acid; Initial %B= 40; Final % B=100; Column: Phenomenex Luna 3.0mm x 50mm S10.



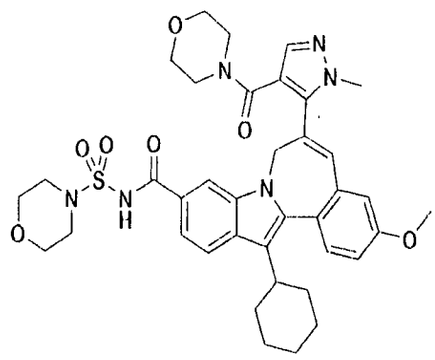
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[methyl(1-methyl-3-pyrrolidinyl)amino]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-. LCMS: m/e 756 (M+H), ret time 2.30 min.



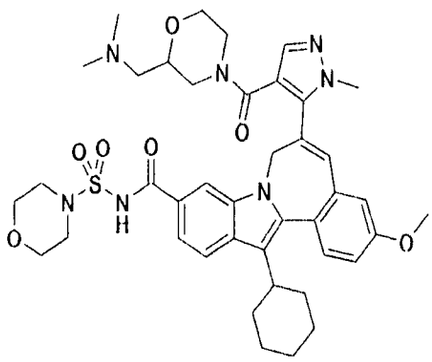
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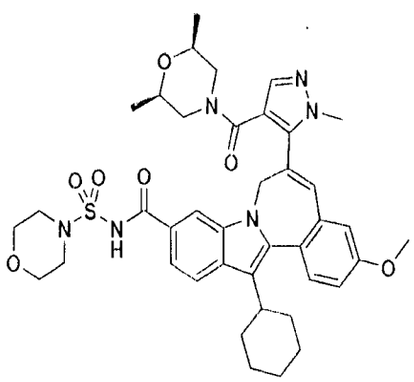
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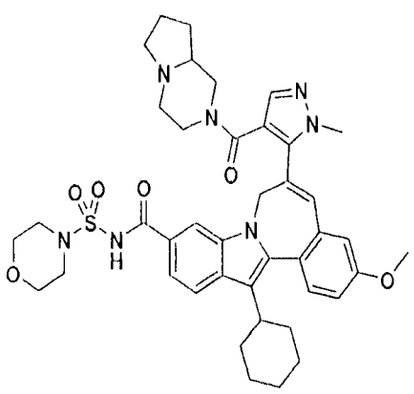
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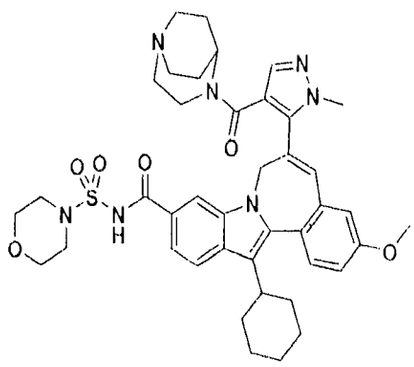
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[2-[(dimethylamino)methyl]-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-. LCMS: m/e 787 (M+H), ret time 2.40 min.



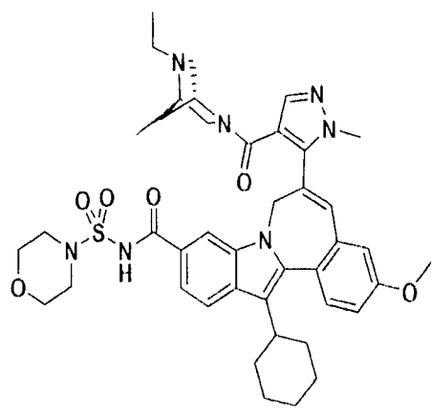
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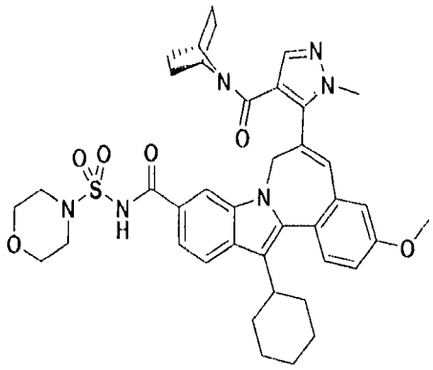
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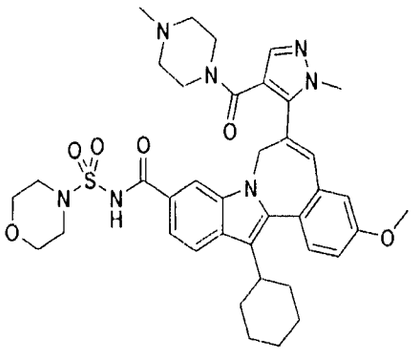
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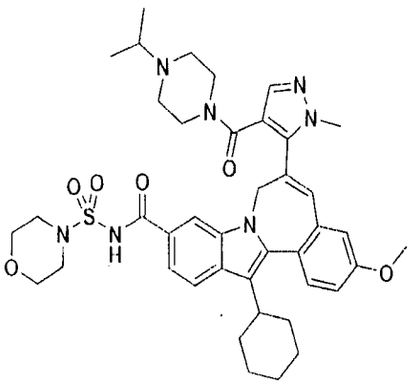
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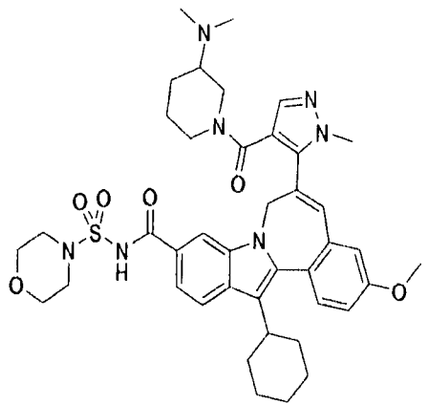
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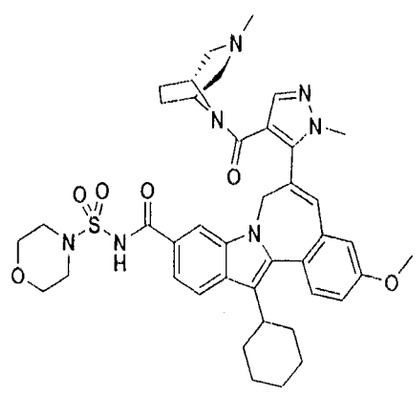
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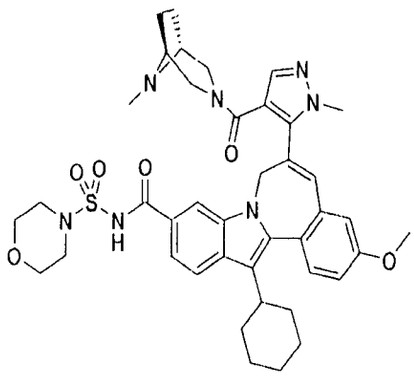
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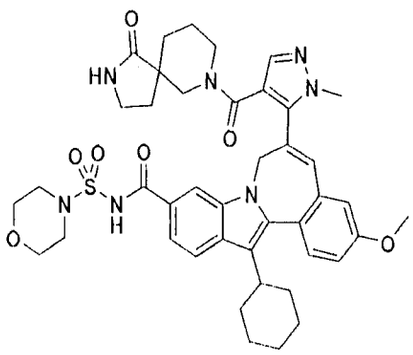
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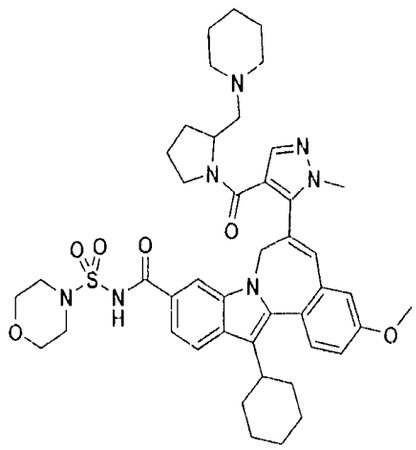
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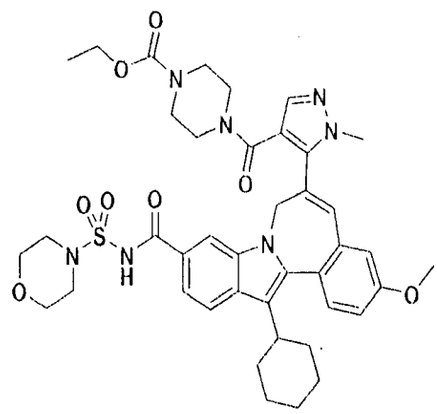
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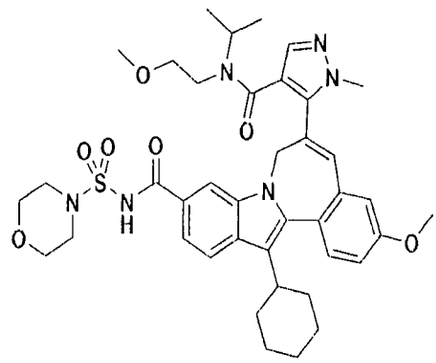
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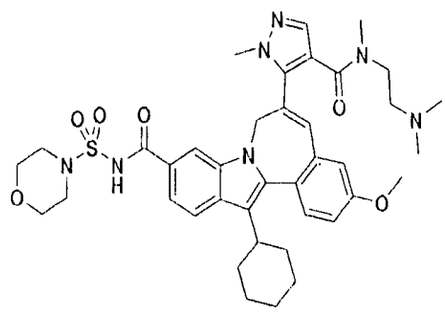
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[2-(1-piperidinylmethyl)-1-pyrrolidinyl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-. LCMS: m/e 811 (M+H), ret time 2.50 min.



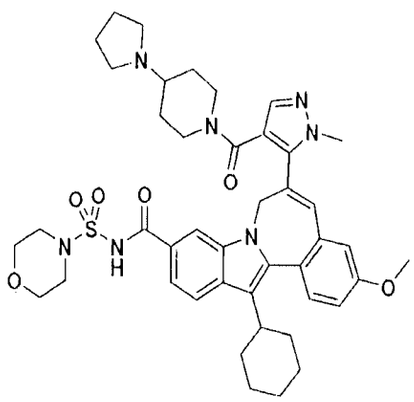
1-piperazinecarboxylic acid, 4-[[5-[13-cyclohexyl-3-methoxy-10-[[(4-morpholinylsulfonyl)amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-1H-pyrazol-4-yl]carbonyl]-, ethyl ester. LCMS: m/e 800 (M+H), ret time 2.60 min.



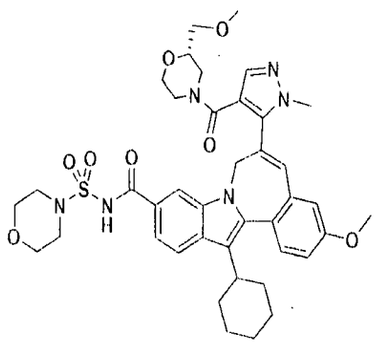
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2-methoxyethyl)(1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-. LCMS: m/e 759 (M+H), ret time 2.80 min.



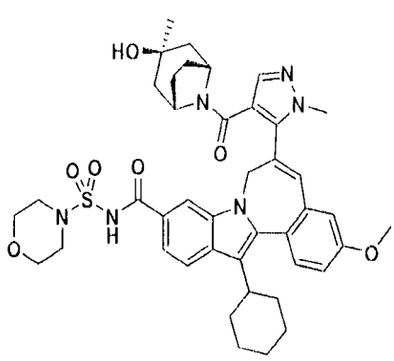
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[[2-(dimethylamino)ethyl]methylamino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-. LCMS: m/e 744 (M+H), ret time 2.20 min.



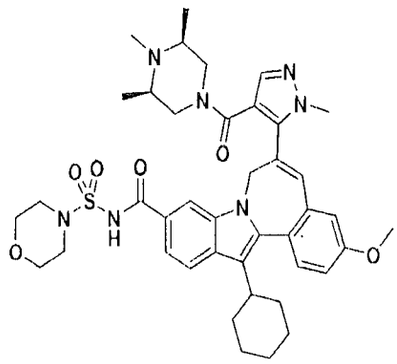
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[4-(1-pyrrolidinyl)-1-piperidinyl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-. LCMS: m/e 797 (M+H), ret time 2.30 min.



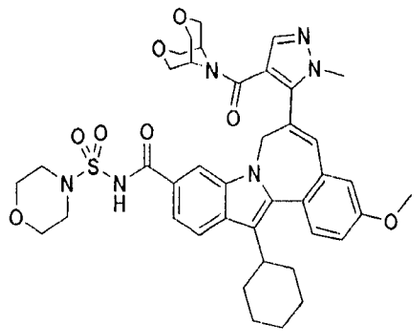
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-. LCMS: m/e 773 (M+H), ret time 2.60 min.



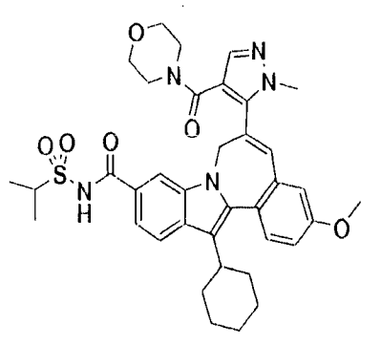
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(3-endo)-3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-. LCMS: m/e 784 (M+H), ret time 2.70 min.



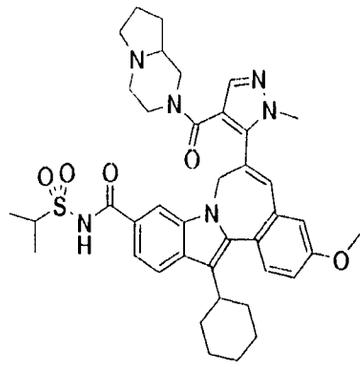
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-. LCMS: m/e 771 (M+H), ret time 2.30 min.



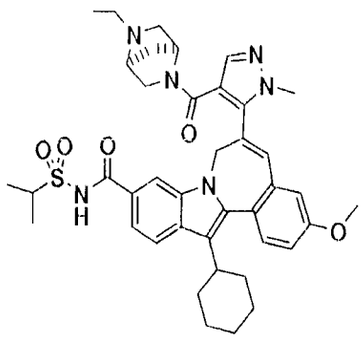
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-. LCMS: m/e 771 (M+H), ret time 2.60 min.



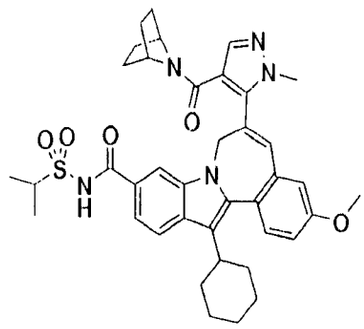
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-: LCMS: m/e 686 (M+H), ret time 3.49 min (method 2).



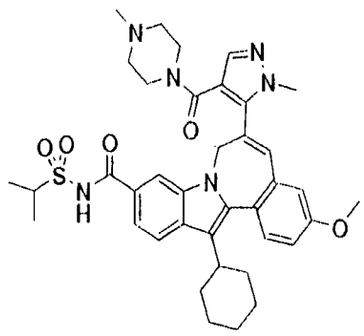
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: LCMS: m/e 725 (M+H), ret time 2.99 min (method 2).



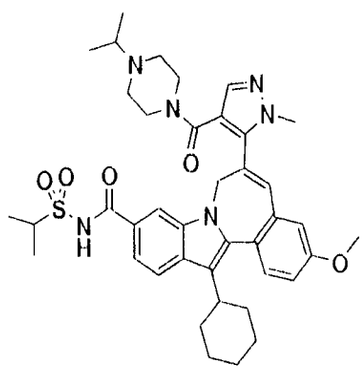
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: LCMS: m/e 725 (M+H), ret time 3.11 min (method 2).



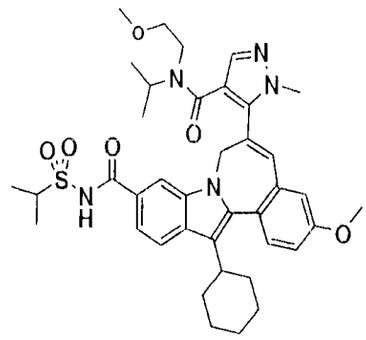
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 6-[4-(7-azabicyclo[2.2.1]hept-7-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-: LCMS: m/e 696 (M+H), ret time 3.32 min (method 2).



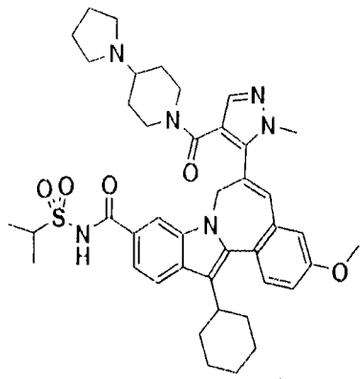
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-: LCMS: m/e 699 (M+H), ret time 3.05 min (method 2).



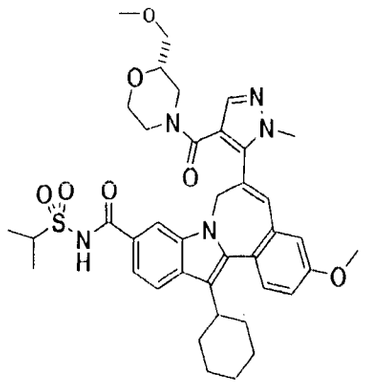
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[4-(1-methylethyl)-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-: LCMS: m/e 727 (M+H), ret time 3.19 min (method 2).



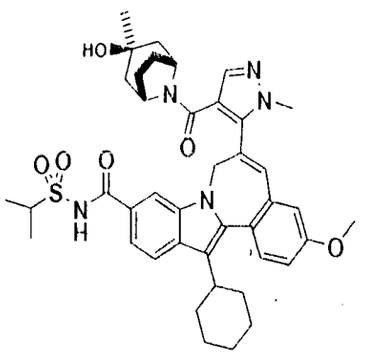
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2-methoxyethyl)(1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: LCMS: m/e 716 (M+H), ret time 3.37 min (method 2).



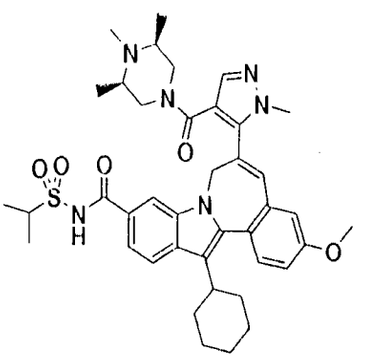
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[4-(1-pyrrolidinyl)-1-piperidinyl]carbonyl]-1H-pyrazol-5-yl]-: LCMS: m/e 753 (M+H), ret time 3.22 min (method 2).



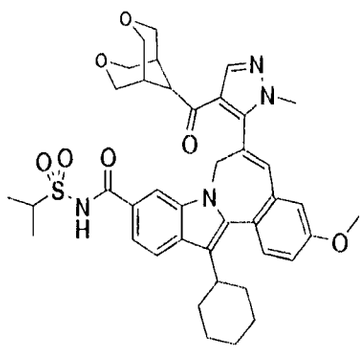
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: LCMS: m/e 730 (M+H), ret time 3.51 min (method 2).



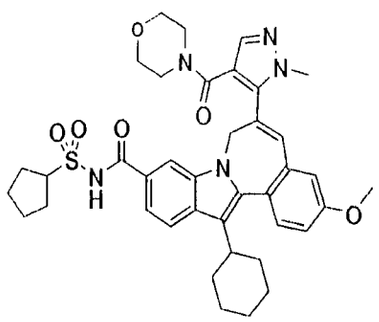
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(3-endo)-3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: LCMS: m/e 740 (M+H), ret time 2.53 min (method 2).



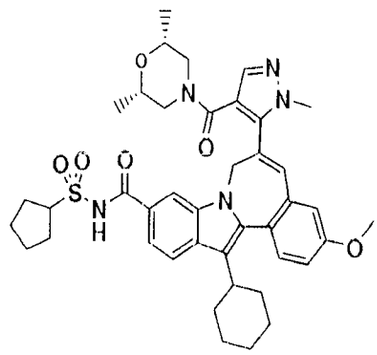
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-: LCMS: m/e 727 (M+H), ret time 2.26 min (method 2).



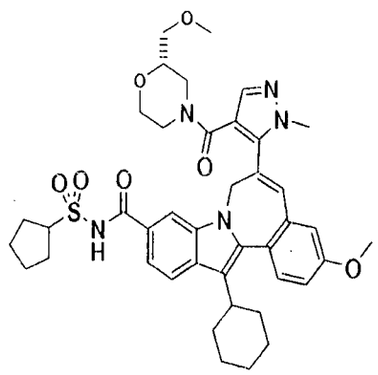
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: LCMS: m/e 727 (M+H), ret time 3.50 min (method 2).



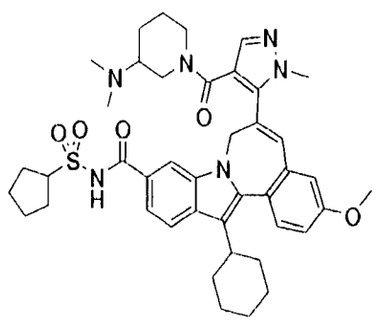
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-: LCMS: m/e 712 (M+H), ret time 2.65 min (method 1).



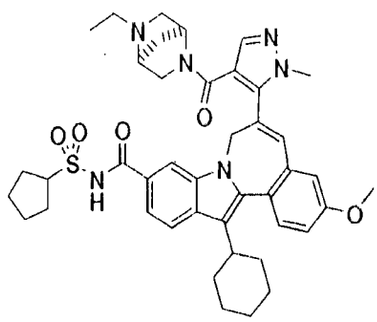
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-: LCMS: m/e 740 (M+H), ret time 2.84 min (method 1).



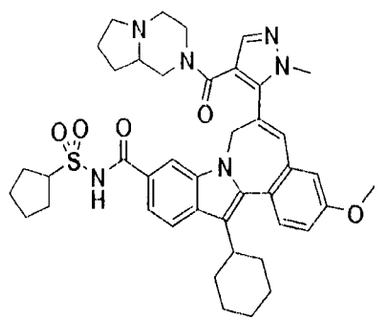
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-: LCMS: m/e 756 (M+H), ret time 2.79 min (method 1).



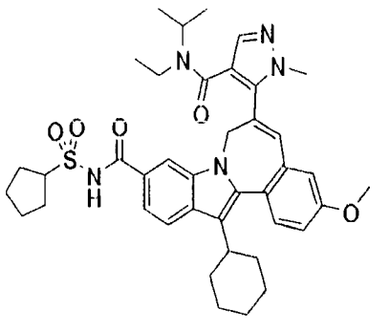
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-: LCMS: m/e 753 (M+H), ret time 2.41 min (method 1).



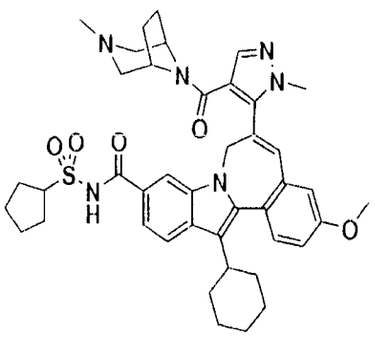
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-: LCMS: m/e 751 (M+H), ret time 2.51 min (method 1).



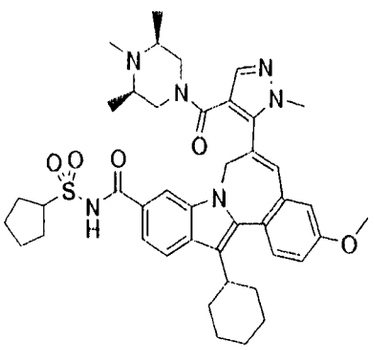
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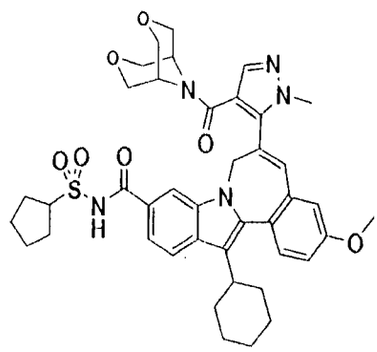
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[[ethyl(1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-: LCMS: m/e 712 (M+H), ret time 2.45 min (method 1).



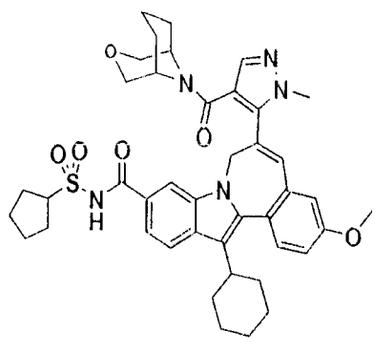
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-: LCMS: m/e 751 (M+H), ret time 2.36 min (method 1).



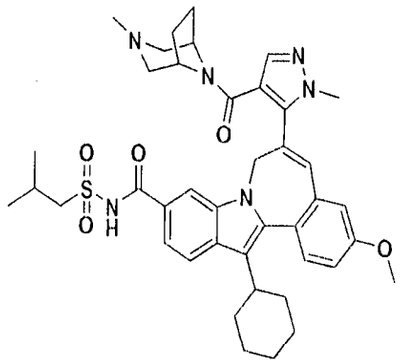
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-: LCMS: m/e 753 (M+H), ret time 2.39 min (method 1).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-: LCMS: m/e 754 (M+H), ret time 2.87 min (method 1).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[1-methyl-4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1H-pyrazol-5-yl]-: LCMS: m/e 752 (M+H), ret time 2.92 min (method 1).

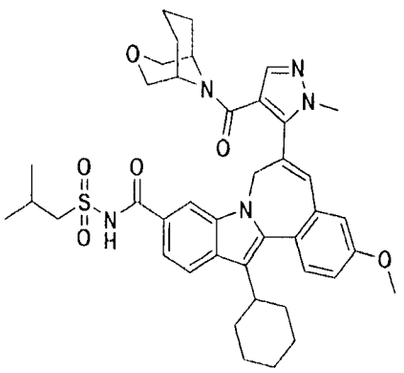


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. 3-methyl-3,8-diazabicyclo[3.2.1]octane, 2HCl (14.21 mg, 0.071 mmol) was then added and the solution was stirred at RT overnight. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated to afford the title compound as a brown colored solid, (36.3 mg, 0.043 mmol, 89 % yield).

MS m/z 739(MH^+), Retention time: 2.070 min.(basic)

IH NMR (500 MHz, MeOD) δ ppm 1.12 (d, *J*=6.71 Hz, 6 H) 1.18 - 2.19 (m, 14 H) 2.24 - 2.37 (m, 1 H) 2.75 (s, 3 H) 2.81 - 3.28 (m, 7 H) 3.45 - 3.52 (m, 2 H) 3.63 - 3.83 (s, br, 3 H) 3.91 (s, 3 H) 4.61 (d, *J*=14.65 Hz, 1 H) 4.90 - 4.94 (m, 1 H) 7.07 - 7.19 (m, 3 H) 7.54 - 7.60 (m, 2 H) 7.81 (s, br, 2 H) 7.93 (d, *J*=8.54 Hz, 1 H).

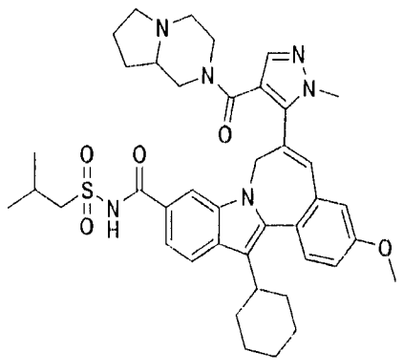


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. 3-oxa-9-azabicyclo[3.3.1]nonane, HCl (11.67 mg, 0.071 mmol) was then added and the solution was stirred at RT overnight. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated under vacuum. The title compound was obtained as a brownish solid, (29.5 mg, 0.040 mmol, 84 % yield).

MS m/z 738($M-H^-$), Retention time: 1.928 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 1.04 - 2.40 (m, 23 H) 2.72 - 3.05 (m, 3 H) 3.41 - 4.02 (m, 12 H) 4.61 - 4.69 (m, br, 1 H) 4.99 - 5.08 (m, br, 1 H) 7.09 - 7.25 (m, 3 H) 7.55 - 7.66 (m, 2 H) 7.66 - 7.73 (m, 1 H) 7.85 - 8.03 (m, 2 H).

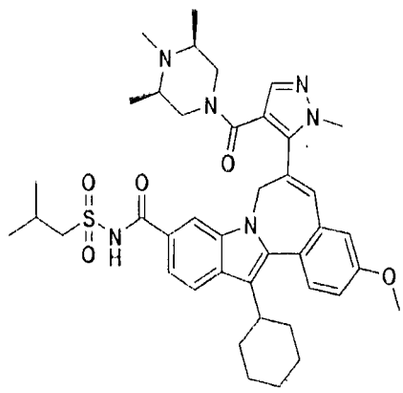


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. Octahydropyrrolo[1,2-a]pyrazine (9.00 mg, 0.071 mmol) was then added and the solution was stirred at RT overnight. The reaction mixture was then purified by preparative HPLC column using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated under speed vacuum. The TFA salt of the title compound was obtained as a brownish solid, (35.5 mg, 0.042 mmol, 88 % yield).

MS m/z 737 ($M-H^+$), Retention time: 1.722 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 1.15 (d, *J*=6.71 Hz, 6 H) 1.19 - 2.23 (m, 14 H) 2.26 - 2.40 (m, 1 H) 2.88 - 3.05 (m, 1 H) 3.11 - 3.58 (m, 11 H) 3.72 (s, 3 H) 3.95 (s, 3 H) 4.60-4.70 (m, br, 1 H) 5.00 - 5.16 (m, br, 1 H) 7.11 (s, 1 H) 7.16 (d, *J*=2.44 Hz, 1 H) 7.20 (dd, *J*=8.54, 2.75 Hz, 1 H) 7.58 - 7.64 (m, 2 H) 7.76 (s, 1 H) 7.91 (s, 1 H) 7.99 (d, *J*=8.55 Hz, 1 H).

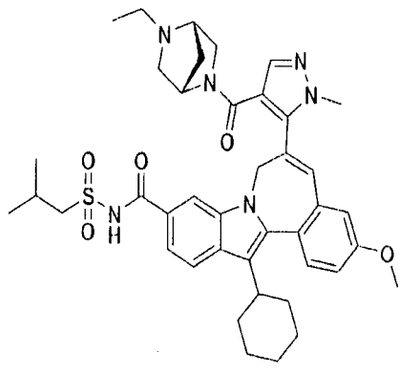


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(2-methylpropyl)sulfonyl]-6-[1-methyl-4-[[cis-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-

To a solution of *1H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-*7H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. Cis-1,2,6-trimethylpiperazine (9.15 mg, 0.071 mmol) was then added and the solution was stirred at RT overnight. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated under vacuum. The TFA salt of the title compound was obtained as a brownish solid, (39.1 mg, 0.046 mmol, 96 % yield).

MS m/z 739 ($M-H^+$), Retention time: 1.723 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 1.15 (d, *J*=7.02 Hz, 6 H) 1.21 - 1.65 (m, 10 H) 1.77 - 2.22 (m, 6 H) 2.28 - 2.40 (m, 1 H) 2.54 - 3.05 (m, 8 H) 3.51 (d, *J*=6.41 Hz, 2 H) 3.74 (s, 3 H) 3.95 (s, 3 H) 4.03 - 4.42 (m, br, 2 H) 4.59 - 4.70 (m, br, 1 H) 5.01 - 5.12 (m, br, 1 H) 7.13 (s, 1 H) 7.16 (d, *J*=2.75 Hz, 1 H) 7.21 (dd, *J*=8.85, 2.75 Hz, 1 H) 7.59 - 7.66 (m, 2 H) 7.74 (s, 1 H) 7.93 (s, 1 H) 8.00 (d, *J*=8.55 Hz, 1 H).

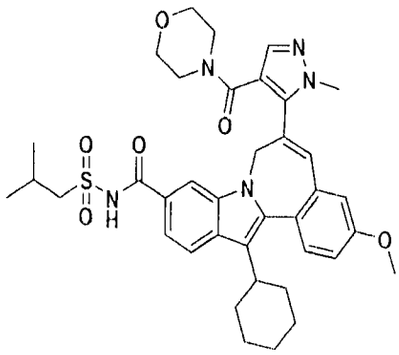


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S, 4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. (1S, 4S)-2-ethyl-2,5-diazabicyclo[2.2.1]heptane, 2TFA (25.3 mg, 0.071 mmol) was then added and the resultant solution was stirred at RT for 3 hours. LC/MS analysis showed that the reaction had progressed to completion. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were collected and concentrated under vacuum. The TFA of the title compound was obtained as a brown colored solid, (35.30 mg, 0.041 mmol, 87 % yield).

MS m/z 737($M-H^+$), Retention time: 1.850 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 1.15 (d, *J*=6.71 Hz, 6 H) 1.21 - 2.22 (m, 15 H) 2.25 - 2.39 (m, 1 H) 2.89 - 3.02 (m, 1 H) 3.05 - 3.80 (m, 12 H) 3.95 (s, 3 H) 4.09 - 4.48 (m, 1 H) 4.57 - 4.70 (m, 1 H) 4.99 - 5.12 (m, 1 H) 6.97 - 7.08 (s, br, 1 H) 7.14 (s, 1 H) 7.20 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.61 (d, *J*=8.85 Hz, 2 H) 7.82 (s, 1 H) 7.88 (s, 1 H) 7.97 (d, *J*=8.55 Hz, 1 H).

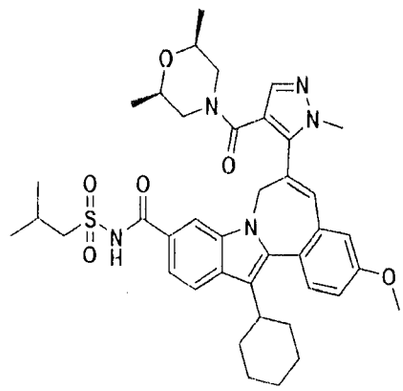


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. Morpholine (6.22 mg, 0.071 mmol) was then added and the resultant solution was stirred at RT for 3 hours. LC/MS analysis showed the reaction had progressed to completion. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated under vacuum. The title compound was obtained as a yellow solid,(28.4 mg, 0.041 mmol, 85 % yield).

MS m/z 698(M-H), Retention time: 1.618 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 1.16 (d, *J*=6.71 Hz, 6 H) 1.21 - 1.36 (m, 1 H) 1.40 - 1.64 (m, 3 H) 1.75 - 1.87 (m, 2 H) 1.94 - 2.25 (m, 4 H) 2.27 - 2.41 (m, 1 H) 2.70 - 3.12 (m, 9 H) 3.49 - 3.55 (m, 2 H) 3.85 (s, 3 H) 3.95 (s, 3 H) 4.69 (d, *J*=14.34 Hz, 1 H) 5.10 (d, *J*=14.95 Hz, 1 H) 7.09 (s, 1 H) 7.16 (d, *J*=2.44 Hz, 1 H) 7.20 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.62 (d, *J*=8.54 Hz, 2 H) 7.66 (s, 1 H) 7.94 (s, 1 H) 7.99 (d, *J*=8.55 Hz, 1 H).

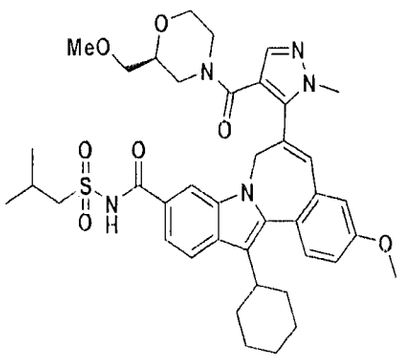


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[cis-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. Cis-2,6-dimethylmorpholine (8.22 mg, 0.071 mmol) was then added and the resultant solution was stirred at RT for 3 hours. LC/MS then showed that the reaction had progressed to completion. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were collected and concentrated under vacuum. The title compound was obtained as a yellow colored solid, (29.6 mg, 0.041 mmol, 85 % yield).

MS m/z 726(M-H$^+$), Retention time: 1.753 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 0.50 - 2.56 (m, 23 H) 2.68 - 3.06 (m, 2 H) 3.21 - 3.63 (m, 7 H) 3.83 - 4.02 (m, 6 H) 4.67 (d, *J*=14.34 Hz, 1 H) 5.04 (d, *J*=14.65 Hz, 1 H) 7.11 - 7.25 (m, 3 H) 7.56 - 7.69 (m, 3 H) 7.93 (s, 1 H) 7.99 (d, *J*=8.24 Hz, 1 H).

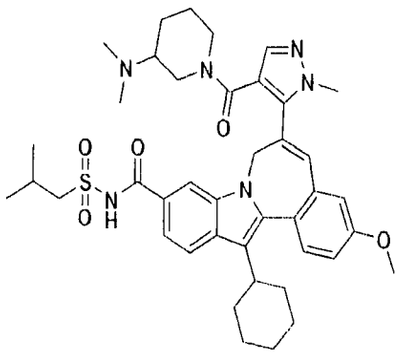


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. (S)-2-(methoxymethyl)morpholine, HCl (11.96 mg, 0.071 mmol) was then added and the resultant solution was stirred at RT for 3 hours. LC/MS analysis then showed the reaction had progressed to completion. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated under vacuum. The title compound was obtained as a yellow colored solid, (28.6 mg, 0.038 mmol, 81 % yield).

MS m/z 742($M-H^+$), Retention time: 1.598 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 1.16 (d, *J*=6.71 Hz, 6 H) 1.22 - 1.65 (m, 4 H) 1.75 - 2.24 (m, 6 H) 2.28 - 2.42 (m, 1 H) 2.88 - 3.63 (m, 15 H) 3.81 (s, 3 H) 3.95 (s, 3 H) 4.61 - 4.72 (m, 1 H) 5.02 - 5.14 (m, 1 H) 7.11 (s, 1 H) 7.17 (d, *J*=2.44 Hz, 1 H) 7.20 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.56 - 7.65 (m, 2 H) 7.66 (s, 1 H) 7.93 (s, 1 H) 7.96 - 8.03 (m, 1 H).

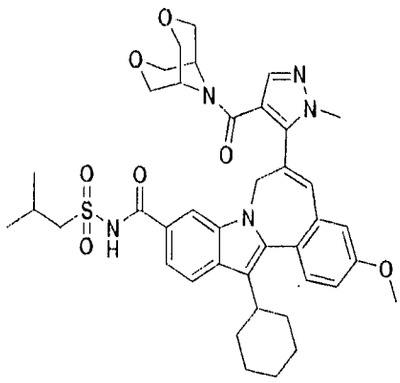


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. N,N-dimethylpiperidin-3-amine, 2HCl (14.35 mg, 0.071 mmol) was then added and the resultant solution was stirred at RT for 3 hours. LC/MS then showed the reaction had progressed to completion. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were collected and concentrated under vacuum. The TFA salt of the title compound was obtained as a yellow colored solid, (36.3 mg, 0.042 mmol, 89 % yield).

MS m/z 739(M-H$^+$), Retention time: 1.810 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 1.16 (d, *J*=6.71 Hz, 6 H) 1.22 - 1.64 (m, 6 H) 1.75 - 2.24 (m, 8 H) 2.29 - 2.39 (m, 1 H) 2.46 - 3.13 (m, 11 H) 3.51 (d, *J*=6.41 Hz, 2 H) 3.83 (s, 3 H) 3.95 (s, 3 H) 4.16 (s, br, 1 H) 4.61 - 4.73 (m, br, 1 H) 5.00 - 5.12 (m, br, 1 H) 7.09 (s, 1 H) 7.16 (d, *J*=2.44 Hz, 1 H) 7.20 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.60 (d, *J*=8.85 Hz, 1 H) 7.64 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.69 (s, 1 H) 7.94 (s, 1 H) 8.01 (d, *J*=8.24 Hz, 1 H).

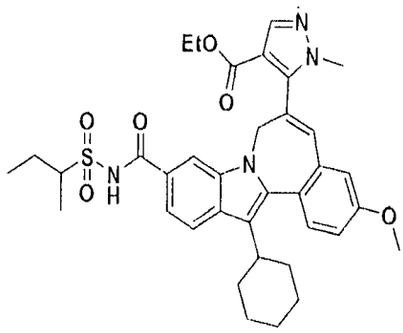


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl 6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (30 mg, 0.048 mmol) in DMSO (1 mL), TBTU (22.91 mg, 0.071 mmol) and DIPEA (0.042 mL, 0.238 mmol) were added. The reaction mixture was stirred at RT for 15 min. 3,7-dioxa-9-azabicyclo[3.3.1]nonane (9.21 mg, 0.071 mmol) was then added and the solution was stirred at RT overnight. LC/MS then showed that only 40% SM had reacted. Two more equivalents of TBTU were then added and the reaction mixture was stirred at RT overnight. LC/MS then showed that the reaction had progressed to completion. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and evaporated under vacuum to give the title compound as a light-yellow colored solid, (26.7 mg, 0.036 mmol, 76 % yield).

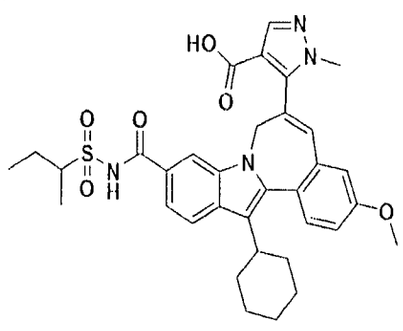
MS m/z 740($M-H^-$), Retention time: 1.887 min.(basic)

1H NMR (500 MHz, MeOD) δ ppm 1.16 (d, *J*=6.71 Hz, 6 H) 1.21 - 1.64 (m, 4 H) 1.71 - 3.15 (m, 10 H) 3.43 - 3.88 (m, 13 H) 3.96 (s, 3 H) 4.63 - 4.72 (m, 1 H) 5.01 - 5.11 (m, 1 H) 7.13 - 7.18 (m, 2 H) 7.22 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.61 (d, *J*=8.55 Hz, 1 H) 7.64 (d, *J*=8.85 Hz, 1 H) 7.74 (s, 1 H) 7.91 (s, 1 H) 7.98 (d, *J*=8.55 Hz, 1 H).



1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl)-, ethyl ester

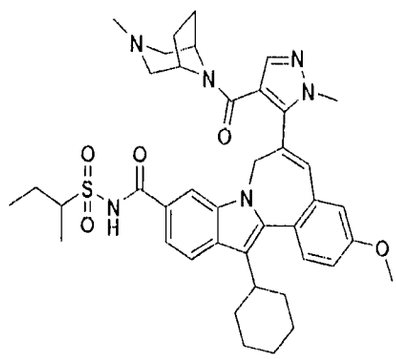
CDI (451 mg, 2.78 mmol) was added to a THF (10 mL) solution of 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-(750 mg, 1.39 mmol) and the resultant mixture was stirred at 60 °C for 1 h. The reaction was then cooled to r.t. and butane-2-sulfonamide (572 mg, 4.17 mmol) and DBU (0.419 mL, 2.78 mmol) were added. The mixture was then heated at 60 °C overnight, after which the solvent was removed and the residue dissolved in EtOAc. The organic layer was washed with sequentially with 1N HCl solution (3 x 20 mL), and Brine (3 x 20 mL) and then dried over Na_2SO_4. The mixture was then filtered and the filtrate was evaporated in vacuo. The residue was purified using a Shimadzu preparative HPLC employing ACN/water and 0.1 % TFA buffer with a Xterra column,30 mm x 100 mm,Gradient over 15 min; Starting conc: 10 %B;Ending conc: 100 %B. Homogeneous fractions were combined and evaporated under reduced pressure to afford the title compound as light yellow solid, (450 mg, 49 %). ESI-MS *m/e* 659 (MH^+).



1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-

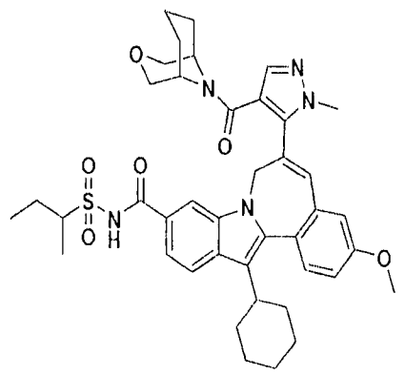
NaOH (1N, 5 mL) was added to a solution of 1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester (250 mg, 0. 379 mmol) in a 1:1 mixture of THF:MeOH (10 mL) and the resultant solution was agitated at r.t. for 48 h. HCl (1N, 5 mL) was then added and the resultant mixture was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with brine (3 x 20 mL) and then dried over Na_2SO_4. The mixture was then filtered and the filtrate was evaporated in vacuo to afford the title product as yellow solid, (235 mg, 98%). ESI-MS *m/e* 631 (MH^+).

Using the standard amide coupling conditions described for related examples, the following examples can be prepared.



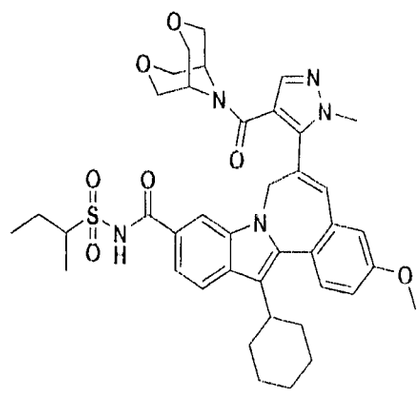
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-N-[(1-methylpropyl)sulfonyl]-

ESI-MS *m/e* 739 (MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.08 (t, *J*=7.32 Hz, 3 H) 1.16 - 1.56 (m, 9 H) 1.58 - 1.85 (m, 4 H) 1.90 - 2.24 (m, 6 H) 2.48 - 2.62 (m, 3 H) 2.81 - 2.99 (m, 3 H) 3.15 - 3.45 (m, 3 H) 3.73 - 4.05 (m, 5 H) 3.94 (s, 3 H) 4.58 - 4.69 (m, 1 H) 4.80 - 5.02 (m, 1 H) 6.92 - 7.01 (m, 2 H) 7.13 (dd, *J*=8.70, 2.29 Hz, 1 H) 7.53 - 7.82 (m, 4 H) 7.92 (d, *J*=8.24 Hz, 1 H) 10.14 (s, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1H-pyrazol-5-yl]-N-[(1-methylpropyl)sulfonyl]-

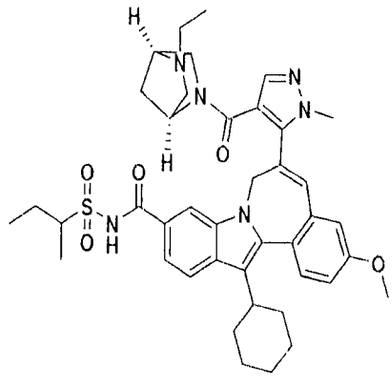
ESI-MS *m/e* 740 (MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.00 - 1.57 (m, 12 H) 1.68 - 1.84 (m, 3 H) 1.91 - 2.48 (m, 9 H) 2.81 - 2.94 (m, 1 H) 3.03 - 3.16 (m, 1 H) 3.18 - 3.72 (m, 5 H) 3.76 - 4.02 (m, 7 H) 4.53 - 4.68 (m, 1 H) 4.94 (d, *J*=15.87 Hz, 1 H) 6.81 - 6.91 (m, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.13 (d, *J*=8.54 Hz, 1 H) 7.54 - 7.62 (m, 1 H) 7.62 - 7.85 (m, 3 H) 7.87 - 7.96 (m, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-

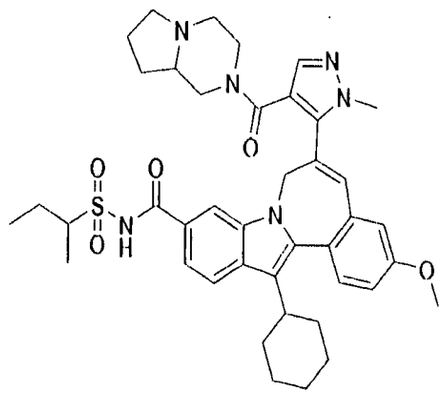
ESI-MS *m/e* 742 (MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.02 - 1.13 (m, 3 H) 1.15 - 1.27 (m, 1 H) 1.31 - 1.56 (m, 6 H) 1.69 - 1.84 (m, 2 H) 1.92 - 2.39 (m, 6 H) 2.62 - 2.70 (m, 1 H) 2.83 - 2.93 (m, 1 H) 3.25 (s, 1 H) 3.30 - 3.49 (m, 3 H) 3.52 - 3.59 (m, 1 H) 3.66 - 3.76 (m, 3 H) 3.80 - 3.86 (m, 2 H) 3.89 (s, 3 H) 3.94 (s, 3 H) 4.63 (d, *J*=15.26 Hz, 1 H) 4.93 (d, *J*=15.56 Hz, 1 H) 6.86 (s, 1 H) 6.95

(d, *J*=2.44 Hz, 1 H) 7.13 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.59 (d, *J*=8.55 Hz, 1 H) 7.63 (d, *J*=8.54 Hz, 1 H) 7.72 (d, *J*=5.49 Hz, 2 H) 7.94 (d, *J*=8.55 Hz, 1 H) 10.08 - 10.26 (m, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-

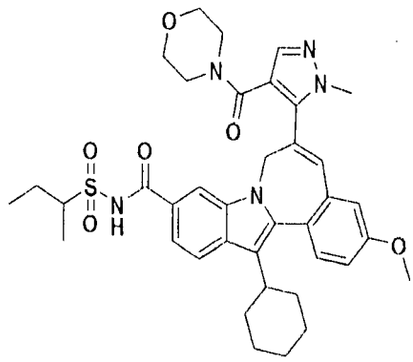
ESI-MS *m/e* 739 (MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.85 - 1.56 (m, 15 H) 1.58 - 2.39 (m, 8 H) 2.68 - 2.96 (m, 4 H) 3.03 - 3.38 (m, 3 H) 3.55 (d, *J*=5.19 Hz, 1 H) 3.72 - 4.03 (m, 5 H) 4.05 - 4.43 (m, 2 H) 4.51 - 5.04 (m, 3 H) 6.68 - 6.86 (m, 1 H) 6.88 - 7.18 (m, 2 H) 7.49 - 7.97 (m, 5 H) 8.17 - 8.28 (m, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-

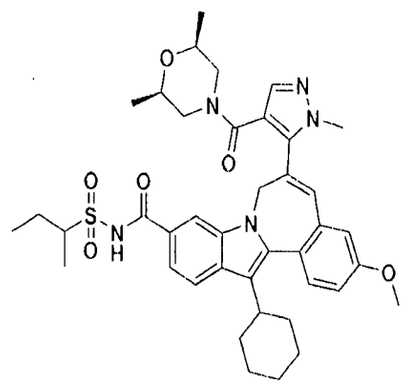
ESI-MS *m/e* 739 (MH^+)1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.00 - 1.13 (m, 3 H) 1.21 - 1.58 (m, 7 H) 1.59 - 1.85 (m, 4 H) 1.90 - 2.49 (m, 11 H) 2.80 - 2.99 (m, 2 H) 3.34 - 3.88 (m, 9 H) 3.92 (s, 3 H) 4.54 - 4.69 (m, 1 H) 4.76 - 5.00 (m, 1

H) 6.83 - 6.94 (m, 1 H) 6.97 (s, 1 H) 7.06 - 7.15 (m, 1 H) 7.48 - 7.68 (m, *J*=35.71 Hz, 3 H) 7.75 (s, 1 H) 7.89 (s, 1 H).



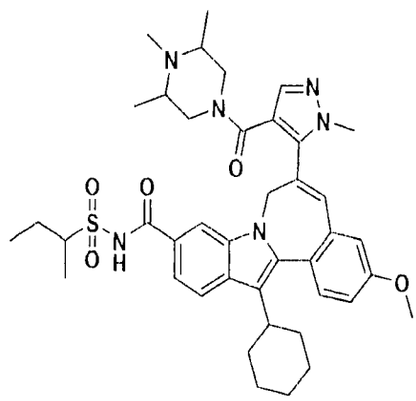
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(1-methylpropyl)sulfonyl]-

ESI-MS *m/e* 700 (MH^+)1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.02 - 1.14 (m, 3 H) 1.16 - 1.30 (m, 1 H) 1.49 (dd, *J*=20.91, 6.87 Hz, 6 H) 1.34 - 1.45 (m, 1 H) 1.93 - 2.40 (m, 7 H) 2.58 - 2.71 (m, 1 H) 2.77 - 2.97 (m, 4 H) 3.04 - 3.25 (m, 2 H) 3.35 - 3.65 (m, 2 H) 3.79 - 3.88 (m, 1 H) 3.90 (s, 3 H) 3.94 (s, 3 H) 4.61 (d, *J*=15.87 Hz, 1 H) 4.90 (d, *J*=15.56 Hz, 1 H) 6.86 (s, 1 H) 6.96 (d, *J*=2.44 Hz, 1 H) 7.13 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.58 (d, *J*=8.55 Hz, 1 H) 7.61 (d, *J*=7.93 Hz, 1 H) 7.65 - 7.74 (m, 2 H) 7.94 (d, *J*=8.54 Hz, 1 H) 10.20 - 10.44 (m, 1 H).



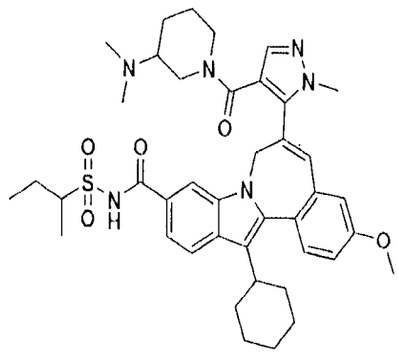
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-

ESI-MS *m/e* 728 (MH^+)1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.98 - 1.13 (m, 3 H) 1.14 - 1.31 (m, 2 H) 1.34 - 1.59 (m, 6 H) 1.70 - 1.86 (m, 3 H) 1.88 - 2.32 (m, 12 H) 2.81 - 2.98 (m, 1 H) 2.95 - 3.14 (m, 1 H) 3.13 - 3.34 (m, 2 H) 3.36 - 3.67 (m, 1 H) 3.83 - 3.93 (m, 1 H) 3.92 (s, 3 H) 3.95 (s, 3 H) 4.61 (d, *J*=14.34 Hz, 1 H) 4.91 (d, *J*=15.56 Hz, 1 H) 6.83 (s, 1 H) 6.96 (s, 1 H) 7.13 (d, *J*=8.55 Hz, 1 H) 7.51 - 7.81 (m, 4 H) 7.92 (d, *J*=7.32 Hz, 1 H) 10.33 - 10.59 (m, 1 H).



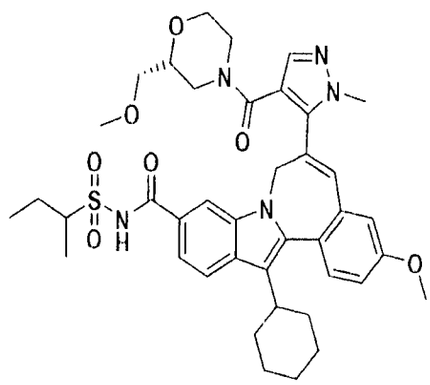
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylpropyl)sulfonyl]-6-[1-methyl-4-[(3,4,5-trimethyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-

ESI-MS *m/e* 741 (MH^+).1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.85 - 2.25 (m, 25 H) 2.27 - 2.64 (m, 3 H) 2.93 (s, 1 H) 3.28 - 3.69 (m, 4 H) 3.71 - 3.87 (m, 5 H) 3.94 (s, 3 H) 4.53 - 4.69 (m, 1 H) 4.83 - 5.01 (m, 1 H) 6.90 (s, 1 H) 6.97 (d, *J*=2.44 Hz, 1 H) 7.08 - 7.15 (m, 1 H) 7.50 - 7.66 (m, 3 H) 7.79 (d, *J*=1.53 Hz, 1 H) 7.93 (d, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-

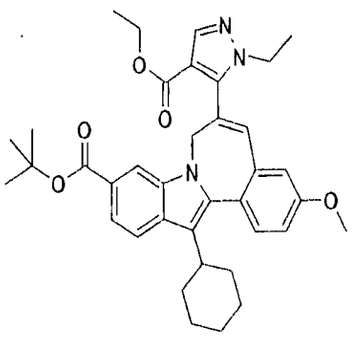
ESI-MS *m/e* 741 (MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.01 - 1.15 (m, 3 H) 1.19 - 1.61 (m, 7 H) 1.64 - 2.28 (m, 15 H) 2.41 - 2.76 (m, 5 H) 2.82 - 2.96 (m, 1 H) 3.35 - 3.83 (m, 3 H) 3.78 - 3.91 (m, 3 H) 3.90 - 3.98 (m, 3 H) 4.19 - 4.40 (m, 1 H) 4.54 - 4.71 (m, 1 H) 4.78 - 4.98 (m, 1 H) 6.84 - 6.96 (m, 1 H) 6.95 - 7.01 (m, 1 H) 7.07 - 7.15 (m, 1 H) 7.50 - 7.58 (m, 1 H) 7.59 - 7.87 (m, 3 H) 7.90 - 7.99 (m, 1 H) 10.02 - 10.36 (m, 1 H).



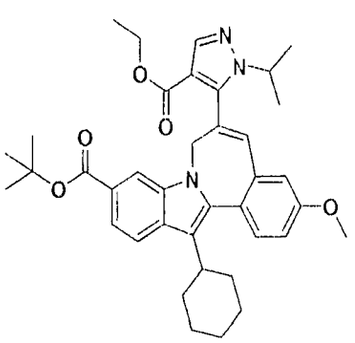
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(1-methylpropyl)sulfonyl]-

ESI-MS *m/e* 744 (MH^+) 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.01 - 1.15 (m, 2 H) 1.23 (d, *J*=15.26 Hz, 1 H) 1.33 - 1.59 (m, 5 H) 1.70 - 2.31 (m, 13 H) 2.36 - 2.53 (m, 1 H) 2.83 - 3.49 (m, 10 H) 3.81 - 3.93 (m, 3 H) 3.94 (s, 3 H) 4.60

(d, *J*=15.26 Hz, 1 H) 4.79 - 5.00 (m, 1 H) 6.85 (s, 1 H) 6.95 (s, 1 H) 7.12 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.50 - 7.81 (m, 4 H) 7.86 - 7.99 (m, 1 H) 10.29 - 10.54 (m, 1 H).

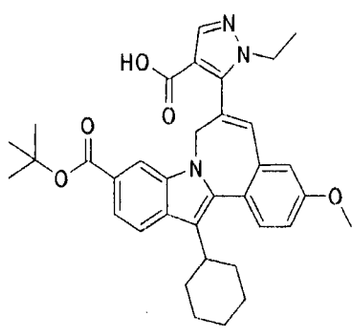


7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-ethyl-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester. tert-butyl 13-cyclohexyl-6-((2E,Z)-3-(dimethylamino)-2-(ethoxycarbonyl)-2-propenoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (370mg, 0.604mmol) was dissolved in ethanol (1.7ml) and the oxylate salt of ethyl hydrazine (100 mg, 0.664 mg) was added to the reaction at room temperature. The reaction was heated to 80 deg C for 3hrs. The reaction was diluted with chloroform and washed with water. The organic phase was concentrated under reduced pressure and purified by prep HPLC under the following conditions: Shimadzu preparative HPLC using Discovery VP software: %A= 10% acetonitrile, 90% water, 0.1% TFA; %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 30; Final % B=100; Gradient= 12min; Runtime=20min; Flow rate= 40ml/min; Column= Waters Sunfire 30 x 100mm S5. This afforded the title compound (265 mg, 72%) as a yellow paste.. MS m/z 610 (MH^+).



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester.

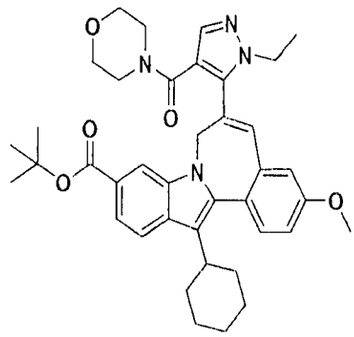
tert-Butyl 13-cyclohexyl-6-((2E,Z)-3-(dimethylamino)-2-(ethoxycarbonyl)-2-propenoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (180mg, 0.294mmol) was dissolved in a solution of ethanol (1ml), triethyl amine (82.0 uL, 0.588mmol) and the hydrochloride salt of 2-propyl hydrazine (36 mg, 0.323 mmol). The reaction was heated in a microwave at 160°C for 2 hours and then concentrated. The resulting solid was purified by preparative HPLC under the following conditions: Shimadzu preparative HPLC using Discovery VP software: %A= 10% acetonitrile, 90% water, 0.1% TFA; %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 30; Final % B=100; Gradient= 12min; Runtime=20min; Flow rate= 40ml/min; Column= Waters Sunfire 30 x 100mm S5. Homogeneous fractions were combined and evaporated in vacuo to afford the title compound (127 mg, 69%) as a yellow paste. MS m/z 624 (MH^+).



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 6-(4-carboxy-1-ethyl-1H-pyrazol-5-yl)-13-cyclohexyl-3-methoxy-, 10-(1,1-dimethylethyl) ester.

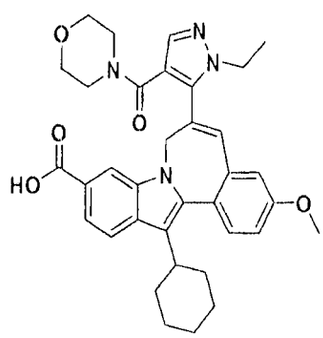
7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-ethyl-1*H*-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester (250mg, 0.410mmol) was dissolved in 12 mL of methanol/THF (1:1, v/v) and 1M aqueous sodium hydroxide (6ml, 6mmol) was added to the reaction. The resulting mixture was stirred at room temperature for 18 hr, and then diluted with 1M aqueous hydrochloric acid and the product was extracted with chloroform. The organic phase was dried over Na_2SO_4, filtered and the filtrate concentrated *in vacuuo* to give the

title compound (251mg, 100%) that was used in subsequent steps without further purification. MS m/z 612 (MH^+).



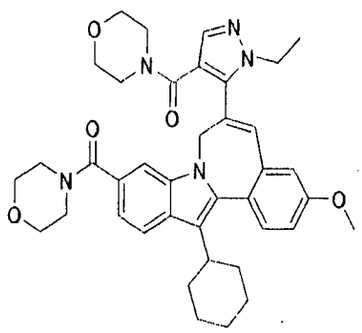
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester.

To a solution of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 6-(4-carboxy-1-ethyl-1*H*-pyrazol-5-yl)-13-cyclohexyl-3-methoxy-, 10-(1,1-dimethylethyl) ester (120mg, 0.206mmol) in THF (1 mL) at 60°C was added carbonyldiimidazole (47mg, 0.288mmol) and the solution stirred for 1hour. Morpholine (36mg, 0.412mmol) and DBU (33mg, 0.268mmol) were then added and the reaction was heated for a further 1hr and was then allowed to stir to room temperature overnight. The reaction was then diluted with 1M aqueous hydrochloric acid and the resultant mixture was extracted with chloroform. The extracts were dried over Na_2SO_4, filtered and then concentrated in vacuo to provide the title compound in quantitative yield. MS m/z 651 (MH^+).



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-.

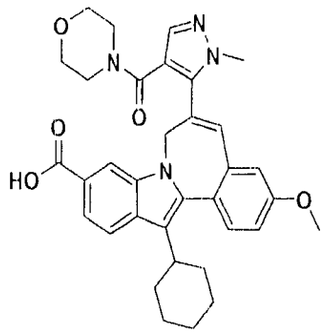
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester (61mg, 0.094 mmol) was dissolved in trifluoroacetic acid (2 mL) and stirred at room temperature for 3 hours and the mixture was then concentrated *in vacuuo*. Residual trifluoroacetic acid was removed by azeotroping with benzene and the final product was dried *in vacuuo* to provide the title compound, (56 mg, 100%) that was used without further purification. MS m/z 595 (MH^+).



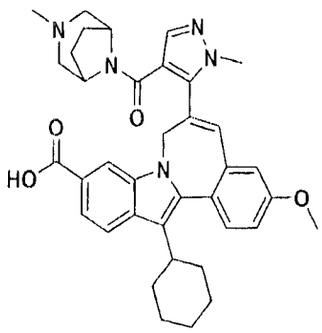
Morpholine, 4-[[13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-7H-indolo[2,1-a][2]benzazepin-10-yl]carbonyl]-.

7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1*H*-pyrazol-5-yl]-3-methoxy-, (60mg, 0.092mmol) was dissolved in THF (0.9 mL) and carbonyldiimidazole (21mg, 0.130mmol) was added. The resultant mixture was then stirred at 60°C for 1hr. Upon cooling to room temperature under a nitrogen atmosphere, morpholine (40 mg, 0.460 mmol) and DBU (0.012 mL, 0.120 mmol) were added. The reaction was heated for 1hr then allowed to stir to room temperature overnight. The resulting mixture was filtered and the resultant filtrate was purified by preparative HPLC under the following conditions: Shimadzu preparative HPLC using Discovery VP software: %A= 10% acetonitrile, 90% water, 0.1% TFA; %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 30; Final % B=100; Gradient= 12min; Runtime=20min; Flow rate= 40 mL/min; Column= Waters Sunfire 30 x 100mm S5. This afforded the title compound (31 mg, 51%) as a yellow paste. MS m/z 664 (MH^+).

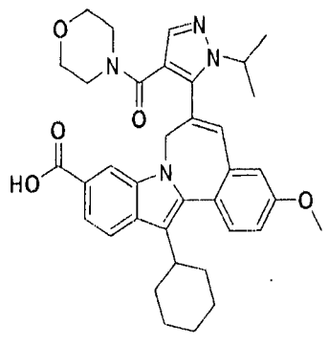
The following compounds were synthesized by an analogous sequence as described above for 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1*H*-pyrazol-5-yl]-3-methoxy-:



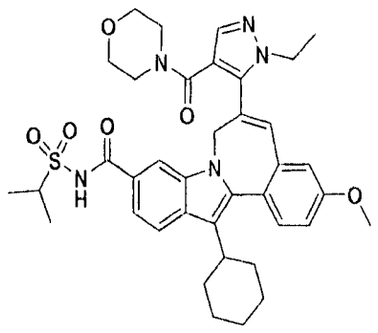
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-. MS m/z 581 (MH^+).



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-. MS m/z 620 (MH^+).



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-. MS m/z 609 (MH^+).

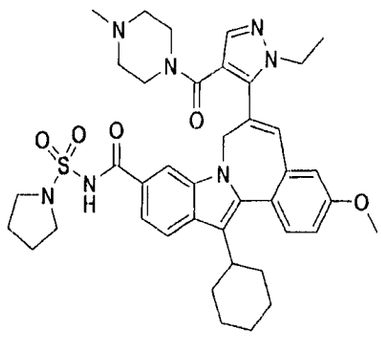


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-.

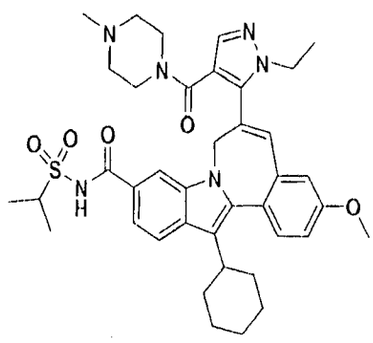
7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1*H*-pyrazol-5-yl]-3-methoxy-, (56mg, 0.094mmol) was dissolved in THF (0.9 mL) and carbonyldiimidazole (21mg, 0.129mmol) added to the reaction at 60°C and the resultant mixture was stirred for 1hr. Propane-2-sulfonamide (57mg,0.246mmol) and DBU (15mg, 0.120mmol) were then added to the reaction and the mixture was heated for a further 1 hour, then allowed to stir to room temperature for 18 hours. The resulting mixture was filtered and the filtrate purified by prep HPLC under the following conditions: Shimadzu preparative HPLC using Discovery VP software: %A= 10% acetonitrile, 90% water, 0.1% TFA; %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 30; Final % B=100; Gradient= 12min; Runtime=20min; Flow rate= 40 mL/min; Column= Waters Sunfire 30 x

100mm S5. This afforded the title compound (40 mg, 61%) as a yellow paste. MS m/z 700 (MH^+).

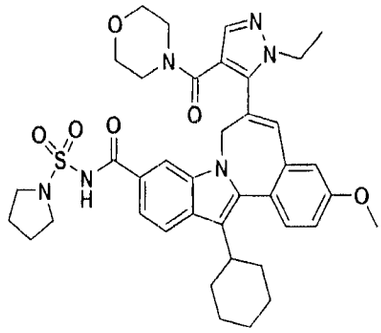
The following compounds were synthesized by an analogous method as described above for 7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-:



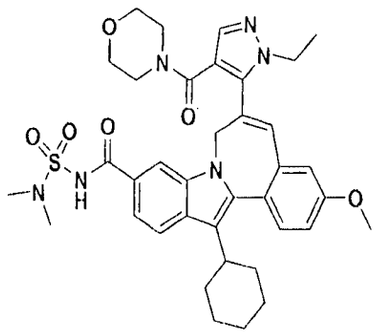
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-(1-pyrrolidinylsulfonyl)-. MS m/z 740 (MH^+).



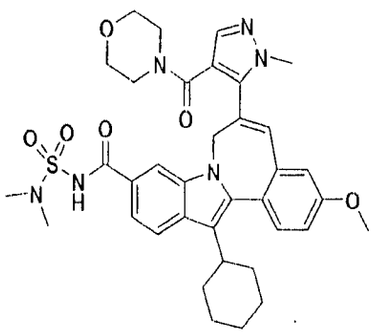
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-. MS m/z 713 (MH^+).



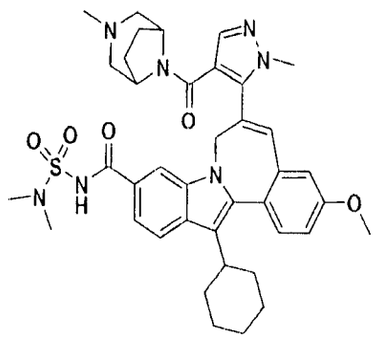
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-(1-pyrrolidinylsulfonyl)-. MS m/z 727 (MH^+).



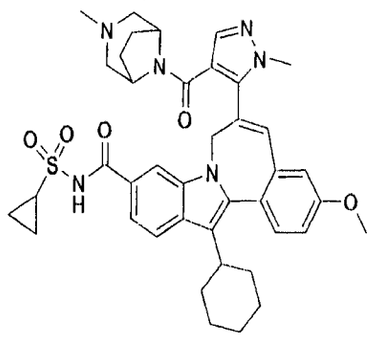
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-. MS m/z 701 (MH^+).



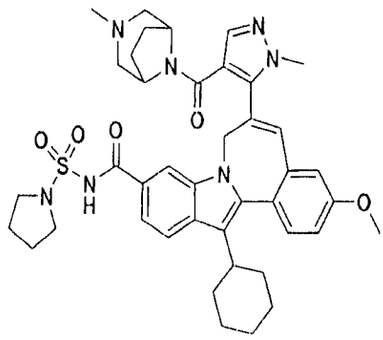
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-. MS m/z 687 (MH^+).



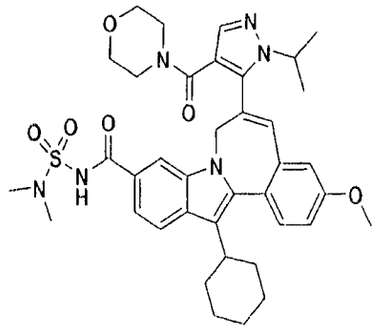
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-. MS m/z 726 (MH^+).



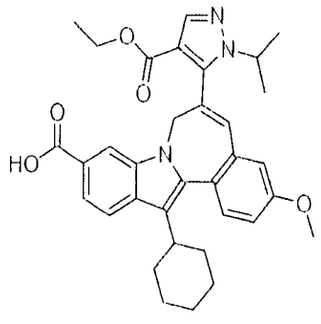
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopropylsulfonyl)-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-. MS m/z 723 (MH^+).



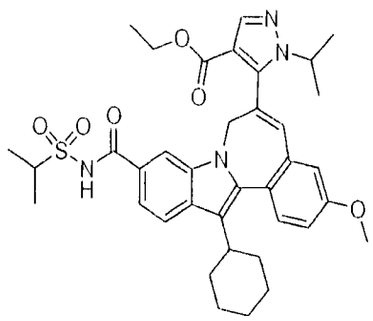
7H-*indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-N-(1-pyrrolidinylsulfonyl)-*. MS m/z 752 (MH^+).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-. MS m/z 715 (MH^+).

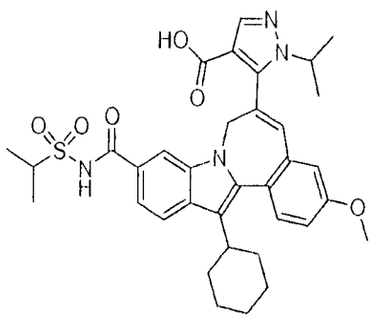


7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-. Dissolve 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester (2.00 g, 3.21 mmol) in 1,2-dichloroethane (6.41 mL), place reaction under a nitrogen atmosphere, then add trifluoroacetic acid (6.41 ml). Stir reaction at room temperature under a nitrogen atmosphere for 2 hours. Remove volatiles in vacuuo and dissolve the reaction product in benzene and remove in vacuuo to aid in removal of trace TFA. Repeat dissolution in benzene and removal in vacuuo. Dry sample at room temperature in vacuuo to obtain the title compound (1.92 g, 100% yield) as a yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.48 (br s, 3H) 1.12 - 1.65 (m, 9 H) 1.72 - 2.19 (m, 7 H) 2.87 (t, *J*=11.29 Hz, 1 H) 3.91 (s, 3 H) 4.22 (m, 1 H) 4.32 (br.s, 2 H) 4.73 (br.s, 1 H) 4.97 (br.s, 1 H) 6.70 (s, 1 H) 6.94 (d, *J*=2.14 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.52 (m, 2 H) 7.64 (d, *J*=8.24 Hz, 1 H) 7.82 (d, *J*=8.24 Hz, 1 H) 7.96 (s, 1 H). LCMS 566 m/z (MH-).



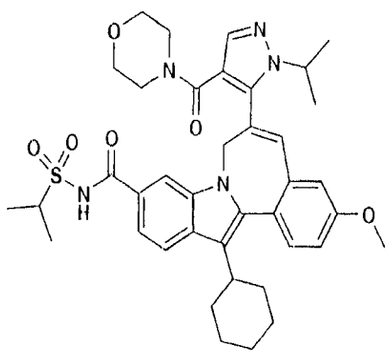
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-1-(1-methylethyl)-, ethyl ester. Dissolve 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)- 1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy- (1.00 g, 1.76 mmol) in THF (5.87 mL). Carbonyldiimidazole (857 mg, 5.28 mmol) was added to the reaction. The reaction was placed under a nitrogen atmosphere and stirred at room temperature for 45 minutes then heated to reflux for 1 hour. The reaction was cooled under a nitrogen atmosphere and propane-2-sulfonamide (868 mg, 7.05 mmol) was added to the reaction followed by DBU

(0.797 mL, 5.28 mmol). The reaction was immerse in oil bath at 80 deg C under nitrogen atmosphere and heated overnight at 70-80 deg C. The reaction was diluted with ethyl acetate (50 mL) and the organic layer washed sequentially with 1.0N aqueous hydrochloric acid (50 mL), 0.1M aqueous NaH2PO4 (50 mL) and brine (25 mL). The organic layer was dried over MgSO4, filtered and volatiles removed *in vacuuo* to yield a yellow foam which was dried *in vacuuo* at room temperature overnight to yield 1.03g (1.57mmol, 87%) of the title compound as a yellow amorphous solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.40 (br s, 3H) 1.12 - 1.70 (m, 15 H) 1.72 - 2.18 (m, 7 H) 2.84 (t, *J*=11.29 Hz, 1 H) 3.90 (s, 3 H) 4.11 (m, 1 H) 4.26 (m, 3 H) 4.66 (br.s, 1 H) 4.97 (br.s, 1 H) 6.68 (s, 1 H) 6.94 (d, *J*=2.14 Hz, 1 H) 7.08 (m, 2 H) 7.52 (d, *J*=8.24 Hz, 1 H) 7.67 (d, *J*=8.24 Hz, 1 H) 7.80 (d, *J*=8.24 Hz, 1 H) 7.89 (s, 1 H). LCMS 671 m/z (MH-).



1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]- 1-(1-methylethyl)-. Dissolve 1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]- 1-(1-methylethyl)-, ethyl ester (1.20 g, 1.78 mmol) was dissolved in THF (15.0 mL) and methanol (15.0 mL) was added to the reaction followed by 1N aqueous sodium hydroxide (15.0 mL). The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 18 hrs. The reaction was diluted with ethyl acetate (25.0 mL) and washed with 1.0N aqueous hydrochloric acid (2 x 20mL). The organic layer was concentrated *in vacuuo* using a rotary evaporator to yield the title compound as a yellow solid (1.15 g, 100%).
MS m/z 645 (MH^+).

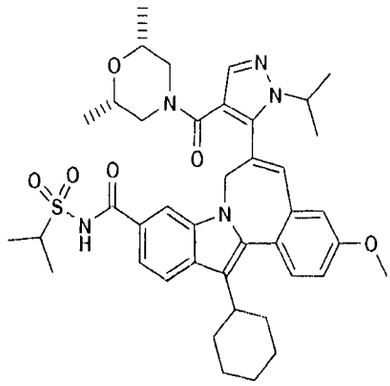
1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.46 (br s, 3H) 1.12 - 1.70 (m, 12 H) 1.72 - 2.15 (m, 7 H) 2.85 (t, *J*=11.29 Hz, 1 H) 3.90 (s, 3 H) 4.26 (m, 1 H) 4.62 (br.s, 1 H) 4.99 (br.s, 1 H) 6.69 (s, 1 H) 6.96 (d, *J*=2.14 Hz, 1 H) 7.06 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.50 (m, 2 H) 7.80 (m, 2 H) 7.85 (s, 1 H) 9.09 (br s , 1 H).



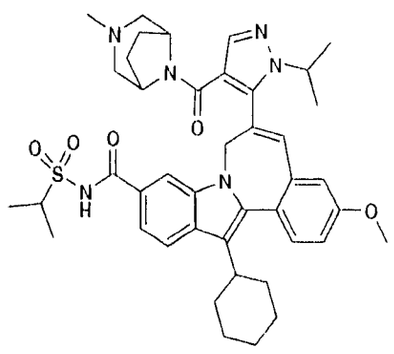
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-:

1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]- 1-(1-methylethyl)- (125 mg, 0.194 mmol) in DMSO (1.94 mL), TBTU (124 mg, 0.388 mmol) and DIPEA (0.100 mg, 0.775 mmol) were added. The reaction mixture was stirred at RT for 15 min. Then morpholine (68 mg, 0.775 mmol) was added. The solution was stirred at RT for overnight. The reaction mixture was purified by prep HPLC column using CH_3CN/H_2O/TFA as solvent system. Fractions were collected and concentrated under speedvac overnight to yield the title compound as a yellow solid (82 mg, 0.114 mmol, 59 % yield). MS m/z 714 ($M-H^+$). 1H NMR (500 MHz, CDCl3) δ ppm 1.20 (m, 1 H) 1.32 - 1.65 (m, 15 H) 1.73 - 2.20 (m, 6 H) 2.63 - 3.24 (m, 7 H) 3.50 (br m, 2 H) 3.93 (s, 3 H) 4.07 (m, 1 H) 4.58 (m, 2 H) 4.90 (m, br, 1 H) 6.78 (s, 1 H) 6.93 (d, *J*=2.44 Hz, 1 H) 7.13 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 - 7.64 (m, 2 H) 7.71 (m, 2 H) 7.93 (d, *J*=8.55 Hz, 1 H) 10.15 (s, br, 1H).

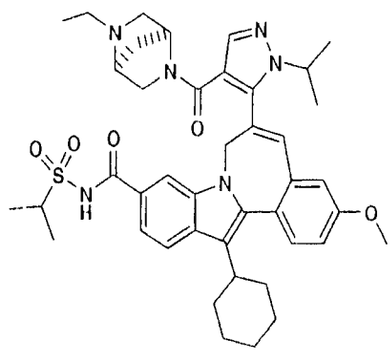
The following compounds were synthesized by an analogous method as described above for 7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-:



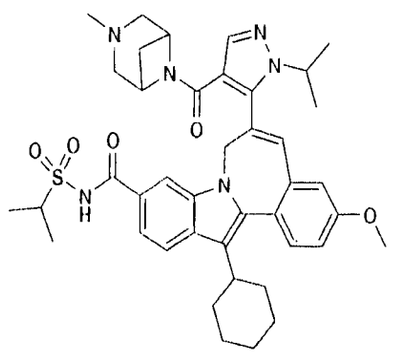
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(2,6-dimethyl-4-morpholinyl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm 0.61-0.92 (m, 6 H) 1.23 (m, 1 H) 1.35 - 1.70 (m, 15 H) 1.73 - 2.20 (m, 6 H) 2.88 (m, 1 H) 3.12-3.70 (m, 6 H) 3.92 (s, 3 H) 4.09 (m, 1 H) 4.58 (m, 2 H) 4.91 (m, br, 1 H) 6.75 (s, 1 H) 6.92 (d, *J*=2.44 Hz, 1 H) 7.12 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 - 7.68 (m, 2 H) 7.75 (m, 2 H) 7.92 (d, *J*=8.55 Hz, 1 H) 10.10 (s, br, 1H). LCMS: m/e 742 (M+H).



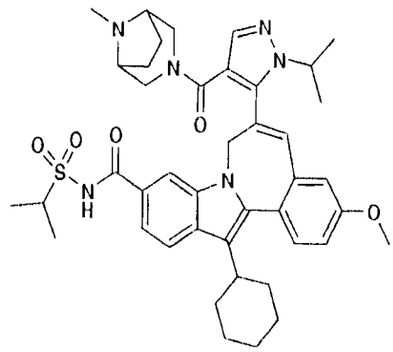
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm 0.02 (m, 2 H) 0.82 (m, 2 H) 1.20-1.82 (m, 16 H) 1.91 - 2.18 (m, 6 H) 2.39-2.70 (m, 4H) 2.88 (m, 1 H) 2.96-3.59 (m, 5 H) 3.94 (s, 3 H) 4.06 (m, 1 H) 4.62 (m, 2 H) 4.85 (m, br, 1 H) 6.92 (m, 2 H) 7.12 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 - 7.69 (m, 3 H) 7.86 (br s, 1 H) 7.92 (d, *J*=8.55 Hz, 1 H) 10.10 (s, br, 1H). LCMS: m/e 753 (M+H).



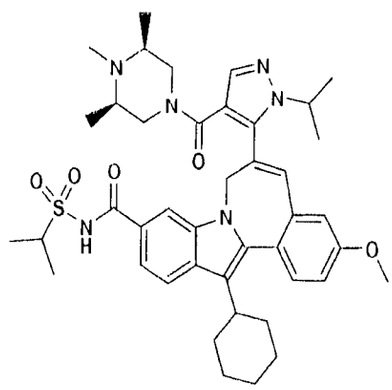
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm 0.02 (m, 1 H) 1.10-1.59 (m, 19 H) 1.91 - 2.49 (m, 8 H) 2.80-3.69 (m, 4H) 2.88 (m, 1 H) 3.81-4.41 (s, 7 H) 4.62 (m, 2 H) 4.90 (m, br, 1 H) 6.97 (m, 2 H) 7.10 (m, 1 H) 7.53 - 7.67 (m, 2 H) 7.71-7.95 (m, 3 H) 10.20 (s, br, 1H). LCMS: m/e 753 (M+H).



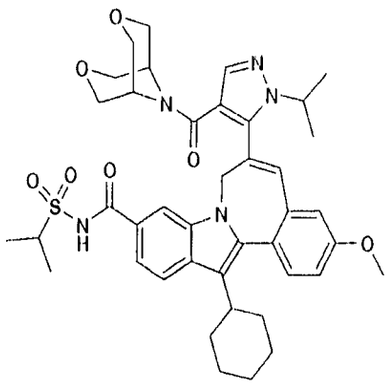
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm 1.17-1.85 (m, 15 H) 1.90 - 2.18 (m, 9 H) 2.59-2.99 (m, 6 H) 3.35-4.10 (m, 8 H) 4.66-5.00 (m, 3 H) 6.92 (m, 2 H) 7.12 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.50 - 7.69 (m, 3 H) 7.75-8.01 (m, 2 H) 10.00 (s, br, 1H). LCMS: m/e 739 (M+H).



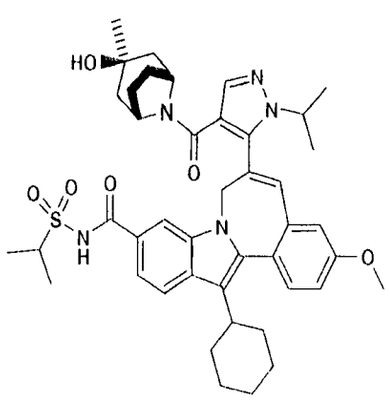
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-:1H NMR (500 MHz, CDCl3) δ ppm 0.021 (m, 2 H) 0.81 (m, 2 H) 1.20-1.86 (m, 16 H) 1.91 - 2.17 (m, 6 H) 2.41-2.71 (m, 4 H) 2.88 (m, 1 H) 2.97-3.70 (m, 5 H) 3.94 (s, 3 H) 4.08 (m, 1 H) 4.62 (m, 2 H) 4.85 (m, br, 1 H) 6.94 (m, 2 H) 7.12 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.52 - 7.69 (m, 3 H) 7.80-7.95 (m, 2 H) 10.10 (s, br, 1H). LCMS: m/e 753 (M+H).



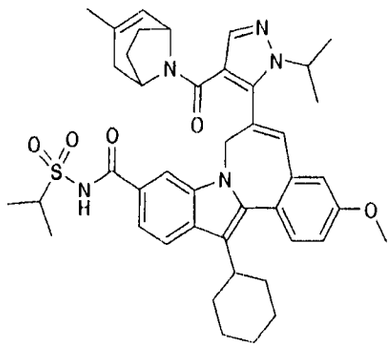
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-(1-methylethyl)-4-[(3,4,5-trimethyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-: 1H NMR (500 MHz, CDCl3) δ ppm 1.20-1.82 (m, 22 H) 1.91 - 2.18 (m, 6 H) 2.50 (br s, 3H) 2.90 (m, 1 H) 3.35-3.69 (m, 7 H) 3.92 (s, 3 H) 4.02 (m, 1 H) 4.61 (br m, 1 H) 4.93 (br m, 1 H) 6.80 (br s , 1 H) 6.95 (s, 1 H) 7.11 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.51 - 7.65 (m, 3 H) 7.80 (br s, 1 H) 7.90 (d, *J*=8.55 Hz, 1 H) 10.20 (s, br, 1H). LCMS: m/e 755 (M+H).



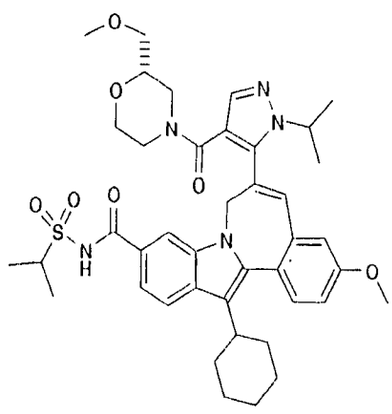
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm 1.15-1.82 (m, 19 H) 1.91 - 2.18 (m, 3 H) 2.88 (m, 1 H) 3.12-3.80 (m, 9 H) 3.92 (s, 3 H) 4.05 (m, 1 H) 4.40 (m, 2 H) 4.61 (br d, 1 H) 4.92 (br d, 1 H) 6.78 (s, 1 H) 6.91 (d, *J*=2.44 Hz, 1 H) 7.13 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.59 - 7.65 (m, 2 H) 7.77 (m, 2 H) 7.93 (d, *J*=8.55 Hz, 1 H) 10.10 (s, br, 1H). LCMS: m/e 756 (M+H).



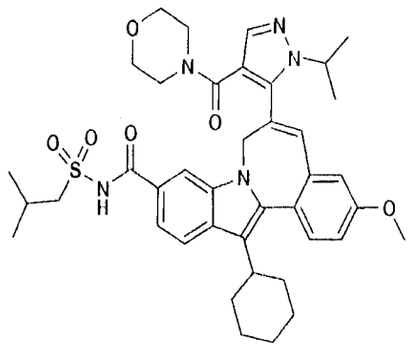
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(3-endo)-3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm -0.25 (m, 1 H) 0.52 (m, 1 H) 1.04 (s, 3 H) 1.15-1.82 (m, 24 H) 1.91 - 2.18 (m, 4 H) 2.89 (m, 1 H) 3.29 (m, 1 H) 3.62 (m, 1 H) 3.92 (s, 3 H) 4.06 (m, 1 H) 4.54-4.71 (m, 2 H) 5.00 (br d, 1 H) 6.82 (br s, 1 H) 6.91 (d, *J*=2.75 Hz, 1 H) 7.12 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.50 - 7.60 (m, 2 H) 7.70 (m, 1 H) 7.80-7.95 (m, 2 H) 10.20 (s, br, 1H). LCMS: m/e 768 (M+H), ret time 2.75 min (method 1).



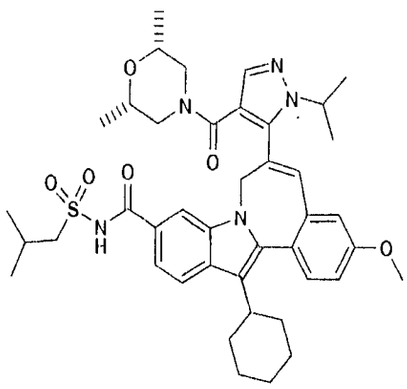
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-8-azabicyclo[3.2.1]oct-2-en-8-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: m/e 750 (M+H), ret time 2.89 min (method 1).



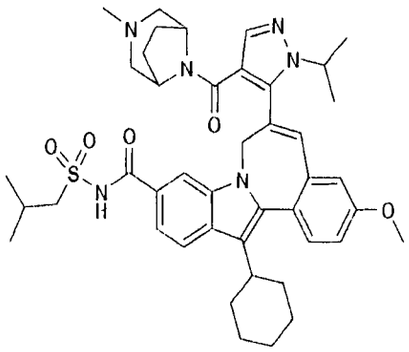
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]- 1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm 1.21 (m, 1 H) 1.32 - 1.70 (m, 15 H) 1.73 - 2.20 (m, 6 H) 2.72-3.47 (m, 8 H) 3.88-4.17 (m, 10 H) 4.61 (m, 1 H) 4 95 (m, br, 1 H) 6.80 (br d, 1 H) 6.93 (br s, 1 H) 7.12 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 - 7.64 (m, 2 H) 7.71-7.96 (m, 3 H) 10.15 (s, br, 1H). LCMS: m/e 758 (M+H).



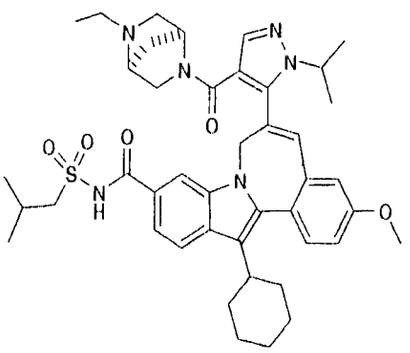
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-: LCMS: m/e 728 (M+H), ret time 3.59 min (method 2).



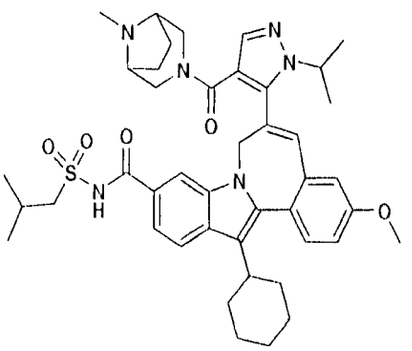
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(2,6-dimethyl-4-morpholinyl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-: LCMS: m/e 756 (M+H), ret time 3.71 min (method 2).



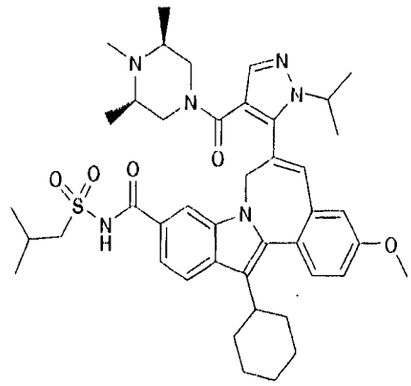
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-: LCMS: m/e 767 (M+H), ret time 3.35 min (method 2).



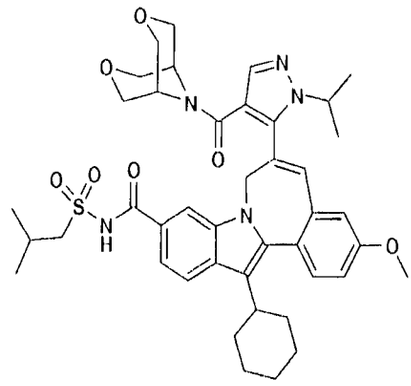
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-: LCMS: m/e 767 (M+H), ret time 3.31 min (method 2).



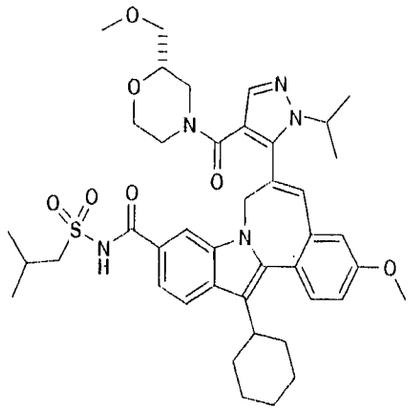
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-: LCMS: m/e 767 (M+H), ret time 3.38 min (method 2).



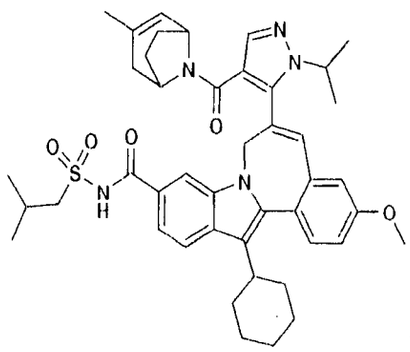
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(2-methylpropyl)sulfonyl]-6-[1-(1-methylethyl)-4-[(3,4,5-trimethyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-: LCMS: m/e 769 (M+H), ret time 3.32 min (method 2).



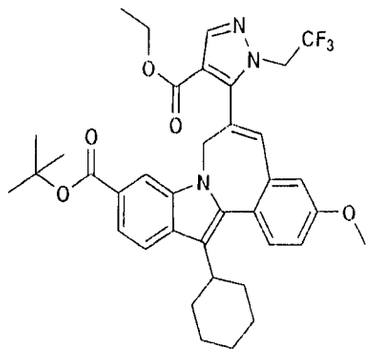
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-:LCMS: m/e 770 (M+H), ret time 3.65 min (method 2).



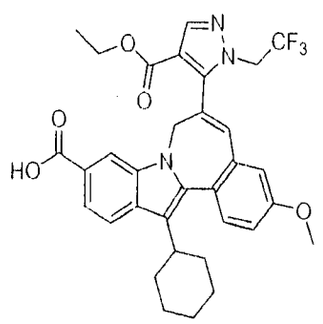
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-: LCMS: m/e 772 (M+H), ret time 3.61 min (method 2).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-8-azabicyclo[3.2.1]oct-2-en-8-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-: LCMS: m/e 764 (M+H), ret time 3.69 min (method 2).

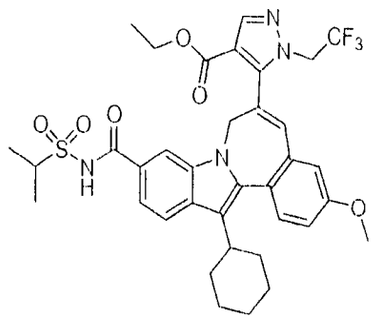


7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester. tert-butyl 13-cyclohexyl-6-((2E,Z)-3-(dimethylamino)-2-(ethoxycarbonyl)-2-propenoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (1.20 g, 1.96 mmol) was dissolved in a solution of ethanol (6.53 mL), triethyl amine (0.396 g, 3.92 mmol), and (2,2,2-trifluoroethyl)hydrazine (0.246 g, 2.15 mmol). The reaction was heated in a microwave at 160 deg C for 2 hours and concentrated. The resulting solid was purified by prep HPLC under the following conditions: Shimadzu prep. HPLC using Discovery VP software: %A= 10% acetonitrile, 90% water, 0.1% TFA; %B= 90% acetonitrile, 10% water, 0.1% TFA; Initial %B= 30; Final % B=100; Gradient= 12min; Runtime=20min; Flow rate= 40ml/min; Column= Waters Sunfire 30 x 100mm S5. This afforded the title compound (1.09 g, 84%) as a yellow paste. MS m/z 664 (MH^+).



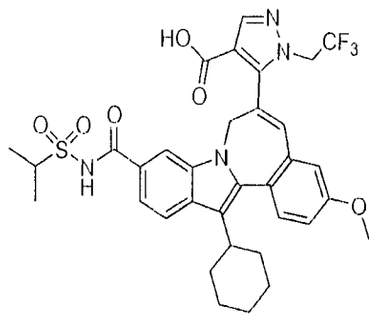
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy-. Dissolve 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-

(ethoxycarbonyl)- 1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester (1.20 g, 1.81 mmol) in 1,2-dichloroethane (3.62 mL), place reaction under a nitrogen atmosphere, then add trifluoroacetic acid (3.62 mL). Stir reaction at room temperature under a nitrogen atmosphere for 2 hours. Remove volatiles in vacuuo and dissolve the reaction product in benzene and remove in vacuuo to aid in removal of trace TFA. Repeat dissolution in benzene and removal in vacuuo. Dried sample at room temperature *in vacuuo* to obtain the title compound (0.923 g, 100% yield) as a yellow solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.20 - 1.62 (m, 7 H) 1.70 - 2.19 (m, 6 H) 2.87 (m, 1 H) 3.91 (s, 3 H) 4.12-4.45 (m, 4 H) 4.76 (br.s, 1 H) 4.97 (br.s, 1 H) 6.82 (s, 1 H) 6.96 (d, *J*=2.14 Hz, 1 H) 7.10 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.56 (d, *J*=8.85 Hz, 1 H) 7.78 (d, *J*=8.24 Hz, 1 H) 7.90 (m, 2 H) 8.11 (s, 1 H). LCMS 608 m/z (MH+).



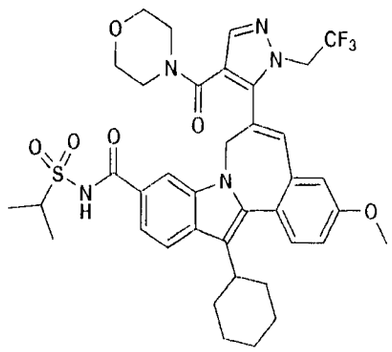
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(2,2,2-trifluoroethyl), ethyl ester. Dissolve 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy- (800 mg, 1.32 mmol) in THF (4.39 mL). Carbonyldiimidazole (640 mg, 3.95 mmol) was added to the reaction. The reaction was placed under a nitrogen atmosphere and stirred at room temperature for 45minutes then heated to reflux for 1 hour. The reaction was cooled under a nitrogen atmosphere and propane-2-sulfonamide (649 mg, 5.27 mmol) was added to the reaction followed by DBU (0.595 mL, 3.95 mmol). The reaction was immerse in oil bath at 80 deg C under nitrogen atmosphere and heated overnight at 70-80 deg C. The reaction was diluted with ethyl acetate (50 mL) and the organic layer washed

sequentially with 1.0N aqueous hydrochloric acid (50 mL), 0.1M aqueous NaH2PO4 (50 mL) and brine (25 mL). The organic layer was dried over MgSO4, filtered and volatiles removed *in vacuuo* to yield a yellow foam which was dried *in vacuuo* at room temperature overnight to yield the title compound (949 mg, 100%) as a yellow amorphous solid. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.20 - 1.62 (m, 13 H) 1.70 - 2.18 (m, 6 H) 2.87 (m, 1 H) 3.90 (s, 3 H) 4.05 (m, 1 H) 4.10-4.40 (m, 4 H) 4.73 (br.s, 1 H) 4.99 (br.s, 1 H) 6.82 (s, 1 H) 6.93 (d, *J*=2.14 Hz, 1 H) 7.10 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.45 (br d, 1 H) 7.52 (d, *J*=8.85 Hz, 1 H) 7.80 (br s , 1 H) 7.88 (d, *J*=8.85 Hz, 1 H) 8.02 (s, 1 H) 8.60 (br s, 1 H). LCMS 713 m/z (MH+).



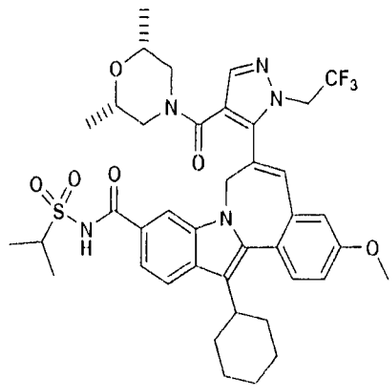
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]- 1-(2,2,2-trifluoroethyl). Dissolve 1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(2,2,2-trifluoroethyl), ethyl ester (0.816 g, 1.15 mmol) in THF (2.86 mL) and methanol (2.86 mL) was added to the reaction followed by 1N aqueous sodium hydroxide (2.29 mL). The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 18 hrs. The reaction was diluted with ethyl acetate (25.0 mL) and washed with 1.0N aqueous hydrochloric acid (2 x 20mL). The organic layer was concentrated *in vacuuo* using a rotary evaporator to yield the title compound as a yellow solid (0.784 g, 100%). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.20 - 1.62 (m, 10 H) 1.70 - 2.18 (m, 6 H) 2.87 (m, 1 H) 3.90 (s, 3 H) 4.05 (m, 1 H) 4.27 (br m, 2 H) 4.73 (br.s, 1 H) 4.99 (br.s, 1 H) 6.82 (s, 1 H) 6.93 (d, *J*=2.14 Hz, 1 H) 7.10 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.45 (br d, 1 H) 7.52 (d,

J=8.85 Hz, 1 H) 7.80 (br s , 1 H) 7.88 (d, *J*=8.85 Hz, 1 H) 8.02 (s, 1 H) 8.60 (br s, 1 H). LCMS 685 m/z (MH+).

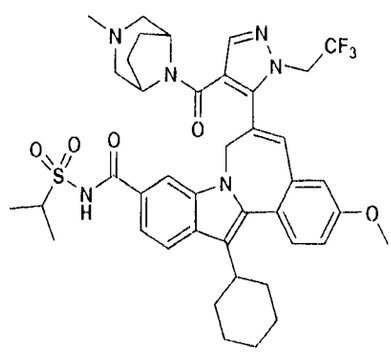


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[4-(4-morpholinylcarbonyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-: 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]- 1-(2,2,2-trifluoroethyl) (90 mg, 0.131 mmol) in DMSO (1.31 mL), TBTU (84 mg, 0.263 mmol) and DIPEA (68 mg, 0.526 mmol) were added. The reaction mixture was stirred at RT for 15 min. Then morpholine (46 mg, 0.526 mmol) was added. The solution was stirred at RT for overnight. The reaction mixture was purified by prep HPLC column using CH_3CN/H_2O/TFA as solvent system. Fractions were collected and concentrated under speedvac overnight to yield the title compound as a yellow solid (53 mg, 0.070 mmol, 53 % yield). MS m/z 754 ($M-H^+$); 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.22 (m, 1 H)1.33 - 1.57 (m, 9 H) 1.70 - 2.18 (m, 6 H) 2.59 (br m, 1 H) 2.70-2.95 (m, 6 H) 3.05-3.21 (m, 2 H) 3.92 (s, 3 H) 4.07 (m, 1 H) 4.73 (br.d, 1 H) 4.76 (br m, 2 H) 4.86 (br.d, 1 H) 6.90 (s, 1 H) 6.94 (d, *J*=2.14 Hz, 1 H) 7.15 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.60 (d, *J*=8.85 Hz, 1 H) 7.63 (d, *J*=8.24 Hz, 1 H) 7.67 (s, 1 H) 7.80 (s, 1 H) 7.93 (d, *J*=8.85 Hz, 1 H).

The following compounds were synthesized by an analogous method as described above for 7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[4-(4-morpholinylcarbonyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-:

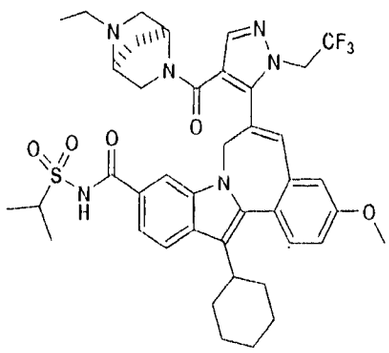


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.64-0.90 (m, 5 H) 1.16-1.28 (m, 2 H) 1.33 - 1.57 (m, 9 H) 1.73 - 2.18 (m, 8 H) 2.30 (br m, 1 H) 2.87 (m, 2 H) 3.05-3.29 (m, 3 H) 3.94 (s, 3 H) 4.07 (m, 1 H) 4.58 (br.d, 1 H) 4.72 (br m, 2 H) 4.93 (br.d, 1 H) 6.87-6.96 (m, 1 H) 7.15 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.52-7.68 (m, 2 H) 7.72-7.85 (m, 2 H) 7.93 (m, 1 H) 8.48 (br s , 1 H). LCMS: m/e 782 (M+H).

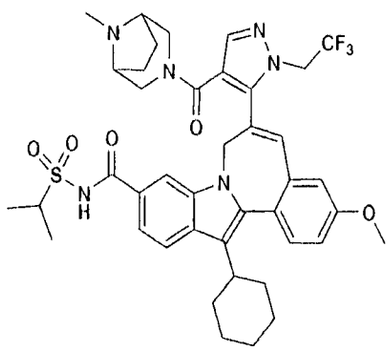


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.19 (br s, 1 H) 0.80 (br s, 1 H) 1.25-1.62 (m, 11 H) 1.76 - 2.18 (m, 7 H) 2.48 (br m, 1 H) 2.62 (br s, 3 H) 2.88 (m, 2 H) 2.95-3.50 (m, 4 H) 3.92 (s, 3 H) 4.06 (m, 1 H) 4.59 (br.d, 1 H) 4.86 (br m, 3 H) 6.93 (s, 1 H) 7.05 (br s, 1

H) 7.17 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.60 (d, *J*=8.85 Hz, 1 H) 7.65 (d, *J*=8.24 Hz, 1 H) 7.86 (br s, 1 H) 7.96 (m, 2 H) 10.0 (br s, 1 H). LCMS: m/e 793 (M+H).

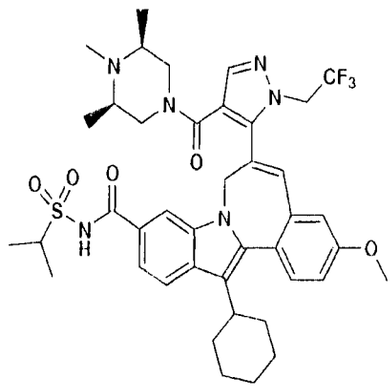


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.10-1.59 (m, 14 H) 1.70 - 2.18 (m, 7 H) 2.38 (m, 1 H) 2.80-3.85 (m, 8 H) 3.95 (s, 3 H) 4.03 (m, 1 H) 4.58 (br.d, 1 H) 4.98 (br.m, 3 H) 6.87-6.96 (m, 1 H) 7.15 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.52-7.68 (m, 2 H) 7.72-7.85 (m, 2 H) 7.93 (m, 1 H) 8.48 (br s , 1 H). LCMS: m/e 793 (M+H).

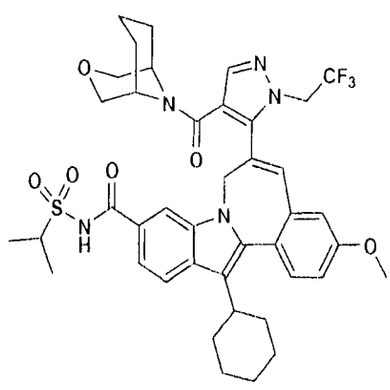


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.18 (br s, 1 H) 0.81 (br s, 1 H) 1.26-1.62 (m, 11 H) 1.80 (m, 2 H) 1.94 - 2.18 (m, 5 H) 2.44 (br m, 1 H) 2.62 (br s, 3 H) 2.90 (m, 2 H) 2.95-

3.55 (m, 4 H) 3.92 (s, 3 H) 4.06 (m, 1 H) 4.59 (br.d, 1 H) 4.86 (br m, 3 H) 6.92 (s, 1 H) 7.03 (br s, 1 H) 7.17 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.58-7.65 (m, 1 H) 7.86 (br s, 1 H) 7.96 (m, 2 H) 10.0 (br s, 1 H). LCMS: m/e 793 (M+H).

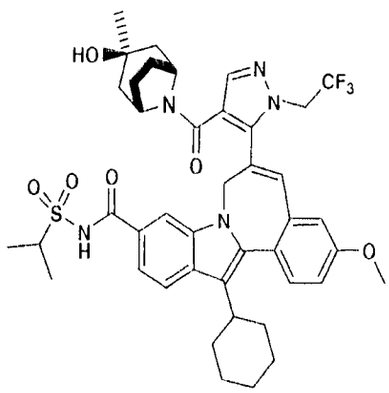


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-(2,2,2-trifluoroethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-: 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.05 - 1.57 (m, 15 H) 1.70 - 2.12 (m, 7 H) 2.30-2.99 (m, 6 H) 3.20-3.65 (m, 4 H) 3.92 (s, 3 H) 4.03 (m, 1 H) 4.60 (br.d, 1 H) 4.65-4.98 (br.m, 3 H) 6.95 (m, 2 H) 7.15 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.57 (m, 2 H) 7.71 (s, 1 H) 7.82 (br s, 1 H) 7.93 (d, *J*=8.85 Hz, 1 H). LCMS: m/e 795 (M+H).

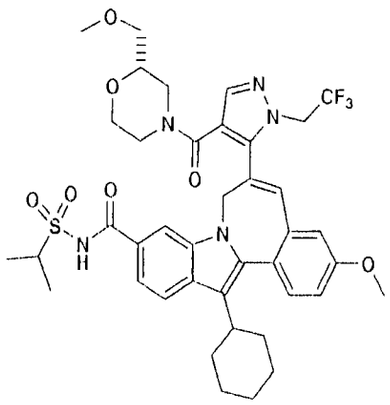


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-: 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.12-1.53 (m, 13 H) 1.70 - 2.40 (m, 9 H) 2.87 (m, 1 H) 3.03-3.62 (m, 6 H) 3.92

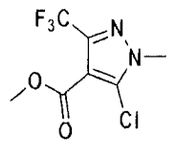
(s, 3 H) 4.07 (m, 1 H) 4.73 (br.d, 1 H) 4.76 (br m, 2 H) 4.86 (br.d, 1 H) 6.90 (s, 1 H) 6.94 (d, *J*=2.14 Hz, 1 H) 7.15 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.60 (d, *J*=8.85 Hz, 1 H) 7.63 (d, *J*=8.24 Hz, 1 H) 7.67 (s, 1 H) 7.80 (s, 1 H) 7.93 (d, *J*=8.85 Hz, 1 H). LCMS: m/e 794 (M+H).



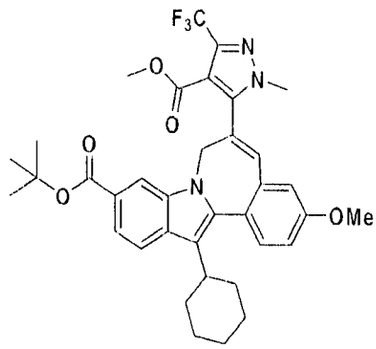
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl)carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm -0.25 (m, 1 H) 0.52 (m, 1 H) 1.06 (s, 3 H) 1.15-1.82 (m, 18 H) 1.91 - 2.18 (m, 4 H) 2.88 (m, 1 H) 3.32 (m, 1 H) 3.60 (m, 1 H) 3.93 (s, 3 H) 4.07 (m, 1 H) 4.56 (br d, 1 H) 4.82 (m, 2 H) 4.97 (br d, 1 H) 6.82 (br s, 2 H) 7.16 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.60 (d, *J*=8.55 Hz , 1 H) 7.70 (d, *J*=8.24 Hz, 1 H) 7.84-7.92 (m, 3 H). LCMS: m/e 808 (M+H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-: 1H NMR (500 MHz, CDCl3) δ ppm 1.21 (m, 1 H) 1.32 - 1.70 (m, 9 H) 1.73 - 2.20 (m, 6 H) 2.72-3.40 (m, 13 H) 3.92 (m, 3 H) 4.10 (m, 1 H) 4.60 (m, 1 H) 4.82 (m, br, 3 H) 6.85-6.96 (m, 2 H) 7.17 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 - 7.72 (m, 3 H) 7.80-7.96 (m, 2 H).LCMS: m/e 798 (M+H).

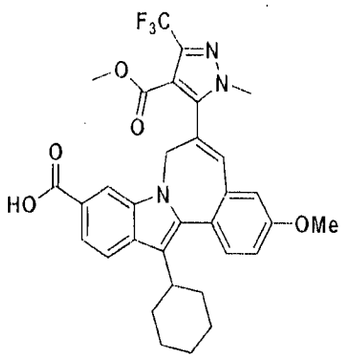


Methyl 5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate . To a solution of 5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxyllic acid (1.00g, 4.38 mmol) in benzene (5.83 mL) and methanol (2.92 mL) at room temperature was added 2M trimethylsilyldiazomethane (8.75 mL). The resulting solution was stirred at room temperature for 3 hours. Solvent was removed at reduced pressure on a rotory evaporator to yield the title compound (1.06 g, 4.38 mmol, 100 % yield) as a white solid. MS m/z 243(MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 3.82 (s, 3 H) 3.89 (s, 3 H).



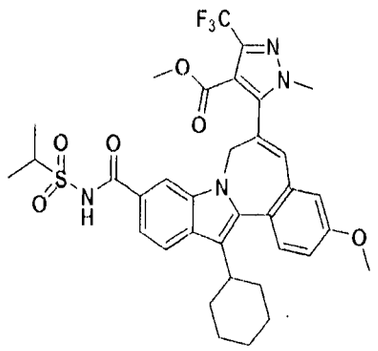
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-, 1,1-dimethylethyl ester. In a microwave tube, 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(tributylstannyl)-, 1,1-dimethylethyl ester (1.00 g, 1.37 mmol), methyl 5-chloro-1-methyl-3-(trifluoromethyl)-1H-

pyrazole-4-carboxylate (497 mg, 2.05 mmol) and bis(dibenzylideneacetone) palladium (78 mg, 0.136 mmol) were added. It was then sealed, degassed and flushed with nitrogen. 1,4-dioxane (6.83 mL) was added. The reaction mixture was heated at 160°C under microwave condition for 3 hours. It was then filtered and the filtrate was concentrated. The residue was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (8 mL) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 25% solvent A / 75% solvent B to 0% solvent A / 100% solvent B, a gradient time of 10 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. The product-containing fractions were collected and concentrated to give title compound as a yellow solid (547 mg, 0.842 mmol, 61% yield). MS m/z 650 (MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.06 - 2.29 (m, 19 H) 2.85 (m, 1 H) 3.30 (s, br, 3 H) 3.78 (s, br, 3H) 3.91 (s, 3 H) 4.76 (m, br, 1 H) 4.97 (m, br, 1 H) 6.80 (s, 1 H) 6.93 (d, *J*=2.44 Hz, 1 H) 7.11 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.56 (d, *J*=8.54 Hz, 1 H) 7.82 (dd, *J*=8.24, 1.22 Hz, 1 H) 7.91 (dd, *J*=8.24, 1.22 Hz, 1 H) 7.98 (s, 1 H).



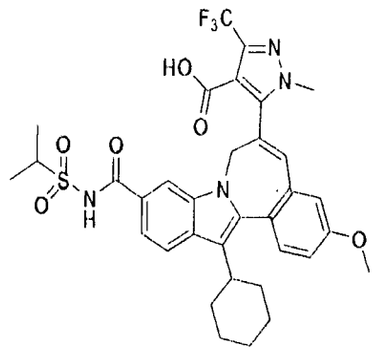
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)- 1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-. To a solution of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-

methoxy-6-[4-(methoxycarbonyl)- 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-, 1,1-dimethylethyl ester (547 mg, 0.842 mmol) in 1,2-dichloroethane (5 mL), TFA (5 mL) was added. The reaction mixture was stirred at RT for 4 hours. Volatiles were removed on a rotary evaporator to give the title compound as a brownish thick oil as crude product (500 mg, 0.842 mmol, 100 % yield). MS m/z 594(MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.06 - 2.28 (m, 10 H) 2.86 (m, 1 H) 3.30 (s, br, 3 H) 3.78 (s, br, 3H) 3.91 (s, 3 H) 4.75 (m, br, 1 H) 4.96 (m, br, 1 H) 6.80 (s, 1 H) 6.93 (d, *J*=2.44 Hz, 1 H) 7.10 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.54 (d, *J*=8.54 Hz, 1 H) 7.81 (dd, *J*=8.24, 1.22 Hz, 1 H) 7.91 (dd, *J*=8.24, 1.22 Hz, 1 H) 7.97 (s, 1 H).

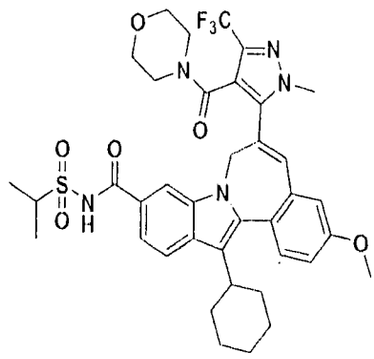


1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]- 1-methyl-3-(trifluoromethyl)-, methyl ester. To a solution of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)- 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]- (480 mg, 0.809 mmol) in tetrahydrofuran (2.70 mL) was added carbonyldiimidazole (393 mg, 2.43 mmol). The reaction mixture was heated at 60°C for one hour and then allowed to cool. Propane-2-sulfonamide (398 mg, 3.23 mmol) and DBU (0.366 mL, 2.43 mmol) were added at room temperature, and the reaction mixture was then heated at 60°C for 4 hours. The resultant mixture was then diluted with 1N HCl (50 mL) solution and extracted with ethyl acetate (2 X 40mL). The organic layers were combined and concentrated on a rotory evaporator to give the product as an orange colored oil. This material was then purified by preparative HPLC column using CH_3CN/H_2O/TFA as solvent system. Homogeneous fractions were collected and concentrated under reduced pressure. The title compound was obtained as a yellow solid, (492 mg,

0.704 mmol, 87 % yield). MS m/z 699 (MH^+). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.16 - 1.61 (m, 10 H) 1.69 - 2.21 (m, 6 H) 2.86 (m, 1 H) 3.34 (s, br, 3H) 3.67 (s, br, 3 H) 3.91 (s, 3 H) 4.01 - 4.19 (m, 1 H) 4.70 (m, br, 1 H) 4.97 (m, br, 1 H) 6.70 (s, 1 H) 6.94 (d, *J*=2.75 Hz, 1 H) 7.09 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.51 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.81 (d, *J*=1.22 Hz, 1 H) 7.88 (d, *J*=8.55 Hz, 1 H) 7.92 (d, *J*=8.55 Hz, 1 H) 8.68 (s, 1 H).

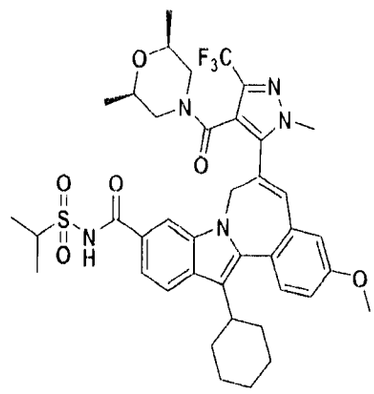


1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]- 1-methyl-3-(trifluoromethyl)-. 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]- 1-methyl-3-(trifluoromethyl)-, methyl ester (0.300 g, 0.429 mmol) was dissolved in THF (1.07 mL) and methanol (1.07 mL) was added followed by 1N aqueous sodium hydroxide (0.900 mL). The reaction was then placed under a nitrogen atmosphere and stirred at room temperature for 18 hrs. The mixture was then diluted with ethyl acetate (50.0 mL) and washed with 1.0 N aqueous hydrochloric acid (2 x 50ml). The organic layer was concentrated *in vacuuo* using a rotary evaporator to yield the title compound as a yellow solid (282 mg, 0.412 mmol, 96%). MS m/z 685(MH^-). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.16 - 1.61 (m, 10 H) 1.69 - 2.21 (m, 6 H) 2.86 (m, 1 H) 3.34 (s, br, 3 H) 3.91 (s, 3 H) 4.01 - 4.19 (m, 1 H) 4.70 (m, br, 1 H) 4.99 (m, br, 1 H) 6.70 (s, 1 H) 6.94 (d, *J*=2.75 Hz, 1 H) 7.10 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.51 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.81 (d, *J*=1.22 Hz, 1 H) 7.88 (d, *J*=8.55 Hz, 1 H) 7.92 (d, *J*=8.55 Hz, 1 H) 9.00 (s, 1 H).

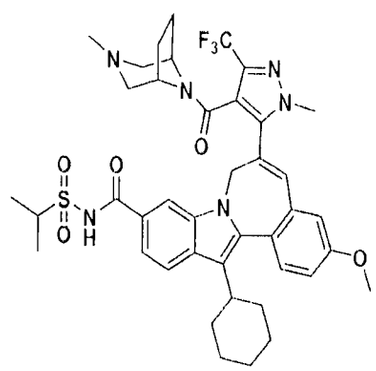


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(4-morpholinylcarbonyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-. To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]- 1-methyl-3-(trifluoromethyl)- (75 mg, 0.11 mmol) in DMSO (1.1 mL), TBTU (70 mg, 0.22 mmol) and DIPEA (0.057 mL, 0.4444 mmol) were added. The reaction mixture was stirred at RT for 15 min. Then morpholine (38 mg, 0.44 mmol) was added. The solution was stirred at RT overnight. The reaction mixture was then purified by preparative HPLC using CH_3CN/H_2O/TFA as solvent system. Homogeneous fractions were collected and concentrated under under reduced pressure to yield the title compound as a yellow solid, (67 mg, 0.089 mmol, 81 % yield). MS m/z 754 ($M-H^+$). 1H NMR (500 MHz, MeOD) δ ppm 1.18 - 1.52 (m, 10 H) 1.75 - 2.25 (m, 6 H) 2.63 - 3.26 (m, 9 H) 3.50 (s, br, 3 H) 3.95 (s, 3 H) 3.96 - 4.03 (m, 1 H) 4.64 (d, br, 1 H) 4.98 (m, br, 1 H) 6,88 (s, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.15 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.55 - 7.65 (m, 2 H) 7.80 (s, br, 1 H) 7.93 (d, *J*=8.55 Hz, 1 H) 10.30 (s, br, 1H).

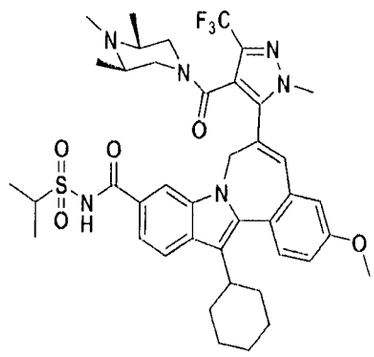
The following compounds were synthesized by an analogous method as described above for 7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(4-morpholinylcarbonyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-:



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-. MS m/z 782 ($M-H^+$). 1H NMR (500 MHz, MeOD) δ ppm 0.71 (s, br, 3H), 0.75 (s, br, 3H) 1.18 - 1.52 (m, 10 H) 1.75 - 2.21 (m, 9 H) 2.35 (m, 1 H) 2.83 - 3.21 (m, 3 H) 3.50 (s, br, 3 H) 3.95 (s, 3 H) 3.96 - 4.03 (m, 1 H) 4.64 (d, br, 1 H) 5.02 (d, br, 1 H) 6.81 (s, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.13 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.55 - 7.65 (m, 2 H) 7.80 (s, br, 1 H) 7.93 (d, *J*=8.55 Hz, 1 H) 10.50 (s, br, 1 H).

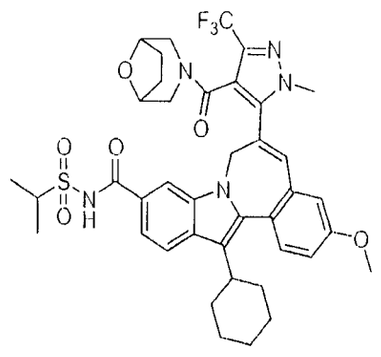


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-. MS m/z 793 ($M-H^+$). 1H NMR (500 MHz, MeOD) δ ppm 1.16 - 2.20 (m, 20 H) 2.40-2.99 (m, 7 H) 3.22-3.71 (m, 3H) 3.90-4.11 (m, 7 H) 4.63 (m, br, 1 H) 4.98 (m, br, 1 H) 6.98 (m, 1 H) 7.03 (m, 1 H) 7.23 (m, 1H) 7.52 - 7.73 (m, 3 H) 7.82 (s, br, 1 H) 10.10 (s, br, 1H).



7H-*indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-3-(trifluoromethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-*. MS m/z 795 ($M-H^+$). 1H NMR (500 MHz, MeOD) δ ppm 1.10 - 1.51 (m, 16 H) 1.71 - 2.50 (m, 11 H) 2.59-2.94 (m, 5 H) 3.50 (s, br, 3 H) 3.96 (s, 3 H) 4.63 (m, br, 2 H) 4.95 (m, br, 1 H) 6.93 (m, 2 H) 7.13 (m, 1 H) 7.49 - 7.65 (m, 2 H) 7.82 (s, br, 1 H) 7.93 (m, 1 H) 10.10 (s, br, 1H).

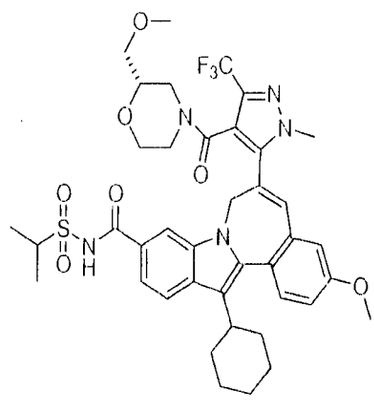
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-ylcarbonyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-



MS m/z 780 ($M-H^+$)

1H NMR (500 MHz, CDCl3) δ ppm 0.70 (m, 1H) 1.21 - 1.52 (m, 13 H) 1.75 - 2.20 (m, 8 H) 2.30 (m, 1H) 2.79 – 2.98 (m, 3 H) 3.11 (m, 1H) 3.87 (m, 1H) 3.98 (s, br, 3 H) 4.05 (s, 3 H) 4.61 (d, br, 1 H) 4.89 (m, br, 1 H) 6.85-6.98 (m, 2 H) 7.17 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.55 - 7.70 (m, 2 H) 7.84-8.03 (m, 1 H) 7.93 (d, *J*=8.55 Hz, 1 H) 10.45 (s, br, 1H).

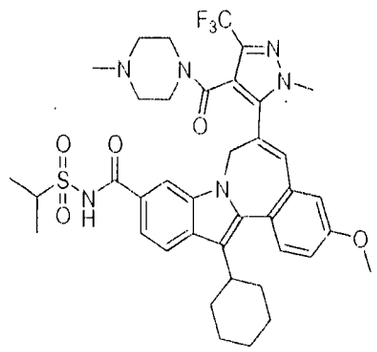
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-



MS m/z 798 ($M-H^+$)

1H NMR (500 MHz, CDCl3) δ ppm 1.11 - 1.61 (m, 10 H) 1.75 - 2.52 (m, 10 H) 2.81 - 3.60 (m, 9 H) 3.95 (s, br, 3 H) 4.03 (s, 3 H) 3.95 - 4.03 (m, 1 H) 4.65 (d, br, 1 H) 5.01 (m, br, 1 H) 6.85 (br s, 1 H) 6.97 (s, 1 H) 7.15 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.50 - 7.71 (m, 2 H) 7.79-7.93 (m,2 H) 10.40 (s, br, 1H).

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(4-methyl-1-piperazinyl)carbonyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-

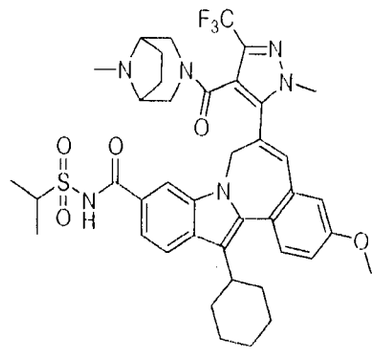


MS m/z 767 ($M-H^+$)

1H NMR (500 MHz, CDCl3) δ ppm 1.13 - 1.58 (m, 10 H) 1.75 - 2.12 (m, 6 H) 2.20 - 2.97 (m, 5 H) 3.19-3.79 (m, 7H) 3.95 (s, 3 H) 3.99 (br s, 3 H) 3.95 - 4.03 (m, 1 H)

4.50 (m, br, 1 H) 4.92 (m, br, 1 H) 6.87-7.01 (m, 2 H) 7.11 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.50 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.59-7.80 (m, 2 H) 7.91 (br s, 1 H) 10.50 (s, br, 1H).

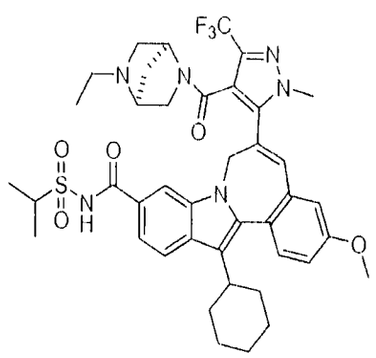
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)carbonyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-



MS m/z 793 ($M-H^+$)

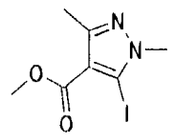
1H NMR (500 MHz, CDCl3) δ ppm 0.37 (br m, 1H) 0.83 (br m, 1H) 1.14 - 1.70 (m, 11 H) 1.75-2.16 (m, 7H) 2.35-2.70 (m, 4 H) 2.86 (m, 2 H) 3.20-3.79 (m, 4H) 3.90-4.11 (m, 7 H) 4.63 (d, br, 1 H) 4.94 (m, br, 1 H) 6.95-7.10 (m, 2 H) 7.15 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.53 - 7.70 (m, 3 H) 7.81 (s, br, 1 H) 10.10 (s, br, 1H).

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-



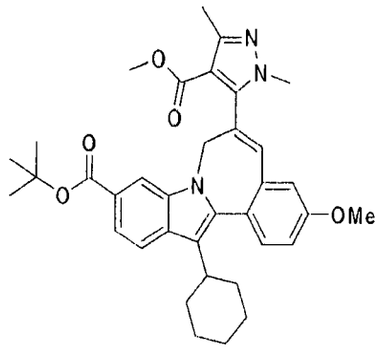
MS m/z 793 ($M-H^-$)

1H NMR (500 MHz, CDCl3) δ ppm 0.55 (br m, 1H) 1.14 - 1.70 (m, 13 H) 1.75-2.16 (m, 7H) 2.52-3.70 (m, 9 H) 3.89-4.11 (m, 7 H) 4.69 (d, br, 1 H) 5.00 (m, br, 1 H) 6.95-7.15 (m, 3 H) 7.50-7.81 (m, 4 H) 10.20 (s, br, 1H).



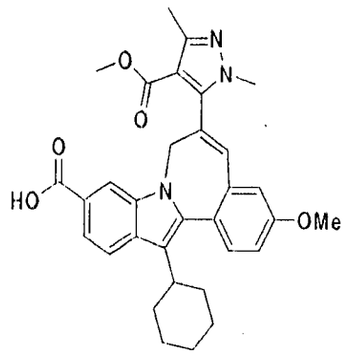
Methyl 5-iodo-1,3-dimethyl-1H-pyrazole-4-carboxylate.

To a solution of methyl 1, 3-dimethyl-1H-pyrazole-4-carboxylate (154 mg, 1 mmol) in dry tetrahydrofuran (10 mL) at -78°C, 2 M solution of BuLi (0.550 mL, 1.100 mmol) in pentane was added dropwise. The reaction mixture was then warmed to -45°C and stirred for 1 h. It was then cooled to -78°C and a solution of IODINE (279 mg, 1.100 mmol) in THF (2 mL) was added. The reaction mixture was warmed to RT and stirred for 1h. It was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate (2X25 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. The crude product was obtained as a brown thick oil. This material was then purified by preparative HPLC using CH_3CN/H_2O/TFA as solvent system. Homogeneous fractions were combined and concentrated in vacuo. The concentrate was then extracted with ethyl acetate and the extracts combined and dried over $MgSO_4$. The suspension was then filtered and the filtrand evaporated under reduced pressure to give the title compound as a white solid, (137 mg, 0.460 mmol, 46.0 % yield). MS m/z 281(MH), Retention time: 1.107 min.(basic). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 2.45 (s, 3 H) 3.84 (s, 3 H) 3.91 (s, 3 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1,3-dimethyl-1H-pyrazol-5-yl]-, 1,1-dimethylethyl ester.

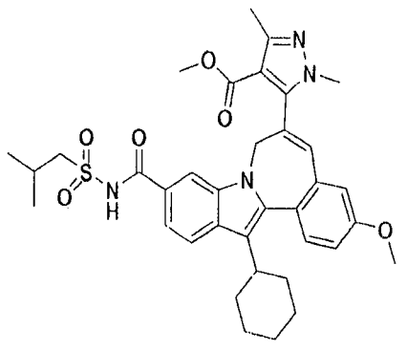
7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(tributylstannyl)-, 1,1-dimethylethyl ester (50 mg, 0.068 mmol), methyl 5-iodo-1,3-dimethyl-1H-pyrazole-4-carboxylate (38.2 mg, 0.136 mmol) and Bis(triphenylphosphine)-palladium(II) chloride (4.79 mg, 6.82 μmol) were added to a standard microwave tube. The vessel was then sealed, degassed and flushed with nitrogen. 1,4-Dioxane (2.0 mL) was added and the resultant mixtue was heated at 120^{0}C under microwave conditions for 2h. It was then filtered and the filtrate concentrated. The residue was purified by preparative.HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were collected and concentrated in vacuo to give the title compound as an orange colored solid, (9.1 mg, 0.015 mmol, 21.26 % yield). MS m/z 596 (MH^+), Retention time: 2.893 min.(basic). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.06 - 2.28 (m, 19 H) 2.47 (s, 3 H) 2.77 - 2.93 (m, 1 H) 3.19 (s, 3 H) 3.53 - 3.83 (s, br, 3 H) 3.90 (s, 3 H) 4.58 - 4.73 (m, br, 1 H) 4.86 - 5.03 (m, br, 1 H) 6.71 (s, 1 H) 6.92 (d, *J*=2.44 Hz, 1 H) 7.06 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.52 (d, *J*=8.54 Hz, 1 H) 7.65 (dd, *J*=8.24, 1.22 Hz, 1 H) 7.80 - 7.85 (m, 2 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1,3-dimethyl-1H-pyrazol-5-yl]-.

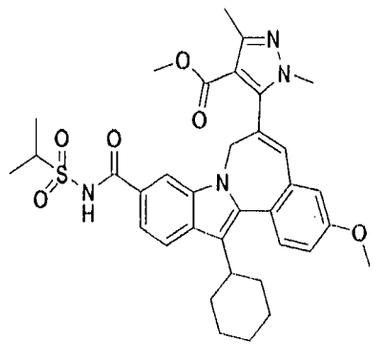
To a solution of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]-, 1,1-dimethylethyl ester (601 mg, 1.009 mmol) in 1,2-Dichloroethane (10 mL), TFA (5 mL, 64.9 mmol) was added. The reaction mixture was stirred at RT for 4 hours. Solvent and TFA were then evaporated to give a brownish thick oil,(650 mg, 1.144 mmol, 113 % yield). 10 mg of this crude product was purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated under reduced pressure to give the title compound as a yellow solid, (3.5 mg, 35% recovery). MS m/z 540(MH^+), Retention time: 1.925 min. (basic). 1H NMR (500 MHz, MeOD) δ ppm 1.15 - 1.59 (m, 4 H) 1.68 - 2.24 (m, 6 H) 2.41 (s, 3 H) 2.84 - 2.97 (m, 1 H) 3.11 - 3.50 (m, br, 6 H) 3.90 (s, 3 H) 4.55 - 4.69 (m, br, 1 H) 4.94 - 5.06 (m, br, 1 H) 6.88 (s, 1 H) 7.07 (d, *J*=2.44 Hz, 1 H) 7.14 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.57 (d, *J*=8.55 Hz, 1 H) 7.67 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.87 (d, *J*=8.54 Hz, 1 H) 7.89 (s, 1 H).

Note: The remaining crude product was used in the subsequent steps without further purification.



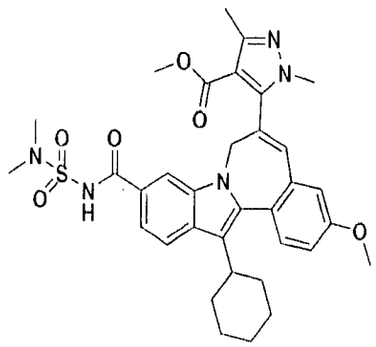
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester.

To a solution of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]- (225 mg, 0.417 mmol) in tetrahydrofuran (10 mL), CDI (101 mg, 0.625 mmol) was added. The reaction mixture was heated at 60°C for one hour and then allowed to cool to RT. 2-Methylpropane-1-sulfonamide (172 mg, 1.251 mmol) and DBU (0.126 mL, 0.834 mmol) were then added and the resultant mixture was heated at 60°C for 4 hours. The reaction was then quenched with 1N HCl solution and the product extracted with ethyl acetate (2 x 40mL). The organic layers were combined, washed with 1N HCl solution, brine, dried ($MgSO_4$) and then filtered. Evaporation of the filtrate gave the product as an orange colored oil. This material was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated in vacuo, to provide the title compound as a yellow colored solid, (46.6 mg, 0.067 mmol, 16.12 % yield). MS m/z 659(MH^+), Retention time: 2.197 min. (basic). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.14 (d, *J*=6.71 Hz, 6 H) 1.19 - 1.60 (m, 4 H) 1.70 - 2.15 (m, 6 H) 2.34 - 2.43 (m, 1 H) 2.49 (s, 3 H) 2.80 - 2.92 (m, 1 H) 3.12 - 3.75 (m, 8 H) 3.91 (s, 3 H) 4.63 - 4.74 (m, br, 1 H) 4.85 - 4.99 (m, br, 1 H) 6.75 (s, 1 H) 6.94 (d, *J*=2.75 Hz, 1 H) 7.09 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.39 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.53 (d, *J*=8.55 Hz, 1 H) 7.75 (d, *J*=1.22 Hz, 1 H) 7.90 (d, *J*=8.55 Hz, 1 H) 8.52 (s, 1 H).



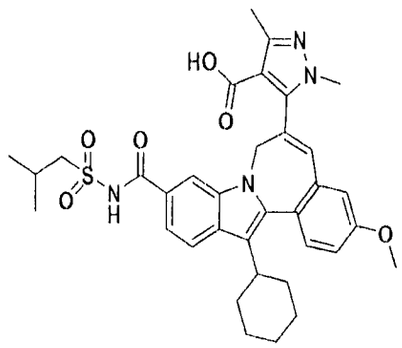
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester.

To a solution of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]- (225 mg, 0.417 mmol) in tetrahydrofuran (10 mL), CDI (101 mg, 0.625 mmol) was added. The reaction mixture was heated at 60°C for one hour and was then allowed to cool to room temperature. Propane-2-sulfonamide (154 mg, 1.251 mmol) and DBU (0.126 mL, 0.834 mmol) were then added and the resultant mixture was heated at 60°C for 4 hours. The reaction was then quenched with 1N HCl solution and the product extracted with ethyl acetate (2 x 40mL). The organic layers were combined, washed with 1N HCl solution, brine, then dried ($MgSO_4$) and filtered. Evaporation of solvents gave the product as an orange colored thick oil. This material was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated in vacuoto provide the title compound as a yellow colored solid, (42.5 mg, 0.066 mmol, 15.81 % yield). MS m/z 645(MH^+), Retention time: 2.105 min. (basic). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.16 - 1.61 (m, 10 H) 1.69 - 2.21 (m, 6 H) 2.48 (s, 3 H) 2.81 - 2.92 (m, 1 H) 3.24 (s, 3 H) 3.66 (s, br, 3 H) 3.91 (s, 3 H) 4.01 - 4.10 (m, 1 H) 4.63 - 4.75 (m, br, 1 H) 4.84 - 4.98 (m, br, 1 H) 6.74 (s, 1 H) 6.94 (d, *J*=2.75 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.39 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.53 (d, *J*=8.55 Hz, 1 H) 7.74 (d, *J*=1.22 Hz, 1 H) 7.90 (d, *J*=8.55 Hz, 1 H) 8.28 (s, 1 H).



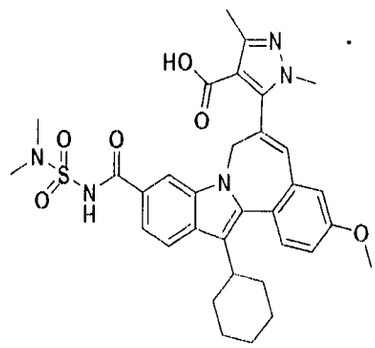
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester.

To a solution of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]- (120 mg, 0.222 mmol) in THF (5 mL), CDI (54.1 mg, 0.334 mmol) was added. The reaction mixture was heated at 60°C for one hour, and then allowed to cool to room temperature. N,N-dimethylsulfamide (83 mg, 0.667 mmol) and DBU (0.067 mL, 0.445 mmol) were then added and the resultant mixture was heated at 60°C overnight. The reaction was then quenched with 1N HCl solution and the product extracted with ethyl acetate (2 x 30mL). The organic layers were combined, washed with 1N HCl solution, brine, dried ($MgSO_4$) and then filtered. Evaporation of solvents gave the curde product as an orange colored thick oil. This material was then purified by preparative HPLC using CH_3CN-H_2O-TFA as a solvent system. Homogeneous fractions were combined and concentrated under vacuum to provide the title compound as an orange colored solid, (31.4 mg, 0.049 mmol, 21.87 % yield). MS m/z 646(MH^+), Retention time: 2.245min. (basic). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.18 - 1.60 (m, 4 H) 1.70 - 2.14 (m, 6 H) 2.49 (s, 3 H) 2.80 - 2.91 (m, 1 H) 3.05 (s, 6 H) 3.24 (s, 3 H) 3.68 (s, br, 3 H) 3.91 (s, 3 H) 4.64 - 4.74 (m, br, 1 H) 4.86 - 5.00 (m, br, 1 H) 6.74 (s, 1 H) 6.94 (d, *J*=2.75 Hz, 1 H) 7.08 (dd, *J*=8.85, 2.75 Hz, 1 H) 7.35 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.53 (d, *J*=8.55 Hz, 1 H) 7.75 (d, *J*=1.22 Hz, 1 H) 7.89 (d, *J*=8.54 Hz, 1 H) 8.44 (s, 1 H).



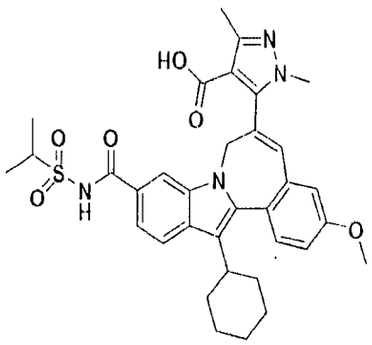
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-.

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester (44.2 mg, 0.067 mmol) in tetrahydrofuran (2.0 mL) and MeOH (2.000 mL), 1N NaOH (0.537 mL, 0.537 mmol) solution was added. The reaction mixture was stirred at RT for 4 days. LC/MS showed that only ~ 25% of the starting ester was hydrolyzed. 0.5 mL of more 1N NaOH solution was added. The reaction mixture was then stirred at RT for three more days. The reaction mixture was concentrated, and the residue was acidified using 1N HCl solution. The resultant mixture was then extracted with ethyl acetate (2 x 20 mL) and the organic layers were combined, washed with brine, dried ($MgSO_4$) and then filtered. Evaporation of filtrate gave the crude product as a viscous orange-colored oil. This material was then purified by preparative HPLC using CH_3CN-H_2O-TFA as a solvent system. Homogeneous fractions were collected concentrated under reduced pressure to give the title compound as a light yellow colored solid, (12.2 mg, 0.019 mmol, 28.2 % yield). MS m/z 645(MH^+), Retention time: 1.847 min.(basic). 1H NMR (500 MHz, DMSO-D6) δ ppm 1.02 (d, *J*=6.71 Hz, 6 H) 1.08 - 1.53 (m, 4 H) 1.64 - 2.09 (m, 6 H) 2.08 - 2.20 (m, 1 H) 2.36 (s, 3 H) 2.71 - 2.85 (m, 1 H) 3.09 (s, 3 H) 3.45 (d, *J*=6.71 Hz, 2 H) 3.88 (s, 3 H) 4.42 - 4.62 (m, br, 1 H) 4.96 - 5.18 (m, br, 1 H) 6.97 (s, 1 H) 7.15 (d, *J*=2.75 Hz, 1 H) 7.21 (dd, *J*=8.85, 2.75 Hz, 1 H) 7.54 (d, *J*=8.85 Hz, 1 H) 7.60 (dd, *J*=8.39, 1.37 Hz, 1 H) 7.90 (d, *J*=8.54 Hz, 1 H) 8.14 (s, 1 H) 11.76 (s, 1 H) 12.37 (s, br, 1 H).



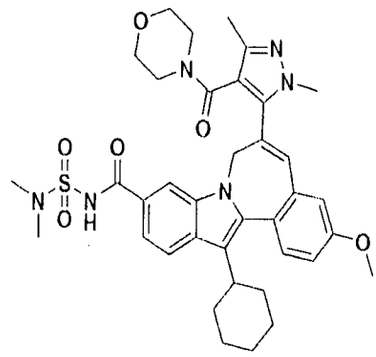
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-.

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester (29.4 mg, 0.046 mmol) in THF (1.5 mL) and MeOH (1.500 mL), 1N NaOH (0.364 mL, 0.364 mmol) solution was added. The reaction mixture was stirred at RT for 4 days. LC/MS showed that only ~ 40% ester was hydrolyzed. 0.5 mL of more 1N NaOH solution was added. The reaction mixture was then stirred at RT for three more days. The reaction mixture was concentrated and the residue acidified using 1N HCl solution. The product was then extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$) and then filtered. Evaporation of filtrate gave the crude product as an orange colored oil. This material was then purified by preparative HPLC using CH_3CN-H_2O-TFA as a solvent system. Homogeneous fractions were combined and concentrated in vacuo to give the title compound as a light yellow colored solid, (9.5 mg, 0.015 mmol, 33.0 % yield). MS m/z 632(MH^+), Retention time: 1.853 min.(basic). 1H NMR (500 MHz, DMSO-D6) δ ppm 1.06 - 1.53 (m, 4 H) 1.58 - 2.07 (m, 6 H) 2.35 (s, 3 H) 2.74 - 2.83 (m, 1 H) 2.87 (s, 6 H) 3.02 - 3.16 (s, br, 3 H) 3.88 (s, 3 H) 4.41 - 4.61 (m, br,1 H) 4.96 - 5.20 (m, br, 1 H) 6.97 (s, 1 H) 7.15 (d, *J*=2.75 Hz, 1 H) 7.20 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.54 (d, *J*=8.55 Hz, 1 H) 7.60 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.89 (d, *J*=8.54 Hz, 1 H) 8.14 (s, 1 H) 11.51 (s, 1 H) 12.35 (s, br, 1 H).



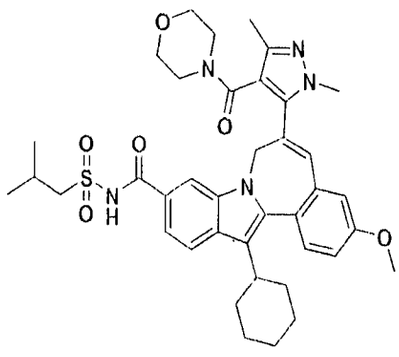
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-.

To a mixture of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester (80 mg, 0.124 mmol) and potassium trimethylsilanolate (TMSOK) (31.8 mg, 0.248 mmol) in a round-bottomed flask, Tetrahydrofuran (8 mL) was added. The resultant mixture was then stirred at RT overnight. LC/MS showed that only 40% of SM reacted. Two more equivalents of TMSOK were added and stirring was contined for 48 hrs. The reaction mixture was then concentrated and 1N HCl solution was added. A yellow solid separated (85 mg). and 10 mg of the matieral was then purified by preparative HPLC using CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and evaporated under vacuum to give the title compound as a yellow colored solid, (7.6 mg, 76% recovery). MS m/z 631(MH^+), Retention time: 1.648 min. (basic). 1H NMR (500 MHz, Acetone) δ ppm 1.11 - 1.61 (m, 10 H) 1.63 - 2.21 (m, 6 H) 2.38 (s, 3 H) 2.85 - 3.00 (m, 1 H) 3.17 (s, 3 H) 3.83 - 3.97 (m, 4 H) 4.54 - 4.72 (m, br, 1 H) 5.09 - 5.29 (m, br, 1 H) 6.93 (s, 1 H) 7.11 (d, *J*=2.75 Hz, 1 H) 7.17 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.61 (d, *J*=8.55 Hz, 1 H) 7.68 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.96 (d, *J*=8.55 Hz, 1 H) 8.21 (s, 1 H) 9.96 (s, 1 H). Note: The crude product describe above can be used without further purification for the preparation of carboxamide examples of the current invention.



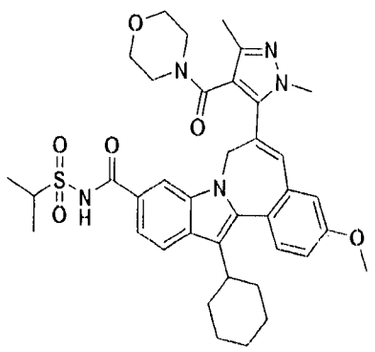
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-[1,3-dimethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-.

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1,3-dimethyl- (9.5 mg, 0.015 mmol) in DMSO (1 mL), TBTU (9.66 mg, 0.030 mmol) and DIPEA (0.013 mL, 0.075 mmol) were added. The reaction mixture was stirred at RT for 15 min. Morpholine (1.965 mg, 0.023 mmol) was then added and the resultant solution was stirred at RT for 48 hours. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as a solvent system. Homogeneous fractions were combined and concentrated under vacuum. The title compound was obtained as a yellow colored solid, (8.0 mg, 0.011 mmol, 74.4 % yield). MS m/z 699 ($M-H^+$), Retention time: 1.990 min.(basic). 1H NMR (500 MHz, MeOD) δ ppm 1.18 - 1.64 (m, 4 H) 1.73 - 2.26 (m, 9 H) 2.59 - 3.09 (m, 15 H) 3.85 (s, 3 H) 3.95 (s, 3 H) 4.67 (d, *J*=14.96 Hz, 1 H) 5.02 - 5.15 (m, 1 H) 7.07 (s, 1 H) 7.15 (d, *J*=2.44 Hz, 1 H) 7.20 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.56 - 7.64 (m, 2 H) 7.92 (s, 1 H) 7.98 (d, *J*=8.55 Hz, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1,3-dimethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-.

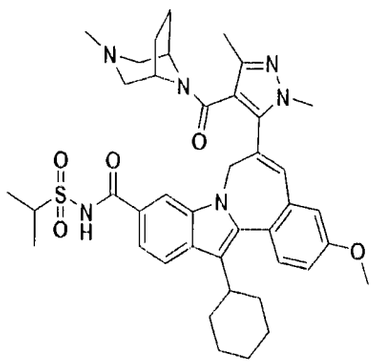
To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1,3-dimethyl- (10 mg, 0.016 mmol) in DMSO (1 mL), TBTU (9.96 mg, 0.031 mmol) and DIPEA (0.014 mL, 0.078 mmol) were added. The reaction mixture was stirred at RT for 15 min. Morpholine (1.351 mg, 0.016 mmol) was then added and the resultant solution was stirred at RT overnight. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as a solvent system. Homogeneous fractions were collected and concentrated under vacuum, to provide the title compound as a yellow colored solid, (10.7 mg, 0.015 mmol, 95 % yield). MS m/z 712(M-H$^-$), Retention time: 1.895 min.(basic). 1H NMR (500 MHz, MeOD) δ ppm 1.16 (d, *J*=6.71 Hz, 6 H) 1.20 - 1.64 (m, 4 H) 1.73 - 2.27 (m, 9 H) 2.29 - 2.43 (m, 1 H) 2.56 - 3.14 (m, 9 H) 3.49 - 3.55 (m, 2 H) 3.85 (s, 3 H) 3.95 (s, 3 H) 4.67 (d, *J*=14.96 Hz, 1 H) 4.98 - 5.16 (m, br, 1 H) 7.07 (s, 1 H) 7.15 (d, *J*=2.44 Hz, 1 H) 7.20 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.55 - 7.66 (m, 2 H) 7.95 (s, 1 H) 7.98 (d, *J*=8.55 Hz, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1,3-dimethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-.

To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1,3-dimethyl- (20 mg, 0.032 mmol) in DMSO (1 mL), TBTU (20.36 mg, 0.063

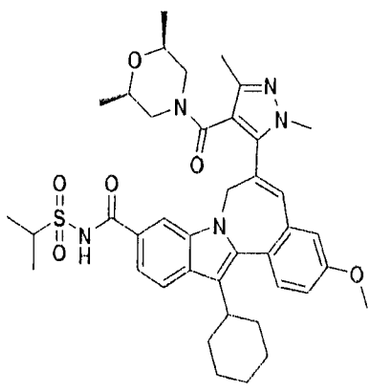
mmol) and DIPEA (0.028 mL, 0.159 mmol) were added. The reaction mixture was stirred at RT for 15 min. Morpholine (4.14 mg, 0.048 mmol) was then added and the resultant solution was stirred at RT overnight. The reaction mixture was then purified by preparative HPLC using CH_3CN-H_2O-TFA as a solvent system. Homogeneous fractions were combined and concentrated under vacuum. The title compound was obtained as a yellow colored solid, (16.8 mg, 0.024 mmol, 74.2 % yield). MS m/z 698(M-H$^-$), Retention time: 1.798 min. (basic). 1H NMR (500 MHz, MeOD) δ ppm 1.18 - 1.62 (m, 10 H) 1.72 - 2.25 (m, 9 H) 2.53 - 3.23 (m, 9 H) 3.84 (s, 3 H) 3.95 (s, 3 H) 3.96 - 4.03 (m, 1 H) 4.64 (d, *J*=14.95 Hz, 1 H) 5.00 - 5.15 (m, br, 1 H) 7.06 (s, 1 H) 7.14 (d, *J*=2.44 Hz, 1 H) 7.19 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.55 - 7.65 (m, 2 H) 7.94 (s, 1 H) 7.98 (d, *J*=8.55 Hz, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6 [1,3-dimethyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl.

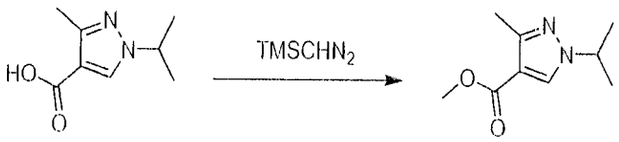
To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1,3-dimethyl- (20 mg, 0.032 mmol) in DMSO (1 mL), TBTU (20.36 mg, 0.063 mmol) and DIPEA (0.028 mL, 0.159 mmol) were added. The reaction mixture was stirred at RT for 15 min. Then 3-methyl-3,8-diazabicyclo[3.2.1]octane.2 HCl (9.47 mg, 0.048 mmol) was added. The solution was then stirred at RT overnight. The crude reaction mixture was then purified by preparative HPLCusing CH_3CN-H_2O-TFA as solvent system. Homogeneous fractions were combined and concentrated under vacuum to afford the title compound as a yellow solid, (19.7 mg, 0.023 mmol,

71.4 % yield) as TFA salt. MS m/z 737(M-H⁻), Retention time: 2.040 min. (basic). 1H NMR (500 MHz, MeOD) δ ppm 1.16 - 1.67 (m, 14 H) 1.74 - 2.25 (m, 6 H) 2.38 (s, 3 H) 2.51 - 2.66 (m, 1 H) 2.72 (s, 3 H) 2.94 - 3.05 (m, 1 H) 3.16 - 3.39 (m, 5 H) 3.84 (s, 3 H) 3.96 (s, 3 H) 3.98 - 4.05 (m, 1 H) 4.59 - 4.71 (m, br, 1 H) 4.94 - 5.05 (m, br, 1 H) 7.14 - 7.28 (m, 3 H) 7.62 - 7.66 (m, 2 H) 7.91 (s, 1 H) 8.00 (d, *J*=8.54 Hz, 1 H).



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1,3-dimethyl-4-[[cis-2,6-dimethyl- 4-morpholinyl]carbonyl]-1H-pyrazol-5-yl] 3-methoxy-N-[(1-methylethyl)sulfonyl]-. To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1,3-dimethyl- (13 mg, 0.021 mmol) in DMSO (1 mL), TBTU (13.24 mg, 0.041 mmol) and DIPEA (0.018 mL, 0.103 mmol) were added. The reaction mixture was stirred at RT for 15 min. Then cis-2,6-dimethylmorpholine (3.56 mg, 0.048 mmol) was added and the resultant mixture was stirred at RT overnight. The crude reaction mixture was purified by preparative HPLC using CH_3CN-H_2O-TFA as a solvent system. Homogeneous fractions were combined and concentrated under vacuum to afford the title compound as a yellow colored solid, (10.1 mg, 0.014 mmol, 67.3 % yield). MS m/z 326(M-H⁻), Retention time: 1.958 min. (basic). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.57 - 2.33 (m, 25 H) 2.81 - 3.60 (m, 5 H) 3.77 - 3.99 (m, 8 H) 4.03 - 4.12 (m, 1 H) 4.57 (d, *J*=15.26 Hz, 1 H) 4.76 - 4.94 (m, 1 H) 6.75 - 6.88 (m, 1 H) 6.95 (s, 1 H) 7.12 (dd, *J*=8.55, 2.14 Hz, 1 H) 7.50 - 7.67 (m, 2 H) 7.71 (s, 1 H) 7.91 (d, *J*=8.24 Hz, 1 H).

Methyl 1-(1-methylethyl)-3-methyl-1H-pyrazole-4-carboxylate

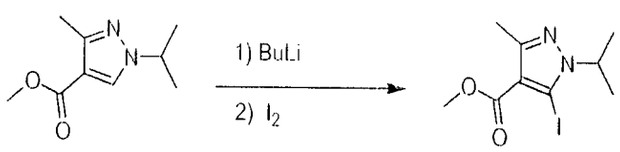


To a solution of 1-(1-methylethyl)-3-methyl-1H-pyrazole-4-carboxyllic acid (2.00g, 11.9 mmol) in benzene (15.9 mL) and methanol (7.93 mL) at room temperature was added 2M trimethylsilyldiazomethane (23.8 mL). The resulting solution was stirred at room temperature for 3 hours. Solvent was removed at reduced pressure on a rotory evaporator to yield the title compound (2.17 g, 11.89 mmol, 100 % yield) as a white solid.

MS m/z 183(MH^+)

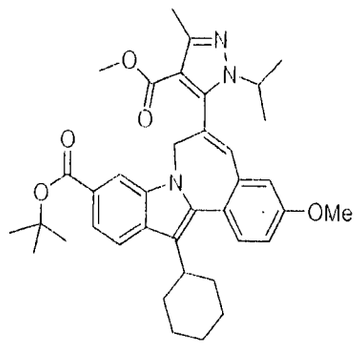
1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.49 (d, 6H) 2.48 (s, 3 H) 3.81 (s, 3 H) 4.42 (m, 1H) 7.86 (s, 1H).

Methyl 5-iodo-1-(1-methylethyl)-3-methyl-1H-pyrazole-4-carboxylate



To a solution of methyl 1-(1-methylethyl)-3-methyl-1H-pyrazole-4-carboxylate (2.00g, 11.0 mmol) in dry tetrahydrofuran (22.0 mL) at -78°C, 2 M solution of butyllithium (6.04 mL, 12.1 mmol) in pentane was added dropwise. The reaction mixture was then warmed to -45°C and stirred for 1 h. It was then cooled to -78°C and a solution of iodine (3.06 g, 12.1 mmol) in THF (11.0 mL) was added. The reaction mixture was warmed to RT and stirred for 1h. Then it was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (2X25 mL). The organic layers were combined, washed with brine and dried ($MgSO_4$). Evaporation of solvent gave a tan solid as title compound (3.38 g, 11.0 mmol, 100 % crude yield). MS m/z 309 (MH^+); 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.41 (d, 6H) 2.47 (s, 3 H) 3.82 (s, 3 H) 4.77 (m, 1H).

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1-(1-methylethyl)-3-methyl-1H-pyrazol-5-yl]-, 1,1-dimethylethyl ester



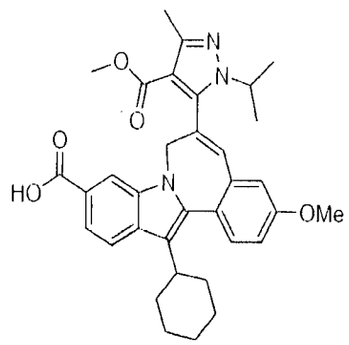
In a microwave tube, 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(tributylstannyl)-, 1,1-dimethylethyl ester (611 mg, 0.834 mmol), methyl 5-iodo-1-(1-methylethyl)-3-methyl-1H-pyrazole-4-carboxylate (360 mg, 1.17 mmol) and bis(triphenylphosphine)palladium II chloride (58.5 mg, 0.083 mmol) were added. It was then sealed, degassed and flushed with nitrogen. 1,4-Dioxane (4.17 mL) was added. The reaction mixture was heated at 160°C under microwave condition for 1 hour. It was then filtered and the filtrate was concentrated. The residue was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (8ml) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 25% solvent A / 75% solvent B to 0% solvent A / 100% solvent B, a gradient time of 10 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system.

The product-containing fractions were collected and concentrated to give title compound as a yellow solid (156 mg, 0.250 mmol, 30% yield).

MS m/z 624 (MH^+); 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.41 (br s, 3H) 1.18 - 1.59 (m, 16 H) 1.72 - 2.20 (m, 6 H) 2.49 (s, 3 H) 2.86 (m, 1 H) 3.68 (m, 1 H)

3.85 (br s, 3 H) 3.92 (s, 3 H) 4.69 (br.d, 1 H) 4.97 (br.d, 1 H) 6.68 (s, 1 H) 6.92 (d, *J*=2.14 Hz, 1 H) 7.06 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.51 (d, *J*=8.55 Hz 1 H) 7.73 (d, *J*=8.24 Hz, 1 H) 7.81 (d, *J*=8.24 Hz, 1 H) 7.87 (s, 1 H).

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)- 1(1-methylethyl)-3-trifluoromethyl-1H-pyrazol-5-yl]-

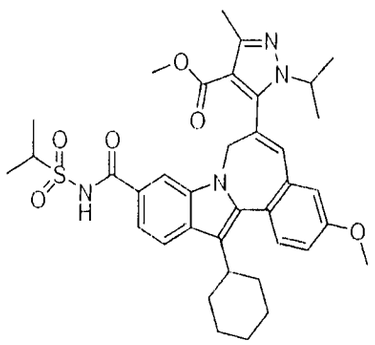


To a solution of 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1-(1-methylethyl)-3-methyl-1H-pyrazol-5-yl]-, 1,1-dimethylethyl ester (156 mg, 0.250 mmol) in 1,2-dichloroethane (4 mL), TFA (4 mL) was added. The reaction mixture was stirred at RT for 2 hours. Volatiles were removed on a rotary evaporator to give the title compound as a brownish thick oil as crude product (142 mg, 0.8250 mmol, 100 % yield).

MS m/z 568(MH^+)

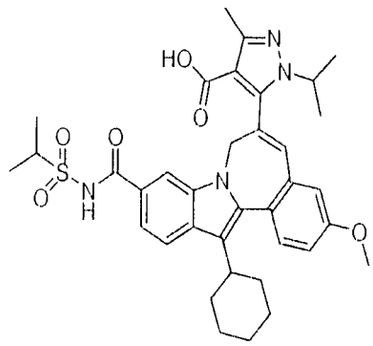
1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.41 (br s, 3H) 1.18 - 1.59 (m, 7 H) 1.72 - 2.20 (m, 6 H) 2.52 (s, 3 H) 2.87 (m, 1 H) 3.63 (m, 1 H) 3.85 (br s, 3 H) 3.91 (s, 3 H) 4.71 (br.d, 1 H) 4.96 (br.d, 1 H) 6.68 (s, 1 H) 6.96 (d, *J*=2.14 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.52 (d, *J*=8.55 Hz 1 H) 7.77 (d, *J*=8.24 Hz, 1 H) 7.87 (d, *J*=8.24 Hz, 1 H) 7.97 (s, 1 H).

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)- 1(1-methylethyl)-3-trifluoromethyl-1H-pyrazol-5-yl]-



To a solution of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)- 1(1-methylethyl)-3-trifluoromethyl-1*H*-pyrazol-5-yl]- (110 mg, 0.194 mmol) in tetrahydrofuran (0.646 mL) was added carbonyldiimidazole (94.0 mg, 0.581 mmol). The reaction mixture was heated at 60^{0}C for one hour. Propane-2-sulfonamide (95 mg, 0.775 mmol) and DBU (0.088 mL, 0.581 mmol) were added at room temperature. The reaction mixture was then heated at 60^{0}C for 4 hours. The reaction mixture was diluted with 1N HCl (50 mL) solution and extracted with ethyl acetate (2 X 40mL). The organic layers were combined and concentrated on a rotory evaporator to give an orange oil as crude product. It was then purified by prep HPLC column using CH_3CN/H_2O/TFA as solvent system. Fractions were collected and concentrated under speedvac for 16h. A yellow solid was obtained as title compound (114 mg, 0.169 mmol, 87 % yield).
MS m/z 673 (MH^+).
1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.41 (br s, 3H) 1.18 - 1.52 (m, 13 H) 1.70 - 2.20 (m, 6 H) 2.51 (s, 3 H) 2.85 (m, 1 H) 3.59 (m, 1 H) 3.87 (s, 3 H) 3.92 (s, 3 H) 4.02 (m, 1 H) 4.73 (br.d, 1 H) 4.97 (br.d, 1 H) 6.67 (s, 1 H) 6.96 (d, *J*=2.14 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.40-7.62 (m, 2 H) 7.78-7.84 (m, 2 H), 9.00 (br s, 1 H).

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]- 1-(1-methylethyl)-3-methyl-

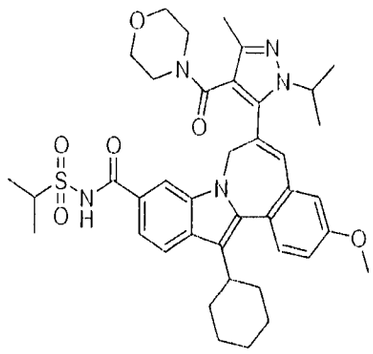


To a mixture of 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)- 1(1-methylethyl)-3-trifluoromethyl-1*H*-pyrazol-5-yl]- (110 mg, 0.163 mmol) was dissolved in THF (0.272 mL) and methanol (0.272 mL) was added to the reaction followed by 1N aqueous sodium hydroxide (0.600 mL). The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 18 hrs. The reaction was diluted with ethyl acetate (25.0 mL) and washed with 1.0N aqueous hydrochloric acid (2 x 20ml). The organic layer was concentrated *in vacuuo* using a rotary evaporator to yield the title compound as a yellow solid (107 mg, 0.163 mmol, 100%).

MS m/z 659(MH^-)

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.39 (br s, 3H) 1.18 - 1.52 (m, 13 H) 1.70 - 2.20 (m, 6 H) 2.48 (s, 3 H) 2.83 (m, 1 H) 3.51 (m, 1 H) 3.87 (s, 3 H) 4.02 (m, 1 H) 4.72 (br.d, 1 H) 4.98 (br.d, 1 H) 6.65 (s, 1 H) 6.95 (d, *J*=2.14 Hz, 1 H) 7.08 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.41-7.60 (m, 2 H) 7.79-7.83 (m, 2 H), 8.96 (br s, 1 H).

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[3-methyl-1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-



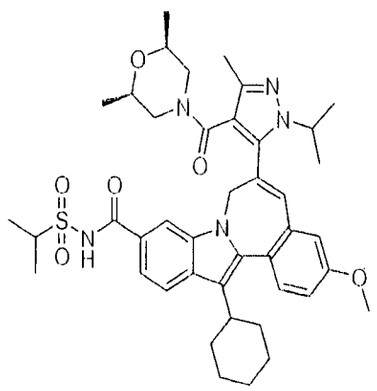
To a solution of 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-(1-methylethyl)-3-methyl- (25 mg, 0.038 mmol) in DMSO (0.38 mL), TBTU (24 mg, 0.076 mmol) and DIPEA (0.020 mg, 0.44 mmol) were added. The reaction mixture was stirred at RT for 15 min. Then morpholine (38 mg, 0.15 mmol) was added. The solution was stirred at RT for overnight. The reaction mixture was purified by prep HPLC column using CH_3CN/H_2O/TFA as solvent system. Fractions were collected and concentrated under speedvac overnight to yield the title compound as a yellow solid (24 mg, 0.031 mmol, 81 % yield).

MS m/z 728 ($M-H^+$)

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.18 - 1.70 (m, 16 H) 1.75 - 2.16 (m, 6 H) 2.30 (s, 3 H) 2.60-3.31 (m, 9 H) 3.94 (m, 3 H) 4.04 (m, 1 H) 4.56 (br.m, 2 H) 4.93 (br.d, 1 H) 6.79 (br s, 1 H) 6.94 (s, 1 H) 7.12 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.57 (d, *J*=8.55 Hz 1 H) 7.66 (br s, 1 H) 7.82 (s, 1 H) 7.97 (d, *J*=8.55 Hz, 1 H), 10.20 (br s, 1 H).

The following compounds were synthesized by an analogous method as described above for 7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[3-methyl-1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-:

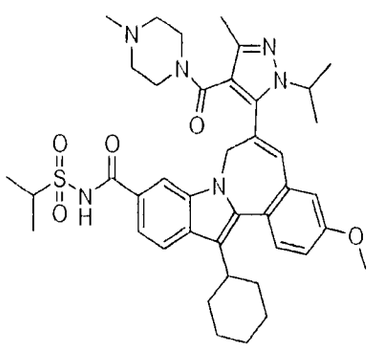
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-



MS m/z 756 ($M-H^+$)

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.70-0.91 (br m, 6 H)1.02 - 1.81 (m, 16 H) 1.86 - 2.16 (m, 6 H) 2.28 (s, 3 H) 2.85-3.29 (m, 5 H) 3.96 (s, 3 H) 4.12 (br m, 3 H) 4.55 (br.m, 2 H) 4.92 (br.d, 1 H) 6.73 (br s, 1 H) 6.94 (br s, 1 H) 7.16 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.51-7.72 (m, 2 H) 7.76-7.98 (m, 2 H), 10.50 (br s, 1 H).

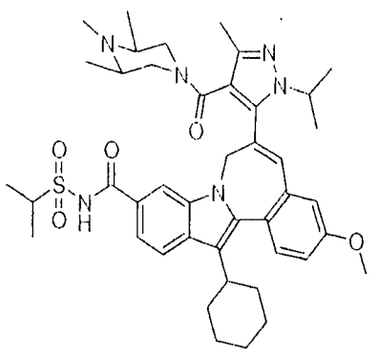
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[3-methyl-1-(1-methylethyl)-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-



MS m/z 741 ($M-H^-$)

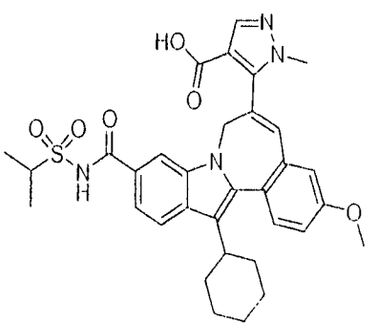
1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.15 - 1.81 (m, 18 H) 1.86 - 2.12 (m, 4 H) 2.21-2.45 (m, 5 H) 2.61-3.05 (m, 6 H) 3.10-3.75 (m, 4 H) 3.93 (s, 3 H) 4.04 (m, 1 H) 4.61 (br.m, 2 H) 4.90 (br.d, 1 H) 6.86 (br s, 1 H) 6.96 (s, 1 H) 7.14 (br m, 1 H) 7.59-7.83 (m, 3 H) 7.93 (br s, 1 H), 10.10 (br s, 1 H).

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[3-methyl-1-(1-methylethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-



MS m/z 769 ($M-H^+$)

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.21 (br s, 1 H) 1.02 (br s, 3 H) 1.15-1.60 (m, 17 H) 1.69 - 2.12 (m, 8 H) 2.28 (m, 4 H) 2.69-3.60 (m, 6 H) 3.96 (s, 3 H) 4.08 (br m, 3 H) 4.60 (br.m, 2 H) 4.88 (br.m, 1 H) 6.82 (br s, 1 H) 6.95 (s, 1 H) 7.15 (br m, 1 H) 7.55-7.74 (m, 2 H) 7.78-7.99 (m, 2 H), 10.12 (br s, 1 H).



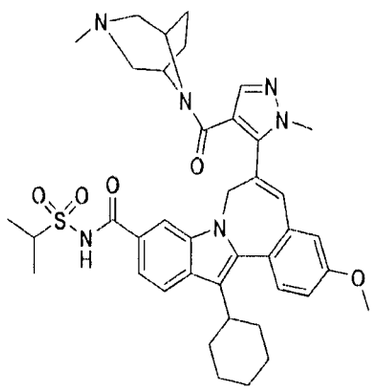
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-

Dissolve 1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester (1.044 g, 1.619 mmol) in a pre-mixed solution of THF(20 mL), MeOH (20 mL) and sodium hydroxide (20 mL, 20.00 mmol). The reaction was homogenous and was stirred at room temperature under a nitrogen atmosphere for 26hrs then concentrated in vacuuo using a rotary evaporator with a bath temperature at 20C. The reaction was poured into 1N aqueous hydrochloric acid and extract using ethyl acetate. The combined organic layers were washed sequentially with 1N aqueous hydrochloric acid and brine, then dried over magnesium sulfate, filtered and solvent removed *in vacuuo*. The crude product dried *in vacuuo* at room temperature to yield 1.68g of an orange amorphous solid. The crude product was dissolved in chloroform (approximately 50mL) with heating and hexanes were added until some material starts to precipitate but re-dissolves on swirling (approximately 10-12ml of hexanes). The mixture was allowed to slowly cool to room temperature and then allowed to stand at room temperature for a few hours. The very fine particulate yellow precipitate was filtered using a Buchner funnel and dried in vacuuo at room temperature to yield 819mg (45%) of purified product as a bright yellow amorphous solid. The title compound 4.6mg was dissolved in CDCl3 (2ml) with the addition of approximately 5 drops of CD3OD to aid in dissolution for 1H NMR acquisition.

1H NMR (500 MHz, CHLOROFORM-D / CD3OD) δ ppm 1.11 - 1.39 (m, 3 H) 1.41 (d, *J*=7.02 Hz, 6 H) 1.47 - 1.65 (m, 1 H) 1.75 (d, *J*=8.85 Hz, 2 H) 1.82 - 2.27 (m, 13 H) 2.77 - 2.90 (m, 1 H) 3.28 (s, 3 H) 3.88 (s, 3 H) 3.97 - 4.06 (m, 1 H) 4.66 (s, 1 H) 5.01 (s, 1 H) 6.76 (s, 1 H) 6.92 (d, *J*=2.75 Hz, 1 H) 7.04 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.47 - 7.54 (m, 2 H) 7.81 (d, *J*=1.22 Hz, 1 H) 7.86 (d, *J*=8.54 Hz, 1 H) 7.91 (s, 1 H).

LC-MS retention time 1.39 min; 615 m/z (MH-). 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 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.



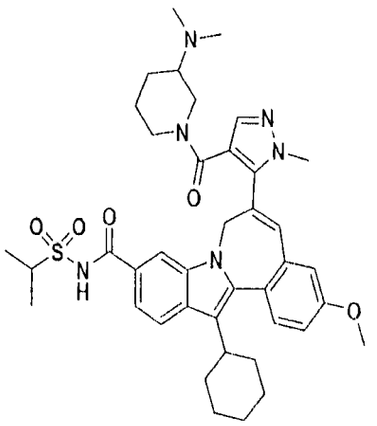
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-

In a 2 dram vial, 900 uL of a stock solution containing 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (0.09M, 0.081mmol) and TBTU (0.19M, 0.171mmol) in DMF was stirred under a nitrogen atmosphere for 1 hour at room temperature. DMAP (40 mg, 0.327 mmol) was added to the reaction and stirred until dissolved then the amine reagent, 3-methyl-3,8-diazabicyclo[3.2.1]octane dihydrochloride (35 mg, 0.176 mmol), was added and the reaction capped under nitrogen and stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid and brine. The organic phase was dried over MgSO4, filtered and solvent removed *in vacuuo*. The crude product was dried *in vacuuo* at room temperature to yield 63mg of an amorphous yellow film/ foam. The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (2mL) purified using a Waters Sunfire Prep C18 OBD, 5uM

19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Sample was purified in two HPLC injections, and the product fractions combined (retention time=5.5min) and volatiles removed *in vacuuo*. The sample was dried *in vacuuo* at room temperature to yield 44.4mg of the title compound as a TFA salt.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.10 - 1.31 (m, 1 H) 1.33 - 1.57 (m, 10 H) 1.80 (s, 2 H) 1.89 - 2.16 (m, 5 H) 2.57 (s, 4 H) 2.74 (s, 9 H) 2.84 - 3.12 (m, 4 H) 3.27 (s, 2 H) 3.32 - 3.72 (m, 4 H) 3.88 (s, 3 H) 3.94 (s, 4 H) 4.00 - 4.14 (m, 1 H) 4.63 (d, *J*=15.56 Hz, 1 H) 4.89 (d, *J*=12.21 Hz, 1 H) 6.96 (d, *J*=2.14 Hz, 2 H) 7.13 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.57 (d, *J*=8.85 Hz, 1 H) 7.63 (d, *J*=7.63 Hz, 2 H) 7.76 (s, 1 H) 7.93 (d, *J*=8.55 Hz, 1 H).

LC-MS retention time 1.81 min; 723 m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-

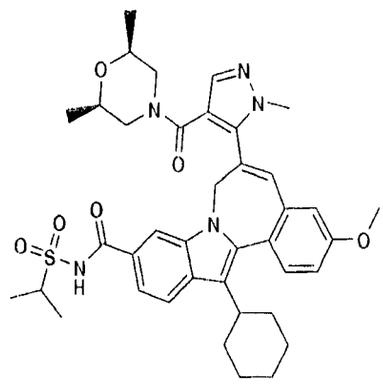
In a 2 dram vial, 900 ul. of a stock solution containing 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (0.09M, 0.081mmol) and TBTU (0.19M, 0.171mmol) in DMF was stirred under a nitrogen atmosphere for 1 hour at room temperature. DMAP (42 mg, 0.344 mmol) was added to the reaction and stirred until dissolved then the amine reagent, N,N-dimethylpiperidin-3-amine dihydrochloride (34 mg, 0.169 mmol) was added and the reaction capped under nitrogen and stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid and brine. The organic phase was dried over MgSO4, filtered and solvent removed *in vacuuo*. The crude product was dried *in vacuuo* at room temperature to yield 67mg as a yellow film. The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (2mL) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run

time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA

Combine product fractions, retention time =5.03min, remove volatiles in vacuuo and dry at room temperature in vacuuo to yield 26.2mg of the title compound as an amorphous yellow solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.04 - 1.18 (m, 1 H) 1.18 - 1.45 (m, 6 H) 1.48 (d, *J*=6.71 Hz, 7 H) 1.80 (d, *J*=8.55 Hz, 3 H) 1.86 - 2.26 (m, 5 H) 2.37 - 2.99 (m, 20 H) 3.12 - 3.72 (m, 4 H) 3.85 (s, 4 H) 3.93 (s, 3 H) 3.98 - 4.08 (m, 1 H) 4.23 (s, 0.4 H) 4.60 (d, *J*=14.34 Hz, 1 H) 4.86 (d, *J*=11.90 Hz, 1 H) 6.82 - 7.02 (m, 2 H) 7.11 (d, *J*=7.02 Hz, 1 H) 7.53 (d, *J*=8.55 Hz, 1 H) 7.58 - 7.88 (m, 3 H) 7.94 (d, *J*=8.24 Hz, 1 H) 10.05 (s, 0.6H)

LC-MS retention time1.54 min; 725 m/z (MH-). 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 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.



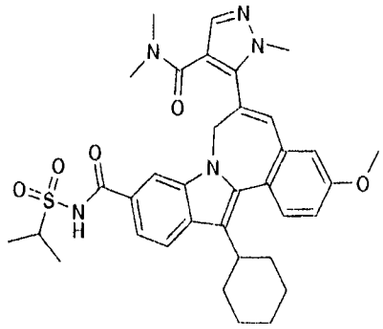
13-cyclohexyl-6-(4-(((2R,6S)-2,6-dimethyl-4-morpholinyl)carbonyl)-1-methyl-1H-pyrazol-5-yl)-N-(isopropylsulfonyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

In a 2 dram vial, 932 uL of a stock solution containing 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (0.087M, 0.081mmol) and TBTU (0.18M, 0.168 mmol), in DMF was stirred under a nitrogen atmosphere for 1.75 hours at room temperature. DMAP (40 mg, 0.327 mmol) was added to the reaction and stirred until dissolved then the amine reagent, (2R,6S)-2,6-dimethylmorpholine (0.030 mL, 0.243 mmol), was added and the reaction capped under nitrogen and stirred at room temperature overnight (19hrs). The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid and brine. The organic phase was dried over MgSO4, filtered and solvent removed *in vacuuo*. The crude product was dried *in vacuuo* at room temperature to yield 65mg of a yellow film. The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (2mL) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA Retention time of product = 12.83 minutes. The sample was purified in two 1ml injections, the second run was cut to a runtime of 20 minutes with the same 15min gradient. Combine product fractions and remove volatiles *in vacuuo* using a rotary evaporator then dry sample *in vacuuo* at room temperature to yield 26.1mg of the title compound as an opaque yellow solid / amorphous film.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.60 - 0.93 (m, 6 H) 1.16 - 1.29 (m, 2 H) 1.30 - 1.58 (m, 9 H) 1.79 (d, *J*=10.68 Hz, 2 H) 1.92 (s, 14 H) 2.05 - 2.27 (m, 3 H) 2.88 (t, *J*=11.44 Hz, 1 H) 3.13 - 3.31 (m, 2 H) 3.46 (br.s, 1 H) 3.91 (s, 3 H) 3.94 (s, 3 H) 4.02 - 4.13 (m, 1 H) 4.60 (d, *J*=15.56 Hz, 1 H) 4.90 (d, *J*=15.56 Hz,

1 H) 6.83 (br. s, 1 H) 6.95 (d, *J*=2.14 Hz, 1 H) 7.06 - 7.17 (m, 1 H) 7.49 - 7.80 (m, 4 H) 7.93 (s, 1 H) 10.12 (br.s, 0.2 H) 10.47 (br.s, 0.6 H).

LC-MS retention time 1.90 min; 712 m/z (MH-). 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 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.



13-cyclohexyl-6-(4-(dimethylcarbamoyl)-1-methyl-1H-pyrazol-5-yl)-N-(isopropylsulfonyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxamide

In a 2 dram vial, 932 uL of a stock solution containing

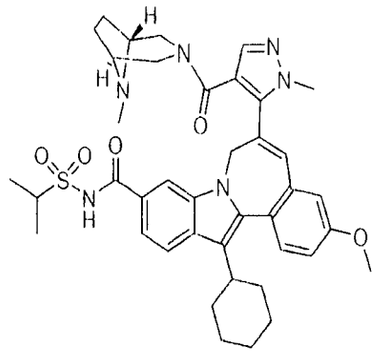
1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (0.087M, 0.081mmol) and TBTU (0.18M, 0.168 mmol), in DMF was stirred under a nitrogen atmosphere for 1.75 hours at room temperature. DMAP (41.8 mg, 0.342 mmol) was added to the reaction and stirred until dissolved then the amine reagent, dimethylamine hydrochloride (17.5 mg, 0.215 mmol), was added and the reaction capped under nitrogen and stirred at room temperature overnight (19hrs). The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid and brine. The organic phase was dried over MgSO4,

filtered and solvent removed *in vacuuo*. The crude product was dried *in vacuuo* at room temperature to yield 57mg as a yellow foam/amorphous solid/film.

The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (2mL) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min, a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA Retention time of product = 12.05 minutes. The sample was purified in two 1ml injections. Combine product fractions and remove volatiles *in vacuuo* using a rotary evaporator then dry sample *in vacuuo* at room temperature to yield 37.6mg (68%) as an amorphous yellow solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.15 - 1.30 (m, 1 H) 1.33 - 1.45 (m, 2 H) 1.49 (br.s, 7 H) 1.79 (d, *J*=8.55 Hz, 2 H) 1.91 - 2.17 (m, 7 H) 2.32 (br.s, 9 H) 2.45 (br.s, 3 H) 2.78 - 2.91 (m, 1 H) 3.50 (br.s, 1 H) 3.82 (s, 3 H) 3.93 (s, 3 H) 4.01 - 4.10 (m, 1 H) 4.60 (d, *J*=14.34 Hz, 1 H) 4.93 (d, *J*=14.65 Hz, 1 H) 6.86 (s, 1 H) 6.96 (d, *J*=2.75 Hz, 1 H) 7.10 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.53 (d, *J*=8.55 Hz, 1 H) 7.58 (d, *J*=8.55 Hz, 1 H) 7.66 (s, 1 H) 7.75 (s, 1 H) 7.91 (d, *J*=8.55 Hz, 1 H) 9.99 (br.s,1 H).

LC-MS retention time 1.74 min;642 m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[(1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl]carbonyl]-1H-pyrazol-5-yl]-

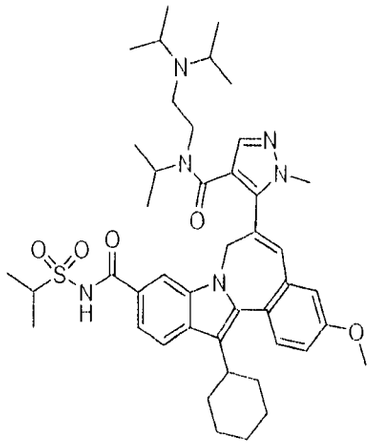
In a 2 dram vial, 900 uL of a stock solution containing 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (0.09M, 0.081mmol) and TBTU (0.19M, 0.171mmol) in DMF was stirred under a nitrogen atmosphere for 1 hour at room temperature. DMAP (41mg, 0.336 mmol) was added to the reaction and stirred until dissolved then the amine reagent, (1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octane dihydrochloride (30mg, 0.151 mmol), was added and the reaction capped under nitrogen and stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid and brine. The organic phase was dried over MgSO4, filtered and solvent removed *in vacuuo*. The crude product was dried *in vacuuo* at room temperature to yield 70mg. The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (2mL) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA.

Retention time of product was 5.56minutes and remove volatiles/solvent *in vacuuo*. HPLC analysis of the first Prep HPLC purification using %A= 10mM Ammonium Acetate, pH=6.8 in Water / Acetonitrile (95%/ 5%) %B= 10mM Ammonium Acetate, pH=6.8 in Water / Acetonitrile (5%/ 95%) solvent system show impurities in the sample. The sample was further purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in 0.5ml DMF/ 1.5ml acetonitrle and purified using a Phenonemex Gemini 30mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 40mL/ min, a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 20 minutes with a run time of 30 minutes using %A= 10mM Ammonium Acetate, pH=6.8 in Water / Acetonitrile (95%/ 5%) %B= 10mM Ammonium Acetate, pH=6.8 in Water / Acetonitrile (5%/ 95%) solvent system. Product elution time is from 9.7minutes to 11.7minutes. Combine product fractions and remove volatiles and dry *in vacuuo*. The trifluoroacetic acid salt of the title compound was made by dissolving the purified product in dichloromethane and adding 10uL of trifluoroacetic acid then removing volatiles *in vacuuo*. Drying *in vacuuo* at room temperature yielded 23.6mg (35%) of the trifluoroacetic acid salt of the title compound as a yellow amorphous solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.11 - 1.29 (m, 1 H) 1.32 - 1.45 (m, 3 H) 1.49 (dd, *J*=11.14, 6.87 Hz, 6 H) 1.79 (d, *J*=10.68 Hz, 2 H) 1.89 - 2.13 (m, 4 H) 2.28 - 2.73 (m, 15 H) 2.84 - 2.95 (m, 1 H) 3.25 (s, 2 H) 3.39 (s, 2 H) 3.76 - 3.92 (m, 3 H) 3.94 (s, 3 H) 4.01 - 4.12 (m, 1 H) 4.63 (d, *J*=15.87 Hz, 1 H) 4.87 (s, 1 H) 6.96 (d, *J*=2.14 Hz, 2 H) 7.13 (dd, *J*=8.85, 2.44 Hz, 1 H) 7.57 (d, *J*=8.55 Hz, 1 H) 7.63 (s, 1 H) 7.77 (s, 1 H) 7.92 (d, *J*=8.55 Hz, 1 H) 10.06 (s, 1 H).

LC-MS retention time 1.73 min; 723 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 6-[4-[[[2-[bis(1-methylethyl)amino]ethyl](1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-

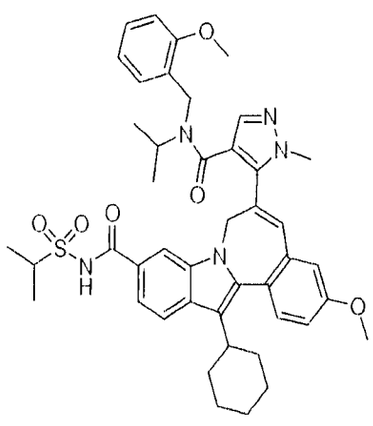
In a 2 dram vial, 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (52.1 mg, 0.084 mmol) was dissolved in DMF(0.9ml) and TBTU (56.2 mg, 0.175 mmol) was added and the reaction stirred under a nitrogen atmosphere for 1 hour at room temperature. DMAP (46mg, 0.377 mmol) was added to the reaction and stirred until dissolved then the amine reagent, N,N,N'-triisopropylethylenediamine (55mg, 0.295 mmol), was added and the reaction capped under nitrogen and stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid and brine. The organic phase was dried over MgSO4, filtered and solvent removed *in vacuuo*. The crude product was dried *in vacuuo* at room temperature to yield 84mg as a yellow glass/film.

The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (2mL) purified using a Waters Sunfire Prep C18 OBD, 5uM

19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA. The retention time of product =6 minutes. Combine product fractions and remove volatiles *in vacuuo* using a rotary evaporator then dry sample *in vacuuo* at room temperature to yield 36.0mg (47%) as a yellow amorphous solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.05 (s, 6 H) 1.18 - 1.43 (m, 15 H) 1.46 (d, *J*=7.02 Hz, 8 H) 1.78 (d, *J*=8.55 Hz, 2 H) 1.87 - 2.12 (m, 4 H) 2.62 (s, 14 H) 2.80 - 2.90 (m, 1 H) 3.12 (s, 2 H) 3.24 - 3.70 (m, 9 H) 3.92 (s, 3 H) 3.97 - 4.06 (m, 1 H) 4.19 (s, 1 H) 4.55 (s, 1 H) 4.99 (s, 1 H) 6.86 (s, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.09 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.48 - 7.57 (m, 3 H) 7.85 (s, 1 H) 7.90 (d, *J*=8.54 Hz, 1 H) 9.33 (s, 1 H) 10.12 (s, 1 H).

LC-MS retention time 1.80 min;783 m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[[(2-methoxyphenyl)methyl](1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-

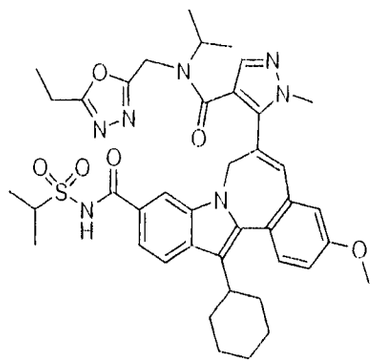
In a 2 dram vial, 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (50 mg, 0.081 mmol) was dissolved in DMF (811 µL) and TBTU (51.5 mg, 0.160 mmol) was added and the reaction stirred under a nitrogen atmosphere for 1.3 hour at room temperature. DMAP (52 mg, 0.426 mmol) was added to the reaction and stirred until dissolved then the amine reagent, N-(2-methoxybenzyl)propan-2-amine hydrochloride (36 mg, 0.167 mmol), was added and the reaction capped under nitrogen and stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid and brine. The organic phase was dried over MgSO4, filtered and solvent removed *in vacuuo*. The crude product was dried *in vacuuo* at room temperature to yield 75mg as a yellow film.

The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF (1:1) (2mL) purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min, a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA Retention time of product = 14.7 minutes. Remove volatiles from product fraction *in vacuuo* using a rotary evaporator then dry sample *in vacuuo* at room temperature to yield 45.4mg (72%) as a amorphous yellow solid. Proton NMR exhibits rotomeric characteristics.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.34 - 1.03 (m, 6.3 H) 1.04 - 1.32 (m, 3.4 H) 1.29 - 1.66 (m, 7.6 H) 1.78 (d, 2.2 H) 1.90 - 2.24 (m, 4.3 H) 2.52 (s, 3.6 H) 2.87 (s, 1.1 H) 3.36 - 3.71 (m, 2.1 H) 3.71 - 3.88 (m, 5.5 H) 3.92 (s, 3.4 H) 4.00-4.06 (m, 0.8 H) 4.13 - 4.39 (m, 1.1 H) 4.63 (d, *J*=12.21 Hz, 1.0 H) 5.08 (d,

J=14.04 Hz, 0.9 H) 6.54 - 6.83 (m, 2.5 H) 6.86 - 6.99 (m, 2.6 H) 7.02 - 7.20 (m, 2.1 H) 7.34 - 7.71 (m, 3.1 H) 7.74 - 7.99 (m, 2.0 H) 9.39 (br.s, 0.4 H) 9.85 (br.s, 0.5 H).

LC-MS retention time 1.99 min;776 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 2 min, and an analysis time of 5 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.



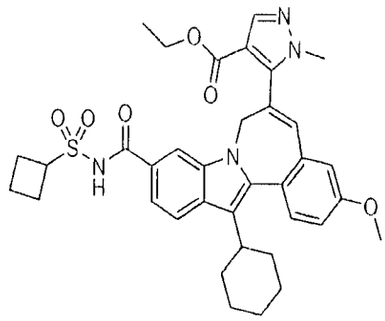
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[[(5-ethyl-1,3,4-oxadiazol-2-yl)methyl](1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-

In a 2 dram vial, 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (50 mg, 0.081 mmol) was dissolved in DMF(811 µL) and TBTU (51.5 mg, 0.160 mmol) was added and the reaction stirred under a nitrogen atmosphere for 1 hour at room temperature. DMAP (43.2 mg, 0.354 mmol) was added to the reaction and stirred until dissolved then the amine reagent, N-((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)propan-2-amine (47.3 mg, 0.280 mmol) dissolved in 0.2ml of DMF, was added to the reaction. The reaction was capped under nitrogen and stirred at room temperature overnight.

The reaction was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was diluted to 2ml volume with acetonitrile and the reaction was purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product is 11.45minutes. Combine product fractions and remove volatiles *in vacuuo* using a rotary evaporator then dry sample *in vacuuo* at room temperature to yield 47.8mg as a yellow amorphous solid/ film.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.07 - 1.24 (m, 5 H) 1.27 (t, *J*=7.48 Hz, 4 H) 1.38 (d, *J*=5.49 Hz, 8 H) 1.56 (d, *J*=9.46 Hz, 1 H) 1.78 (d, *J*=9.46 Hz, 2 H) 1.88 - 1.99 (m, 1 H) 2.00 - 2.17 (m, 3 H) 2.55 - 2.82 (m, 4 H) 2.83 - 2.94 (m, 1 H) 3.73 (s, 3 H) 3.89 (s, 3 H) 3.97 - 4.08 (m, 1 H) 4.15 - 4.80 (m, 4 H) 5.22 (d, *J*=16.79 Hz, 1 H) 6.88 (s, 1 H) 6.94 (d, *J*=2.75 Hz, 1 H) 7.04 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.46 (d, *J*=8.85 Hz, 1 H) 7.59 - 7.67 (m, 2 H) 7.91 (d, *J*=8.55 Hz, 1 H) 8.31 (br.s, 1 H) 9.62 (br.s, 1 H).

LC-MS retention time 1.75 min;766 m/z (MH-). 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 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.



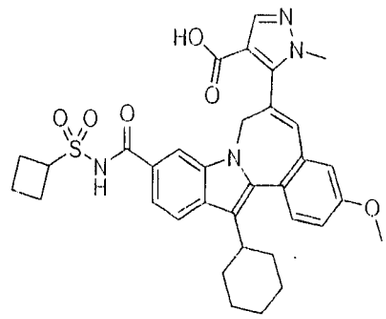
1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester

Dissolve 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-(653mg, 1.210 mmol) in THF (12ml) in a 50ml RB flask. Carbonyldiimidazole (1.308 g, 8.07 mmol) was added to the reaction. The flask fitted with a condenser was placed under a nitrogen atmosphere and the reaction allowed to stir at room temperature for 1hr then refluxed for 50 minutes. The reaction was cooled under a nitrogen atmosphere and cyclobutanesulfonamide (825 mg, 6.10 mmol) was added to the reaction followed by DBU (0.383 ml, 2.54 mmol). The reaction was heated overnight at 70C under a nitrogen atmosphere. LC-MS analysis indicated primarily imidazolide but an insignificant amount of product, therefore cyclobutylsulfonamide (700mg, 5.17mmol) was added to the reaction followed by DBU (0.383 ml, 2.54 mmol). The reacton was heated to reflux under a nitrogen atmosphere for 3.5 hours and progress rechecked by LCMS. Additional cyclobutylsulfonamide (357mg, 2.64mmol) and DBU (0.383 ml, 2.54 mmol) was added to the reaction and the reaction heated to reflux for 3.25hrs. The reaction was cooled and ethyl acetate and washed two times with 1.0N aqueous hydrochloric acid. The aqueous layer was back extracted with ethyl acetate. The organic layers were combined and wash sequentially with 1.0N aqueous hydrochloric acid, 0.1M NaH2PO4, and again with 1.0N aqueous hydrochloric acid and finally brine. The organic phase was dried over magnesium sulfate, filtered and solvent removed *in vacuuo* to yield 949mg of a crude product as a yellow solid. The crude product was adsorbed onto 2.6g of silica gel and chromatographed on 28.7g of silica gel slurry packed using 2% methanol in dichloromethane and eluted using 2% methanol in dichloromethane. Pure product fractions were combined and the volatiles removed *in vacuuo* using a rotary

evaporator to yield 465mg (59%) of the title compound as an amorphous yellow solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.20 (m, 1 H) 1.30 (t, *J*=7.17 Hz, 3 H) 1.33 - 1.48 (m, 2 H) 1.55 (br.s, 4 H) 1.78 (d, *J*=9.46 Hz, 2 H) 1.87 - 2.14 (m, 6 H) 2.32 - 2.42 (m, 2 H) 2.55 - 2.69 (m, 2 H) 2.79 - 2.92 (m, 1 H) 3.28 (s, 3 H) 3.90 (s, 3 H) 4.25 (br.s, 2 H) 4.53 - 4.63 (m, 1 H) 4.71 (d, *J*=10.68 Hz, 1 H) 4.97 (d, *J*=14.34 Hz, 1 H) 6.77 (s, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.07 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.35 (dd, *J*=8.39, 1.37 Hz, 1 H) 7.52 (d, *J*=8.85 Hz, 1 H) 7.73 (d, *J*=1.22 Hz, 1 H) 7.88 (d, *J*=8.55 Hz, 1 H) 7.91 (s, 1 H) 8.24 (s, 1 H).

LC-MS retention time 1.78 min; 655 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.



1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-

1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester (463mg, 0.705mmol) was dissolved in THF (6.8mL), then diluted using methanol (6.8mL) with heating and the mixture cooled to room temperature. To the reaction suspension in THF/methanol was added 1.0N aqueous sodium hydroxide (6.8mL,

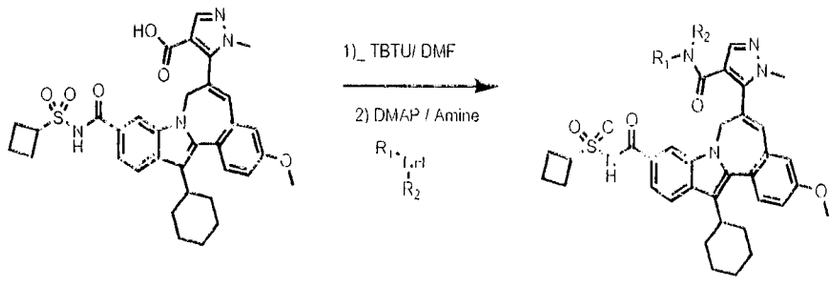
6.8mmol). Upon addition of the sodium hydroxide solution the reaction became a clear homogeneous solution. The reaction was stirred at room temperature under a nitrogen atmosphere for 20hrs. Concentrate reaction *in vacuuo* using a rotary evaporator with room temperature bath (20C). Partition the reaction between 200ml of ethyl acetate and 1.0N aqueous hydrochloric acid. Extract aqueous phase using ethyl acetate. Combine organic phases and wash sequentially with 1.0N aqueous hydrochloric acid and brine. Dry the organic layer over magnesium sulfate, filter and remove volatiles from the filtrate *in vacuuo* to yield 457mg of the title compound as a light yellow colored solid.

1H NMR (500 MHz, MeOD) δ ppm 0.83 (br.s, 1 H) 1.11 - 1.29 (m, 3 H) 1.30 - 1.60 (m, 4 H) 1.74 (d, *J*=7.93 Hz, 2 H) 1.87 (br.s, 1 H) 1.94 - 2.07 (m, 5 H) 2.25 - 2.35 (m, 2 H) 2.50 - 2.60 (m, 2 H) 2.78 - 2.87 (m, 1 H) 3.24 (s, 3 H) 3.87 (s, 3 H) 4.46 - 4.55 (m, 1 H) 4.67 (br.s, 1 H) 4.99 (br.s, 1 H) 6.78 (s, 1 H) 6.93 (d, *J*=2.44 Hz, 1 H) 7.05 (dd, *J*=8.55, 2.75 Hz, 1 H) 7.49 (d, *J*=8.55 Hz, 1 H) 7.52 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.81 (d, *J*=1.53 Hz, 1 H) 7.84 (d, *J*=8.55 Hz, 1 H) 7.89 (s, 1 H).

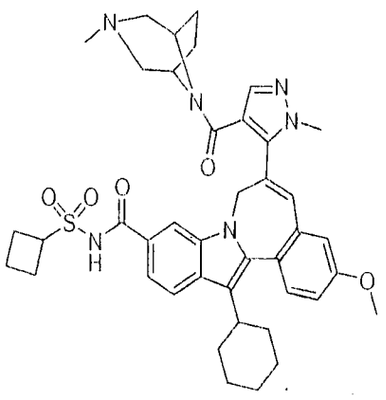
LC-MS retention time 1.42 min; 627m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 ml/min , a gradient 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 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.

General Procedure for amide couplings on:

1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-



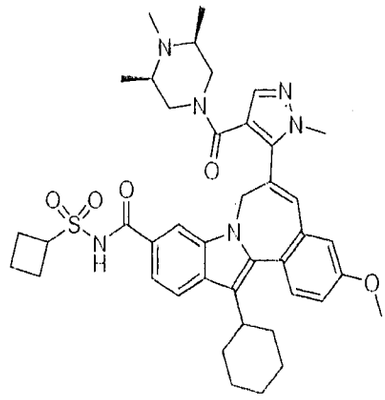
Into a 2 dram vial place 639ul of a stock solution containing 1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl- (0.639 mL, 0.072 mmol) and TBTU (0.639 mL, 0.138 mmol) which was pre-mixed for 1.25hr at room temperature. To the reaction mixture add 239ul of a stock solution containing DMAP (0.239 mL, 0.358 mmol), then add the amine reagent (0.159 mmol). Cap the reaction under a nitrogen atmosphere and stir at room temperature overnight. The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was diluted to 2ml (or 4ml) using acetonitrile and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes (or 25minutes) using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Volatiles from the product fraction(s) are removed *in vacuuo* using a speed vac overnight with heating.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.13 - 1.30 (m, 1 H) 1.31 - 1.56 (m, 4 H) 1.79 (d, *J*=10.68 Hz, 2 H) 1.88 - 2.15 (m, 7 H) 2.37 (s, 4 H) 2.54 (s, 4 H) 2.67 (d, *J*=9.16 Hz, 4 H) 2.83 - 2.96 (m, 2 H) 3.05 - 3.64 (m, 5 H) 3.89 (s, 3 H) 3.93 (s, 3 H) 4.54 - 4.69 (m, 2 H) 4.88 (s, 1 H) 6.95 (t, *J*=2.14 Hz, 1 H) 7.13 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.57 (d, *J*=8.55 Hz, 1 H) 7.60 (d, *J*=6.71 Hz, 1 H) 7.77 (s, 1 H) 7.91 (d, *J*=8.24 Hz, 1 H) 10.17 (s, 1 H).

LC-MS retention time 1.55 min; 735m/z (MH-). 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 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.



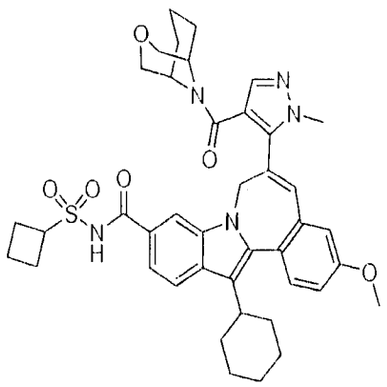
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-

See procedure for general amide coupling. The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was solubilized by diluting to 2ml using acetonitrile and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 90% solvent A / 10% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product = 8.3 minutes.

1H NMR (500 MHz, CHLOROFORM-D) d ppm 0.99 - 1.32 (m, 7 H) 1.32 - 1.66 (m, 3 H) 1.80 (d, *J*=8.55 Hz, 2 H) 1.88 - 2.13 (m, 6 H) 2.35 (s, 2 H) 2.54 (s, 2 H) 2.66 (s, 2 H) 2.92 (s, 2 H) 3.02 - 3.71 (m, 10 H) 3.80 (s, 3 H) 3.93 (s, 3 H) 4.08 (s, 1 H) 4.49 - 4.67 (m, 2 H) 4.92 (d, *J*=12.21 Hz, 1 H) 6.91 (s, 1 H) 6.97 (d, *J*=2.44 Hz, 1 H) 7.11 (dd, *J*=8.39, 2.29 Hz, 1 H) 7.54 (d, *J*=8.54 Hz, 1 H) 7.56 - 7.65 (m, 2 H) 7.78 (s, 1 H) 7.92 (d, *J*=8.55 Hz, 1 H) 9.71 (s, 1 H).

LC-MS retention time1.49 min;737 m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[1-methyl-4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1H-pyrazol-5-yl]-

See procedure for general amide coupling.

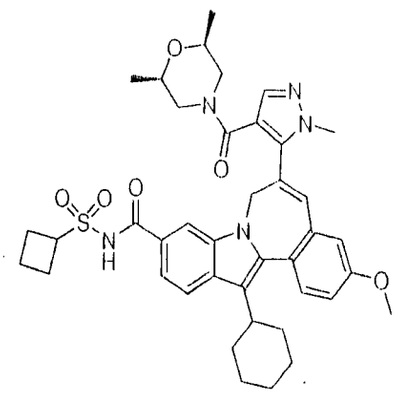
Sample was diluted to 4ml using acetonitrile. The sample needed more than 2ml volume to completely solubilize in acetonitrile indicating lower solubility than previous run samples.

The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was diluted to 4ml using acetonitrile and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. The purification was performed as two 2ml injections. Retention time of product was 13.9 minutes.

Volatiles from the product fractions were removed *in vacuuo* using a speed vac overnight with heating. Weight of isolated title compound was 38.6mg.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.85 (m, 1 H) 1.21 (m, 2 H) 1.31 - 1.57 (m, 6 H) 1.77 (d, *J*=8.24 Hz, 3 H) 1.89 - 2.14 (m, 6 H) 2.15 - 2.24 (m, 1 H) 2.30 (d, *J*=11.29 Hz, 1 H) 2.34 - 2.43 (m, 2 H) 2.57 - 2.79 (m, 2 H) 2.86 (t, *J*=10.53 Hz, 1 H) 2.94 - 3.41 (m, 9 H) 3.51 (d, *J*=14.65 Hz, 1 H) 3.62 (d, *J*=10.68 Hz, 1 H) 3.86 (s, 1 H) 3.93 (s, 5 H) 4.51 - 4.68 (m, 2 H) 4.83 - 5.06 (m, 1 H) 6.78 - 6.89 (m, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.08 - 7.17 (m, 1 H) 7.58 (d, *J*=8.54 Hz, 1 H) 7.63 (d, *J*=7.93 Hz, 1 H) 7.66 - 7.81 (m, 2 H) 7.90 (t, *J*=9.16 Hz, 1 H) 10.19 (s, 0.2 H) 10.44 (s, 0.7 H).

LC-MS retention time 1.62min; 736m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-

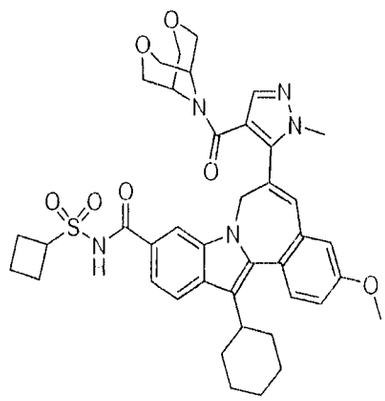
See procedure for general amide coupling.

The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was diluted to 2ml using acetonitrile and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product = 13.5minutes.

Volatiles from the product fractions were removed *in vacuuo* using a speed vac overnight with heating.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.68 (br.s, 3 H) 0.78 (m, 1 H) 0.81 - 0.91 (m, 1 H) 1.12 - 1.32 (m, 2 H) 1.32 - 1.50 (m, 3 H) 1.79 (d, *J*=11.29 Hz, 2 H) 1.90 - 2.01 (m, 3 H) 2.01 - 2.16 (m, 5 H) 2.18 - 2.27 (m, 1 H) 2.28 - 2.36 (m, 1 H) 2.35 - 2.46 (m, 1 H) 2.60 - 2.82 (m, 3 H) 2.83 - 3.11 (m, 5 H) 3.12 - 3.31 (m, 2 H) 3.42 (s, 1 H) 3.81 - 3.94 (m, 3 H) 3.94 (s, 3 H) 4.51 - 4.70 (m, 2 H) 4.90 (d, *J*=14.34 Hz, 1 H) 6.79 - 6.90 (m, 1 H) 6.95 (d, *J*=1.83 Hz, 1 H) 7.13 (dd, *J*=8.55, 2.14 Hz, 1 H) 7.60 (dd, *J*=24.57, 8.39 Hz, 2 H) 7.69 (d, *J*=16.48 Hz, 1 H) 7.91 (d, *J*=8.24 Hz, 1 H) 10.03 (s, 0.3 H) 10.42 (s, 0.7 H).

LC-MS retention time1.85 min; 724m/z (MH-). 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 4 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 2 min, and an analysis time of 5 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-

Into a 2 dram vial place 639ul of a stock solution containing 1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl- (0.639 mL, 0.072 mmol) and TBTU (0.639 mL, 0.138 mmol) which was pre-mixed for 1.25 hr at room temperature. To the reaction mixture add 239ul of a stock solution containing DMAP (0.239 mL, 0.358 mmol), then add the amine reagent 3,7-dioxa-9-azabicyclo[3.3.1]nonane hydrochloride (38.0 mg, 0.229 mmol). Cap the reaction under a nitrogen atmosphere and stir at room temperature. Analysis of the reaction mixture by LCMS indicated only a trace of product present. The reaction was allowed to sit capped at room temperature for 3 days then HATU (92 mg, 0.242 mmol). The reaction was capped and stirred at room temperature overnight. LCMS indicated a complete reaction. The reaction was allowed to stir at room temperature for 2 more days (weekend).

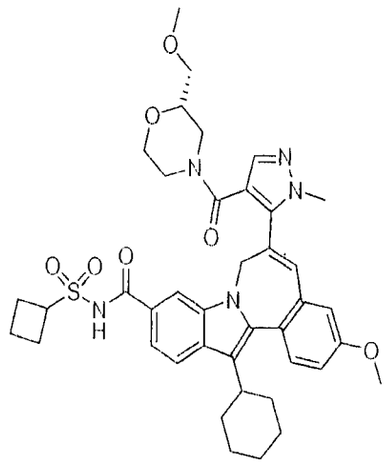
The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was diluted to 2ml using acetonitrile and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A=

10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. The retention time of product was observed as split peaks at 10.72min and 11.03minutes. Volatiles from the product fractions were removed *in vacuuo* using a speed vac overnight with heating.

1H NMR analysis of each product fraction provided identical NMR spectrums. The product fraction were combined and into a vial and dried *in vacuuo* at room temperature to yield 34.5mg (65%) of the title compound as a yellow amorphous solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.11 - 1.27 (m, 1 H) 1.31 - 1.52 (m, 3 H) 1.71 - 1.83 (m, *J*=8.85 Hz, 2 H) 1.92 - 2.15 (m, 6 H) 2.31 (s, 1 H) 2.38 (s, 1 H) 2.55 - 2.77 (m, 3 H) 2.81 - 2.91 (m, 1 H) 3.25 (s, 1 H) 3.33 (d, *J*=9.46 Hz, 1 H) 3.42 (s, 2 H) 3.55 (d, *J*=10.07 Hz, 1 H) 3.62 - 3.80 (m, 3 H) 3.89 (s, 3 H) 3.93 (s, 3 H) 4.23 (s, 3 H) 4.53 - 4.66 (m, 2 H) 4.93 (d, *J*=15.26 Hz, 1 H) 6.87 (s, 1 H) 6.95 (d, *J*=2.44 Hz, 1 H) 7.13 (dd, *J*=8.54, 2.75 Hz, 1 H) 7.58 (d, *J*=8.55 Hz, 1 H) 7.61 (d, *J*=8.55 Hz, 1 H) 7.70 (s, 1 H) 7.74 (s, 1 H) 7.93 (d, *J*=8.54 Hz, 1 H) 10.09 (s, 1 H).

LC-MS retention time 1.50 min; 738 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-

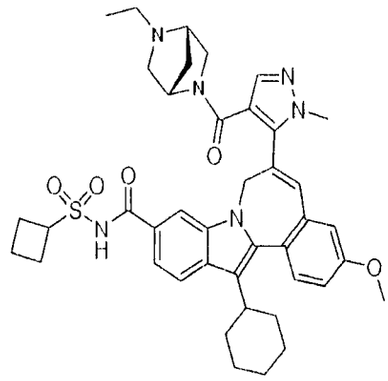
Into a 2 dram vial place 787ul of a stock solution containing 1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl- (0.091M) (0.787 mL, 0.072 mmol) and TBTU (0.213M) (0.787 mL, 0.168 mmol) which was pre-mixed for 1.25hr at room temperature. To the reaction mixture add DMAP (48.0 mg, 0.393 mmol), then add the amine reagent then add the amine reagent, in this case, (S)-2-(methoxymethyl)morpholine hydrochloride (30.4 mg, 0.181 mmol). Cap the reaction under a nitrogen atmosphere and stir at room temperature overnight. The reaction is diluted with acetonitrile and purified by reverse phase Prep HPLC.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.19 (m, 1 H) 1.31 - 1.54 (m, 3 H) 1.79 (d, *J*=10.38 Hz, 2 H) 1.90 - 2.20 (m, 7 H) 2.23 - 2.55 (m, 3 H) 2.58 - 2.82 (m, 4 H) 2.82 - 3.13 (m, 6 H) 3.11 - 3.49 (m, 5 H) 3.90 (s, 3 H) 3.94 (s, 3 H) 4.51 - 4.67 (m, 2 H) 4.78 - 4.96 (m, 1 H) 6.85 (s, 1 H) 6.95 (s, 1 H) 7.12 (dd, *J*=8.55, 2.44 Hz, 1 H) 7.56 (d, *J*=8.55 Hz, 1 H) 7.59 (d, *J*=7.63 Hz, 1 H) 7.63 - 7.74 (m, 2 H) 7.90 (t, *J*=9.00 Hz, 1 H) 10.09 (s, 0.3 H) 10.41 (s, 0.6 H).

LC-MS retention time1.62 min; 740 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 2 min, and an analysis time of 5 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.

The following examples can be prepared in an analogous fashion.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-

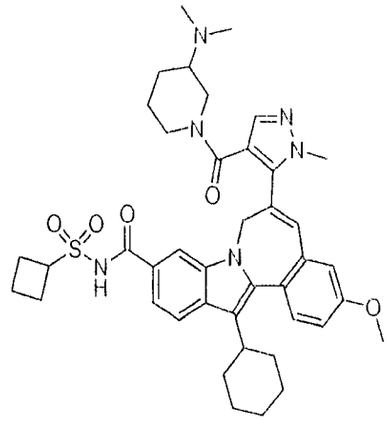
HPLC Method: The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction mixture was diluted to 2ml using acetonitrile and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. The product retention time is 5.71minutes. Volatiles from the product fractions were removed *in vacuuo* using a speed vac with a medium heat setting.

The proton NMR of this sample exhibited characteristics of rotomers.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.49 (s, 0.3 H) 0.96 - 1.29 (m, 2.2 H) 1.30 - 1.59 (m, 3.3 H) 1.79 (d, *J*=11.60 Hz, 1.8 H) 1.86 - 2.17 (m, 3.8 H)

2.19 - 2.46 (m, 2.1 H) 2.49 - 3.74 (m, 6.4 H) 3.76 - 4.21 (m, 5.1 H) 4.24 - 4.39 (m, 0.8 H) 4.43 - 4.70 (m, 1.4 H) 4.73 - 5.07 (m, 1.0 H) 5.23 (s, 0.1 H) 6.73 (d, *J*=29.30 Hz, 0.4 H) 6.88 - 7.00 (m, 0.8 H) 7.04-7.13 (m, 0.7 H) 7.44 - 7.60 (m, 0.9 H) 7.58 - 7.96 (m, 2.0 H) 8.19 (s, 0.1 H) 10.43 (d, *J*=81.79 Hz, 0.4 H) 11.20 (d, *J*=87.28 Hz, 0.5 H) 12.46 (s, 0.6 H)

LC-MS retention time1.60 min;737 m/z (MH+). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-

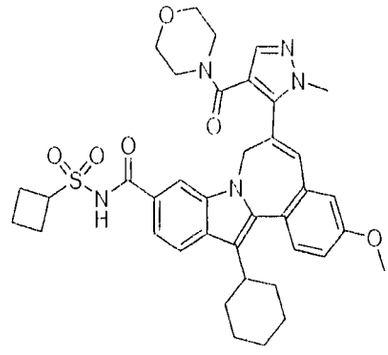
HPLC Method: The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was diluted to 4ml using acetonitrile with a very small amount of methanol and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM.

The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. The retention time of product was 5.37minutes. The compound was purified as two 2ml injections.

Peaks in proton NMR spectra are generally broad, characteristic of restricted rotation in molecule.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.13 - 1.32 (m, 2 H) 1.32 - 1.59 (m, 5 H) 1.79 (s, 3 H) 1.89 - 2.18 (m, 7 H) 2.36 (s, 2 H) 2.48 - 2.76 (m, 8 H) 2.88 (s, 1 H) 3.51 (s, 1 H) 3.60 - 3.91 (m, 7 H) 3.93 (s, 3 H) 4.24 (s, 0.6 H) 4.47 - 4.68 (m, 2 H) 4.84 (d, *J*=13.43 Hz, 1 H) 6.86 - 6.98 (m, 1 H) 7.07 - 7.17 (m, 1 H) 7.53 (d, *J*=8.55 Hz, 1 H) 7.58 - 7.84 (m, 2 H) 7.93 (d, *J*=7.93 Hz, 1 H) 10.07 (s, 1 H).

LC-MS retention time 1.56 min; 739m/z (MH+). 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 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.



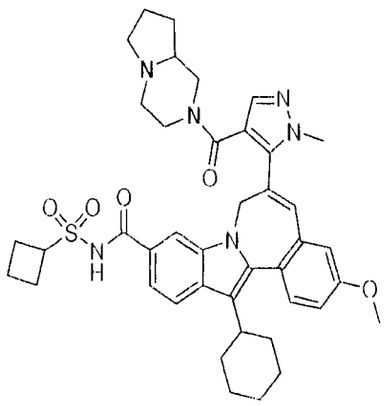
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-

HPLC Method: The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction mixture was diluted to 4 ml using acetonitrile and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 50% solvent A / 50% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 20 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. The compound was purified as two 2ml injections.

Volatiles from the product fractions were removed *in vacuuo* using a speed vac overnight with heating. The product fractions were combined using dichoromethane and solvent removed in vacuuo to give 35.4mg (71%) of the title compound as a yellow amorphous solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.22 (m, 1 H) 1.33 - 1.55 (m, 3 H) 1.79 (d, *J*=10.68 Hz, 2 H) 1.91 - 2.21 (m, 7 H) 2.37 (d, *J*=29.60 Hz, 3 H) 2.56 - 2.79 (m, 4 H) 2.78 - 2.96 (m, 4 H) 3.12 (s, 3 H) 3.90 (s, 3 H) 3.94 (s, 3 H) 4.53 - 4.65 (m, 2 H) 4.89 (d, *J*=14.95 Hz, 1 H) 6.86 (s, 1 H) 6.95 (d, *J*=2.44 Hz, 1 H) 7.12 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.57 (d, *J*=8.85 Hz, 1 H) 7.59 (d, *J*=8.55 Hz, 1 H) 7.67 (s, 1 H) 7.69 (s, 1 H) 7.93 (d, *J*=8.54 Hz, 1 H) 10.24 (s, 1 H).

LCMS for 74814-024-a: LC-MS retention time 1.61min;696 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.



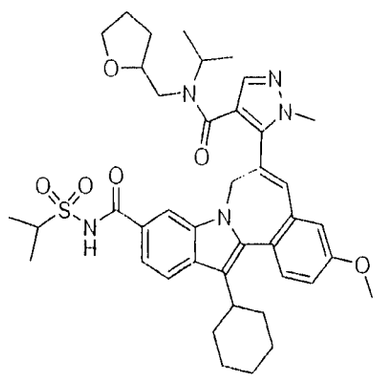
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-

HPLC Method: The sample was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was diluted to 4ml using acetonitrile and a trace of methanol and in purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product = 5.72minutes.

The compound was purified as two 2ml injections. Volatiles were removed from the product fractions *in vacuuo* overnight using a speed-vac set at medium heating.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.24 (s, 1 H) 1.30 - 1.45 (m, 2 H) 1.31 - 1.45 (m, 2 H) 1.58 (none, 2 H) 1.78 (s, 4 H) 1.88 - 2.24 (m, 9 H) 2.34 (s, 2 H) 2.65 (s, 3 H) 2.74 - 3.18 (m, 3 H) 3.18 - 3.87 (m, 9 H) 3.89 - 3.96 (m, 3 H) 3.96 - 4.35 (m, 3 H) 4.45 - 4.68 (m, 2 H) 4.76 - 5.00 (m, 1 H) 6.80 - 6.95 (m, 1 H) 6.96 (s, 1 H) 7.05 - 7.15 (m, *J*=8.24 Hz, 1 H) 7.47 - 7.68 (m, 3 H) 7.68 - 7.81 (m, 1 H) 7.88 (s, 1 H) 9.94 (s, 1 H) 12.54 (s, 1 H).

LC-MS retention time 1.61 min;735 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.



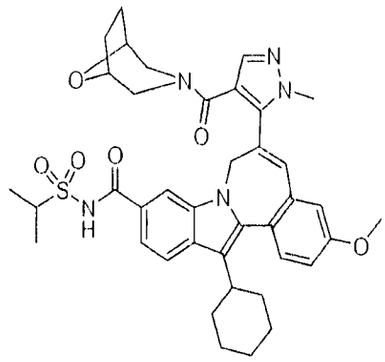
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[(1-methylethyl)[(tetrahydro-2-furanyl)methyl]amino]carbonyl]-1H-pyrazol-5-yl]-

In a 2 dram vial, 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (51.1mg, 0.083 mmol) was dissolved in DMF (829 µl) and HATU (66.3 mg, 0.174 mmol) was added to the reaction. The reaction was stirred under a nitrogen atmosphere for 1.2 hours at room temperature. DMAP (41.5 mg, 0.340 mmol) was added to the reaction and stirred until dissolved then the amine reagent, Isopropyl-(tetrahydro-furan-2-ylmethyl)-amine (36µl, 0.251 mmol), was added and the reaction capped under nitrogen and stirred at room temperature for 17 hours. Note-assume density of amine reagent is 1g/cc, important aspect is not exact stoichometry but excess amine present. The product was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction

collector. The sample was dissolved in acetonitrile / DMF (1:1) (2ml) and purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product is 13.3minutes. Take product fraction and remove volatiles *in vacuuo* using a rotary evaporator. The title compound was isolated (47.4mg, 77%) as an amorphous yellow solid. Proton NMR spectra exhibits characteristics of restricted rotation (broad and rotomeric peaks).

1H NMR (500 MHz, CHLOROFORM-D) d ppm 0.61 (s, 1.6 H) 0.80 - 1.11 (m, 5.1 H) 1.23 (s, 2.7 H) 1.31 - 1.57 (m, 10.7 H) 1.76 (s, 4.0 H) 1.87 - 2.13 (m, 5.9 H) 2.20 (s, 2.4 H) 2.38 - 2.75 (m, 0.7 H) 2.78 - 2.92 (m, 1.2 H) 3.06-3.25 (m, 1.3 H) 3.37 - 3.82 (m, 6.9 H) 3.91 (s, 3.9 H) 3.97 - 4.27 (m, 2.0 H) 4.56 (d, *J*=12.82 Hz, 0.9 H) 4.93 - 5.23 (m, 0.9 H) 6.87 (s, 1.0 H) 6.94 (d, *J*=2.44 Hz, 1.0 H) 7.07 (d, *J*=7.93 Hz, 1.0 H) 7.51 (d, *J*=7.93 Hz, 1.1 H) 7.57 (s, 2.2 H) 7.81 - 8.01 (m, 2.1 H) 9.48 - 9.81 (m, 0.6 H) 9.98 (s, 0.5 H).

LC-MS retention time 1.76 min;740 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u 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 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.



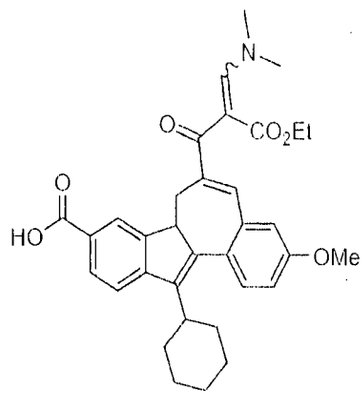
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-ylcarbonyl)-1H-pyrazol-5-yl]-

In a 2 dram vial, 1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-methyl- (50.8 mg, 0.082 mmol) was dissolved in DMF(824 µL) and HATU (72.2mg, 0.190 mmol) was added and the reaction stirred under a nitrogen atmosphere for 1 hour at room temperature. DMAP (41.8mg, 0.342 mmol) was added to the reaction and stirred until dissolved then the amine reagent, 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (30.6 mg, 0.205 mmol). The reaction capped under nitrogen and stirred at room temperature overnight. The product was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was acidified with aqueous acetic acid then diluted to 2ml with acetonitrile and filtered using a 0.45uM syringe filter. The filtrate was purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 20 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. The product was collected as a single fraction from 13.99 to 14.70minutes. Volatiles from the product fraction were removed *in vacuuo* using a speed vac at medium heat setting.

The title compound was isolated (46.0mg, 78% yield) as a yellow amorphous solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.26 - 1.05 (m, 1.2 H) 1.14 - 1.32 (m, 1.9 H) 1.33 - 1.45 (m, 2.3 H) 1.49 (dd, *J*=14.04, 6.71 Hz, 7.1 H) 1.53 - 1.72 (m, 3.4 H) 1.79 (d, *J*=9.77 Hz, 2.2 H) 1.97 (d, *J*=10.99 Hz, 1.2 H) 2.02 - 2.15 (m, 3.1 H) 2.27 (d, *J*=11.29 Hz, 0.7 H) 2.86 (t, *J*=11.60 Hz, 1.6 H) 3.02 (d, *J*=8.85 Hz, 1.5 H) 3.16 (s, 3.9 H) 3.32 (d, *J*=11.60 Hz, 1.1 H) 3.73 - 3.87 (m, 2.1 H) 3.90 (s, 2.8 H) 3.92 - 3.97 (m, 3.4 H) 4.00 - 4.11 (m, 1.4 H) 4.59 (d, *J*=15.26 Hz, 1.0 H) 4.86 (d, *J*=14.34 Hz, 0.8 H) 5.04 (s, 0.3 H) 6.86 (s, 1.0 H) 6.95 (s, 1.0 H) 7.11 (dd, *J*=8.55, 2.44 Hz, 1.0 H) 7.54 (d, *J*=8.85 Hz, 1.2 H) 7.57 - 7.77 (m, 2.7 H) 7.80 - 8.02 (m, 1.3 H) 9.74 (s, 0.2 H) 10.11 (s, 0.7 H).

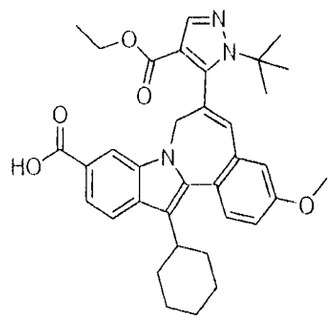
LC-MS retention time 1.61min;710 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min , a gradient 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 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.



13-cyclohexyl-6-((2E,Z)-3-(dimethylamino)-2-(ethoxycarbonyl)-2-propenoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid

In a 50ml round bottom flask dissolve tert-butyl 13-cyclohexyl-6-((2E,Z)-3-(dimethylamino)-2-(ethoxycarbonyl)-2-propenoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (538mg, 0.879 mmol) in 1,2-dichloroethane (5mL) then add TFA (5 mL). The reaction mixture turned a darker reddish color upon addition of TFA. Place the reaction under a nitrogen atmosphere and stir at room temperature for 2.25hrs. Remove volatiles *in vacuuo* using a rotary evaporator, dissolve oily red residue in dichloromethane/benzene and remove volatiles *in vacuuo* on rotary evaporator. Take resulting red oil dissolve in ethyl acetate wash with 1.0N aqueous hydrochloric acid. The aqueous layer was back extracted with ethyl acetate. The organic layers were combined and sequentially washed with 1.0N aqueous hydrochloric acid and brine. The organic layer was dried over MgSO4, filtered and the solvents removed *in vacuuo* to give a reddish-orange oil which was dissolved in benzene and volatiles removed *in vacuuo* to yield 519mg of the title compound a red-orange foam. The compound was used without further purification.

LC-MS retention time 1.86 min; 555 m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-(1,1-dimethylethyl)-4-(ethoxycarbonyl)-1H-pyrazol-5-yl]-3-methoxy-

7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[(2*E*,*Z*)-3-(dimethylamino)-2-[[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-oxo-2-propenyl]-3-methoxy- (101 mg, 0.181 mmol) was dissolved in ethanol (726 µL) and dioxane (181 µL). Triethyl amine(59 µL, 0.423 mmol) was added to the reaction followed by the hydrazine reagent, tert-butylhydrazine hydrochloride (23.6 mg, 0.189 mmol). The reaction was capped under a nitrogen atmosphere and heated in a microwave to 160C for 45minutes. The reaction was concentrated *in vacuuo* using a rotary evaporator and the residue was dissolved in ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric acid then brine. The organic layer was dried over magnesium sulfate, filtered and volatiles removed *in vacuuo* to give 91mg of a yellow amorphous solid. The product was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample was dissolved in acetonitrile / DMF mixture purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 20 minutes with a run time of 30 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system.

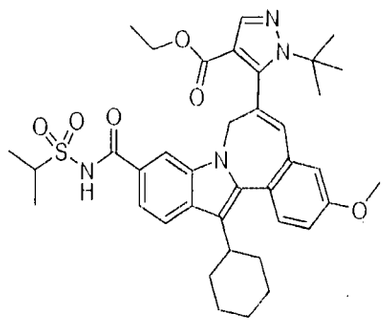
The above isomeric major product retention time was 18.54minutes. The minor region-isomeric alkylated pyrazole was collected with retention time of 20.54minutes.

The volatiles were removed from product fractions *in vacuuo* to obtain 29.8mg of the title compound as a yellow amorphous solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.09 (s, 9 H) 1.18 - 1.56 (m, 8 H) 1.63 (d, 1 H) 1.78 (d, *J*=8.55 Hz, 2 H) 1.88 - 2.22 (m, 5 H) 2.89 (t, *J*=11.75 Hz, 1 H) 3.89 (s, 3 H) 4.27 (s, 2 H) 4.84 (d, *J*=14.65 Hz, 1 H) 4.96 (d, *J*=14.95 Hz, 1 H) 6.81 (s, 1 H) 6.90 (d, *J*=2.14 Hz, 1 H) 7.05 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.52 (d, *J*=8.54

Hz, 1 H) 7.76 (dd, *J*=8.55, 1.22 Hz, 1 H) 7.88 (d, *J*=8.55 Hz, 1 H) 7.92 (s, 1 H) 8.01 (s, 1 H).

LC-MS retention time 2.20 min; 580 m/z (MH-). 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 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.



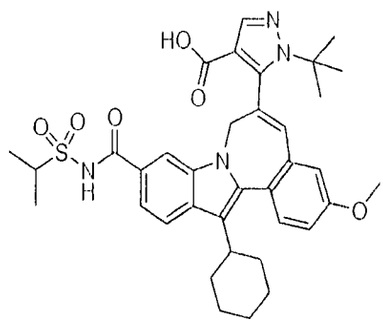
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(1,1-dimethylethyl)-, ethyl ester

In a 2 dram vial, 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-(1,1-dimethylethyl)-4-(ethoxycarbonyl)-1H-pyrazol-5-yl]-3-methoxy- (139mg, 0.239 mmol) was dissolved in dichloromethane (2.4ml) and propane-2-sulfonamide (98 mg, 0.796 mmol) and DMAP (90 mg, 0.737 mmol) were added to the reaction followed by EDC (70.3 mg, 0.367 mmol). The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 18hrs. The reaction was monitored by HPLC then allowed to continue stirring under a nitrogen atmosphere at room temperature for 24hrs.

Subsequent HPLC analysis revealed no discernable change in reaction composition over the last 24hrs. Volatiles were removed from the reaction in vacuuo using a rotary evaporator and the reaction residue was diluted with ethyl acetate and

washed sequentially with 1.0N aqueous hydrochloric acid, 0.1M aqueous NaH2PO4 and 1.0N aqueous hydrochloric acid then brine. The organic phase was dried over MgSO4, filtered and solvent removed *in vacuuo*. The product was dried *in vacuuo* at room temperature to give 165mg of product as an amorphous yellow solid. The product was used without any further purification.

LC-MS retention time 2.03min; 685m/z (MH-). 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 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.

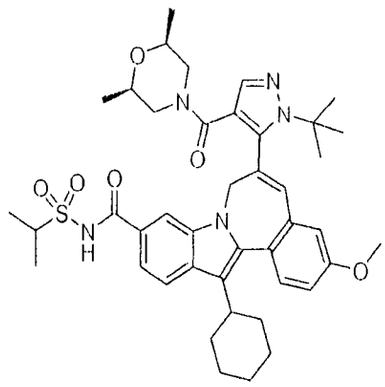


1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(1,1-dimethylethyl)-

1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-(1,1-dimethylethyl)-, ethyl ester (164 mg, 0.239 mmol) was dissolved in THF (3 mL) and methanol (3.00 mL) then 1.0 N aqueous sodium hydroxide (3.00 mL) was added to the reaction and the reaction was placed under a nitrogen atmosphere and stirred at room temperature for 25hrs. The reaction was concentrated in vacuuo using a rotary evaporator without heating then partitioned between ethyl acetate and 1.0N aqueous hydrochloric acid. Wash ethyl acetate with 1N aqueous hydrochloric acid, combine

aqueous layers and back extract with ethyl acetate. The organic layers were combined and wash with brine, dry over magnesium sulfate and solvent removed *in vacuuo* using a rotary evaporator. The product was dried *in vacuuo* at room temperature to give 158.4mg as a yellow amorphous solid. The product was carried on without any further purification.

LC-MS retention time 1.54min; 657 m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-(1,1-dimethylethyl)-4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-

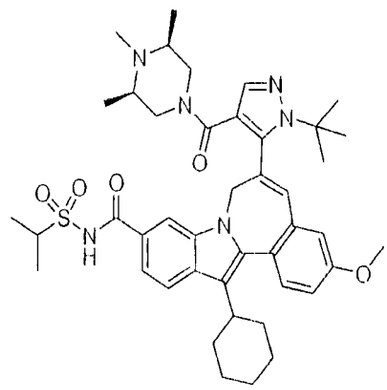
1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-(1,1-dimethylethyl)- (60mg, 0.091 mmol) was dissolved in DMF (911 µL). HATU (81.5 mg, 0.214 mmol) was added to the reaction and the reaction was capped under a nitrogen atmosphere and stir at room temperature for 1.25hrs. DMAP (45.9 mg, 0.376 mmol) was added to reaction followed by amine reagent, (2R,6S)-2,6-dimethylmorpholine (34 µL, 0.275 mmol). The reaction was capped under a nitrogen

atmosphere and stir at room temperature for 18hr. The product was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was diluted to 2ml with acetonitrile and a couple of drops of aqueous acetic acid then purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 20 minutes with a run time of 30 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product was 18.5 minutes. Product fractions were combined and volatiles removed *in vacuuo* using a rotary evaporator. The sample was dried *in vacuuo* at room temperature to give 32.5mg as a yellow amorphous film. 1H NMR results are characteristic of restricted rotation with broadening and splitting of peaks.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.66 (d, *J*=6.10 Hz, 2.4 H) 0.71 (d, *J*=6.10 Hz, 2.3 H) 0.78 (dd, *J*=11.29, 6.10 Hz, 1.8 H) 1.10 (s, 1.2 H) 1.25 (dd, *J*=13.73, 6.71 Hz, 3.0 H) 1.35 - 1.44 (m, 2.5 H) 1.46 (t, *J*=7.02 Hz, 4.7 H) 1.54 (d, *J*=6.71 Hz, 3.7 H) 1.67 (s, 0.6 H) 1.71 (s, 6.8 H) 1.72 - 1.75 (m, 2.7 H) 1.79 (d, *J*=11.90 Hz, 2.5 H) 1.83 - 1.92 (m, 1.0 H) 1.98 (d, *J*=12.51 Hz, 2.2 H) 2.02 - 2.21 (m, 7.9 H) 2.21 - 2.30 (m, 1.4 H) 2.80 - 2.95 (m, 2.3 H) 3.04 (d, *J*=42.42 Hz, 0.6 H) 3.23 (d, *J*=13.73 Hz, 0.3 H) 3.34 (d, *J*=12.82 Hz, 0.8 H) 3.92 (d, *J*=4.88 Hz, 0.5 H) 3.95 (s, 3.0 H) 4.04 - 4.13 (m, 1.1 H) 4.49 - 4.58 (m, 1.0 H) 4.79 (d, *J*=14.65 Hz, 0.3 H) 4.86 (d, *J*=15.26 Hz, 0.7 H) 6.78 (s, 0.8 H) 6.85 (s, 0.3 H) 6.87 (d, *J*=2.75 Hz, 0.8 H) 6.91 (s, 0.3 H) 7.14 (dd, *J*=8.55, 2.44 Hz, 1.0 H) 7.55 - 7.60 (m, 0.9 H) 7.60 - 7.64 (m, 2.3 H) 7.64 - 7.68 (m, 1.0 H) 7.83 - 7.95 (m, 1.3 H) 10.32 (s, 0.3 H) 10.60 (s, 0.7 H).

LC-MS retention time 2.10 min; 754m/z (MH-). 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 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.



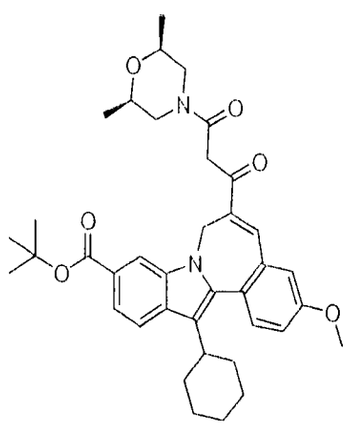
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-(1,1-dimethylethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-

1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-(1,1-dimethylethyl)- (48.8 mg, 0.074 mmol) was dissolved in DMF (741 µL). HATU (65.3 mg, 0.172 mmol) was added to the reaction and the reaction was capped under a nitrogen atmosphere and stir at room temperature for 1hrs. DMAP (53.8 mg, 0.440 mmol) was added to reaction followed by amine reagent, (2R,6S)-1,2,6-trimethylpiperazine dihydrochloride (34.5 mg, 0.172 mmol). The reaction was capped under a nitrogen atmosphere and stir at room temperature for 18hr. The product was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was acidified with a few drops of aqueous acetic acid and diluted to 2ml with acetonitrile then purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 100mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 ml. / min , a gradient of 70 solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 20 minutes with a run time of 25 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Product was collected from 8.14

minutes to 9.45minutes. Volatiles were removed *in vacuuo* from the combined product fractions to ultimately yield 11.1mg of the title compound as a yellow amorphous film.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.93 - 1.34 (m, 9.7 H) 1.37 - 1.52 (m, 9.5 H) 1.56 - 1.68 (m, 1.6 H) 1.68 - 1.83 (m, 9.2 H) 1.87 - 2.20 (m, 5.4 H) 2.28 - 2.52 (m, 2.0 H) 2.55 - 3.01 (m, 9.4 H) 3.19 (d, *J*=40.59 Hz, 0.8 H) 3.63 (d, *J*=134.28 Hz, 2.4 H) 3.83 - 4.04 (m, 4.0 H) 4.54 (d, *J*=14.65 Hz, 0.8 H) 4.76 (d, *J*=14.34 Hz, 0.8 H) 6.72 - 6.97 (m, 2.0 H) 7.08 (d, *J*=7.32 Hz, 1.0 H) 7.36 - 7.76 (m, 3.4 H) 7.88 (s, 1.2 H) 10.86 (s, 0.5 H) 11.26 (s, 0.4 H).

LC-MS retention time 1.81min;767 m/z (MH-). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[3-[(2R,6S)-2,6-dimethyl-4-morpholinyl]-1,3-dioxopropyl]-3-methoxy-, 1,1-dimethylethyl ester

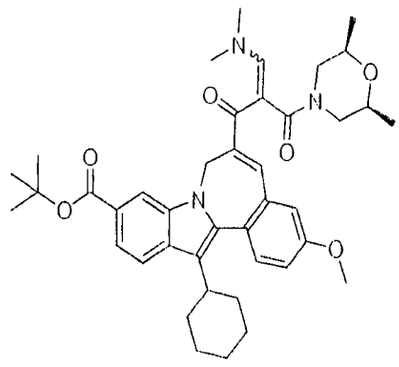
In a 250ml round bottom flask dissolve tert-butyl 13-cyclohexyl-6-(3-ethoxy-3-oxopropanoyl)-3-methoxy-7H-indolo[2,1-a][2]benzazepine-10-carboxylate (3.13g,

5.61 mmol) in toluene (56 mL) and add cis-2,6-Dimethylmorpholine (2.6 mL, 20.99 mmol) to the reaction. Place reaction under a nitrogen atmosphere and heat to reflux for 9hours. The reaction was partitioned between ethyl acetate and 1.0M aqueous citric acid. The organic layer was washed sequentially with 1.0M aqueous citric acid, 0.1M NaH2PO4, and brine. Dry organic phase over magnesium sulfate, filter and remove solvent in vacuuo to give 3.01g of crude product as a orange-amber foam. Dissolve the crude product in dichloromethane and adsorb onto 8.2g of silica gel. Chromatograph crude product on 90g of silica gel slurry packed in 5% ethyl acetate in dichloromethane, elute with gradient of 5% ethyl acetate in dichloromethane to10% ethyl acetate in dichloromethane. Pure product fractions were combined and solvent removed *in vacuuo* using a rotary evaporator to yield a yellow amorphous solid which was further dried *in vacuuo* at room temperature to yield 1.28g of the title compound. Less pure fractions yielded another 0.48g of product. LCMS analysis gave two peaks of equivalent mass to that of the desired product. Resolution of the two peaks by Prep HPLC under the following conditions yielded peaks which inter-converted when analyzed after isolation: Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The sample 76816-035-a (63mg) was dissolved in acetonitrile / DMF mixture (2:1, 2ml) purified using a Phenonmenex Luna C18 30 x 100mm 10u column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 40mL/ min , a gradient of 60% solvent A / 40% solvent B to 0% solvent A / 100% solvent B, a gradient time of 15 minutes with a run time of 25 minutes using %A= 10mM Ammonium Acetate in 95:5 Water/Acetonitrile %B= 10mM Ammonium Acetate in 5:95 Water/Acetonitrile solvent system. Two peaks were isolated from the sample: First peak at RT= 16.3 minutes. Both samples exhibited identical HPLC spectra after isolation indicating inter-conversion.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.89 (s, 2.0 H) 1.01 (s, 3.3 H) 1.19 (d, *J*=26.25 Hz, 3.5 H) 1.30 - 1.47 (m, 4.5 H) 1.55 (s, 4.2 H) 1.60 (s, 3.6 H) 1.63 (s, 9.0 H) 1.76 (d, *J*=8.24 Hz, 3.1 H) 1.93 (d, *J*=9.46 Hz, 1.9 H) 1.98 - 2.15 (m, 4.2 H) 2.23 (s, 1.2 H) 2.39 (s, 0.4 H) 2.56 - 2.72 (m, 1.6 H) 2.74 - 2.86 (m, 1.6 H) 2.91 (s, 0.8 H) 3.47 - 3.65 (m, 2.8 H) 3.74 - 3.85 (m, 1.6 H) 3.90 (s, 1.4 H) 3.91 (s,

3.1 H) 3.93 - 4.04 (m, 1.8 H) 4.19 (d, *J*=12.82 Hz, 0.5 H) 4.26 (d, *J*=14.65 Hz,0.5 H) 4.39 (s, 0.5 H) 4.47 (d, *J*=11.29 Hz, 0.4 H) 5.18 (s, 0.3 H) 5.71 - 5.92 (m, 1.1 H) 7.01 (d, *J*=2.75 Hz, 0.4 H) 7.03 - 7.06 (m, 1.4 H) 7.11 (dd, *J*=8.70, 2.59 Hz, 1.0 H) 7.47 - 7.51 (m, 0.9 H) 7.52 (s, 0.5 H) 7.57 (s, 0.4 H) 7.65 (d, *J*=1.53 Hz, 0.2 H) 7.68 (dd, *J*=8.55, 1.22 Hz, 1.2 H) 7.80 (s, 0.6 H) 7.80 - 7.82 (m, 0.7 H) 7.84 (s, 0.2 H) 7.91 (s, 0.4 H) 8.04 (s, 0.5 H) 8.19 (s, 0.3 H) 8.21 (d, *J*=1.22 Hz, 1.0 H) 15.15 (d, *J*=23.80 Hz, 0.4 H).

LC-MS retention time 4.21min (88%); 625m/z (MH-) and 5.23min (12%); 625m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u 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 70% solvent A / 30% solvent B to 0% solvent A / 100% solvent B, a gradient time of 5min, a hold time of 2 min, and an analysis time of 7 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.

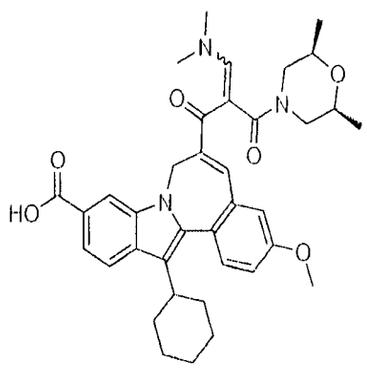


7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[(2E,Z)-3-(dimethylamino)-2-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-oxo-2-propenyl]-3-methoxy-, 1,1-dimethylethyl ester

7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[3-[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]-1,3-dioxopropyl]-3-methoxy-, 1,1-dimethylethyl ester was dissolved in N,N-Dimethylformamide dimethyl acetal (10 mL,). The reaction was fitted with a condenser and placed under a nitrogen

atmosphere. The reaction was heated to reflux for 3hrs, cooled then the volatiles were removed *in vacuuo* using a rotary evaporator, then dry *in vacuuo* at room temperature to obtain the product as an amorphous orange solid (517mg, 86%).

LC-MS retention time 4.60min;682 m/z (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u 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 4 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 5min, a hold time of 2 min, and an analysis time of 7 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. The intermediate was used without further purification.

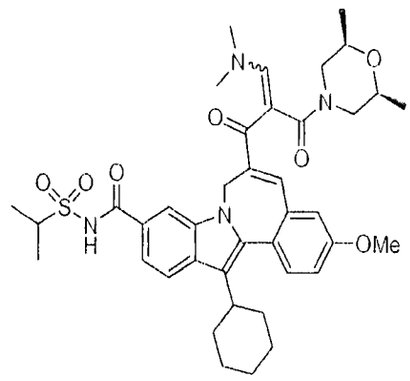


7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[(2E,Z)-3-(dimethylamino)-2-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-oxo-2-propenyl]-3-methoxy-

7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[(2*E*,*Z*)-3-(dimethylamino)-2-[[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-oxo-2-propenyl]-3-methoxy-, 1,1-dimethylethyl ester was dissolved in 1,2-dichloroethane (5mL) and TFA (5mL) was added to the reaction. The reaction was placed under a nitrogen atmosphere and stirred for 2.5hrs. Volatiles were removed *in vacuuo* from the reaction using a rotary evaporator to give a reddish oil. The product was dissolved in benzene/dichloromethane and the volatiles again removed *in vacuuo* to give a red foam. The product was dissolved in ethyl acetate and washed with 1.0N

aqueous hydrochloric acid. The aqueous layer was back extracted with ethyl acetate. The organic extracts were combined, washed with brine and dried over magnesium sulfate. The organic solution was filtered and the volatiles removed *in vacuuo* using a rotary evaporator to give a amber-orange foam. The product was dried *in vacuuo* at room temperature to give 388mg of amorphous amber-orange solid.

LC-MS retention time 2.83 min; 624 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u 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 4 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 5min, a hold time of 2 min, and an analysis time of 7 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.



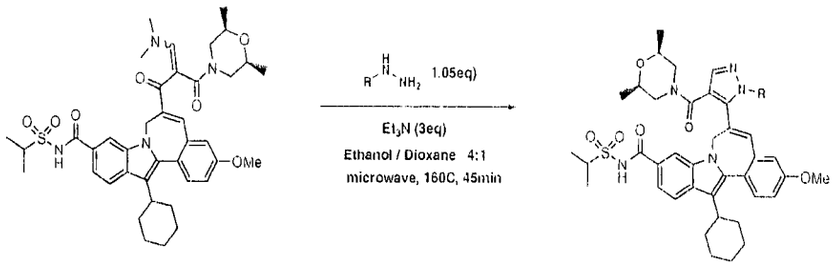
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[(2E,Z)-3-(dimethylamino)-2-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-oxo-2-propenyl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-

In a 25ml rb flask, dissolve 7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[(2*E*,*Z*)-3-(dimethylamino)-2-[[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-oxo-2-propenyl]-3-methoxy- (385mg, 0.616 mmol) in dichloromethane (6.2 mL), add propane-2-sulfonamide (233 mg, 1.892 mmol) and DMAP (230 mg, 1.880 mmol) to the reaction followed by EDC (177 mg, 0.924 mmol). The reaction was placed under a nitrogen atmosphere and stirred at room temperature for 18.5hrs. The reaction was diluted with ethyl acetate and washed with

1.0N aqueous hydrochloric acid. The aqueous phases were combined and back extracted with ethyl acetate. The organic layers were combined and sequentially washed with 1.0N aqueous hydrochloric acid and brine. The organic solution was dried over magnesium sulfate, filtered and the solvent removed *in vacuuo* using a rotary evaporator to give an amorphous orange solid/foam which was dried *in vacuuo* to give 415mg of crude product.

LC-MS retention time 3.00 min; 729m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u 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 5min, a hold time of 2 min, and an analysis time of 7 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.

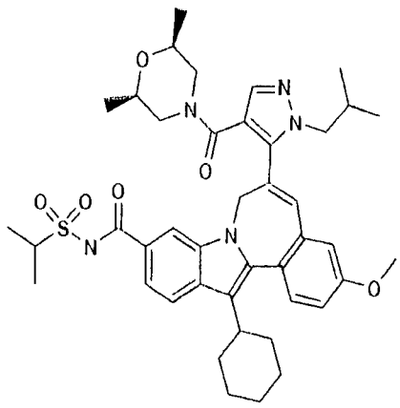
The crude product was used without any further purification in subsequent pyrazole synthesis.



The following analog can be prepared using the general methodology described below.

7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[(2*E*,*Z*)-3-(dimethylamino)-2-[[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-oxo-2-propenyl]-3-methoxy-*N*-[(1-methylethyl)sulfonyl]- (100 mg, 0.137 mmol) in ethanol (547 µL) and dioxane (137 µL). Add the hydrazine reagent (0.146 mmol) followed by TEA (58.2 µL, 0.417 mmol) to the reaction in a 0.5-2mL microwave reaction vessel. The vessel was capped under a nitrogen atmosphere and heated at 160C for

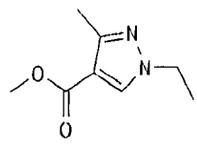
45 minutes. The reaction was diluted in DMF/Acetonitrile and product compound purified by reverse phase HPLC.

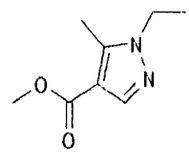


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-(2-methylpropyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-

This compound was isolated using reverse phase HPLC with the instrumentation listed below using gradient method Bin# 16. Dionex APS-3000; Chromeleon 6.70 sp1 LC software; Thermo-Finnigan Xcalibur MS software; Dionex P680 binary pump for analytical; Dionex PP150 binary pump prep; Dionex UVD340U UV spectrometer; Polymer Labs PL-ELS 1000 ELS detector; Thermo-Finnigen MSQ Surveyor Plus mass spectrometer. **LC Conditions:** Column; Waters Xbridge 19x200mm 5 um C18; Guard Column; Waters Xbridge 19x10mm 5 um C18; Mobile Phase; A = Water, 20 mM NH4OH; B = CAN. LC-MS retention time 5.47 min; 756.87m/z (MH+). LC data was recorded using Masslynx 4.0 SP4 with a system equipped with: CTC-Leap HTS-PAL autosampler with Harney 4-port injection module, Waters 1525 binary pump, Waters 2488 UV detector at 220 nm, Polymer Lab 1000 ELS detector (evap. Temp.=90C, Neb. Temp.= 80C) and a Waters LCT mass spectrometer with 4 way MUX source. The sample was analyzed using an Ascentis 4.6x50mm 5uM C18 column. The elution conditions employed a flow rate of 2 ml/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 8min, a hold time of 1 min, and an analysis time of 9 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

ionization using a Waters LCT mass spectrometer in ESI positive mode.





Methyl 1-ethyl-3-methyl-1H-pyrazole-4-carboxylate, and Methyl 1-ethyl-5-methyl-1H-pyrazole-4-carboxylate

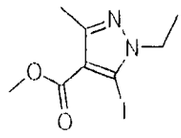
Methyl 2-((dimethylamino)methylene)-3-oxobutanoate (1.712 g, 10 mmol) in was suspended in diethyl ether (50 mL), under a nitrogen atmosphere to 0°C. Ethylhydrazine oxalate (1.651 g, 11 mmol) in diethyl ether (13 mL), triethyl amine (7.0 mL, 50.2 mmol) and ethanol (6 mL) were then added. The resultant mixture slowly became more homogeneous and stirring was continued 0°C for 40min, afterwhich the ice bath was removed and the mixture stirred for an additional 1.5 hours. The reaction was then partitioned between ethyl acetate and 1.0N aqueous hydrochloric acid. Extract aqueous phase with ethyl acetate. Combine the organic layers and wash sequentially with 1.0N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine. Dry organic layer over magnesium sulfate, filter and remove volatiles *in vacuuo* to yield a yellow oil, transfer to a small pear shaped flask in benzene, remove volatiles *in vacuuo* using rotary evaporator. The sample was briefly dried in vacuuo on a rotary evaporator to yield 1.549g of a yellow liquid/oil.

1H NMR analysis indicated an mixture of isomers of 53:46 ratio.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.40 (t, *J*=7.32 Hz, 3.01 H) 1.46 (t, *J*=7.32 Hz, 3.56 H) 2.44 (s, 3.45 H) 2.52 (s, 2.99 H) 3.79 (s, 3.49 H) 3.79 (s, 2.79 H) 4.05 - 4.13 (m, 4.44 H) 7.80 (s, 1.09 H) 7.82 (s, 0.86 H).

LC-MS retention time 0.80min; 169m/z (MH+). 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 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.



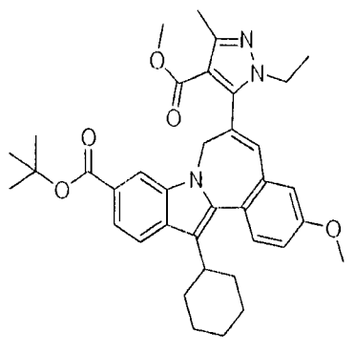
Methyl 1-ethyl-5-iodo-3-methyl-1H-pyrazole-4-carboxylate

In a 100ml RB a mixture of methyl 1-ethyl-3-methyl-1H-pyrazole-4-carboxylate, and methyl 1-ethyl-5-methyl-1H-pyrazole-4-carboxylatemixture (1.539 g, 9.15 mmol) was dissolved in anhydrous THF (44 mL). The reaction was placed under a nitrogen atmosphere and cooled to -78C, then n-butyl lithium (5.49 mL, 10.98 mmol) 2.0M in pentane was added in a dropwise fashion. The orange solution at -78C was then immersed in a acetonitrile/CO2 bath at -44C and stirred for 1 hour. The reaction was cooled to -78C and a solution of iodine (2.55 g, 10.07 mmol) in tetrahydrofuran (10 mL) was added by cannua over approximately 10minutes. The reaction was stirred at -78C for 10 minutes after the addition of iodine then the cold bath removed and the reaction allowed to warm to room temperature over 1hr. The reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted into ethyl acetate. The reaction was partitioned between ethyl acetate and aqueous saturated ammonium chloride, washed with aqueous sodium sulfite and again with saturated aqueous ammonium chloride and brine. The product solution was dried over magnesium sulfate and volatiles removed in vacuuo using rotary evaporator. The crude product was isolated as an amber oil (approx 2.1g). The title compound (Rf=0.66 in 50% ethyl acetate / hexanes on Analtech Uniplate silica gel GHLF 250 micron TLC plate) was isolated by silica gel chromatography. The crude reaction was adsorbed onto 5.5g of silica gel using dichloromethane and chromatographed on 55.9g of silica gel slurry packed in a column using 10% ethyl acetate in hexanes. Elution with 10% ethyl acetate in hexanes then a step gradient of 15%, 20%, 25%, 30%, 40%, 50% and finally to 70% ethyl acetate in hexanes yielded the purified product and separation of crude reaction components.

The title compound (424mg, 30%) was isolated as a nearly colorless solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.40 (t, *J*=7.17 Hz, 3 H) 2.45 (s, 3 H) 3.84 (s, 3 H) 4.24 (q, *J*=7.32 Hz, 2 H).

LC-MS retention time1.19 min;295 m/z (MH+). 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 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.



7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(methoxycarbonyl)-3-methyl-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester

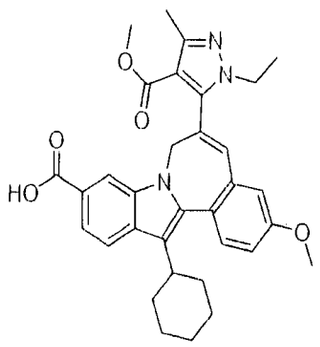
Into a 20 ml microwave vessel charge, 7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-(tributylstannyl)-, 1,1-dimethylethyl ester (300 mg, 0.409 mmol), methyl 1-ethyl-5-iodo-3-methyl-1H-pyrazole-4-carboxylate (169 mg, 0.573 mmol), bis(triphenylphosphine)palladium(II) dichloride (29.6 mg, 0.042 mmol) and 1g of activated 3A molecular sieves. Cap reaction vessel and evacuate and fill with nitrogen through three cycles. Dioxane was added to the reaction and the reagents dissolved at room temperature. The sealed reaction was heated at 120C for 17hrs. Ethyl acetate was added to the reaction and the reaction filtered through a 0.45uM Whatman autovial filter. The filter cake was rinsed with ethyl acetate and the volatiles were removed from the filtrate *in vacuuo* to give a

508mg of yellow oil. The crude product with an odor of tin was dissolved in 13ml of dioxane and stirred for 2hrs with a aqueous solution of potassium fluoride. An attempt to filter the solution was unsuccessful and the aqueous /organic suspension was poured into a separatory funnel and ethyl acetate added and the aqueous layer extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate, filtered and volatiles removed *in vacuuo* to obtain 446mg of amber oil that still has an odor of tin. The crude product was adsorbed onto 1.1g of silica gel using dichloromethane and purified on a 15.0g of silica gel column slurry loaded in dichloromethane. The column was eluted with a step gradient of dichloromethane to 2% ethyl acetate in dichloromethane and finally flushed with 5% ethyl acetate in dichloromethane. The product fraction were combined and solvent removed in vacuuo to give the title compound (152mg, 61%) as a amorphous yellow solid. The compound had a faint odor indicating trace amount of tin may be present. The product was used in subsequent steps without further purification.

1H NMR shows sample probably contains a butyl tin impurity. 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.64 (s, 3 H) 0.81 - 0.89 (m, 2 H) 0.91 (t, *J*=7.32 Hz, 2.5 H, Sn compound?) 1.20 - 1.31 (m, 7 H) 1.31 - 1.41 (m, 3 H) 1.43 - 1.55 (m, 3 H) 1.56 (s, 5 H) 1.58 (s, 8 H) 1.60 - 1.68 (m, 2 H) 1.77 (d, *J*=9.46 Hz, 2 H) 1.94 (d, *J*=7.63 Hz, 1 H) 2.03 (s, 0.9 H, EtOAc) 2.07 (s, 2 H) 2.45 (s, 0.4 H) 2.47 (s, 3 H) 2.53 (s, 0.3 H) 2.85 (t, *J*=11.90 Hz, 1 H) 3.50 (d, *J*=54.93 Hz, 3 H) 3.73 - 3.85 (m, 3 H) 3.90 (s, 3 H) 4.08 - 4.14 (m, 0.8 H, EtOAc and impurity) 4.59 (q, *J*=7.22 Hz, 1 H) 4.66 (d, *J*=13.43 Hz, 1 H) 4.95 (d, *J*=14.04 Hz, 1 H) 6.72 (s, 1 H) 6.92 (d, *J*=2.44 Hz, 1 H) 7.05 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.51 (d, *J*=8.54 Hz, 1 H) 7.63 (dd, *J*=8.55, 1.53 Hz, 1 H) 7.78 - 7.83 (m, 1 H) 7.85 (s, 1 H).

LC-MS retention time 2.74 min; 610 m/z (MH+). 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 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.



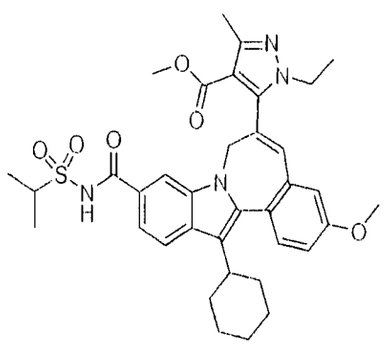
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(methoxycarbonyl)-3-methyl-1H-pyrazol-5-yl]-3-methoxy-

7*H*-indolo[2,1-*a*][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(methoxycarbonyl)-3-methyl-1*H*-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester (151mg, 0.248 mmol) was dissolved in 1,2-dichloroethane (2ml) and TFA (2.000 ml) added. The reaction was stirred under a nitrogen atmosphere at room temperature for 2.5hrs. Volatiles from the reaction were removed *in vacuuo* using a rotary evaporator to give a orange/amber oil. The oily product was dissolved in a mixture of dichloromethane and benzene and the volatiles were removed *in vacuuo* to obtain a yellow amorphous solid. The solid was suspended in benzene-dichloromethane and again volatiles removed *in vacuuo*. The product was dried *in vacuuo* at room temperature to give 151mg of a yellow solid with a trace odor of tin. The product was triturated with the addition of 1.5 to 2mls of dichloromethane and several milliliters of hexanes. The suspension was heated to reflux then allowed to cool. The product as a pale yellow amorphous solid was filtered and rinsed with hexanes and dried *in vacuuo* at room temperature to yield 114.7mg of the title compound.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.60 (s, 3 H) 0.88 (t, *J*=7.02 Hz, 1 H) 1.19 - 1.33 (m, 3 H) 1.34 - 1.58 (m, 3 H) 1.79 (d, *J*=8.85 Hz, 2 H) 1.96 (s, 1 H) 2.08 (s, 3 H) 2.51 (s, 3 H) 2.86 (t, *J*=11.60 Hz, 1 H) 3.41 - 3.71 (m, 3 H) 3.73 - 3.89 (m, 2 H) 3.91 (s, 3 H) 4.49 (s, 6 H) 4.70 (d, *J*=12.21 Hz, 1 H) 4.96 (d, *J*=12.21

Hz, 1 H) 6.76 (s, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.08 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.54 (d, *J*=8.54 Hz, 1 H) 7.76 (dd, *J*=8.39, 1.37 Hz, 1 H) 7.89 (d, *J*=8.54 Hz, 1 H) 7.95 (s, 1 H).

LC-MS retention time1.87 min;552 m/z (MH-). 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 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.



1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-ethyl-3-methyl-, methyl ester

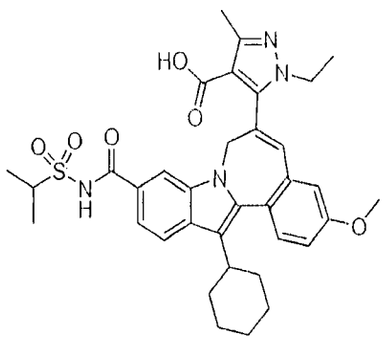
7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(methoxycarbonyl)-3-methyl-1H-pyrazol-5-yl]-3-methoxy- (109.4 mg, 0.198 mmol) was suspended in dichloromethane (2ml) and propane-2-sulfonamide (82 mg, 0.666 mmol) and DMAP (77.8 mg, 0.637 mmol) were added to the reaction. Upon addition of DMAP the reaction became a homogeneous yellow solution. EDC (57.7 mg, 0.301 mmol) was added to the reaction and the reaction was capped under a nitrogen atmosphere and stir at room temperature for 2 days. The reaction was diluted with ethyl acetate and washed sequentially with 1.0N aqueous hydrochloric

acid and brine. The organic phase was dried over MgSO4, filtered and solvent removed *in vacuuo* to obtain 128mg of product as a yellow foam.

1H NMR analysis shows the presence of ethyl acetate and approximately 0.24 equivilents of propane-2-sulfonamide reagent. The material was used without further purification.

LC-MS retention time 1.84min; 657m/z (MH-). 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 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.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.66 (s, 2 H) 0.79 - 0.94 (m, 2 H) 1.28 - 1.39 (m, 2 H) 1.45 - 1.49 (m, 6 H) 1.50 - 1.56 (m, 1 H) 1.79 (d, *J*=8.85 Hz, 2 H) 1.96 (s, 2 H) 2.05 - 2.11 (m, 2 H) 2.26 (s, 7 H, H2O peak) 2.49 (s, 3 H) 2.81 - 2.91 (m, 1 H) 3.38 - 3.71 (m, 4 H) 3.74 - 3.88 (m, 2 H) 3.91 (s, 3 H) 4.01 - 4.08 (m, 1 H) 4.69 (d, *J*=15.26 Hz, 1 H) 4.94 (d, *J*=12.51 Hz, 1 H) 6.76 (s, 1 H) 6.94 (d, *J*=2.75 Hz, 1 H) 7.08 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.38 (d, *J*=8.55 Hz, 1 H) 7.53 (d, *J*=8.55 Hz, 1 H) 7.76 (s, 1 H) 7.89 (d, *J*=8.54 Hz, 1 H) 8.30 (s, 1 H).



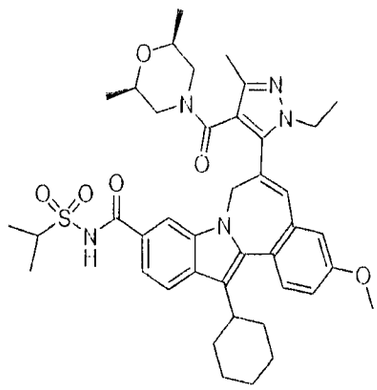
1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-ethyl-3-methyl-

1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-ethyl-3-methyl-, methyl ester (127mg, 0.193 mmol) was dissolved in THF (3ml) and methanol (3 ml) added to the solution.. Sodium hydroxide (3 ml, 3.00 mmol, 1.0N aqueous solution) was added to the homogeneous yellow solution reaction. The reaction turned to a rose-reddish cloudy color after complete addition of sodium hydroxide solution. The reaction was stirred at room temperature under a nitrogen atmosphere and eventually became a clear rose colored solution. The reaction was stirred at room temperature under a nitrogen atmosphere. HPLC analysis after 40hours revealed 78% conversion to product. Sodium hydroxide (1.0ml, 1.00mmol, 1.0N aqueous solution) was added to the reaction and the reaction stirred under a nitrogen atmosphere for an additional 24hrs. The reaction was concentrated to dryness *in vacuuo* using a rotary evaporator with bath at ambient temperature. The pink solid residue was partitioned between ethyl acetate and 1.0N aqueous hydrochloric acid. The aqueous phase was extracted with ethyl acetate and the organic layers combined and washed sequentially with 1.0N aqueous hydrochloric acid and brine. The organic layer was dried over magnesium sulfate, filtered and solvents removed *in vacuuo* to give a yellow solid which was dried *in vacuuo* at room temperature to give 108mg of the title compound as a amorphous yellow solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.71 (s, 3 H) 0.81 - 0.94 (m, 2 H) 0.96 - 1.20 (m, 3 H) 1.23 - 1.27 (m, 3 H) 1.27 - 1.37 (m, 3 H) 1.41 (t, *J*=7.17 Hz, 6 H) 1.45 - 1.53 (m, 2 H) 1.60 - 1.73 (m, 1 H) 1.77 (d, *J*=11.90 Hz, 2 H) 1.86 - 2.02 (m, 2 H) 2.04 - 2.08 (m, 1 H) 2.47 (s, 2 H) 2.77 - 2.89 (m, 1 H) 3.43 - 3.69 (m, 4 H) 3.70 - 3.86 (m, 2 H) 3.99 - 4.06 (m, 2 H) 4.61 (d, *J*=10.07 Hz, 1 H) 4.95 (d, *J*=13.73 Hz, 1 H) 6.75 (s, 1 H) 6.94 (d, *J*=2.44 Hz, 1 H) 7.03 - 7.10 (m, 1 H) 7.42 (d, *J*=8.24 Hz, 1 H) 7.47 - 7.54 (m, 1 H) 7.79 - 7.91 (m, 2 H) 8.76 (s, 1 H).

LC-MS retention time 1.50 min; 643 m/z (MH-). 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 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.



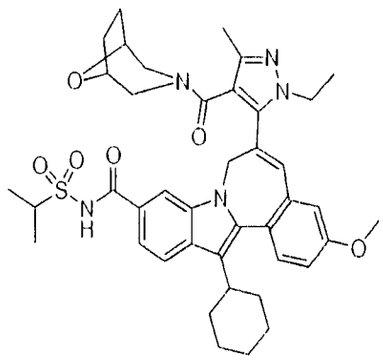
7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-ethyl-3-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-

1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-ethyl-3-methyl- (61.1 mg, 0.095 mmol) was dissolved in DMF (948 µL) and HATU (80 mg, 0.210 mmol) added to the reaction. The reaction was capped under a nitrogen atmosphere and stirred at room temperature for 1hr. DMAP (36.7 mg, 0.300 mmol) was added to the reaction followed by the amine reagent, (2R,6S)-2,6-dimethylmorpholine (35.2 µL, 0.284 mmol). The clear yellow reaction solution was capped under a nitrogen atmosphere and the reaction stirred at room temperature for 42 hours. The product was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was diluted to 2ml with acetonitrile purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 150mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 50% solvent A / 50% solvent B to 0% solvent A / 100% solvent B, a gradient time of 25 minutes with a run time of 30 minutes using %A=

10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product was from 16.16 to 17.47 minutes. The product fractions were combined and volatiles removed *in vacuuo* using a rotary evaporator. The title compound was dried in vacuuo at room temperature to yield 36.3mg as a yellow amorphous solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.68 (s, 4 H) 0.75 - 0.93 (m, 2 H) 1.05 (s, 1 H) 1.30 - 1.45 (m, 6 H) 1.51 (dd, *J*=21.82, 6.26 Hz, 7 H) 1.79 (d, *J*=10.68 Hz, 2 H) 1.89 - 2.02 (m, 3 H) 2.03 - 2.16 (m, 3 H) 2.26 (s, 12 H) 2.88 (t, *J*=10.68 Hz, 1 H) 2.95 - 3.31 (m, 3 H) 3.34 - 3.75 (m, 1 H) 3.94 (s, 3 H) 4.03 - 4.11 (m, 1 H) 4.17 (s, 2 H) 4.57 (d, *J*=14.65 Hz, 1 H) 4.87 (d, *J*=15.56 Hz, 1 H) 6.74 - 6.86 (m, 1 H) 6.93 (s, 1 H) 7.12 (d, *J*=7.02 Hz, 1 H) 7.58 (d, *J*=8.54 Hz, 1 H) 7.66 (s, 1 H) 7.73 (s, 1 H) 7.90 (d, *J*=8.24 Hz, 1 H) 10.66 (s, 1 H).

LC-MS retention time 1.93 min; 740m/z (MH-). 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 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.

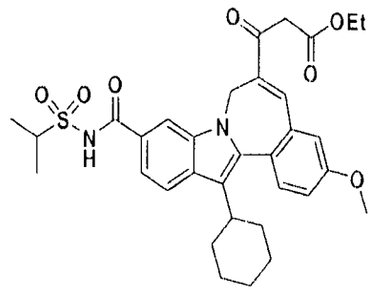


7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-3-methyl-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-ylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-

1*H*-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-1-ethyl-3-methyl- (45.8mg, 0.071 mmol) was dissolved DMF (710 µL) and HATU (62.7 mg, 0.165 mmol) was added to the reaction. The reaction was capped under a nitrogen atmosphere and stirred for 1hr at room temperature. DMAP (37.1 mg, 0.304 mmol), was added to the reaction followed by the amine reagent 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (23.3 mg, 0.156 mmol). The reaction was again capped under a nitrogen atmosphere and stirred at room temperature for 42hrs. The product was purified on a Shimadzu high pressure liquid chromatography system employing Discovery VP software interfaced with a SCL-10A controller, SIL-10A autosampler and FRC-10A fraction collector. The reaction was diluted to 2ml with acetonitrile purified using a Waters Sunfire Prep C18 OBD, 5uM 19mm x 150mm column and monitored using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 25 mL / min , a gradient of 50% solvent A / 50% solvent B to 0% solvent A / 100% solvent B, a gradient time of 25 minutes with a run time of 35 minutes using %A= 10% acetonitrile, 90% water, 0.1% TFA %B= 90% acetonitrile, 10% water, 0.1% TFA solvent system. Retention time of product was from 14.77 to 15.57 minutes. Volatiles were removed from the product fraction *in vacuuo* using a rotary evaporator. The title compound was dried *in vacuuo* at room temperature to yield 28.2mg of a yellow amorphous solid.

1H NMR (500 MHz, CHLOROFORM-D) δ ppm 0.68 (s, 1 H) 1.14 - 1.30 (m, 2 H) 1.32 - 1.55 (m, 11 H) 1.55 - 1.72 (m, 3 H) 1.80 (t, *J*=10.68 Hz, 2 H) 1.90 2.02 (m, 2 H) 2.11 (s, 12 H) 2.19 - 2.34 (m, 4 H) 2.85 (t, *J*=11.75 Hz, 1 H) 2.98 (d, *J*=11.90 Hz, 1 H) 3.13 (s, 1 H) 3.25 - 3.68 (m, 2 H) 3.74 - 3.91 (m, 2 H) 3.94 (s, 3 H) 4.00 - 4.10 (m, 1 H) 4.19 (d, *J*=27.77 Hz, 2 H) 4.55 (d, *J*=14.95 Hz, 1 H) 4.80 (d, *J*=14.65 Hz, 1 H) 5.03 (s, 0.15 H) 6.82 (s, 1 H) 6.93 (s, 1 H) 7.11 (dd, *J*=8.70, 2.59 Hz, 1 H) 7.54 (d, *J*=8.55 Hz, 1 H) 7.62 (d, *J*=7.63 Hz, 2 H) 7.81 - 8.01 (m, 1 H) 10.51 (s, 1 H).

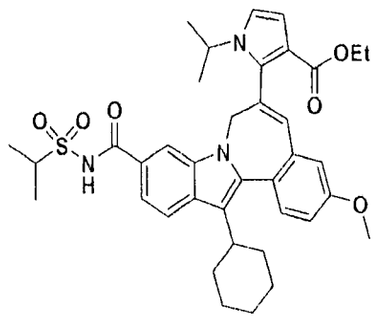
LC-MS retention time 1.79 min; 738 m/z (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 ml/min , a gradient 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 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.



7H-indolo[2,1-a][2]benzazepine-6-propanoic acid, 13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-beta-oxo-, ethyl ester.

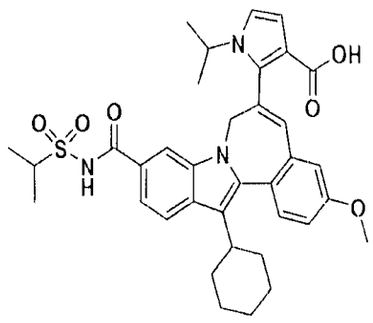
To a stirred solution of 7H-indolo[2,1-a][2]benzazepine-6-carboxylic acid, 13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]- (4 g, 7.45 mmol) in THF (20 mL) was added CDI (1.151 g, 7.10 mmol) and the mixture was heated at 45 °C for 0.5 h and the reaction mixture was cooled and transferred into a suspension of magnesium chloride (1.419 g, 14.91 mmol) and potassium ethyl malonate (2.54 g, 14.91 mmol) in THF (15 mL). Additional THF (40 mL) was added to dissolve the ensuing precipitation. The reaction mixture was stirred for 0.5 h at r. t. and then heated at 60 °C overnight. Rxn mixture was cooled to rt and diluted with EtOAc, washed with 1N HCl, brine and dried (Mg2SO4). Crude product was purified on a Thomson 160g column (MeOH/DCM: 0 to 25%) to afford the product as a reddish solid (3.8 g, 84%). LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O

/ 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.418 min, m/z 607 (MH^+).



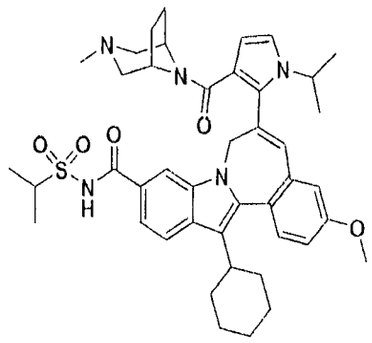
1H-pyrrole-3-carboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(1-methylethyl)-, ethyl ester.

To a solution of 7H-indolo[2,1-a][2]benzazepine-6-propanoic acid, 13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-beta-oxo-, ethyl ester (0.8 g, 1.055 mmol) in THF (3 mL) was added propan-2-amine (0.624 g, 10.55 mmol) and Tosic Acid (10.03 mg, 0.053 mmol). The mixture was stirred at r.t. for 0.5 h and 1,2-dibromoethyl acetate (0.337 g, 1.371 mmol) was added at 0 °C. The reaction mixture was stirred at r.t. for 0.5 h and then sodium hydride (0.051 g, 2.110 mmol) was added and stirred for 10 min at r.t. The mixture was heated at 60 °C for 3 h and cooled to r.t., diluted with EtOAc and washed with ice cold HCl (1N), brine and dried (MgSO4). Crude product was purified on a Biotage 25M column, (EtOAc/hexane: 5-100%) to afford the compound as a beige foam (0.26 g, 35%). LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.631 min, m/z 672 (MH^+).



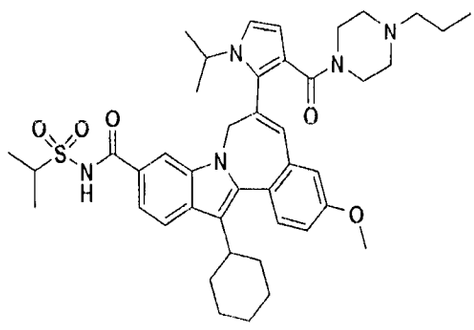
1H-pyrrole-3-carboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(1-methylethyl)-.

To a solution of 1H-pyrrole-3-carboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(1-methylethyl)-, ethyl ester (80 mg, 0.119 mmol) in THF (2 mL) and was added potassium trimethylsilanolate (45.8 mg, 0.357 mmol). The mixture was stirred under nitrogen for 30 min and another portion of potassium trimethylsilanolate (100 mg) was added. The reaction mixture was stirred at r.t. for 2 days and diluted with EtOAc, washed with cold 1 N HCl, brine, dried (MgSO4) and removed the solvent to afford the acid as a beige solid (71 mg, 88%). 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.80 (1 H, br. s.), 7.81 - 7.89 (1 H, m), 7.76 (1 H, s), 7.45 - 7.52 (1 H, m), 7.42 (1 H, d, *J*=6.29 Hz), 7.03 (1 H, dd, *J*=8.69, 2.64 Hz), 6.93 (1 H, d, *J*=2.27 Hz), 6.47 - 6.76 (3 H, m), 4.98 (1 H, d, *J*=13.85 Hz), 4.61 (1 H, d, *J*=14.60 Hz), 3.97 - 4.07 (1 H, m), 3.89 (1 H, s), 3.34 - 3.52 (1 H, m), 2.73 - 2.89 (1 H, m), 1.87 - 2.12 (4 H, m), 1.66 - 1.84 (2 H, m), 0.81 - 1.55 (19 H, m). LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.503 min, m/z 644 (MH^+).



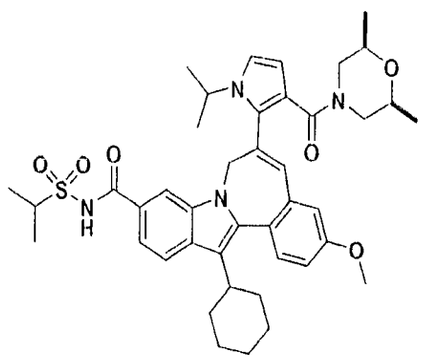
13-Cyclohexyl-6-(1-isopropyl-3-(3-methyl-3,8-diazabicyclo[3.2.1]octane-8-carbonyl)-1H-pyrrol-2-yl)-3-methoxy-N-(isopropylsulfonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.87 (1 H, d, *J*=8.56 Hz), 7.78 (1 H, s), 7.66 (1 H, d, *J*=8.06 Hz), 7.54 (1 H, d, *J*=8.31 Hz), 7.02 - 7.09 (1 H, m), 6.89 (1 H, d, *J*=2.77 Hz), 6.83 (1 H, br. s.), 6.69 (1 H, br. s.), 6.48 (1 H, br. s.), 4.91 (1 H, d, *J*=15.36 Hz), 4.55 (1 H, d, *J*=15.61 Hz), 4.48 (1 H, br. s.), 4.01 - 4.13 (1 H, m), 3.93 (3 H, s), 3.58 (1 H, br. s.), 3.12 (1 H, br. s.), 2.78 - 2.92 (1 H, m), 1.70 - 2.34 (14 H, m), 1.13 - 1.68 (16 H, m), 1.05 (1 H, br. s.), 0.52 (1 H, br. s.), -0.30 (1 H, br. s.). LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.331 min, m/z 752 (MH^+).

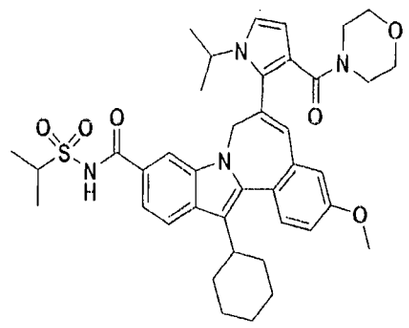


13-Cyclohexyl-6-(1-isopropyl-3-(4-propylpiperazine-1-carbonyl)-1H-pyrrol-2-yl)-3-methoxy-N-(isopropylsulfonyl)- 7H-indolo[2,1-a][2]benzazepine-10-carboxamide. 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.87 (1 H, d, *J*=8.56 Hz), 7.79 (1 H, s), 7.59 (1 H, d, *J*=8.31 Hz), 7.53 (1 H, d, *J*=8.56 Hz), 7.05 (1 H, dd,

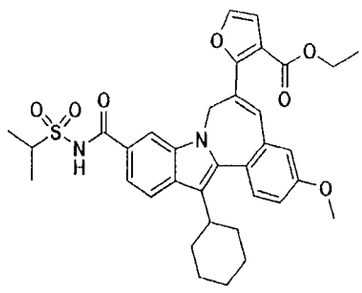
J=8.69, 2.64 Hz), 6.90 (1 H, d, *J*=2.52 Hz), 6.78 (1 H, br. s.), 6.68 (1 H, s), 6.32 (1 H, d, *J*=2.27 Hz), 4.91 (1 H, d, *J*=14.60 Hz), 4.55 (2 H, d, *J*=14.86 Hz), 3.99 - 4.50 (2 H, m), 3.95 - 4.32 (1 H, m), 3.92 (3 H, s), 2.70 - 3.19 (5 H, m), 1.86 - 2.16 (8 H, m), 1.67 - 1.84 (2 H, m), 1.09 - 1.64 (18 H, m), 0.65 - 0.83 (3 H, m). LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.330 min, m/z 754 (MH^+).

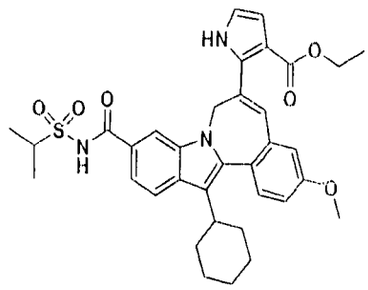


13-Cyclohexyl-6-(3-((2S,6R)-2,6-dimethylmorpholine-4-carbonyl)-1-isopropyl-1H-pyrrol-2-yl)-3-methoxy-N-(isopropylsulfonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide. 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.87 - 7.93 (1 H, m), 7.75 (1 H, br. s.), 7.44 - 7.66 (2 H, m), 7.01 - 7.12 (1 H, m), 6.90 (1 H, br. s.), 6.83 (1 H, br. s.), 6.64 (1 H, br. s.), 6.37 (1 H, br. s.), 4.90 (0 H, d, *J*=14.86 Hz), 4.57 (1 H, s), 4.31 - 4.50 (1 H, m), 4.05 - 4.16 (1 H, m), 3.94 (3 H, s), 3.85 - 3.92 (1 H, m), 2.70 - 3.74 (5 H, m), 1.84 - 2.25 (7 H, m), 1.66 - 1.84 (2 H, m), 0.97 - 1.66 (20 H, m), 0.53 - 0.93 (5 H, m); LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.550 min, m/z 741 (MH^+).



13-Cyclohexyl-6-(1-isopropyl-3-(morpholine-4-carbonyl)-1H-pyrrol-2-yl)-3-methoxy-N-(isopropylsulfonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 10.21 (1 H, br. s.), 7.92 (1 H, d, *J*=8.56 Hz), 7.84 (1 H, s), 7.61 (1 H, d, *J*=8.31 Hz), 7.56 (1 H, d, *J*=8.81 Hz), 7.09 (1 H, dd, *J*=8.69, 2.64 Hz), 6.90 (1 H, d, *J*=2.77 Hz), 6.82 (1 H, br. s.), 6.69 (1 H, s), 6.36 (1 H, d, *J*=2.52 Hz), 4.94 (1 H, d, *J*=14.86 Hz), 4.56 (1 H, d, *J*=15.11 Hz), 4.38 (1 H, br. s.), 4.02 - 4.12 (1 H, m), 3.94 (3 H, s), 3.58 - 4.14 (2 H, m), 2.53 - 3.28 (6 H, m), 1.95 (1 H, br. s.), 1.88 - 2.30 (4 H, m), 1.72 - 1.85 (2 H, m), 1.08 - 1.64 (16 H, m).



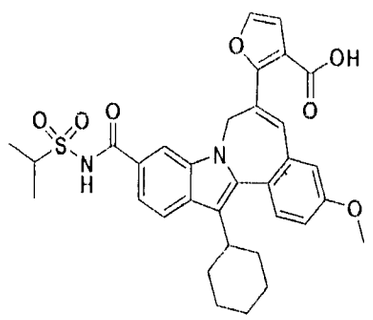


3-Furancarboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-, ethyl ester

1H-pyrrole-3-carboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-, ethyl ester

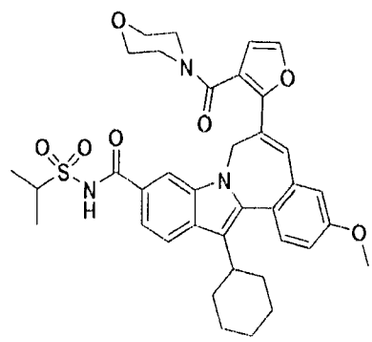
To a solution of starting 7H-indolo[2,1-a][2]benzazepine-6-propanoic acid, 13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-beta-oxo-, ethyl ester (1.200 g, 1.978 mmol) in THF (20 mL) was added 1,2-dibromoethyl acetate in THF (0.26 M, 9.13 mL, 2.373 mmol). NH_3 was then bubbled through the

mixture for 10 min and the reaction was maintained under ammonia (1 atmosphere) overnight. The mixture was then heated at 60° C for 2 h and then cooled to room termperature., diluted with EtOAc and washed with cold 0.5 N HCl (3x) and brine. The organic layer was then dried ($MgSO_4$) and filtered and the filtrate evaporated under reduced pressure. The crude product was purified on a Biotage 40M Column (EtOAc/hexane 0% to 100%) to afford a yellow solid which was further purified by preparative HPLC to afford the title furan (65 mg, 5%) and title pyrrole (145 mg, 11%). Furan product: 1H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 8.10 (1 H, s), 7.90 (1 H, d, *J*=8.56 Hz), 7.81 (1 H, s), 7.49 - 7.63 (3 H, m), 7.05 - 7.18 (2 H, m), 6.86 (1 H, d, *J*=2.01 Hz), 5.93 (1 H, d, *J*=14.35 Hz), 4.28 - 4.47 (3 H, m), 3.94 - 4.02 (1 H, m), 3.92 (3 H, s), 2.79 - 2.96 (1 H, m), 1.86 - 2.23 (4 H, m), 1.69 - 1.84 (2 H, m), 1.44 (6 H, d, *J*=6.80 Hz), 1.35 (3 H, t, *J*=7.05 Hz), 1.27 - 1.60 (4 H, m). LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.736 min, m/z 631 (MH^+). Pyrrole product: 1H NMR (400 MHz, *MeOD*) δ ppm 11.02 (1 H, br. s.), 8.03 (1 H, br. s.), 7.84 (1 H, d, *J*=8.56 Hz), 7.81 (1 H, s), 7.47 - 7.56 (2 H, m), 7.01 - 7.11 (2 H, m), 6.90 (1 H, s), 6.58 - 6.64 (2 H, m), 5.44 (1 H, d, *J*=17.63 Hz), 4.51 (1 H, d, *J*=14.10 Hz), 4.18 - 4.35 (2 H, m), 3.87 (3 H, s), 3.81 - 3.97 (1 H, m), 2.82 - 2.95 (1 H, m), 1.86 - 2.20 (4 H, m), 1.68 - 1.84 (2 H, m), 1.12 - 1.55 (13 H, m). LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.475 min, m/z 630 (MH^+).



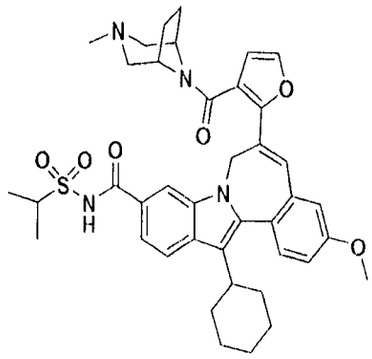
3-Furancarboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-.

To a mixture of 3-Furancarboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-, ethyl ester (63 mg, 0.100 mmol) and potassium trimethylsilanolate (128 mg, 0.999 mmol) was added THF (2 mL). The mixture was stirred at r. t. under nitrogen for 2 h. Diluted with EtOAc and washed with cold 1N HCl and dried (MgSO4), removed the solvents to afford acid (48 mg, 80%). LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.558 min, m/z 603 (MH^+).

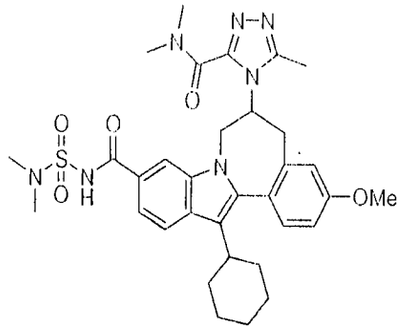


13-cyclohexyl-6-(3-(morpholine-4-carbonyl)furan-2-yl)-3-methoxy-N-(isopropylsulfonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide.

1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.08 (1 H, d, *J*=1.01 Hz), 7.86 (1 H, d, *J*=8.56 Hz), 7.66 (1 H, dd, *J*=8.44, 1.38 Hz), 7.49 (1 H, d, *J*=8.56 Hz), 7.40 (1 H, d, *J*=1.76 Hz), 7.33 (1 H, s), 7.04 (1 H, dd, *J*=8.56, 2.77 Hz), 6.96 (1 H, d, *J*=2.52 Hz), 6.48 (1 H, d), 5.23 (1 H, d), 4.40 (1 H, d), 3.99 - 4.18 (2 H, m), 3.90 (3 H, s), 3.79 - 3.95 (1 H, m), 3.67 - 3.78 (2 H, m), 3.42 - 3.51 (2 H, m), 3.33 - 3.41 (1 H, m), 3.19 - 3.31 (1 H, m), 2.75 - 2.88 (1 H, m), 1.86 - 2.13 (4 H, m), 1.14 - 1.83 (12 H, m); LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.276 min, m/z 711 (MH^+).

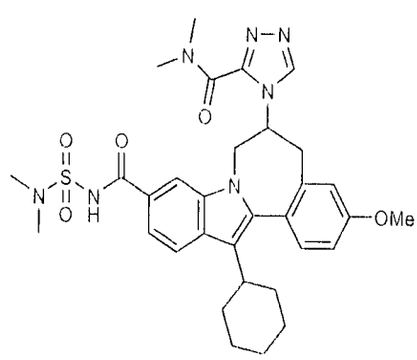


13-cyclohexyl-6-(3-(3-methyl-3,8-diazabicyclo[3.2.1]octane-8-carbonyl)furan-2-yl)-1H-pyrrol-2-yl)-3-methoxy-N-(isopropylsulfonyl)-7H-indolo[2,1-a][2]benzazepine-10-carboxamide. LC/MS method: Start % B: 0; Final % B: 100; Gradient time: 3 min; Stop time: 4 min; Flow rate: 4 mL/min; Wavelength: 220 Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid; Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid; Column: XBridge 4.6 x 50 mm S5. LC/MS: retention time 3.503 min, m/z 644 (MH^+).



5H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[3-[(dimethylamino)carbonyl]-5-methyl-4H-1,2,4-triazol-4-yl]-N-[(dimethylamino)sulfonyl]-6,7-dihydro-3-methoxy-. To a mixture of ethanediamide, *N'*-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-6,7-dihydro-3-methoxy-5*H*-indolo[2,1-*a*][2]benzazepin-6-yl]-*N*,*N*-dimethyl- (19.9 mg, 0.033 mmol) in CH_2Cl_2 (1 mL) at 0 °C under N_2 was added phosphorus pentachloride (20.4 mg, 0.098 mmol). The mixture was stirred at 0 °C for 2 hours, and then added with acetylhydrazine (7.25 mg, 0.098 mmol). The mixture was stirred at 0 °C for 1 hour, and then at r.t. for 21 hours. The mixture was added another 14.5 mg (0.196 mmol)

of acetylhydrazine, evaporated to dryness, added $PhCH_3$ (1 mL), and then stirred at 120 °C for 6 hours. The mixture was cooled to r.t. and then evaporated. The residue was diluted with MeOH and purified by using Shimadzu-VP preparative reverse phase HPLC to obtain the TFA salt of the product 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 = 60, Final %B = 90, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, Fraction Collection: 7.02 – 7.62 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% 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: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 648.41, HPLC R_t = 1.787 min. HPLC method: Solvent A = 5% MeCN–95% H_2O–10 mM NH_4OAc, Solvent B = 95% MeCN–5%H_2O–10 mM NH_4OAc, Start %B = 0, Final %B = 100, Gradient time = 2 min, Stop time = 3 min, Flow Rate = 5 ml/min, Column: Phenomenex Lina C18 5um 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 648.38, HPLC R_t = 1.260 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 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 = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um; R_t = 10.46 min; Column: Waters Xbridge Phenyl 4.6 x 150 mm, 3.5 um; R_t = 9.42 min.



5H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[3-[(dimethylamino)carbonyl]-4H-1,2,4-triazol-4-yl]-N-[(dimethylamino)sulfonyl]-6,7-dihydro-3-methoxy-. This example was prepared in a similar manner as described by using formylhydrazine as the coupling partner. Purification by Shimadzu-VP preparative reverse phase HPLC to obtain the TFA salt of the product 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 = 40, Final %B = 90, Gradient time = 10 min, Stop time = 12 min, Flow Rate = 30 mL/min, Column: Xterra Prep MS C18 5u 30x50mm, Fraction Collection: 9.57 – 9.99 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% 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: Xterra MS C18 S7 3.0 x 50mm; (ES+) m/z $(M+H)^+$ = 634.45, HPLC R_t = 1.785 min. Analytical HPLC were performed by using Shimadzu-VP instrument with UV detection at 254 nm and 256 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 = 10, Final %B = 100, Gradient time = 10 min, Stop time = 20 min, Flow Rate = 1 ml/min, Column: Waters Sunfire C-18, 4.6 x 150 mm, 3.5 um; R_t = 10.33 min; Column: Waters Xbridge Phenyl 4.6 x 150 mm, 3.5 um; R_t = 9.44 min.

Biological Methods

The compounds demonstrated activity against HCV NS5B as determined in the following HCV RdRp assays.

HCV NS5B RdRp cloning, expression, and purification. 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.

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 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).

The protein was purified using three sequential chromatography steps: Heparin sepharose CL-6B, polyU sepharose 4B, and Hitrap SP sepharose (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. 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. HCV RdRp genotype 1b assays were run in a final volume of 60 μl in 96 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 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 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. A modified enzyme assay was performed essentially as described for the standard enzyme assay except for the following: The biotinylated oligo dT12 primer 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 μg/μl beads. Order of addition in the assay: enzyme (14 nM) was added to 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° C.

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

FRET Assay Preparation. To perform the HCV FRET screening assay, 96-well cell culture plates were used. The FRET peptide (Anaspec, Inc.) (Taliani et al., *Anal. Biochem.* **1996**, *240*, 60-67) 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 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.

To prepare plates, HCV replicon cells, with or without a Renilla luciferase 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 CO_2 incubator at 37 °C.

Assays. 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 Cytoflour 4000 instrument (PE Biosystems), plates were rinsed with PBS and then used for FRET assay by the addition of 30 ul of the FRET peptide assay reagent described above (FRET Assay Preparation) per well. The plate was then placed into the Cytoflour 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 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.

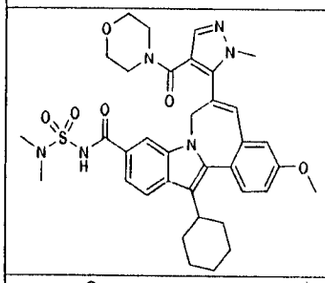
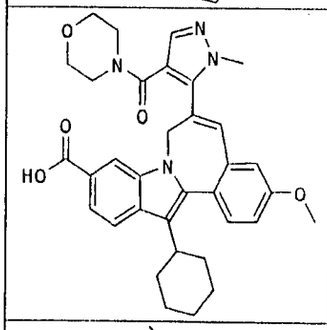
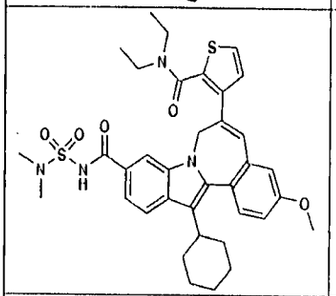
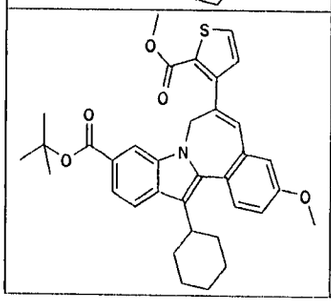
Compound analysis was determined by quantification of the relative HCV replicon inhibition and the relative cytotoxicity values. To calculate cytoxicity values, the average Alamar Blue fluorescence signals from the control wells were set as 100% non-toxic. The individual signals in each of the compound 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 HCV protease inhibitor at the end of the assay period. These numbers were similar to those obtained from naïve Huh-7 cells.

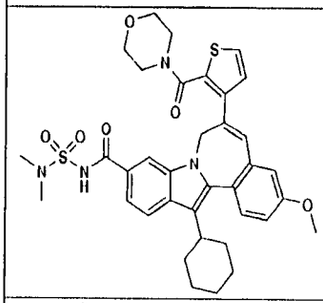
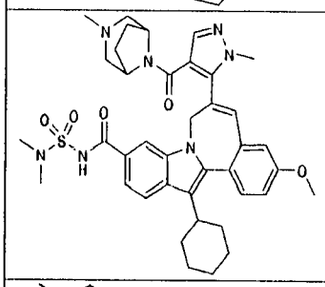
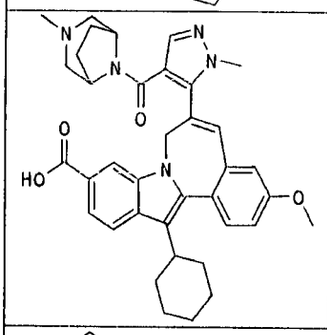
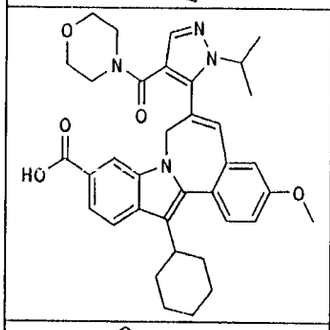
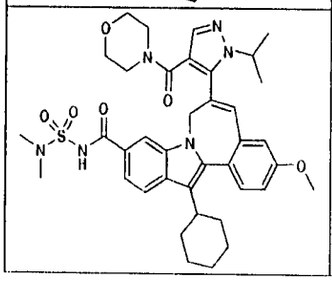
The background numbers were then subtracted from the average signal obtained from the control wells and this number was used as 100% activity. The individual signals in each of the compound test wells were then divided by the averaged control values after background subtraction and multiplied by 100%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

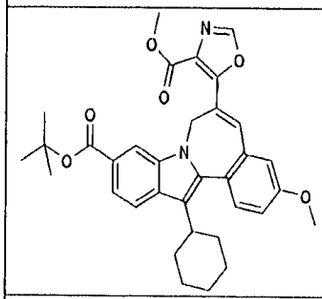
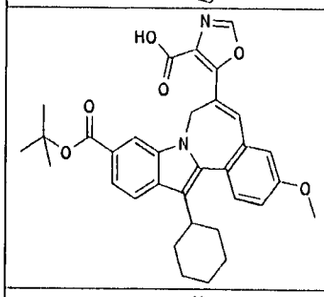
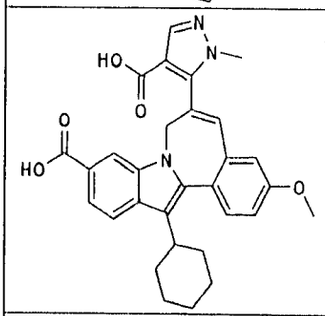
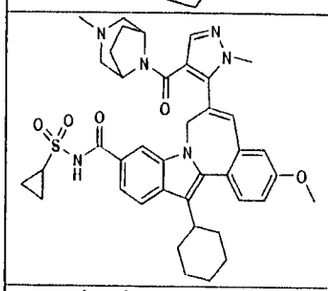
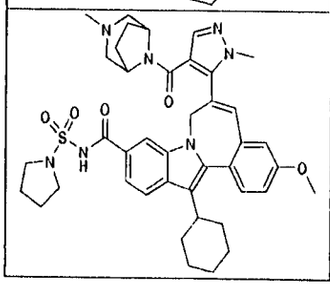
activity. The two numbers generated for the compound plate, percent cytoxicity and percent activity were used to determine compounds of interest for further analysis.

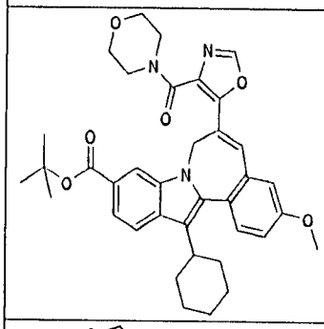
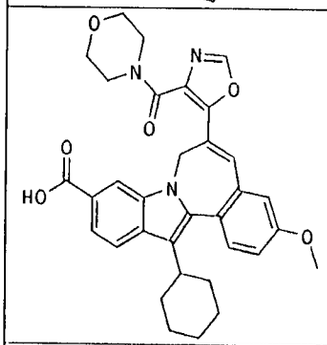
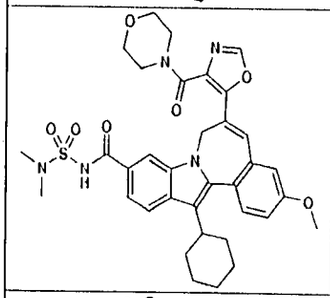
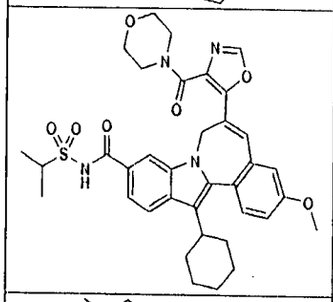
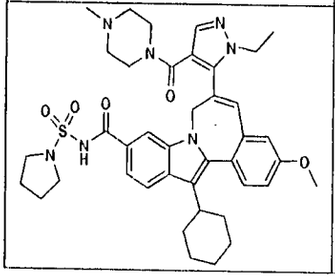
Representative data for some compounds are reported in Table 1.

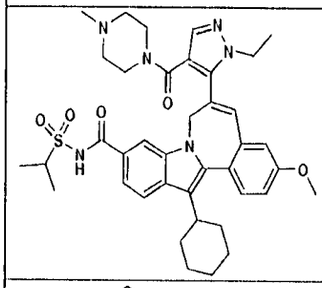
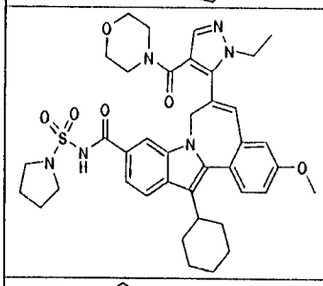
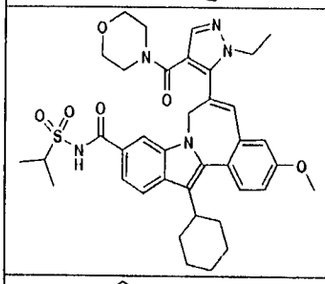
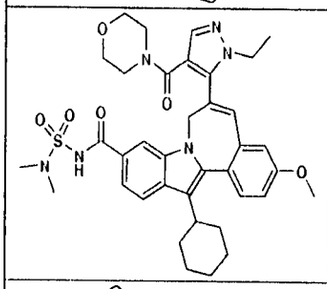
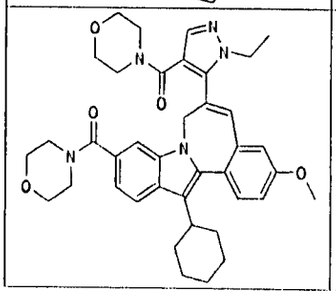
Table 1.

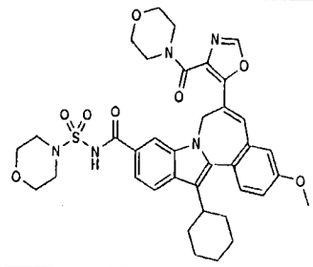
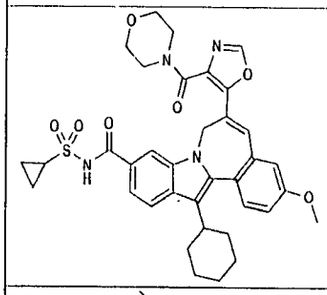
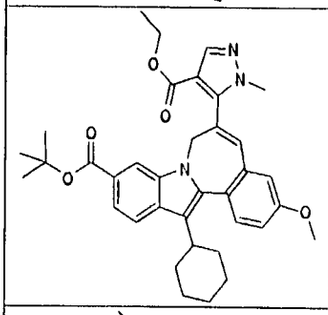
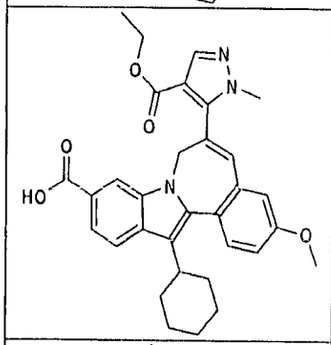
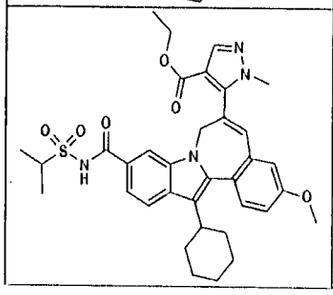
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
		

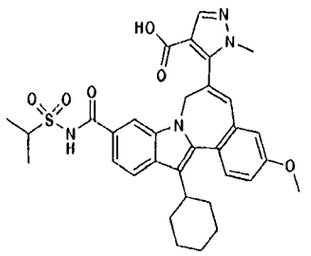
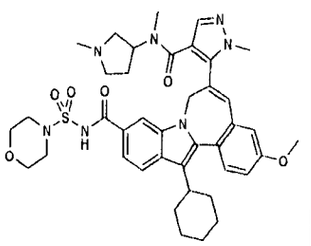
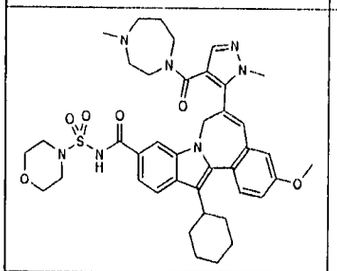
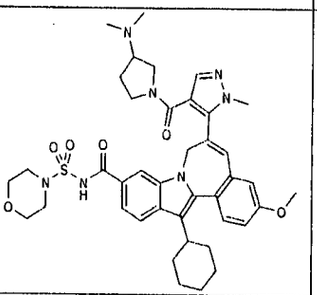
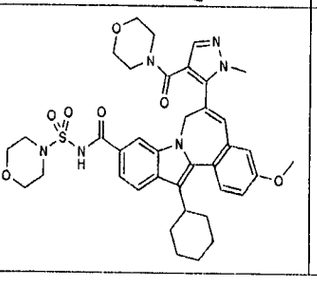
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	A	B
	B	B
	B	B

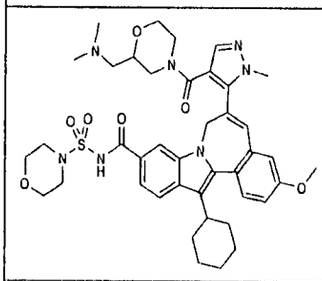
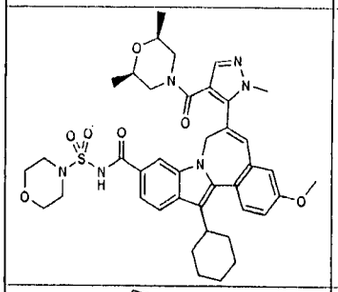
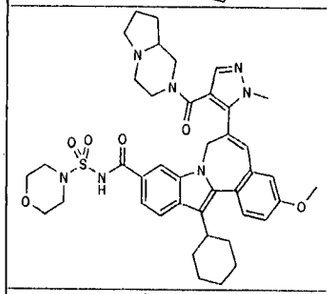
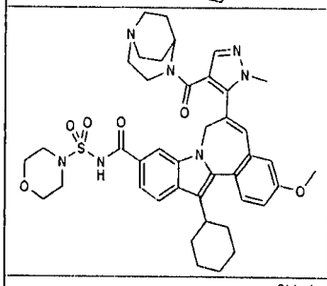
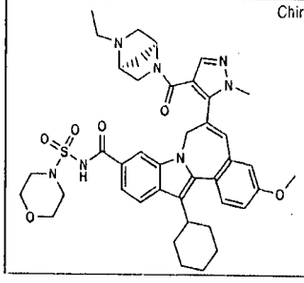
Structure	IC_{50} (μM)	EC_{50} (μM)
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	D	D
	B	D
	B	B
	B	B

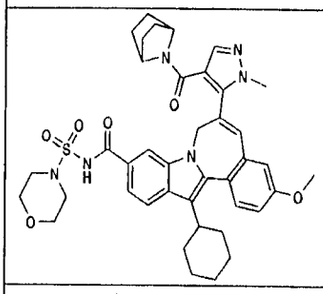
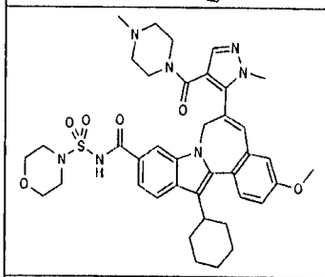
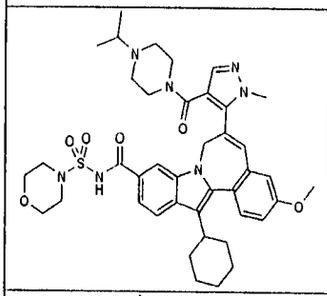
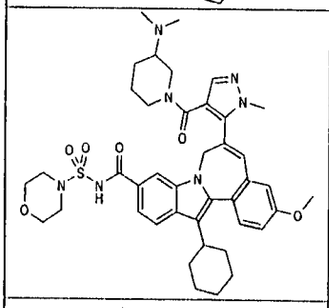
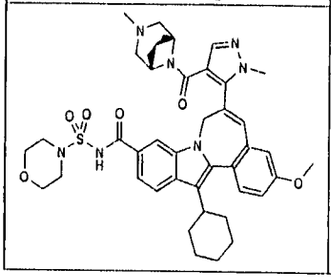
Structure	IC_{50} (μM)	EC_{50} (μM)
	D	D
	B	B
	B	B
	B	B
	B	B

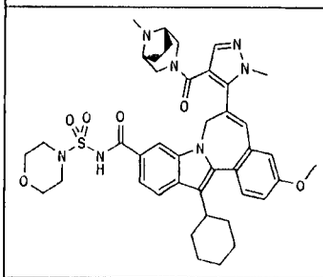
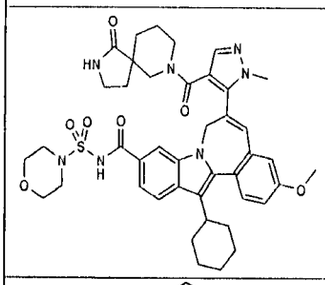
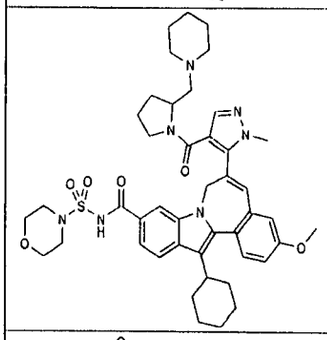
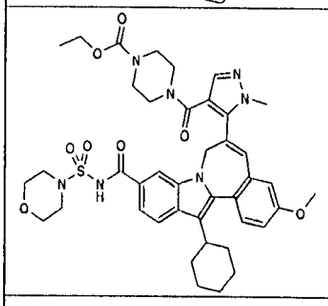
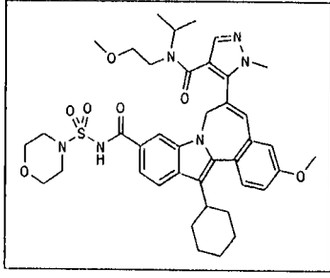
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B
	A	B

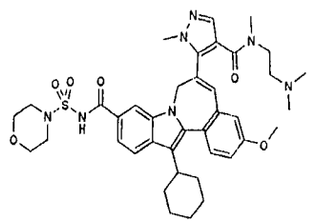
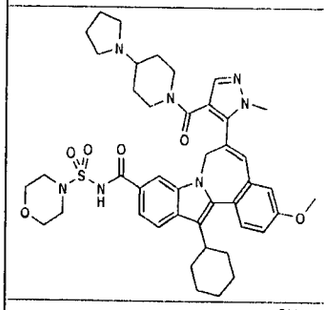
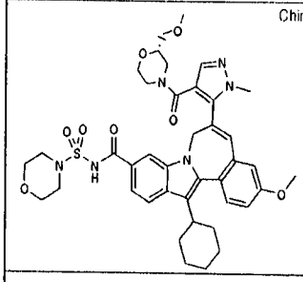
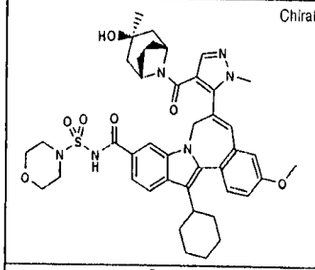
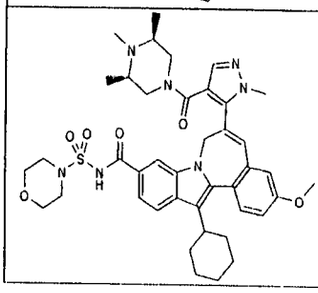
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	D	B
	B	B
	B	B

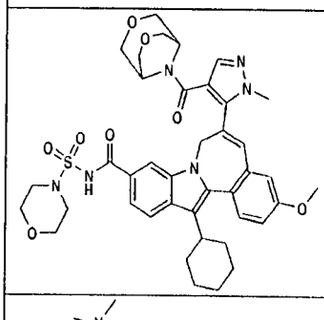
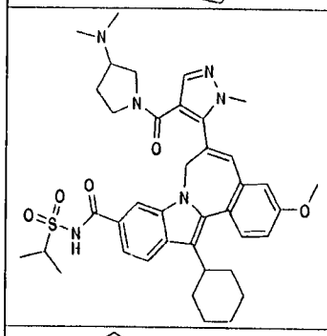
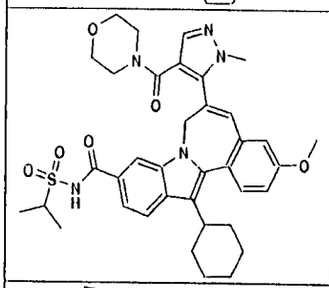
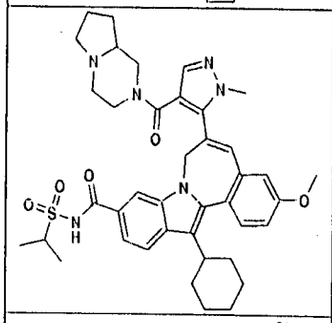
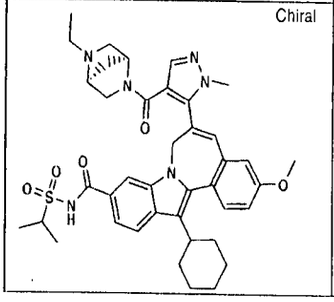
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	
	B	B
	C	B
	B	B
	C	B

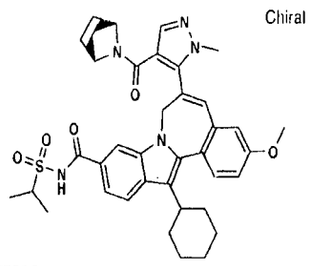
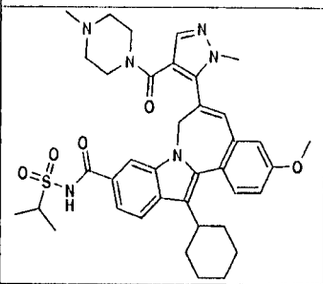
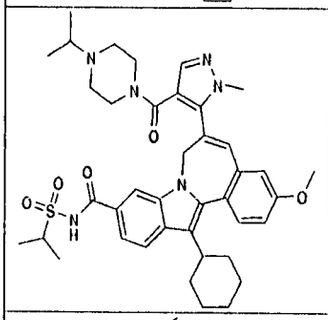
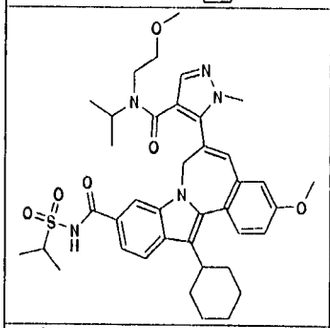
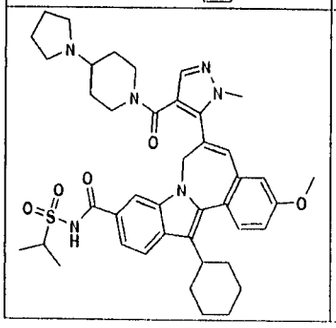
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B
Chiral 	B	B

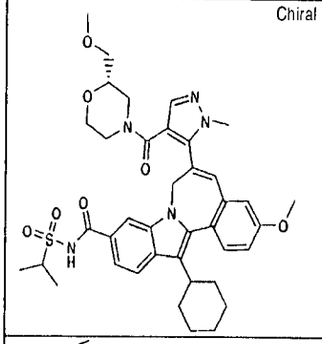
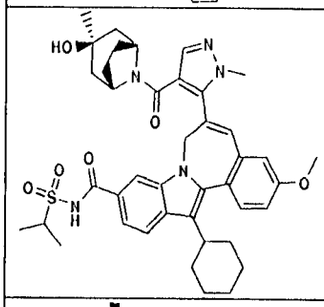
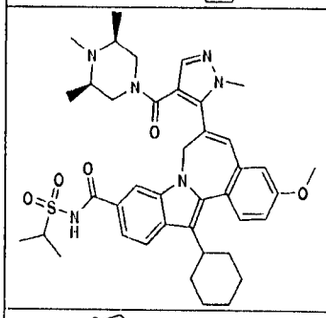
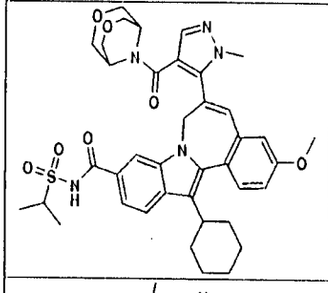
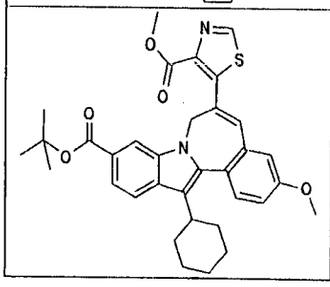
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B
	B	B

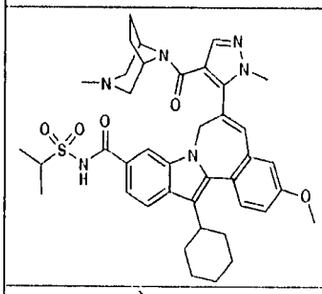
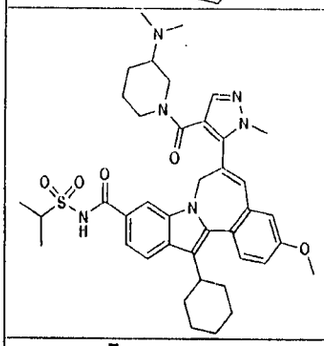
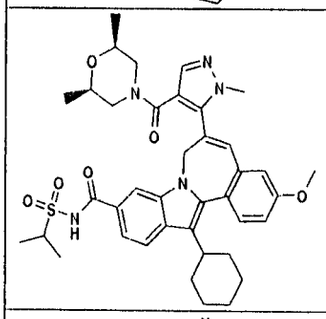
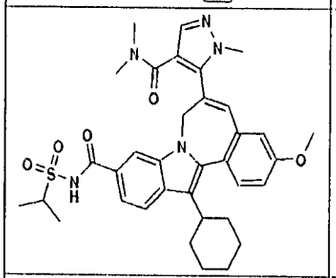
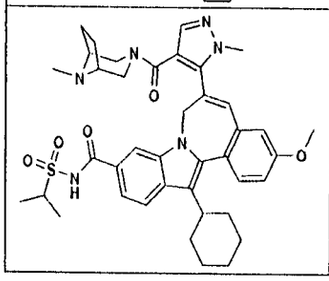
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B
	B	B

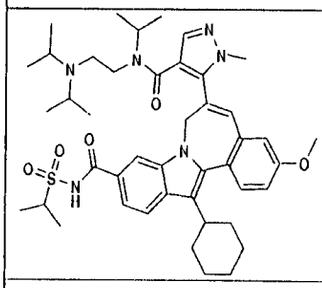
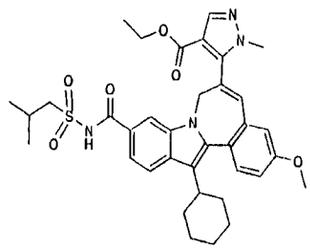
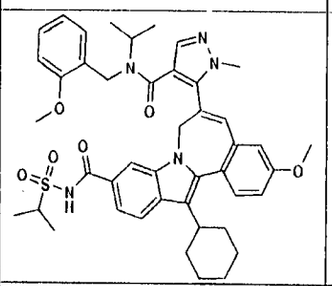
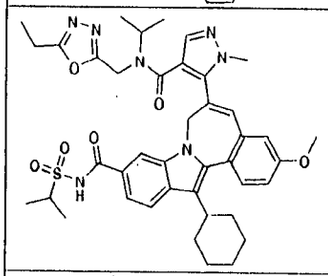
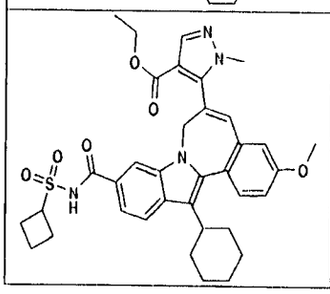
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	A
Chiral 	B	B
Chiral 	B	B
	B	B

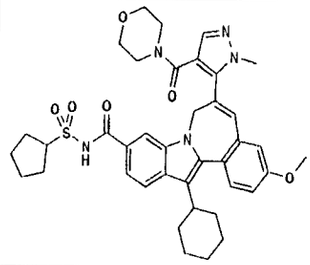
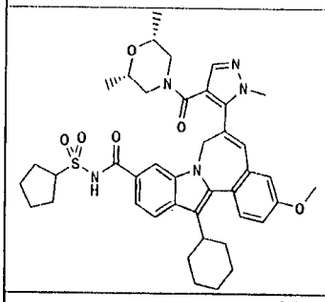
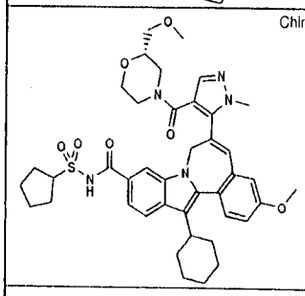
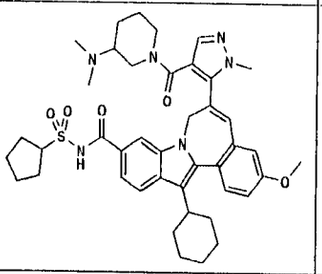
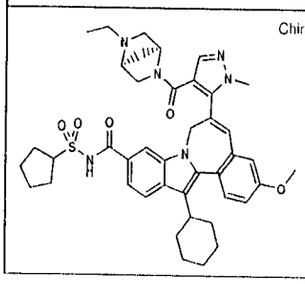
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B
Chiral 	B	B

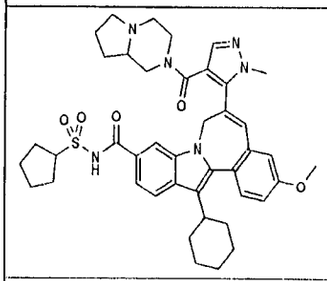
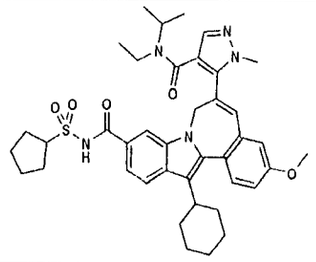
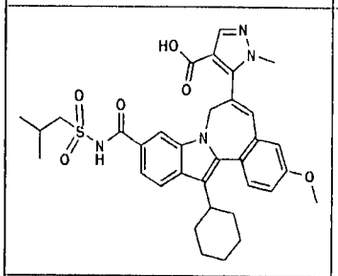
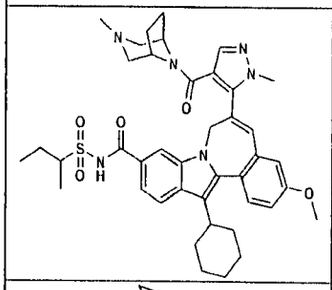
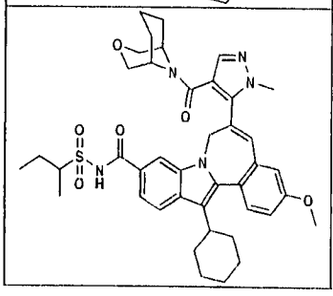
Structure	IC_{50} (μM)	EC_{50} (μM)
 Chiral	B	B
	B	B
	B	B
	B	B
	B	B

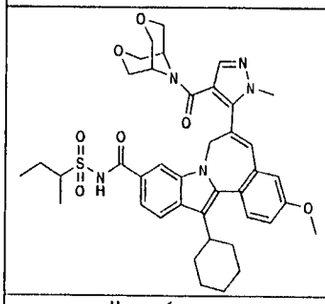
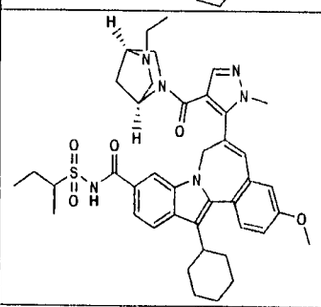
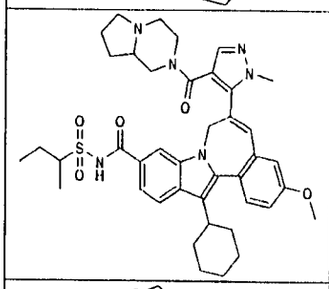
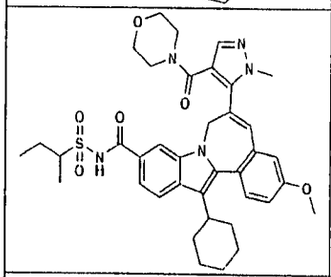
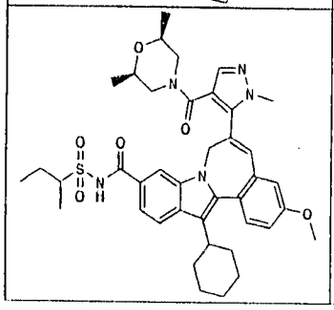
Structure	IC_{50} (μM)	EC_{50} (μM)
Chiral 	B	B
	B	B
	B	B
	B	B
		

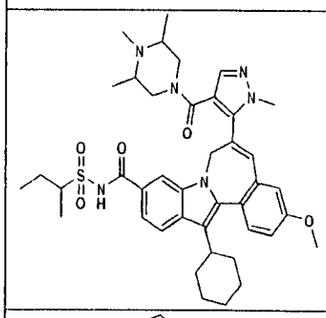
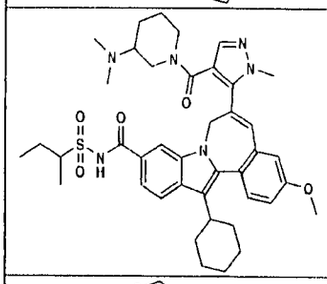
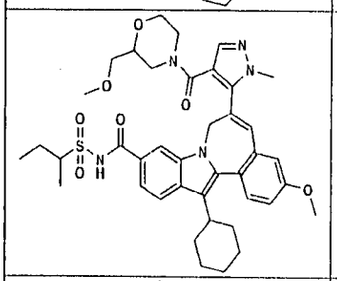
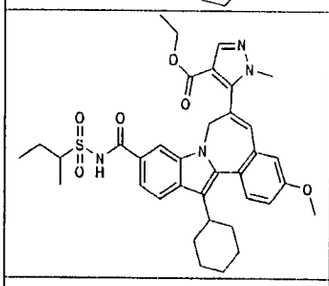
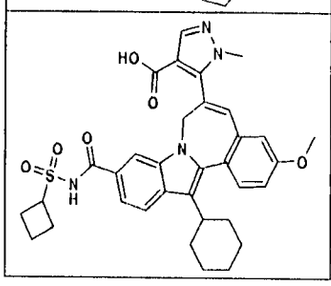
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B
	B	B

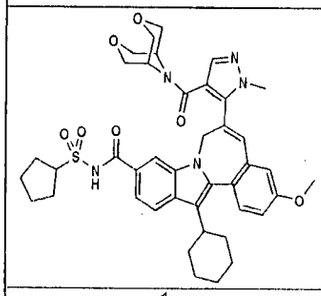
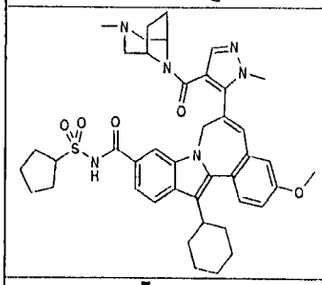
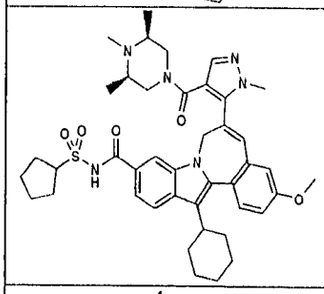
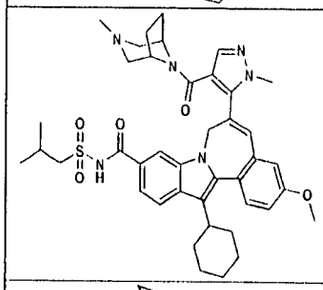
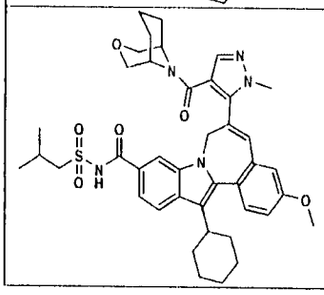
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	
	B	
	B	
	B	

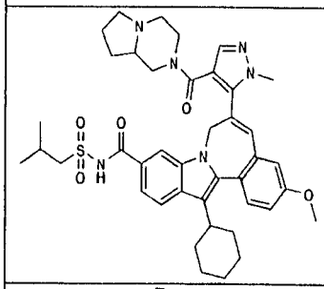
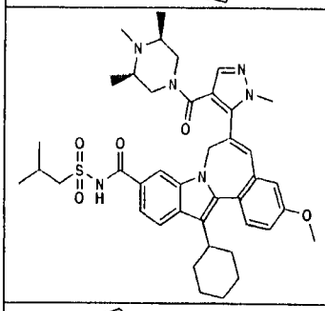
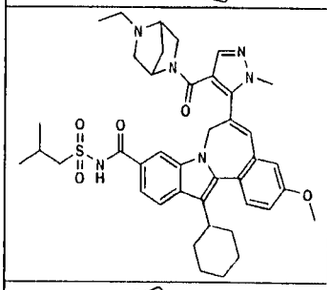
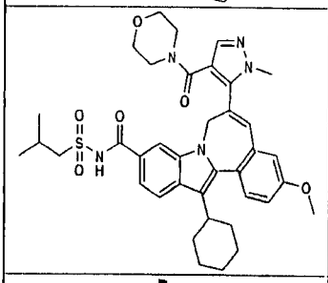
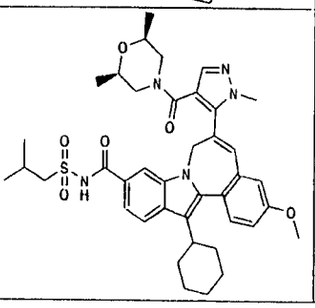
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	
Chiral 	B	B
	B	
Chiral 	B	

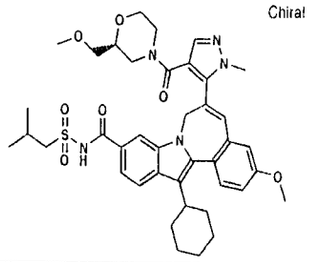
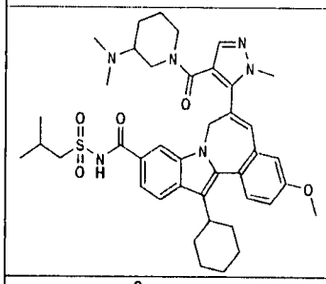
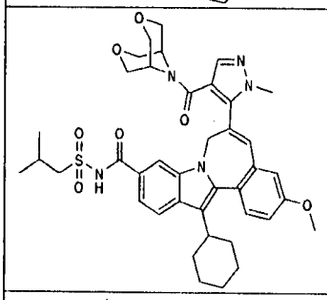
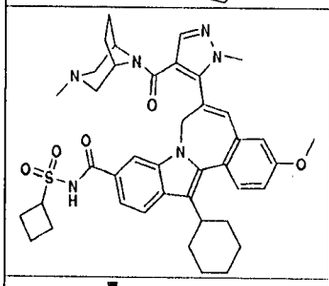
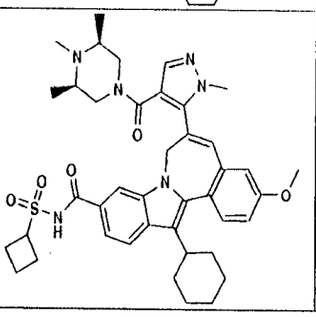
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	
	B	
		
	B	B
	B	B

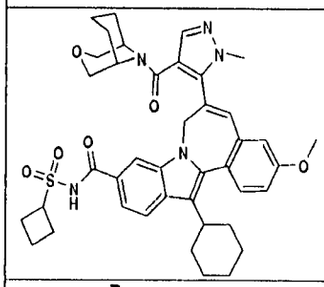
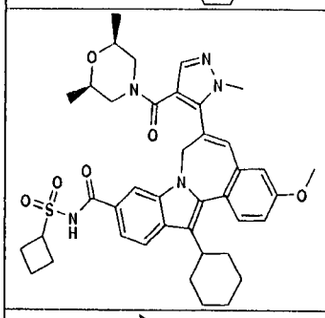
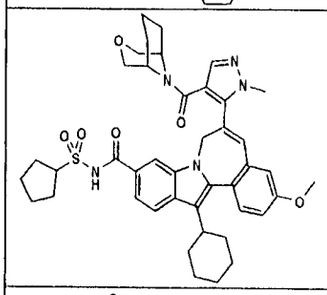
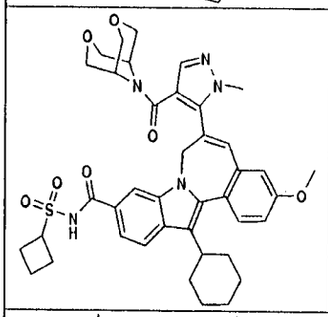
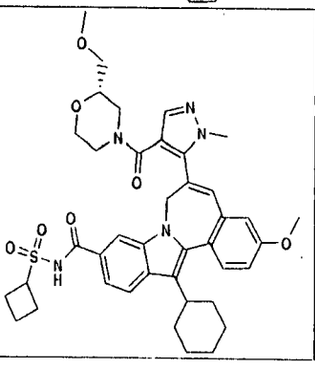
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	
	B	
	B	B
	B	B

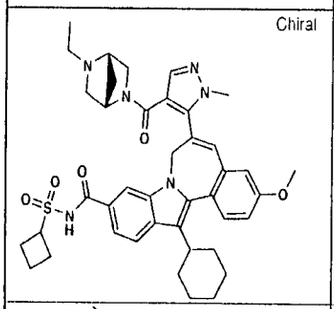
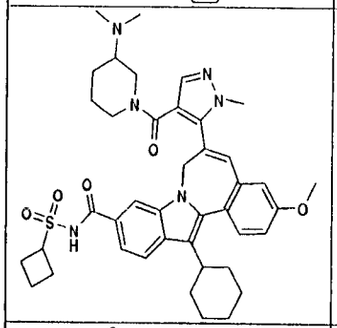
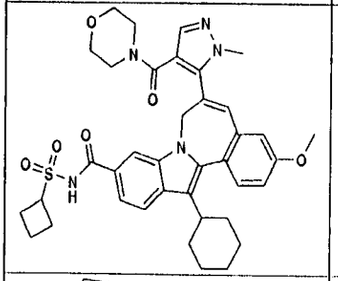
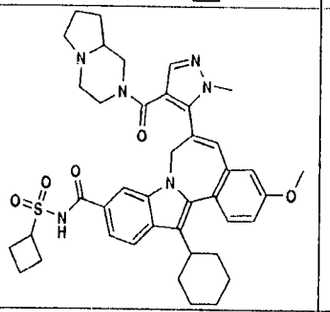
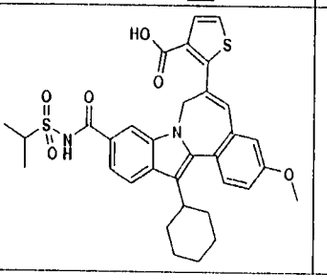
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	
	B	

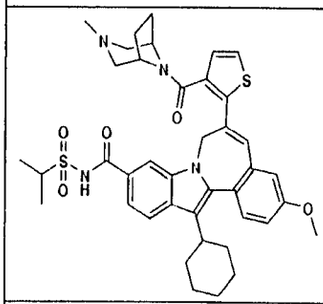
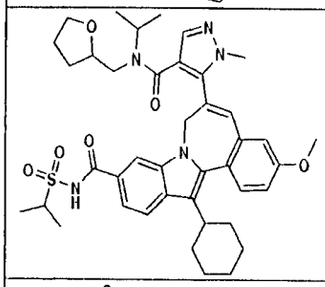
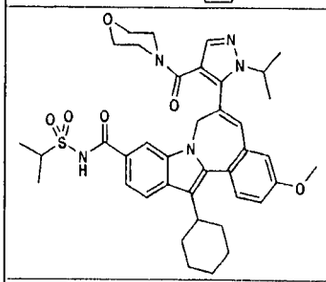
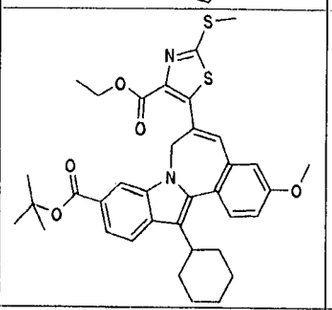
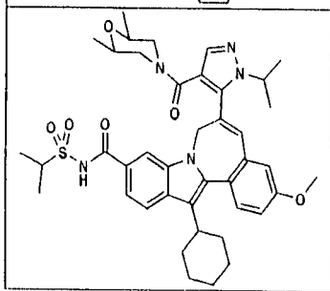
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	
	B	B
	B	B

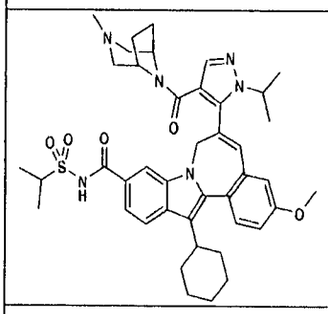
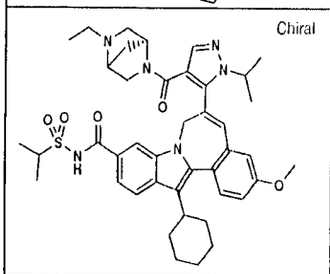
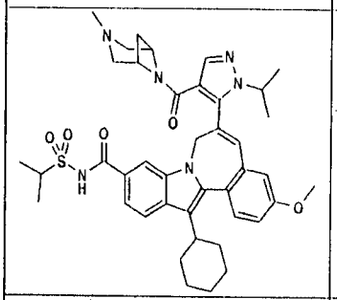
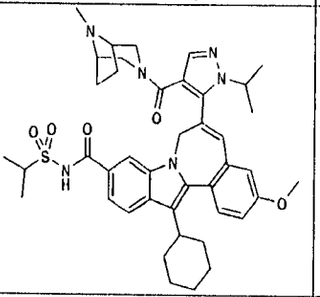
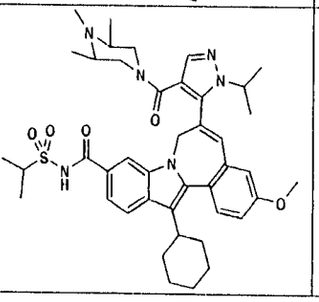
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	
	B	
	B	
	B	B
	B	B

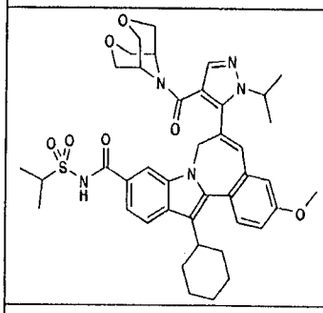
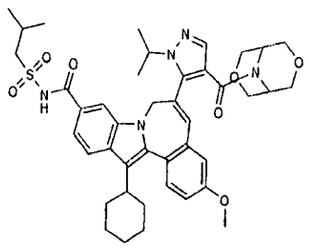
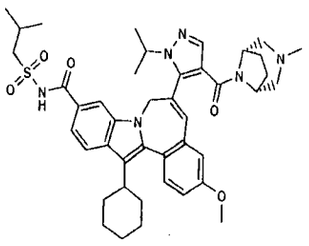
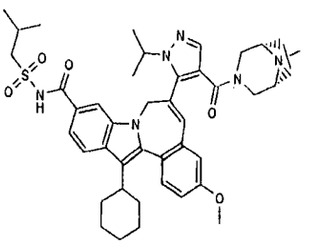
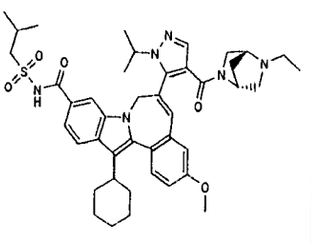
Structure	IC_{50} (μM)	EC_{50} (μM)
 Chiral	B	B
	B	
	B	B
	B	B
	B	

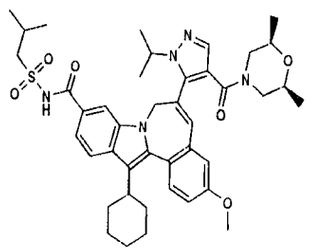
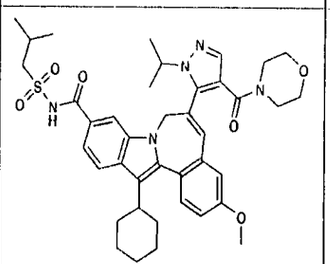
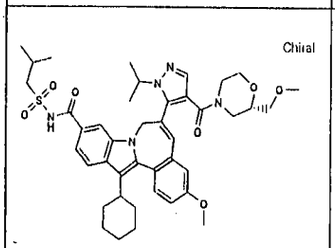
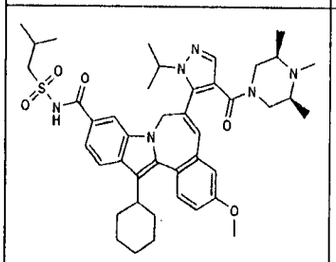
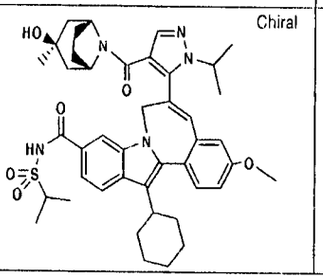
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	
	B	B
	B	B
	B	B

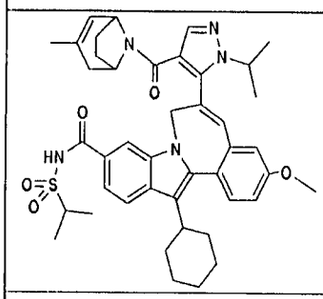
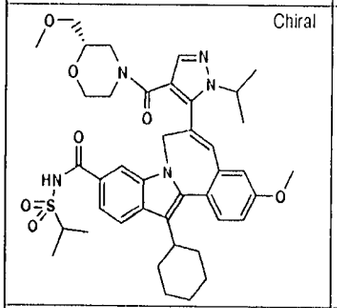
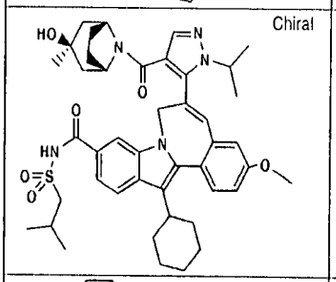
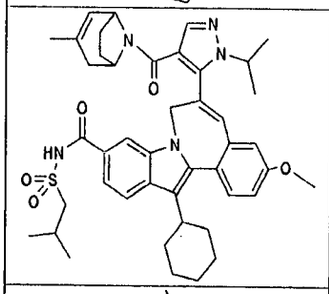
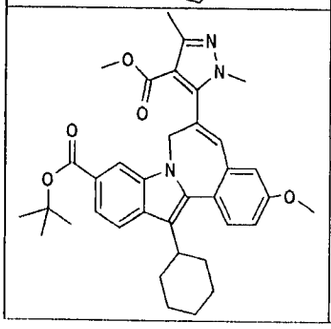
Structure	IC_{50} (μM)	EC_{50} (μM)
 Chiral	B	B
	B	B
	B	B
	B	B
	B	D

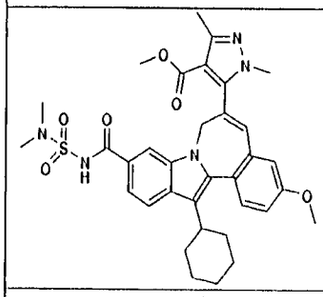
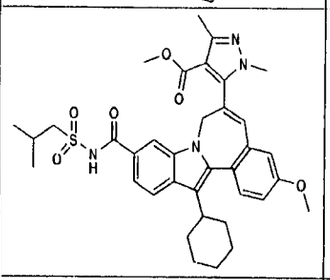
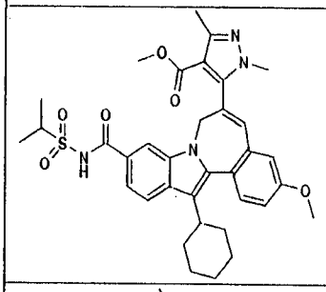
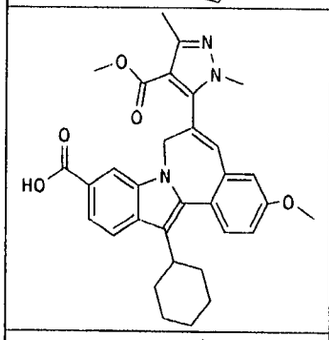
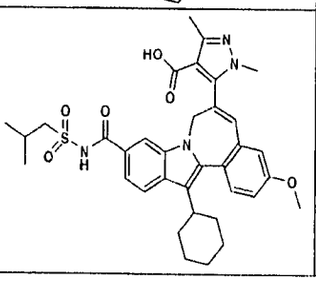
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
		
	B	B

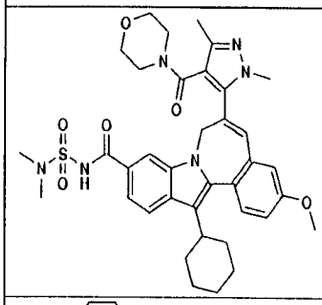
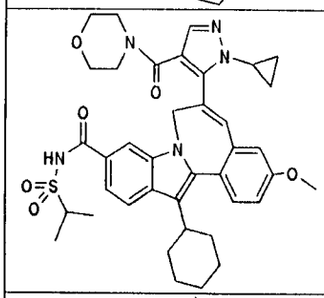
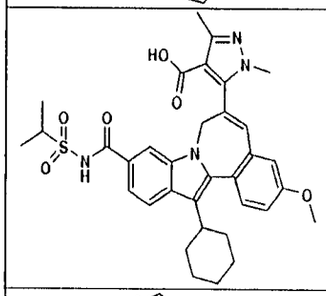
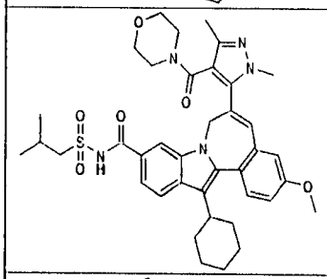
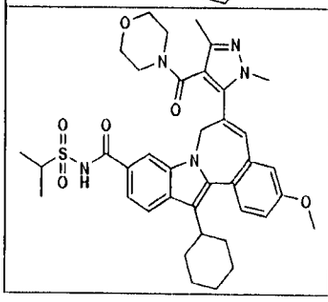
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
 Chiral	B	B
	B	B
	B	B
	B	B

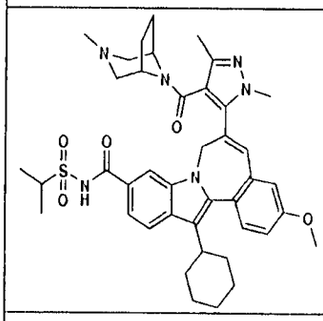
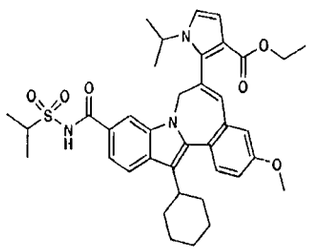
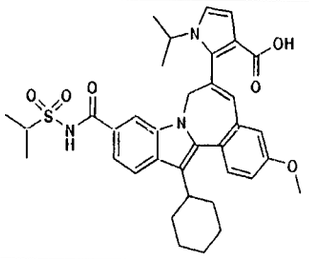
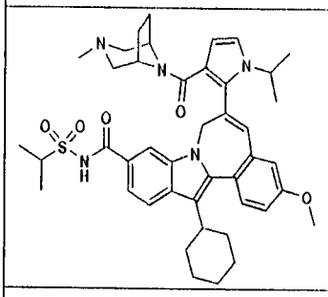
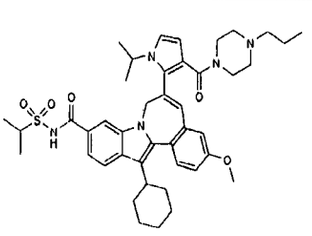
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B
	B	B

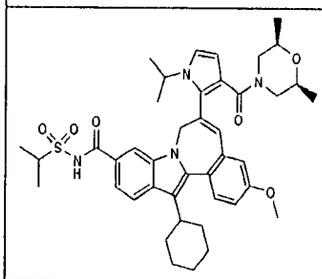
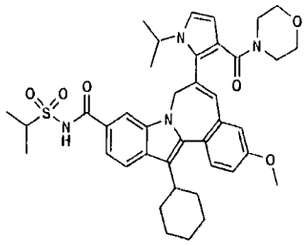
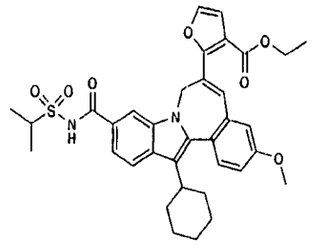
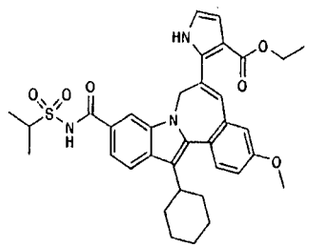
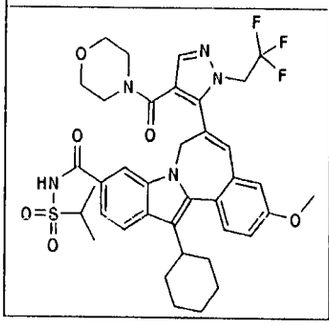
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
 Chiral	B	B
	B	B
 Chiral	B	B

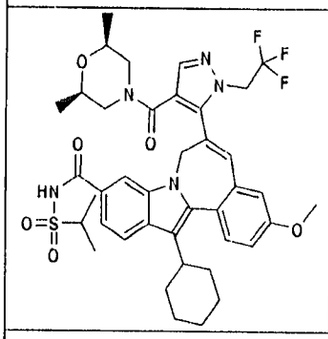
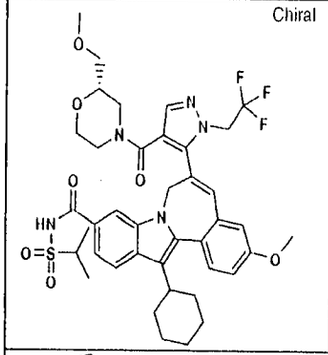
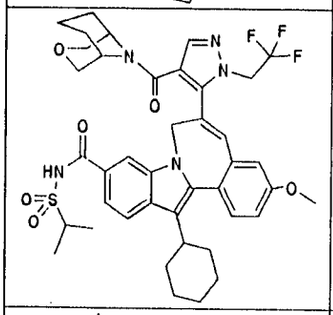
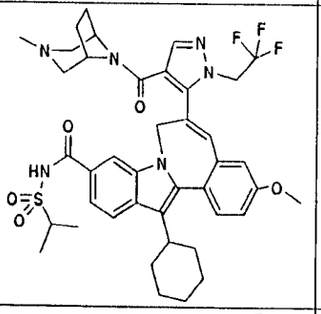
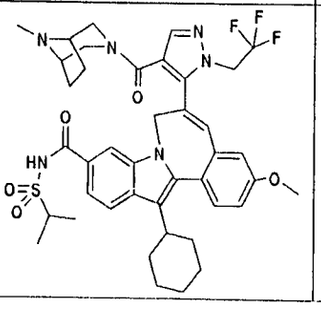
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
Chiral 	B	B
Chiral 	B	B
	B	B
		

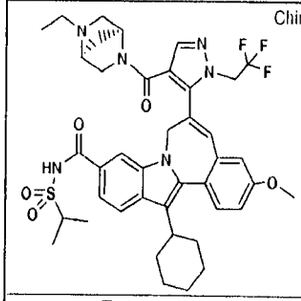
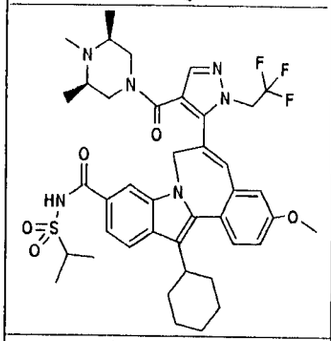
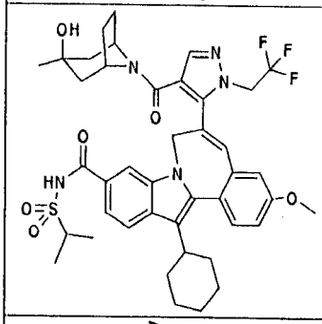
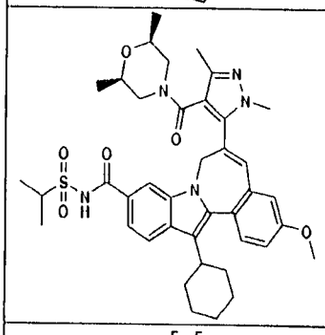
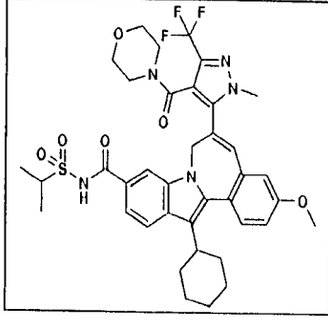
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	
	B	
		
	B	B
	B	D

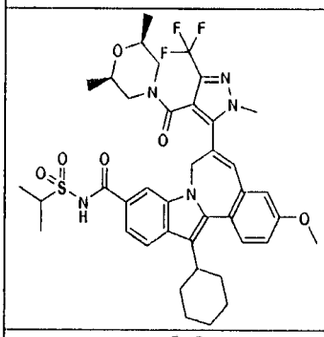
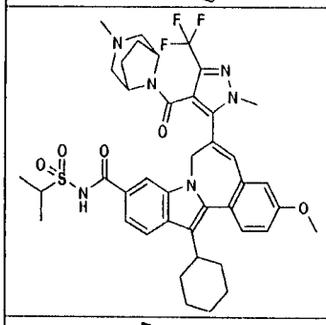
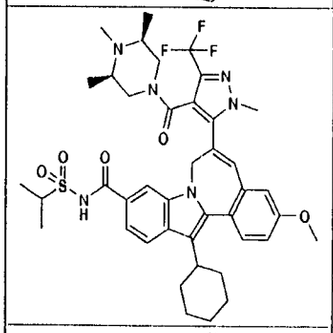
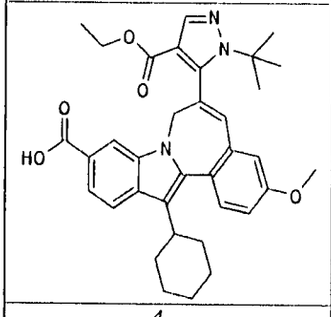
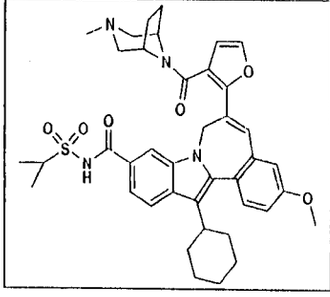
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	A
	B	B
	B	B

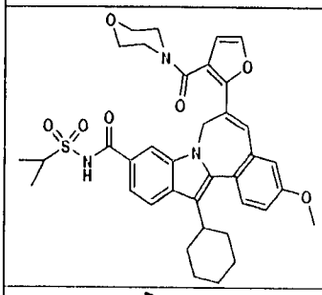
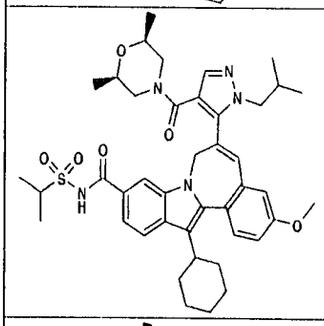
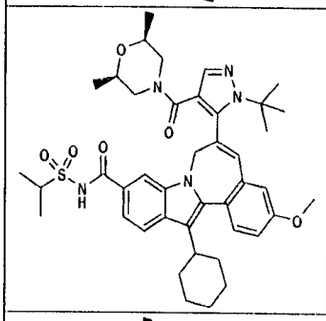
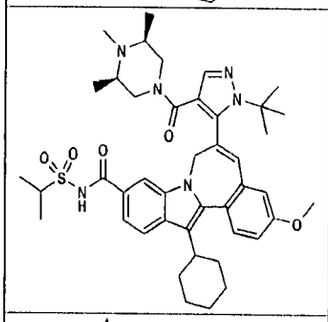
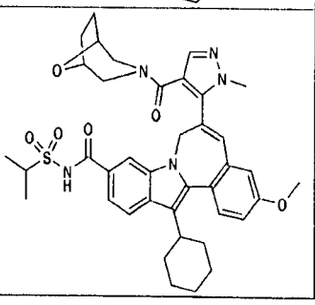
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
		
	B	A
	B	B
	B	B

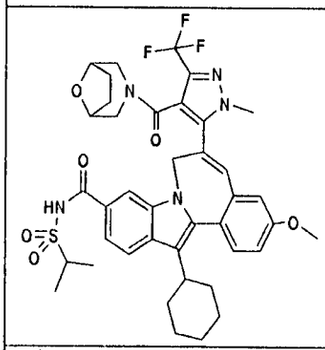
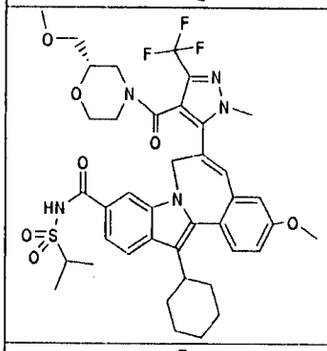
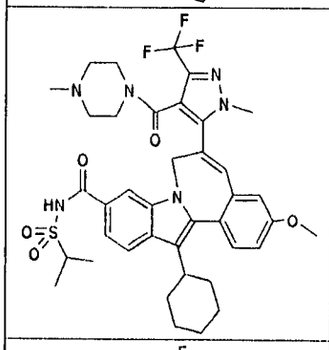
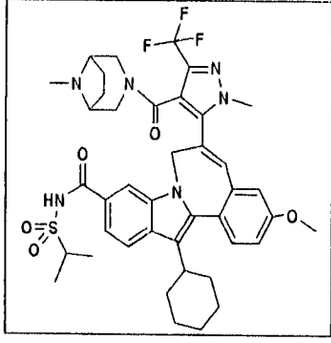
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	A
	B	B
	B	B

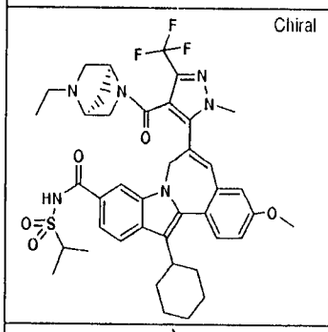
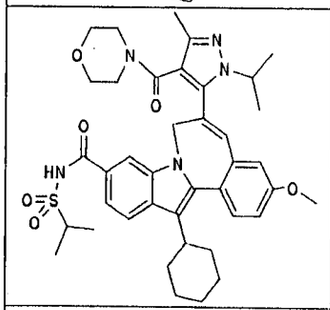
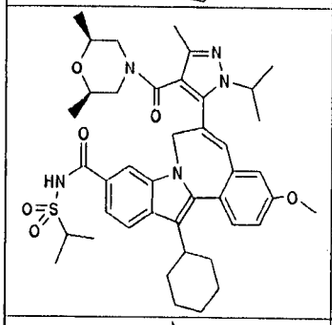
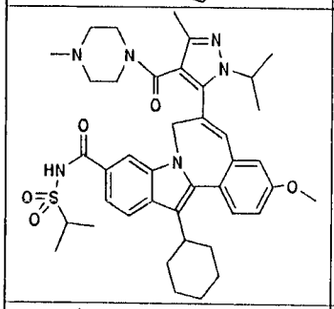
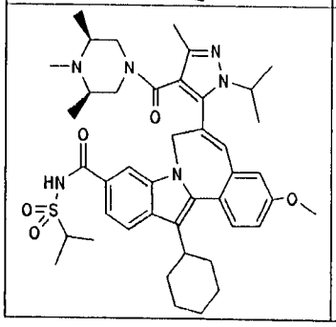
Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
Chiral 	B	B
	B	B
	B	B
	B	B

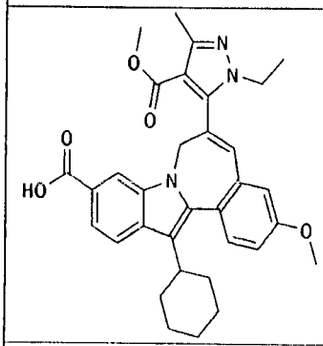
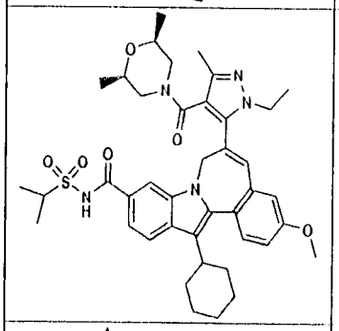
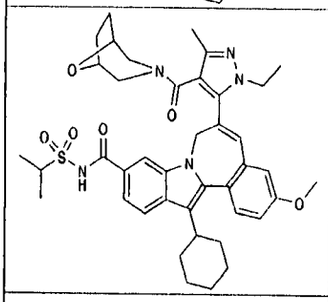
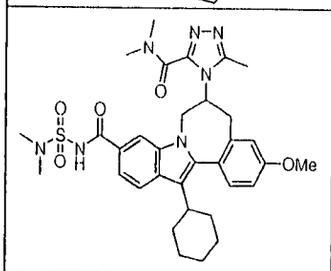
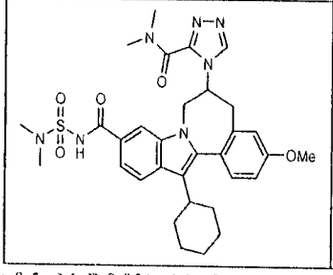
Structure	IC_{50} (μM)	EC_{50} (μM)
Chiral 	B	B
	B	B
	B	B
	B	B
	C	B

Structure	IC_{50} (μM)	EC_{50} (μM)
	C	B
	B	B
	B	B
		
	B	B

Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B
	C	B

Structure	IC_{50} (μM)	EC_{50} (μM)
	B	B
	B	B
	B	B
	B	B

Structure	IC_{50} (μM)	EC_{50} (μM)
 Chiral	B	B
	B	B
	B	B
	B	B
	B	B

Structure	IC_{50} (μM)	EC_{50} (μM)
		
		
		
	B	B
	B	B

A>0.5 μM; B 0.001 μM 0.5 μM; C <0.02 μM but an exact value was not determined; D>0.04 μM; but an exact value was not determined.

Pharmaceutical Compositions and Methods of Treatment

The compounds demonstrate activity against HCV NS5B and can be useful in treating HCV and HCV infection. Therefore, another aspect of the invention is a composition comprising a compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a composition further comprising a compound having anti-HCV activity.

Another aspect of the invention is a composition where the compound having anti-HCV activity is an interferon. Another aspect of the invention is where the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

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.

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, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

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.

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.

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

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 or a pharmaceutically acceptable salt thereof.

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 of a compound or a pharmaceutically acceptable salt thereof. In another embodiment the compound is effective to inhibit the function of the HCV replicon. In another embodiment the compound is effective to inhibit the function of the HCV NS5B protein.

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 of a compound, or a pharmaceutically acceptable salt thereof, in conjunction with (prior to, after, or concurrently) another compound having anti-HCV activity.

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

Another aspect of the invention is the method where the interferon is selected from interferon alpha 2B, pegylated interferon alpha, concensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

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

Another aspect of the invention is the method where the cyclosporin is cyclosporin A.

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, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

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 HCV infection.

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.

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

"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.

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

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. A therapeutically effective amount is that which is needed to provide a meaningful patient benefit. Pharmaceutically acceptable carriers are those conventionally known carriers having acceptable safety profiles. Compositions encompass all common solid and liquid forms including capsules, tablets, losenges, and powders as well as liquid suspensions, syrups, elixers, 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.

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 that class used clinically. Typically, this is 0.25-1000 mg/unit.

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 clinically. Typically, this is 1-100 mg/mL.

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. The specific dosing regime, however, will be determined by a physician using sound medical judgement.

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 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 judgement.

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

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-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ribavirin	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
CellCept	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Wellferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Albuferon - α	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Levovirin	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
IDN-6556	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
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 Phamaceuticals Inc., New York, NY
JTK-003	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Pegasys and Ceplene	PEGylated IFN-α2a/ 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

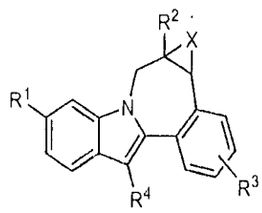
Brand Name	Type of Inhibitor or Target	Source Company
Intron A and Zadaxin	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Levovirin	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Viramidine	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
Intron A	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Rebetron	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Ribavirin	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Zadazim	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Rebif	IFN-β1a	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
Omniferon	natural IFN-α	Viragen Inc., Plantation, FL

Brand Name	Type of Inhibitor or Target	Source Company
XTL-6865 (XTL-002)	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
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-2005047288 26 May 2005	HCV Inhibitors	Arrow Therapeutics Ltd.
2'C Methyl adenosine	NS5B Replicase Inhibitor	Merck
GS-9132 (ACH-806)	HCV Inhibitor	Achillion / Gilead

CLAIMS

We claim:

1. A compound of formula I



I

where:

R^1 is CO_2R^5 or $CONR^6R^7$;

R^2 is furanyl, pyrrolyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, or tetrazolyl, and is substituted with 0-2 substituents selected from oxo, amino, alkylthio, alkyl, and haloalkyl, and 1 substituent selected from CO_2R^5, $CON(R^{12})_2$, and COR^{13};

R^3 is hydrogen, halo, alkyl, alkenyl, hydroxy, benzyloxy, or alkoxy;

R^4 is cycloalkyl;

R^5 is hydrogen or alkyl;

R^6 is hydrogen, alkyl, $alkylSO_2$, $cycloalkylSO_2$, $haloalkylSO_2$, $(R^9)(R^{10})NSO_2$, or $(R^{11})SO_2$;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, alkylcarbonyl, cycloalkylcarbonyl, haloalkylcarbonyl, alkoxycarbonyl, alkylSO_2, cycloalkylSO_2, haloalkylSO_2, aminocarbonyl, (alkylamino)carbonyl, (dialkylamino)carbonyl, benzyl, benzyloxycarbonyl, or pyridinyl;

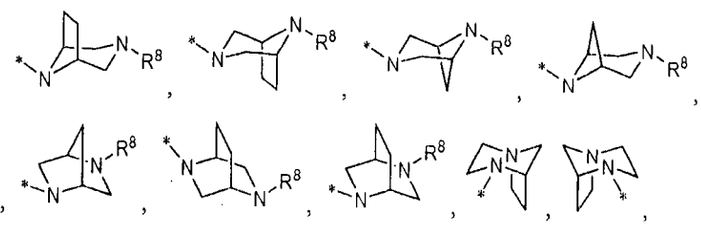
R^9 is hydrogen or alkyl;

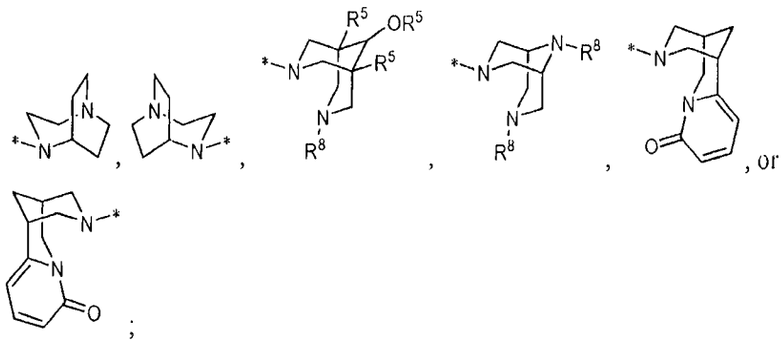
R^{10} is hydrogen or alkyl;

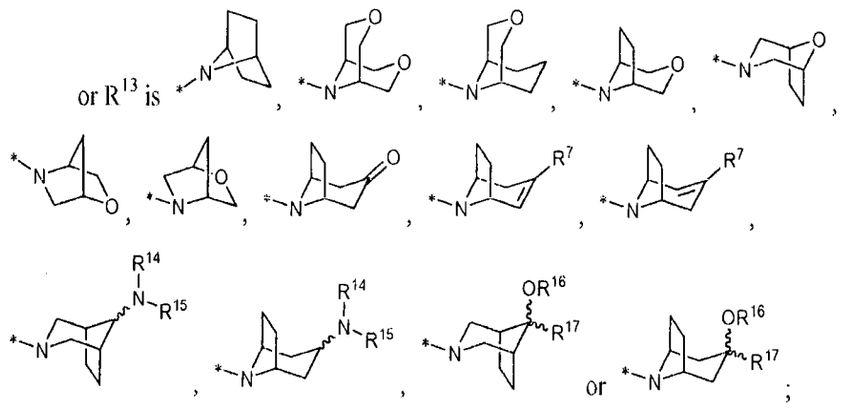
R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-1 alkyl substituents;

R^{12} is hydrogen, alkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or (R^{11})alkyl;

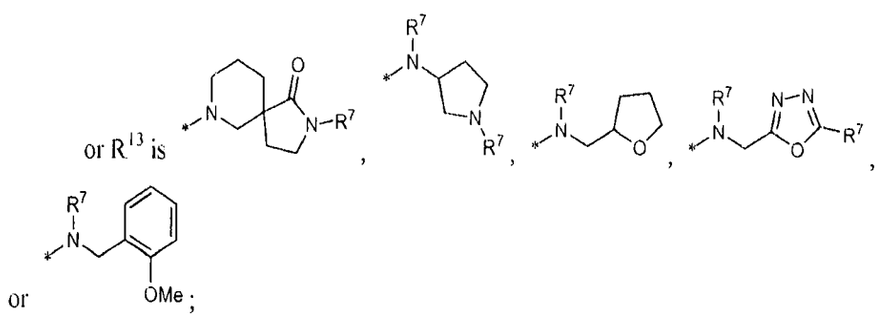
R^{13} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkoxyalkyl, amino, alkylamino, dialkylamino, R^{11}, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (R^{11})alkyl, or CO_2R^5;

or R^{13} is 



or R^{13} is 

or R^{13} is a [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents;

or R^{13} is 

R^{14} is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or benzyl;

R^{15} is is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or benzyl;

or $NR^{14}R^{15}$ taken together is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-(alkyl)piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, or homomorpholinyl;

R^{16} is hydrogen or alkyl;

R^{17} is hydrogen, alkyl, or cycloalkyl; and

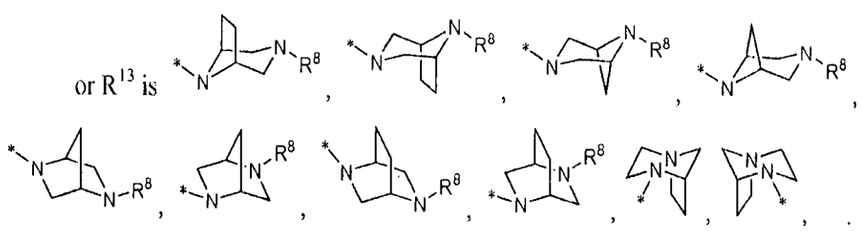
X is methylene, a bond, or absent;

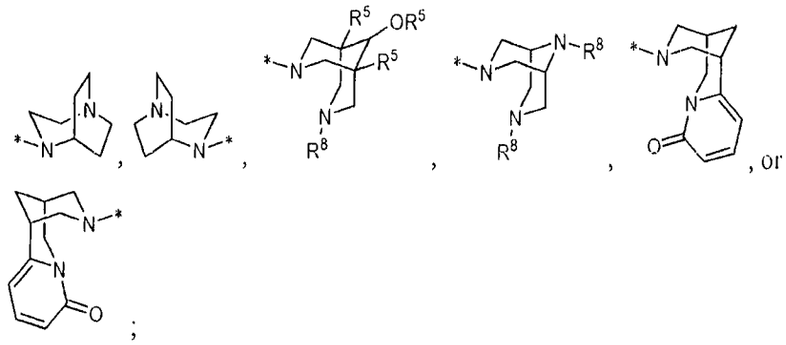
or a pharmaceutically acceptable salt thereof.

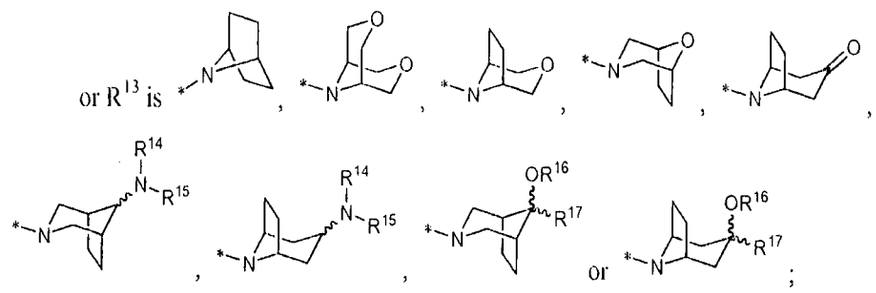
2. A compound of claim 1 where:

R^2 is furanyl, pyrrolyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, or tetrazolyl, and is substituted with 0-2 substituents selected from oxo, amino, alkyl, and haloalkyl, and 1 substituent selected from CO_2R^5, $CON(R^{12})_2$, and COR^{13}; and

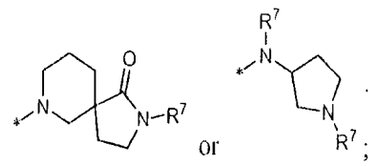
R^{13} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, alkoxyalkyl, amino, alkylamino, dialkylamino, R^{11}, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (R^{11})alkyl, or CO_2R^5;

or R^{13} is 



or R^{13} is 

or R^{13} is a [4.3.0] or [3.3.0] bicyclic diamine attached to the carbonyl through one nitrogen, and is substituted with 0-2 R^8 substituents;

or R^{13} is 

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 where:

R^2 is furanyl, pyrrolyl, thienyl, pyrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, or tetrazolyl, and is substituted with 0-2 substituents selected from oxo, amino, and alkyl, and 1 substituent selected from CO_2R^5, $CON(R^{12})_2$, and COR^{13};

R^{11} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl; and

R^{13} is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperidinyl, homopiperazinyl, or homomorpholinyl, and is substituted with 0-3 substituents selected from alkyl, amino, alkylamino, dialkylamino, R^{11}, aminoalkyl, (alkylamino)alkyl, (dialkylamino)alkyl, or (R^{11})alkyl;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 where R^1 is $CONR^6R^7$; R^6 is alkylSO_2, cycloalkylSO_2, haloalkylSO_2, $(R^9)_2NSO_2$, or $(R^{10})SO_2$; and R^7 is hydrogen.

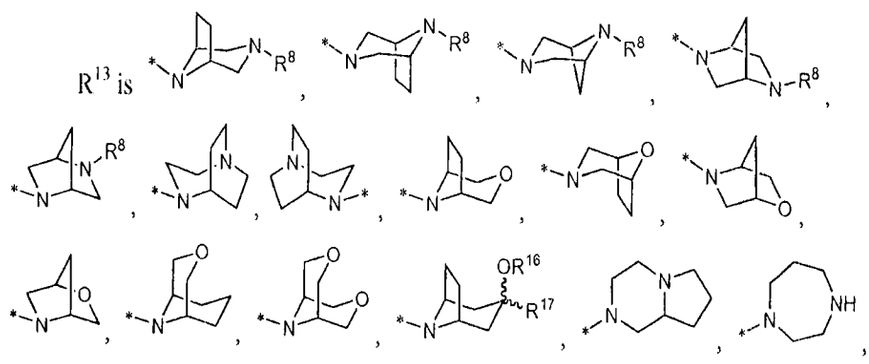
5. A compound of claim 1 where R^3 is hydrogen.

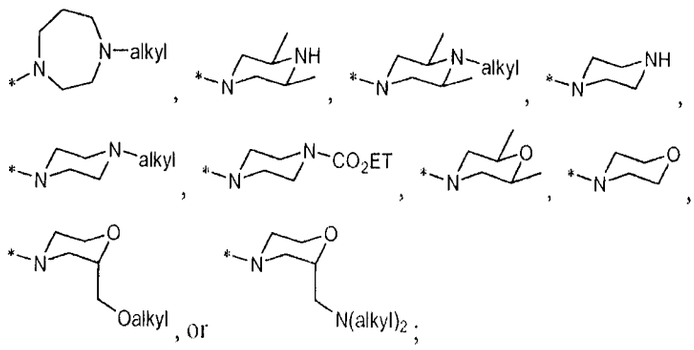
6. A compound of claim 1 where R^3 is methoxy.

7. A compound of claim 1 where R^4 is cyclohexyl.

8. A compound of claim 1 where R^6 is alkylSO_2, cycloalkylSO_2, $(R^9)(R^{10})NSO_2$ or $(R^{11})SO_2$.

9. A compound of claim 1 where R^2 is pyrazolyl substituted with 2 substituents selected from alkyl and haloalkyl and 1 COR^{13} substituent;

R^{13} is 



R^8 is hydrogen or alkyl;

R^{16} is hydrogen or alkyl; and

R^{17} is alkyl;

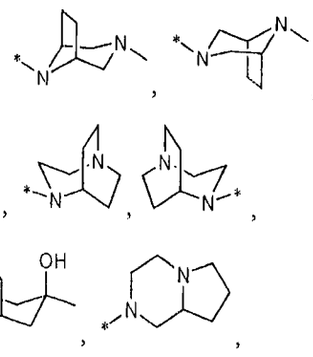
or a pharmaceutically acceptable salt thereof.

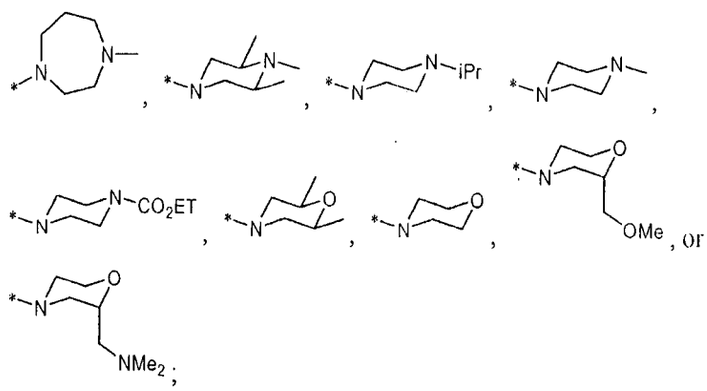
10. A compound of claim 1 where X is methylene.

11. A compound of claim 1 where X is absent.

12. A compound of claim 1 where X is a bond.

13. A compound of claim 12 where R^1 is $CONR^6R^7$;

R^2 is pyrazolyl substituted with 2 substituents selected from alkyl and haloalkyl and 1 COR^{13} substituent where R^{13} is 



R^3 is hydrogen or methoxy;

R^4 is cyclohexyl;

R^6 is alkylSO$_2$, cycloalkylSO$_2$, haloalkylSO$_2$, $(R^9)_2NSO_2$, or $(R^{10})SO_2$;

and R^7 is hydrogen;

or a pharmaceutically acceptable salt thereof.

14. A compound of claim 1 selected from the group consisting of

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[2-(methoxycarbonyl)-3-thienyl]-, 1,1-dimethylethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 6-(4-carboxy-1-methyl-1H-pyrazol-5-yl)-13-cyclohexyl-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(1,4-diazabicyclo[3.2.2]non-4-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[(1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-5-thiazolyl]-, 1,1-dimethylethyl ester;

3-thiophenecarboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-(1-methylethyl)-4-[(3,4,5-trimethyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(1R,5S)-3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1,3-dimethyl-1H-pyrazol-5-yl]-, 1,1-dimethylethyl ester;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-;

1H-pyrrole-3-carboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(1-methylethyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(4-morpholinylcarbonyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(4-methyl-1-piperazinyl)carbonyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-3-methyl-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-ylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[2-[(diethylamino)carbonyl]-3-thienyl]-N-[(dimethylamino)sulfonyl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-5-oxazolyl]-, 1,1-dimethylethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(4-morpholinylcarbonyl)-5-oxazolyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-(4-morpholinylcarbonyl)-5-oxazolyl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[methyl(1-methyl-3-pyrrolidinyl)amino]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[2-[(dimethylamino)methyl]-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[(1R,5S)-3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[4-(1-methylethyl)-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[4-(1-pyrrolidinyl)-1-piperidinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-N-[(1-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(1-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-cyclopropyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

1H-pyrrole-3-carboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-, ethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-(1,1-dimethylethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[2-(4-morpholinylcarbonyl)-3-thienyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 6-[4-(7-azabicyclo[2.2.1]hept-7-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-13-cyclohexyl-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-pyrrolidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 6-[4-(7-azabicyclo[2.2.1]hept-7-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)carbonyl]-1H-pyrazol-5-yl]-;

1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[1-methyl-4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1R,4R)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-8-azabicyclo[3.2.1]oct-2-en-8-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-10-[[[(dimethylamino)sulfonyl]amino]carbonyl]-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[4-(4-morpholinylcarbonyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-(2,2,2-trifluoroethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-3-methyl-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[3-methyl-1-(1-methylethyl)-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[3-methyl-1-(1-methylethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-ethyl-3-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-N-(1-pyrrolidinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[4-(4-morpholinylcarbonyl)-5-oxazolyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-(1-pyrrolidinylsulfonyl)-morpholine, 4-[[13-cyclohexyl-6-[1-ethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-7H-indolo[2,1-a][2]benzazepin-10-yl]carbonyl]-;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

1-piperazinecarboxylic acid, 4-[[5-[13-cyclohexyl-3-methoxy-10-[[(4-morpholinylsulfonyl)amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-1H-pyrazol-4-yl]carbonyl]-, ethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[4-(1-pyrrolidinyl)-1-piperidinyl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[[(2-methoxyphenyl)methyl](1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1H-pyrazol-5-yl]-N-[(1-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1,3-dimethyl-, methyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1,3-dimethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl) sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[3-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-(1-methylethyl)-1H-pyrrol-2-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-3-(4-morpholinylcarbonyl)-1H-pyrrol-2-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl)carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[4-(4-morpholinylcarbonyl)-5-oxazolyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[[2-(dimethylamino)ethyl]methylamino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(2-methylpropyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[[(5-ethyl-1,3,4-oxadiazol-2-yl)methyl](1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(1-methylpropyl)sulfonyl]-;

1H-pyrazole-4-carboxylic acid, 5-[10-[[(cyclobutylsulfonyl)amino]carbonyl]-13-cyclohexyl-3-methoxy-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(2-methylpropyl)sulfonyl]-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(2,6-dimethyl-4-morpholinyl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-8-azabicyclo[3.2.1]oct-2-en-8-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[3-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1-(1-methylethyl)-1H-pyrrol-2-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-3-[(4-propyl-1-piperazinyl)carbonyl]-1H-pyrrol-2-yl]-N-[(1-methylethyl)sulfonyl]-;

3-furancarboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-, ethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl)carbonyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 6-(4-carboxy-5-oxazolyl)-13-cyclohexyl-3-methoxy-, 10-(1,1-dimethylethyl) ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-(1-pyrrolidinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-ethyl-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopropylsulfonyl)-3-methoxy-6-[4-(4-morpholinylcarbonyl)-5-oxazolyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(3-endo)-3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[(4-methyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-6-[4-[[ethyl(1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-[[(1-methylethyl)[(tetrahydro-2-furanyl)methyl]amino]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]oct-3-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(methoxycarbonyl)-1,3-dimethyl-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1,3-dimethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-3-(trifluoromethyl)-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopropylsulfonyl)-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[4-(4-morpholinylcarbonyl)-5-oxazolyl]-, 1,1-dimethylethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-, 1,1-dimethylethyl ester;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-pyrrolidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(1-oxo-2,7-diazaspiro[4.5]dec-7-yl)carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2-methoxyethyl)(1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[[(2-methoxyethyl)(1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(3-endo)-3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(dimethylamino)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-[[(1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[4-[(3-methyl-3,6-diazabicyclo[3.1.1]hept-6-yl)carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(3-endo)-3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(3-endo)-3-hydroxy-3-methyl-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

1H-pyrrole-3-carboxylic acid, 2-[13-cyclohexyl-3-methoxy-10-[[[(1-methylethyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-(1-methylethyl)-, ethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1,3-dimethyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1-(1,1-dimethylethyl)-4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-ylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(8-oxa-3-azabicyclo[3.2.1]oct-3-ylcarbonyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[3-methyl-1-(1-methylethyl)-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[4-(1-methylethyl)-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[3-(dimethylamino)-1-piperidinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[2-(1-piperidinylmethyl)-1-pyrrolidinyl]carbonyl]-1H-pyrazol-5-yl]-N-(4-morpholinylsulfonyl)-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 6-[4-[[[2-[bis(1-methylethyl)amino]ethyl](1-methylethyl)amino]carbonyl]-1-methyl-1H-pyrazol-5-yl]-13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-(cyclopentylsulfonyl)-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylpropyl)sulfonyl]-6-[1-methyl-4-[(3,4,5-trimethyl-1-piperazinyl)carbonyl]-1H-pyrazol-5-yl]-;

1H-pyrazole-4-carboxylic acid, 5-[13-cyclohexyl-3-methoxy-10-[[[(1-methylpropyl)sulfonyl]amino]carbonyl]-7H-indolo[2,1-a][2]benzazepin-6-yl]-1-methyl-, ethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[1-methyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-N-[(2-methylpropyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[1-methyl-4-[[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]carbonyl]-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[1-methyl-4-(3-oxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-6-[4-(3,7-dioxa-9-azabicyclo[3.3.1]non-9-ylcarbonyl)-1-methyl-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, N-(cyclobutylsulfonyl)-13-cyclohexyl-3-methoxy-6-[4-[[(2S)-2-(methoxymethyl)-4-morpholinyl]carbonyl]-1-methyl-1H-pyrazol-5-yl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[3-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-2-thienyl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[4-(ethoxycarbonyl)-2-(methylthio)-5-thiazolyl]-3-methoxy-, 1,1-dimethylethyl ester;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(1S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl]-1-(1-methylethyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-N-[(dimethylamino)sulfonyl]-6-[1,3-dimethyl-4-(4-morpholinylcarbonyl)-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[1,3-dimethyl-4-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-(1,1-dimethylethyl)-4-(ethoxycarbonyl)-1H-pyrazol-5-yl]-3-methoxy-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-6-[3-[(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)carbonyl]-2-furanyl]-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-3-methoxy-N-[(1-methylethyl)sulfonyl]-6-[3-(4-morpholinylcarbonyl)-2-furanyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[4-[[(2R,6S)-2,6-dimethyl-4-morpholinyl]carbonyl]-1-(2-methylpropyl)-1H-pyrazol-5-yl]-3-methoxy-N-[(1-methylethyl)sulfonyl]-;

7H-indolo[2,1-a][2]benzazepine-10-carboxylic acid, 13-cyclohexyl-6-[1-ethyl-4-(methoxycarbonyl)-3-methyl-1H-pyrazol-5-yl]-3-methoxy-;

5*H*-indolo[2,1-*a*][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[3-[(dimethylamino)carbonyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]-*N*-[(dimethylamino)sulfonyl]-6,7-dihydro-3-methoxy-; and

5*H*-indolo[2,1-*a*][2]benzazepine-10-carboxamide, 13-cyclohexyl-6-[3-[(dimethylamino)carbonyl]-4*H*-1,2,4-triazol-4-yl]-*N*-[(dimethylamino)sulfonyl]-6,7-dihydro-3-methoxy-;

or a pharmaceutically acceptable salt thereof.

15. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. The composition of claim 15 further comprising at least one additional compound having therapeutic benefits for HCV wherein the compound is selected from the group consisting of interferons, cyclosporins, interleukins, HCV metalloprotease inhibitors, HCV serine protease inhibitors, HCV polymerase inhibitors, HCV helicase inhibitors, HCV NS4B protein inhibitors, HCV entry inhibitors, HCV assembly inhibitors, HCV egress inhibitors, HCV NS5A protein inhibitors, HCV NS5B protein inhibitors, and HCV replicon inhibitors.

17. A method of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of claim 1 to a patient.

18. The method of claim 17 further comprising administering at least one additional compound having therapeutic benefits for HCV wherein the compound is selected from the group consisting of interferons, cyclosporins, interleukins, HCV metalloprotease inhibitors, HCV serine protease inhibitors, HCV polymerase inhibitors, HCV helicase inhibitors, HCV NS4B protein inhibitors, HCV entry

inhibitors, HCV assembly inhibitors, HCV egress inhibitors, HCV NS5A protein inhibitors, HCV NS5B protein inhibitors, and HCV replicon inhibitors.

COMPUESTOS PARA EL TRATAMIENTO DE HEPATITIS C

REFERENCIA A SOLICITUDES RELACIONADAS

Esta solicitud reivindica el beneficio de las solicitudes provisionales de Estados Unidos números de serie 61/049,944 presentada el 2 de mayo de 2008 y 60/954,814 presentada el 9 de agosto de 2007.

ANTECEDENTES DE LA INVENCIÓN

El virus de la Hepatitis C (VHC) es un patógeno humano importante, que se estima infecta a 170 millones de personas en todo el mundo - aproximadamente cinco veces el número de infectados por el virus de la inmunodeficiencia humana tipo 1. Una fracción sustancial de estos individuos infectados por VHC desarrolla enfermedad hepática progresiva grave, incluyendo cirrosis y carcinoma hepatocelular (Lauer, G. M.; Walker, B. D *N. Engl. J. Med.* **2001**, *345*, 41-52).

El VHC es un virus ARN de cadena positiva. En base a la comparación de la secuencia de aminoácidos deducida y a la extensa similitud en la región sin traducir 5', el VHC se ha clasificado como un género separado en la familia de Flaviviridae. Todos los miembros de la familia Flaviviridae tienen viriones encapsulados que contienen un genoma de ARN de cadena positiva que codifica todas las proteínas específicas de virus conocidas mediante traducción de un marco de lectura abierto no interrumpido único.

Dentro de la secuencia de nucleótidos y aminoácidos codificados en todo el genoma del VHC se encuentra una considerable heterogeneidad. Se han caracterizado al menos seis genotipos principales y se han descrito más de 50 subtipos. Los genotipos principales del VHC se diferencian en su distribución en todo el mundo y la significación clínica de la heterogeneidad genética del VHC sigue siendo difícil de conseguir a pesar de numerosos estudios del efecto positivo de genotipos sobre la patogénesis y tratamiento.

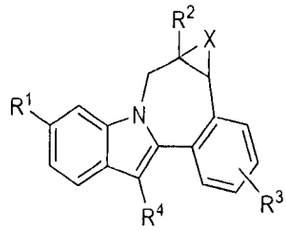
El genoma del ARN del VHC es de aproximadamente 9500 nucleótidos y tiene un marco de lectura abierto (ORF) que codifica una única poliproteína grande de aproximadamente 3000 aminoácidos. En células infectadas, esta poliproteína se corta en múltiples sitios por proteasas celulares y virales para producir las proteínas estructurales y no estructurales (NS). En el caso del VHC, la generación de proteínas estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A y NS5B) se efectúa por dos proteasas virales. Se cree que la primera es una metaloproteasa y corta la unión NS2-NS3; la segunda es una serina proteasa contenida en la región N-terminal de NS3 (también denominada proteasa NS3) y media todas los cortes posteriores cadena abajo de NS3, ambos en cis, en el sitio de corte NS3-NS4A, y en trans, para los sitios NS4A-NS4B, NS4B-NS5A, NS5A-NS5B restantes. La proteína NS4A parece servir para múltiples funciones, actuando como cofactor para la NS3 proteasa y posiblemente ayudando en la localización de membrana de NS3 y otros componentes de replicasa viral. La compleja formación de la proteína NS3 con NS4A parece necesaria para los sucesos de procesamiento, potenciando la eficacia proteolítica en todos los sitios. La proteína NS3 también presenta

actividades nucleósido trifosfatasa y ARN helicasa. NS5B (también denominada polimerasa del VHC) es una ARN polimerasa dependiente de ARN que está implicada en la replicación del VHC. La proteína NS5B del VHC se describe en "Structural Analysis of the Hepatitis C Virus RNA Polymerase in Complex with Ribonucleotides (Bressanelli; S. et al., *Journal of Virology* **2002**, 3482-3492; and Defrancesco and Rice, *Clinics in Liver Disease* **2003**, 7, 211-242.

En la actualidad, el tratamiento más eficaz contra el VHC emplea una combinación de interferón alfa y ribavirina, que conduce a una eficacia sostenida en el 40 por ciento de pacientes (Poynard, T. et al. *Lancet* **1998**, 352, 1426-1432). Recientes estudios clínicos demuestran que el interferón alfa pegilado es superior al interferón alfa no modificado como monotratamiento (Zeuzem, S. et al. *N. Engl. J. Med.* **2000**, 343, 1666-1672). No obstante, incluso con pautas terapéuticas experimentales que conllevan combinaciones de interferón alfa pegilado y ribavirina, una fracción sustancial de pacientes no experimenta una reducción sostenida en la carga viral. Así, existe una necesidad evidente y no satisfecha de desarrollar terapias terapéuticas eficaces para el tratamiento de infección por VHC.

DESCRIPCIÓN DE LA INVENCIÓN

Un aspecto de la invención es un compuesto de fórmula I



I

en la que:

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es furanilo, pirrolilo, tienilo, pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, triazolilo o tetrazolilo, y está sustituido con 0-2 sustituyentes seleccionados de oxo, amino, alquiltio, alquilo y haloalquilo, y 1 sustituyente seleccionado de CO_2R^5, $CON(R^{12})_2$ y COR^{13};

R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, $alquilSO_2$, $cicloalquilSO_2$, $haloalquilSO_2$, $(R^9)(R^{10})NSO_2$ o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquilSO_2, cicloalquilSO_2, haloalquilSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo o piridinilo;

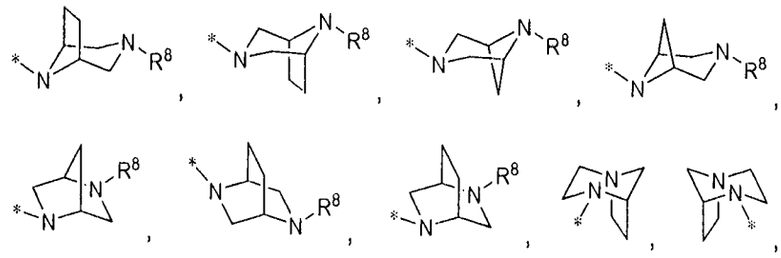
R^9 es hidrógeno o alquilo;

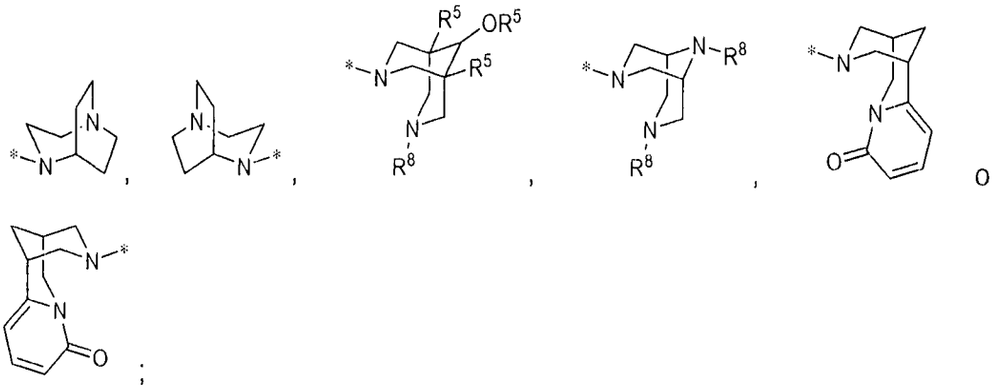
R^{10} es hidrógeno o alquilo;

R^{11} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-1 sustituyentes alquilo;

R^{12} es hidrógeno, alquilo, alcoxialquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o (R^{11})alquilo;

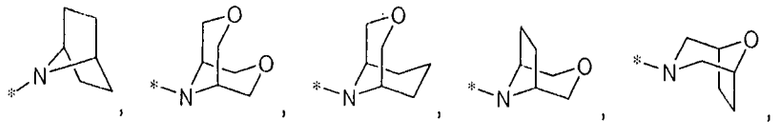
R^{13} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-3 sustituyentes seleccionados de alquilo, alcoxialquilo, amino, alquilamino, dialquilamino, R^{11}, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo, (R^{11})alquilo o CO_2R^5;

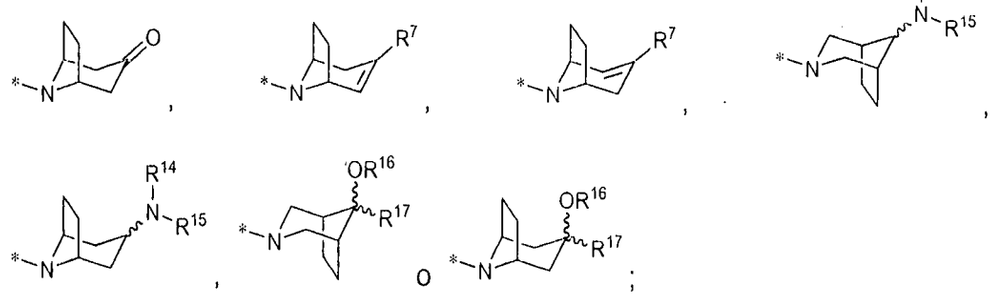
o R^{13} es 



;

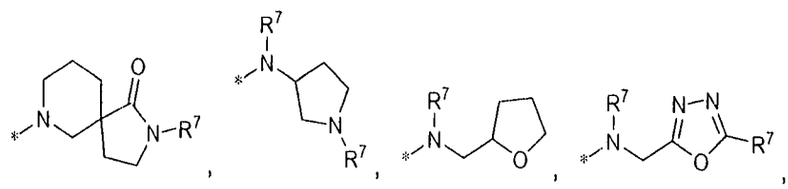
o R^{13} es

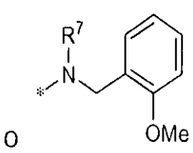




o R^{13} es una diamina bicíclica [4.3.0] o [3.3.0] unida al carbonilo a través de un nitrógeno, y está sustituido con 0-2 sustituyentes R^8;

o R^{13} es





;

R^{14} es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o bencilo;

R^{15} es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o bencilo;

o $NR^{14}R^{15}$ tomados conjuntamente es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-(alquil)piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo o homomorfolinilo;

R^{16} es hidrógeno o alquilo;

R^{17} es hidrógeno, alquilo o cicloalquilo; y

X es metileno, un enlace o no está presente;

o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un compuesto de fórmula I en la que:

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es furanilo, pirrolilo, tienilo, pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, triazolilo o tetrazolilo, y está sustituido con 0-2 sustituyentes seleccionados de oxo, amino, alquilo y haloalquilo, y 1 sustituyente seleccionado de CO_2R^5, $CON(R^{12})_2$ y COR^{13};

R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquilSO_2, cicloalquilSO_2, haloalquilSO_2, $(R^9)(R^{10})NSO_2$ o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquilSO_2, cicloalquilSO_2, haloalquilSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo o piridinilo;

R^9 es hidrógeno o alquilo;

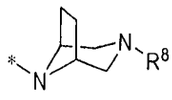
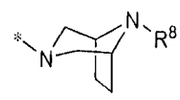
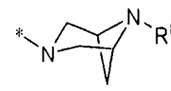
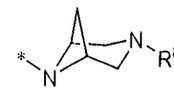
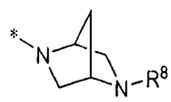
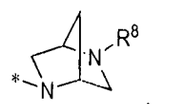
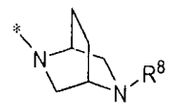
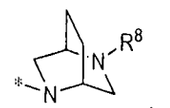
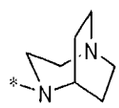
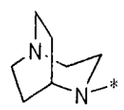
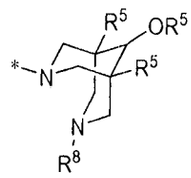
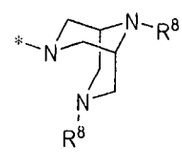
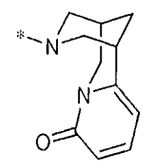
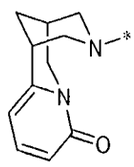
R^{10} es hidrógeno o alquilo;

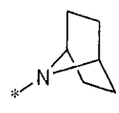
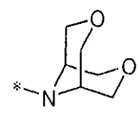
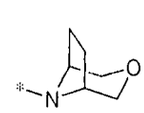
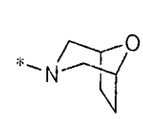
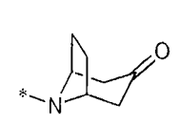
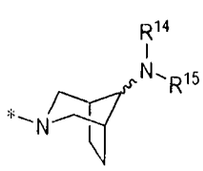
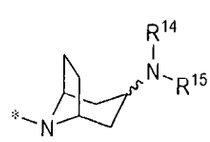
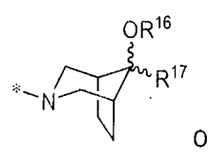
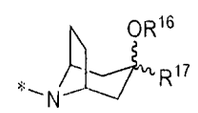
R^{11} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-1 sustituyentes alquilo;

R^{12} es hidrógeno, alquilo, alcoxialquilo, aminoalquilo,

(alquilamino)alquilo, (dialquilamino)alquilo o (R^{11})alquilo;

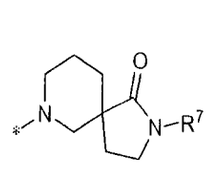
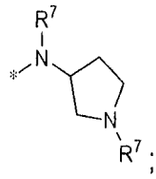
R^{13} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-3 sustituyentes seleccionados de alquilo, alcoxialquilo, amino, alquilamino, dialquilamino, R^{11}, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo, (R^{11})alquilo o CO_2R^5;

o R^{13} es  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , o  ;

o R^{13} es  ,  ,  ,  ,  ,  ,  ,  , o  ;

o R^{13} es una diamina bicíclica [4.3.0] o [3.3.0] unida al carbonilo a través

de un nitrógeno, y está sustituido con 0-2 sustituyentes R^8;

o R^{13} es  o  ;

R^{14} es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o bencilo;

R^{15} es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o bencilo;

o $NR^{14}R^{15}$ tomados conjuntamente es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-(alquil)piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo o homomorfolinilo;

R^{16} es hidrógeno o alquilo;

R^{17} es hidrógeno, alquilo o cicloalquilo; y

X es metileno, un enlace o no está presente;

o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un compuesto de fórmula I en la que:

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es furanilo, pirrolilo, tienilo, pirazolilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo o tetrazolilo, y está sustituido con 0-2 sustituyentes seleccionados de oxo, amino y alquilo, y 1 sustituyente seleccionado de CO_2R^5, $CON(R^{12})_2$ y COR^{13};

R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquilSO_2, cicloalquilSO_2, haloalquilSO_2, $(R^9)(R^{10})NSO_2$ o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquilSO_2, cicloalquilSO_2, haloalquilSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo o piridinilo;

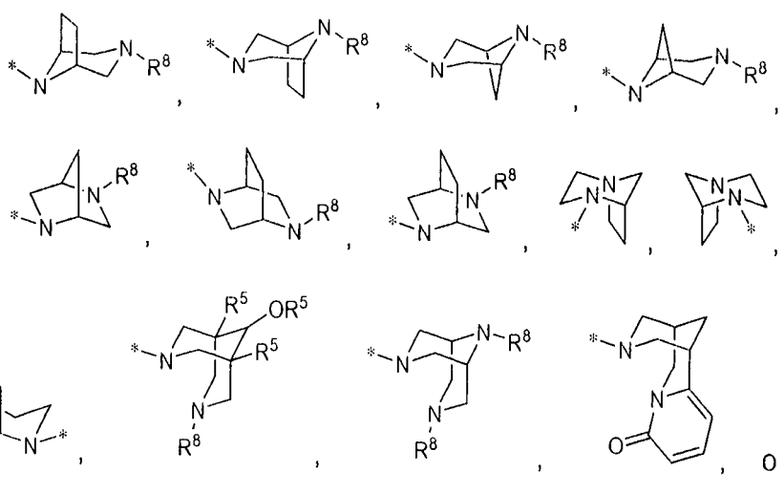
R^9 es hidrógeno o alquilo;

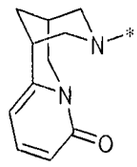
R^{10} es hidrógeno o alquilo;

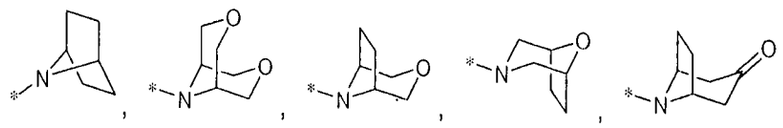
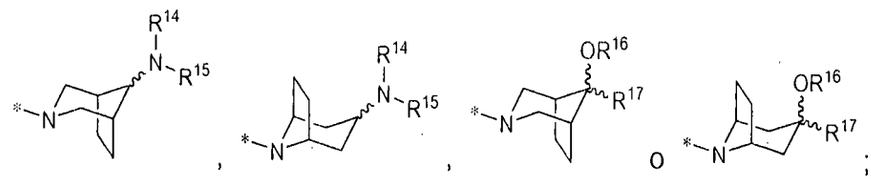
R^{11} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-alquilpiperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo;

R^{12} es hidrógeno, alquilo, alcoxialquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o (R^{11})alquilo;

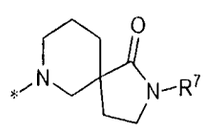
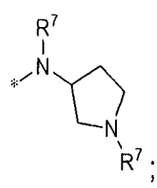
R^{13} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-3 sustituyentes seleccionados de alquilo, amino, alquilamino, dialquilamino, R^{11}, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o (R^{11})alquilo;

o R^{13} es 


;

o R^{13} es 

o
;

o R^{13} es una diamina bicíclica [4.3.0] o [3.3.0] unida al carbonilo a través de un nitrógeno, y está sustituido con 0-2 sustituyentes R^8;

o R^{13} es 
o 
;

R^{14} es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o bencilo;

R^{15} es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o bencilo;

o $NR^{14}R^{15}$ tomados conjuntamente es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-(alquil)piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo o homomorfolinilo;

R^{16} es hidrógeno o alquilo;

R^{17} es hidrógeno, alquilo o cicloalquilo; y

X es metileno, un enlace o no está presente;

o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un compuesto de fórmula I en la que R^1 es $CONR^6R^7$; R^6 es alquilSO_2, cicloalquilSO_2, haloalquilSO_2, $(R^9)_2NSO_2$ o $(R^{10})SO_2$; y R^7 es hidrógeno.

Otro aspecto de la invención es un compuesto de fórmula I en la que R^3 es hidrógeno.

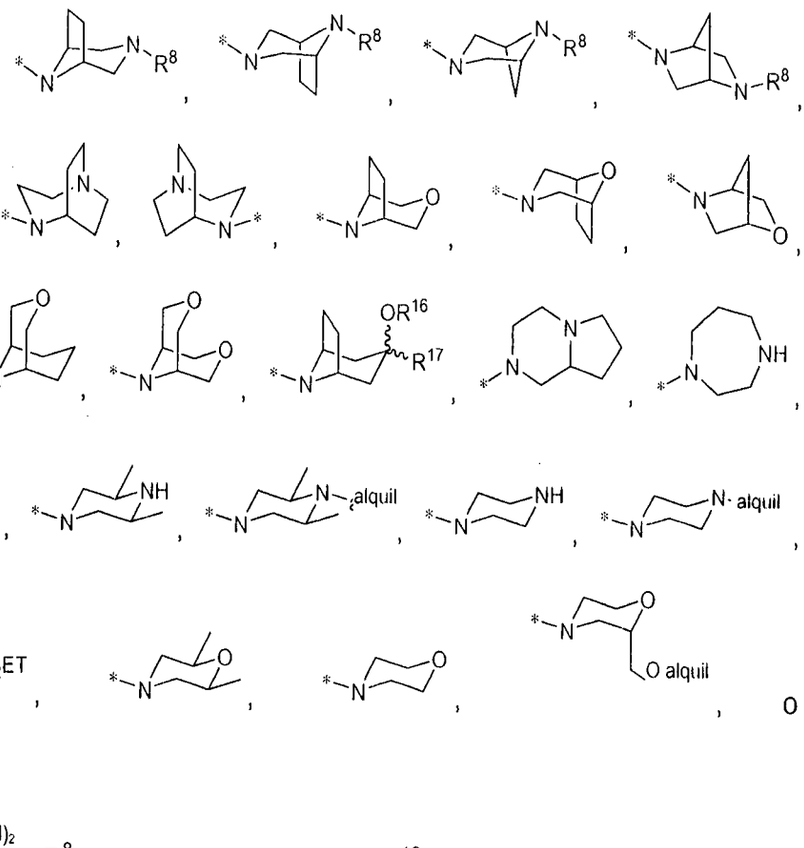
Otro aspecto de la invención es un compuesto de fórmula I en la que R^3 es metoxi.

Otro aspecto de la invención es un compuesto de fórmula I en la que R^4 es ciclohexilo.

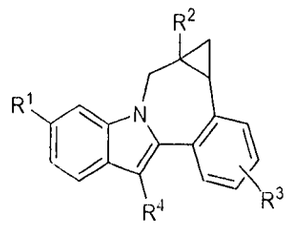
Otro aspecto de la invención es un compuesto de fórmula I en la que R^6 es alquilSO_2, cicloalquilSO_2, $(R^9)(R^{10})NSO_2$ o $(R^{11})SO_2$.

Otro aspecto de la invención es un compuesto de fórmula I en la que R^2

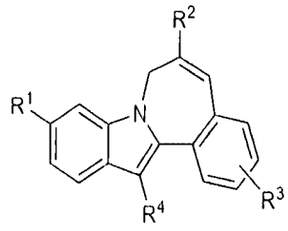
es pirazolilo sustituido con 2 sustituyentes seleccionados de alquilo y haloalquilo y 1 sustituyente COR^{13}

R^{13} es 
; R^8 es hidrógeno o alquilo; R^{16} es hidrógeno o alquilo; y R^{17} es alquilo.

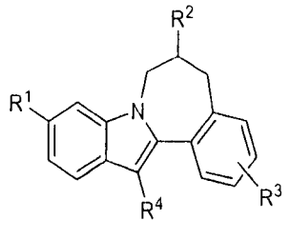
Otro aspecto de la invención es un compuesto de fórmula I en la que X es metileno.



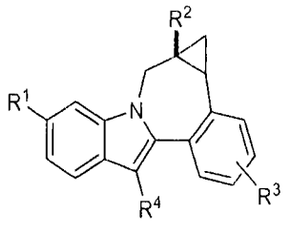
Otro aspecto de la invención es un compuesto de fórmula I en la que X es un enlace.



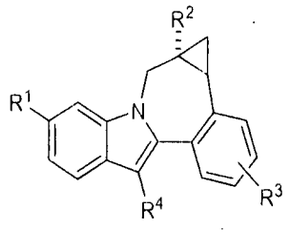
Otro aspecto de la invención es un compuesto de fórmula I en la que X no está presente.



Otro aspecto de la invención es un compuesto de fórmula I de acuerdo con la siguiente estereoquímica.

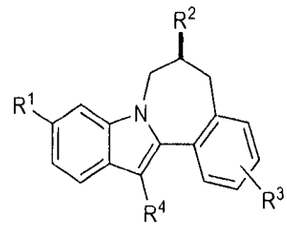


Otro aspecto de la invención es un compuesto de fórmula I de acuerdo con la siguiente estereoquímica.

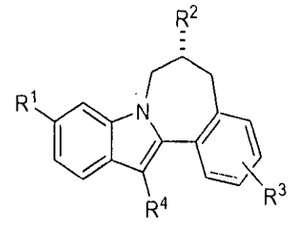


Otro aspecto de la invención es un compuesto de fórmula I de acuerdo

con la siguiente estereoquímica.



Otro aspecto de la invención es un compuesto de fórmula I de acuerdo con la siguiente estereoquímica.



Se puede usar cualquier alcance de cualquiera de las variables, incluyendo 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} y X independientemente con el alcance de cualquier otro caso de una variable.

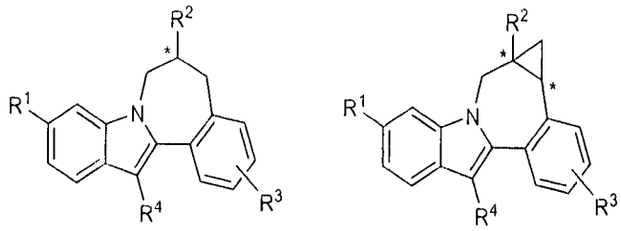
A no ser que se indique de otro modo, estos términos tienen los siguientes significados. "Alquilo" se refiere a un grupo alquilo lineal o ramificado formado por 1 a 6 carbonos. "Alquenilo" se refiere a un grupo alquilo lineal o ramificado formado por 2 a 6 carbonos con al menos un doble enlace. "Cicloalquilo" se refiere a un sistema de anillo monocíclico formado por 3 a 7 carbonos. "Hidroxialquilo," "alcoxi" y otros términos con un resto alquilo sustituido incluyen isómeros lineales y ramificados formados por 1 a 6 átomos de carbono para el resto alquilo. "Haloalquilo" y "haloalcoxi" incluyen todos los isómeros halogenados desde alquilo monosustituido con halo hasta alquilo persustituido con halo. "Arilo" incluye sustituyentes aromáticos carbocíclicos y

heterocíclicos. Los términos entre paréntesis y multiparéntesis se desea que aclaren las relaciones de enlace a los expertos en la técnica. Por ejemplo, un término tal como ((R)alquilo) significa un sustituyente alquilo que está además sustituido con el sustituyente R.

La invención incluye todas las formas de sal farmacéuticamente aceptables de los compuestos. Sales farmacéuticamente aceptables son aquellas en las que el ion contrario no contribuye de forma significativa a la actividad fisiológica o toxicidad de los compuestos y como tales, funcionan como equivalentes farmacéuticos. Estas sales se pueden preparar de acuerdo con técnicas orgánicas convencionales que emplean reactivos disponibles de forma comercial. Algunas formas de sal aniónica 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 de sal catiónica 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 asimétricos (véase, por ejemplo, el siguiente compuesto). La invención incluye todas las formas estereoisoméricas, incluyendo enantiómeros y diastereoisómeros, así como mezclas de estereoisómeros tales como racematos. Algunos estereoisómeros se pueden preparar usando procedimientos conocidos en la técnica. Las mezclas estereoisoméricas de los

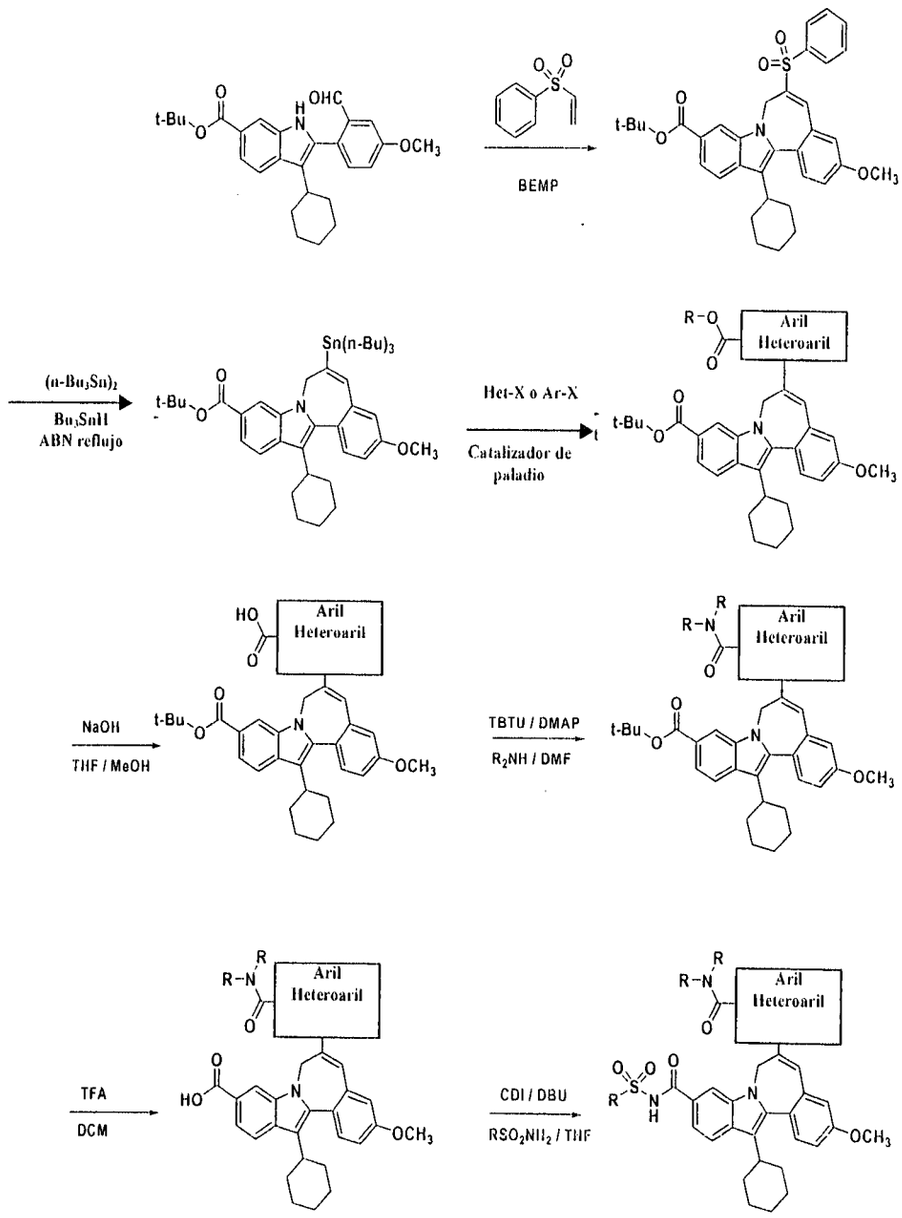
compuestos e intermedios relacionados se pueden separar en isómeros individuales de acuerdo con procedimientos conocidos habitualmente en la técnica.



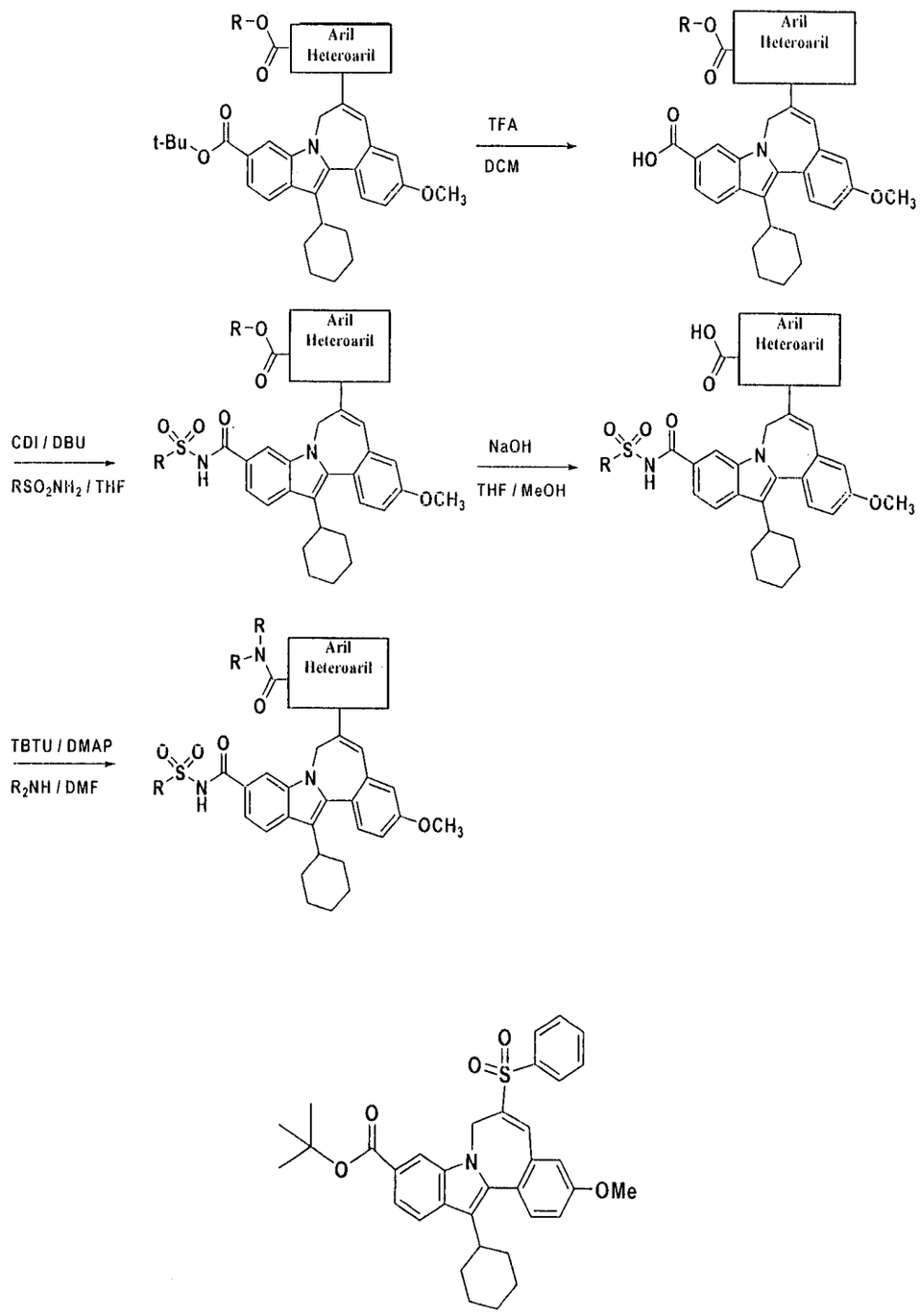
Procedimientos de síntesis

Los compuestos se pueden preparar por procedimientos conocidos en la técnica, incluyendo los descritos más adelante. Algunos reactivos e intermedios son conocidos en la técnica. Otros reactivos e intermedios se pueden preparar por procedimientos conocidos en la técnica usando materiales disponibles. Las variables (por ejemplo, sustituyentes "R" numerados) usadas para describir la síntesis de los compuestos están destinadas únicamente a ilustrar el modo de preparar los compuestos y no se confundirán con las variables usadas en las reivindicaciones y otras secciones de la memoria descriptiva. Las abreviaturas usadas en los esquemas siguen por lo general los convenios usados en la técnica.

El esquema mostrado a continuación ilustra procedimientos que se pueden usar para preparar intermedios y compuestos.



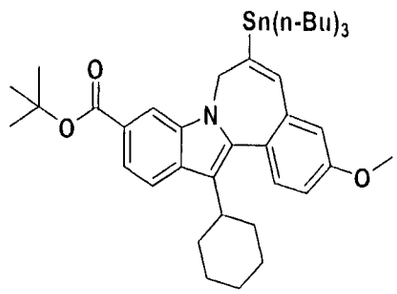
Como alternativa, la secuencia de reacción se puede modificar como se muestra a continuación.



Éster terc-butílico del ácido 13-ciclohexil-3-metoxi-6-(fenilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

A una solución de 2-(2-formil-4-metoxifenil)-1H-indol-6-carboxilato de 3-

ciclohexilo (6,00 g, 13,8 mmol) en dioxano (28,0 ml) y BEMP (7,97 ml, 27,6 mmol) se añadió fenil vinil sulfona (27,6 g, 2,21 mmol). La mezcla resultante se agitó en un tubo sellado en un microondas a 120°C durante 15 min. La solución resultante se concentró a presión reducida. La cromatografía sobre gel de sílice (CH_2Cl_2) del concentrado proporcionó el compuesto del epígrafe 6,36 g (79%) como un aceite amarillo. MS (Espectro de Masas) m/z 584 (MH^+). RMN de ^1H (500 MHz, CLOROFORMO-d) δ ppm 1,18-1,33 (1 H, m), 1,34-1,45 (2 H, m), 1,49-57 (1 H, m), 1,64 (9 H, s.), 1,74-1,82 (2 H, m), 1,90-2,09 (4 H, m), 2,73 (1 H, m,), 3,93 (3 H, s), 4,38 (1 H, d ancho), 5,08 (1 H, d ancho), 7,09 (1 H, d, *J*=2,75 Hz), 7,12-7,18 (3 H, m), 7,22 (1 H, d, *J*=7,45 Hz), 7,30 (1 H, s), 7,48 (1 H, d, *J*=8,85 Hz), 7,54 (1 H, dd, *J*=8,55, 1,22 Hz), 7,61 (2 H, m), 7,67 (1 H, d, *J*=8,55), 8,01 (1 H, s).



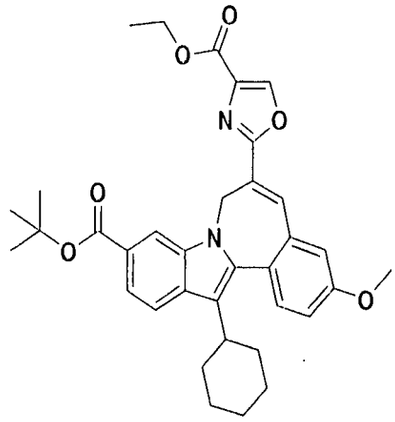
Éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(tributilestannil)-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. 13-ciclohexil-3-(metiloxi)-6-(tributilestannanil)-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de 1,1-dimetiletilo. Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(fenilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico (1,00 g, 1,71 mmol) en 26 ml de benceno junto con bis(tributilestaño) (2,8 ml, 5,54 mmol),

hidruro de tributilestaño (136 ul, 0,513 mmol) y trietilamina (1,05 ml, 7,5 mmol). La solución se roció durante aproximadamente 10 minutos con nitrógeno y luego se añadió a la reacción 2,2'-bisazoisobutironitrilo (AIBN) (96 mg, 0,58 mmol). La reacción se calentó hasta reflujo en nitrógeno durante 2 h. La reacción se siguió por LC-MS usando las siguientes condiciones HPLC: HPLC analítica Shimadzu usando software Discovery VP: %A= 5% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B inicial= 0; %B final=100; Gradiente= 3 min; Tiempo de ejecución= 10 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Waters Xterra, 3mm x 50mm, S7. A la reacción se añadió hidruro de tributilestaño (0,45 ml, 1,7 mmol) y AIBN (95 mg, 0,58 mmol), la reacción se calentó hasta reflujo durante 2 horas y se analizó para determinar el progreso. Se añadió AIBN (99 mg, 0,60 mmol) a la reacción y la reacción se calentó hasta reflujo durante otras 6 horas usando un programador. El progreso de la reacción se analizó por LC-MS (Cromatografía de Líquidos - Espectrometría de Masas) y luego se añadió hidruro de tributilestaño (1,0ml, 3,8 mmol) y AIBN (97 mg, 0,59 mmol) y la reacción se calentó hasta reflujo durante 2 horas 20 minutos. La reacción se analizó por LC-MS y se añadió a la reacción AIBN (97 mg, 0,59 mmol). La reacción se calentó durante 1 hora en nitrógeno a reflujo y se enfrió y analizó por LC-MS. Los volátiles se eliminaron a vacío de la reacción y la reacción se purificó por cromatografía en columna usando un relleno para C_{18} de 190g de YMC GEL ODS-A, 120A esférica 75 uM. El residuo de reacción (6,67g de aceite amarillo) se disolvió en un mínimo de diclorometano y la solución se aplicó en la columna de fase inversa rellena en diclorometano al 10% en acetonitrilo. Se realizó una elución inicial usando

diclorometano al usando diclorometano al 10% en acetonitrilo seguido por elución con diclorometano al 15% en acetonitrilo. La cromatografía se controló por TLC usando placas de TLC de 200 uM de espesor de 2,54 cm x 37,62 cm de fase inversa Whatman MKC18F eluyendo usando diclorometano al 15% en acetonitrilo. La observación del compuesto se llevó a cabo por una lámpara UV por una lámpara UV a 254 nm y tinción con yodo de las placas TLC. Se recogieron las fracciones de producto y se eliminaron los volátiles a vacío proporcionando 647mg (52%) como una espuma amarillo pálido. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,71 - 0,83 (m, 9 H) 0,85 - 0,96 (m, 3 H) 0,95 - 1,08 (m, 6 H) 1,15 - 1,27 (m, 7 H) 1,27 - 1,49 (m, 11 H) 1,53 (s, 5 H) 1,60 - 1,67 (m, 9 H) 1,68 - 1,82 (m, 2 H) 1,84 - 1,96 (m, 1 H) 1,96 - 2,16 (m, 3 H) 2,74 - 2,91 (m, 1 H) 3,90 (s, 3 H) 4,16 - 4,40 (m, 1 H) 4,82 - 5,03 (m, 1 H) 6,72 - 6,90 (m, 2 H) 6,96 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,43 (d, *J*=8,55 Hz, 1 H) 7,66 (dd, *J*=8,39, 1,37 Hz, 1 H) 7,81 (d, *J*=8,55 Hz, 1 H) 8,04 (s, 1 H); LC-MS: HPLC Analítica Shimadzu usando software Discovery VP: %A= 10% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B inicial= 0; %B final=100; Gradiente= 3 min; Tiempo de ejecución= 5 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Waters Xterra, 3mm x 50mm, S7. Tiempo de retención= 4,2min, MS m/z 734(MH^+).

Éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(tributilestannil)-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. 13-ciclohexil-3-(metiloxi)-6-(tributilestannanil)-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de 1,1-dimetiletilo.

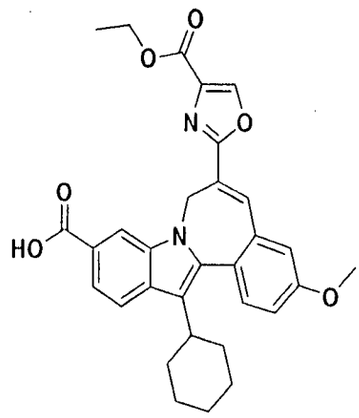
Se secó a la llama un conjunto de matraz de tres bocas provisto de burbujeador de argón, condensador de reflujo y embudo de adición y luego se enfrió en una corriente de argón. Se cargó entonces el matraz con benceno (5 ml) y éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(fenilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxílico 1 (500 mg, 0,857 mmol). La mezcla resultante se sometió a ultrasonidos en argón durante 5 minutos (para eliminar el oxígeno) y luego se calentó hasta reflujo. Se añadió entonces al embudo de adición una solución de hidruro de tri-N-butilestaño (0,459 ml, 1,713 mmol) y 2,2'-azobis(2-metilpropionitrilo (52,0 mg, 0,317 mmol) en benceno desgasificado (5 ml). Se añadieron aproximadamente 2,5 ml de esta solución gota a gota durante un período de aproximadamente 30 minutos y la solución resultante se dejó agitando a reflujo durante 1,5 horas. La solución restante se añadió gota a gota, lentamente durante un período de aproximadamente 30 minutos y se continuó calentando durante otras 1,5 horas. La mezcla se evaporó entonces a presión reducida para eliminar los volátiles. El residuo se suspendió en hexano y se cargó en un cartucho de gel de sílice Biotage y luego se cargó en una columna de gel de sílice equilibrada en hexanos al 100%. El producto eluyó entonces usando un gradiente de etapas de acetato de etilo-hexano: 0 -100%, luego 2-98%, luego 5-95%. Las fracciones homogéneas se reunieron y evaporaron dando un aceite amarillo. Este se colocó en alto vacío durante la noche para dar el compuesto del epígrafe como un aceite color amarillo viscoso. [373 mg, 57%]. El producto se almacenó en nitrógeno en un frigorífico.



13-ciclohexil-6-(4-(etoxicarbonil)-1,3-oxazol-2-il)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo.

Se disolvió 13-ciclohexil-3-(metiloxi)-6-(tributilestannanil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxilato de 1,1-dimetiletilo (266 mg, 0,36 mmol) en 3,4 ml de 1,4-dioxano en un vial de 2 dram (dracma inglés =1,772 gramos). Se disolvió 2-cloorooxazol-4-carboxilato de etilo (83,4 mg, 0,47 mmol) en la reacción seguido por la adición de cloruro de bis(trifenilfosfina)paladio(II) (17,7 mg, 0,025 mmol). La reacción se tapó en nitrógeno y se calentó en un baño de aceite a 100ºC durante 17 horas, después de lo cual la reacción se enfrió y se midió el progreso de la reacción por LC-MS. Se añadió a la mezcla de reacción cloruro de bis(trifenilfosfina)palacio(II) (10mg, 0,014mmol). La reacción se tapó en nitrógeno y se calentó durante otras 5 horas a 100ºC. La reacción se concentró a vacío y el residuo se adsorbió sobre gel de sílice y se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano a acetato de etilo al 2% en diclorometano proporcionando 233 mg de un producto sólido amarillo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,13 - 1,37 (m, 4 H) 1,37 - 1,44 (m, 4 H) 1,46 - 1,55 (m, 1 H) 1,64 (s, 9 H) 1,68 - 1,81 (m, 2 H) 1,83 - 1,98 (m, 3 H) 1,98 - 2,13 (m, 3 H) 2,74 - 2,88 (m, 1 H) 3,91 (s, 3 H)

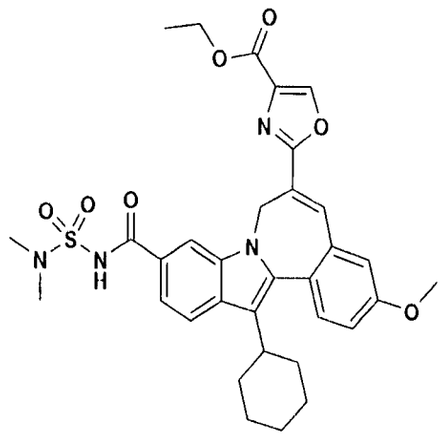
4,34 - 4,48 (m, 3 H) 5,84 - 6,00 (m, 1 H) 7,00 (d, J=2,44 Hz, 1 H) 7,08 (dd, J=8,55, 2,75 Hz, 1 H) 7,53 (d, J=8,85 Hz, 1 H) 7,69 (dd, J=8,55, 1,22 Hz, 1 H) 7,74 (s, 1 H) 7,82 (d, J=8,24 Hz, 1 H) 8,21 (s, 1 H) 8,30 (s, 1 H); LC-MS: HPLC analítica Shimadzu usando software Discovery VP: %A= 10% de metanol, 90% de agua, 0,1% de ácido trifluoracético, %B= 90% de metanol, 10% de agua, 0,1% de ácido trifluoracético; %B inicial= 0; %B final=100; Gradiente= 3 min; Tiempo de ejecución= 5 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Phenomenex Luna 3,0mm x 50mm S10; Tiempo de retención= 3,4 min, MS m/z 583(MH^+).



Ácido 13-ciclohexil-6-[4-(etoxicarbonil)-2-oxazolil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

Se disolvió 13-ciclohexil-6-(4-(etoxicarbonil)-1,3-oxazol-2-il)-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxilato de terc-butilo (109 mg, 0,19 mmol) en 2 ml de 1,2-dicloroetano y se añadieron a la reacción 2 ml de ácido trifluoracético. La reacción se agitó a temperatura ambiente durante 1,5 horas. Se eliminaron los volátiles y el producto se secó a vacío proporcionando 102 mg de un sólido amarillo. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm

1,11 - 1,37 (m, 4 H) 1,42 (t, *J*=7,02 Hz, 4 H) 1,48 - 1,62 (m, 1 H) 1,77 (d, *J*=10,07 Hz, 2 H) 1,86 - 2,13 (m, 4 H) 2,73 - 2,90 (m, 1 H) 2,98 - 3,39 (m, 6 H) 3,92 (s, 3 H) 4,30 - 4,53 (m, 3 H) 5,87 - 6,03 (m, 1 H) 7,02 (d, *J*=2,44 Hz, 1 H) 7,09 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,75 (s, 1 H) 7,79 (dd, *J*=8,39, 1,37 Hz, 1 H) 7,88 (d, *J*=8,55 Hz, 1 H) 8,24 (s, 1 H) 8,50 (s, 1 H); LC-MS: HPLC analítica Shimadzu usando software Discovery VP: %A= 5% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B Inicial= 0; %B Final=100; Gradiente= 2 min; Tiempo de ejecución= 3 min; Caudal= 5 ml/min; Longitud de onda= 220nm; Columna= Phenomenex Luna 3,0mm x 50mm S10; Tiempo de retención= 1,7min, MS m/z 525(MH^+).

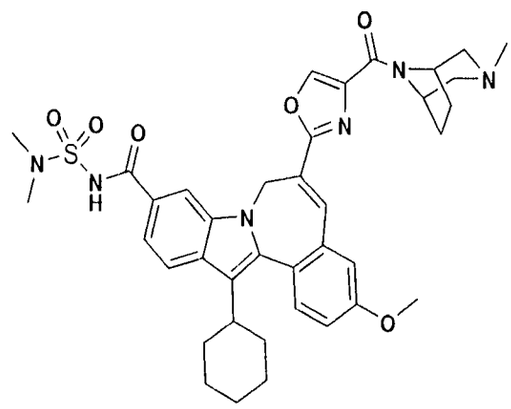


2-(13-Ciclohexil-10-(((dimetilamino)sulfonil)carbamoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il)-1,3-oxazol-4-carboxilato de etilo.

2-(13-Ciclohexil-10-(((dimetilamino)sulfonil)carbamoil)-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-6-il)-1,3-oxazol-4-carboxilato de etilo. Se disolvió ácido 13-ciclohexil-6-[4-(etoxicarbonil)-2-oxazolil]-3-metoxi-7*H*-indolo[2,1-

a][2]benzazepin-10-carboxílico, (115 mg, 0,22 mmol) en 3 ml de THF anhidro y se añadió 1,1'-carbonildiimidazol (61 mg, 0,38 mmol) a la reacción. La reacción se agitó en nitrógeno durante 1 h 20 min a temperatura ambiente luego se calentó hasta reflujo en nitrógeno durante 45 minutos. La reacción se enfrió y se añadió dimetilsulfamida (186 mg, 1,49 mmol) a la reacción seguido por 1,8-diazabiciclo[5.4.0]undec-7-eno (39ul,0,26 mmol) (DBU). La reacción se calentó a 55ºC durante 16 horas en nitrógeno. La reacción se repartió entre diclorometano y fosfato monosódico 0,1M. El extracto de diclorometano se lavó con fosfato monosódico 0,1M y luego se secó sobre sulfato sódico. Los volátiles se eliminaron a vacío proporcionando 167 mg de producto amarillo bruto. La mitad de la muestra bruta se disolvió en una mezcla de acetonitrilo y metanol y se purificó por HPLC preparativa de fase inversa en las siguientes condiciones: HPLC Prep Shimadzu usando software Discovery VP, %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 50; %B final=100; Gradiente= 12 min; Tiempo de ejecución= 17 min; Caudal= 25 ml/min; Longitud de onda= 220 nm; Columna= Waters Sunfire 19mm x 100mm. Tiempo de retención del producto= 12,25 min hasta 17 min (cola debido a solubilidad). Se obtuvieron 25,2 mg de sólido amarillo amorfo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,18 - 1,30 (m, 2 H) 1,34 - 1,46 (m, 5 H) 1,47 - 1,62 (m, 1 H) 1,70 - 1,85 (m, 2 H) 1,86 - 2,21 (m, 4 H) 2,72 - 2,92 (m, 1 H) 3,07 (s, 6 H) 3,92 (s, 3 H) 4,08 - 4,34 (m, 2 H) 4,41 (c, *J*=7,22 Hz, 3 H) 5,75 - 5,99 (m, 1 H) 7,02 (d, *J*=2,75 Hz, 1 H) 7,10 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,45 - 7,65 (m, 2 H) 7,71 (s, 1 H) 7,89 (d, *J*=8,55 Hz, 1 H) 8,20 (s, 1 H) 8,29 (s, 1 H) 9,36 (s, 1 H); LC-MS: HPLC analítica Shimadzu usando software Discovery VP: %A= 5% de acetonitrilo, 95% de agua, Acetato

Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B Inicial= 0; %B Final=100; Gradiente= 2 min; Tiempo de ejecución= 4 min; Caudal= 5 ml/min; Longitud de onda= 220nm; Columna= Phenomenex Luna 3,0mm x 50mm S10; Tiempo de retención= 1,9 min, MS m/z 631 (MH^-), m/z 633(MH^+).

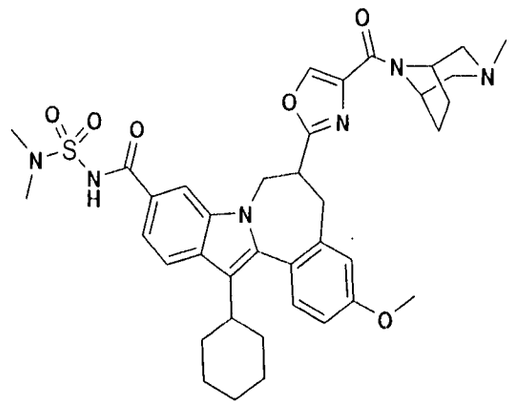


13-ciclohexil-N-((dimetilamino)sulfonil)-3-metoxi-6-(4-((3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil)-1,3-oxazol-2-il)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

Se disolvió 2-(13-ciclohexil-10-(((dimetilamino)sulfonil)carbamoil)-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-6-il)-1,3-oxazol-4-carboxilato de etilo (35,7mg, 0,056mmol) en 0,6 ml de THF en un vial de 2 dram. Se añadió a la reacción hidróxido de tetrabutilamonio (170ul, 0,17 mmol) como una solución 1M en metanol. La reacción se tapó y se agitó durante 3 horas a temperatura ambiente. La reacción se repartió entre ácido clorhídrico 1N y diclorometano. La fase orgánica se lavó con ácido clorhídrico 1N y se secó sobre sulfato sódico. El material se concentró hasta sequedad, se secó a vacío y se usó sin purificación posterior. Se disolvió el producto de hidrólisis (0,056 mmol) en 1 ml de DMF y se añadió TBTU (39 mg, 0,12 mmol). La reacción se agitó a temperatura ambiente en nitrógeno durante aproximadamente 50 minutos y

luego se añadió DMAP (37,9 mg, 0,31 mmol) seguido por diclorhidrato de 3-metil-3,8-diaza-biciclo[3.2.1]octano (23 mg, 0,11 mmol). La reacción se agitó durante 4 horas a temperatura ambiente en atmósfera de nitrógeno hasta su finalización, luego se añadió a 20 ml de agua y se extrajo con diclorometano, se lavó la fase orgánica con agua y se secó sobre sulfato sódico proporcionando 50 mg de producto bruto. El producto se purificó por HPLC prep en las siguientes condiciones: HPLC Preparativa Shimadzu usando software Discovery VP, %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 30; %B final=100; Gradiente= 12 min; Tiempo de ejecución= 20 min; Caudal= 25 ml/min; Longitud de onda= 220 nm; Columna= Waters Sunfire 19mm x 100mm. Tiempo de retención del producto= 6,1min. Las fracciones de producto se concentraron a vacío proporcionando 30,5mg del compuesto del epígrafe como una sal trifluoracetato. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,09 - 1,30 (m, 1 H) 1,31 - 1,61 (m, 3 H) 1,68 - 1,85 (m, 2 H) 1,87 - 2,20 (m, 5 H) 2,26 - 2,44 (m, 2 H) 2,51 - 2,66 (m, 1 H) 2,77 - 2,90 (m, 1 H) 2,91 - 3,01 (m, 3 H) 3,04 (s, 6 H) 3,12 (d, J=11,90 Hz, 1 H) 3,23 (d, J=11,60 Hz, 1 H) 3,78 (d, J=12,21 Hz, 1 H) 3,94 (s, 3 H) 4,24 (d, J=13,12 Hz, 1 H) 4,43 (d, J=14,34 Hz, 1 H) 5,01 (d, J=5,30 Hz, 1 H) 5,13 - 5,47 (m, 1 H) 5,85 (d, J=14,04 Hz, 1 H) 6,02 (s, 1 H) 7,03 (d, J=2,75 Hz, 1 H) 7,12 (dd, J=8,70, 2,59 Hz, 1 H) 7,25 - 7,32 (m, 1 H) 7,56 (d, J=8,55 Hz, 1 H) 7,69 (s, 1 H) 7,88 (d, J=8,24 Hz, 1 H) 8,18 (s, 1 H) 8,28 (s, 1 H) 8,52 (s, 1 H) 11,72 (s, 1 H); LC-MS: HPLC analítica Shimadzu usando software Discovery VP: %A= 5% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B inicial= 0; %B final=100; Gradiente= 2 min; Tiempo de ejecución= 3

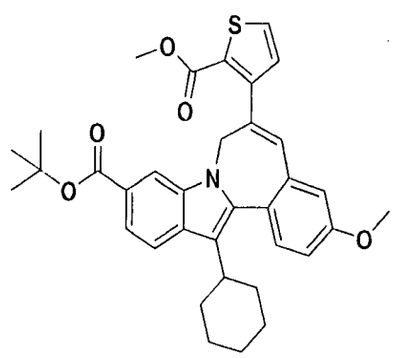
min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Phenomenex Luna 3,0mm x 50mm S10 Tiempo de retención= 1,7 min, MS m/z 711 (MH -), m/z 713(MH+).



13-Ciclohexil-N-((dimetilamino)sulfonil)-3-metoxi-6-(4-((3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil)-1,3-oxazol-2-il)-6,7-dihidro-5H-indolo[2,1-a][2]benzazepin-10-carboxamida.

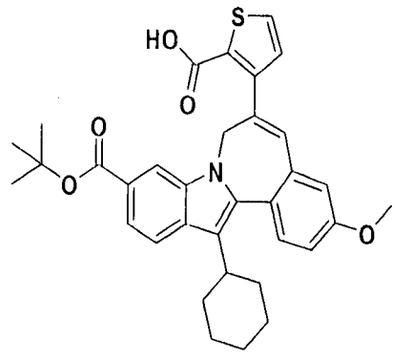
Se disolvió 13-ciclohexil-*N*-((dimetilamino)sulfonil)-3-metoxi-6-(4-((3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil)-1,3-oxazol-2-il)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxamida (26,5mg, 0,037mmol) en 1 ml de THF y se añadieron 0,3 ml de metanol seguido por 10 mg de paladio al 10% sobre carbón. La reacción se colocó en hidrógeno a 1 atmósfera (balón) y se agitó durante 18 horas a temperatura ambiente. La reacción se filtró a través de un lecho corto de Celite y se aclaró con acetonitrilo. Los volátiles se eliminaron del filtrado a vacío y el residuo se disolvió en acetonitrilo y purificó por HPLC Preparativa en las siguientes condiciones: HPLC Prep Shimadzu usando software Discovery VP, %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 30; %B

final=100; Gradiente= 12 min; Tiempo de ejecución= 17 min; Caudal= 25 ml/min; Longitud de onda= 220 nm; Columna= Waters Sunfire 19mm x 100mm. Tiempo de retención del producto= 5,3 minutos. El compuesto del epígrafe se aisló como una sal TFA, se obtuvieron 17,6 mg. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,20 - 1,33 (m, 1,1H) 1,33 - 1,54 (m, 2,1 H) 1,65 (t, *J*=10,99 Hz, 1,1 H) 1,74 - 1,86 (m, 1,9 H) 1,89 - 2,11 (m, 5,6 H) 2,11 - 2,44 (m, 3,0H) 2,71 - 2,86 (m, 3,2 H) 2,87 - 2,98 (m, 2,9 H) 2,98 - 3,10 (m, 7,7 H) 3,08 - 3,45 (m, 6,1 H) 3,72 - 3,83 (m, 0,9 H) 3,82 - 3,93 (m, 3,1 H) 3,92 - 4,00 (m, 0,8 H) 4,05 (dd, *J*=14,80, 5,65 Hz, 0,8 H) 4,55 - 5,12 (m, 2,6 H) 5,60 (d, *J*=12,82 Hz, 0,3 H) 6,64 - 7,12 (m, 2,0 H) 7,29 - 7,62 (m, 1,8 H) 7,77 - 7,97 (m, 1,2 H) 7,97 - 8,45 (m, 1,2 H) 8,55 - 9,33 (m, 0,7 H) 11,70 (s, 0,5 H). LC-MS: HPLC analítica Shimadzu usando software Discovery VP: %A= 5% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B inicial= 0; %B final=100; Gradiente= 3 min; Tiempo de ejecución= 5 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Gemini 4,6mm x 50mm S5; Tiempo de retención= 2,2 min, MS m/z 715(MH^+), m/z 713(MH^-).



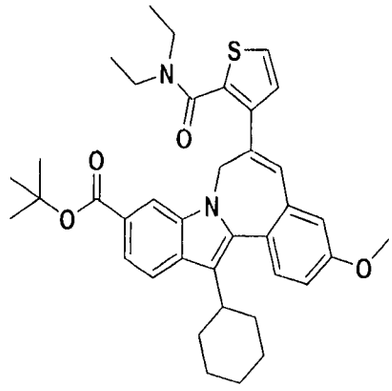
Éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[2-

(metoxicarbonil)-3-tienil]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(tributilestannil)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (140 mg, 0,19 mmol) en 2 ml de 1,4-dioxano junto con 3-bromotiofen-2-carboxilato de metilo (79 mg, 0,36 mmol) en un vial de 2 dram. Se añadió a la reacción dicloruro de bis(trifenilfosfina)paladio (9,2 mg, 0,013 mmol). La reacción se tapó en una atmósfera de nitrógeno y se calentó hasta 100ºC durante 4,5 horas. La reacción se enfrió y se filtró a través de un filtro de jeringa de nailon de 0,45 µm y los volátiles se eliminaron a vacío proporcionando 226 mg de un aceite amarillo. El compuesto del epígrafe se purificó por cromatografía sobre gel de sílice eluyendo con hexanos al 30% en diclorometano proporcionando 73 mg (66%) de producto. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,92 (t, J=7,32 Hz, 2 H) 1,24 - 1,44 (m, 6 H) 1,57 (s, 9 H) 1,58 - 1,71 (m, 2 H) 1,77 (d, J=8,85 Hz, 2 H) 1,85 - 1,99 (m, 1 H) 2,00 - 2,17 (m, 3 H) 2,83 - 2,93 (m, 1 H) 3,82 (s, 3 H) 3,88 (s, 3 H) 4,71 (s, 1 H) 5,10 (s, 1 H) 6,80 (s, 1 H) 6,83 (d, J=4,88 Hz, 1 H) 6,90 (d, J=2,75 Hz, 1 H) 7,01 (dd, J=8,55, 2,75 Hz, 1 H) 7,40 (d, J=5,19 Hz, 1 H) 7,51 (d, J=8,85 Hz, 1 H) 7,63 (dd, J=8,55, 1,22 Hz, 1 H) 7,82 (d, J=8,55 Hz, 1 H) 7,88 (s, 1 H); LC-MS: HPLC analítica Shimadzu usando software Discovery VP: %A= 10% de metanol, 90% de agua, 0,1% de ácido trifluoracético %B= 90% de metanol, 10% de agua, 0,1% de ácido trifluoracético; %B inicial= 0; %B final=100; Gradiente= 2 min; Tiempo de ejecución= 5 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Phenomenex Luna 3,0mm x 50mm S10; Tiempo de retención= 2,95 min, 2,95 min, MS m/z 584(MH^+).



Éster 10-(1,1-dimetiletílico) del ácido 6-(2-carboxi-3-tienil)-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

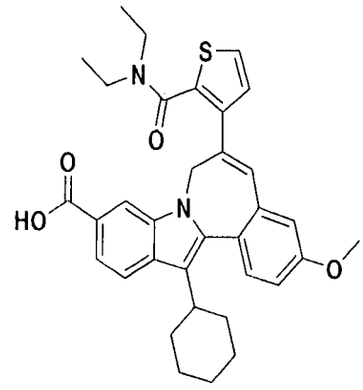
Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[2-(metoxicarbonil)-3-tienil]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico, (65 mg, 0,11 mmol) en 1 ml de THF en un vial de 2 dram. A esta solución se añadió hidróxido de tetrabutilamonio 1,0M (0,33 ml, 0,33 mmol) en metanol. La reacción se tapó y se agitó a temperatura ambiente durante 3 horas, luego se controló por HPLC. Se añadió más hidróxido de tetrabutilamonio 1,0 M (0,10 ml, 0,1mmol) en metanol a la reacción y la reacción se tapó a temperatura ambiente durante otras 21 horas. La reacción se repartió entre diclorometano y ácido cítrico 0,1M. La fase acuosa se extrajo con diclorometano y los extractos orgánicos se reunieron y se secaron sobre sulfato sódico. Los volátiles se eliminaron a vacío proporcionando 72 mg de producto bruto. Usando Discovery VP Software: %A= 5% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B inicial= 0; %B final=100; Gradiente= 3 min; Tiempo de ejecución= 5 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Phenomenex Luna 3,0mm x 50mm S10; Tiempo de retención= 2,50min, MS m/z 570(MH^+).



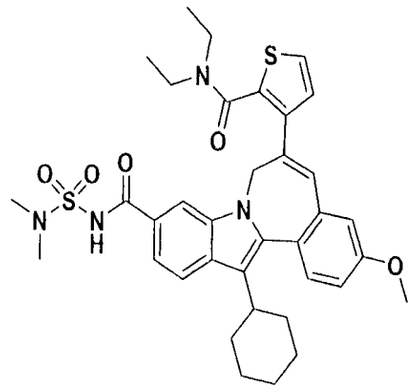
Éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[2-[(dietilamino)carbonil]-3-tienil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

Se disolvió éster 10-(1,1-dimetiletílico) del ácido 6-(2-carboxi-3-tienil)-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico, (36 mg, 0,063 mmol) en 0,7 ml de DMF anhidro y se añadió TBTU (36,5 mg, 0,114 mmol) a la reacción. La reacción se tapó en nitrógeno y se agitó a temperatura ambiente durante 1,5 horas. Se disolvió entonces DMAP (29 mg, 0,24 mmol) en la reacción y luego se añadió dietilamina (26 ul, 0,25 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó durante 21 horas a temperatura ambiente. La reacción se añadió a 15 ml de agua y la suspensión acuosa se extrajo con diclorometano. La fase orgánica se lavó secuencialmente con ácido cítrico 0,1M, agua y se secó sobre sulfato sódico, se filtró y los volátiles se eliminaron a vacío proporcionando un aceite ámbar. LC-MS: HPLC analítica Shimadzu usando software Discovery VP: %A= 10% de metanol, 90% de agua, 0,1% de ácido trifluoracético %B= 90% de metanol, 10% de agua, 0,1% de ácido trifluoracético; %B inicial= 50; %B final=100; Gradiente= 5 min; Tiempo de ejecución= 6 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna=

Phenomenex Luna 3,0mm x 50mm S10; Tiempo de retención= 4,64 min, MS m/z 625(MH^+), 647$(M+Na)^+$.

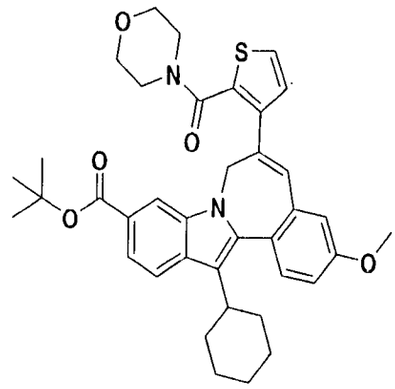


Ácido 13-ciclohexil-6-[2-[(dietilamino)carbonil]-3-tienil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[2-[(dietilamino)carbonil]-3-tienil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (39 mg, 0,06 mmol) en 1 ml de 1,2-dicloroetano y se añadió 1 ml de ácido trifluoracético. La reacción se agitó a temperatura ambiente durante 2 horas y luego se eliminaron los volátiles a vacío. El producto de reacción se disolvió repetidamente en benceno y los volátiles se eliminaron a vacío para ayudar a la eliminación del TFA residual. El peso del producto fue 39 mg como un sólido amorfo. Usando Discovery VP Software: %A= 5% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B inicial= 0; %B final=100; Gradiente= 3 min; Tiempo de ejecución= 5 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Phenomenex Luna 3,0mm x 50mm S10; Tiempo de retención= 2,31min, MS m/z 569(MH^+).



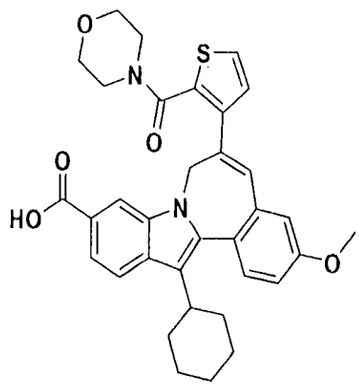
13-Ciclohexil-6-[2-[(dietilamino)carbonil]-3-tienil]-N-[(dimetilamino)sulfonil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. Se disolvió ácido 13-ciclohexil-6-[2-[(dietilamino)carbonil]-3-tienil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (36,7 mg, 0,064 mmol) en THF (1ml) y se añadió carbonildiimidazol (19 mg, 0,117 mmol) a la reacción. La reacción se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 1,5 horas. La reacción se calentó entonces hasta 60ºC durante 1,5 horas, luego se enfrió y se añadió dimetilsulfamida (55 mg, 0,444 mmol) a la reacción seguido por DBU (13,3 ul, 0,089 mmol). La reacción se tapó en una atmósfera de nitrógeno y se calentó a 65ºC hasta 70ºC durante la noche. La reacción se enfrió y luego se repartió entre diclorometano y ácido clorhídrico acuoso 1N. La fase acuosa se volvió a extraer con diclorometano y se reunieron las fases orgánicas y se lavaron secuencialmente con ácido clorhídrico acuoso 1N, NaH_2PO_4 0,1M acuoso. La fase de diclorometano se secó sobre sulfato sódico, se filtró y se eliminaron los volátiles a vacío proporcionando 47 mg de película marrón. La muestra se disolvió en acetonitrilo / DMF (1:1) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de

elución emplearon un caudal de 25 ml / min, un gradiente de 50% de disolvente A / 50% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El disolvente se eliminó de la fracción de producto a vacío proporcionando 18,1mg de sólido amarillo amorfo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,53 (s ancho, 3 H) 0,96 (s ancho, 3 H) 1,04 - 1,44 (m, 4 H) 1,51 (d, J=10,07 Hz, 1 H) 1,78 (d, J=9,46 Hz, 2 H) 1,88 - 2,13 (m, 4 H) 2,40 - 2,52 (m, 1 H) 2,80 - 2,97 (m, 3 H) 3,05 (s, 6 H) 3,57 (s ancho, 1 H) 3,89 (s, 3 H) 4,49 (d, J=14,65 Hz, 1 H) 5,20 (d, J=14,04 Hz, 1 H) 6,93 (d, J=2,75 Hz, 1 H) 6,98 (s, 1 H) 7,02 (dd, J=8,70, 2,59 Hz, 1 H) 7,11 (d, J=5,19 Hz, 1 H) 7,38 (d, J=4,88 Hz, 1 H) 7,41 - 7,52 (m, 2 H) 7,86 (d, J=8,55 Hz, 1 H) 8,01 (s, 1 H) 9,18 (s, 1 H); Tiempo de retención LC-MS 2,19 min; 673 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



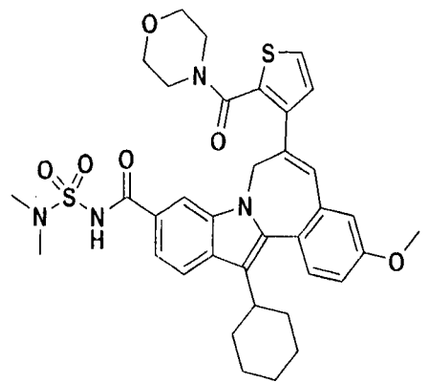
13-Ciclohexil-3-metoxi-6-(2-(4-morfolinilcarbonil)-3-tienil)-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo. En un vial de 2 dram, se disolvió éster 10-(1,1-dimetiletílico) del ácido 6-(2-carboxi-3-tienil)-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (33,7 mg, 0,059 mmol) y tetrafluorborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (34,2 mg, 0,106 mmol) en DMF (0,7 ml) dando una solución amarillo transparente. La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 1 hora 20 minutos. Se disolvió DMAP (28,9 mg, 0,237 mmol) en la reacción y luego se añadió morfolina (10,5 µl, 0,121 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 2 días. Se vertió la reacción en 15 ml de agua. Se formó un precipitado amarillo pálido. Se extrajo en diclorometano. Se lavó la solución de diclorometano con ácido cítrico acuoso 0,1M, se volvió a extraer el extracto acuoso usando diclorometano. Las fases de diclorometano reunidas se lavaron 1x con agua y se secaron sobre sulfato sódico. Los volátiles se eliminaron a vacío proporcionando 45 mg del producto del título como un aceite amarillo. LC-MS: HPLC analítica Shimadzu usando software Discovery VP: %A= 10% de metanol, 90% de agua, 0,1% de ácido trifluoracético %B= 90% de metanol,

10% de agua, 0,1% de ácido trifluoracético; %B inicial= 50; %B final=100; Gradiente= 6 min; Tiempo de ejecución= 6 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Phenomenex Luna 3,0mm x 50mm S10; Tiempo de retención= 4,38 min, MS m/z 639(MH^+).



Ácido 13-ciclohexil-3-metoxi-6-(2-(4-morfolinilcarbonil)-3-tienil)-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. En un vial de 2 dram, se disolvió 13-ciclohexil-3-metoxi-6-(2-(4-morfolinilcarbonil)-3-tienil)-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo (37,7 mg, 0,059 mmol) en 1,2-dicloroetano (1 ml) y se añadió TFA (1 ml, 12,98 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 1,5 horas. Se transfieren los contenidos de la reacción a un matraz en forma de pera de 25 ml usando benceno para aclarar. Los volátiles se eliminan a vacío. El producto se disuelve en benceno y se trata por evaporación rotatoria para ayudar a eliminar las trazas de TFA. Se obtienen 41 mg del compuesto del epígrafe como una película marrón amarillo. Se obtuvo una LC-MS para confirmar el producto y el producto se usó en la etapa siguiente sin purificación

posterior. LC-MS: HPLC Analítica Shimadzu usando software Discovery VP: %A= 5% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B inicial= 0; %B final=100; Gradiente= 3 min; Tiempo de ejecución= 5 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Waters Xterra, 3mm x 50mm, S7. Tiempo de retención= 1,73 min, MS m/z 583(MH^+), m/z 581$(M-H)^-$.



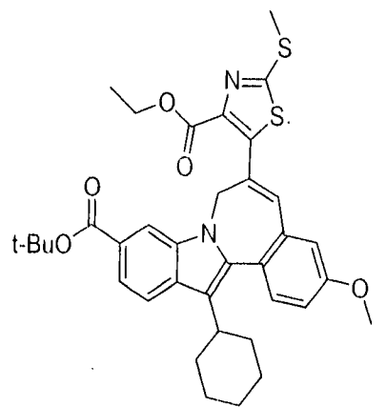
13-Ciclohexil-N-(dimetilsulfamoil)-3-metoxi-6-(2-(4-morfolinilcarbonil)-3-tienil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

En un vial de 2 dram, se disuelve ácido 13-ciclohexil-3-metoxi-6-(2-(4-morfolinilcarbonil)-3-tienil)-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (38 mg, 0,065 mmol) en 1 ml de THF anhidro y se añade CDI (19,03 mg, 0,117 mmol) a la reacción. La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante aproximadamente 1 hora. La reacción se tapó caliente en nitrógeno a 65ºC durante 1 hora, luego se enfrió hasta temperatura ambiente y se añadió a la reacción N,N-dimetilsulfamida (44,3 mg, 0,357 mmol) y luego DBU (13,8 µl, 0,092 mmol). La reacción se tapó y se calentó en nitrógeno durante la noche a 65ºC. El análisis de una alícuota por LC-MS indicó

que la reacción estaba incompleta. Se añadió a la reacción más dimetilsulfamida (19 mg, 0,153 mmol) y DBU (13,8ul, 0,092 mmol). La reacción se tapó en una atmósfera de nitrógeno y se calentó a 69°C durante 3,25 horas. El análisis de la reacción por LC-MS indicó que la reacción estaba completa. La reacción se repartió entre diclorometano y ácido clorhídrico acuoso 1N. La fase acuosa se extrajo con diclorometano. Las fases orgánicas se reunieron y se lavaron secuencialmente con ácido clorhídrico acuoso 1N y luego dihidrógenofosfato sódico 0,1M (NaH_2PO_4) y se secó sobre sulfato sódico. Los volátiles se eliminaron a vacío dando un aceite amarillo/película. El compuesto del epígrafe bruto se secó a vacío durante la noche a temperatura ambiente. El peso del producto bruto es 43 mg como un sólido amarillo/marrón. Se disuelve en una mezcla de acetonitrilo y DMF y se purifica por HPLC de fase inversa en las siguientes condiciones: HPLC Preparativa Shimadzu usando software Discovery VP, %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 50; %B final=100; Gradiente= 15 min; Tiempo de ejecución= 25 min; Caudal= 25 ml/min; Longitud de onda= 220 nm; Columna= Waters Sunfire 19mm x 100mm. Tiempo de recogida del producto= 9,72 min. a 10,49 min. Los volátiles se eliminaron a vacío de la fracción de producto proporcionando 14,2 mg del compuesto del epígrafe como un sólido amarillo. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,17 - 1,30 (m, 1 H) 1,32 - 1,50 (m, 2 H) 1,55 (d, *J*=11,29 Hz, 1 H) 1,78 (d, *J*=10,99 Hz, 2 H) 1,90 - 2,16 (m, 4 H) 2,42 - 2,58 (m, 1 H) 2,60 - 2,86 (m, 4 H) 2,85 - 2,94 (m, 2 H) 2,95 - 3,04 (m, 2 H) 3,06 (s, 6 H) 3,10 - 3,30 (m, 1 H) 3,91 (s, 3 H) 4,56 (d, *J*=14,65 Hz, 1 H) 5,09 (d, *J*=14,65 Hz, 1 H) 6,87 (s, 1 H) 6,93 (d, *J*=2,75 Hz, 1 H) 7,05 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,08 (d, *J*=4,88 Hz, 1 H)

7,45 (d, *J*=4,88 Hz, 1 H) 7,47 - 7,54 (m, 2 H) 7,83 (s, 1 H) 7,91 (d, *J*=8,55 Hz, 1 H) 9,59 (s, 1 H). LC-MS: HPLC Analítica Shimadzu usando software Discovery VP: %A= 4% de acetonitrilo, 95% de agua, Acetato Amónico 10 mmol; %B= 95% de acetonitrilo, 5% de agua, Acetato Amónico 10 mmol; %B inicial= 0; %B final=100; Gradiente= 3 min; Tiempo de ejecución= 5 min; Caudal= 5 ml/min; Longitud de onda= 220 nm; Columna= Waters Xterra, 3mm x 50mm, S7. Tiempo de retención= 2,05min min, MS m/z 689 (MH^+), m/z 687 $(M-H)^-$.

éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-2-(metiltio)-5-tiazolil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico



Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(tributilestannil)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (203 mg, 0,277 mmol) en 1,4-dioxano (2,7 ml)) en un recipiente de microondas tapado de 2-5 ml con barra de agitación magnética. Se añadió a la reacción 5-bromo-2-(metiltio)tiazol-4-carboxilato de etilo (171 mg, 0,606 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (14,9 mg, 0,021 mmol). La reacción se tapó en una atmósfera de nitrógeno y se calentó hasta 100°C durante 17,5 horas. El análisis HPLC de la reacción indicó solo aproximadamente 45% de conversión del

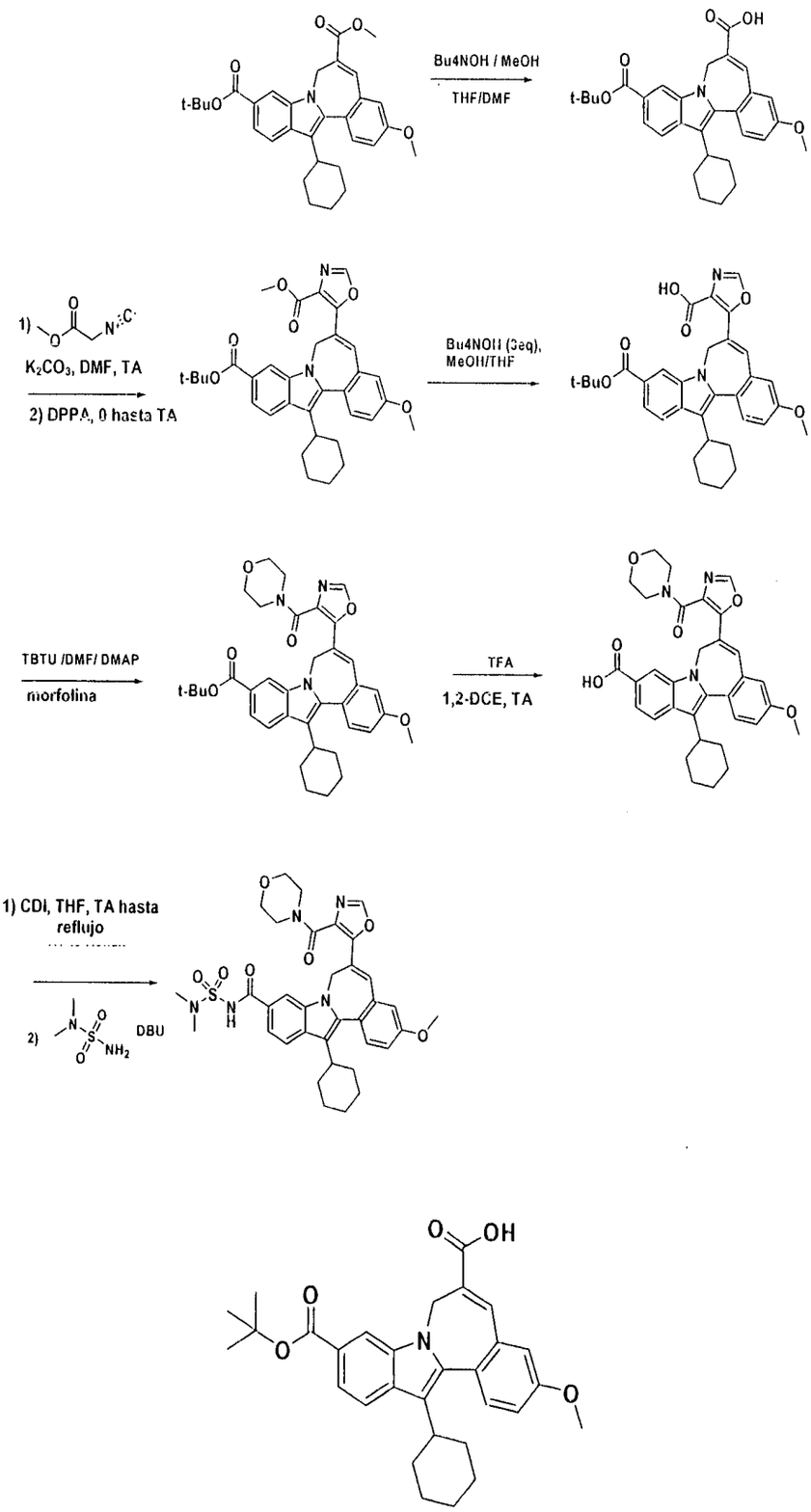
material de partida. Se añadió más cloruro de bis(trifenilfosfina)paladio(II) catalizador (5,7 mg) a la reacción y ésta se calentó en atmósfera de nitrógeno a 110°C durante 23 horas. Se eliminaron los volátiles de la mezcla de reacción a vacío y se disolvió la mezcla de reacción bruta en una mezcla de 8 ml de DMF/acetonitrilo y se purificó como cuatro inyecciones de 2 ml usando HPLC de fase inversa. La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu usando software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo y DMF y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 30 ml / min, un gradiente de 40% de disolvente A / 60% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. Tiempo de retención del producto= 26,6 min. Los volátiles de las fracciones de producto se eliminaron a vacío usando un SpeedVac en posición de calentamiento medio.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,16 - 1,26 (m, 1 H) 1,30 (t, *J*=7,02 Hz, 3 H) 1,33 - 1,56 (m, 3 H) 1,60 (s, 10 H) 1,63 - 1,83 (m, 5 H) 1,94 (s ancho, 1 H) 1,98 - 2,16 (m, 3 H) 2,71 (s, 3 H) 2,82 - 2,92 (m, 1 H) 3,90 (s, 3 H) 4,28 (c, *J*=7,02 Hz, 2 H) 4,53 (d, *J*=14,95 Hz, 1 H) 5,52 (d, *J*=14,65 Hz, 1 H) 6,98 (d, *J*=2,75 Hz, 1 H) 7,03 (dd, *J*=8,85, 2,75 Hz, 1 H) 7,49 - 7,54 (m, 2 H) 7,65 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,81 (d, *J*=8,55 Hz, 1 H) 8,13 (d, *J*=1,22 Hz, 1

H).

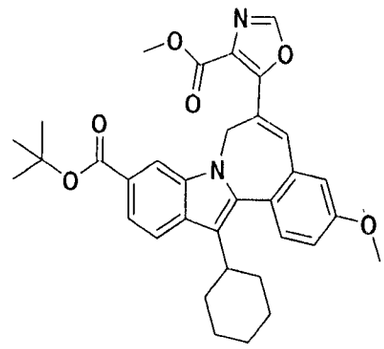
Tiempo de retención LC-MS 3,08 min; 645 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

El esquema mostrado a continuación es ilustrativo de los procedimientos que se pueden usar para preparar intermedios y compuestos.


Bu4NOH / MeOH
THF/DMF
1) K2CO3, DMF, TA
2) DPPA, 0 hasta TA
Bu4NOH (3eq), MeOH/THF
TBTU /DMF/ DMAP
morfolina
TFA
1,2-DCE, TA
1) CDI, THF, TA hasta reflujo
2)
DBU

Ácido 10-(terc-butoxicarbonil)-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-carboxílico. Se disuelve 6-metil13-ciclohexil-3-(metiloxi)-7*H*-indolo[2,1-*a*][2]benzazepin-6,10-dicarboxilato de 10-(1,1-dimetiletílico) (5,53 g, 11,02 mmol) en THF (70 ml) con calentamiento, se añade DMF (20 ml) para mantener la solubilidad, dejando enfriar hasta temperatura ambiente y luego se añade hidróxido de tetrabutilamonio (33,1 ml, 33,1 mmol) 1,0M en metanol. La reacción se agita a temperatura ambiente durante 2 horas y luego se añade ácido clorhídrico 0,1N a la reacción seguido por NaH_2PO_4 acuoso 0,1M. Se separan las fases, se lava la fase orgánica secuencialmente con ácido clorhídrico acuoso 1,0N, NaH_2PO_4 acuoso 0,1M. Se vuelve a extraer la fase acuosa 1x usando acetato de etilo. Se combinan las fracciones de acetato de etilo y se lavan secuencialmente con NaH_2PO_4 acuoso 0,1M y salmuera. Se seca sobre sulfato de magnesio, se filtra y se eliminan los disolventes a vacío proporcionando un sólido amarillo brillante. Se seca el producto a vacío a temperatura ambiente dando 5,21 g (97%). RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,12 - 1,28 (m, 2 H) 1,28 - 1,45 (m, 2 H) 1,46 - 1,60 (m, 2 H) 1,63 (s, 9 H) 1,66 - 1,96 (m, 4 H) 1,96 - 2,16 (m, 3 H) 2,76 - 2,84 (m, 1 H) 3,91 (s, 3 H) 4,18 (s ancho, 1 H) 5,66 (s ancho, 1 H) 7,00 (d, *J*=2,44 Hz, 1 H) 7,10 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 (d, *J*=8,54 Hz, 1 H) 7,65 - 7,71 (m, 1 H) 7,82 (d, *J*=8,24 Hz, 1 H) 7,93 (s, 1 H) 8,22 (s, 1 H). Tiempo de retención LC-MS 1,47 min; 486 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta

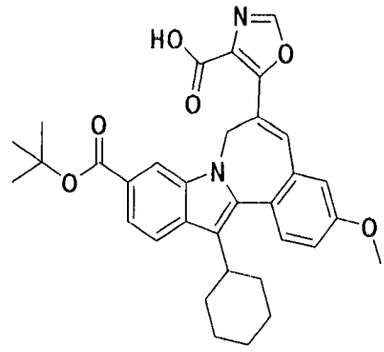
0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-Ciclohexil-3-metoxi-6-(4-(metoxicarbonil)-1,3-oxazol-5-il)-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo. Se disolvió ácido 10-(*terc*-butoxicarbonil)-13-ciclohexil-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-6-carboxílico (1,00 g, 2,051 mmol) en DMF (10 ml) y se añadió carbonato potásico (0,624 g, 4,51 mmol) a la reacción seguido por isocianoacetato de metilo (0,24 ml, 2,64 mmol). La reacción se agitó en una atmósfera de nitrógeno a temperatura ambiente durante aproximadamente 5 minutos y luego se enfrió hasta 0ºC. Se añadió lentamente azida de difenilfosforilo (0,5 ml, 2,320 mmol) a la reacción durante 10 minutos. La reacción se agitó a 0ºC en una atmósfera de nitrógeno y se dejó calentar lentamente hasta temperatura ambiente durante la noche. Se diluyó la reacción con 100 ml de

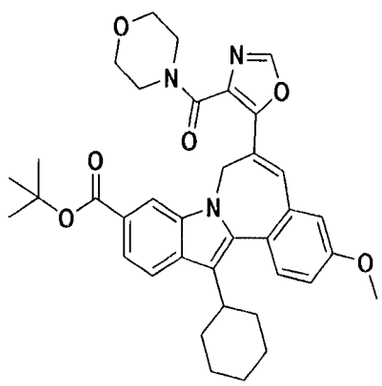
benceno/acetato de etilo (1:1) y se lavó con agua. Se volvió a extraer la fase acuosa usando acetato de etilo. Los orgánicos se reunieron y se lavaron sucesivamente con ácido cítrico acuoso 0,1M, bicarbonato sódico acuoso saturado y luego salmuera y se secaron sobre sulfato de magnesio. Se filtró y los volátiles se eliminaron a vacío. Se sometió a cromatografía en 43,4 g de suspensión de gel de sílice rellena en acetato de etilo al 5% /diclorometano. Se eluyó con acetato de etilo al 5% / diclorometano. La combinación de las fracciones de producto puro y eliminación de volátiles a vacío proporcionó 215 mg de sólido amarillo amorfo. La combinación de las fracciones menos puras proporcionó otros 189 mg de producto con pureza mayor que 92%. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,11 - 1,29 (m, 2 H) 1,30 - 1,48 (m, 3 H) 1,57 (s, 2 H) 1,61 (s, 10 H) 1,69 - 1,80 (m, 2 H) 1,86 - 1,98 (m, 1 H) 1,99 - 2,13 (m, 4 H) 2,76 - 2,90 (m, 1 H) 3,92 (s, 3 H) 3,98 (s, 3 H) 4,47 (d, *J*=12,82 Hz, 1 H) 5,84 (d, *J*=14,65 Hz, 1 H) 7,02 (d, *J*=2,44 Hz, 1 H) 7,07 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 (d, *J*=8,55 Hz, 1 H) 7,65 - 7,71 (m, 1 H) 7,82 (d, *J*=8,24 Hz, 1 H) 7,87 (s, 1 H) 8,08 (s, 1 H) 8,16 (s, 1 H). Tiempo de retención LC-MS 2,75 min; m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 0 min y un tiempo de análisis de 3 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los

datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



Ácido 5-(10-(terc-butoxicarbonil)-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il)-1,3-oxazol-4-carboxílico. Se disolvió 13-ciclohexil-3-metoxi-6-(4-(metoxicarbonil)-1,3-oxazol-5-il)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxilato de terc-butilo (205 mg, 0,360 mmol) en THF (3,0ml) y se añadió a la reacción hidróxido de tetrabutilamonio (1,1 ml, 1,100 mmol) (1,0M en metanol). La reacción se tapó y se agitó a temperatura ambiente durante 2 horas. Se añadió una solución acuosa NaH_2PO_4 0,1M a la reacción seguido por ácido clorhídrico acuoso 0,1N. El producto se extrajo en acetato de etilo y la fase orgánica se lavó secuencialmente con ácido clorhídrico acuoso 0,1N, NaH_2PO_4 acuoso 0,1M, salmuera y se secó sobre sulfato de magnesio. La solución de producto se filtró, se eliminó el disolvente y se secó el producto a vacío proporcionando 191 mg de un sólido amarillo. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,77 - 0,94 (m, 1 H) 1,12 - 1,31 (m, 3 H) 1,30 - 1,59 (m, 5 H) 1,62 (s, 9 H) 1,76 (d, *J*=11,29 Hz, 2 H) 1,87 - 2,18 (m, 4 H) 2,76 - 2,90 (m, 1 H) 3,91 (s, 3 H) 4,45 (d, *J*=14,04 Hz, 1 H) 6,03 (d, *J*=12,21 Hz, 1 H) 7,03

(d, *J*=2,44 Hz, 1 H) 7,08 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 (d, *J*=8,85 Hz, 1 H) 7,68 (d, *J*=8,24 Hz, 1 H) 7,82 (d, *J*=8,55 Hz, 1 H) 7,91 (s, 1 H) 8,21 (d, *J*=5,80 Hz, 2 H). Tiempo de retención LC-MS 1,86 min; m/z 553 (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

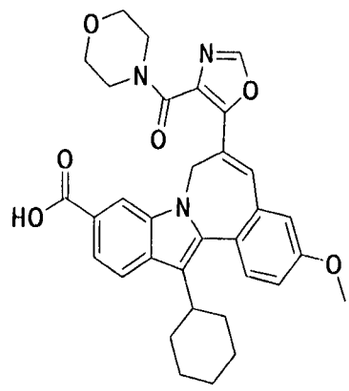


13-Ciclohexil-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo.

Se disolvió ácido 5-(10-(*terc*-butoxicarbonil)-13-ciclohexil-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-6-il)-1,3-oxazol-4-carboxílico (185 mg, 0,334 mmol)

en DMF (3,2 ml) y se añadió tetrafluorborato de O-benzotriazol-1-il-N,N,N',N'-tetra-metiluronio (193 mg, 0,600 mmol). La reacción se agitó tapada a temperatura ambiente durante 25 minutos y se disolvió DMAP (163 mg, 1,334 mmol) en la reacción y luego se añadió morfolina (0,058 ml, 0,667 mmol). La reacción se tapó y se agitó a temperatura ambiente durante la noche. La reacción se vertió en 30 ml de agua y se extrajo con diclorometano. La fase orgánica se lavó secuencialmente con ácido cítrico acuoso 0,1M, NaH_2PO_4 acuoso 0,1M, luego se secó sobre sulfato sódico anhidro. La muestra se filtró, se eliminaron los volátiles y se secó la muestra a vacío obteniendo 227 mg de un sólido naranja amorfo. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,16 - 1,50 (m, 7 H) 1,53 - 1,61 (m, 6 H) 1,62 (s, 10 H) 1,76 (d, *J*=10,38 Hz, 2 H) 1,83 - 2,15 (m, 5 H) 3,40 - 3,84 (m, 7 H) 3,83 - 3,95 (m, 5 H) 4,40 (d, *J*=11,60 Hz, 1 H) 5,64 (d, *J*=12,21 Hz, 1 H) 6,97 (d, *J*=2,75 Hz, 1 H) 7,05 (dd, *J*=8,39, 2,59 Hz, 1 H) 7,50 (d, *J*=8,55 Hz, 1 H) 7,53 (s, 1 H) 7,65 (d, *J*=8,24 Hz, 1 H) 7,77 - 7,86 (m, 2 H) 7,97 - 8,04 (m, 1 H) 8,10 (s, 1 H). Tiempo de retención LC-MS 2,64 min m/z 624 (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 2 min y un tiempo de análisis de 5 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una

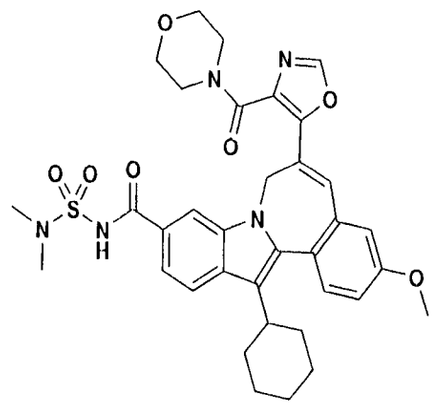
plataforma Micromass para LC en modo electronebulización.



*Ácido 13-ciclohexil-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-*7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

Se disolvió 13-ciclohexil-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo (203 mg, 0,325 mmol) en 1,2-dicloroetano (3 ml) y se añadió TFA (3 ml, 38,9 mmol). La reacción se tapó en una atmósfera de nitrógeno a 25ºC durante 2 horas. Se eliminaron los volátiles de la reacción a vacío y el residuo se disolvió en 80 ml de acetato de etilo con calentamiento. La solución se lavó con ácido clorhídrico acuoso 1N (2x40 ml), salmuera y se secó sobre sulfato de magnesio. La solución de producto se filtró, se eliminaron los volátiles y la muestra se secó a vacío a temperatura ambiente durante la noche dando 179 mg (97%) de un sólido amarillo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,74 - 1,03 (m, 4 H) 1,06 - 1,31 (m, 6 H) 1,32 - 1,50 (m, 3 H) 1,56 (d, *J*=9,16 Hz, 2 H) 1,77 (d, *J*=8,85 Hz, 2 H) 1,86 - 2,18 (m, 5 H) 2,83 - 2,91 (m, 1 H) 3,60 (s, 3 H) 3,64 - 3,89 (m, 4 H) 3,88 - 3,93 (m, 4 H) 3,95 - 4,08 (m, 1 H) 4,43 (d, *J*=15,56 Hz, 1 H) 5,64 (d, *J*=14,95 Hz, 1 H) 6,99 (d, *J*=2,75 Hz, 1 H) 7,07 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,48 - 7,56 (m, 2 H) 7,85 - 7,94 (m, 2 H) 8,15 (s, 1 H). Tiempo de retención

LC-MS 1,65 min; 568 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

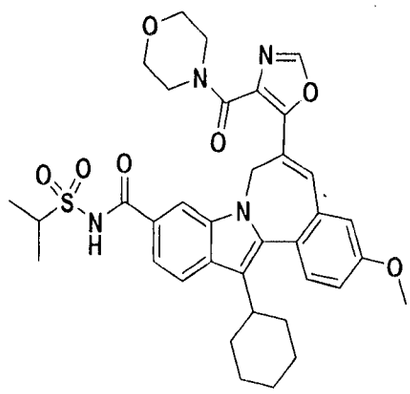


13-Ciclohexil-N-(dimetilsulfamoil)-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

En un vial de 2 dram, se añadió a la reacción ácido 13-ciclohexil-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (40 mg, 0,070 mmol) en THF (1 ml) y CDI (23,8 mg, 0,147 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó a

temperatura ambiente durante 1 hora. La reacción se calentó entonces a 60ºC durante 1 hora, se enfrió y se añadió N,N-dimetilsulfamida (46,5 mg, 0,375 mmol) a la reacción seguido por DBU (0,014 ml, 0,092 mmol). La reacción se tapó en una atmósfera de nitrógeno y se calentó durante la noche (16 horas) a 60ºC. La reacción se controló por HPLC y se añadieron más N,N-dimetilsulfamida (22,9 mg, 0,184 mmol) y DBU (0,015 ml, 0,099 mmol) y la reacción se calentó hasta 70ºC en una atmósfera de nitrógeno durante 5 horas. La mezcla de reacción se repartió entre ácido clorhídrico acuoso 1N y diclorometano. La fase orgánica se lavó secuencialmente con ácido clorhídrico acuoso 1N y NaH_2PO_4 acuoso 0,1M y se secó sobre sulfato sódico. El disolvente se eliminó a vacío proporcionando 46 mg de producto bruto. El compuesto del epígrafe se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP y que está conectado con un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 12 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,05 - 1,28 (m, 1,2 H) 1,29 - 1,62 (m, 3,7 H) 1,64 - 1,84 (m, 4,0 H) 1,84 - 2,20 (m, 4,6 H) 2,47 (d, *J*=14,04 Hz, 0,1 H) 2,78

- 2,88 (m, 1,1 H) 3,04 (s, 5,9 H) 3,10 (s, 0,9 H) 3,35 - 3,89 (m, 9,0 H) 3,91 (s, 3,0 H) 4,09 (s, 0,4 H) 4,18 (d, *J*=1,83 Hz, 0,9 H) 4,41 (d, *J*=15,56 Hz, 0,9 H) 4,55 (d, *J*=16,48 Hz, 0,1 H) 5,59 (d, *J*=14,95 Hz, 0,9 H) 6,62 (d, *J*=14,34 Hz, 0,1 H) 6,97 (d, *J*=2,44 Hz, 1,0 H) 7,07 (dd, *J*=8,70, 2,59 Hz, 1,0 H) 7,27 - 7,36 (m, 0,3 H) 7,46 - 7,54 (m, 1,9 H) 7,59 (d, *J*=8,55 Hz, 0,9 H) 7,75 (d, *J*=7,93 Hz, 0,1 H) 7,82 (s, 1,0 H) 7,87 (d, *J*=8,54 Hz, 0,9 H) 8,15 (s, 0,1 H) 8,28 - 8,35 (m, 0,2 H) 8,44 (s, 0,9 H) 8,94 (d, *J*=9,16 Hz, 0,1 H) 9,43 (s, 0,9 H) 9,88 (s, 0,1 H) 12,11 (s, 0,1 H). Tiempo de retención LC-MS 1,40min; 672 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

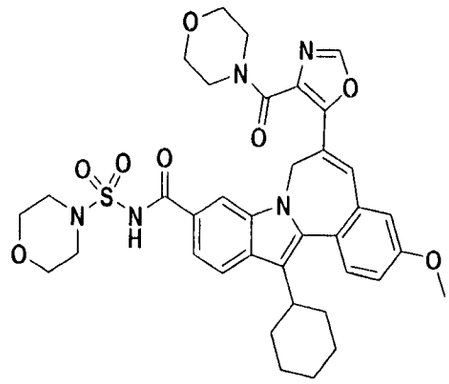


13-ciclohexil-N-(isopropilsulfonil)-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

Se disolvió ácido 13-ciclohexil-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico (40,8 mg, 0,072 mmol) en THF (1ml) y se añadió CDI (26 mg, 0,160 mmol) a la reacción. La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 50 min y luego se calentó en un baño de aceite a 60°C durante 1,5 horas. La reacción se enfrió y se añadió propano-2-sulfonamida (46 mg, 0,373 mmol) a la reacción seguido por DBU (0,022 ml, 0,144 mmol). La reacción se tapó en una atmósfera de nitrógeno y se calentó a 65°C durante la noche (16 horas). La reacción se repartió entre diclorometano y ácido clorhídrico acuoso 1,0N. La fase orgánica se lavó secuencialmente con ácido clorhídrico acuoso 1N, NaH_2PO_4 acuoso 0,1M. La fase orgánica se secó sobre sulfato sódico y se eliminó el disolvente a vacío proporcionando 50 mg de sólido amarillo amorfo. El compuesto del epígrafe se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) y se purificó usando una columna de 5 um 19mm x 100 mm Waters

Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 12 minutos con un tiempo de ejecución de 15 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. La eliminación de disolventes y secado a vacío proporcionó 28,3 mg de un sólido amarillo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,15 - 1,28 (m, 1,2 H) 1,29 - 1,60 (m, 10,9 H) 1,59 - 1,85 (m, 6,7 H) 1,86 - 2,15 (m, 4,7 H) 2,73 - 2,87 (m, 1,0 H) 3,37 - 3,50 (m, 1,4 H) 3,51 - 3,89 (m, 7,3 H) 3,91 (s, 3,3 H) 4,02 - 4,12 (m, 1,5 H) 4,15 - 4,26 (m, 0,9 H) 4,42 (d, *J*=13,73 Hz, 0,9 H) 4,54 (d, *J*=15,26 Hz, 0,1 H) 5,54 (d, *J*=14,65 Hz, 0,9 H) 6,57(d, *J*=14,04Hz, 0,1H) 6,97 (d, *J*=2,44 Hz, 0,9 H) 7,07 (dd, *J*=8,55, 2,44 Hz, 1,0 H) 7,28 - 7,35 (m, 0,3 H) 7,48 - 7,54 (m, 2,0 H) 7,62 - 7,67 (m, 1,0 H) 7,75 (d, *J*=7,93 Hz, 0,1 H) 7,82 (s, 1,0 H) 7,87 (d, *J*=8,55 Hz, 1,0 H) 8,21 (s, 0,9 H) 8,31 (s, 0,2 H) 8,48 (s, 1,0 H) 8,94 (d, *J*=9,15 Hz, 0,1 H) 9,46 (s, 0,9 H) 9,86 (s, 0,1 H). Tiempo de retención LC-MS 1,26 min; 671 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O

/ acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

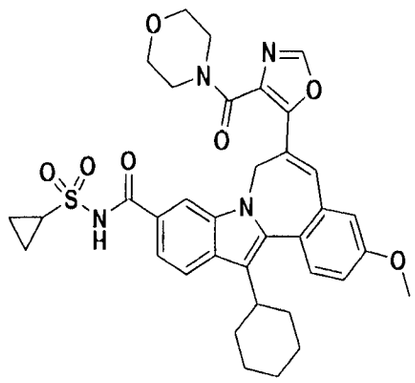


13-Ciclohexil-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

Se disolvió ácido 13-ciclohexil-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (40,8 mg, 0,072 mmol) en THF (1ml) y se añadió CDI (26 mg, 0,160 mmol) a la reacción. La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 50 min y luego se calentó en un baño de aceite a 60°C durante 1,5 horas. La reacción se enfrió y se añadió propano-2-sulfonamida (46 mg, 0,373 mmol) a la reacción seguido por DBU (0,022 ml, 0,144 mmol). La reacción se tapó en una atmósfera de nitrógeno y se calentó a 65°C durante la noche (16 horas). La reacción se repartió entre diclorometano y ácido clorhídrico acuoso 1,0N. La fase orgánica se lavó secuencialmente con ácido clorhídrico acuoso 1N, NaH_2PO_4 acuoso 0,1M. La fase orgánica se secó sobre sulfato sódico y se eliminó el disolvente a vacío proporcionando 50 mg de sólido amarillo amorfo. El compuesto del epígrafe se purificó en un sistema de

cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 12 minutos con un tiempo de ejecución de 15 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. La eliminación de disolventes y secado a vacío proporcionó 28,3 mg de un sólido amarillo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,15 - 1,28 (m, 1,3 H) 1,30 - 1,46 (m, 2,4 H) 1,48 - 1,61 (m, *J*=16,48 Hz, 1,2 H) 1,77 (d, *J*=9,77 Hz, 2,3 H) 1,87 - 2,15 (m, 4,8 H) 2,22 - 2,52 (m, 4,6 H) 2,78 - 2,90 (m, 1,1 H) 3,37 - 3,72 (m, 6,9 H) 3,76 (s, 6,2 H) 3,80 - 3,89 (m, 3,2 H) 3,91 (s, 3,6 H) 4,08 (s, 0,3 H) 4,13 - 4,23 (m, 1,0 H) 4,42 (d, *J*=13,73 Hz, 0,9 H) 4,65 (d, *J*=14,95 Hz, 0,1 H) 5,55 (d, *J*=14,04 Hz, 1,0 H) 6,97 (d, *J*=2,44 Hz, 1,0 H) 7,07 (dd, *J*=8,70, 2,59 Hz, 1,0 H) 7,27 - 7,33 (m, 0,2 H) 7,38 (s, 0,1 H) 7,46 - 7,55 (m, 2,0 H) 7,60 (d, *J*=9,77 Hz, 1,0 H) 7,78 (d, *J*=8,24 Hz, 0,1 H) 7,83 (s, 1,0 H) 7,87 (d, *J*=8,55 Hz, 1 H) 8,07 (s, 0,1 H) 8,10 (d, *J*=4,27 Hz, 0,1 H) 8,31 (d, *J*=8,54 Hz, 0,1 H) 8,42 (s, 0,9 H) 8,94 (d, *J*=9,16 Hz, 0,1 H) 9,55 (s, 0,9 H) 9,60 (s, 0,1 H). Tiempo de retención LC-MS 1,63 min; 714 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a

una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



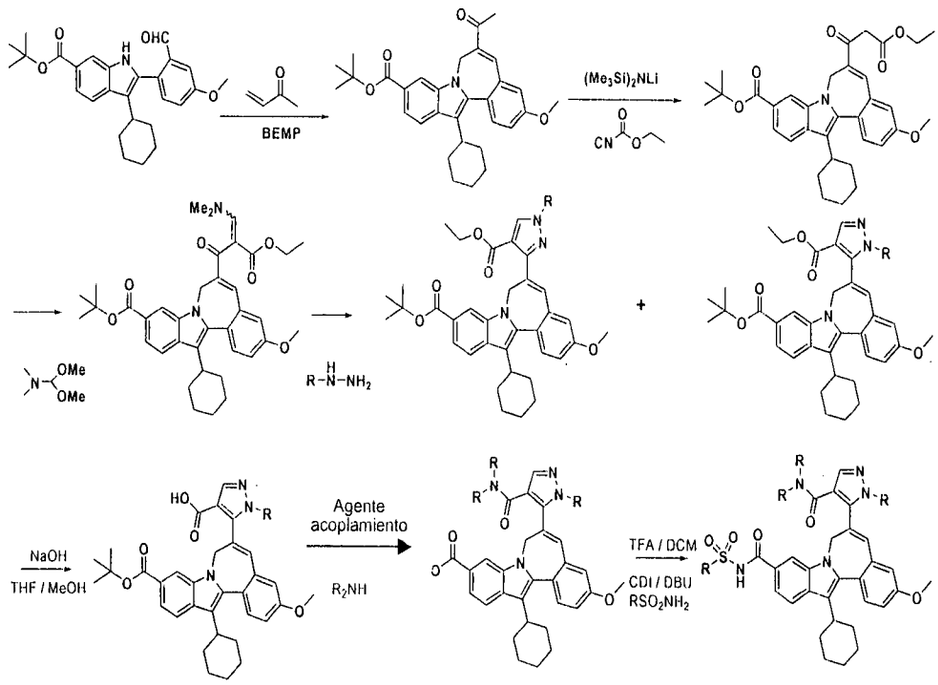
13-ciclohexil-N-(ciclopropilsulfonil)-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

Se disolvió ácido 13-ciclohexil-3-metoxi-6-(4-(4-morfolinilcarbonil)-1,3-oxazol-5-il)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (40 mg, 0,070 mmol) en THF (1ml) y se añadió CDI (26 mg, 0,160 mmol) a la reacción. La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 1 hora 50 minutos y luego se calentó en un baño de aceite a 65ºC durante 1 hora 10 minutos. La reacción se enfrió y se añadió ciclopropanosulfonamida (48 mg, 0,396 mmol) y luego DBU (0,022 ml, 0,146 mmol) a la reacción. La reacción se tapó en una atmósfera de nitrógeno y se

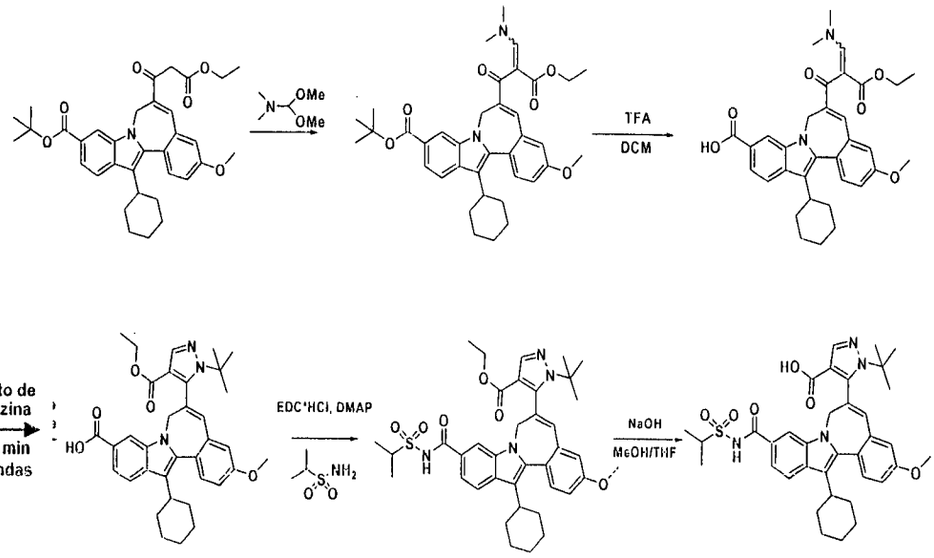
calentó a 68ºC durante la noche (18 horas). La reacción se repartió entre diclorometano y ácido clorhídrico acuoso 1,0N. La fase orgánica se lavó secuencialmente con ácido clorhídrico acuoso 1N, NaH_2PO_4 acuoso 0,1M. La fase orgánica se secó sobre sulfato sódico y se eliminó el disolvente a vacío proporcionando 62 mg de sólido amarillo amorfo. El compuesto del epígrafe se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. La eliminación de disolventes y secado a vacío proporcionó 30,8 mg del compuesto del epígrafe como un sólido amorfo amarillo. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,99 - 1,28 (m, 4,0 H) 1,29 - 1,45 (m, 3,9 H) 1,47 - 1,68 (m, 7,9 H) 1,75 (m, 2,3 H) 1,84 - 2,17 (m, 4,5 H) 2,77 - 2,88 (m, 1,0 H) 3,14 - 3,23 (m, 1,2 H) 3,33 - 3,89 (m, 8,3 H) 3,91 (s, 3,3 H) 4,09 (s, 0,5 H) 4,17 (s, 0,9 H) 4,42 (d, *J*=14,34 Hz, 0,9 H) 5,54 (d, *J*=15,56 Hz, 0,9 H) 6,60 (d, 0,1 H) 6,97 (d, *J*=2,44 Hz, 1,0 H) 7,07 (dd, *J*=8,55, 2,75 Hz, 1,0 H) 7,27 - 7,35 (m, 0,3 H) 7,49 (s, 1,0 H) 7,52 (d, *J*=8,85 Hz, 1,0 H) 7,64 (dd, *J*=8,55, 1,53 Hz, 1,0 H) 7,75 (d, *J*=7,94 Hz, 0,2 H) 7,82 (s, 1,0 H) 7,87

(d, *J*=8,55 Hz, 1,0 H) 8,21 (s, 0,1 H) 8,31 - 8,36 (m, 0,3 H) 8,43 (d, *J*=1,53 Hz, 1,0 H) 8,95 (d, *J*=9,16 Hz, 0,2 H) 9,61 (s, 1,0 H) 9,82 (s, 0,1 H). Tiempo de retención LC-MS 1,59 min; 669 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

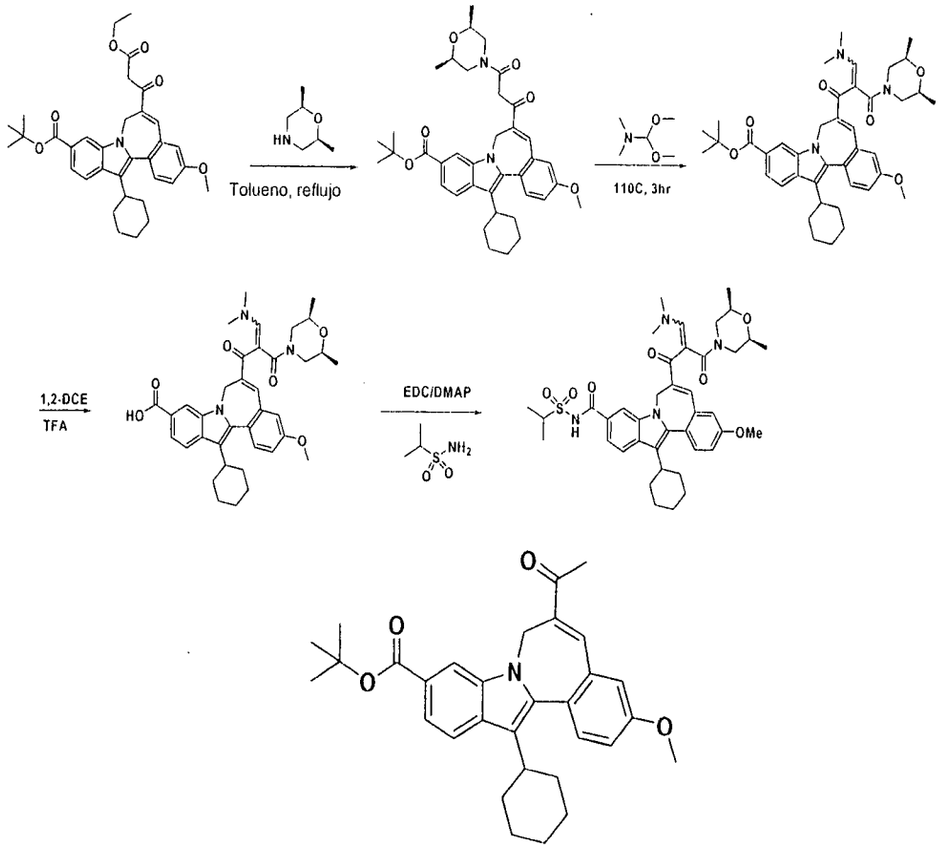
El esquema mostrado a continuación es ilustrativo de los procedimientos que se pueden usar para preparar intermedios y compuestos.



Una variación adicional que se puede emplear para la síntesis de intermedios y compuestos se muestra en el esquema siguiente.



Una variación adicional de la metodología que se puede usar para la síntesis de otros intermedios y compuestos se representa en el esquema mostrado a continuación.

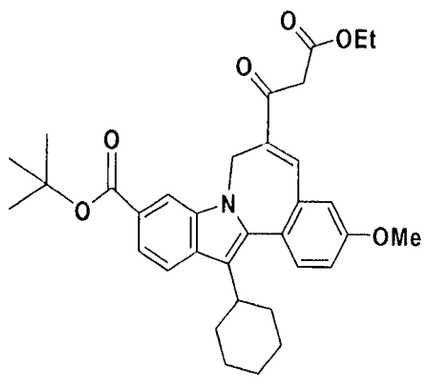


6-Acetil-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo.

Se añadió a una suspensión de 3-ciclohexil-2-(2-formil-4-metoxifenil)-1H-indol-6-carboxilato de terc-butilo (2 g, 4,61 mmol) en dioxano (9,2 ml) de 2-terc-butilimino-2-dietilamino-1,3-di- metilperhidrodiazafosforina (2,00 ml, 6,92 mmol) y luego but-3-en-2-ona (0,756 ml, 9,23 mmol) en un recipiente de microondas de 20 ml. Se tapó la reacción heterogénea en nitrógeno y se calentó en el microondas a 120°C durante 40 minutos. Esta reacción se repitió dos veces más en la escala anterior y una última vez con 3-ciclohexil-2-(2-formil-4-metoxifenil)-1H-indol-6-carboxilato de terc-butilo (2,51g, 5,79 mmol), se disolvió

en dioxano (11,5ml), se añadió BEMP (2,5ml, 8,64 mmol) seguido por but-3-en-2-ona (0,95ml, 11,46 mmol). Se trató cada segmento de reacción mientras que la secuencia siguiente se ejecutaba en el microondas. El tratamiento consistía en el reparto de la reacción entre acetato de etilo y ácido clorhídrico acuoso 1N en un embudo de separación de 250 ml. La fase acuosa se volvió a extraer una vez más con acetato de etilo y las fases orgánicas se reunieron y lavaron secuencialmente con ácido clorhídrico acuoso 1N, NaH_2PO_4 0,1M y salmuera. La solución se reunió entonces con un tratamiento previo en un matraz de Erlenmeyer de 1 litro que contenía sulfato de magnesio. Se filtró y se eliminaron los materiales volátiles, se secó a vacío a temperatura ambiente durante la noche obteniendo 10,67 g de una espuma amarillo-naranja. Se adsorbió el material bruto sobre 25 g de gel de sílice usando diclorometano, eliminando los volátiles a vacío. Se realizó una cromatografía en 299 g de suspensión de gel de sílice rellena en acetato de etilo al 20% en hexanos y eluyendo con acetato de etilo al 20% en hexanos. Se reunieron las fracciones de producto puro de la cromatografía y se eliminaron los disolventes a vacío. El residuo se disolvió en benceno y se eliminó a vacío para ayudar en la eliminación de las trazas de acetato de etilo. El compuesto del epígrafe como una espuma amarilla /sólido amorfo se secó a vacío durante la noche a temperatura ambiente proporcionando 6,83 g (71,7%). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,12 - 1,29 (m, 1 H) 1,30 - 1,61 (m, 4 H) 1,64 (s, 10 H) 1,67 - 2,00 (m, 4 H) 1,98 - 2,19 (m, 3 H) 2,43 (s, 3 H) 2,75 - 2,87 (m, 1 H) 3,85 - 4,01 (m, 4 H) 5,86 (s, 1 H) 7,00 (d, *J*=2,75 Hz, 1 H) 7,11 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,35 (s, 1,8 H, benceno) 7,69 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,82 (d, *J*=8,24 Hz, 1 H) 8,24 (s, 1 H). Tiempo de retención LC-MS 3,28 min; m/z

(MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 30% de disolvente A / 70% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 6 min en el que el disolvente A fue 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético y el disolvente B fue 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

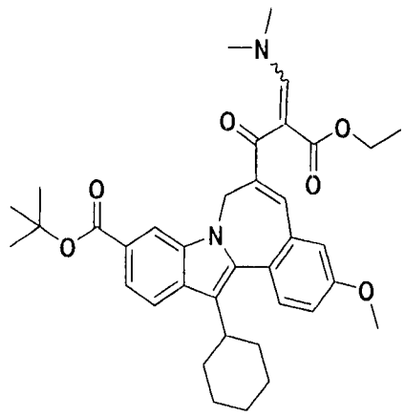


Éster etílico del ácido 13-ciclohexil-10-[(1,1-dimetiletoxi)carbonil]-3-metoxi-beta-oxo-7H-Indolo[2,1-a][2]benzazepin-6-propanoico.

A una solución del éster 1,1-dimetiletílico del ácido 6-acetil-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (2,50 g, 5,15 mmol) en THF (15,0 ml) se añadió una solución 1M de LHMDS (5,41 ml, 5,41 mmol) en THF a -78ºC y se agitó durante 15 min. Se añadió cianoformiato de etilo (0,510

ml, 5,15 mmol) a -78ºC a la solución resultante y se continuó agitando durante 30 minutos. Se añadió NH_4Cl acuoso saturado (50 ml) y la fase acuosa se extrajo con $CHCl_3$ (2 x 50 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. La cromatografía sobre gel de sílice (cloruro de metileno:hexanos 2:1) del concentrado proporcionó el compuesto del epígrafe (1,75 g, 61%) como un aceite amarillo. MS m/z 558 (MH^+). Se separó en las siguientes condiciones una reacción previa que se ejecutó de una forma análoga a la reacción anterior y en la que el material de partida éster 1,1-dimetiletílico del ácido 6-acetil-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico estaba todavía presente: Este procedimiento describe la separación de 13-ciclohexil-6-(3-etoxi-3-oxopropanoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo (producto deseado) del material de partida cetona, 6-acetil-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo. El peso total de materiales se estimó que era 2,6g. Se disolvieron 3,9 g de una mezcla de muestra como un aceite naranja en diclorometano y se adsorbió sobre 10g de gel de sílice. Los volátiles se eliminaron a vacío usando un evaporador rotatorio. Se cargó la muestra adsorbida sobre gel de sílice en una columna de 294 g de gel de sílice que se había rellenado en suspensión en éter dietílico al 30% en hexanos. Se colocó un lecho de arena sobre la parte superior de la muestra adsorbida para ayudar a añadir el disolvente. El tamaño aproximado del relleno de la columna de gel de sílice fue 75mm de diámetro x 175mm de altura. El producto eluyó usando un gradiente de éter dietílico al 30% en hexanos hasta éter dietílico al 35% en hexanos hasta éter dietílico al 40% en hexanos. Eluyó con aproximadamente 1 l de Et_2O al 30%/hexanos, luego 1 l de Et_2O al

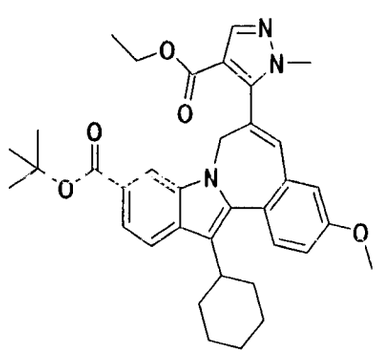
35%/hexanos y finalmente usando Et_2O al 40%/hexanos. Los volúmenes de las fracciones fueron aproximadamente 125 ml a 150 ml. Las fracciones producto se reunieron y se eliminaron los volátiles y se secó el ceto-éster del epígrafe a vacío proporcionando 1,63 g de un sólido amorfo amarillo-naranja. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,12 (t, *J*=7,02 Hz, 2,5 H) 1,15 - 1,28 (m, 1,6 H) 1,32 (c, *J*=7,12 Hz, 1,0 H) 1,35 - 1,43 (m, 1,5 H) 1,59 (s, 1,5 H) 1,61 - 1,69 (m, 9,4 H) 1,72 - 1,82 (m, 2,0 H) 1,94 (s, 1,2 H) 2,04 (s, 2,9 H) 2,76 - 2,85 (m, 1,0 H) 3,64 - 3,79 (m, 0,8 H) 3,88 (s, 0,7 H) 3,90 (s, 0,7 H) 3,92 (s, 2,6 H) 3,94 - 4,06 (m, 0,7 H) 4,12 (c, *J*=7,22 Hz, 1,9 H) 4,21 - 4,33 (m, 0,7 H) 4,39 (c, *J*=7,12 Hz, 0,2 H) 5,67 (s, 0,2 H) 5,71 - 5,90 (m, 0,7 H) 6,95 - 7,02 (m, 1,0 H) 7,06 (dd, *J*=8,55, 2,75 Hz, 0,2 H) 7,12 (dd, *J*=8,70, 2,59 Hz, 0,82 H) 7,46 - 7,57 (m, 1,2 H) 7,64 (s, 0,8 H) 7,69 (d, *J*=8,55 Hz, 0,9 H) 7,76 - 7,85 (m, 0,9 H) 8,14 (s, 0,2 H) 8,22 (s, 0,8 H) 12,40 (s, 0,1 H). Tiempo de retención LC-MS 2,78 min; 556 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

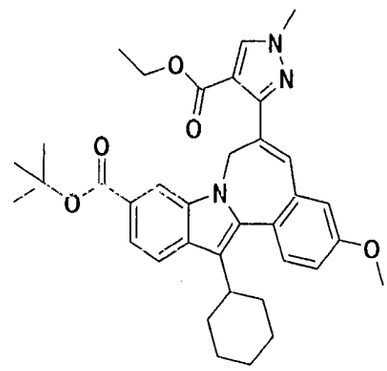


13-Ciclohexil-6-((2E,Z)-3-(dimetilamino)-2-(etoxicarbonil)-2-propenoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo.

Se disolvió 13-ciclohexil-6-(3-etoxi-3-oxopropanoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo (1,63 g, 2,92 mmol) en dimetil acetal de N,N-dimetilformamida (7,0 ml, 52,7 mmol) en un matraz de fondo redondo de 50 ml. La reacción se mantuvo en una atmósfera de nitrógeno y se calentó en un baño de aceite en condiciones de reflujo (110°C) durante 2,75 horas. Seguidamente se enfrió la reacción en una atmósfera de nitrógeno y los volátiles se evaporaron a vacío dando una espuma color naranja. El análisis por TLC (placa de SiO_2, elución - éter dietílico al 50% en hexanos) confirmó que se había completado la reacción. Este material se secó a vacío a temperatura ambiente durante la noche proporcionando 1,87 g del intermedio enamina como espuma naranja ámbar que se usó en la etapa siguiente sin ninguna purificación adicional. LC-MS del intermedio enamina: Tiempo de retención LC-MS 2,81 min; 613 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las

condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 2 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 3 min en el que el disolvente A fue 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético y el disolvente B fue 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.





éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico y éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-3-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

Se disolvió el intermedio enamina, 13-ciclohexil-6-((2E,Z)-3-(dimetilamino)-2-(etoxicarbonil)-2-propenoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo, (1,63 g, 2,99 mmol) en etanol absoluto (10 ml). En unos pocos minutos de disolución en etanol, la reacción se volvió heterogénea con formación de un precipitado amarillo/naranja fino. Se

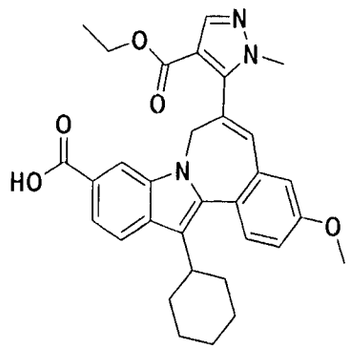
añadió metilhidrazina (0,173 ml, 3,29 mmol) a la reacción y la reacción se colocó en una atmósfera de nitrógeno con un condensador. La reacción se calentó hasta 80°C y permaneció heterogénea a 80°C. Se añadieron otros 5 ml más de etanol absoluto y la reacción se agitó a 80°C durante 15 minutos. La reacción era todavía heterogénea y se añadió 1,4-dioxano (5 ml) y la reacción se volvió lentamente homogénea. La reacción se calentó durante 2 horas y luego se enfrió y se eliminaron los volátiles a vacío obteniendo una espuma naranja ámbar. El residuo se disolvió en benceno y luego se eliminaron los volátiles a vacío y la muestra se secó a temperatura ambiente durante la noche a vacío proporcionando 1,79 g de un sólido/espuma amarillo amorfo. El análisis LC-MS indicó dos posibles productos isoméricos. Se purificaron 102 mg del producto bruto por HPLC de fase inversa. La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu usando software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y un recogedor de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (4ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 25% de disolvente A / 75% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 10 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El primer producto en eluir es éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-

10-carboxílico con tiempo de retención de 11,7 minutos, siendo el producto componente minoritario éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-3-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico con un tiempo de retención de 14,5 minutos.

Éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,13 - 1,27 (m, 1 H) 1,30 (t, *J*=7,02 Hz, 3 H) 1,34 - 1,55 (m, 3 H) 1,58 (s, 9 H) 1,61 - 1,84 (m, 3 H) 1,85 - 2,00 (m, 1 H) 1,99 - 2,18 (m, 3 H) 2,86 (t, *J*=11,75 Hz, 1 H) 3,28 (s, 3 H) 3,90 (s, 3 H) 4,27 (d, *J*=4,27 Hz, 2 H) 4,71 (s, 1 H) 4,97 (s, 1 H) 6,77 (s, 1 H) 6,93 (d, *J*=2,44 Hz, 1 H) 7,07 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,65 (d, *J*=8,55 Hz, 1 H) 7,79 - 7,88 (m, 2 H) 7,97 (s, 1 H). Tiempo de retención LC-MS 3,92 min; 596 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 6 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

Éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-3-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,13 - 1,26 (m, 1 H) 1,30 (t, *J*=7,17 Hz, 3 H) 1,33 - 1,60 (m, 3 H) 1,61 (s, 9 H) 1,64 - 1,83 (m, 3 H) 1,91 (s, 2 H) 1,98 - 2,16 (m, 3 H) 2,82 - 2,91 (m, 1 H) 3,90 (s, 3 H) 3,94 (s, 3 H) 4,20 - 4,30 (m, 2 H) 4,41 (d, *J*=14,04 Hz, 1 H) 5,76 (d, *J*=14,04 Hz, 1 H) 6,96 - 7,03 (m, 2 H) 7,49 - 7,54 (m, 1 H) 7,64 (dd, *J*=8,39, 1,37 Hz, 1 H) 7,79 (d, *J*=8,55 Hz, 1 H) 7,84 (s, 1 H) 7,90 (s, 1 H) 8,26 (s, 1 H). Tiempo de retención LC-MS 4,26 min; 596 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 6 ml/min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 1% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de 0 min y un tiempo de análisis de 5 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización. El resto de la muestra (1,615 g) se adsorbió sobre 4 g de gel de sílice usando diclorometano y se sometió a cromatografía en 50 g de suspensión de gel de sílice rellena usando acetato de etilo al 2% en diclorometano y eluyendo con acetato de etilo al 2% en diclorometano. El primer componente en eluir es el producto minoritario, éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-3-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico, 179 mg aislados. El segundo

componente, éster 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-1,1-dimetiletílico del ácido 7H-indolo[2,1-a][2]benzazepin-10-carboxílico, fue el componente mayoritario en la elución y proporcionó 966 mg.

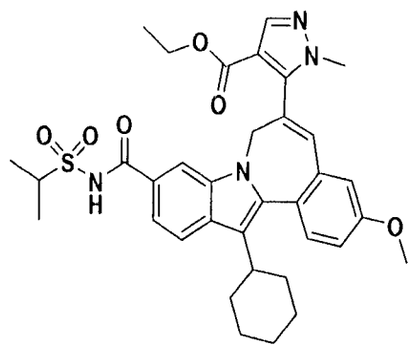


Ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (53 mg, 0,089 mmol) en 1,2-dicloroetano (2 ml) en una atmósfera de nitrógeno. Se añadió entonces ácido trifluoracético (2 ml, 26,0 mmol) y la reacción se agitó a temperatura ambiente durante 2,5 horas. Se eliminaron entonces los volátiles a vacío y el residuo se disolvió en benceno y se evaporó la solución resultante a presión reducida para eliminar el TFA residual. Este proceso se repitió una vez. Esto dio el compuesto del epígrafe como un sólido amarillo, (46,2 mg).

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,12 - 1,26 (m, 1 H) 1,31 (t, *J*=7,02 Hz, 3 H) 1,40 (s, 2 H) 1,51 - 1,89 (m, 3 H) 1,87 - 2,23 (m, 4 H) 2,87 (t, *J*=11,29 Hz, 1 H) 3,29 (s, 3 H) 3,91 (s, 3 H) 4,27 (s ancho, 2 H) 4,73 (s ancho, 1

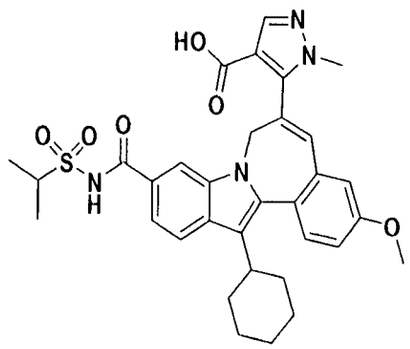
H) 4,97 (s ancho, 1 H) 6,78 (s, 1 H) 6,94 (d, *J*=2,14 Hz, 1 H) 7,08 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,54 (d, *J*=8,85 Hz, 1 H) 7,77 (d, *J*=8,24 Hz, 1 H) 7,86 - 7,95 (m, 2 H) 7,98 (s, 1 H) 8,36 (s ancho, 2 H). Tiempo de retención LC-MS 1,84 min; 538 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de 0 min y un tiempo de análisis de 5 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



Éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico.

Se disolvió ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (981 mg, 1,818 mmol) en THF (18 ml). Se añade carbonildiimidazol (649 mg, 4,00 mmol) a la reacción. La reacción se colocó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 45 minutos y luego se calentó hasta reflujo durante 1 hora. La reacción se enfrió en una atmósfera de nitrógeno y se añadió propano-2-sulfonamida (1164 mg, 9,45 mmol) a la reacción seguido por DBU (0,548 ml, 3,64 mmol). La reacción se sumergió entonces en un baño de aceite a 80°C en atmósfera de nitrógeno y se calentó durante la noche a 70-80°C. La reacción se diluyó entonces con acetato de etilo y la fase orgánica se lavó secuencialmente con ácido clorhídrico acuoso 1,0 N, NaH_2PO_4 acuoso 0,1M y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se eliminaron los volátiles a vacío proporcionando una espuma amarilla que se secó a vacío a temperatura ambiente durante la noche proporcionando 1,170 g de un sólido amarillo amorfo. El análisis de RMN de protón reveló la presencia de propano-2-sulfonamida (1,41 ppm, d, 500MHz, $CDCl_3$) en la muestra. La muestra bruta se disolvió en aproximadamente 200 ml de diclorometano y se lavó 2x con 125 ml de agua, luego secuencialmente con ácido clorhídrico acuoso 1N, 2x con NaH_2PO_4 0,1M y luego de nuevo con ácido clorhídrico acuoso 1N. La solución en diclorometano se secó sobre sulfato sódico, se filtró y se eliminaron los volátiles y el producto se secó a vacío a temperatura ambiente durante la noche proporcionando 1,046 g (89%) del compuesto del epígrafe como un sólido amarillo amorfo. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,80 - 0,90 (m, 1 H) 1,20 - 1,27 (m, 4 H) 1,30 (t, *J*=7,02 Hz, 4 H) 1,32 - 1,43 (m, 3 H) 1,46 (d, *J*=7,02 Hz, 6 H) 1,53 - 1,64 (m, 3

H) 1,79 (d, *J*=9,77 Hz, 3 H) 1,85 - 2,13 (m, 5 H) 2,81 - 2,91 (m, 1 H) 3,90 (s, 3 H) 4,00 - 4,10 (m, 1 H) 4,24 (s, 2 H) 4,71 (d, *J*=12,21 Hz, 1 H) 4,99 (d, *J*=16,48 Hz, 1 H) 6,77 (s, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,08 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,38 (dd, *J*=8,55, 1,22 Hz, 1 H) 7,52 (d, *J*=8,85 Hz, 1 H) 7,76 (d, *J*=1,22 Hz, 1 H) 7,86 - 7,92 (m, 2 H) 8,26 (s ancho, 1 H). Tiempo de retención LC-MS 1,79 min; 643 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xtena MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]-carbonil]-

7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico.

Se disolvió éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico (1,044 g, 1,619 mmol) en THF (11 ml) con calentamiento. Se añadió entonces DMF (5 ml) y la mezcla se calentó suavemente para asegurar la disolución. La mezcla se calentó entonces hasta temperatura ambiente y se añadió hidróxido de tetrabutilamonio (6,5 ml, 6,50 mmol) (1,0M en metanol). La mezcla resultante se calentó seguidamente a temperatura ambiente en nitrógeno durante 2,5 horas y se controló el progreso por LC-MS. Los resultados mostraron fundamentalmente ésteres metílicos y etílicos. La mezcla se agitó entonces durante otras 3 horas más, después de lo cual se añadieron otros 2,0 ml (2 mmol) de hidróxido de tetrabutilamonio (1,0M en metanol) y la reacción se agitó a temperatura ambiente en nitrógeno durante otros 2 días. El análisis posterior mostró que la reacción había transcurrido hasta aproximadamente 22% de conversión al producto ácido deseado. Se eliminaron los volátiles (metanol, etanol, THF) de la reacción a vacío (30oC) usando un evaporador rotatorio. Se añadieron a la reacción 200 ul de hidróxido sódico acuoso 10N y 4 ml de THF. La reacción se mezcló colocando en un evaporador rotatorio, se calentó suavemente (25ºC, 3 horas) y luego se añaden 6 ml de DMF y se calienta 35ºC durante 3 horas y usando vacío para eliminar los volátiles generados por la hidrólisis. El análisis de la reacción por LC-MS indicó una conversión de aproximadamente 83% al producto ácido. La reacción se agitó durante la noche a temperatura ambiente y el posterior análisis no mostró conversión adicional al producto. Se añadieron otros 4,0 ml de hidróxido de tetrabutilamonio 1,0M en metanol a la reacción. La reacción se colocó en un

evaporador rotatorio y se eliminaron los volátiles a vacío y se continuó calentando la reacción a 40-45ºC durante aproximadamente 6 horas. La reacción se trató entonces añadiendo ácido clorhídrico acuoso 1N (100 ml) a la reacción y luego se lavó la mezcla en un embudo de separación de 500 ml usando acetato de etilo para llevar el volumen de orgánicos hasta aproximadamente 200ml. Se repartió la reacción entre acetato de etilo y ácido clorhídrico acuoso 1,0N. La fase orgánica se lavó 3x (~300ml cada vez) con ácido clorhídrico acuoso 1,0N, luego salmuera y se secó sobre MgSO4, se filtró y se eliminaron los volátiles a vacío proporcionando 1,03 g de una espuma película amarilla. La muestra se secó a vacío a temperatura ambiente hasta 0,92 g (92%) del compuesto del epígrafe. Tiempo de retención LC-MS 1,48 min; 615 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

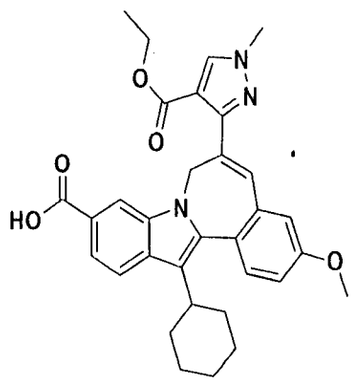
A continuación se describe un procedimiento alternativo para la preparación del compuesto del epígrafe.

Se disuelve éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico (1,044 g, 1,619 mmol) en una solución premezclada de THF (20 ml), MeOH (20 ml) e hidróxido sódico (20 ml, 20,00 mmol). La reacción era homogénea y se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 26 horas y luego se concentró a vacío usando un evaporador rotatorio con un baño de temperatura a 20°C. La reacción se vertió en ácido clorhídrico acuoso 1N y se extrajo usando acetato de etilo. Las fases orgánicas reunidas se lavaron secuencialmente con ácido clorhídrico acuoso 1N y salmuera, luego se secaron sobre sulfato de magnesio, se filtraron y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando 1,68 g de un sólido amorfo naranja. El producto bruto se disolvió en cloroformo (aproximadamente 50 ml) con calentamiento y se añadieron hexanos hasta que parte del material comenzó a precipitar pero se volvió a disolver al agitar (aproximadamente 10-12 ml de hexanos) La mezcla se dejó enfriar lentamente hasta temperatura ambiente y luego se dejó reposar a temperatura ambiente durante unas pocas horas. El precipitado amarillo en forma de partículas finas se filtró usando un embudo de Buchner y se secó a vacío a temperatura ambiente proporcionando 819 mg (45%) de producto purificado como un sólido amorfo amarillo brillante. El compuesto del epígrafe, 4,6 mg se disolvió en $CDCl_3$ (2 ml) con la adición de aproximadamente 5 gotas de CD_3OD para ayudar a disolver para la adquisición de RMN de ^1H.

RMN de ^1H (500 MHz, CLOROFORMO-D / CD_3OD) δ ppm 1,11 - 1,39 (m, 3 H) 1,41 (d, *J*=7,02 Hz, 6 H) 1,47 - 1,65 (m, 1 H) 1,75 (d, *J*=8,85 Hz, 2 H) 1,82 -

2,27 (m, 13 H) 2,77 - 2,90 (m, 1 H) 3,28 (s, 3 H) 3,88 (s, 3 H) 3,97 - 4,06 (m, 1 H) 4,66 (s, 1 H) 5,01 (s, 1 H) 6,76 (s, 1 H) 6,92 (d, *J*=2,75 Hz, 1 H) 7,04 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,47 - 7,54 (m, 2 H) 7,81 (d, *J*=1,22 Hz, 1 H) 7,86 (d, *J*=8,54 Hz, 1 H) 7,91 (s, 1 H)

Tiempo de retención LC-MS 1,39 min; 615 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

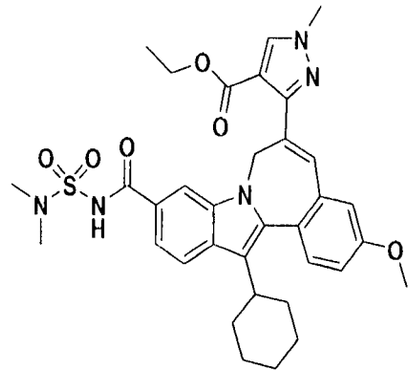


Ácido 13-ciclohexil-6-[4-(eloxicarbonil)-1-metil-1H-pirazol-3-il]-3-metoxi-

7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

Se disuelve éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-3-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (176 mg, 0,295 mmol) en 1,2-dicloroetano (3 ml), se coloca la reacción en una atmósfera de nitrógeno, luego se añade ácido trifluoracético (3 ml, 38,9 mmol). Se agita la reacción a temperatura ambiente en una atmósfera de nitrógeno durante 2 h 20 min y luego se eliminan los volátiles a vacío. Se disuelve el producto en una mezcla de benceno y diclorometano y luego se eliminan los volátiles a vacío. Se repite la disolución en benceno y diclorometano y se eliminan los volátiles para ayudar a eliminar las trazas de ácido trifluoracético. El compuesto del epígrafe se secó a vacío a temperatura ambiente proporcionando 164 mg de un sólido amorfo amarillo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,01 - 1,29 (m, 3 H) 1,32 (t, *J*=7,17 Hz, 3 H) 1,35 - 1,53 (m, 2 H) 1,52 - 1,85 (m, 3 H) 1,86 - 2,20 (m, 4 H) 2,79 - 2,95 (m, 1 H) 3,91 (s, 3 H) 3,97 (s, 3 H) 4,27 (c, *J*=7,22 Hz, 2 H) 4,41 (d, *J*=14,34 Hz, 1 H) 5,84 (d, *J*=14,34 Hz, 1 H) 6,97 - 7,08 (m, 2 H) 7,54 (d, *J*=8,24 Hz, 1 H) 7,76 (d, *J*=8,55 Hz, 1 H) 7,85 (d, *J*=8,54 Hz, 1 H) 7,91 (s, 1 H) 7,95 (s, 1 H) 8,50 (s, 1 H). Tiempo de retención LC-MS 2,08 min; 538 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 6 min en el que el disolvente A fue 5% de

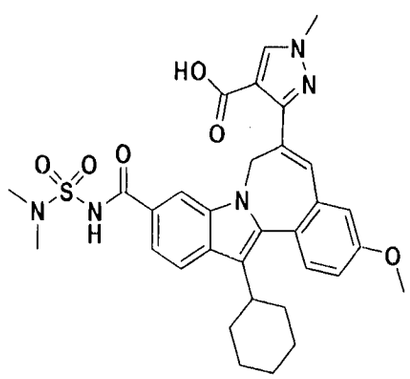
acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



Éster etílico del ácido 3-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico.

Se disuelve ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-3-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico, (60 mg, 0,111 mmol) en THF (1,0 ml), luego se añade carbonil diimidazol (42 mg, 0,259 mmol) a la reacción. La reacción se agitó en una atmósfera de nitrógeno durante 1 hora a temperatura ambiente. La reacción se calentó entonces a 70°C durante 1 hora y luego se enfrió y se añadió N,N-dimetilsulfamida (70 mg, 0,564 mmol) a la reacción seguido por DBU (0,034 ml, 0,222 mmol). La reacción se tapó de nuevo en una atmósfera de nitrógeno y se calentó a 70°C durante 16,5 horas. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N, NaH_2PO_4 acuoso 0,1M y de nuevo con ácido clorhídrico acuoso 1,0N y finalmente con salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente y el producto se

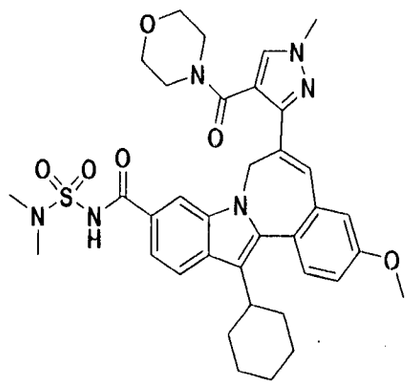
secó a vacío a temperatura ambiente proporcionando 70 mg de sólido amarillo amorfo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,76 - 0,95 (m, 2 H) 1,12 - 1,26 (m, 5 H) 1,32 (t, *J*=7,17 Hz, 3 H) 1,38 (s, 2 H) 1,51 - 1,61 (m, 4 H) 1,67 - 1,81 (m, 3 H) 1,87 - 2,01 (m, 2 H) 2,01 - 2,11 (m, 3 H) 2,82 - 2,92 (m, 1 H) 3,06 (s, 6 H) 3,91 (s, 3 H) 3,96 (s, 3 H) 4,26 (d, *J*=7,02 Hz, 2 H) 4,42 (d, *J*=14,34 Hz, 1 H) 5,75 (d, *J*=14,04 Hz, 1 H) 6,99 - 7,05 (m, 2 H) 7,38 (d, *J*=8,24 Hz, 1 H) 7,52 (d, *J*=8,24 Hz, 1 H) 7,85 (d, *J*=8,55 Hz, 1 H) 7,89 - 7,96 (m, 2 H) 8,18 (s, 1 H) 8,36 (s ancho, 1 H). Tiempo de retención LC-MS 2,34 min; 644 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



Ácido 3-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico.

Se disolvió éster etílico del ácido 3-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (66 mg, 0,102 mmol) en THF (1 ml) y se añadió a la reacción una solución 1,0M de hidróxido de tetrabutilamonio (0,41 ml, 0,410 mmol) en metanol. La reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno y luego se analizó por LC-MS. La reacción se concentró a vacío en un evaporador rotatorio y luego se añadió 1 ml de THF a la reacción y se tapó la reacción una vez más en una atmósfera de nitrógeno. La reacción se colocó en un baño de agua a 40°C y se dejó agitando durante la noche. En algún momento durante la noche falló el elemento calefactor en el baño de agua y se observó la reacción hasta una temperatura ambiente la mañana siguiente. El análisis por LC-MS de la reacción indicó que se había completado. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N, luego de nuevo con ácido clorhídrico acuoso 1,0N y finalmente con salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó a vacío. El compuesto del epígrafe se secó a vacío proporcionando 63 mg de sólido amarillo amorfo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,81 - 0,97 (m, 3 H) 1,18 - 1,30 (m, 4 H) 1,30 - 1,65 (m, 6 H) 1,66 - 1,83 (m, 3 H) 1,84 - 2,10 (m, 6 H) 2,84 - 2,92 (m, 3 H) 3,04 (s, 6 H) 3,88 (s, 3 H) 3,97 (s, 3 H) 4,43 (d, *J*=14,34 Hz, 1 H) 5,68 (d, *J*=13,73 Hz, 1 H).6,99 (d, *J*=2,75 Hz, 1 H) 7,02 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,35 (d, *J*=8,24 Hz, 1 H) 7,52 (d, *J*=8,55 Hz, 1 H) 7,77 (s, 1 H) 7,83 (d, *J*=8,24 Hz, 1 H) 7,98 (s, 1 H) 8,15 (s, 1 H) 8,71 (s, 1 H).

Tiempo de retención LC-MS1,53 min; 616 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

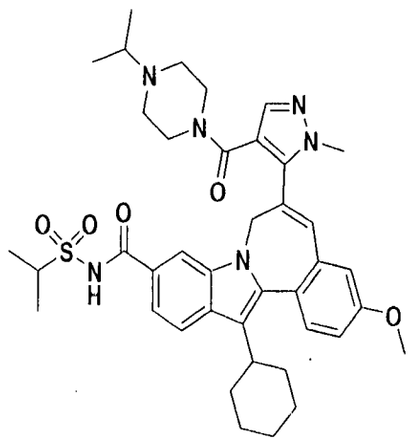


13-ciclohexil-N-[(dimetilamino)sulfonil]-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-3-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

Se disolvió ácido 3-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi-7*H*-indolo[2,1-

a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico, (57 mg, 0,092 mmol) en DMF (1,0 ml) y se añadió TBTU (55,8 mg, 0,174 mmol) a la reacción. La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 1 hora y luego se añadió DMAP (47 mg, 0,385 mmol) a la reacción seguido por morfolina (16 µl, 0,184 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante la noche. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N, NaH_2PO_4 acuoso 0,1M y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El compuesto del epígrafe se secó durante la noche a vacío a temperatura ambiente proporcionando 63 mg de un sólido amorfo amarillo. El compuesto del epígrafe se purificó adicionalmente en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (volumen total 2ml) purificado usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 60% de disolvente A / 40% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 12 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. La muestra se trató como dos inyecciones de 1 ml. El tiempo de experimento de la segunda HPLC Prep se limitó hasta 15 minutos en base a los datos del primer

experimento. Las fracciones de producto (Tiempo de retención= 8,75 min.) se reunieron y se eliminó el disolvente a vacío. El compuesto se secó a temperatura ambiente a vacío proporcionando 38 mg del compuesto del epígrafe como un sólido amorfo amarillo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,23 (c, *J*=12,21 Hz, 1 H) 1,30 - 1,56 (m, 3 H) 1,77 (d, *J*=10,38 Hz, 2 H) 1,90 - 2,14 (m, 4 H) 2,54 - 2,81 (m, 4 H) 2,82 - 2,95 (m, 2 H) 2,95 - 3,05 (m, 2 H) 3,07 (s, 6 H) 3,09 - 3,39 (m, 5 H) 3,90 (s, 3 H) 3,97 (s, 3 H) 4,45 (d, *J*=14,65 Hz, 1 H) 5,45 (d, *J*=14,65 Hz, 1 H) 6,95 (d, *J*=2,75 Hz, 1 H) 6,97 (s, 1 H) 7,04 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,46 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,52 (d, *J*=8,55 Hz, 1 H) 7,55 (s, 1 H) 7,89 (d, *J*=8,55 Hz, 1 H) 7,94 (d, *J*=1,22 Hz, 1 H) 9,13 (s ancho, 1 H). Tiempo de retención LC-MS 1,82 min; 685 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-Ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[[4-(1-metiletil)-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

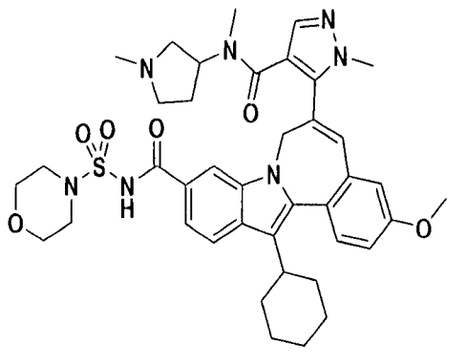
Se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (0,92g, 1,5 mmol) en DMF (25ml) y se añadió HATU (1141 mg, 3,0 mmol) seguido por diisopropiletilamina (1306 ul, 7,5 mmol). Se traspasó 1 ml de la solución de reacción que contenía ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico / HATU / DIEA a un vial Wheaton de 16x100 mm que contenía 1-isopropilpiperazina (36,9 mg, 0,288 mmol). La reacción se tapó y se agitó a temperatura ambiente durante la noche. La reacción se traspasó a un placa de 96 pocillos y el vial de reacción se aclaró con DMF (800 ul) llevando el volumen final de reacción hasta 1,800 ml. La mezcla de reacción se purificó por HPLC de fase inversa en las siguientes condiciones. La HPLC Prep estaba controlada por software Dionex Chromeleon 6,70 sp1 LC usando una bomba binaria Varian Prostar con una carga de

bombeo de 50 ml/min y detección usando un detector Sedex 75 ELS para obtener las fracciones. Para observar las trazas UV del experimento HPLC se usó un espectrómetro Dionex UVD340U UV. Para el aislamiento se empleó una columna Waters Sunfire C18 19mm x 25mm de 10u usando un sistema disolvente de A= agua y acetato amónico 20mM, B= acetonitrilo. Se usó el siguiente gradiente: 80% de A y 20% de B mantenido durante 3 minutos seguido por un gradiente de 19 minutos hasta 5% de A y 95% de B con un mantenimiento final a 5% de A y 95% de B de 5 minutos. El caudal para la purificación fue 20ml/ min. Las fracciones de interés se recogieron y concentraron hasta sequedad usando un evaporador Zymark Turbo Vap Evaporator. El análisis de RMN se llevó a cabo en los picos de interés (tiempo de retención analítica 5,69 minutos y 6,30 minutos). Se determinó que el compuesto del epígrafe era el pico con tiempo de retención analítica de 6,30 minutos por análisis de RMN (rotómeros). RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,17 (s, 0,5 H) 0,91 (t, *J*=6,87 Hz, 3,3 H) 1,10 (t, *J*=14,95 Hz, 1,2 H) 1,17 - 1,32 (m, 2,6 H) 1,33 - 1,59 (m, 13,1 H) 1,68 - 1,83 (m, 3,5 H) 1,88 - 2,18 (m, 8,7H) 2,20 - 2,67 (m, 7,8 H) 2,76 - 3,05 (m, 3,3 H) 3,23 (d, *J*=10,99 Hz, 1,3 H) 3,29 - 3,53 (m, 1,6 H) 3,63 - 3,86 (m, 2,7 H) 3,88 - 3,98 (m, 6,0 H) 4,02 - 4,10 (m, 1,0 H) 4,61 (d, *J*=14,65 Hz, 1,3 H) 4,89 (d, *J*=14,95 Hz, 0,9 H) 6,76 - 6,86 (m, 0,8 H) 6,91 - 7,00 (m, 1,9 H) 7,06 - 7,13 (m, 1,3 H) 7,51 - 7,57 (m, 1,4 H) 7,57 - 7,66 (m, 1,6 H) 7,66 - 7,75 (m, 1,9 H) 7,89 (d, *J*=8,55 Hz, 1,5 H). Análisis LCMS usando software de LC-MS MassLynx 4,0 SP4, un automuestreador CTC-Leap HTS-PAL, con una bomba binaria Agilent 1100, detector UV Agilent 1100 fotodiodo, detector Polymer Lab 2100 ELS (Temp=45ºC, temperatura de nebulización 35ºC) y un espectrómetro de masas

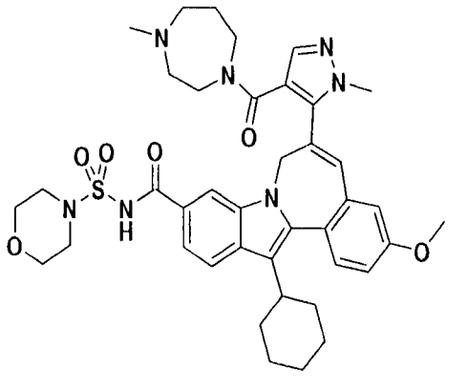
Waters ZQ con ESCi. El análisis se llevó a cabo usando una columna Phenomenex Gemini 4,6x 150mm C18 de 3u con un sistema disolvente de fase móvil de A= agua y acetato amónico 20mM, B= acetonitrilo con un caudal de 1,0 ml/min y un gradiente que comienza a 70% de A y 30% de B y una composición final de 5% de A y 95% de B, tiempo de gradiente de 11 minutos y un tiempo de mantenimiento de 2 minutos dando un tiempo de ejecución del análisis de 13 minutos.

Tiempo de retención = 6,63 minutos, m/z= 725 (MH+).

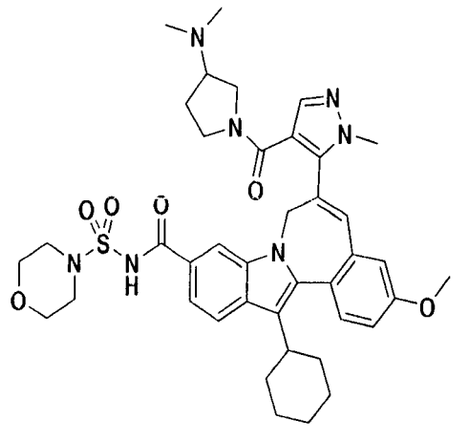
Los siguientes compuestos se sintetizaron por un procedimiento análogo al descrito antes para 13-ciclohexil-*N*-[(dimetilamino)sulfonil]-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-3-il]-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxamida y 13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-[[4-(1-metiletil)-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida. Los datos de LCMS analítica de los siguientes ejemplos se adquirieron usando las siguientes columnas y condiciones. Procedimiento 1: Gradiente: 3 minutos; Caudal: 5 ml/min; Tiempo de parada: Tiempo de gradiente + 1 minuto; Eluyente A: 5% de CH_3CN / 95% de H_2O con NH_4OAc 10 mM; Eluyente B: 95% de CH_3CN / 5% de H_2O con NH_4OAc 10 mM; %B Inicial= 30; %B Final=100; Columna: Waters Xterra, 3mm x 50mm, S7. Procedimiento 2: Gradiente: 3 minutos; Caudal: 5 ml/min; Tiempo de parada: Tiempo de gradiente + 1 minuto; Eluyente A= 10% de metanol, 90% de agua, 0,1% de ácido trifluoracético; %B= 90% de metanol, 10% de agua, 0,1% de ácido trifluoracético; %B Inicial= 40; %B Final=100; Columna: Phenomenex Luna 3,0mm x 50mm S10.



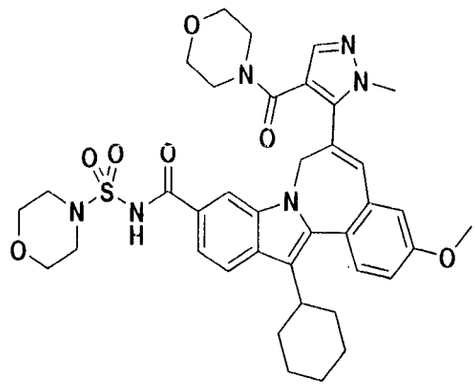
13-ciclohexil-3-metoxi-6-[1-metil-4-[[metil(1-metil-3-pirrolidinil)amino]carbonil]-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.: LCMS m/e 756 (M+H), tiempo de retención 2,30 min.



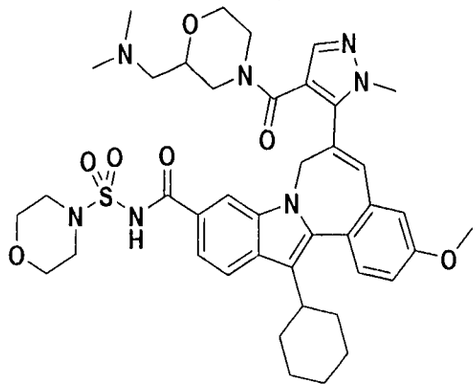
13-ciclohexil-6-[4-[(hexahidro-4-metil-1H-1,4-diazepin-1-il)carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. LCMS m/e 756 (M+H), tiempo de retención 2,10 min.



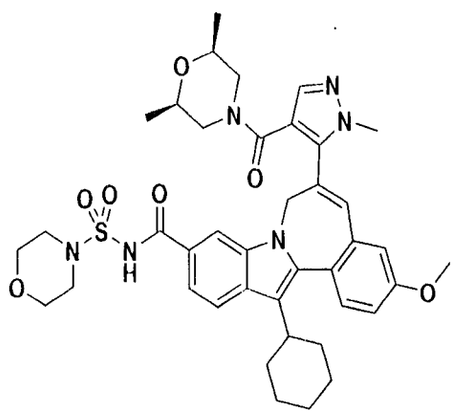
13-ciclohexil-6-[4-[[3-(dimetilamino)-1-pirrolidinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 756 (M+H), tiempo de retención 2,40 min.



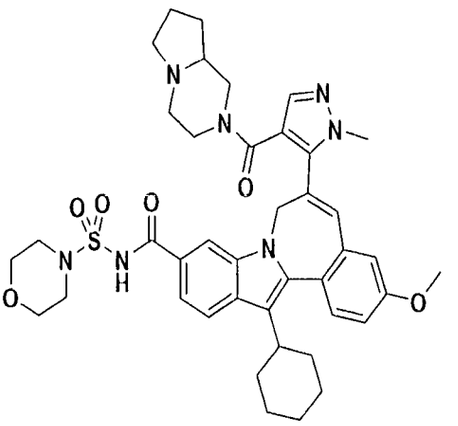
13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 729 (M+H), tiempo de retención 2,60 min.



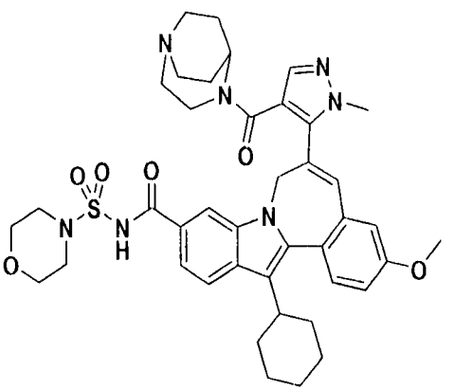
13-ciclohexil-6-[4-[[2-[(dimetilamino)metil]-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 787 (M+H), tiempo de retención 2,40 min.



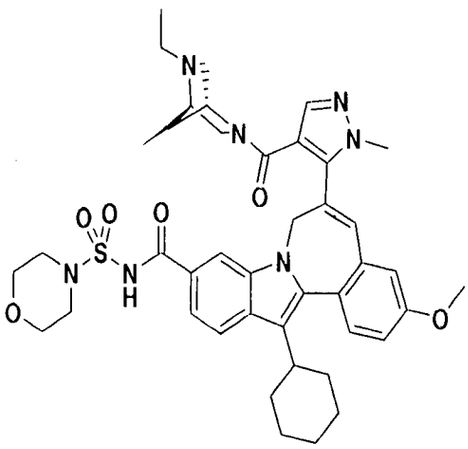
13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 757 (M+H), tiempo de retención 2,80 min.



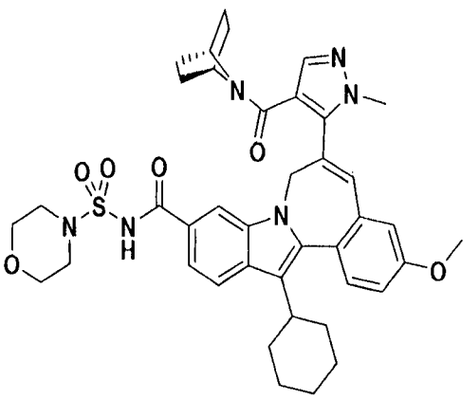
13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 768 (M+H), tiempo de retención 2,40 min.



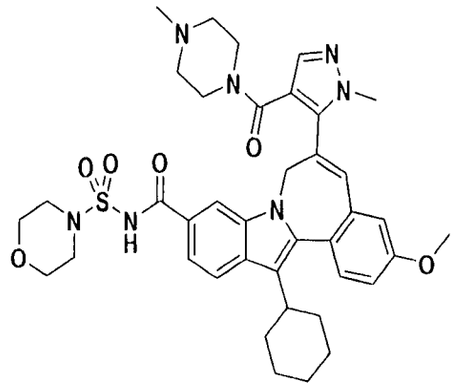
13-ciclohexil-6-[4-(1,4-diazabiciclo[3.2.2]non-4-ilcarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. LCMS m/e 768 (M+H), tiempo de retención 2,10 min.



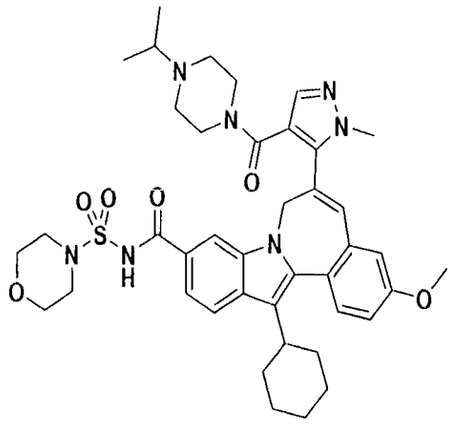
13-ciclohexil-6-[4-[[(1R,4R)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. LCMS m/e 768 (M+H), tiempo de retención 2,30 min.



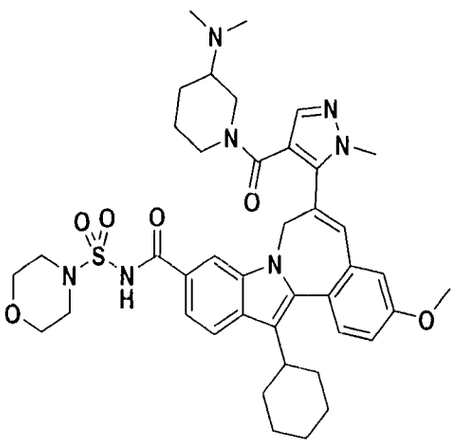
6-[4-(7-azabiciclo[2.2.1]hept-7-ilcarbonil)-1-metil-1H-pirazol-5-il]-13-ciclohexil-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. LCMS m/e 739 (M+H), tiempo de retención 3,10 min.



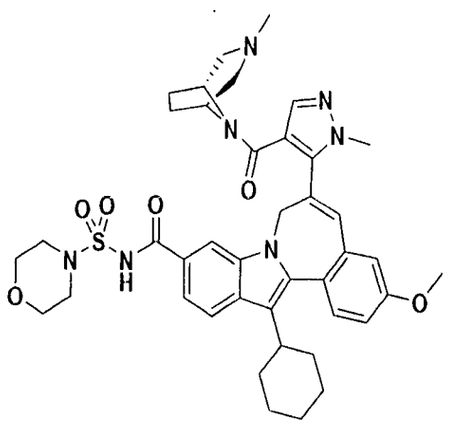
13-ciclohexil-3-metoxi-6-[1-metil-4-[(4-metil-1-piperazinil)carbonil]-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. LCMS m/e 742 (M+H), tiempo de retención 2,30 min.



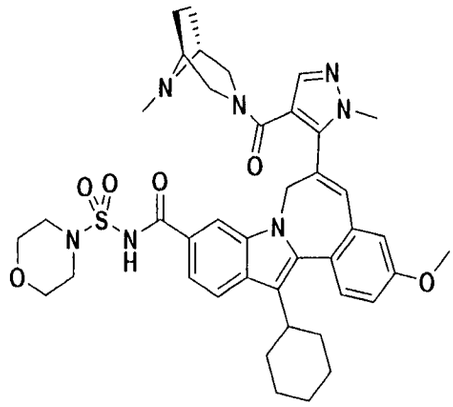
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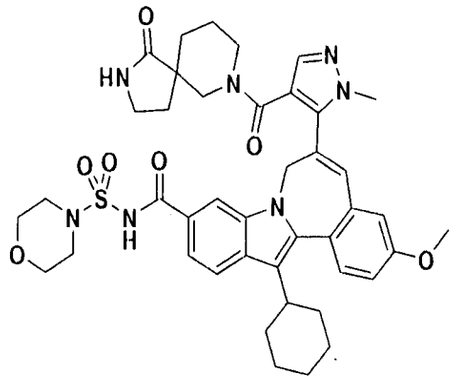
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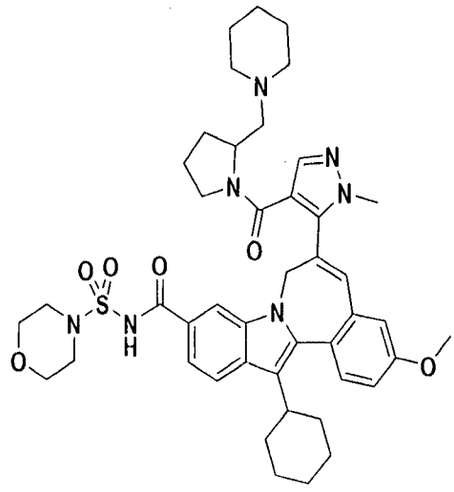
13-ciclohexil-3-metoxi-6-[1-metil-4-[[(1R,5S)-3-metil-3,8-diazabiciclo[3.2.1]oct-8-il]carbonil]-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 768 (M+H), tiempo de retención 2,60 min.



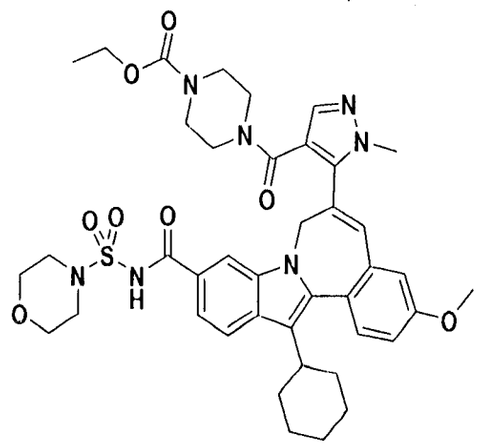
13-ciclohexil-3-metoxi-6-[1-metil-4-[[(1R,5S)-8-metil-3,8-diazabiciclo[3.2.1]oct-3-il]carbonil]-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 768 (M+H), tiempo de retención 2,60 min.



13-ciclohexil-3-metoxi-6-[1-metil-4-[(1-oxo-2,7-diazaspiro[4.5]dec-7-il)carbonil]-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 797 (M+H), tiempo de retención 2,40 min.

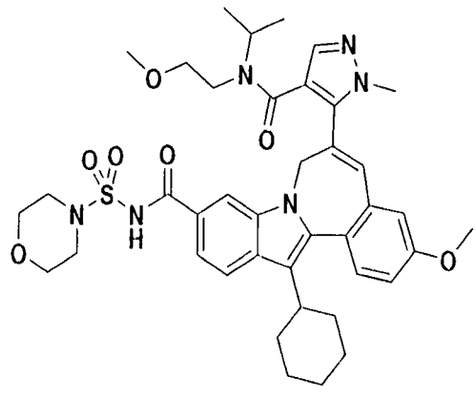


13-ciclohexil-3-metoxi-6-[1-metil-4-[[2-(1-piperidinilmetil)-1-pirrolidinil]carbonil]-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 811 (M+H), tiempo de retención 2,50 min.

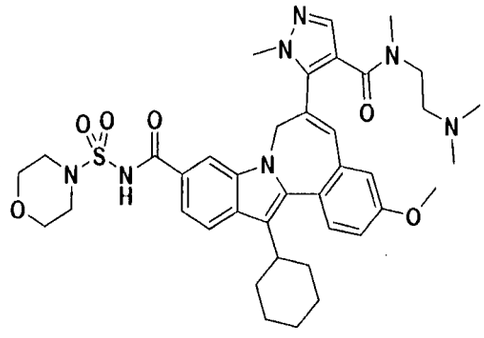


éster etílico del ácido 4-[[5-[13-ciclohexil-3-metoxi-10-[[(4-morfolinilsulfonil)amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-il]carbonil]-1-piperazincarboxílico. CMS m/e 800 (M+H), tiempo de

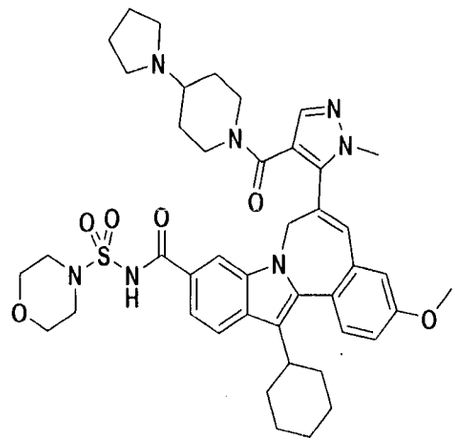
retención 2,60 min.



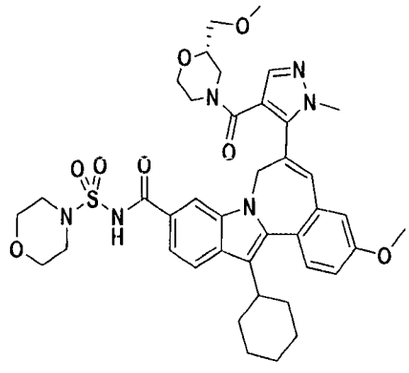
13-ciclohexil-3-metoxi-6-[4-[[(2-metoxietil)(1-metiletil)amino]carbonil]-1-metil-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 759 (M+H), tiempo de retención 2,80 min.



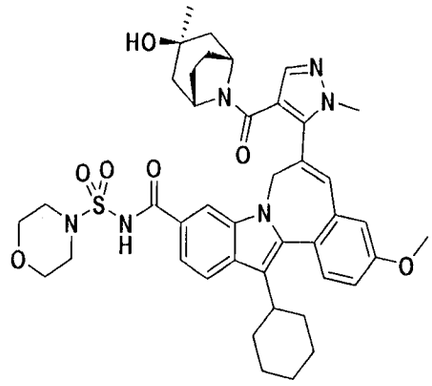
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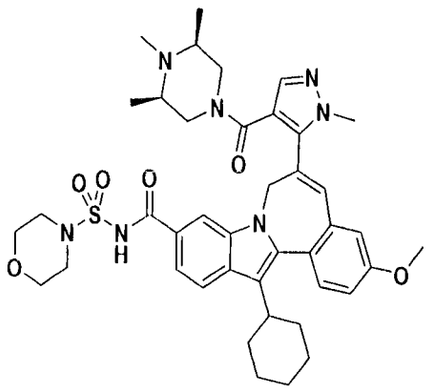
13-ciclohexil-3-metoxi-6-[1-metil-4-[[4-(1-pirrolidinil)-1-piperidinil]carbonil]-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. LCMS m/e 797 (M+H), tiempo de retención 2,30 min.



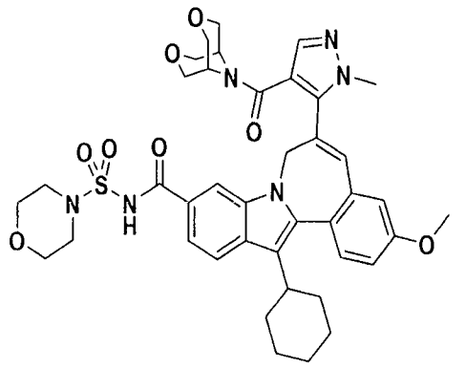
13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(meloximetil)-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 773 (M+H), tiempo de retención 2,60 min.



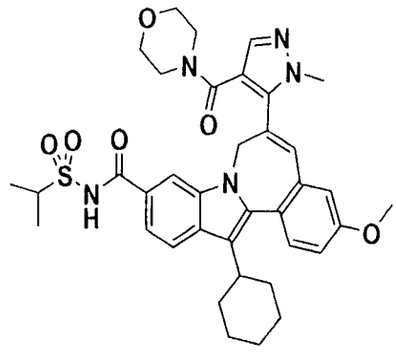
13-ciclohexil-6-[4-[[(3-endo)-3-hidroxi-3-metil-8-azabiciclo[3.2.1]oct-8-il]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 784 (M+H), tiempo de retención 2,70 min.



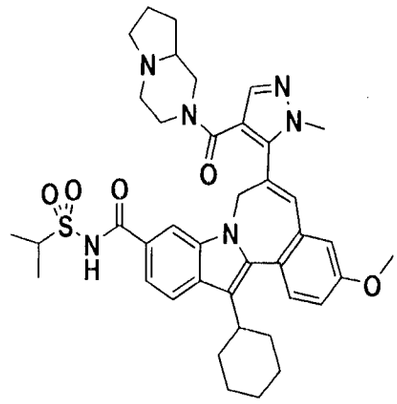
13-ciclohexil-3-metoxi-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. LCMS m/e 771 (M+H), tiempo de retención 2,30 min.



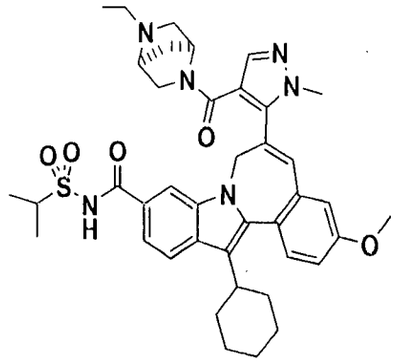
13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. CMS m/e 771 (M+H), tiempo de retención 2,60 min.



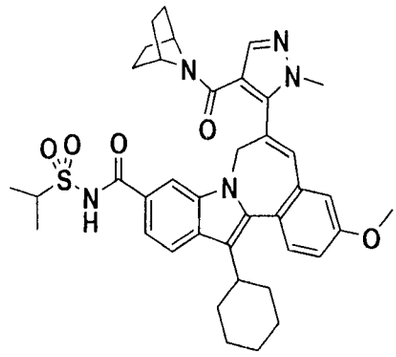
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 686 (M+H), tiempo de retención 3,49 min (procedimiento 2).



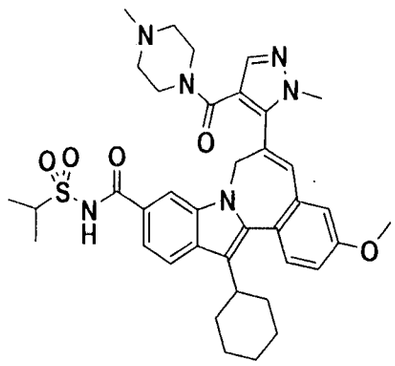
13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 725 (M+H), tiempo de retención 2,99 min (procedimiento 2).



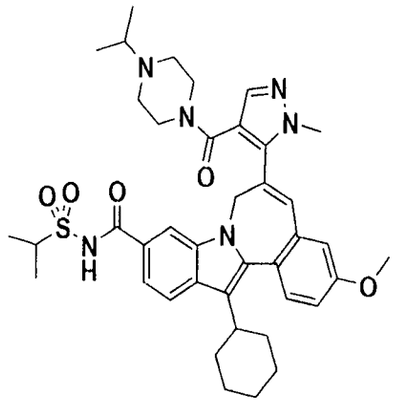
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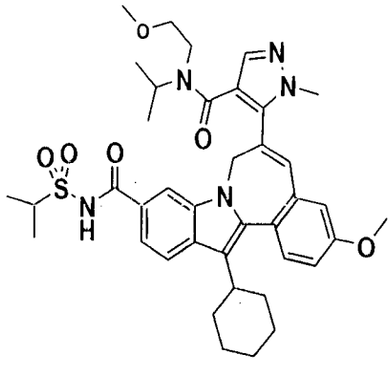
6-[4-(7-azabiciclo[2.2.1]hept-7-ilcarbonil)-1-metil-1H-pirazol-5-il]-13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 696 (M+H), tiempo de retención 3,32 min (procedimiento 2).



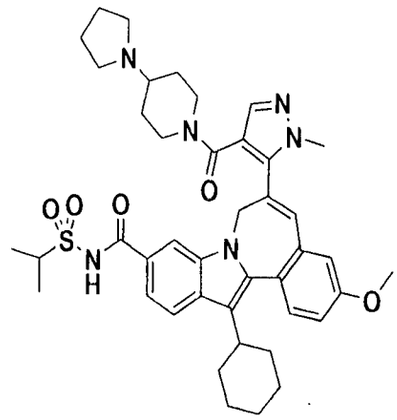
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[(4-metil-1-piperazinil)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 699 (M+H), tiempo de retención 3,05 min (procedimiento 2).



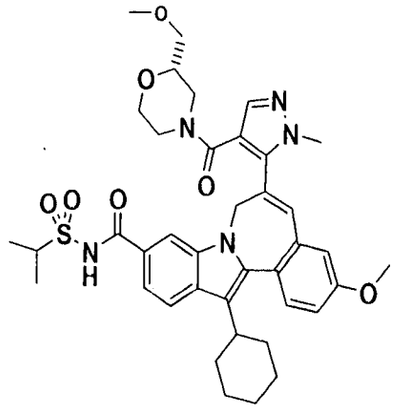
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[[4-(1-metiletil)-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 727 (M+H), tiempo de retención 3,19 min (procedimiento 2).



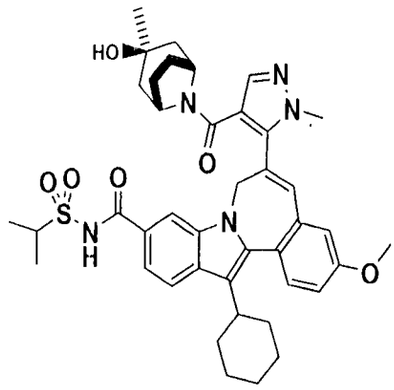
13-ciclohexil-3-metoxi-6-[4-[[(2-metoxietil)(1-metiletil)amino]carbonil]-1-metil-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 716 (M+H), tiempo de retención 3,37 min (procedimiento 2).



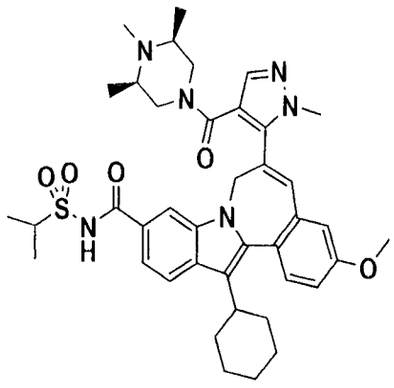
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[[4-(1-pirrolidinil)-1-piperidinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 753 (M+H), tiempo de retención 3,22 min (procedimiento 2).



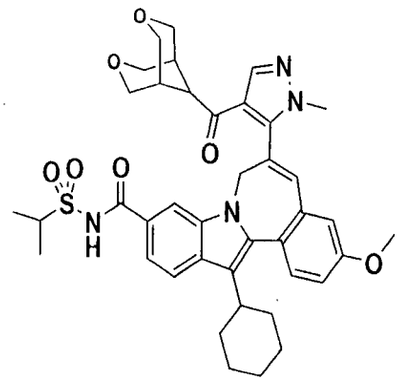
13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 730 (M+H), tiempo de retención 3,51 min (procedimiento 2).



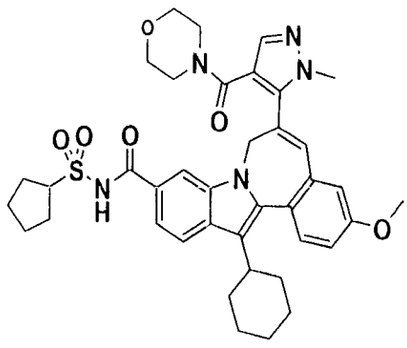
13-ciclohexil-6-[4-[[(3-endo)-3-hidroxi-3-metil-8-azabiciclo[3.2.1]oct-8-il]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 740 (M+H), tiempo de retención 2,53 min (procedimiento 2).



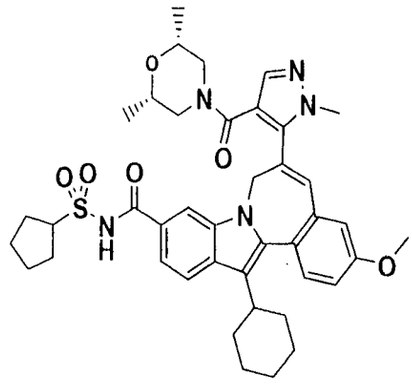
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 727 (M+H), tiempo de retención 2,26 min (procedimiento 2).



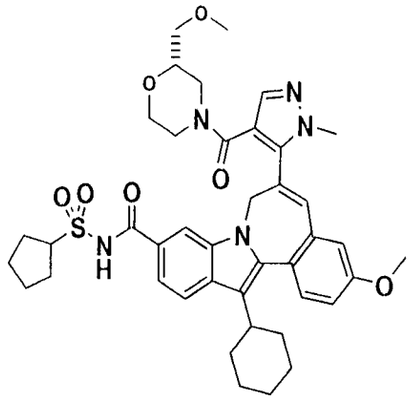
13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 727 (M+H), tiempo de retención 3,50 min (procedimiento 2).



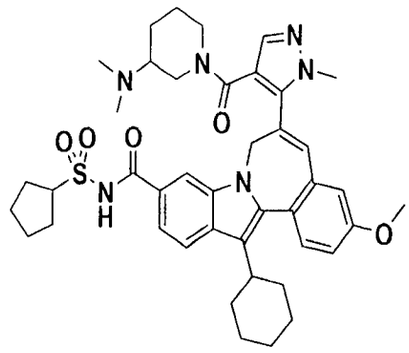
13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 712 (M+H), tiempo de retención 2,65 min (procedimiento 1).



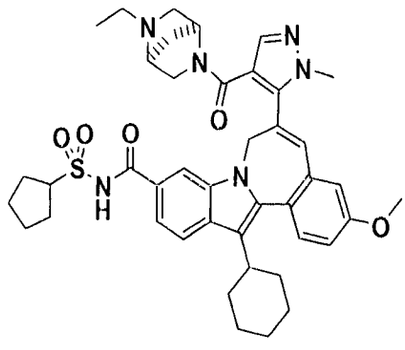
13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 740 (M+H), tiempo de retención 2,84 min (procedimiento 1).



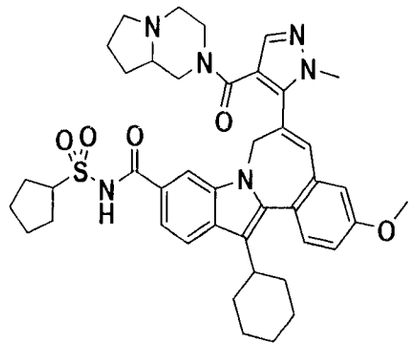
13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 756 (M+H), tiempo de retención 2,79 min (procedimiento 1).



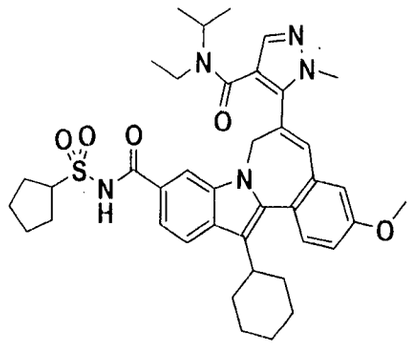
13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 753 (M+H), tiempo de retención 2,41 min (procedimiento 1).



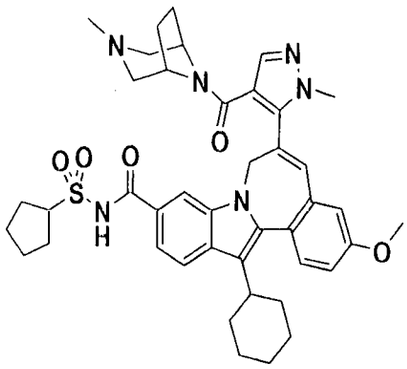
13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 751 (M+H), tiempo de retención 2,51 min (procedimiento 1).



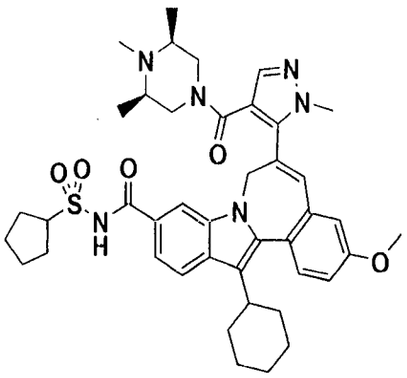
13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 751 (M+H), tiempo de retención 2,29 min (procedimiento 1).



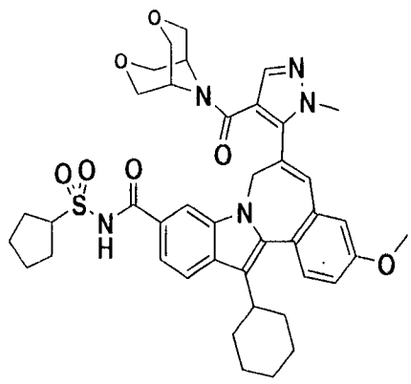
13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[[etil(1-metiletil)amino]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 712 (M+H), tiempo de retención 2,45 min (procedimiento 1).



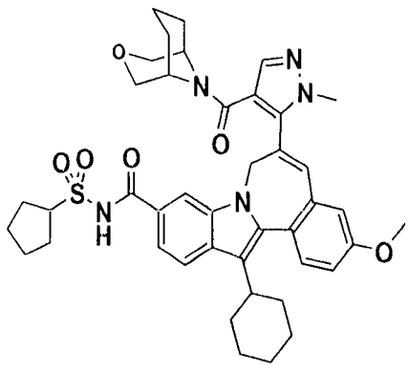
13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 751 (M+H), tiempo de retención 2,36 min (procedimiento 1).



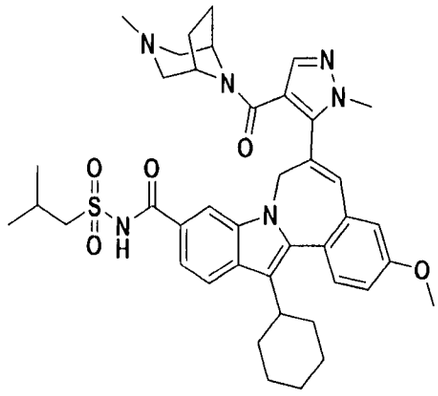
13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 753 (M+H), tiempo de retención 2,39 min (procedimiento 1).



13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 754 (M+H), tiempo de retención 2,87 min (procedimiento 1).



13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[1-metil-4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 752 (M+H), tiempo de retención 2,92 min (procedimiento 1).



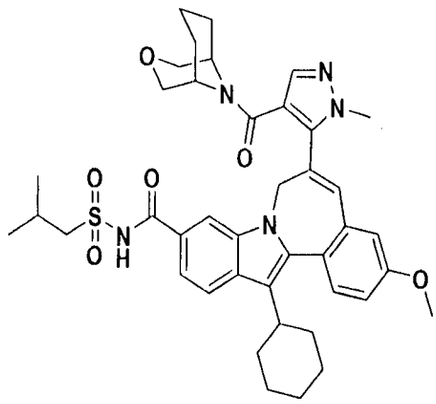
13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-N-(2-metilpropil)sulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces 3-metil-3,8-diazabiciclo[3.2.1]octano, 2HCl (14,21 mg, 0,071 mmol) y la solución se agitó a TA durante la noche. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron proporcionando el compuesto del epígrafe como un sólido color marrón, (36,3 mg, 0,043 mmol, 89 % de rendimiento).

MS m/z 739(MH^+), Tiempo de retención: 2,070 min (básico).

RMN de ^1H (500 MHz, MeOD) δ ppm 1,12 (d, *J*=6,71 Hz, 6 H) 1,18 - 2,19

(m, 14 H) 2,24 - 2,37 (m, 1 H) 2,75 (s, 3 H) 2,81 - 3,28 (m, 7 H) 3,45 - 3,52 (m, 2 H) 3,63 - 3,83 (s ancho, 3 H) 3,91 (s, 3 H) 4,61 (d, *J*=14,65 Hz, 1 H) 4,90 - 4,94 (m, 1 H) 7,07 - 7,19 (m, 3 H) 7,54 - 7,60 (m, 2 H) 7,81 (s ancho, 2 H) 7,93 (d, *J*=8,54 Hz, 1 H).



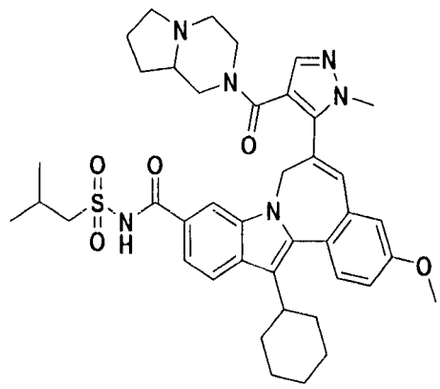
13-ciclohexil-3-metoxi-6-[1-metil-4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1H-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces 3-oxa-9-azabiciclo[3.3.1]nonano, HCl (11,67 mg, 0,071 mmol) y la solución se agitó a TA durante la noche. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío. El compuesto del epígrafe se obtuvo como un sólido parduzco, (29,5 mg, 0,040 mmol, 84 % de

rendimiento).

MS m/z 738(M-H$^-$), Tiempo de retención: 1,928 min.(básico)

RMN de ^{1}H (500 MHz, MeOD) δ ppm 1,04 - 2,40 (m, 23 H) 2,72 - 3,05 (m, 3 H) 3,41 - 4,02 (m, 12 H) 4,61 - 4,69 (m ancho, 1 H) 4,99 - 5,08 (m ancho, 1 H) 7,09 - 7,25 (m, 3 H) 7,55 - 7,66 (m, 2 H) 7,66 - 7,73 (m, 1 H) 7,85 - 8,03 (m, 2 H).



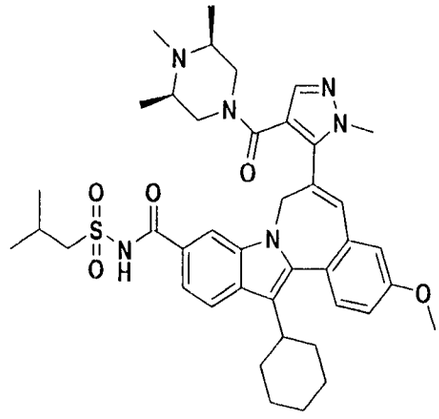
13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces octahidropirrolo[1,2-a]pirazina (9,00 mg, 0,071 mmol) y se agitó la solución a TA durante la noche. La mezcla de reacción se purificó entonces por columna

de HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron en un Speed Vac. La sal TFA del compuesto del epígrafe se obtuvo como un sólido parduzco, (35,5 mg, 0,042 mmol, 88 % de rendimiento).

MS m/z 737 ($M-H^+$), Tiempo de retención: 1,722 min. (básico)

RMN de ^1H (500 MHz, MeOD) δ ppm 1,15 (d, *J*=6,71 Hz, 6 H) 1,19 - 2,23 (m, 14 H) 2,26 - 2,40 (m, 1 H) 2,88 - 3,05 (m, 1 H) 3,11 - 3,58 (m, 11 H) 3,72 (s, 3 H) 3,95 (s, 3 H) 4,60-4,70 (m ancho, 1 H) 5,00 - 5,16 (m ancho, 1 H) 7,11 (s, 1 H) 7,16 (d, *J*=2,44 Hz, 1 H) 7,20 (dd, *J*=8,54, 2,75 Hz, 1 H) 7,58 - 7,64 (m, 2 H) 7,76 (s, 1 H) 7,91 (s, 1 H) 7,99 (d, *J*=8,55 Hz, 1 H).



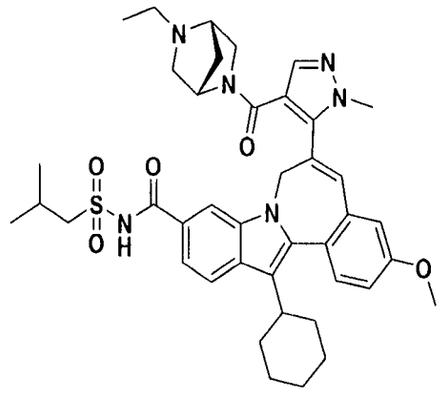
13-ciclohexil-3-metoxi-N-[(2-metilpropil)sulfonil]-6-[1-metil-4-[[cis-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de

reacción se agitó a TA durante 15 minutos. Se añadió entonces cis-1,2,6-trimetilpirazina (9,15 mg, 0,071 mmol) y se agitó la solución a TA durante la noche. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío. La sal TFA del compuesto del epígrafe se obtuvo como un sólido parduzco, (39,1 mg, 0,046 mmol, 96 % de rendimiento).

MS m/z 739 ($M-H^+$), Tiempo de retención: 1,723 min. (básico)

RMN de ^1H (500 MHz, MeOD) δ ppm 1,15 (d, *J*=7,02 Hz, 6 H) 1,21 - 1,65 (m, 10 H) 1,77 - 2,22 (m, 6 H) 2,29 - 2,40 (m, 1 H) 2,54 - 3,05 (m, 8 H) 3,51 (d, *J*=6,41 Hz, 2 H) 3,74 (s, 3 H) 3,95 (s, 3 H) 4,03 - 4,42 (m ancho, 2 H) 4,59 - 4,70 (m ancho, 1 H) 5,01 - 5,12 (m ancho, 1 H) 7,13 (s, 1 H) 7,16 (d, *J*=2,75 Hz, 1 H) 7,21 (dd, *J*=8,85, 2,75 Hz, 1 H) 7,59 - 7,66 (m, 2 H) 7,74 (s, 1 H) 7,93 (s, 1 H) 8,00 (d, *J*=8,55 Hz, 1 H).



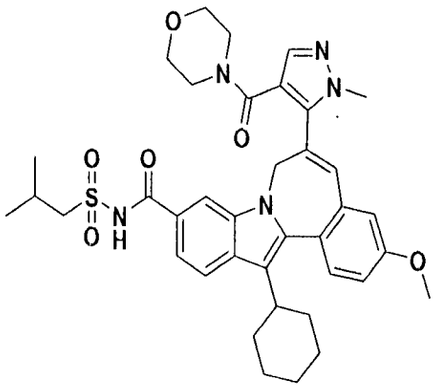
13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-

a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces (1S, 4S)-2-etil-2,5-diazabiciclo[2.2.1]heptano, 2TFA (25,3 mg, 0,071 mmol) y la solución resultante se agitó a TA durante 3 horas. El análisis LC/MS mostró que la reacción había progresado hasta completarse. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se recogieron y concentraron a vacío. La sal TFA del compuesto del epígrafe se obtuvo como un sólido color marrón, (35,30 mg, 0,041 mmol, 87 % de rendimiento).

MS m/z 737($M-H^+$), Tiempo de retención: 1,850 min. (básico)

RMN de ^1H (500 MHz, MeOD) δ ppm 1,15 (d, *J*=6,71 Hz, 6 H) 1,21 - 2,22 (m, 15 H) 2,25 - 2,39 (m, 1 H) 2,89 - 3,02 (m, 1 H) 3,05 - 3,80 (m, 12 H) 3,95 (s, 3 H) 4,09 - 4,48 (m, 1 H) 4,57 - 4,70 (m, 1 H) 4,99 - 5,12 (m, 1 H) 6,97 - 7,08 (s ancho, 1 H) 7,14 (s, 1 H) 7,20 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,61 (d, *J*=8,85 Hz, 2 H) 7,82 (s, 1 H) 7,88 (s, 1 H) 7,97 (d, *J*=8,55 Hz, 1 H).



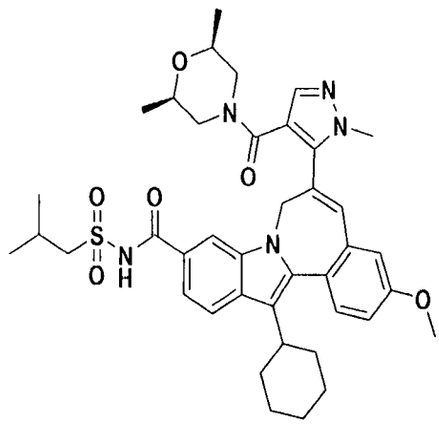
13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces morfolina (6,22 mg, 0,071 mmol) y la solución resultante se agitó a TA durante 3 horas. El análisis LC/MS mostró que la reacción había progresado hasta completarse. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío. El compuesto del epígrafe se obtuvo como un sólido amarillo, (28,4 mg, 0,041 mmol, 85 % de rendimiento).

MS m/z 698($M-H^+$), Tiempo de retención: 1,618 min. (básico)

RMN de ^1H (500 MHz, MeOD) δ ppm 1,16 (d, *J*=6,71 Hz, 6 H) 1,21 - 1,36 (m, 1 H) 1,40 - 1,64 (m, 3 H) 1,75 - 1,87 (m, 2 H) 1,94 - 2,25 (m, 4 H) 2,27 - 2,41 (m, 1 H) 2,70 - 3,12 (m, 9 H) 3,49 - 3,55 (m, 2 H) 3,85 (s, 3 H) 3,95 (s, 3 H) 4,69 (d, *J*=14,34 Hz, 1 H) 5,10 (d, *J*=14,95 Hz, 1 H) 7,09 (s, 1 H) 7,16 (d, *J*=2,44

Hz, 1 H) 7,20 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,62 (d, *J*=8,54 Hz, 2 H) 7,66 (s, 1 H) 7,94 (s, 1 H) 7,99 (d, *J*=8,55 Hz, 1 H).



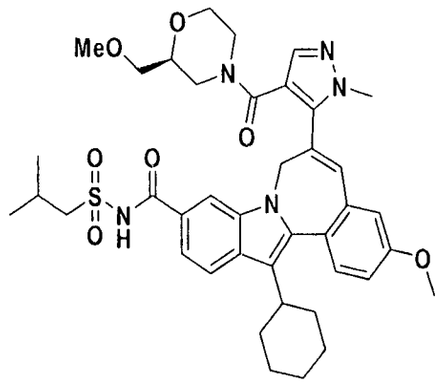
13-ciclohexil-6-[4-[[cis-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces cis-2,6-dimetilmorfolina (8,22 mg, 0,071 mmol) y la solución resultante se agitó a TA durante 3 horas. La LC/MS mostró entonces que la reacción había progresado hasta completarse. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se recogieron y concentraron a vacío. El compuesto del epígrafe se obtuvo como un sólido amarillo, (29,6 mg, 0,041 mmol, 85 % de

rendimiento).

MS m/z 726($M-H^-$), Tiempo de retención: 1,753 min. (básico)

RMN de ^1H (500 MHz, MeOD) δ ppm 0,50 - 2,56 (m, 23 H) 2,68 - 3,06 (m, 2 H) 3,21 - 3,63 (m, 7 H) 3,63 - 4,02 (m, 6 H) 4,67 (d, *J*=14,34 Hz, 1 H) 5,04 (d, *J*=14,65 Hz, 1 H) 7,11 - 7,25 (m, 3 H) 7,56 - 7,69 (m, 3 H) 7,93 (s, 1 H) 7,99 (d, *J*=8,24 Hz, 1 H).



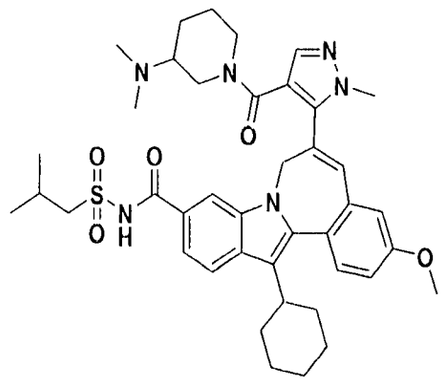
13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces (S)-2-(metoximetil)morfolina, HCl (11,96 mg, 0,071 mmol) y la solución resultante se agitó a TAdurante 3 horas. El análisis LC/MS mostró entonces que la reacción había progresado hasta completarse. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema

disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío. El compuesto del epígrafe se obtuvo como un sólido amarillo, (28,6 mg, 0,038 mmol, 81 % de rendimiento).

MS m/z 742($M-H^-$), Tiempo de retención: 1,598 min. (básico)

RMN de ^1H (500 MHz, MeOD) δ ppm 1,16 (d, *J*=6,71 Hz, 6 H) 1,22 - 1,65 (m, 4 H) 1,75 - 2,24 (m, 6 H) 2,28 - 2,42 (m, 1 H) 2,88 - 3,63 (m, 15 H) 3,81 (s, 3 H) 3,95 (s, 3 H) 4,61 - 4,72 (m, 1 H) 5,02 - 5,14 (m, 1 H) 7,11 (s, 1 H) 7,17 (d, *J*=2,44 Hz, 1 H) 7,20 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,56 - 7,65 (m, 2 H) 7,66 (s, 1 H) 7,93 (s, 1 H) 7,96 - 8,03 (m, 1 H).



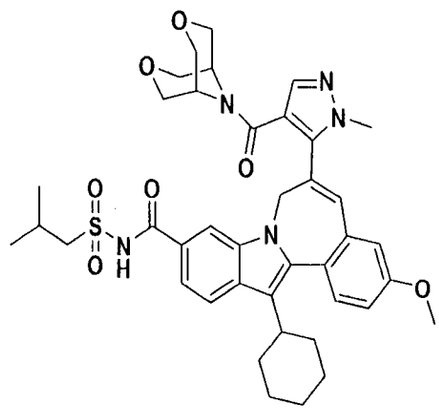
13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces 1,N-dimetilpiperidin-3-amina, 2HCl (14,35 mg, 0,071 mmol) y la solución resultante

se agitó a TA durante 3 horas. La LC/MS mostró entonces que la reacción había progresado hasta completarse. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se recogieron y concentraron a vacío. La sal TFA del compuesto del epígrafe se obtuvo como un sólido amarillo, (36,3 mg, 0,042 mmol, 89 % de rendimiento).

MS m/z 739($M-H^+$), Tiempo de retención: 1,810 min. (básico)

RMN de ^1H (500 MHz, MeOD) δ ppm 1,16 (d, *J*=6,71 Hz, 6 H) 1,22 - 1,64 (m, 6 H) 1,75 - 2,24 (m, 8 H) 2,29 - 2,39 (m, 1 H) 2,46 - 3,13 (m, 11 H) 3,51 (d, *J*=6,41 Hz, 2 H) 3,83 (s, 3 H) 3,95 (s, 3 H) 4,16 (s ancho, 1 H) 4,61 - 4,73 (m ancho, 1 H) 5,00 - 5,12 (m ancho, 1 H) 7,09 (s, 1 H) 7,16 (d, *J*=2,44 Hz, 1 H) 7,20 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,60 (d, *J*=8,85 Hz, 1 H) 7,64 (dd, *J*=8,55, 1,22 Hz, 1 H) 7,69 (s, 1 H) 7,94 (s, 1 H) 8,01 (d, *J*=8,24 Hz, 1 H).

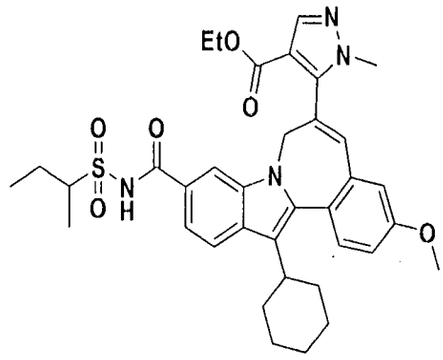


13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (30 mg, 0,048 mmol) en DMSO (1 ml) se añadieron TBTU (22,91 mg, 0,071 mmol) y DIPEA (0,042 ml, 0,238 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces 3,7-dioxa-9-azabiciclo[3.3.1]nonano (9,21 mg, 0,071 mmol) y la solución se agitó a TA durante la noche. La LC/MS mostró entonces que solo había reaccionado el 40% del material de partida. Se añadieron entonces dos equivalentes más de TBTU y la mezcla de reacción e agitó a TAdurante la noche. La LC/MS mostró entonces que la reacción había progresado hasta completarse. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y evaporaron a vacío dando el compuesto del epígrafe como un sólido color amarillo claro, (26,7 mg, 0,036 mmol, 76 % de rendimiento).

MS m/z 740($M-H^-$), Tiempo de retención: 1,887 min. (básico)

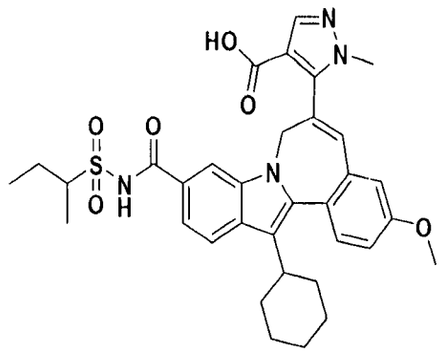
RMN de ^1H (500 MHz, MeOD) δ ppm 1,16 (d, *J*=6,71 Hz, 6 H) 1,21 - 1,64 (m, 4 H) 1,71 - 3,15 (m, 10 H) 3,43 - 3,88 (m, 13 H) 3,96 (s, 3 H) 4,63 - 4,72 (m, 1 H) 5,01 - 5,11 (m, 1 H) 7,13 - 7,18 (m, 2 H) 7,22 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,61 (d, *J*=8,55 Hz, 1 H) 7,64 (d, *J*=8,85 Hz, 1 H) 7,74 (s, 1 H) 7,91 (s, 1 H) 7,98 (d, *J*=8,55 Hz, 1 H).



Éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico.

Se añadió CDI (451 mg, 2,78 mmol) a una solución en THF (10 ml) de ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (750 mg, 1,39 mmol) y la mezcla resultante se agitó a 60ºC durante 1 h. La reacción se enfrió entonces hasta temperatura ambiente y se añadieron butano-2-sulfonamida (572 mg, 4,17 mmol) y DBU (0,419 ml, 2,78 mmol). La mezcla se calentó entonces a 60ºC durante la noche, después de lo cual el disolvente se eliminó a vacío y el residuo se disolvió en EtOAc. La fase orgánica se lavó secuencialmente con solución 1N de HCl (3 x 20 ml) y salmuera (3 x 20 ml) y luego se secó sobre Na_2SO_4. La mezcla se filtró entonces y el filtrado se evaporó a vacío. El residuo se purificó usando una HPLC preparativa Shimadzu usando ACN/agua y tampón TFAal 0,1 % con una columna Xterra, 30 mm x 100 mm, Gradiente durante 15 min; Concentración inicial: 10 % B; Concentración final: 100 % B. Las fracciones homogéneas se reunieron y evaporaron a presión reducida proporcionando el compuesto del epígrafe como un sólido amarillo claro, (450

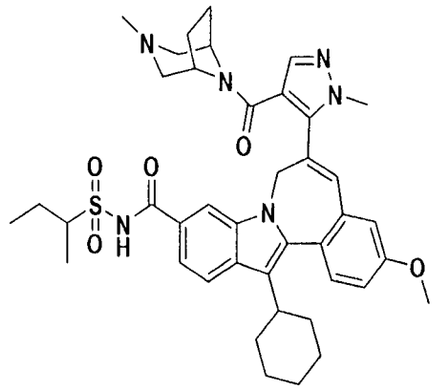
mg, 49 %). ESI-MS *m/e* 659 (MH^+).



Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]-carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico.

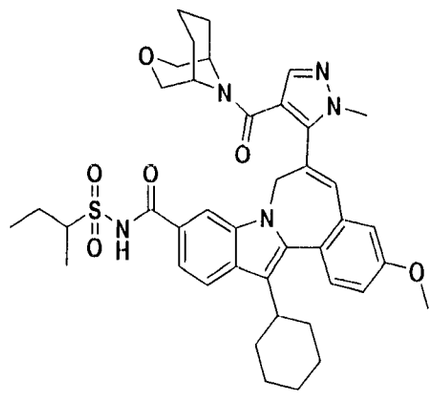
Se añadió NaOH (1N, 5 ml) a una solución de éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico (250 mg, 0. 379 mmol) en una mezcla 1:1 de THF:MeOH (10 ml) y la solución resultante se agitó a TA durante 43 horas. Se añadió entonces HCl (1N, 5 ml) y la mezcla resultante se evaporó a presión reducida. El residuo se disolvió en EtOAc y se lavó con salmuera (3 x 20 ml) y luego se secó sobre Na_2SO_4. La mezcla se filtró seguidamente y el filtrado se evaporó a vacío proporcionando el producto del epígrafe como un sólido amarillo, (235 mg, 98%). ESI-MS *m/e* 631 (MH^+).

Usando las condiciones de acoplamiento de amida convencionales descritas para los ejemplos relacionados se pueden preparar los siguientes ejemplos.



13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

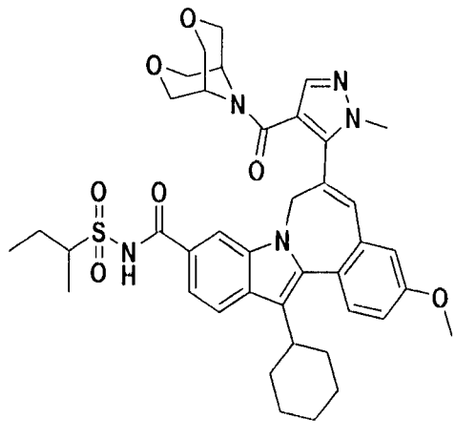
ESI-MS *m/e* 739 (MH^+). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,08 (t, *J*=7,32 Hz, 3 H) 1,16 - 1,56 (m, 9 H) 1,58 - 1,85 (m, 4 H) 1,90 - 2,24 (m, 6 H) 2,48 - 2,62 (m, 3 H) 2,81 - 2,99 (m, 3 H) 3,15 - 3,45 (m, 3 H) 3,73 - 4,05 (m, 5 H) 3,94 (s, 3 H) 4,58 - 4,69 (m, 1 H) 4,80 - 5,02 (m, 1 H) 6,92 - 7,01 (m, 2 H) 7,13 (dd, *J*=8,70, 2,29 Hz, 1 H) 7,53 - 7,82 (m, 4 H) 7,92 (d, *J*=8,24 Hz, 1 H) 10,14 (s, 1 H).



13-ciclohexil-3-metoxi-6-[1-metil-4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1H-pirazol-5-il]-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-

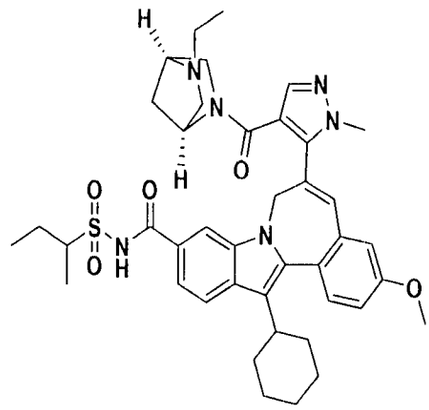
a][2]benzazepin-10-carboxamida

ESI-MS *m/e* 740 (MH^+). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,00 - 1,57 (m, 12 H) 1,68 - 1,84 (m, 3 H) 1,91 - 2,48 (m, 9 H) 2,81 - 2,94 (m, 1 H) 3,03 - 3,16 (m, 1 H) 3,18 - 3,72 (m, 5 H) 3,76 - 4,02 (m, 7 H) 4,53 - 4,68 (m, 1 H) 4,94 (d, *J*=15,87 Hz, 1 H) 6,81 - 6,91 (m, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,13 (d, *J*=8,54 Hz, 1 H) 7,54 - 7,62 (m, 1 H) 7,62 - 7,85 (m, 3 H) 7,87 - 7,96 (m, 1 H).



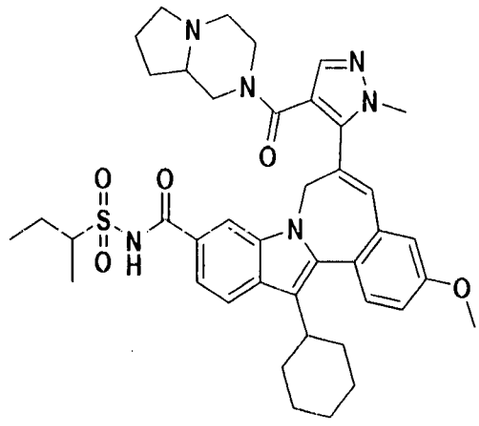
13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

ESI-MS *m/e* 742 (MH^+). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,02 - 1,13 (m, 3 H) 1,15 - 1,27 (m, 1 H) 1,31 - 1,56 (m, 6 H) 1,69 - 1,84 (m, 2 H) 1,92 - 2,39 (m, 6 H) 2,62 - 2,70 (m, 1 H) 2,83 - 2,93 (m, 1 H) 3,25 (s, 1 H) 3,30 - 3,49 (m, 3 H) 3,52 - 3,59 (m, 1 H) 3,66 - 3,76 (m, 3 H) 3,80 - 3,86 (m, 2 H) 3,89 (s, 3 H) 3,94 (s, 3 H) 4,63 (d, *J*=15,26 Hz, 1 H) 4,93 (d, *J*=15,56 Hz, 1 H) 6,86 (s, 1 H) 6,95 (d, *J*=2,44 Hz, 1 H) 7,13 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,59 (d, *J*=8,55 Hz, 1 H) 7,63 (d, *J*=8,54 Hz, 1 H) 7,72 (d, *J*=5,49 Hz, 2 H) 7,94 (d, *J*=8,55 Hz, 1 H) 10,08 - 10,26 (m, 1 H).



13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

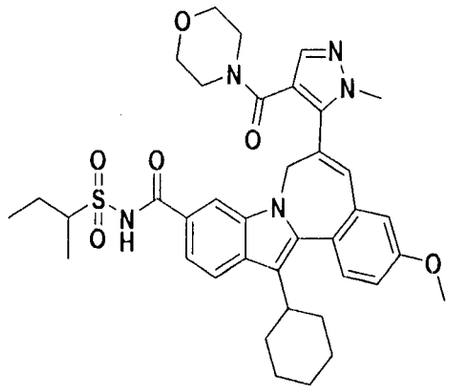
ESI-MS *m/e* 739 (MH^+). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,85 - 1,56 (m, 15 H) 1,58 - 2,39 (m, 8 H) 2,68 - 2,96 (m, 4 H) 3,03 - 3,38 (m, 3 H) 3,55 (d, *J*=5,19 Hz, 1 H) 3,72 - 4,03 (m, 5 H) 4,05 - 4,43 (m, 2 H) 4,51 - 5,04 (m, 3 H) 6,68 - 6,86 (m, 1 H) 6,88 - 7,18 (m, 2 H) 7,49 - 7,97 (m, 5 H) 8,17 - 8,28 (m, 1 H).



13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

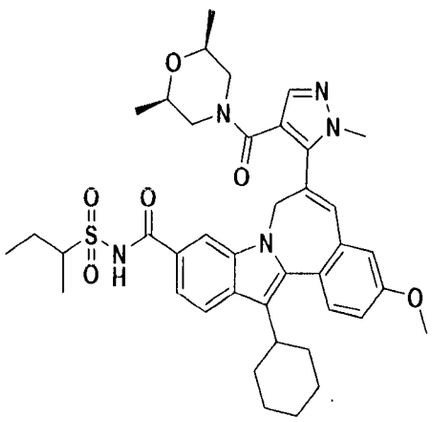
ESI-MS *m/e* 739 (MH^+)RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm

1,00 - 1,13 (m, 3 H) 1,21 - 1,58 (m, 7 H) 1,59 - 1,85 (m, 4 H) 1,90 - 2,49 (m, 11 H) 2,80 - 2,99 (m, 2 H) 3,34 - 3,88 (m, 9 H) 3,92 (s, 3 H) 4,54 - 4,69 (m, 1 H) 4,76 - 5,00 (m, 1 H) 6,83 - 6,94 (m, 1 H) 6,97 (s, 1 H) 7,06 - 7,15 (m, 1 H) 7,48 - 7,68 (m, *J*=35,71 Hz, 3 H) 7,75 (s, 1 H) 7,89 (s, 1 H).



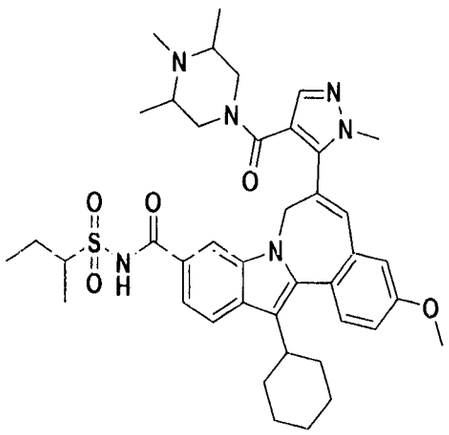
13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

ESI-MS *m/e* 700 (MH^+)RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,02 - 1,14 (m, 3 H) 1,16 - 1,30 (m, 1 H) 1,49 (dd, *J*=20,91, 6,87 Hz, 6 H) 1,34 - 1,45 (m, 1 H) 1,93 - 2,40 (m, 7 H) 2,58 - 2,71 (m, 1 H) 2,77 - 2,97 (m, 4 H) 3,04 - 3,25 (m, 2 H) 3,35 - 3,65 (m, 2 H) 3,79 - 3,88 (m, 1 H) 3,90 (s, 3 H) 3,94 (s, 3 H) 4,61 (d, *J*=15,87 Hz, 1 H) 4,90 (d, *J*=15,56 Hz, 1 H) 6,86 (s, 1 H) 6,96 (d, *J*=2,44 Hz, 1 H) 7,13 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,58 (d, *J*=8,55 Hz, 1 H) 7,61 (d, *J*=7,93 Hz, 1 H) 7,65 - 7,74 (m, 2 H) 7,94 (d, *J*=8,54 Hz, 1 H) 10,20 - 10,44 (m, 1 H).



13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

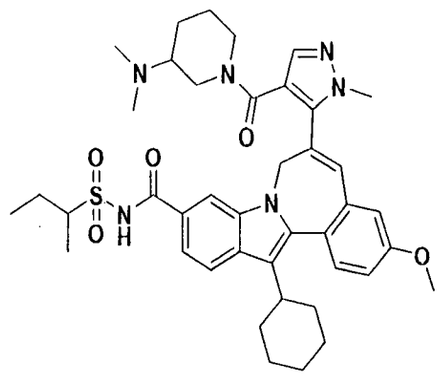
ESI-MS *m/e* 728 (MH^+)RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,98 - 1,13 (m, 3 H) 1,14 - 1,31 (m, 2 H) 1,34 - 1,59 (m, 6 H) 1,70 - 1,86 (m, 3 H) 1,88 - 2,32 (m, 12 H) 2,81 - 2,98 (m, 1 H) 2,95 - 3,14 (m, 1 H) 3,13 - 3,34 (m, 2 H) 3,36 - 3,67 (m, 1 H) 3,83 - 3,93 (m, 1 H) 3,92 (s, 3 H) 3,95 (s, 3 H) 4,61 (d, *J*=14,34 Hz, 1 H) 4,91 (d, *J*=15,56 Hz, 1 H) 6,83 (s, 1 H) 6,96 (s, 1 H) 7,13 (d, *J*=8,55 Hz, 1 H) 7,51 - 7,81 (m, 4 H) 7,92 (d, *J*=7,32 Hz, 1 H) 10,33 - 10,59 (m, 1 H).



13-ciclohexil-3-metoxi-N-[(1-metilpropil)sulfonil]-6-[1-metil-4-[(3,4,5-

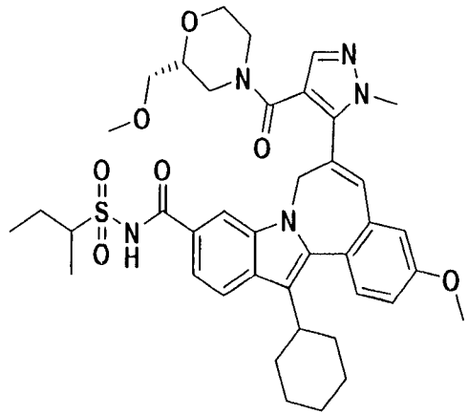
trimetil-1-piperazinil)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

ESI-MS *m/e* 741 (MH^+).RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,85 - 2,25 (m, 25 H) 2,27 - 2,64 (m, 3 H) 2,93 (s, 1 H) 3,28 - 3,69 (m, 4 H) 3,71 - 3,87 (m, 5 H) 3,94 (s, 3 H) 4,53 - 4,69 (m, 1 H) 4,83 - 5,01 (m, 1 H) 6,90 (s, 1 H) 6,97 (d, *J*=2,44 Hz, 1 H) 7,08 - 7,15 (m, 1 H) 7,50 - 7,66 (m, 3 H) 7,79 (d, *J*=1,53 Hz, 1 H) 7,93 (d, 1 H).



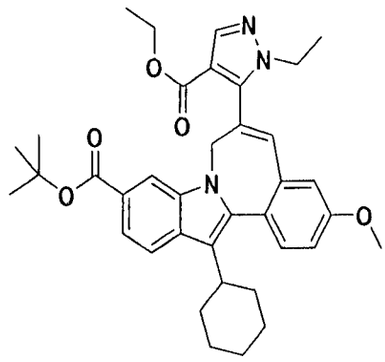
13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

ESI-MS *m/e* 741 (MH^+). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,01 - 1,15 (m, 3 H) 1,19 - 1,61 (m, 7 H) 1,64 - 2,28 (m, 15 H) 2,41 - 2,76 (m, 5 H) 2,82 - 2,96 (m, 1 H) 3,35 - 3,83 (m, 3 H) 3,78 - 3,91 (m, 3 H) 3,90 - 3,98 (m, 3 H) 4,19 - 4,40 (m, 1 H) 4,54 - 4,71 (m, 1 H) 4,78 - 4,98 (m, 1 H) 6,84 - 6,96 (m, 1 H) 6,95 - 7,01 (m, 1 H) 7,07 - 7,15 (m, 1 H) 7,50 - 7,58 (m, 1 H) 7,59 - 7,87 (m, 3 H) 7,90 - 7,99 (m, 1 H) 10,02 - 10,36 (m, 1 H).



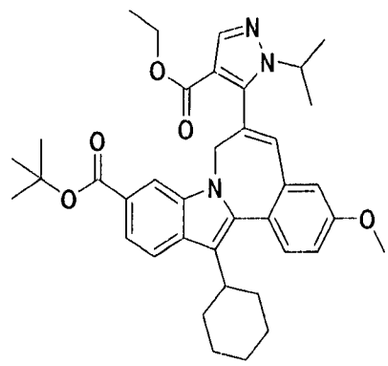
13-ciclohexil-3-metoxi-6-[4-[[2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-N-[(1-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

ESI-MS *m/e* 744 (MH^+) RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,01 - 1,15 (m, 2 H) 1,23 (d, *J*=15,26 Hz, 1 H) 1,33 - 1,59 (m, 5 H) 1,70 - 2,31 (m, 13 H) 2,36 - 2,53 (m, 1 H) 2,83 - 3,49 (m, 10 H) 3,81 - 3,93 (m, 3 H) 3,94 (s, 3 H) 4,60 (d, *J*=15,26 Hz, 1 H) 4,79 - 5,00 (m, 1 H) 6,85 (s, 1 H) 6,95 (s, 1 H) 7,12 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,50 - 7,81 (m, 4 H) 7,86 - 7,99 (m, 1 H) 10,29 - 10,54 (m, 1 H).



Éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-etil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. Se

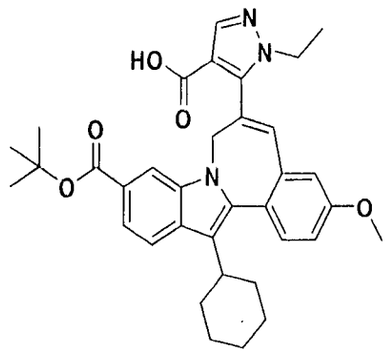
disolvió 13-ciclohexil-6-((2E,Z)-3-(dimetilamino)-2-(etoxicarbonil)-2-propenoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo (370mg, 0,604mmol) en etanol (1,7 ml) y se añadió la sal oxilato de etilhidrazina (100 mg, 0,664 mg) a la reacción a temperatura ambiente. La reacción se calentó hasta 80°C durante 3 horas. La reacción se diluyó con cloroformo y se lavó con agua. La fase orgánica se concentró a presión reducida y se purificó por HPLC Preparativa en las siguientes condiciones: HPLX prep. Shimadzu usando software Discovery VP: %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 30; %B final=100; Gradiente= 12min; Tiempo de ejecución= 20min; Caudal= 40ml/min; Columna= Waters Sunfire 30 x 100mm S5. Esto proporcionó el compuesto del epígrafe (265 mg, 72%) como una pasta amarilla. MS m/z 610 (MH^+).



Éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-(1-metiletil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico .

Se disolvió 13-ciclohexil-6-((2E,Z)-3-(dimetilamino)-2-(etoxicarbonil)-2-propenoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo (180 mg, 0,294 mmol) en una solución de etanol (1ml), trietilamina (82,0 ul, 0,588 mmol) y la sal clorhidrato de 2-propilhidrazina (36 mg, 0,323 mmol). La

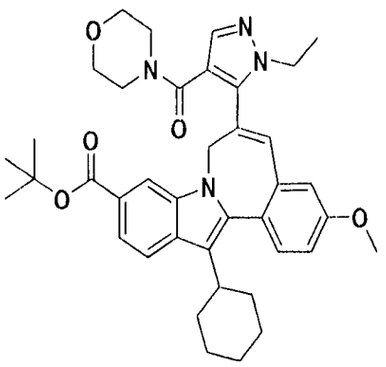
reacción se calentó en un microondas a 160°C durante 2 horas y luego se concentró. El sólido resultante se purificó por HPLC preparativa en las siguientes condiciones: HPLC preparativa Shimadzu usando software Discovery VP: %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 30; %B final=100; Gradiente= 12min; Tiempo de ejecución= 20min; Caudal= 40ml/min; Columna= Waters Sunfire 30 x 100mm S5. Las fracciones homogéneas se reunieron y evaporaron a vacío proporcionando el compuesto del epígrafe (127 mg, 69%) como una pasta amarilla. MS m/z 624 (MH^+).



*Éster 10-(1,1-dimetiletílico) del ácido 6-(4-carboxi-1-etil-1*H*-pirazol-5-il)-13-ciclohexil-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico.*

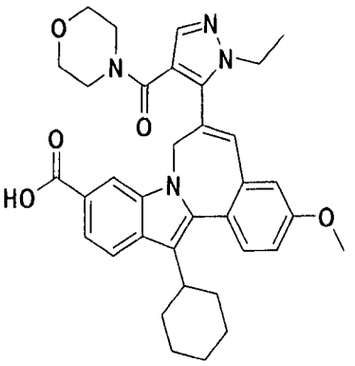
Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-etil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico (250 mg, 0,410 mmol) en 12 ml de metanol/THF (1:1, v/v) y se añadió hidróxido sódico acuoso 1M (6 ml, 6 mmol) a la reacción. La mezcla resultante se agitó a temperatura ambiente durante 18 horas y luego se diluyó con ácido clorhídrico acuoso 1M y el producto se extrajo con cloroformo. La

fase orgánica se secó sobre Na_2SO_4, se filtró y el filtrado se concentró a vacío dando el compuesto del epígrafe (251mg, 100%) que se usó en etapas posteriores sin purificación adicional. MS m/z 612 (MH^+).



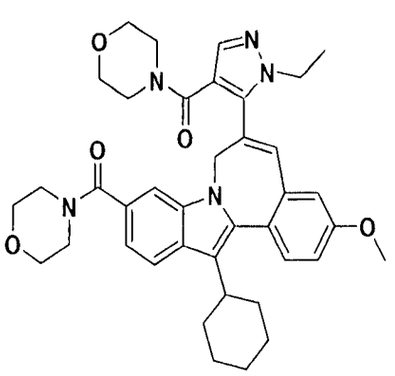
Éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

A una solución de éster 10-(1,1-dimetiletílico) del ácido 6-(4-carboxi-1-etil-1*H*-pirazol-5-il)-13-ciclohexil-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (120 mg, 0,206 mmol) en THF (1ml) a 60ºC se añadió carbonildiimidazol (47 mg, 0,288 mmol) y la solución se agitó durante 1 hora. Se añadieron entonces morfolina (36 mg, 0,412 mmol) y DBU (33 mg, 0,268 mmol) y la reacción se calentó durante una hora más y luego se dejó agitando hasta temperatura ambiente durante la noche. La reacción se diluyó entonces con ácido clorhídrico acuoso 1M y la mezcla resultante se extrajo con cloroformo. Los extractos se secaron sobre Na_2SO_4, se filtraron y luego se concentraron a vacío proporcionando el compuesto del epígrafe con rendimiento cuantitativo. MS m/z 651 (MH^+).



Ácido 13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

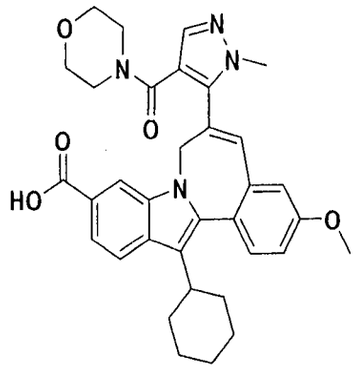
Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (61mg, 0,094 mmol) en ácido trifluoracético (2 ml) y se agitó a temperatura ambiente durante 3 horas y la mezcla se concentró entonces a vacío. Se eliminó el ácido trifluoracético residual por destilación azeotrópica con benceno y el producto final se secó a vacío proporcionando el compuesto del epígrafe (56 mg, 100%) que se usó sin purificación posterior. MS m/z 595 (MH^+).



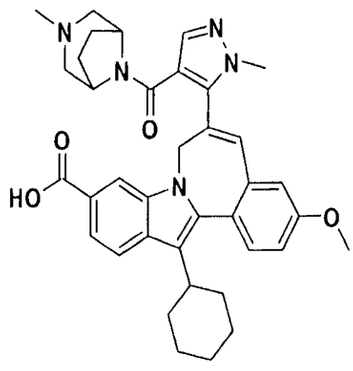
4-[[13-Ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-il]carbonil]-morfolina.

Se disolvió ácido 13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (60 mg, 0,092 mmol) en THF (0,9 ml) y se añadió carbonildiimidazol (21 mg, 0,130 mmol). La mezcla resultante se agitó entonces a 60°C durante 1 hora. Tras enfriar hasta temperatura ambiente en una atmósfera de nitrógeno, se añadieron morfolina (40 mg, 0,460 mmol) y DBU (0,012 ml, 0,120 mmol). La reacción se calentó durante 1 hora y luego se dejó agitando hasta temperatura ambiente durante la noche. La mezcla resultante se filtró el filtrado resultante se purificó por HPLC preparativa en las siguientes condiciones: HPLC preparativa Shimadzu usando software Discovery VP: %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 30; %B final=100; Gradiente= 12min; Tiempo de ejecución= 20min; Caudal= 40ml/min; Columna= Waters Sunfire 30 x 100mm S5. Esto proporcionó el compuesto del epígrafe (31 mg, 51%) como una pasta amarilla. MS m/z 664 (MH^+).

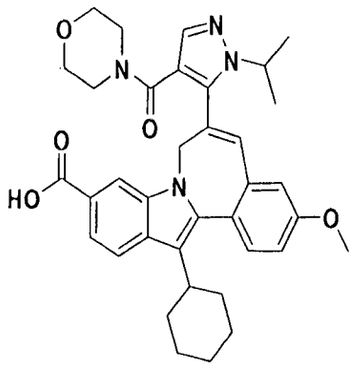
Los siguientes compuestos se sintetizaron por una secuencia análoga a la descrita antes para el ácido 13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico:



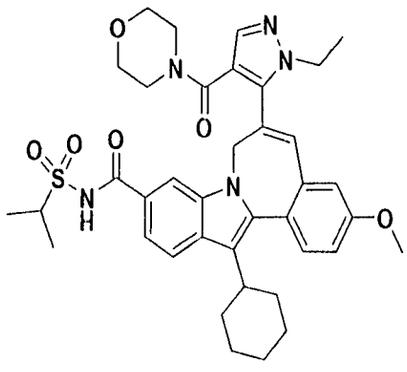
Ácido 13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. MS m/z 581 (MH^+).



Ácido 13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. MS m/z 620 (MH^+).



Ácido 13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. MS m/z 609 (MH^+).

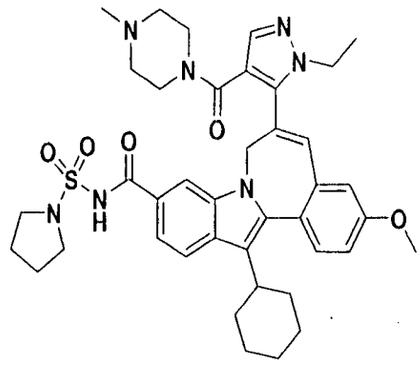


13-Ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

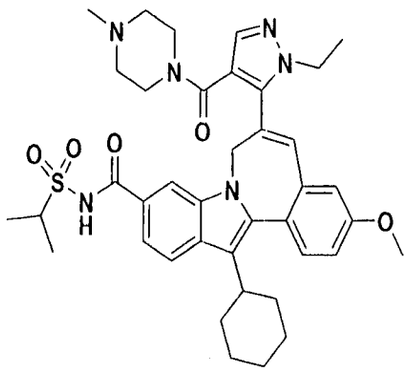
Se disolvió ácido 13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (56 mg, 0,094 mmol) se volvió a disolver en THF (0,9 ml) y se añadió carbonildiimidazol (21 mg, 0,129 mmol) a la reacción a 60ºC y la mezcla resultante se agitó durante 1 hora. Se añadieron entonces a la reacción propano-2-sulfonamida (57 mg, 0,246 mmol) y DBU (15 mg, 0,120 mmol) y la mezcla se calentó

durante 1 hora más, luego se dejó agitando hasta temperatura ambiente durante 18 horas. La mezcla resultante se filtró el filtrado se purificó por HPLC preparativa en las siguientes condiciones: HPLC preparativa Shimadzu usando software Discovery VP: %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 30; %B final=100; Gradiente= 12min; Tiempo de ejecución= 20min; Caudal= 40ml/min; Columna= Waters Sunfire 30 x 100mm S5. Esto proporcionó el compuesto del epígrafe (40 mg, 61%) como una pasta amarilla. MS m/z 700 (MH^+).

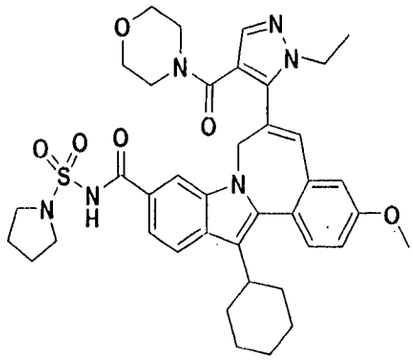
Los siguientes compuestos se sintetizaron por un procedimiento análogo al descrito antes para 13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida:



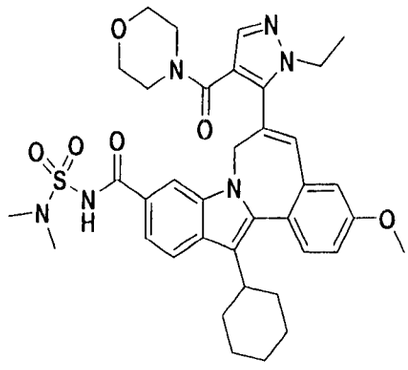
13-Ciclohexil-6-[1-etil-4-[(4-metil-1-piperazinil)carbonil]-1H-pirazol-5-il]-3-metoxi-N-(1-pirrolidinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 740 (MH^+).



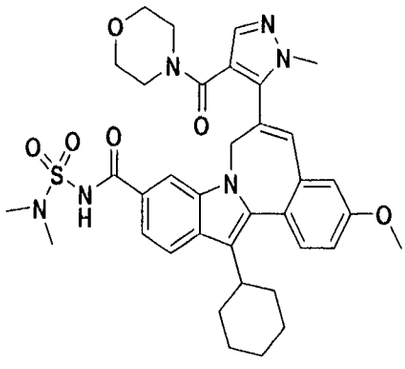
13-Ciclohexil-6-[1-etil-4-[(4-metil-1-piperazinil)carbonil]-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 713 (MH^+).



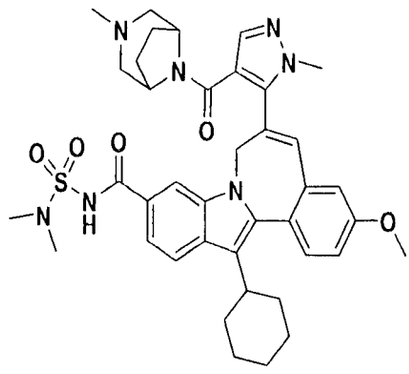
13-Ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-N-(1-pirrolidinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 727 (MH^+).



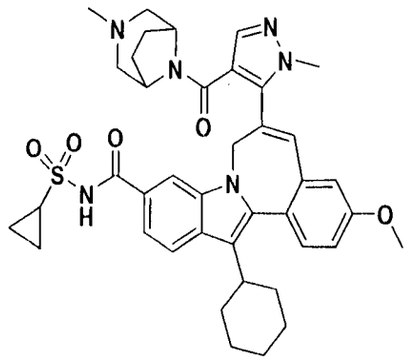
13-Ciclohexil-N-[(dimetilamino)sulfonil]-6-[1-etil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 701 (MH^+).



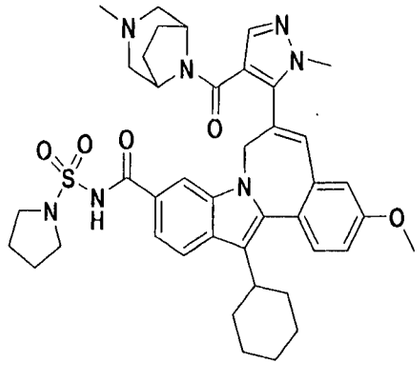
13-ciclohexil-N-[(dimetilamino)sulfonil]-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 687 (MH^+).



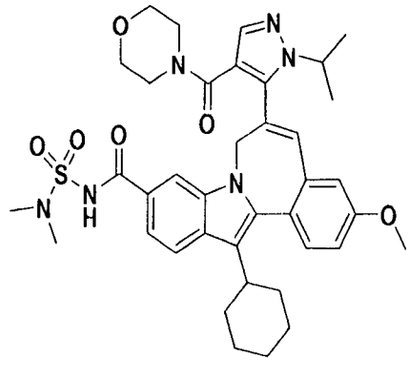
13-Ciclohexil-N-[(dimetilamino)sulfonil]-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 726 (MH^+).



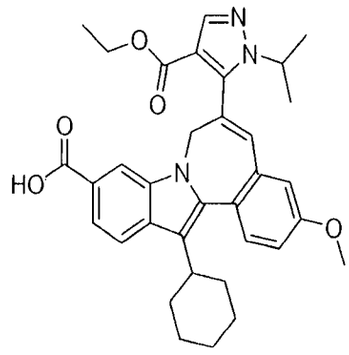
13-Ciclohexil-N-(ciclopropilsulfonil)-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 723 (MH^+).



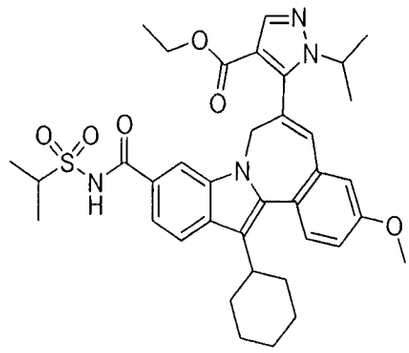
13-Ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-N-(1-pirolidinilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 752 (MH^+).



13-Ciclohexil-N-[(dimetilamino)sulfonil]-3-metoxi-6-[1-(1-metiletil)-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 715 (MH^+).

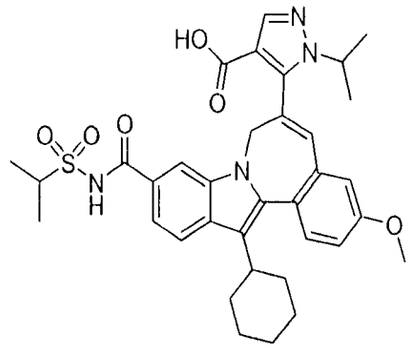


Ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-(1-metiletil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. Se disuelve éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-(1-metiletil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][6,41]benzazepin-10-carboxílico (2,00 g, 3,21 mmol) en 1,2-dicloroetano (6,41 ml), se coloca la reacción en una atmósfera de nitrógeno, luego se añade ácido trifluoracético (6,41 ml). Se agita la reacción a temperatura ambiente en una atmósfera de nitrógeno durante 2 horas. Los volátiles se eliminan a vacío y se disuelve el producto de reacción en benceno y se elimina a vacío para ayudar a eliminar las trazas de TFA. Se repite la disolución en benceno y eliminación a vacío. Se seca la muestra a temperatura ambiente a vacío obteniendo el compuesto del epígrafe (1,92 g, 100% de rendimiento) como un sólido amarillo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,48 (s ancho, 3H) 1,12 - 1,65 (m, 9 H) 1,72 - 2,19 (m, 7 H) 2,87 (t, *J*=11,29 Hz, 1 H) 3,91 (s, 3 H) 4,22 (m, 1 H) 4,32 (s ancho, 2 H) 4,73 (s ancho, 1 H) 4,97 (s ancho, 1 H) 6,70 (s, 1 H) 6,94 (d, *J*=2,14 Hz, 1 H) 7,08 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,52 (m, 2 H) 7,64 (d, *J*=8,24 Hz, 1 H) 7,82 (d, *J*=8,24 Hz, 1 H) 7,96 (s, 1 H). LCMS 566 m/z (MH-).



Éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(metiletil)-1H-pirazol-4-carboxílico. Se disuelve ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-(metiletil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (1,0 g, 1,76 mmol) en THF (5,87 ml). Se añade carbonildiimidazol (857 mg, 5,28 mmol) a la reacción. La reacción se colocó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 45 minutos y luego se calentó hasta reflujo durante 1 hora. La reacción se enfrió en una atmósfera de nitrógeno y se añadió propano-2-sulfonamida (868 mg, 7,05 mmol) a la reacción seguido por DBU (0,797 ml, 5,28 mmol). La reacción se sumergió en un baño de aceite a 80ºC en atmósfera de nitrógeno y se calentó durante la noche a 70-80ºC. La reacción se diluyó con acetato de etilo (50 ml) y la fase orgánica se lavó secuencialmente con ácido clorhídrico 1,0N (50 ml), NaH_2PO_4 acuoso 0,1M (50 ml) y salmuera (25 ml). La fase orgánica se secó sobre MgSO4, se filtró y se eliminaron los volátiles a vacío proporcionando una espuma amarilla que se secó a vacío a temperatura ambiente durante la noche proporcionando 1,03 g (1,57 mmol, 87%) del compuesto del epígrafe como un sólido amarillo amorfo.

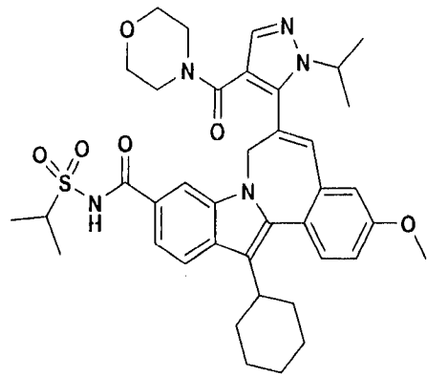
RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,40 (s ancho, 3H) 1,12 - 1,70 (m, 15 H) 1,72 - 2,18 (m, 7 H) 2,84 (t, *J*=11,29 Hz, 1 H) 3,90 (s, 3 H) 4,11 (m, 1 H) 4,26 (m, 3 H) 4,66 (s ancho, 1 H) 4,97 (s ancho, 1 H) 6,68 (s, 1 H) 6,94 (d, *J*=2,14 Hz, 1 H) 7,08 (m, 2 H) 7,52 (d, *J*=8,24 Hz, 1 H) 7,67 (d, *J*=8,24 Hz, 1 H) 7,80 (d, *J*=8,24 Hz, 1 H) 7,89 (s, 1 H). LCMS 671 m/z (MH-).



Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]-carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(metiletil)-1H-pirazol-4-carboxílico. Se disolvió éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(1-metiletil)-1H-pirazol-4-carboxílico (1,20 g, 1,78 mmol) en THF (15,0 ml) y se añadió metanol (15,0 ml) a la reacción seguido por hidróxido sódico acuoso 1N (15,0 ml). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18 horas. La reacción se diluyó con acetato de etilo (25,0 ml) y se lavó con ácido clorhídrico acuoso 1,0N (2 x 20 ml). La fase orgánica se concentró a vacío usando un evaporador rotatorio proporcionando el compuesto del epígrafe como un sólido amarillo (1,15 mg, 100%).

MS m/z 645 (MH^+).

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,46 (s ancho, 3H) 1,12 - 1,70 (m, 12 H) 1,72 - 2,15 (m, 7 H) 2,85 (t, *J*=11,29 Hz, 1 H) 3,90 (s, 3 H) 4,26 (m, 1 H) 4,62 (s ancho, 1 H) 4,99 (s ancho, 1 H) 6,69 (s, 1 H) 6,96 (d, *J*=2,14 Hz, 1 H) 7,06 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,50 (m, 2 H) 7,80 (m, 2 H) 7,85 (s, 1 H) 9,09 (s ancho, 1 H).

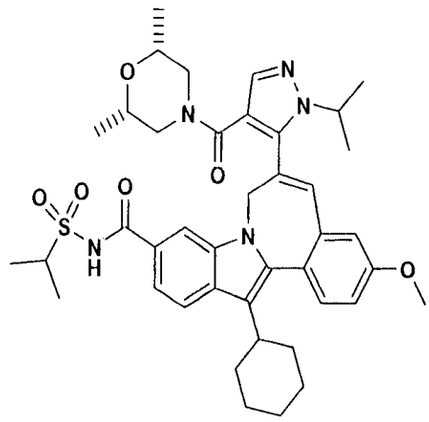


13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida:

Se añadieron ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-(1-metiletil)-1*H*-pirazol-4-carboxílico (125 mg, 0,194 mmol) en DMSO (1,94 ml), TBTU (124 mg, 0,368 mmol) y DIPEA (0,100 mg, 0,775 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. A continuación se añadió morfolina (68 mg, 0,775 mmol). La solución se agitó a TA durante la noche. La mezcla de reacción se purificó por una columna HPLC prep usando CH_3CN/H_2O/TFA como sistema disolvente. Las fracciones se recogieron y concentraron en SpeedVAc durante la noche proporcionando el compuesto del epígrafe como

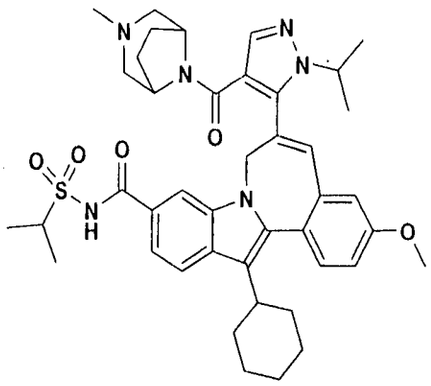
un sólido amarillo (82 mg, 0,114 mmol, 59% de rendimiento). MS m/z 714 ($M-H^+$). RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 1,20 (m, 1 H) 1,32 - 1,65 (m, 15 H) 1,73 - 2,20 (m, 6 H) 2,63 - 3,24 (m, 7 H) 3,50 (m ancho, 2 H) 3,93 (s, 3 H) 4,07 (m, 1 H) 4,58 (m, 2 H) 4,90 (m ancho, 1 H) 6,78 (s, 1 H) 6,93 (d, *J*=2,44 Hz, 1 H) 7,13 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 - 7,64 (m, 2 H) 7,71 (m, 2 H) 7,93 (d, *J*=8,55 Hz, 1 H) 10,15 (s ancho, 1H).

Los siguientes compuestos se sintetizaron por un procedimiento análogo al descrito antes para 13-ciclohexil-3-metoxi-6-[1-(metiletil)-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida:

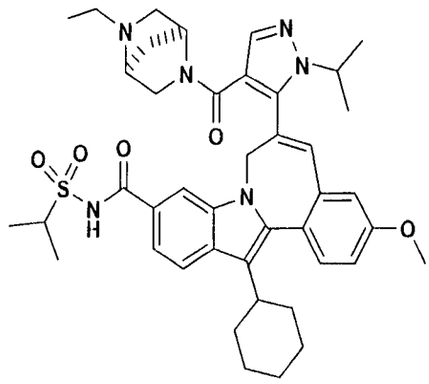


13-ciclohexil-6-[4-[(2,6-dimetil-4-morfolinil)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 0,61-0,92 (m, 6 H) 1,23 (m, 1 H) 1,35 - 1,70 (m, 15 H) 1,73 - 2,20 (m, 6 H) 2,88 (m, 1 H) 3,12-3,70 (m, 6 H) 3,92 (s, 3 H) 4,09 (m, 1 H) 4,58 (m, 2 H) 4,91 (m ancho, 1 H) 6,75 (s, 1 H) 6,92

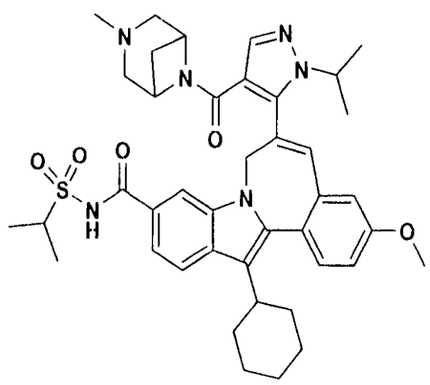
(d, *J*=2,44 Hz, 1 H) 7,12 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 - 7,68 (m, 2 H) 7,75 (m, 2 H) 7,92 (d, *J*=8,55 Hz, 1 H) 10,10 (s ancho, 1H). LCMS: m/e 742 (M+H).



13-ciclohexil-3-metoxi-6-[4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 0,02 (m, 2 H) 0,82 (m, 2 H) 1,20-1,82 (m, 16 H) 1,91 - 2,18 (m, 6 H) 2,39-2,70 (m, 4H) 2,88 (m, 1 H) 2,96-3,59 (m, 5 H) 3,94 (s, 3 H) 4,06 (m, 1 H) 4,62 (m, 2 H) 4,85 (m ancho, 1 H) 6,92 (m, 2 H) 7,12 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 - 7,69 (m, 3 H) 7,86 (s ancho, 1 H) 7,92 (d, *J*=8,55 Hz, 1 H) 10,10 (s ancho, 1H). LCMS: m/e 753 (M+H).

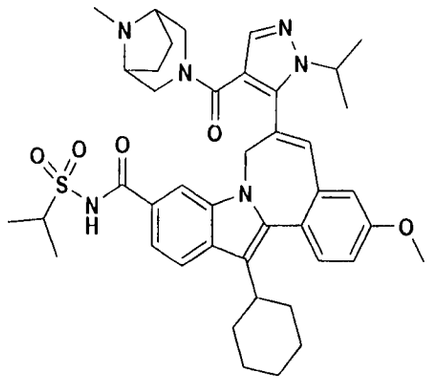


13-ciclohexil-6-[4-[[(1S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 0,02 (m, 1 H) 1,10-1,59 (m, 19 H) 1,91 - 2,49 (m, 8 H) 2,80-3,69 (m, 4H) 2,88 (m, 1 H) 3,81-4,41 (s, 7 H) 4,62 (m, 2 H) 4,90 (m ancho, 1 H) 6,97 (m, 2 H) 7,10 (m, 1 H) 7,53 - 7,67 (m, 2 H) 7,71-7,95 (m, 3 H) 10,20 (s ancho, 1H). LCMS: m/e 753 (M+H).

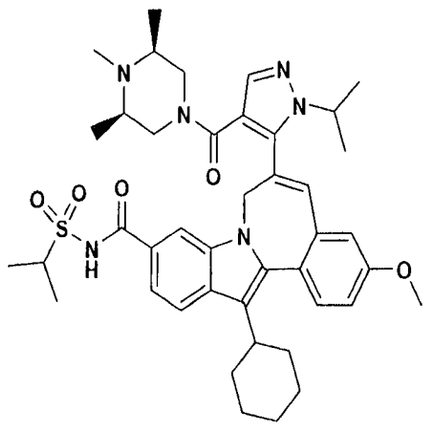


13-ciclohexil-3-metoxi-6-[4-[(3-metil-3,6-diazabiciclo[3,1,1]hept-6-il)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-

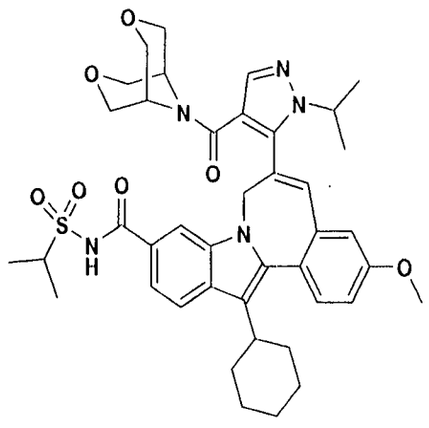
a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 1,17-1,85 (m, 15 H) 1,90 - 2,18 (m, 9 H) 2,59-2,99 (m, 6 H) 3,35-4,10 (m, 8 H) 4,66-5,00 (m, 3 H) 6,92 (m, 2 H) 7,12 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,50 - 7,69 (m, 3 H) 7,75-8,01 (m, 2 H) 10,00 (s ancho, 1H). LCMS: m/e 739 (M+H).



13-ciclohexil-3-metoxi-6-[4-[(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 0,021 (m, 2 H) 0,81 (m, 2 H) 1,20-1,86 (m, 16 H) 1,91 - 2,17 (m, 6 H) 2,41-2,71 (m, 4 H) 2,88 (m, 1 H) 2,97-3,70 (m, 5 H) 3,94 (s, 3 H) 4,08 (m, 1 H) 4,62 (m, 2 H) 4,85 (m ancho, 1 H) 6,94 (m, 2 H) 7,12 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,52 - 7,69 (m, 3 H) 7,80-7,95 (m, 2 H) 10,10 (s ancho, 1H). LCMS: m/e 753 (M+H).

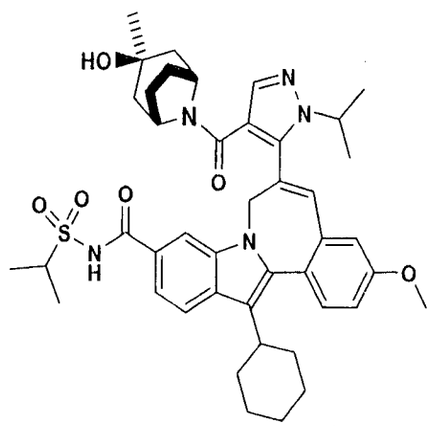


13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-(1-metiletil)-4-[(3,4,5-trimetil-1-piperazinil)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 1,20-1,82 (m, 22 H) 1,91 - 2,18 (m, 6 H) 2,50 (s ancho, 3H) 2,90 (m, 1 H) 3,35-3,69 (m, 7 H) 3,92 (s, 3 H) 4,02 (m, 1 H) 4,61 (m ancho, 1 H) 4,93 (m ancho, 1 H) 6,80 (s ancho, 1 H) 6,95 (s, 1 H) 7,11 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,51 - 7,65 (m, 3 H) 7,80 (s ancho, 1 H) 7,90 (d, *J*=8,55 Hz, 1 H) 10,20 (s ancho, 1H). LCMS: m/e 755 (M+H).

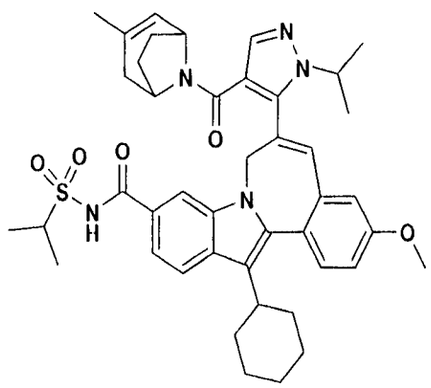


13-ciclohexil-6-[1-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-(1-

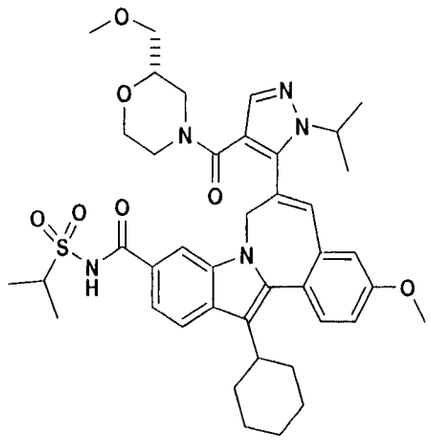
metiletil)-1H-pirazol-5-il]-3-meloxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 1,15-1,82 (m, 19 H) 1,91 - 2,18 (m, 3 H) 2,88 (m, 1 H) 3,12-3,80 (m, 9 H) 3,92 (s, 3 H) 4,05 (m, 1 H) 4,40 (m, 2 H) 4,61 (d ancho, 1 H) 4,92 (d ancho, 1 H) 6,78 (s, 1 H) 6,91 (d, *J*=2,44 Hz, 1 H) 7,13 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,59 - 7,65 (m, 2 H) 7,77 (m, 2 H) 7,93 (d, *J*=8,55 Hz, 1 H) 10,10 (s ancho, 1H). LCMS: m/e 756 (M+H).



13-ciclohexil-6-[4-[[(3-endo)-3-hidroxi-3-metil-8-azabiciclo[3.2.1]oct-8-il]carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-3-meloxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm -0,25 (m, 1 H) 0,52 (m, 1 H) 1,04 (s, 3 H) 1,15-1,82 (m, 24 H) 1,91 - 2,13 (m, 4 H) 2,89 (m, 1 H) 3,29 (m, 1 H) 3,62 (m, 1 H) 3,92 (s, 3 H) 4,06 (m, 1 H) 4,54-4,71 (m, 2 H) 5,00 (d ancho, 1 H) 6,82 (s ancho, 1 H) 6,91 (d, *J*=2,75 Hz, 1 H) 7,12 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,50 - 7,60 (m, 2 H) 7,70 (m, 1 H) 7,80-7,95 (m, 2 H) 10,20 (s ancho, 1H). LCMS: m/e 768 (M+H), tiempo de retención 2,75 min (procedimiento 1).

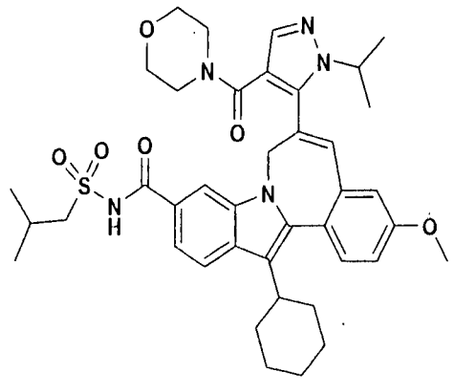


13-ciclohexil-3-metoxi-6-[4-[(3-metil-8-azabiciclo[3.2.1]oct-2-en-8-il)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: m/e 750 (M+H), tiempo de retención 2,89 min (procedimiento 1).

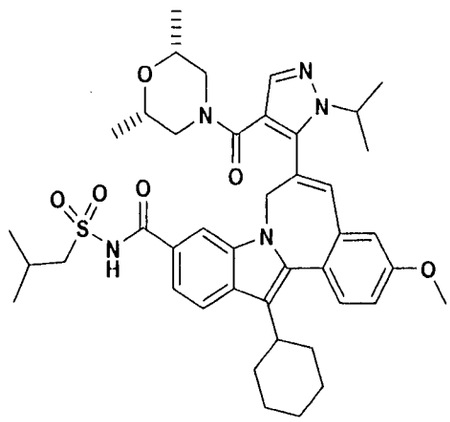


13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]- 1-(1-metiletil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 1,21 (m, 1 H) 1,32 - 1,70 (m, 15 H) 1,73 - 2,20 (m, 6 H) 2,72-3,47 (m, 8 H) 3,88-4,17 (m, 10 H) 4,61 (m, 1 H) 4,95 (m ancho, 1 H) 6,80 (d ancho, 1 H) 6,93 (s ancho, 1 H) 7,12 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 - 7,64 (m, 2 H) 7,71-7,96 (m, 3 H) 10,15 (s ancho, 1H).

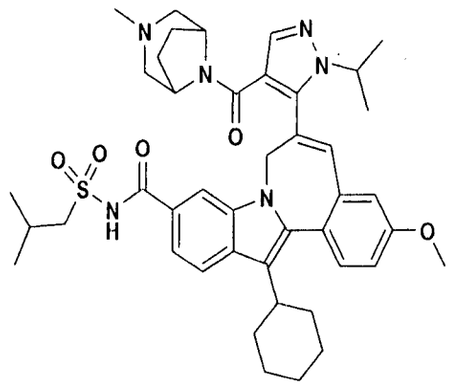
LCMS: m/e 758 (M+H).



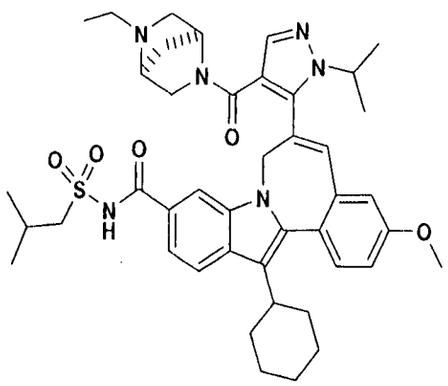
13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 728 (M+H), tiempo de retención 3,59 min (procedimiento 2).



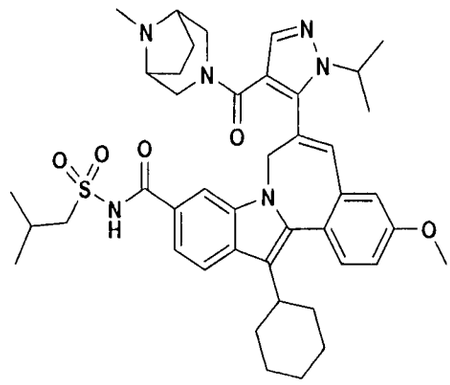
13-ciclohexil-6-[4-[(2,6-dimetil-4-morfolinil)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 756 (M+H), tiempo de retención 3,71 min (procedimiento 2).



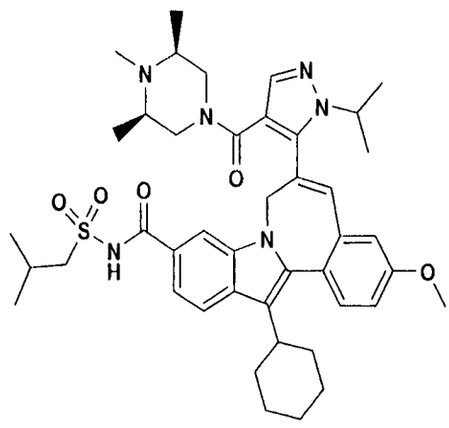
13-ciclohexil-3-metoxi-6-[4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 767 (M+H), tiempo de retención 3,35 min (procedimiento 2).



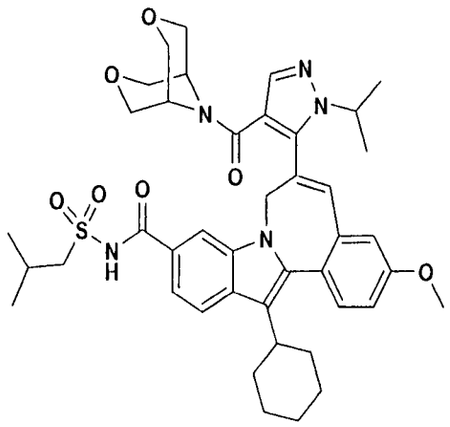
13-ciclohexil-6-[4-[[(1S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 767 (M+H), tiempo de retención 3,31 min (procedimiento 2).



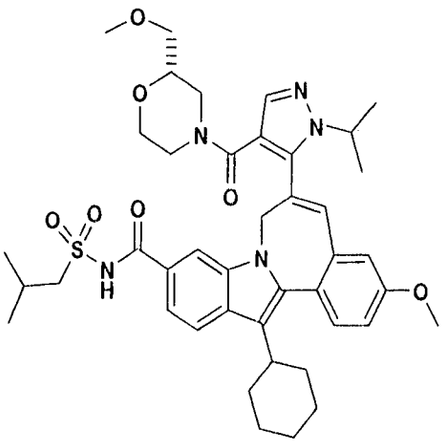
13-ciclohexil-3-metoxi-6-[4-[(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 767 (M+H), tiempo de retención 3,38 min (procedimiento 2).



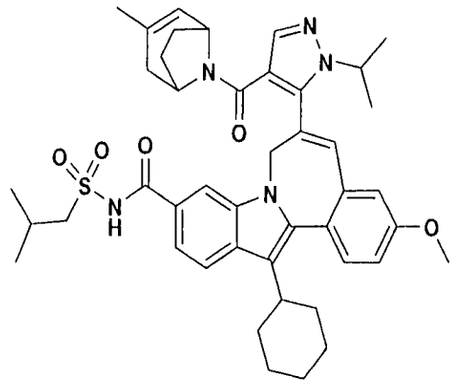
13-ciclohexil-3-metoxi-N-[(2-metilpropil)sulfonil]-6-[1-(1-metiletil)-4-[(3,4,5-trimetil-1-piperazinil)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 769 (M+H), tiempo de retención 3,32 min (procedimiento 2).



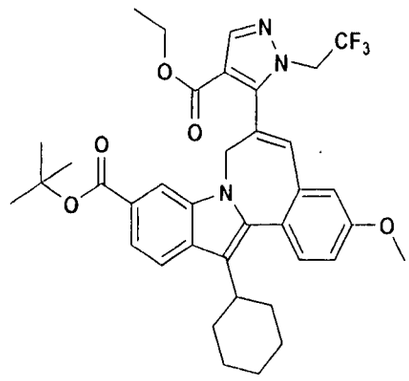
13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-(1-metiletil)-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 770 (M+H), tiempo de retención 3,65 min (procedimiento 2).



13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 772 (M+H), tiempo de retención 3,61 min (procedimiento 2).

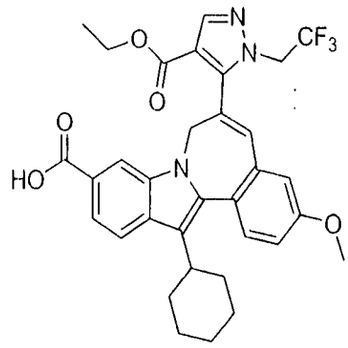


13-ciclohexil-3-metoxi-6-[4-[(3-metil-8-azabiciclo[3.2.1]oct-2-en-8-il)carbonil]-1-(1-metiletil)-1H-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: LCMS: m/e 764 (M+H), tiempo de retención 3,69 min (procedimiento 2).



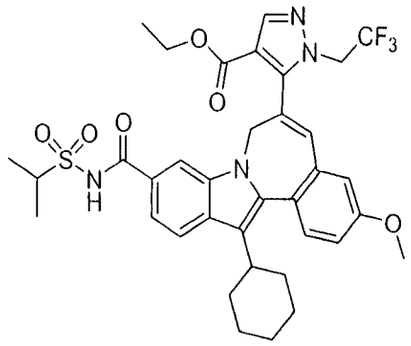
éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. Se disolvió 13-ciclohexil-6-((2E,Z)-3-(dimetilamino)-2-(etoxicarbonil)-2-propenoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-

carboxilato de terc-butilo (1,20 g, 1,96 mmol) en una solución de etanol (6,53 ml), trietilamina (0,396 g, 3,92 mmol) y (2,2,2-trifluoroetil)hidrazina (0,246 g, 2,15 mmol). La reacción se calentó en un microondas a 160ºC durante 2 horas y se concentró. El sólido resultante se purificó por HPLC prep en las siguientes condiciones: HPLC prep Shimadzu usando software Discovery VP: %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA; %B inicial= 30; %B final=100; Gradiente= 12min; Tiempo de ejecución= 20min; Caudal= 40ml/min; Columna= Waters Sunfire 30 x 100mm S5. Esto proporcionó el compuesto del epígrafe (1,09 g, 84%) como una pasta amarilla. MS m/z 664 (MH^+).



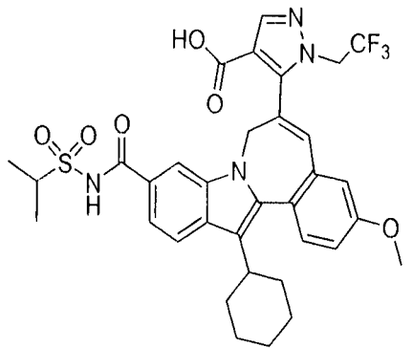
Ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. Se disuelve éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][3,62]benzazepin-10-carboxílico (1,20 g, 1,81 mmol) en 1,2-dicloroetano (3,62 ml), se coloca la reacción en una atmósfera de nitrógeno, luego se añade ácido trifluoracético (3,62 ml). Se agita la reacción a temperatura ambiente en una atmósfera de nitrógeno durante 2

horas. Los volátiles se eliminan a vacío y se disuelve el producto de reacción en benceno y se elimina a vacío para ayudar a eliminar las trazas de TFA. Se repite la disolución en benceno y eliminación a vacío. Se seca la muestra a temperatura ambiente a vacío obteniendo el compuesto del epígrafe (0,923 g, 100% de rendimiento) como un sólido amarillo. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,20 - 1,62 (m, 7 H) 1,70 - 2,19 (m, 6 H) 2,87 (m, 1 H) 3,91 (s, 3 H) 4,12-4,45 (m, 4 H) 4,76 (s ancho, 1 H) 4,97 (s ancho, 1 H) 6,82 (s, 1 H) 6,96 (d, *J*=2,14 Hz, 1 H) 7,10 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,56 (d, *J*=8,85 Hz, 1 H) 7,78 (d, *J*=8,24 Hz, 1 H) 7,90 (m, 2 H) 8,11 (s, 1 H). LCMS 608 m/z (MH+).



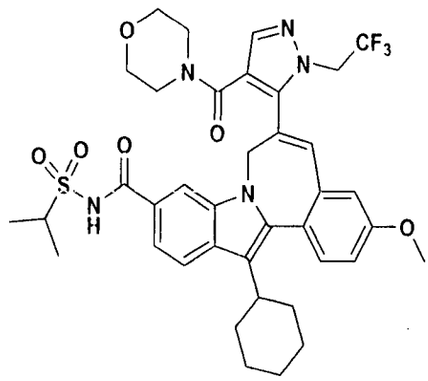
Éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(2,2,2-trifluoroetil)-1H-pirazol-4-carboxílico. Se disuelve ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (800 mg, 1,32 mmol) en THF (4,39 ml). Se añade carbonildiimidazol (640 mg, 3,95 mmol) a la reacción. La reacción se colocó en una atmósfera de nitrógeno y se agitó a temperatura ambiente

durante 45 minutos y luego se calentó hasta reflujo durante 1 hora. La reacción se enfrió en una atmósfera de nitrógeno y se añadió propano-2-sulfonamida (649 mg, 5,27 mmol) a la reacción seguido por DBU (0,595 ml, 3,95 mmol). La reacción se sumergió en un baño de aceite a 80°C en atmósfera de nitrógeno y se calentó durante la noche a 70-80°C. La reacción se diluyó con acetato de etilo (50 ml) y la fase orgánica se lavó secuencialmente con ácido clorhídrico 1,0N (50 ml), NaH_2PO_4 acuoso 0,1M (50 ml) y salmuera (25 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se eliminaron los volátiles a vacío proporcionando una espuma amarilla que se secó a vacío a temperatura ambiente durante la noche proporcionando el compuesto del epígrafe (949 mg, 100%) como un sólido amarillo amorfo. RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,20 - 1,62 (m, 13 H) 1,70 - 2,18 (m, 6 H) 2,87 (m, 1 H) 3,90 (s, 3 H) 4,05 (m, 1 H) 4,10-4,40 (m, 4 H) 4,73 (s ancho, 1 H) 4,99 (s ancho, 1 H) 6,82 (s, 1 H) 6,93 (d, *J*=2,14 Hz, 1 H) 7,10 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,45 (d ancho, 1 H) 7,52 (d, *J*=8,85 Hz, 1 H) 7,80 (s ancho, 1 H) 7,88 (d, *J*=8,85 Hz, 1 H) 8,02 (s, 1 H) 8,60 (s ancho, 1 H). LCMS 713 m/z (MH+).



Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-meliletil)sulfonil]amino]carbonil]-

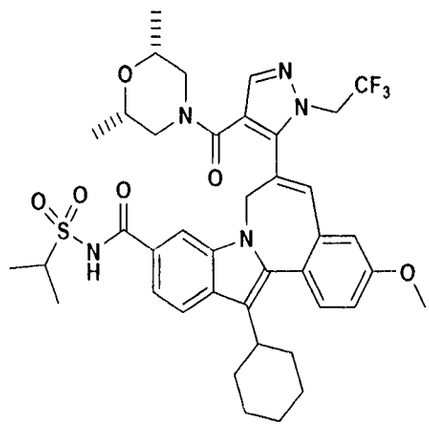
7H-indolo[2,1-a][2]benzazepin-6-il]-1-(2,2,2-trifluoroetil)-1H-pirazol-4-carboxílico. Se disolvió éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(2,2,2-trifluoroetil)-1H-pirazol-4-carboxílico (0,816 g, 1,15 mmol) en THF (2,86 ml) y se añadió metanol (2,86 ml) a la reacción seguido por hidróxido sódico acuoso 1N (2,29 ml). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18 horas. La reacción se diluyó con acetato de etilo (25,0 ml) y se lavó con ácido clorhídrico acuoso 1,0N (2 x 20 ml). La fase orgánica se concentró a vacío usando un evaporador rotatorio proporcionando el compuesto del epígrafe como un sólido amarillo (0,734 mg, 100%). RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,20 - 1,62 (m, 10 H) 1,70 - 2,18 (m, 6 H) 2,87 (m, 1 H) 3,90 (s, 3 H) 4,05 (m, 1 H) 4,27 (m ancho, 2 H) 4,73 (s ancho, 1 H) 4,99 (s ancho, 1 H) 6,82 (s, 1 H) 6,93 (d, *J*=2,14 Hz, 1 H) 7,10 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,45 (d ancho, 1 H) 7,52 (d, *J*=8,85 Hz, 1 H) 7,80 (s ancho, 1 H) 7,88 (d, *J*=8,85 Hz, 1 H) 8,02 (s, 1 H) 8,60 (s ancho, 1 H). LCMS 685 m/z (MH+).



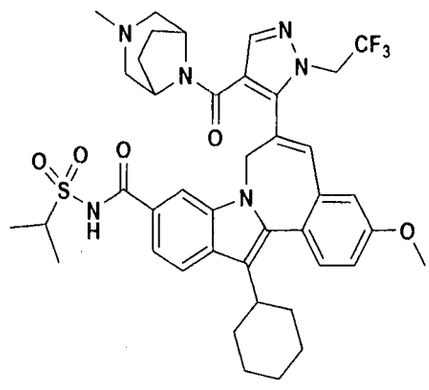
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[4-(4-morfolinilcarbonil)-1-

(2,2,2-trifluoroetil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: Se añadieron ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-(2,2,2-trifluoroetil)1*H*-pirazol-4-carboxílico (90 mg, 0,131 mmol) en DMSO (1,31 ml), TBTU (84 mg, 0,263 mmol) y DIPEA (68 mg, 0,526 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. A continuación se añadió morfolina (46 mg, 0,526 mmol). La solución se agitó a TA durante la noche. La mezcla de reacción se purificó por una columna HPLC prep usando CH_3CN/H_2O/TFA como sistema disolvente. Las fracciones se recogieron y concentraron en SpeedVAc durante la noche proporcionando el compuesto del epígrafe como un sólido amarillo (53 mg, 0,070 mmol, 53% de rendimiento). MS m/z 754 ($M-H^+$); RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,22 (m, 1 H)1,33 - 1,57 (m, 9 H) 1,70 - 2,18 (m, 6 H) 2,59 (m ancho, 1 H) 2,70-2,95 (m, 6 H) 3,05-3,21 (m, 2 H) 3,92 (s, 3 H) 4,07 (m, 1 H) 4,73 (d ancho, 1 H) 4,76 (m ancho, 2 H) 4,86 (d ancho, 1 H) 6,90 (s, 1 H) 6,94 (d, *J*=2,14 Hz, 1 H) 7,15 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,60 (d, *J*=8,85 Hz, 1 H) 7,63 (d, *J*=8,24 Hz, 1 H) 7,67 (s, 1 H) 7,80 (s, 1 H) 7,93 (d, *J*=8,85 Hz, 1 H).

Los siguientes compuestos se sintetizaron por un procedimiento análogo al descrito antes para 13-ciclohexil-3-metoxi-11-[(1-metiletil)sulfonil]–6–[4-(4–morfolinilcarbonil)-1-(2,2,2-trifluoroetil)-1H–pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida:

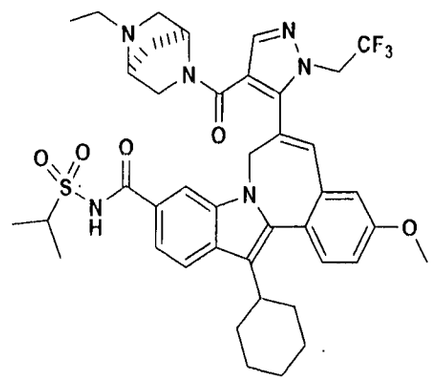


13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,64-0,90 (m, 5 H) 1,16-1,26 (m, 2 H) 1,33 - 1,57 (m, 9 H) 1,73 - 2,18 (m, 8 H) 2,30 (m ancho, 1 H) 2,87 (m, 2 H) 3,05-3,29 (m, 3 H) 3,94 (s, 3 H) 4,07 (m, 1 H) 4,58 (d ancho, 1 H) 4,72 (m ancho, 2 H) 4,93 (d ancho, 1 H) 6,87-6,96 (m, 1 H) 7,15 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,52-7,68 (m, 2 H) 7,72-7,85 (m, 2 H) 7,93 (m, 1 H) 8,48 (s ancho, 1 H). LCMS: m/e 782 (M+H).

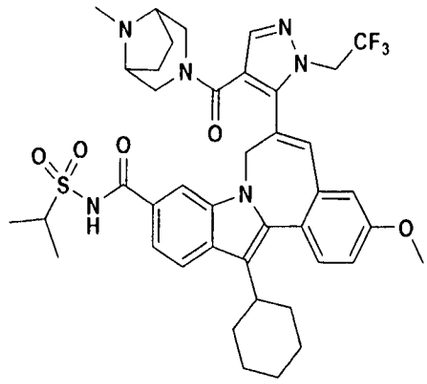


13-ciclohexil-3-metoxi-6-[4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-

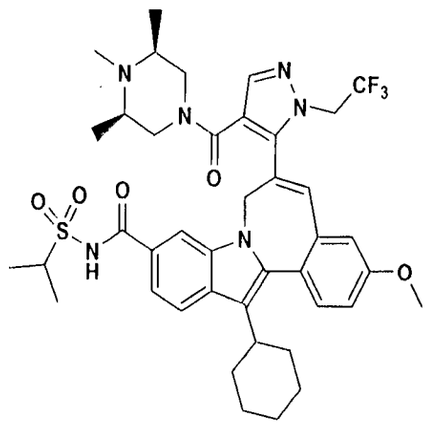
il)carbonil]-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,19 (s ancho, 1 H) 0,80 (s ancho, 1 H) 1,25-1,62 (m, 11 H) 1,76 - 2,18 (m, 7 H) 2,48 (m ancho, 1 H) 2,62 (s ancho, 3 H) 2,88 (m, 2 H) 2,95-3,50 (m, 4 H) 3,92 (s, 3 H) 4,06 (m, 1 H) 4,59 (d ancho, 1 H) 4,86 (m ancho, 3 H) 6,93 (s, 1 H) 7,05 (s ancho, 1 H) 7,17 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,60 (d, *J*=8,85 Hz, 1 H) 7,65 (d, *J*=8,24 Hz, 1 H) 7,86 (s ancho, 1 H) 7,96 (m, 2 H) 10,0 (s ancho, 1 H). LCMS: m/e 793 (M+H).



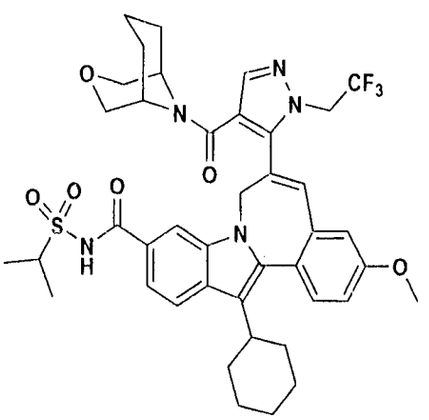
13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-3-meloxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,10-1,59 (m, 14 H) 1,70 - 2,18 (m, 7 H) 2,38 (m, 1 H) 2,80-3,85 (m, 8 H) 3,95 (s, 3 H) 4,03 (m, 1 H) 4,58 (d ancho, 1 H) 4,98 (m ancho, 3 H) 6,87-6,96 (m, 1 H) 7,15 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,52-7,68 (m, 2 H) 7,72-7,85 (m, 2 H) 7,93 (m, 1 H) 8,48 (s ancho, 1 H). LCMS: m/e 793 (M+H).



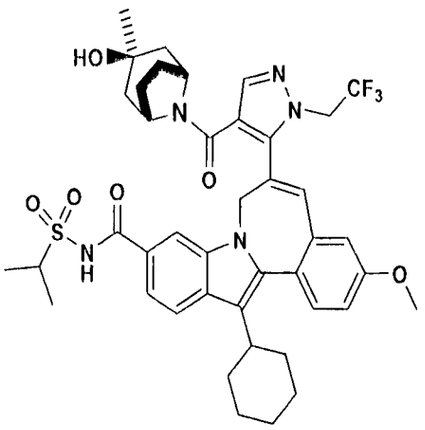
13-ciclohexil-3-metoxi-6-[4-[(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)carbonil]-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,18 (s ancho, 1 H) 0,81 (s ancho, 1 H) 1,26-1,62 (m, 11 H) 1,30 (m, 2 H) 1,94 - 2,18 (m, 5 H) 2,44 (m ancho, 1 H) 2,62 (s ancho, 3 H) 2,90 (m, 2 H) 2,95-3,55 (m, 4 H) 3,92 (s, 3 H) 4,06 (m, 1 H) 4,59 (d ancho, 1 H) 4,86 (m ancho, 3 H) 6,92 (s, 1 H) 7,03 (s ancho, 1 H) 7,17 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,58-7,65 (m, 1 H) 7,86 (s ancho, 1 H) 7,98 (m, 2 H) 10,0 (s ancho, 1 H). LCMS: m/e 793 (M+H).



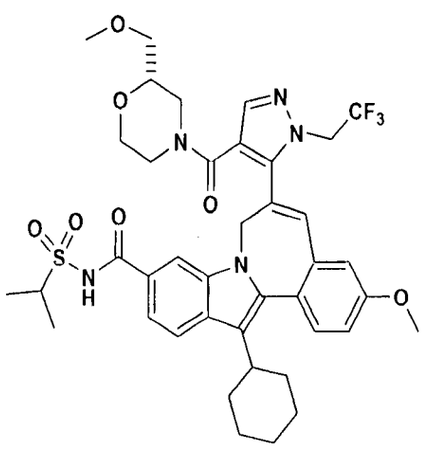
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-(2,2,2-trifluoroetil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,05 - 1,57 (m, 15 H) 1,70 - 2,12 (m, 7 H) 2,30-2,99 (m, 6 H) 3,20-3,65 (m, 4 H) 3,92 (s, 3 H) 4,03 (m, 1 H) 4,60 (d ancho, 1 H) 4,65-4,98 (m ancho, 3 H) 6,95 (m, 2 H) 7,15 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,57 (m, 2 H) 7,71 (s, 1 H) 7,82 (s ancho, 1 H) 7,93 (d, *J*=8,85 Hz, 1 H). LCMS: m/e 795 (M+H).



13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,12-1,53 (m, 13 H) 1,70 - 2,40 (m, 9 H) 2,37 (m, 1 H) 3,03-3,62 (m, 6 H) 3,92 (s, 3 H) 4,07 (m, 1 H) 4,73 (d ancho, 1 H) 4,76 (m ancho, 2 H) 4,36 (d ancho, 1 H) 6,90 (s, 1 H) 6,94 (d, *J*=2,14 Hz, 1 H) 7,15 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,60 (d, *J*=8,85 Hz, 1 H) 7,63 (d, *J*=8,24 Hz, 1 H) 7,67 (s, 1 H) 7,80 (s, 1 H) 7,93 (d, *J*=8,85 Hz, 1 H). LCMS: m/e 794 (M+H).



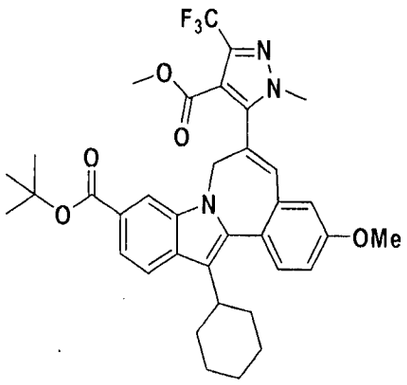
13-ciclohexil-6-[4-[(3-hidroxi-3-metil-8-azabiciclo[3.2.1]oct-8-il)carbonil]-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm -0,25 (m, 1 H) 0,52 (m, 1 H) 1,06 (s, 3 H) 1,15-1,82 (m, 18 H) 1,91 - 2,18 (m, 4 H) 2,88 (m, 1 H) 3,32 (m, 1 H) 3,60 (m, 1 H) 3,93 (s, 3 H) 4,07 (m, 1 H) 4,56 (d ancho, 1 H) 4,82 (m, 2 H) 4,97 (d ancho, 1 H) 6,82 (s ancho, 2 H) 7,16 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,60 (d, *J*=8,55 Hz , 1 H) 7,70 (d, *J*=8,24 Hz, 1 H) 7,84-7,92 (m, 3 H). LCMS: m/e 808 (M+H).



13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-(2,2,2-trifluoroetil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 1,21 (m, 1 H) 1,32 - 1,70 (m, 9 H) 1,73 - 2,20 (m, 6 H) 2,72-3,40 (m, 13 H) 3,92 (m, 3 H) 4,10 (m, 1 H) 4,60 (m, 1 H) 4,82 (m ancho, 3 H) 6,85-6,96 (m, 2 H) 7,17 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 - 7,72 (m, 3 H) 7,80-7,96 (m, 2 H). LCMS: m/e 798 (M+H).

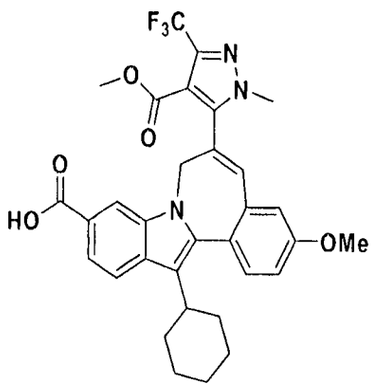


5-Cloro-1-metil-3-(trifluorometil)-1H-pirazol-4-carboxilato de metilo. A una solución de ácido 5-cloro-1-metil-3-(trifluorometil)-1H-pirazol-4-carboxílico (1,00g, 4,38 mmol) en benceno (5,83 ml) y metanol (2,92 ml) a temperatura ambiente se añadió trimetilsilildiazometano 2M (8,75 ml). La solución resultante se agitó a temperatura ambiente durante 3 horas. El disolvente se eliminó a presión reducida en un evaporador rotatorio proporcionando el compuesto del epígrafe (1,06 g, 4,38 mmol, 100% de rendimiento) como un sólido blanco. MS m/z 243(MH^+). RMN de 1H (500 MHz, CLOROFORMO-D) δ ppm 3,82 (s, 3 H) 3,89 (s, 3 H).



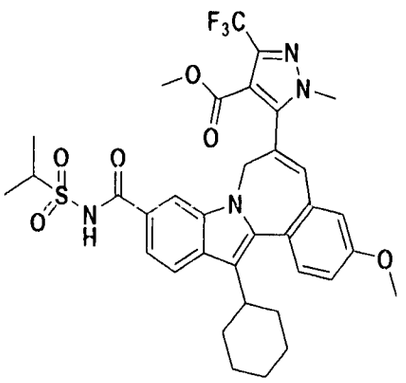
Éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1-metil-3-(trifluorometil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. En un tubo de microondas, se añadieron éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(tributilestannil)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (1,00 g, 1,37 mmol), 5-cloro-1-metil-3-(trifluorometil)-1H-pirazol-4-carboxilato de metilo (497 mg, 2,05 mmol) y bis(dibencilidenacetona)paladio (78 mg, 0,136 mmol). Seguidamente se selló, se desgasificó y se llenó con nitrógeno. Se añadió 1,4-dioxano (6,83 ml). La mezcla de reacción se calentó a 160ºC en condiciones de microondas durante 3 horas. Luego se filtró y se concentró el filtrado. El residuo se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FPC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (8 ml) purificado usando una columna de 5 um 19 mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 25% de disolvente A / 75% de disolvente B hasta 0% de disolvente A / 100% de

disolvente B, un tiempo de gradiente de 10 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. Las fracciones que contenían producto se recogieron y se concentraron dando el compuesto del epígrafe como un sólido amarillo (547 mg, 0,842 mmol, 61% de rendimiento). MS m/z 650 (MH^+). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,06 - 2,29 (m, 19 H) 2,85 (m, 1 H) 3,30 (s ancho, 3 H) 3,78 (s ancho, 3H) 3,91 (s, 3 H) 4,76 (m ancho, 1 H) 4,97 (m ancho, 1 H) 6,80 (s, 1 H) 6,93 (d, *J*=2,44 Hz, 1 H) 7,11 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,56 (d, *J*=8,54 Hz, 1 H) 7,82 (dd, *J*=8,24, 1,22 Hz, 1 H) 7,91 (dd, *J*=8,24, 1,22 Hz, 1 H) 7,98 (s, 1 H).



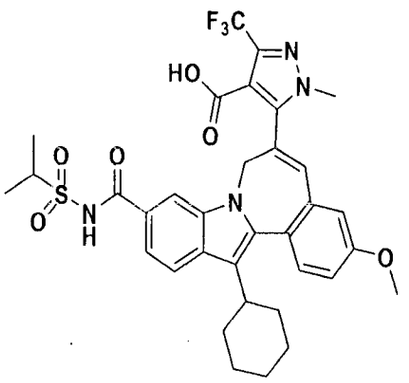
Ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1-metil-3-(trifluorometil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico. Se añadió TFA (5 ml) a una solución de éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1-metil-3-(trifluorometil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (547 mg, 0,842 mmol) en 1,2-dicloroetano (5 ml). La mezcla de reacción se agitó a TA durante 4 horas. Los volátiles se eliminaron en un evaporador rotatorio dando el compuesto del

epígrafe como un aceite parduzco espeso como producto bruto (500 mg, 0,642 mmol, 100% de rendimiento). MS m/z 594(MH^+). RMN de *1H (500 MHz, CLOROFORMO-D) δ ppm 1,06 - 2,28 (m, 10 H) 2,86 (m, 1 H) 3,30 (s ancho, 3 H) 3,78 (s ancho, 3H) 3,91 (s, 3 H) 4,75 (m ancho, 1 H) 4,96 (m ancho, 1 H) 6,80 (s, 1 H) 6,93 (d, J*=2,44 Hz, 1 H) 7,10 (dd, J=8,55, 2,75 Hz, 1 H) 7,54 (d, J=8,54 Hz, 1 H) 7,81 (dd, J=8,24, 1,22 Hz, 1 H) 7,91 (dd, J=8,24, 1,22 Hz, 1 H) 7,97 (s, 1 H).



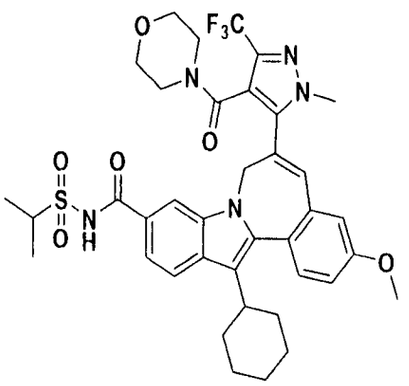
Éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-3-(trifluorometil)-1H-pirazol-4-carboxílico. A una solución de ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1-metil-3-(trifluorometil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico, (480 mg, 0,809 mmol) en tetrahidrofurano (2,70 ml) se añadió carbonildiimidazol (393 mg, 2,43 mmol). La mezcla de reacción se calentó a 60ºC durante una hora y luego se dejó enfriar Se añadieron propano-2-sulfonamida (398 mg, 3,23 mmol) y DBU (0,366 ml, 2,43 mmol) a temperatura ambiente y la mezcla de reacción se calentó a 60ºC durante 4 horas. La mezcla resultante se diluyó entonces con solución de HCl

1N (50 ml) y se extrajo con acetato de etilo (2 X 40 ml). Las fases orgánicas se reunieron y concentraron en un evaporador rotatorio dando el producto como un aceite naranja. Este material se purificó entonces por columna de HPLC Preparativa usando CH_3CN/H_2O/TFA como sistema disolvente. Las fracciones homogéneas se recogieron y concentraron a presión reducida. El compuesto del epígrafe se obtuvo como un sólido amarillo, (492 mg, 0,704 mmol, 37 % de rendimiento). MS m/z 699 (MH^+). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,16 - 1,61 (m, 10 H) 1,69 - 2,21 (m, 6 H) 2,86 (m, 1 H) 3,34 (s ancho, 3H) 3,67 (s ancho, 3 H) 3,91 (s, 3 H) 4,01 - 4,19 (m, 1 H) 4,70 (m ancho, 1 H) 4,97 (m ancho, 1 H) 6,70 (s, 1 H) 6,94 (d, *J*=2,75 Hz, 1 H) 7,09 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,51 (dd, *J*=8,55, 1,22 Hz, 1 H) 7,81 (d, *J*=1,22 Hz, 1 H) 7,88 (d, *J*=8,55 Hz, 1 H) 7,92 (d, *J*=8,55 Hz, 1 H) 8,68 (s, 1 H).



Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]-carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-3-(trifluorometil)-1H-pirazol-4-carboxílico. Se disolvió en THF (1,07 ml) éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-3-(trifluorometil)-1*H*-pirazol-4-carboxílico (0,300 g,

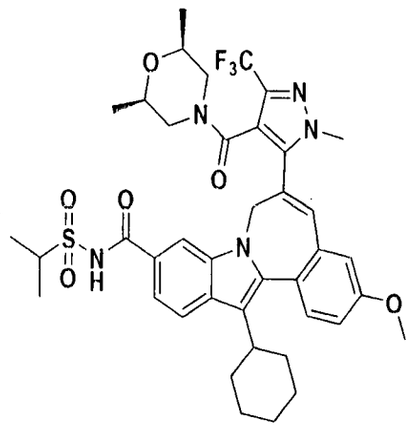
0,429 mmol) y se añadió metanol (1,07 ml) seguido por hidróxido sódico acuoso 1N (0,900 ml). La reacción se colocó entonces en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18 horas. La mezcla se diluyó entonces con acetato de etilo (50,0 ml) y se lavó con ácido clorhídrico acuoso 1,0N (2 x 50 ml). La fase orgánica se concentró a vacío usando un evaporador rotatorio proporcionando el compuesto del epígrafe como un sólido amarillo (282 mg, 0,412 mmol, 96%). MS m/z 685(MH^+). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,16 - 1,61 (m, 10 H) 1,69 - 2,21 (m, 6 H) 2,86 (m, 1 H) 3,34 (s ancho, 3 H) 3,91 (s, 3 H) 4,01 - 4,19 (m, 1 H) 4,70 (m ancho, 1 H) 4,99 (m ancho, 1 H) 6,70 (s, 1 H) 6,94 (d, *J*=2,75 Hz, 1 H) 7,10 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,51 (dd, *J*=8,55, 1,22 Hz, 1 H) 7,81 (d, *J*=1,22 Hz, 1 H) 7,88 (d, *J*=8,55 Hz, 1 H) 7,92 (d, *J*=8,55 Hz, 1 H) 9,00 (s, 1 H).



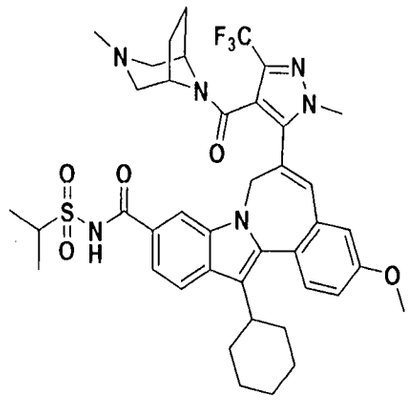
13-Ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-(4-morfolinilcarbonil)-3-(trifluorometil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-

6-il]-1-metil-3-(trifluorometil)-1*H*-pirazol-4-carboxílico (75 mg, 0,11 mmol) en DMSO (1,1 ml) se añadieron TBTU (70 mg, 0,22 mmol) y DIPEA (0,057 ml, 0,4444 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. A continuación se añadió morfolina (38 mg, 0,44 mmol). La solución se agitó a TA durante la noche. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN/H_2O/TFA como sistema disolvente. Las fracciones homogéneas se recogieron y concentraron a presión reducida proporcionando el compuesto del epígrafe como un sólido amarillo (67 mg, 0,089 mmol, 81% de rendimiento). MS m/z 754 ($M-H^+$). RMN de ^1H (500 MHz, MeOD) δ ppm 1,13 - 1,52 (m, 10 H) 1,75 - 2,25 (m, 6 H) 2,63 - 3,26 (m, 9 H) 3,50 (s ancho, 3 H) 3,95 (s, 3 H) 3,96 - 4,03 (m, 1 H) 4,64 (d ancho, 1 H) 4,93 (m ancho, 1 H) 6,83 (s, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,15 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,55 - 7,65 (m, 2 H) 7,80 (s ancho, 1 H) 7,93 (d, *J*=8,55 Hz, 1 H) 10,30 (s ancho, 1H).

Los siguientes compuestos se sintetizaron por un procedimiento análogo al descrito antes para 13-ciclohexil-3-meloxi-N-1-metiletil)sulfonil]–6–[1–metil-4-4–morfolinilcarbonil)-3-trifluorometil)-1H–pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida:

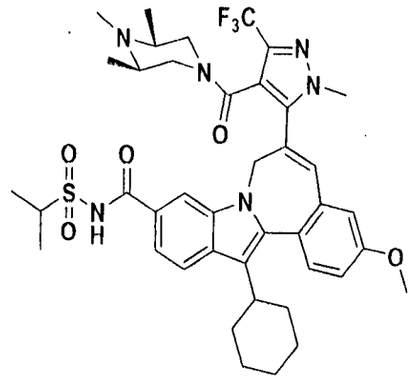


13-Ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-3-(trifluorometil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 782 ($M-H^+$). RMN de ^1H (500 MHz, MeOD) δ ppm 0,71 (s ancho, 3H), 0,75 (s ancho, 3H) 1,13 - 1,52 (m, 10 H) 1,75 - 2,21 (m, 9 H) 2,35 (m, 1 H) 2,83 - 3,21 (m, 3 H) 3,50 (s ancho, 3 H) 3,95 (s, 3 H) 3,96 - 4,03 (m, 1 H) 4,64 (d ancho, 1 H) 5,02 (d ancho, 1 H) 6,81 (s, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,13 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,55 - 7,65 (m, 2 H) 7,80 (s ancho, 1 H) 7,93 (d, *J*=8,55 Hz, 1 H) 10,50 (s ancho, 1 H).



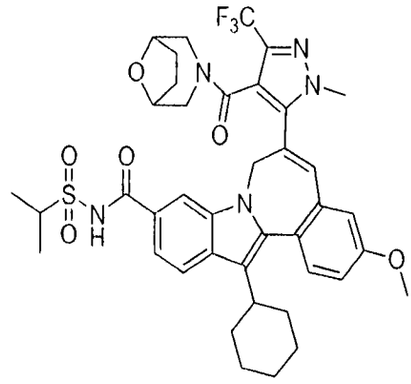
13-Ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[(3-metil-3,8-

diazabiciclo[3.2.1]oct-8-il)carbonil]-3-(trifluorometil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 793 ($M-H^+$). RMN de ^1H (500 MHz, MeOD) δ ppm 1,16 - 2,20 (m, 20 H) 2,40-2,99 (m, 7 H) 3,22-3,71 (m, 3H) 3,90-4,11 (m, 7 H) 4,63 (m ancho, 1 H) 4,98 (m ancho, 1 H) 6,98 (m, 1 H) 7,03 (m, 1 H) 7,23 (m, 1H) 7,52 - 7,73 (m, 3 H) 7,82 (s ancho, 1 H) 10,10 (s ancho, 1H).



13-Ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-3-(trifluorometil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. MS m/z 795 ($M-H^+$). RMN de ^1H (500 MHz, MeOD) δ ppm 1,10 - 1,51 (m, 16 H) 1,71 - 2,50 (m, 11 H) 2,59-2,94 (m, 5 H) 3,50 (s ancho, 3 H) 3,96 (s, 3 H) 4,63 (m ancho, 2 H) 4,95 (m ancho, 1 H) 6,93 (m, 2 H) 7,13 (m, 1 H) 7,49 - 7,65 (m, 2 H) 7,82 (s ancho, 1 H) 7,93 (m, 1 H) 10,10 (s ancho, 1H).

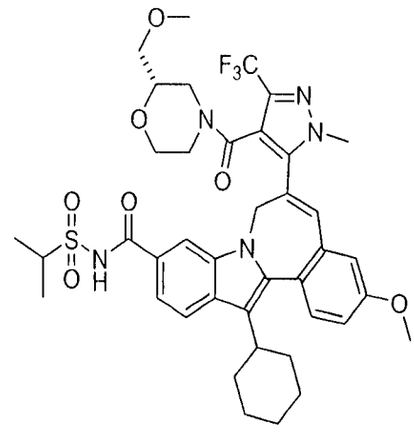
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-(3-oxa-3-azabiciclo[3.2.1]oct-3-ilcarbonil)-3-(trifluorometil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



MS m/z 780 ($M-H^+$)

RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 0,70 (m, 1H) 1,21 - 1,52 (m, 13 H) 1,75 - 2,20 (m, 8 H) 2,30 (m, 1H) 2,79 – 2,98 (m, 3 H) 3,11 (m, 1H) 3,87 (m, 1H) 3,98 (s ancho, 3 H) 4,05 (s, 3 H) 4,61 (d ancho, 1 H) 4,89 (m ancho, 1 H) 6,85-6,98 (m, 2 H) 7,17 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,55 - 7,70 (m, 2 H) 7,84-8,03 (m, 1 H) 7,93 (d, *J*=8,55 Hz, 1 H) 10,45 (s ancho, 1H).

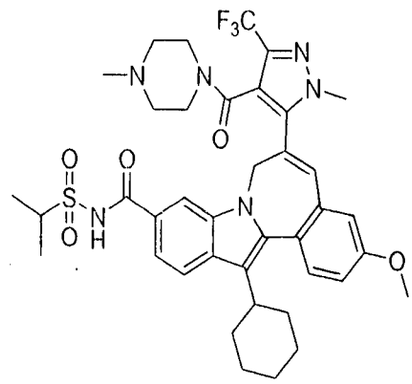
13-ciclohexil-3-metoxi-6-[1-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-3-(trifluorometil)-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



MS m/z 798 ($M-H^+$).

RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 1,11 - 1,61 (m, 10 H) 1,75 - 2,52 (m, 10 H) 2,81 - 3,60 (m, 9 H) 3,95 (s ancho, 3 H) 4,03 (s, 3 H) 3,95 - 4,03 (m, 1 H) 4,65 (d ancho, 1 H) 5,01 (m ancho, 1 H) 6,85 (s ancho, 1 H) 6,97 (s, 1 H) 7,15 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,50 - 7,71 (m, 2 H) 7,79-7,93 (m,2 H) 10,40 (s ancho, 1H).

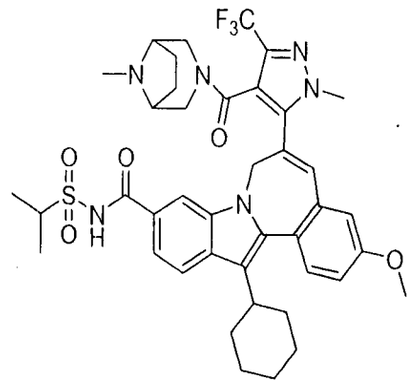
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[(4-metil-1-piperazinil)carbonil]-3-(trifluorometil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



MS m/z 767 ($M-H^+$).

RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 1,13 - 1,58 (m, 10 H) 1,75 - 2,12 (m, 6 H) 2,20 – 2,97 (m, 5 H) 3,19-3,79 (m, 7H) 3,95 (s, 3 H) 3,99 (s ancho, 3 H) 3,95 - 4,03 (m, 1 H) 4,50 (m ancho, 1 H) 4,92 (m ancho, 1 H) 6,87-7,01 (m, 2 H) 7,11 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,50 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,59-7,80 (m, 2 H) 7,91 (s ancho, 1 H) 10,50 (s ancho, 1H).

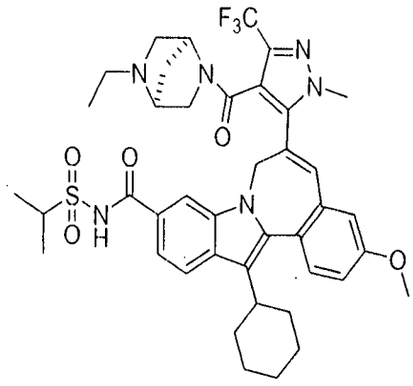
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[(3-metil-3,3-diazabiciclo[3.2.1]oct-3-il)carbonil]-3-(trifluorometil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



MS m/z 793 ($M-H^+$)

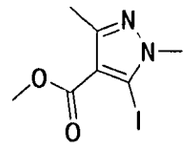
PMR de ^1H (500 MHz, $CDCl_3$) δ ppm 0,37 (m ancho, 1H) 0,83 (m ancho, 1H) 1,14 - 1,70 (m, 11 H) 1,75-2,16 (m, 7H) 2,35-2,70 (m, 4 H) 2,86 (m, 2 H) 3,20-3,79 (m, 4H) 3,90-4,11 (m, 7 H) 4,63 (d ancho, 1 H) 4,94 (m ancho, 1 H) 6,95-7,10 (m, 2 H) 7,15 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,53 - 7,70 (m, 3 H) 7,81 (s ancho, 1 H) 10,10 (s ancho, 1H).

13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-3-(trifluorometil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



MS m/z 793 ($M-H^+$)

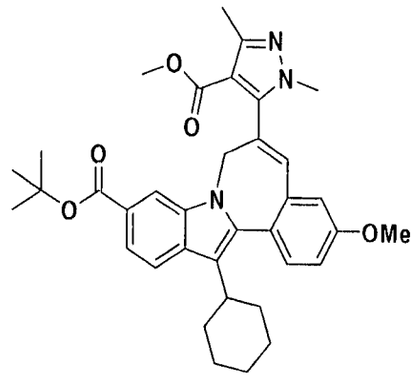
RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 0,55 (m ancho, 1H) 1,14 - 1,70 (m, 13 H) 1,75-2,16 (m, 7H) 2,52-3,70 (m, 9 H) 3,89-4,11 (m, 7 H) 4,69 (d ancho, 1 H) 5,00 (m ancho, 1 H) 6,95-7,15 (m, 3 H) 7,50-7,31 (m, 4 H) 10,20 (s ancho, 1H).



5-Yodo-1,3-dimetil-1H-pirazol-4-carboxilato de metilo.

A una solución de 1,3-dimetil-1H-pirazol-4-carboxilato de metilo (154 mg, 1 mmol) en tetrahidrofurano seco (10 ml) a -78ºC se añadió gota a gota una solución 2M de BuLi (0,550 ml, 1,100 mmol) en pentano. La mezcla de reacción se calentó entonces hasta -45ºC y se agitó durante 1 hora. Esta se enfrió hasta -78ºC y se añadió una solución de yodo (279 mg, 1,100 mmol) en THF (2 ml). La mezcla de reacción se calentó hasta TA y se agitó durante 1 hora. Seguidamente se inactivó con solución saturada de NH_4Cl y se extrajo con

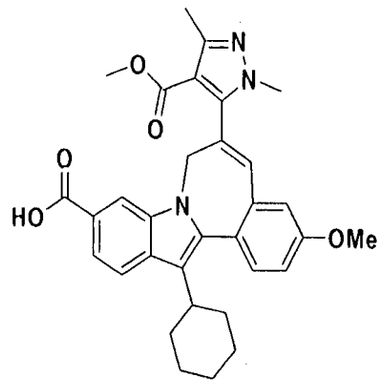
acetato de etilo (2X25 ml). Las fases orgánicas se reunieron, se lavaron con salmuera, se secaron sobre $MgSO_4$, y luego se concentraron a vacío. El producto bruto se obtuvo como un aceite espeso marrón. Este material se purificó entonces por HPLC Preparativa usando CH_3CN/H_2O/TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío. El concentrado se extrajo entonces con acetato de etilo y los extractos se reunieron y secaron sobre $MgSO_4$. La suspensión se filtró entonces y el filtrado se evaporó a presión reducida dando el compuesto del epígrafe como un sólido blanco, (137 mg, 0,460 mmol, 46,0 % de rendimiento). MS m/z 281(MH^+), Tiempo de retención: 1,107 min (básico). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 2,45 (s, 3 H) 3,84 (s, 3 H) 3,91 (s, 3 H).



Éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1,3-dimetil-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

Se añadieron a un tubo de microondas convencional éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(tributilestannil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico, (50 mg, 0,068 mmol), 5-yodo-1,3-dimetil-1H-

pirazol-4-carboxilato de metilo (33,2 mg, 0,136 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (4,79 mg, 6,82 µmol). El recipiente se selló, se desgasificó y se llenó con nitrógeno. Se añadió 1,4-dioxano (2,0 ml) y la mezcla resultante se calentó a 120°C en condiciones de microondas durante 2 horas. Luego se filtró y se concentró el filtrado. El residuo se purificó por HPLC preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se recogieron y concentraron a vacío dando el compuesto del epígrafe como un sólido color naranja, (9,1 mg, 0,015 mmol, 21,26 % de rendimiento). MS m/z 596(MH^+), Tiempo de retención: 2,893 min (básico). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,06 - 2,28 (m, 19 H) 2,47 (s, 3 H) 2,77 - 2,93 (m, 1 H) 3,19 (s, 3 H) 3,53 - 3,83 (s ancho, 3 H) 3,90 (s, 3 H) 4,58 - 4,73 (m ancho, 1 H) 4,86 - 5,03 (m ancho, 1 H) 6,71 (s, 1 H) 6,92 (d, *J*=2,44 Hz, 1 H) 7,06 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,52 (d, *J*=8,54 Hz, 1 H) 7,65 (dd, *J*=3,24, 1,22 Hz, 1 H) 7,80 - 7,85 (m, 2 H).

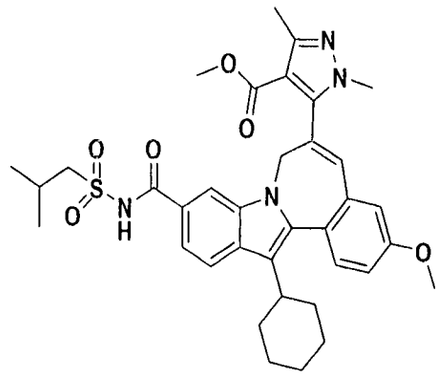


Ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1,3-dimetil-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico.

A una solución de éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1,3-dimetil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-

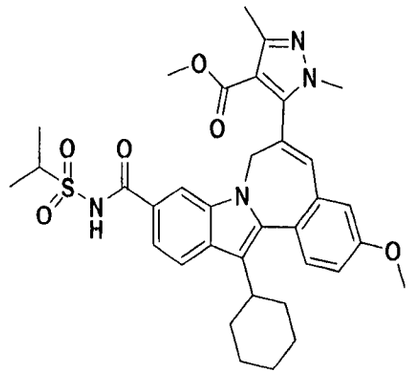
a][2]benzazepin-10-carboxílico (601 mg, 1,009 mmol) en 1,2-dicloroetano (10 ml) se añadió TFA (5 ml, 64,9 mmol). La mezcla de reacción se agitó a TA durante 4 horas. Se evaporaron entonces el disolvente y TFA dando un aceite parduzco espeso (650 mg, 1,144 mmol, 113% de rendimiento). Se purificaron 10 mg de producto bruto por HPLC preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a presión reducida dando el compuesto del epígrafe como un sólido amarillo claro, (3,5 mg, 35 % de recuperación). MS m/z 540(MH^+), Tiempo de retención: 1,925 min (básico). RMN de ^1H (500 MHz, MeOD) δ ppm 1,15 - 1,59 (m, 4 H) 1,68 - 2,24 (m, 6 H) 2,41 (s, 3 H) 2,84 - 2,97 (m, 1 H) 3,11 - 3,50 (m ancho, 6 H) 3,90 (s, 3 H) 4,55 - 4,69 (m ancho, 1 H) 4,94 - 5,06 (m ancho, 1 H) 6,88 (s, 1 H) 7,07 (d, *J*=2,44 Hz, 1 H) 7,14 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,57 (d, *J*=8,55 Hz, 1 H) 7,67 (dd, *J*=8,55, 1,22 Hz, 1 H) 7,87 (d, *J*=3,54 Hz, 1 H) 7,89 (s, 1 H).

Nota: El producto bruto restante se usó en las etapas siguientes sin purificación adicional.



Éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1H-pirazol-4-carboxílico.

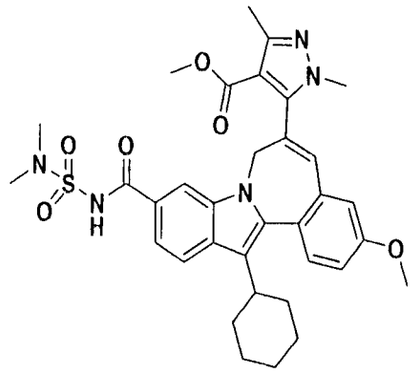
A una solución de ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1,3-dimetil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (225 mg, 0,417 mmol) en tetrahidrofurano (10 ml) se añadió CDI (101 mg, 0,625 mmol). La mezcla de reacción se calentó a 60ºC durante una hora y luego se dejó enfriar hasta temperatura ambiente. Se añadieron entonces 2-metilpropano-1-sulfonamida (172 mg, 1,251 mmol) y DBU (0,126 ml, 0,834 mmol) y la mezcla resultante se calentó a 60ºC durante 4 horas. La reacción se inactivó entonces con solución de HCl 1N y el producto se extrajo con acetato de etilo (2*40 ml). Las fases orgánicas se reunieron, se lavaron con solución de HCl 1N, salmuera, se secaron ($MgSO_4$) y luego se filtraron. La evaporación del filtrado dio el producto como un aceite color naranja. Este material se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío, proporcionando el compuesto del epígrafe como un sólido color amarillo, (46,6 mg, 0,067 mmol, 16,12 % de rendimiento). MS m/z 659(MH^+), Tiempo de retención: 2,197 min (básico). RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,14 (d, *J*=6,71 Hz, 6 H) 1,19 - 1,60 (m, 4 H) 1,70 - 2,15 (m, 6 H) 2,34 - 2,43 (m, 1 H) 2,49 (s, 3 H) 2,80 - 2,92 (m, 1 H) 3,12 - 3,75 (m, 8 H) 3,91 (s, 3 H) 4,63 - 4,74 (m ancho, 1 H) 4,85 - 4,99 (m ancho, 1 H) 6,75 (s, 1 H) 6,94 (d, *J*=2,75 Hz, 1 H) 7,09 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,39 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,53 (d, *J*=3,55 Hz, 1 H) 7,75 (d, *J*=1,22 Hz, 1 H) 7,90 (d, *J*=8,55 Hz, 1 H) 8,52 (s, 1 H).



Éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1H-pirazol-4-carboxílico.

A una solución de ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1,3-dimetil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (225 mg, 0,417 mmol) en tetrahidrofurano (10 ml) se añadió CDI (101 mg, 0,625 mmol). La mezcla de reacción se calentó a 60ºC durante una hora y luego se dejó enfriar hasta temperatura ambiente. Se añadieron entonces propano-2-sulfonamida (154 mg, 1,251 mmol) y DBU (0,126 ml, 0,834 mmol) y la mezcla resultante se calentó a 60ºC durante 4 horas. La reacción se inactivó entonces con solución de HCl 1N y el producto se extrajo con acetato de etilo (2X40 ml). Las fases orgánicas se reunieron, se lavaron con solución de HCl 1N, salmuera, luego se secaron ($MgSO_4$) y filtraron. La evaporación de los disolventes dio el producto como un aceite espeso color naranja. Este material se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío proporcionando el compuesto del epígrafe como un sólido color amarillo, (42,5 mg, 0,066 mmol, 15,81 % de rendimiento). MS m/z 645(MH^+), Tiempo de

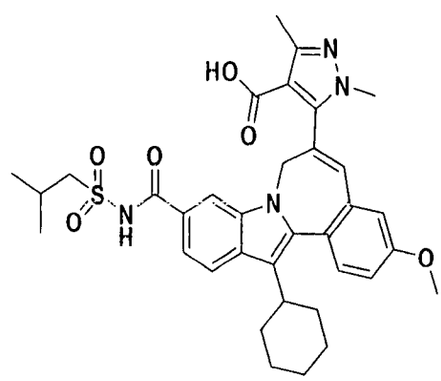
retención: 2,105 min (básico). RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,16 - 1,61 (m, 10 H) 1,69 - 2,21 (m, 6 H) 2,46 (s, 3 H) 2,81 - 2,92 (m, 1 H) 3,24 (s, 3 H) 3,66 (s ancho, 3 H) 3,91 (s, 3 H) 4,01 - 4,10 (m, 1 H) 4,63 - 4,75 (m ancho, 1 H) 4,84 - 4,98 (m ancho, 1 H) 6,74 (s, 1 H) 6,94 (d, *J*=2,75 Hz, 1 H) 7,00 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,39 (dd, *J*=8,55, 1,22 Hz, 1 H) 7,53 (d, *J*=8,55 Hz, 1 H) 7,74 (d, *J*=1,22 Hz, 1 H) 7,90 (d, *J*=8,55 Hz, 1 H) 8,28 (s, 1 H).



Éster metílico del ácido 5-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]-amino]carbonil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1H-pirazol-4-carboxílico.

A una solución de ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1,3-dimetil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (120 mg, 0,222 mmol) en THF (5 ml) se añadió CDI (54,1 mg, 0,334 mmol). La mezcla de reacción se calentó a 60ºC durante una hora y luego se dejó enfriar hasta temperatura ambiente. Se añadieron entonces N,N-dimetilsulfamida (83 mg, 0,667 mmol) y DBU (0,067 ml, 0,445 mmol) y la mezcla resultante se calentó a 60ºC durante la noche. La reacción se inactivó entonces con solución de HCl 1N y el producto se extrajo con acetato de etilo (2X30 ml). Las fases orgánicas

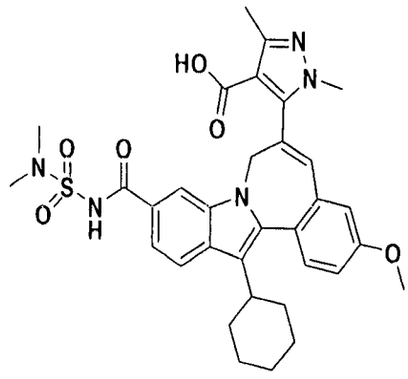
se reunieron, se lavaron con solución de HCl 1N, salmuera, se secaron ($MgSO_4$) y luego se filtraron. La evaporación de los disolventes dio el producto bruto como un aceite espeso color naranja. Este material se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y se concentraron a vacío proporcionando el compuesto del epígrafe como un sólido color naranja, (31,4 mg, 0,049 mmol, 21,87 % de rendimiento). MS m/z 646(MH^+), Tiempo de retención: 2,245 min (básico). PMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,18 - 1,60 (m, 4 H) 1,70 - 2,14 (m, 6 H) 2,49 (s, 3 H) 2,80 - 2,91 (m, 1 H) 3,05 (s, 6 H) 3,24 (s, 3 H) 3,68 (s ancho, 3 H) 3,91 (s, 3 H) 4,64 - 4,74 (m ancho, 1 H) 4,86 - 5,00 (m ancho, 1 H) 6,74 (s, 1 H) 6,94 (d, *J*=2,75 Hz, 1 H) 7,03 (dd, *J*=8,85, 2,75 Hz, 1 H) 7,35 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,53 (d, *J*=8,55 Hz, 1 H) 7,75 (d, *J*=1,22 Hz, 1 H) 7,89 (d, *J*=8,54 Hz, 1 H) 8,44 (s, 1 H).



Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]-carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1H-pirazol-4-carboxílico.

A una solución de éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-

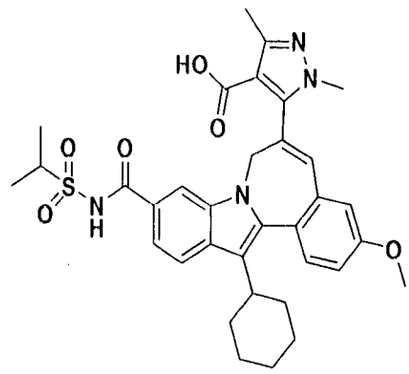
[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico (44,2 mg, 0,067 mmol) en tetrahidrofurano (2,0 ml) y MeOH (2,000 ml), se añadió solución de NaOH 1N (0,537 ml, 0,537 mmol). La mezcla de reacción se agitó a TA durante 4 días. La LC/MS mostró que solo ~ 25% del éster de partida se había hidrolizado. Se añadieron 0,5 ml más de solución de NaOH 1N. La mezcla de reacción se agitó entonces a TA durante tres días más. La mezcla de reacción se concentró y el residuo se acidificó usando solución de HCl 1N. La mezcla resultante se extrajo entonces con acetato de etilo (2 x 20 ml) y se reunieron las fases orgánicas, se lavaron con salmuera, se secaron ($MgSO_4$) y luego se filtraron. La evaporación del filtrado dio el producto bruto como un aceite color naranja viscoso. Este material se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se recogieron y concentraron a presión reducida dando el compuesto del epígrafe como un sólido amarillo claro (12,2 mg, 0,019 mmol, 28,2% de rendimiento). MS m/z 645(MH^+), Tiempo de retención: 1,847 min (básico). RMN de ^1H (500 MHz, DMSO-D6) δ ppm 1,02 (d, *J*=6,71 Hz, 6 H) 1,08 - 1,53 (m, 4 H) 1,64 - 2,09 (m, 6 H) 2,08 - 2,20 (m, 1 H) 2,36 (s, 3 H) 2,71 - 2,85 (m, 1 H) 3,09 (s, 3 H) 3,45 (d, *J*=6,71 Hz, 2 H) 3,88 (s, 3 H) 4,42 - 4,62 (m ancho, 1 H) 4,96 - 5,13 (m ancho, 1 H) 6,97 (s, 1 H) 7,15 (d, *J*=2,75 Hz, 1 H) 7,21 (dd, *J*=8,85, 2,75 Hz, 1 H) 7,54 (d, *J*=8,85 Hz, 1 H) 7,60 (dd, *J*=8,39, 1,37 Hz, 1 H) 7,90 (d, *J*=8,54 Hz, 1 H) 8,14 (s, 1 H) 11,76 (s, 1 H) 12,37 (s ancho, 1 H).



Ácido 5-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1H-pirazol-4-carboxílico.

A una solución de éster metílico del ácido 5-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico (29,4 mg, 0,046 mmol) en THF (1,5 ml) y MeOH (1,500 ml), se añadió solución de NaOH 1N (0,364 ml, 0,364 mmol). La mezcla de reacción se agitó a TA durante 4 días. La LC/MS mostró que solo ~ 40% del éster se había hidrolizado. Se añadieron 0,5 ml más de solución de NaOH 1N. La mezcla de reacción se agitó entonces a TA durante tres días más. La mezcla de reacción se concentró y el residuo se acidificó usando solución de HCl 1N. El producto se extrajo entonces con acetato de etilo (2 x 20 ml). Las fases orgánicas se reunieron, se lavaron con salmuera, se secaron ($MgSO_4$) y luego se filtraron. La evaporación del filtrado dio el producto bruto como un aceite color naranja. Este material se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío dando el compuesto del epígrafe como un sólido color amarillo claro, (9,5 mg, 0,015 mmol, 33,0 % de rendimiento). MS m/z 632(MH^+), Tiempo de retención:

1,853 min (básico). RMN de ^{1}H (500 MHz, DMSO-D6) δ ppm 1,06 - 1,53 (m, 4 H) 1,53 - 2,07 (m, 6 H) 2,35 (s, 3 H) 2,74 - 2,83 (m, 1 H) 2,87 (s, 6 H) 3,02 - 3,16 (s ancho, 3 H) 3,83 (s, 3 H) 4,41 - 4,61 (m ancho,1 H) 4,96 - 5,20 (m ancho, 1 H) 6,97 (s, 1 H) 7,15 (d, *J*=2,75 Hz, 1 H) 7,20 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,54 (d, *J*=8,55 Hz, 1 H) 7,60 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,89 (d, *J*=8,54 Hz, 1 H) 8,14 (s, 1 H) 11,51 (s, 1 H) 12,35 (s ancho, 1 H).

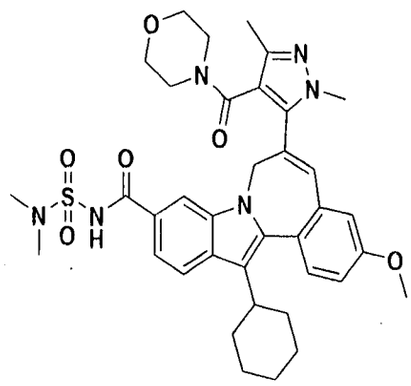


Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]-carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1H-pirazol-4-carboxílico.

A una mezcla de éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico (80 mg, 0,124 mmol) y trimetilsilanolato potásico (TMSOK) (31,8 mg, 0,248 mmol) en un matraz de fondo redondo se añadió tetrahidrofurano (8 ml). La mezcla resultante se agitó entonces a RT durante la noche. La LC/MS mostró que solo el 40% de material de partida había reaccionado. Se añadieron dos equivalentes más de TMSOK y se continuó agitando durante 48 horas. La mezcla de reacción se concentró entonces y se añadió solución de HCl 1N. Se separó un sólido amarillo (35 mg) y se purificaron entonces 10 mg del material por HPLC preparativa usando

CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y evaporaron a vacío dando el compuesto del epígrafe como un sólido color amarillo, (7,6 mg, 76 % de recuperación). MS m/z 631(MH^+), Tiempo de retención: 1,648 min (básico). RMN de ^1H (500 MHz, Acetona) δ ppm 1,11 - 1,61 (m, 10 H) 1,63 - 2,21 (m, 6 H) 2,38 (s, 3 H) 2,85 - 3,00 (m, 1 H) 3,17 (s, 3 H) 3,83 - 3,97 (m, 4 H) 4,54 - 4,72 (m ancho, 1 H) 5,09 - 5,29 (m ancho, 1 H) 6,93 (s, 1 H) 7,11 (d, *J*=2,75 Hz, 1 H) 7,17 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,61 (d, *J*=8,55 Hz, 1 H) 7,68 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,96 (d, *J*=8,55 Hz, 1 H) 8,21 (s, 1 H) 9,96 (s, 1 H).

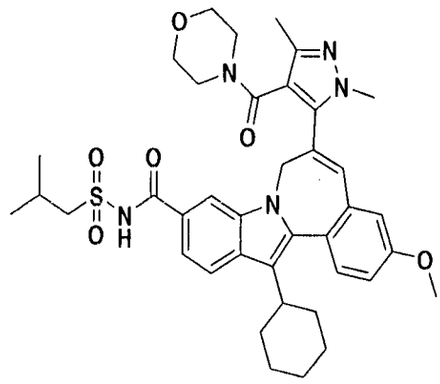
Nota: El producto bruto descrito antes se puede usar sin purificación posterior para la preparación de los ejemplos carboxamida de la presente invención.



13-Ciclohexil-N-[(dimetilamino)sulfonil]-6-[1,3-dimetil-4-(4-morfolinilcarbonil)-1H-pirazol-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

A una solución de ácido 5-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico (9,5 mg, 0,015 mmol) en DMSO (1 ml) se añadieron TBTU (9,66 mg, 0,030 mmol) y DIPEA (0,013 ml,

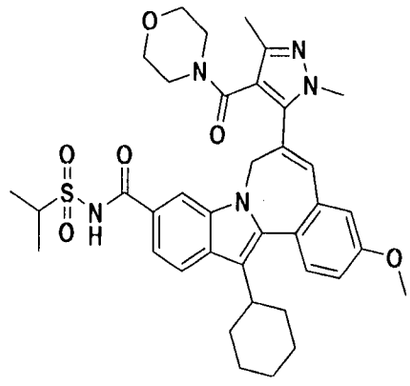
0,075 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces morfolina (1,965 mg, 0,023 mmol) y la solución resultante se agitó a TA durante 48 horas. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío. El compuesto del epígrafe se obtuvo como un sólido color amarillo, (5,0 mg, 0,011 mmol, 74,4 % de rendimiento). MS m/z 699(M-H$^-$), Tiempo de retención: 1,990 min (básico). PMN de ^{1}H (500 MHz, MeOD) δ ppm 1,18 - 1,64 (m, 4 H) 1,73 - 2,26 (m, 9 H) 2,59 - 3,09 (m, 15 H) 3,85 (s, 3 H) 3,95 (s, 3 H) 4,67 (d, *J*=14,96 Hz, 1 H) 5,02 - 5,15 (m, 1 H) 7,07 (s, 1 H) 7,15 (d, *J*=2,44 Hz, 1 H) 7,20 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,56 - 7,64 (m, 2 H) 7,92 (s, 1 H) 7,98 (d, *J*=8,55 Hz, 1 H).



13-Ciclohexil-6-[1,3-dimetil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico (10 mg, 0,016 mmol) en DMSO (1 ml) se

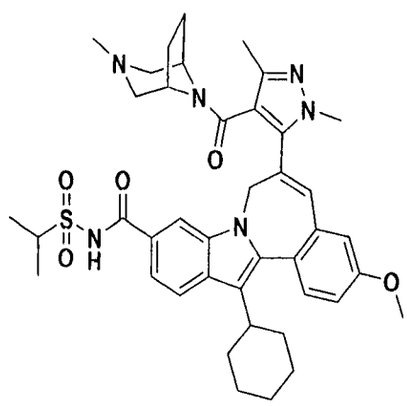
añadieron TBTU (9,96 mg, 0,031 mmol) y DIPEA (0,014 ml, 0,078 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces morfolina (1,351 mg, 0,016 mmol) y la solución resultante se agitó a TA durante la noche. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se recogieron y concentraron a vacío proporcionando el compuesto del epígrafe como un sólido color amarillo (10,7 mg, 0,015 mmol, 95% de rendimiento). MS m/z 712($M-H^-$), Tiempo de retención: 1,895 min (básico). RMN de ^1H (500 MHz, MeOD) δ ppm 1,16 (d, *J*=6,71 Hz, 6 H) 1,20 - 1,64 (m, 4 H) 1,73 - 2,27 (m, 9 H) 2,29 - 2,43 (m, 1 H) 2,56 - 3,14 (m, 9 H) 3,49 - 3,55 (m, 2 H) 3,85 (s, 3 H) 3,95 (s, 3 H) 4,67 (d, *J*=14,96 Hz, 1 H) 4,98 - 5,16 (m ancho, 1 H) 7,07 (s, 1 H) 7,15 (d, *J*=2,44 Hz, 1 H) 7,20 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,55 - 7,66 (m, 2 H) 7,95 (s, 1 H) 7,98 (d, *J*=8,55 Hz, 1 H).



13-Ciclohexil-6-[1,3-dimetil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1,3-dimetil-

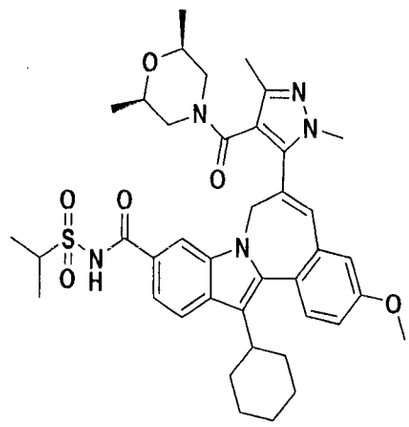
1*H*-pirazol-4-carboxílico (20 mg, 0,032 mmol) en DMSO (1 ml) se añadieron TBTU (20,36 mg, 0,063 mmol) y DIPEA (0,028 ml, 0,159 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Se añadió entonces morfolina (4,14 mg, 0,048 mmol) y la solución resultante se agitó a TA durante la noche. La mezcla de reacción se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío. El compuesto del epígrafe se obtuvo como un sólido color amarillo, (16,8 mg, 0,024 mmol, 74,2 % de rendimiento). MS m/z 698(M-H$^-$), Tiempo de retención: 1,798 min (básico). RMN de ^{1}H (500 MHz, MeOD) δ ppm 1,18 - 1,62 (m, 10 H) 1,72 - 2,25 (m, 9 H) 2,53 - 3,23 (m, 9 H) 3,84 (s, 3 H) 3,95 (s, 3 H) 3,96 - 4,03 (m, 1 H) 4,64 (d, *J*=14,95 Hz, 1 H) 5,00 - 5,15 (m ancho, 1 H) 7,06 (s, 1 H) 7,14 (d, *J*=2,44 Hz, 1 H) 7,19 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,55 - 7,65 (m, 2 H) 7,94 (s, 1 H) 7,98 (d, *J*=8,55 Hz, 1 H).



13-Ciclohexil-6-[1,3-dimetil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-3-il)carbonil]-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-

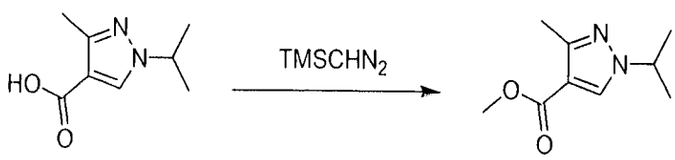
metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico (20 mg, 0,032 mmol) en DMSO (1 ml) se añadieron TBTU (20,36 mg, 0,063 mmol) y DIPEA (0,028 ml, 0,159 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Seguidamente, se añadió 3-metil-3,8-diazabiciclo[3.2.1]octano,2 HCl (9,47 mg, 0,048 mmol). La solución se agitó entonces a TA durante la noche. La mezcla de reacción bruta se purificó entonces por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío proporcionando el compuesto del epígrafe como un sólido color amarillo (19,7 mg, 0,023 mmol, 71,4% de rendimiento). MS m/z 737($M-H^+$), Tiempo de retención: 2,040 min (básico). RMN de ^1H (500 MHz, MeOD) δ ppm 1,16 - 1,67 (m, 14 H) 1,74 - 2,25 (m, 6 H) 2,33 (s, 3 H) 2,51 - 2,66 (m, 1 H) 2,72 (s, 3 H) 2,94 - 3,05 (m, 1 H) 3,16 - 3,39 (m, 5 H) 3,84 (s, 3 H) 3,96 (s, 3 H) 3,98 - 4,05 (m, 1 H) 4,59 - 4,71 (m ancho, 1 H) 4,94 - 5,05 (m ancho, 1 H) 7,14 - 7,28 (m, 3 H) 7,62 - 7,66 (m, 2 H) 7,91 (s, 1 H) 8,00 (d, *J*=8,54 Hz, 1 H).



13-Ciclohexil-6-[1,3-dimetil-4-[[cis-2,6-dimetil-4-morfolinil]carbonil]-1H-

pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico (13 mg, 0,021 mmol) en DMSO (1 ml) se añadieron TBTU (13,24 mg, 0,041 mmol) y DIPEA (0,018 ml, 0,103 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. Seguidamente, se añadió cis-2,6-dimetilmorfolina (3,56 mg, 0,048 mmol) y la mezcla resultante se agitó a TA durante la noche. La mezcla de reacción bruta se purificó por HPLC Preparativa usando CH_3CN-H_2O-TFA como sistema disolvente. Las fracciones homogéneas se reunieron y concentraron a vacío proporcionando el compuesto del epígrafe como un sólido color amarillo (10,1 mg, 0,014 mmol, 67,3% de rendimiento). MS m/z 326(M-H$^+$), Tiempo de retención: 1,958 min (básico). RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,57 - 2,33 (m, 25 H) 2,81 - 3,60 (m, 5 H) 3,77 - 3,99 (m, 8 H) 4,03 - 4,12 (m, 1 H) 4,57 (d, *J*=15,26 Hz, 1 H) 4,76 - 4,94 (m, 1 H) 6,75 - 6,83 (m, 1 H) 6,95 (s, 1 H) 7,12 (dd, *J*=8,55, 2,14 Hz, 1 H) 7,50 - 7,67 (m, 2 H) 7,71 (s, 1 H) 7,91 (d, *J*=8,24 Hz, 1 H).

1-(1-Metiletil)-3-metil-1H-pirazol-4-carboxilato de metilo



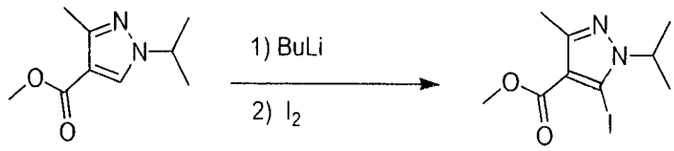
Se añadió trimetilsilildiazometano (23,8 ml) a una solución de ácido 1-(1-metiletil)-3-metil-1H-pirazol-4-carboxílico (2,00 g, 11,9 mmol) en benceno (15,9 ml) y metanol (7,93 ml) a temperatura ambiente. La solución resultante se agitó

a temperatura ambiente durante 3 horas. El disolvente se eliminó a presión reducida en un evaporador rotatorio proporcionando el compuesto del epígrafe (2,17 g, 11,89 mmol, 100% de rendimiento) como un sólido blanco.

MS m/z 183 (MH^+)

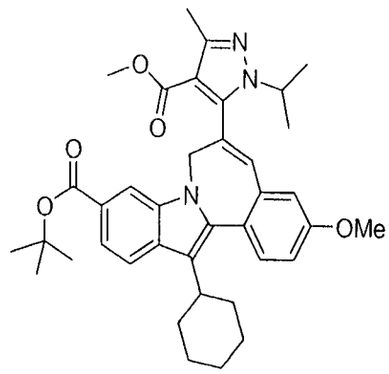
RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,49 (d, 6H) 2,43 (s, 3 H) 3,81 (s, 3 H) 4,42 (m, 1H) 7,86 (s, 1H).

5-yodo-1-(1-metiletil)-3-metil-1H-pirazol-4-carboxilato de metilo



A una solución de 1-(1-metiletil)-3-metil-1H-pirazol-4-carboxilato de metilo (2,00 g, 11,0 mmol) en tetrahidrofurano seco (22,0 ml) a -78°C, se añadió gota a gota una solución 2 M de butil litio (6,04 ml, 12,1 mmol) en pentano. La mezcla de reacción se calentó entonces hasta -45°C y se agitó durante 1 hora. Esta se enfrió hasta -78°C y se añadió una solución de yodo (3,06 g, 12,1 mmol) en THF (11,0 ml). La mezcla de reacción se calentó hasta TA y se agitó durante 1 hora. Seguidamente se inactivó con solución saturada de NH_4Cl y se extrajo con acetato de etilo (2X25 ml). Las fases orgánicas se reunieron, se lavaron con salmuera y se secaron ($MgSO_4$). La evaporación del disolvente dio un sólido color castaño como compuesto del epígrafe (3,38 g, 11,0 mmol, 100 % rendimiento bruto). MS m/z 309 (MH^+); RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,41 (d, 6H) 2,47 (s, 3 H) 3,82 (s, 3 H) 4,77 (m, 1H).

éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1-(1-metiletil)-3-metil-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico



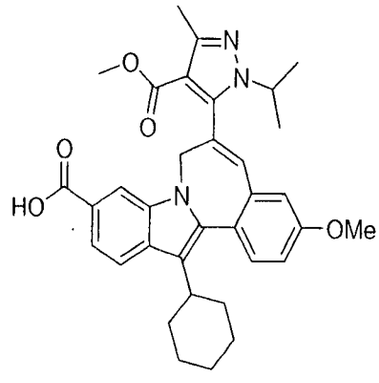
En un tubo de microondas se añadieron éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(tributilestannil)-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (611 mg, 0,834 mmol), 5-yodo-1-(1-metiletil)-3-metil-1H-pirazol-4-carboxilato de metilo (360 mg, 1,17 mmol) y cloruro de bis(trifenilfosfina)paladio II (58,5 mg, 0,083 mmol). Seguidamente se selló, se desgasificó y se llenó con nitrógeno. Se añadió 1,4-dioxano (4,17 ml). La mezcla de reacción se calentó a 160ºC en condiciones de microondas durante 1 hora. Luego se filtró y se concentró el filtrado. El residuo se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (3 ml) purificado usando una columna de 5 um 19 mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud

de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 25% de disolvente A / 75% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 10 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente.

Las fracciones que contenían producto se recogieron y se concentraron dando el compuesto del epígrafe como un sólido amarillo (156 mg, 0,250 mmol, 30% de rendimiento).

MS m/z 624 (MH^+); RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,41 (s ancho, 3H) 1,18 - 1,59 (m, 16 H) 1,72 - 2,20 (m, 6 H) 2,49 (s, 3 H) 2,86 (m, 1 H) 3,68 (m, 1 H) 3,85 (s ancho, 3 H) 3,92 (s, 3 H) 4,69 (d ancho, 1 H) 4,97 (d ancho, 1 H) 6,68 (s, 1 H) 6,92 (d, *J*=2,14 Hz, 1 H) 7,06 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,51 (d, *J*=8,55 Hz 1 H) 7,73 (d, *J*=8,24 Hz, 1 H) 7,81 (d, *J*=8,24 Hz, 1 H) 7,87 (s, 1 H).

ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1(1-metiletil)-3-trifluorometil-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico

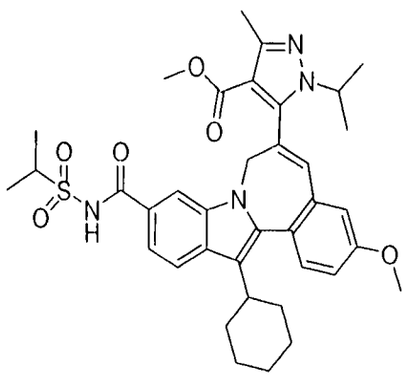


Se añadió TFA (4 ml) a una solución de éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1-(1-metiletil)-3-(trifluorometil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (156 mg, 0,250 mmol) en 1,2-dicloroetano (4 ml). La mezcla de reacción se agitó a TA durante 2 horas. Los volátiles se eliminaron en un evaporador rotatorio dando el compuesto del epígrafe como un aceite parduzco espeso como producto bruto (142 mg, 0,8250 mmol, 100% de rendimiento).

MS m/z 568 (MH^+)

RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,41 (s ancho, 3H) 1,13 - 1,59 (m, 7 H) 1,72 - 2,20 (m, 6 H) 2,52 (s, 3 H) 2,87 (m, 1 H) 3,63 (m, 1 H) 3,85 (s ancho, 3 H) 3,91 (s, 3 H) 4,71 (d ancho, 1 H) 4,96 (d ancho, 1 H) 6,68 (s, 1 H) 6,96 (d, *J*=2,14 Hz, 1 H) 7,08 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,52 (d, *J*=8,55 Hz 1 H) 7,77 (d, *J*=8,24 Hz, 1 H) 7,87 (d, *J*=8,24 Hz, 1 H) 7,97 (s, 1 H).

ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)- 1(1-metiletil)-3-trifluorometil-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxílico



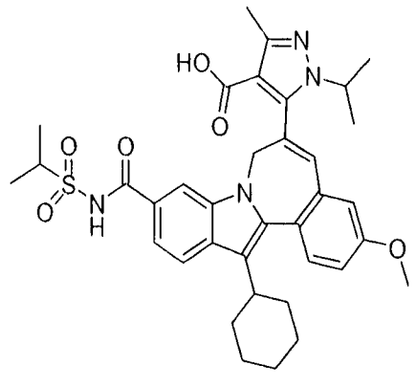
A una solución de ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-

1(1-metiletil)-3-trifluorometil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico (110 mg, 0,194 mmol) en tetrahidrofurano (0,646 ml) se añadió carbonildiimidazol (94,0 mg, 0,581 mmol). La mezcla de reacción se calentó a 60ºC durante una hora. Se añadieron propano-2-sulfonamida (95 mg, 0,775 mmol) y DBU (0,088 ml, 0,581 mmol) a temperatura ambiente. La mezcla de reacción se calentó entonces a 60ºC durante 4 horas. La mezcla de reacción se diluyó con solución de HCl 1N (50 ml) y se extrajo con acetato de etilo (2 X 40 ml). Las fases orgánicas se reunieron y concentraron en un evaporador rotatorio dando un aceite naranja como producto bruto. Este se purificó por columna HPLC prep usando CH_3CN/H_2O/TFA como sistema disolvente. Las fracciones se recogieron y concentraron en un SpeedVAc durante 16h. Se obtuvo un sólido amarillo como compuesto del epígrafe (114 mg, 0,169 mmol, 87% de rendimiento).

MS m/z 673 (MH^+)

RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,41 (s ancho, 3H) 1,13 - 1,52 (m, 13 H) 1,70 - 2,20 (m, 6 H) 2,51 (s, 3 H) 2,85 (m, 1 H) 3,59 (m, 1 H) 3,87 (s, 3 H) 3,92 (s, 3 H) 4,02 (m, 1 H) 4,73 (d ancho, 1 H) 4,97 (d ancho, 1 H) 6,67 (s, 1 H) 6,96 (d, *J*=2,14 Hz, 1 H) 7,08 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,40-7,62 (m, 2 H) 7,78-7,84 (m, 2 H), 9,00 (s ancho, 1 H).

Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]-carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(metiletil)-3-metil-1H-pirazol-4-carboxílico.



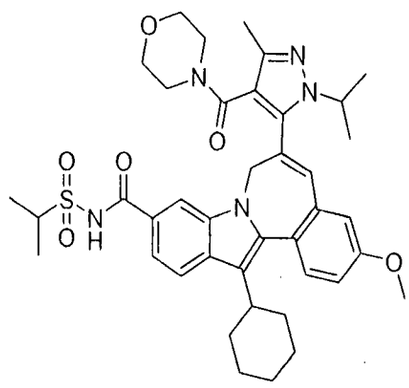
Una mezcla de ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)- 1(1-metiletil)-3-trifluorometil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (110 mg, 0,163 mmol) se disolvió en THF (0,272 ml) y se añadió a la reacción metanol (0,272 ml) seguido por hidróxido sódico acuoso 1N (0,600 ml). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18 horas. La reacción se diluyó con acetato de etilo (25,0 ml) y se lavó con ácido clorhídrico acuoso 1,0N (2 x 20 ml). La fase orgánica se concentró a vacío usando un evaporador rotatorio proporcionando el compuesto del epígrafe como un sólido amarillo (107 mg, 0,163 mmol, 100%).

MS m/z 659 (MH^+)

PMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,39 (s ancho, 3H) 1,18 - 1,52 (m, 13 H) 1,70 - 2,20 (m, 6 H) 2,48 (s, 3 H) 2,83 (m, 1 H) 3,51 (m, 1 H) 3,87 (s, 3 H) 4,02 (m, 1 H) 4,72 (d ancho, 1 H) 4,98 (d ancho, 1 H) 6,65 (s, 1 H) 6,95 (d, *J*=2,14 Hz, 1 H) 7,08 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,41-7,60 (m, 2 H) 7,79-7,83 (m, 2 H), 8,96 (s ancho, 1 H).

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[3-metil-1-(1-metiletil)-4-

(4-morfolinilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



A una solución de ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-(1-metiletil)-3-metil-1*H*-pirazol-4-carboxílico (25 mg, 0,038 mmol) en DMSO (0,38 ml) se añadieron TBTU (24 mg, 0,076 mmol) y DIPEA (0,020 mg, 0,44 mmol). La mezcla de reacción se agitó a TA durante 15 minutos. A continuación se añadió morfolina (38 mg, 15 mmol). La solución se agitó a TA durante la noche. La mezcla de reacción se purificó por una columna HPLC prep usando CH_3CN/H_2O/TFA como sistema disolvente. Las fracciones se recogieron y concentraron en SpeedVAc durante la noche proporcionando el compuesto del epígrafe como un sólido amarillo (24 mg, 0,031 mmol, 81% de rendimiento).

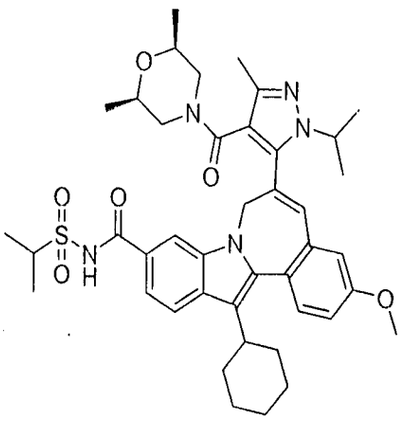
MS m/z 728 ($M-H^+$).

RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,18 - 1,70 (m, 16 H) 1,75 - 2,16 (m, 6 H) 2,30 (s, 3 H) 2,60-3,31 (m, 9 H) 3,94 (m, 3 H) 4,04 (m, 1 H) 4,56 (m ancho, 2 H) 4,93 (d ancho, 1 H) 6,79 (s ancho, 1 H) 6,94 (s, 1 H) 7,12 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,57 (d, *J*=8,55 Hz 1 H) 7,66 (s ancho, 1 H) 7,82 (s, 1 H)

7,97 (d, *J*=8,55 Hz, 1 H), 10,20 (s ancho, 1 H).

Los siguientes compuestos se sintetizaron por un procedimiento análogo al descrito antes para 13-ciclohexil-3-metoxi-N-1-metiletil)sulfonil]–6–[3–metil-1-(1-metiletil)-4-4–morfolinilcarbonil)-1H–pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida:

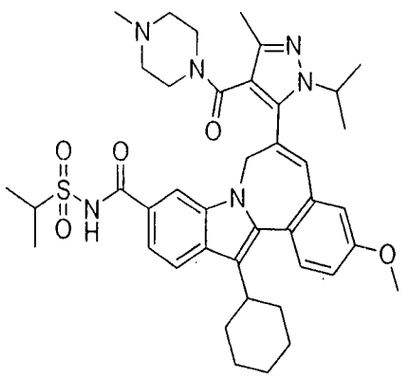
13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-3-metil-1-(1-metiletil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



MS m/z 756 ($M-H^+$).

RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,70-0,91 (m ancho, 6 H)1,02 - 1,81 (m, 16 H) 1,86 - 2,16 (m, 6 H) 2,29 (s, 3 H) 2,85-3,29 (m, 5 H) 3,96 (s, 3 H) 4,12 (m ancho, 3 H) 4,55 (m ancho, 2 H) 4,92 (d ancho, 1 H) 6,73 (s ancho, 1 H) 6,94 (s ancho, 1 H) 7,16 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,51-7,72 (m, 2 H) 7,76-7,98 (m, 2 H), 10,50 (s ancho, 1 H).

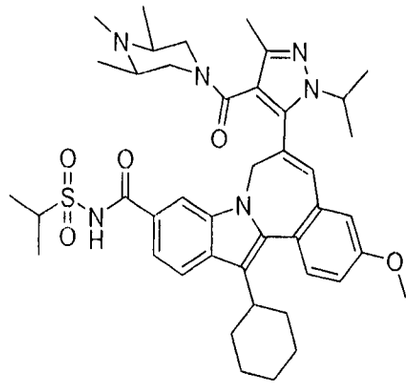
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[3-metil-1-(1-metiletil)-4-[(4-metil-1-piperazinil)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



MS m/z 741 ($M-H^+$).

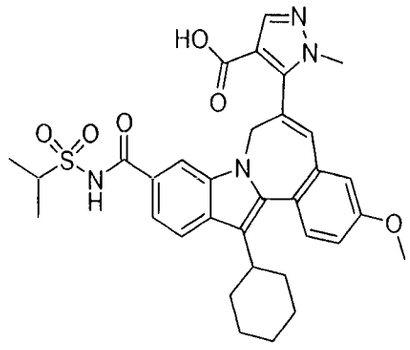
RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 1,15 - 1,81 (m, 18 H) 1,86 - 2,12 (m, 4 H) 2,21-2,45 (m, 5 H) 2,61-3,05 (m, 6 H) 3,10-3,75 (m, 4 H) 3,93 (s, 3 H) 4,04 (m, 1 H) 4,61 (m ancho, 2 H) 4,90 (d ancho, 1 H) 6,86 (s ancho, 1 H) 6,96 (s, 1 H) 7,14 (m ancho, 1 H) 7,59-7,63 (m, 3 H) 7,93 (s ancho, 1 H), 10,10 (s ancho, 1 H).

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[3-metil-1-(1-metiletil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida



MS m/z 769 ($M-H^+$).

RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,21 (s ancho, 1 H) 1,02 (s ancho, 3 H) 1,15-1,60 (m, 17 H) 1,69 - 2,12 (m, 8 H) 2,28 (m, 4 H) 2,69-3,60 (m, 6 H) 3,96 (s, 3 H) 4,08 (m ancho, 3 H) 4,60 (m ancho, 2 H) 4,88 (m ancho, 1 H) 6,82 (s ancho, 1 H) 6,95 (s, 1 H) 7,15 (m ancho, 1 H) 7,55-7,74 (m, 2 H) 7,78-7,99 (m, 2 H), 10,12 (s ancho, 1 H).



Ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]-carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico.

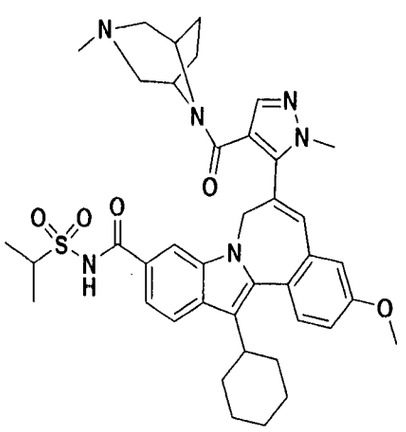
Se disuelve éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-

pirazol-4-carboxílico (1,044 g, 1,619 mmol) en una solución premezclada de THF (20 ml), MeOH (20 ml) e hidróxido sódico (20 ml, 20,00 mmol). La reacción era homogénea y se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 26 horas y luego se concentró a vacío usando un evaporador rotatorio con una temperatura de baño a 20°C. La reacción se vertió en ácido clorhídrico acuoso 1N y se extrajo usando acetato de etilo. Las fases orgánicas reunidas se lavaron secuencialmente con ácido clorhídrico acuoso y salmuera, luego se secaron sobre sulfato de magnesio, se filtraron y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando 1,68 g de un sólido amorfo naranja. El producto bruto se disolvió en cloroformo (aproximadamente 50 ml) con calentamiento y se añadieron hexanos hasta que el material comenzó a precipitar pero se volvió a disolver al agitar (aproximadamente 10-12 ml de hexanos). La mezcla se dejó enfriar lentamente hasta temperatura ambiente y luego se dejó reposar a temperatura ambiente durante unas pocas horas. El precipitado amarillo en forma de partículas finas se filtró usando un embudo Buchner y se secó a vacío a temperatura ambiente proporcionando 819 mg (45%) de producto purificado como un sólido amorfo amarillo brillante. El compuesto del epígrafe, 4,6 mg, se disolvió en $CDCl_3$ (2ml) con la adición de aproximadamente 5 gotas de CD_3OD para ayudar en la disolución para la adquisición de RMN de ^1H.

RMN de ^1H (500 MHz, CLOROFORMO-D / CD3OD) δ ppm 1,11 - 1,39 (m, 3 H) 1,41 (d, *J*=7,02 Hz, 6 H) 1,47 - 1,65 (m, 1 H) 1,75 (d, *J*=8,85 Hz, 2 H) 1,82 - 2,27 (m, 13 H) 2,77 - 2,90 (m, 1 H) 3,28 (s, 3 H) 3,88 (s, 3 H) 3,97 - 4,06 (m, 1 H) 4,66 (s, 1 H) 5,01 (s, 1 H) 6,76 (s, 1 H) 6,92 (d, *J*=2,75 Hz, 1 H) 7,04 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,47 - 7,54 (m, 2 H) 7,81 (d, *J*=1,22 Hz, 1 H) 7,86 (d,

J=8,54 Hz, 1 H) 7,91 (s, 1 H).

Tiempo de retención LC-MS 1,39 min; 615 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



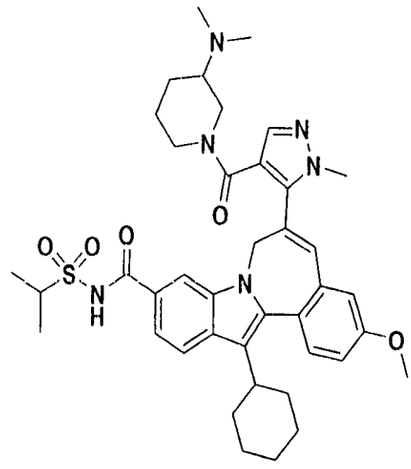
13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En vial de 2 dram, se agitaron 900 ul de una solución madre que contenía ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (0,09M, 0,081mmol) y TBTU (0,19M, 0,171mmol) en DMF en una atmósfera de nitrógeno durante 1 hora a temperatura ambiente. Se añadió DMAP (40 mg, 0,327 mmol) a la reacción y se agitó hasta disolución y luego se añadió el reactivo amina, diclorhidrato de 3-metil-3,8-diazabiciclo[3.2.1]octano (35 mg, 0,176 mmol) y la reacción se tapó en nitrógeno y se agitó a temperatura ambiente. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando 63 mg de una película/espuma amarillo amorfo. La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (2 ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. La muestra se purificó en dos inyecciones HPLC, y

las fracciones de producto se reunieron (Tiempo de retención=5,5min) y se eliminaron los volátiles a vacío. La muestra se secó a vacío a temperatura ambiente proporcionando 44,4 mg del compuesto del epígrafe como una sal TFA.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,10 - 1,31 (m, 1 H) 1,33 - 1,57 (m, 10 H) 1,80 (s, 2 H) 1,89 - 2,16 (m, 5 H) 2,57 (s, 4 H) 2,74 (s, 9 H) 2,84 - 3,12 (m, 4 H) 3,27 (s, 2 H) 3,32 - 3,72 (m, 4 H) 3,88 (s, 3 H) 3,94 (s, 4 H) 4,00 - 4,14 (m, 1 H) 4,63 (d, *J*=15,56 Hz, 1 H) 4,89 (d, *J*=12,21 Hz, 1 H) 6,96 (d, *J*=2,14 Hz, 2 H) 7,13 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,57 (d, *J*=8,85 Hz, 1 H) 7,63 (d, *J*=7,63 Hz, 2 H) 7,76 (s, 1 H) 7,93 (d, *J*=8,55 Hz, 1 H).

Tiempo de retención LC-MS 1,31 min; 723 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En un vial de 2 dram, se agitaron en una atmósfera de nitrógeno durante 1 hora a temperatura ambiente 900 ul de una solución madre que contenía ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (0,09M, 0,081mmol) y TBTU (0,19M, 0,171mmol) en DMF. Se añadió DMAP (42 mg, 0,344 mmol) a la reacción y se agitó hasta disolución y luego se añadió el reactivo amina, diclorhidrato de N,N-dimetilpiperidin-3-amina (34 mg, 0,169 mmol) y la reacción se tapó en nitrógeno y se agitó a temperatura ambiente durante la noche. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando 67 mg como una película amarilla. La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea

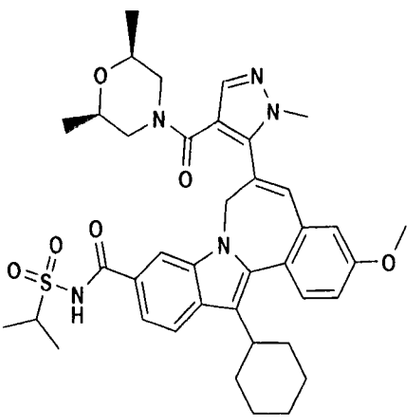
software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A.. La muestra se disolvió en acetonitrilo / DMF (1:1) (2 ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA.

Se reúnen las fracciones producto, tiempo de retención =5,03min, se eliminan los volátiles a vacío y se secó a temperatura ambiente a vacío proporcionando 26,2mg del compuesto del epígrafe como un sólido amarillo amorfo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,04 - 1,18 (m, 1 H) 1,18 - 1,45 (m, 6 H) 1,48 (d, *J*=6,71 Hz, 7 H) 1,80 (d, *J*=8,55 Hz, 3 H) 1,86 - 2,26 (m, 5 H) 2,37 - 2,99 (m, 20 H) 3,12 - 3,72 (m, 4 H) 3,85 (s, 4 H) 3,93 (s, 3 H) 3,98 - 4,08 (m, 1 H) 4,23 (s, 0,4 H) 4,60 (d, *J*=14,34 Hz, 1 H) 4,86 (d, *J*=11,90 Hz, 1 H) 6,82 - 7,02 (m, 2 H) 7,11 (d, *J*=7,02 Hz, 1 H) 7,53 (d, *J*=8,55 Hz, 1 H) 7,58 - 7,88 (m, 3 H) 7,94 (d, *J*=8,24 Hz, 1 H) 10,05 (s, 0,6H)

Tiempo de retención LC-MS 1,54 min; 725 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las

condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



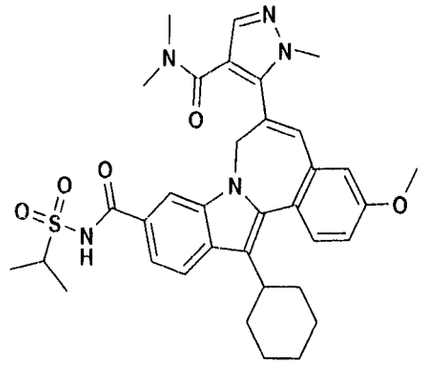
13-ciclohexil-6-(4-(((2R,6S)-2,6-dimetil-4-morfolinil)carbonil)-1-metil-1H-pirazol-5-il)-N-(isopropilsulfonil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

En un vial de 2 dram, se agitaron en una atmósfera de nitrógeno durante 1,75 horas a temperatura ambiente 932 ul de una solución madre que contenía ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (0,087M, 0,081mmol) y TBTU (0,18M, 0,168 mmol), en DMF. Se añadió DMAP (40 mg,

0,327 mmol) a la reacción y se agitó hasta disolución, a continuación se añadió el reactivo amina, (2R,6S)-2,6-dimetilmorfolina (0,030 ml, 0,243 mmol) y la reacción se tapó en nitrógeno y se agitó a temperatura ambiente durante la noche (19 horas). La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando 65 mg como una película amarilla. La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (2 ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA. Tiempo de retención del producto= 12,83 minutos. La muestra se purificó en dos inyecciones de 1 ml, se cortó la segunda operación a un tiempo de operación de 20 minutos con el mismo gradiente de 15 minutos. Las fracciones de producto se reunieron y se eliminaron los volátiles a vacío usando un evaporador rotatorio y luego se secó la muestra a vacío a temperatura ambiente proporcionando 26,1 mg del compuesto del epígrafe como un sólido amarillo/película amorfa.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,60 - 0,93 (m, 6 H) 1,16 - 1,29 (m, 2 H) 1,30 - 1,58 (m, 9 H) 1,79 (d, *J*=10,68 Hz, 2 H) 1,92 (s, 14 H) 2,05 - 2,27 (m, 3 H) 2,88 (t, *J*=11,44 Hz, 1 H) 3,13 - 3,31 (m, 2 H) 3,46 (s ancho, 1 H) 3,91 (s, 3 H) 3,94 (s, 3 H) 4,02 - 4,13 (m, 1 H) 4,60 (d, *J*=15,56 Hz, 1 H) 4,90 (d, *J*=15,56 Hz, 1 H) 6,83 (s ancho, 1 H) 6,95 (d, *J*=2,14 Hz, 1 H) 7,06 - 7,17 (m, 1 H) 7,49 - 7,80 (m, 4 H) 7,93 (s, 1 H) 10,12 (s ancho, 0,2 H) 10,47 (s ancho, 0,6 H).

Tiempo de retención LC-MS 1,90 min; 712 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-6-(4-(dimetilcarbamoil)-1-metil-1H-pirazol-5-il)-N-(isopropilsulfonil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En un vial de 2 dram, se agitaron en una almósfera de nitrógeno durante 1,75 horas a temperatura ambiente 932 ul de una solución madre que contenía ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (0,087M, 0,081mmol) y TBTU (0,18M, 0,168 mmol) en DMF. Se añadió DMAP (41,8 mg, 0,342 mmol) a la reacción y se agitó hasta disolución, a continuación se añadió el reactivo amina, clorhidrato de dimetilamina (17,5 mg, 0,215 mmol) y la reacción se tapó en nitrógeno y se agitó a temperatura ambiente durante la noche (19 horas). La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando 57 mg como una espuma amarilla/sólido amorfo/película.

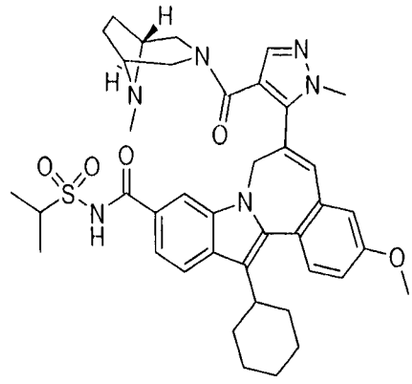
La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de

fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (2 ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA. Tiempo de retención del producto= 12,05 minutos. La muestra se purificó en dos inyecciones de 1 ml. Se reúnen las fracciones de producto y se eliminan los volátiles a vacío usando un evaporador rotatorio y luego se seca la muestra a vacío a temperatura ambiente proporcionando37,6mg (68%) como un sólido amarillo amorfo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,15 - 1,30 (m, 1 H) 1,33 - 1,45 (m, 2 H) 1,49 (s ancho, 7 H) 1,79 (d, *J*=8,55 Hz, 2 H) 1,91 - 2,17 (m, 7 H) 2,32 (s ancho, 9 H) 2,45 (s ancho, 3 H) 2,78 - 2,91 (m, 1 H) 3,50 (s ancho, 1 H) 3,82 (s, 3 H) 3,93 (s, 3 H) 4,01 - 4,10 (m, 1 H) 4,60 (d, *J*=14,34 Hz, 1 H) 4,93 (d, *J*=14,65 Hz, 1 H) 6,86 (s, 1 H) 6,96 (d, *J*=2,75 Hz, 1 H) 7,10 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,53 (d, *J*=8,55 Hz, 1 H) 7,58 (d, *J*=8,55 Hz, 1 H) 7,66 (s, 1 H) 7,75 (s, 1 H) 7,91 (d, *J*=8,55 Hz, 1 H) 9,99 (s ancho,1 H).

Tiempo de retención LC-MS 1,74 min; 642 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de

100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[[(1R,5S)-3-metil-3,8-diazabiciclo[3.2.1]oct-3-il]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En un vial de 2 dram, se agitaron en una atmósfera de nitrógeno durante 1 hora a temperatura ambiente 900 ul de una solución madre que contenía ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (0,09M, 0,081mmol) y TBTU (0,19M, 0,171mmol) en DMF. Se añadió DMAP (41mg, 0,336 mmol) a la reacción y se agitó hasta disolución, a continuación se añadió el reactivo amina, diclorhidrato de (1R,5S)-8-metil-3,8-diazabiciclo[3.2.1]octano (30 mg, 0,151 mmol) y la reacción se tapó en nitrógeno y se agitó a

temperatura ambiente durante la noche. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando70 mg. La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (2 ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA.

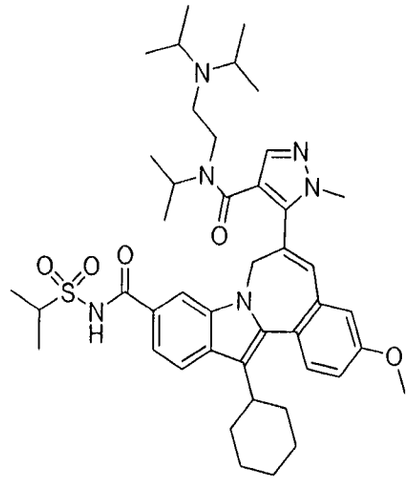
El tiempo de retención del producto fue 5,56 minutos y los volátiles/disolvente se eliminaron a vacío. El análisis HPLC de la primera purificación por HPLC preparativa usando %A= Acetato Amónico 10mM, pH=6,8 en Agua / Acetonitrilo (95%/ 5%) %B= Acetato Amónico 10mM, pH=6,8 en Agua / Acetonitrilo (5%/ 95%) como sistema disolvente mostró impurezas en la muestra. La muestra se purificó luego en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en 0,5ml de DMF/ 1,5 ml de

acetonitrilo y se purificó usando una columna Phenonemex Gemini 30mm x 100mm y se controló usando un detector UV-Vis SPD-10AV UV-Vis a una longitud de onda de 220 nm. Las condiciones de elución emplearon un caudal de 40ml/ min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, a tiempo de gradiente de 20 minutos con un tiempo de ejecución de 30 minutos usando %A= Acetato Amónico 10mM, pH=6,8 en Agua / Acetonitrilo (95%/ 5%) %B= Acetato Amónico 10mM, pH=6,8 en Agua / Acetonitrilo (5%/ 95%) como sistema disolvente. El tiempo de elución del producto varía de 9,7 minutos hasta 11,7 minutos. Se reúnen las fracciones de producto y se eliminan los volátiles y se secan a vacío. Se preparó la sal trifluoracetato del compuesto del epígrafe disolviendo el producto purificado en diclorometano y añadiendo 10 ul de ácido trifluoracético y eliminando luego los volátiles a vacío. El secado a vacío proporcionó 23,6 mg (35%) de la sal trifluoracetato del compuesto del epígrafe como un sólido amarillo amorfo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,11 - 1,29 (m, 1 H) 1,32 - 1,45 (m, 3 H) 1,49 (dd, *J*=11,14, 6,87 Hz, 6 H) 1,79 (d, *J*=10,68 Hz, 2 H) 1,89 - 2,13 (m, 4 H) 2,28 - 2,73 (m, 15 H) 2,84 - 2,95 (m, 1 H) 3,25 (s, 2 H) 3,39 (s, 2 H) 3,76 - 3,92 (m, 3 H) 3,94 (s, 3 H) 4,01 - 4,12 (m, 1 H) 4,63 (d, *J*=15,87 Hz, 1 H) 4,87 (s, 1 H) 6,96 (d, *J*=2,14 Hz, 2 H) 7,13 (dd, *J*=8,85, 2,44 Hz, 1 H) 7,57 (d, *J*=8,55 Hz, 1 H) 7,63 (s, 1 H) 7,77 (s, 1 H) 7,92 (d, *J*=8,55 Hz, 1 H) 10,06 (s, 1 H).

Tiempo de retención LC-MS 1,73 min; 723 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector

UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



6-[1-[[[2-[bis(1-metiletil)amino]etil](1-metiletil)amino]carbonil]-1-metil-1H-pirazol-5-il]-13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

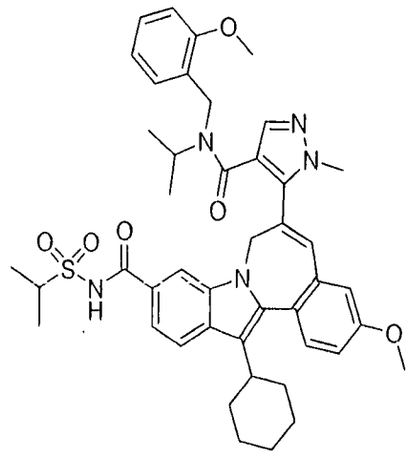
En un vial de 2 dram se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (52,1 mg, 0,034 mmol) en DMF (0,9ml) y se añadió TBTU

(56,2 mg, 0,175 mmol) y la reacción se agitó en una atmósfera de nitrógeno durante 1 hora a temperatura ambiente. Se añadió DMAP (46mg, 0,377 mmol) a la reacción y se agitó hasta disolución, a continuación se añadió el reactivo amina, N,N,N'-triisopropiletilendiamina (55mg, 0,295 mmol) y la reacción se tapó en nitrógeno y se agitó a temperatura ambiente durante la noche. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando 84 mg como un vidrio/ película amarillo.

La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (2 ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA. El tiempo de retención del producto =6 minutos. Se reúnen las fracciones de producto y se eliminan los volátiles a vacío usando un evaporador rotatorio y luego se seca la muestra a vacío a temperatura ambiente proporcionando 36,0 mg (47%) como un sólido amarillo amorfo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,05 (s, 6 H) 1,18 - 1,43 (m, 15 H) 1,46 (d, *J*=7,02 Hz, 3 H) 1,78 (d, *J*=8,55 Hz, 2 H) 1,87 - 2,12 (m, 4 H) 2,62 (s, 14 H) 2,80 - 2,90 (m, 1 H) 3,12 (s, 2 H) 3,24 - 3,70 (m, 9 H) 3,92 (s, 3 H) 3,97 - 4,06 (m, 1 H) 4,19 (s, 1 H) 4,55 (s, 1 H) 4,99 (s, 1 H) 6,86 (s, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,09 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,43 - 7,57 (m, 3 H) 7,85 (s, 1 H) 7,90 (d, *J*=8,54 Hz, 1 H) 9,33 (s, 1 H) 10,12 (s, 1 H).

Tiempo de retención LC-MS 1,80 min; 733 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-3-metoxi-6-[4-[[[(2-metoxifenil)metil](1-metiletil)amino]carbonil]-1-metil-1H-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En un vial de 2 dram se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (50 mg, 0,081 mmol) en DMF (811 µl) y se añadió TBTU (51,5 mg, 0,160 mmol) y la reacción se agitó en una atmósfera de nitrógeno durante 1,3 horas a temperatura ambiente. Se añadió DMAP (52 mg, 0,426 mmol) a la reacción y se agitó hasta disolución, a continuación se añadió el reactivo amina, clorhidrato de N-(2-metoxibencil)propan-2-amina (36 mg, 0,167 mmol) y la reacción se tapó en nitrógeno y se agitó a temperatura ambiente durante la noche. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El producto bruto se secó a vacío a temperatura ambiente proporcionando 75 mg como una película amarilla.

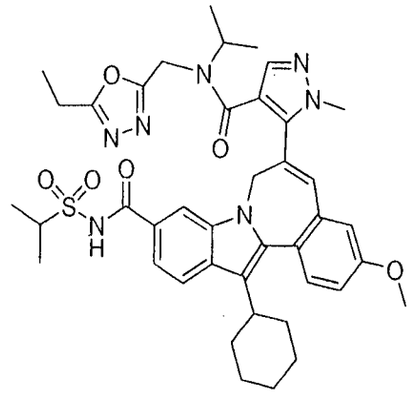
La muestra se purificó en un sistema de cromatografía líquida de alta

presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (2 ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA. Tiempo de retención del producto= 14,07 minutos. Los volátiles se eliminaron de la fracción de producto a vacío usando un evaporador rotatorio y luego se secó la muestra a vacío a temperatura ambiente proporcionando 45,4 mg (72%) como un sólido amarillo amorfo. La RMN de protón mostró características rotómeras.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,34 - 1,03 (m, 6,3 H) 1,04 - 1,32 (m, 3,4 H) 1,29 - 1,66 (m, 7,6 H) 1,78 (d, 2,2 H) 1,90 - 2,24 (m, 4,3 H) 2,52 (s, 3,6 H) 2,87 (s, 1,1 H) 3,36 - 3,71 (m, 2,1 H) 3,71 - 3,83 (m, 5,5 H) 3,92 (s, 3,4 H) 4,00-4,06 (m, 0,3 H) 4,13 - 4,39 (m, 1,1 H) 4,63 (d, *J*=12,21 Hz, 1,0 H) 5,08 (d, *J*=14,04 Hz, 0,9 H) 6,54 - 6,83 (m, 2,5 H) 6,86 - 6,99 (m, 2,6 H) 7,02 - 7,20 (m, 2,1 H) 7,34 - 7,71 (m, 3,1 H) 7,74 - 7,99 (m, 2,0 H) 9,39 (s ancho, 0,4 H) 9,85 (s ancho, 0,5 H).

Tiempo de retención LC-MS 1,99 min; 776 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector

UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 2 min y un tiempo de análisis de 5 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-6-[1-[[[(5-etil-1,3,4-oxadiazol-2-il)metil](1-metiletil)amino]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En un vial de 2 dram, se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (50 mg, 0,081 mmol) en DMF (811 µl) y se añadió TBTU (51,5 mg, 0,160 mmol) y la reacción se agitó en una atmósfera de nitrógeno durante 1 hora a temperatura ambiente. Se añadió a la reacción DMAP (43,2

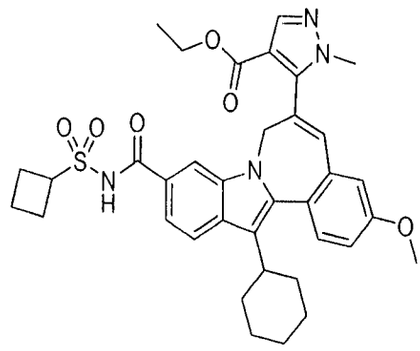
mg, 0,354 mmol) y se agitó hasta disolución, a continuación se añadió a la reacción el reactivo amina, N-((5-etil-1,3,4-oxadiazol-2-il)metil)propan-2-amina (47,3 mg, 0,280 mmol) disuelto en 0,2 ml de DMF. La reacción se lapó en nitrógeno y se agitó a temperatura ambiente durante la noche.

La reacción se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La reacción se diluyó hasta un volumen de 2 ml con acetonitrilo y se purificó la reacción usando una columna Waters Sunfire Prep C18 OBD, de 5uM 19mm x 100mm y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda de detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. Tiempo de retención del producto es 11,45 minutos. Se reúnen las fracciones de producto y se eliminan los volátiles a vacío usando un evaporador rotatorio y luego se seca la muestra a vacío a temperatura ambiente proporcionando 47,8 mg como un sólido /película amarillo amorfo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,07 - 1,24 (m, 5 H) 1,27 (t, *J*=7,48 Hz, 4 H) 1,38 (d, *J*=5,49 Hz, 8 H) 1,56 (d, *J*=9,46 Hz, 1 H) 1,73 (d, *J*=9,46 Hz, 2 H) 1,88 - 1,99 (m, 1 H) 2,00 - 2,17 (m, 3 H) 2,55 - 2,82 (m, 4 H) 2,83 - 2,94 (m, 1 H) 3,73 (s, 3 H) 3,89 (s, 3 H) 3,97 - 4,08 (m, 1 H) 4,15 - 4,80 (m, 4 H) 5,22 (d, *J*=16,79 Hz, 1 H) 6,88 (s, 1 H) 6,94 (d, *J*=2,75 Hz, 1 H) 7,04

(dd, *J*=8,55, 2,44 Hz, 1 H) 7,46 (d, *J*=8,85 Hz, 1 H) 7,59 - 7,67 (m, 2 H) 7,91 (d, *J*=8,55 Hz, 1 H) 8,31 (s ancho, 1 H) 9,62 (s ancho, 1 H).

Tiempo de retención LC-MS 1,75 min; 766 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



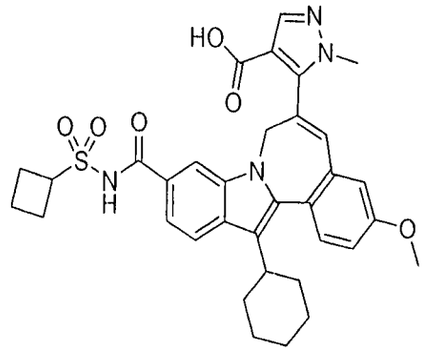
éster etílico del ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico

Se disuelve ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (653mg, 1,210 mmol) en THF (12ml) en un matraz de fondo redondo de 50 ml. Se añadió carbonildiimidazol (1,308 g, 8,07 mmol) a la reacción. El matraz con un condensador se colocó en una atmósfera de nitrógeno y se dejó agitando la reacción a temperatura ambiente durante 1 hora y luego se llevó a reflujo durante 50 minutos. La reacción se enfrió en una atmósfera de nitrógeno y se añadió a la reacción ciclobutanosulfonamida (825 mg, 6,10 mmol) seguido por DBU (0,383 ml, 2,54 mmol). La reacción se calentó durante la noche a 70°C en una atmósfera de nitrógeno. El análisis LC-MS indicó principalmente imidazolida pero una cantidad insignificante de producto, por tanto, se añadió ciclobutilsulfonamida (700 mg, 5,17 mmol) a la reacción seguido por DBU (0,383 ml, 2,54 mmol). La reacción se calentó hasta reflujo en una atmósfera de nitrógeno durante 3,5 horas y se volvió a comprobar el progreso por LCMS. Se añadió más ciclobutilsulfonamida (357mg, 2,64mmol) y DBU (0,383 ml, 2,54 mmol) a la reacción y ésta se calentó hasta reflujo durante 3,25 horas. La reacción se enfrió y se añadió acetato de etilo y se lavó dos veces con ácido clorhídrico acuoso 1,0 N. Se volvió a extraer la fase acuosa con acetato de etilo. Las fases orgánicas se reunieron y se lavaron secuencialmente con ácido clorhídrico acuoso 1,0N, NaH_2PO_4 0,1M, y de nuevo con ácido clorhídrico acuoso 1,0N y finalmente salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío proporcionando 949 mg de un producto bruto como un sólido amarillo. El producto bruto se adsorbió sobre 2,6g de gel de sílice y se sometió a cromatografía en 28,7g de suspensión de gel de sílice rellenada usando 2% de metanol en diclorometano y eluyendo

usando 2% de metanol en diclorometano. Las fracciones de producto puras se reunieron y los volátiles se eliminaron a vacío usando un evaporador rotatorio proporcionando 465 mg (59%) del compuesto del epígrafe como un sólido amarillo amorfo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,20 (m, 1 H) 1,30 (t, *J*=7,17 Hz, 3 H) 1,33 - 1,48 (m, 2 H) 1,55 (s ancho, 4 H) 1,73 (d, *J*=9,46 Hz, 2 H) 1,97 - 2,14 (m, 6 H) 2,32 - 2,42 (m, 2 H) 2,55 - 2,69 (m, 2 H) 2,79 - 2,92 (m, 1 H) 3,28 (s, 3 H) 3,90 (s, 3 H) 4,25 (s ancho, 2 H) 4,53 - 4,63 (m, 1 H) 4,71 (d, *J*=10,68 Hz, 1 H) 4,97 (d, *J*=14,34 Hz, 1 H) 6,77 (s, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,07 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,35 (dd, *J*=8,39, 1,37 Hz, 1 H) 7,52 (d, *J*=8,85 Hz, 1 H) 7,73 (d, *J*=1,22 Hz, 1 H) 7,88 (d, *J*=8,55 Hz, 1 H) 7,91 (s, 1 H) 8,24 (s, 1 H).

Tiempo de retención LC-MS 1,78 min; 655 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico

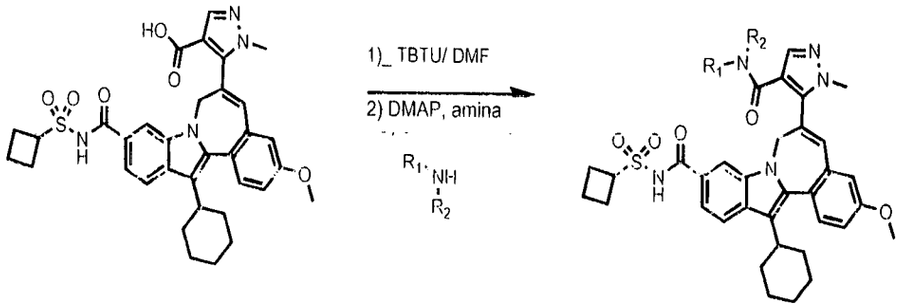
Se disolvió éster etílico del ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico (463mg, 0,705mmol) en THF (6,8 ml), luego se diluyó usando metanol (6,8 ml) con calentamiento y se enfrió la mezcla hasta temperatura ambiente. Se añadió a la suspensión de reacción en THF/metanol hidróxido sódico acuoso 1,0N (6,8 ml, 6,8mmol). Tras la adición de la solución de hidróxido sódico la reacción se convirtió en una solución homogénea transparente. La reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 20 horas. La reacción se concentró a vacío usando un evaporador rotatorio con temperatura de baño ambiente (20°C). Se repartió la reacción entre 200 ml de acetato de etilo y ácido clorhídrico acuoso 1,0N. La fase acuosa se extrajo usando acetato de etilo. Las fases orgánicas se reunieron y lavaron secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. Se secó la fase orgánica sobre sulfato de magnesio, se filtró y se eliminaron los volátiles del filtrado a vacío proporcionando 457 mg del compuesto del epígrafe como un sólido color amarillo claro.

RMN de ^{1}H (500 MHz, MeOD) δ ppm 0,83 (s ancho, 1 H) 1,11 - 1,29 (m, 3 H) 1,30 - 1,60 (m, 4 H) 1,74 (d, *J*=7,93 Hz, 2 H) 1,87 (s ancho, 1 H) 1,94 - 2,07 (m, 5 H) 2,25 - 2,35 (m, 2 H) 2,50 - 2,60 (m, 2 H) 2,78 - 2,87 (m, 1 H) 3,24 (s, 3 H) 3,87 (s, 3 H) 4,46 - 4,55 (m, 1 H) 4,67 (s ancho, 1 H) 4,99 (s ancho, 1 H) 6,73 (s, 1 H) 6,93 (d, *J*=2,44 Hz, 1 H) 7,05 (dd, *J*=8,55, 2,75 Hz, 1 H) 7,49 (d, *J*=8,55 Hz, 1 H) 7,52 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,81 (d, *J*=1,53 Hz, 1 H) 7,84 (d, *J*=8,55 Hz, 1 H) 7,89 (s, 1 H).

Tiempo de retención LC-MS 1,42 min; 627m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

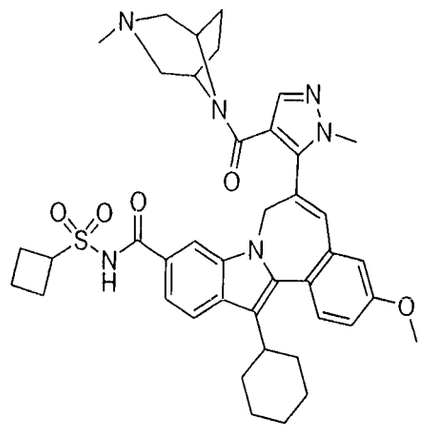
Procedimiento general para acoplamientos de amida en:

ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico



En un vial de 2 dram se colocaron 639 ul de una solución madre que contenía ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico (0,639 ml, 0,072 mmol) y TBTU (0,639 ml, 0,138 mmol) que se premezcló durante 1,25 horas a temperatura ambiente. Se añadieron a la mezcla de reacción 239ul de una solución madre que contenía DMAP (0,239 ml, 0,358 mmol), luego se añadió el reactivo amina (0,159 mmol). Se tapó la reacción en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante la noche. La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se diluyó hasta 2 ml (o 4 ml) usando acetonitrilo y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 20 minutos (o 25 minutos) usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. Los volátiles de la fracción(es) de

producto se eliminaron a vacío usando un SpeedVac durante la noche con calentamiento.

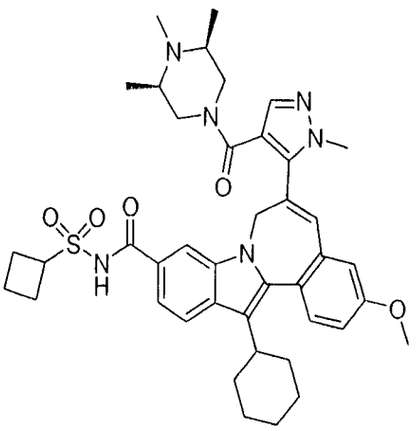


N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,13 - 1,30 (m, 1 H) 1,31 - 1,56 (m, 4 H) 1,79 (d, *J*=10,68 Hz, 2 H) 1,88 - 2,15 (m, 7 H) 2,37 (s, 4 H) 2,54 (s, 4 H) 2,67 (d, *J*=9,16 Hz, 4 H) 2,83 - 2,96 (m, 2 H) 3,05 - 3,64 (m, 5 H) 3,89 (s, 3 H) 3,93 (s, 3 H) 4,54 - 4,69 (m, 2 H) 4,88 (s, 1 H) 6,95 (t, *J*=2,14 Hz, 1 H) 7,13 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,57 (d, *J*=8,55 Hz, 1 H) 7,60 (d, *J*=6,71 Hz, 1 H) 7,77 (s, 1 H) 7,91 (d, *J*=8,24 Hz, 1 H) 10,17 (s, 1 H).

Tiempo de retención LC-MS 1,55 min; 735m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las

condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

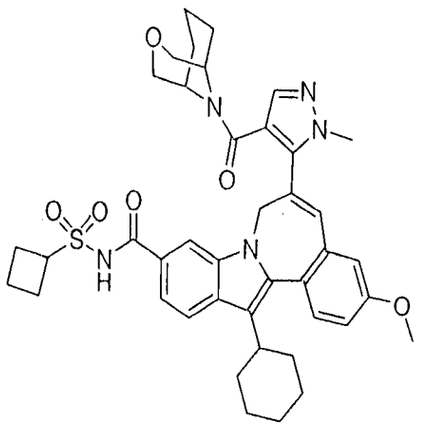
Véase el procedimiento para el acoplamiento general de amidas. La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se solubilizó diluyendo hasta 2 ml usando acetonitrilo y se purificó

usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 90% de disolvente A / 10% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto =8,3 minutos.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,99 - 1,32 (m, 7 H) 1,32 - 1,66 (m, 3 H) 1,80 (d, *J*=8,55 Hz, 2 H) 1,88 - 2,13 (m, 6 H) 2,35 (s, 2 H) 2,54 (s, 2 H) 2,66 (s, 2 H) 2,92 (s, 2 H) 3,02 - 3,71 (m, 10 H) 3,80 (s, 3 H) 3,93 (s, 3 H) 4,03 (s, 1 H) 4,49 - 4,67 (m, 2 H) 4,92 (d, *J*=12,21 Hz, 1 H) 6,91 (s, 1 H) 6,97 (d, *J*=2,44 Hz, 1 H) 7,11 (dd, *J*=8,39, 2,29 Hz, 1 H) 7,54 (d, *J*=8,54 Hz, 1 H) 7,56 - 7,65 (m, 2 H) 7,78 (s, 1 H) 7,92 (d, *J*=8,55 Hz, 1 H) 9,71 (s, 1 H).

Tiempo de retención LC-MS1,49 min; 737 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo

electronebulización.



N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[1-metil-4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

Véase el procedimiento para el acoplamiento general de amidas.

La muestra se diluyó hasta 4 ml usando acetonitrilo. La muestra necesitó más de 2 ml de volumen para solubilizarse totalmente en acetonitrilo indicando una menor solubilidad que las muestras tratadas anteriormente.

La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se diluyó hasta 4 ml usando acetonitrilo y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de

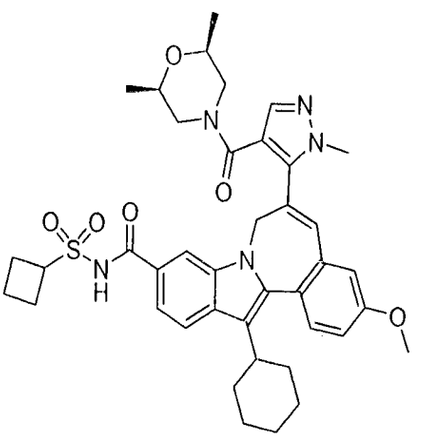
15 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. La purificación se llevó a cabo como dos inyecciones de 2 ml. El tiempo de retención del producto fue 13,9 minutos.

Los volátiles de las fracciones de producto se eliminaron a vacío usando un SpeedVac durante la noche con calentamiento. El peso del compuesto del epígrafe aislado fue 38,6 mg.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,85 (m, 1 H) 1,21 (m, 2 H) 1,31 - 1,57 (m, 6 H) 1,77 (d, *J*=8,24 Hz, 3 H) 1,89 - 2,14 (m, 6 H) 2,15 - 2,24 (m, 1 H) 2,30 (d, *J*=11,29 Hz, 1 H) 2,34 - 2,43 (m, 2 H) 2,57 - 2,79 (m, 2 H) 2,86 (t, *J*=10,53 Hz, 1 H) 2,94 - 3,41 (m, 9 H) 3,51 (d, *J*=14,65 Hz, 1 H) 3,62 (d, *J*=10,68 Hz, 1 H) 3,86 (s, 1 H) 3,93 (s, 5 H) 4,51 - 4,68 (m, 2 H) 4,83 - 5,06 (m, 1 H) 6,78 - 6,89 (m, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,08 - 7,17 (m, 1 H) 7,58 (d, *J*=8,54 Hz, 1 H) 7,63 (d, *J*=7,93 Hz, 1 H) 7,66 - 7,81 (m, 2 H) 7,90 (t, *J*=9,16 Hz, 1 H) 10,19 (s, 0,2 H) 10,44 (s, 0,7 H).

Tiempo de retención LC-MS 1,62min; 736m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de

H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

Véase el procedimiento para el acoplamiento general de amidas.

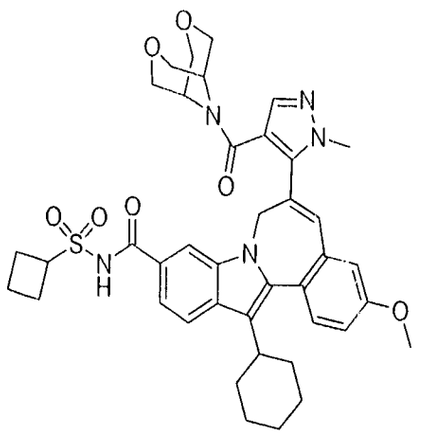
La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se diluyó hasta 2 ml usando acetonitrilo y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de

agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto =13,5 minutos.

Los volátiles de las fracciones de producto se eliminaron a vacío usando un SpeedVac durante la noche con calentamiento.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,68 (s ancho, 3 H) 0,78 (m, 1 H) 0,81 - 0,91 (m, 1 H) 1,12 - 1,32 (m, 2 H) 1,32 - 1,50 (m, 3 H) 1,79 (d, *J*=11,29 Hz, 2 H) 1,90 - 2,01 (m, 3 H) 2,01 - 2,16 (m, 5 H) 2,16 - 2,27 (m, 1 H) 2,28 - 2,36 (m, 1 H) 2,35 - 2,46 (m, 1 H) 2,60 - 2,82 (m, 3 H) 2,83 - 3,11 (m, 5 H) 3,12 - 3,31 (m, 2 H) 3,42 (s, 1 H) 3,81 - 3,94 (m, 3 H) 3,94 (s, 3 H) 4,51 - 4,70 (m, 2 H) 4,90 (d, *J*=14,34 Hz, 1 H) 6,79 - 6,90 (m, 1 H) 6,95 (d, *J*=1,83 Hz, 1 H) 7,13 (dd, *J*=8,55, 2,14 Hz, 1 H) 7,60 (dd, *J*=24,57, 8,39 Hz, 2 H) 7,69 (d, *J*=16,48 Hz, 1 H) 7,91 (d, *J*=8,24 Hz, 1 H) 10,03 (s, 0,3 H) 10,42 (s, 0,7 H).

Tiempo de retención LC-MS 1,55 min; 724m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 2 min y un tiempo de análisis de 5 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En un vial de 2 dram se colocaron 639ul de una solución madre que contenía ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico (0,639 ml, 0,072 mmol) y TBTU (0,639 ml, 0,138 mmol) que se había premezclado durante 1,25 horas a temperatura ambiente. Se añadieron a la mezcla de reacción 239 ul de una solución madre que contenía DMAP (0,239 ml, 0,358 mmol), luego se añadió el reactivo amina, clorhidrato de 3,7-dioxa-9-azabiciclo[3.3.1]nonano (38,0 mg, 0,229 mmol). Se tapó la reacción en una atmósfera de nitrógeno y se agitó a temperatura ambiente. El análisis de la mezcla de reacción por LCMS indicó solo trazas del producto presentes. La reacción se dejó reposar tapada a temperatura ambiente durante 3 días y luego se añadió HATU (92 mg, 0,242 mmol). La reacción se tapó y se agitó a temperatura ambiente durante la noche. LCMS indicó reacción completa. La reacción se dejó agitando a temperatura ambiente durante 2 días más (fin de

semana).

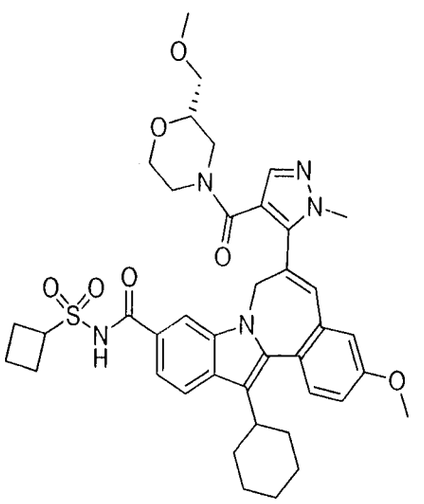
La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se diluyó hasta 2 ml usando acetonitrilo y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto se observó como picos separados a 10,72 minutos y 11,03 minutos. Los volátiles de las fracciones de producto se eliminaron a vacío usando un SpeedVac durante la noche con calentamiento.

El análisis de RMN de ^{1}H de cada fracción de producto proporcionó idénticos espectros de RMN. Las fracciones de producto se reunieron en un vial y se secaron a vacío a temperatura ambiente proporcionando 34,5mg (65%) del compuesto del epígrafe como un sólido amorfo amarillo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,11 - 1,27 (m, 1 H) 1,31 - 1,52 (m, 3 H) 1,71 - 1,83 (m, *J*=8,85 Hz, 2 H) 1,92 - 2,15 (m, 6 H) 2,31 (s, 1 H) 2,38 (s, 1 H) 2,55 - 2,77 (m, 3 H) 2,81 - 2,91 (m, 1 H) 3,25 (s, 1 H) 3,33 (d, *J*=9,46 Hz, 1 H) 3,42 (s, 2 H) 3,55 (d, *J*=10,07 Hz, 1 H) 3,62 - 3,80 (m, 3 H) 3,89 (s, 3 H) 3,93 (s, 3 H) 4,23 (s, 3 H) 4,53 - 4,66 (m, 2 H) 4,93 (d, *J*=15,26 Hz, 1 H)

6,87 (s, 1 H) 6,95 (d, *J*=2,44 Hz, 1 H) 7,13 (dd, *J*=8,54, 2,75 Hz, 1 H) 7,58 (d, *J*=8,55 Hz, 1 H) 7,61 (d, *J*=8,55 Hz, 1 H) 7,70 (s, 1 H) 7,74 (s, 1 H) 7,93 (d, *J*=8,54 Hz, 1 H) 10,09 (s, 1 H).

Tiempo de retención LC-MS 1,50 min; 733 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-

morfolinil]carbonil]-1-metil-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

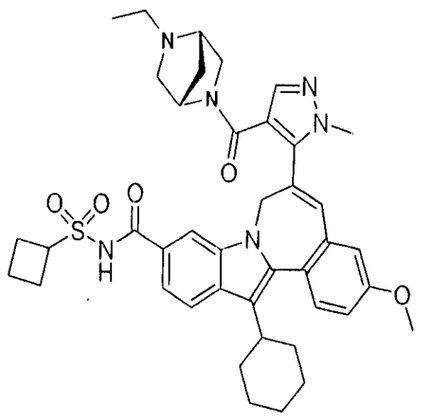
En un vial de 2 dram se colocaron 787ul de una solución madre que contenía ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7H-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1H-pirazol-4-carboxílico (0,091M) (0,787 ml, 0,072 mmol) y TBTU (0,213M) (0,787 ml, 0,168 mmol) que se había premezclado durante 1,25 horas a temperatura ambiente. Se añadió a la mezcla de reacción DMAP (48,0 mg, 0,393 mmol), luego se añadió el reactivo amina, en este caso clorhidrato de (S)-2-(metoximetil)morfolina (30,4 mg, 0,181 mmol). Se tapó la reacción en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante la noche. La reacción se diluyó con acetonitrilo y se purificó por HPLC preparativa de fase inversa.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,19 (m, 1 H) 1,31 - 1,54 (m, 3 H) 1,79 (d, *J*=10,38 Hz, 2 H) 1,90 - 2,20 (m, 7 H) 2,23 - 2,55 (m, 3 H) 2,58 - 2,82 (m, 4 H) 2,82 - 3,13 (m, 6 H) 3,11 - 3,49 (m, 5 H) 3,90 (s, 3 H) 3,94 (s, 3 H) 4,51 - 4,67 (m, 2 H) 4,73 - 4,96 (m, 1 H) 6,85 (s, 1 H) 6,95 (s, 1 H) 7,12 (dd, *J*=8,55, 2,44 Hz, 1 H) 7,56 (d, *J*=8,55 Hz, 1 H) 7,59 (d, *J*=7,63 Hz, 1 H) 7,63 - 7,74 (m, 2 H) 7,90 (t, *J*=9,00 Hz, 1 H) 10,09 (s, 0,3 H) 10,41 (s, 0,6 H).

Tiempo de retención LC-MS1,62 min; 740 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de

2 min y un tiempo de análisis de 5 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

Los siguientes ejemplos se pueden preparar de una forma análoga.



N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

Procedimiento HPLC: La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La mezcla de reacción se diluyó hasta 2 ml usando acetonitrilo y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de

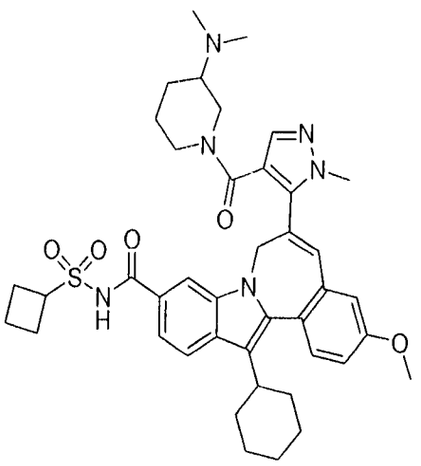
elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto es 5,71 minutos. Los volátiles de las fracciones de producto se eliminaron a vacío usando un SpeedVac en una posición de calentamiento medio.

La RMN de protón de esta muestra presentó características de rotómeros.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,49 (s, 0,3 H) 0,96 - 1,29 (m, 2,2 H) 1,30 - 1,59 (m, 3,3 H) 1,79 (d, *J*=11,60 Hz, 1,3 H) 1,86 - 2,17 (m, 3,8 H) 2,19 - 2,46 (m, 2,1 H) 2,49 - 3,74 (m, 6,4 H) 3,76 - 4,21 (m, 5,1 H) 4,24 - 4,39 (m, 0,8 H) 4,43 - 4,70 (m, 1,4 H) 4,73 - 5,07 (m, 1,0 H) 5,23 (s, 0,1 H) 6,73 (d, *J*=29,30 Hz, 0,4 H) 6,88 - 7,00 (m, 0,8 H) 7,04-7,13 (m, 0,7 H) 7,44 - 7,60 (m, 0,9 H) 7,58 - 7,96 (m, 2,0 H) 8,19 (s, 0,1 H) 10,43 (d, *J*=81,79 Hz, 0,4 H) 11,20 (d, *J*=87,28 Hz, 0,5 H) 12,46 (s, 0,6 H)

Tiempo de retención LC-MS1,60 min; 737 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de

acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

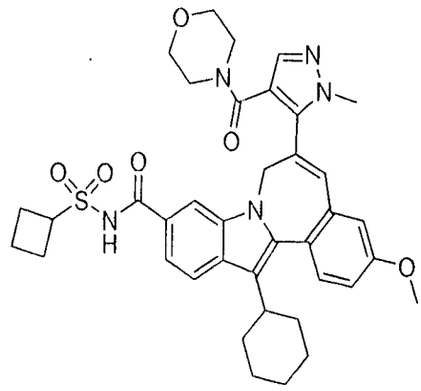
Procedimiento HPLC: La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La reacción se diluyó hasta 4 ml usando acetonitrilo con una cantidad muy pequeña de metanol y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con

un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto fue 5,37 minutos. El compuesto se purificó como dos inyecciones de 2 ml.

Los picos del espectro de RMN de protón son por lo general ancho, característica de rotación limitada en la molécula.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,13 - 1,32 (m, 2 H) 1,32 - 1,59 (m, 5 H) 1,79 (s, 3 H) 1,89 - 2,18 (m, 7 H) 2,36 (s, 2 H) 2,48 - 2,76 (m, 3 H) 2,88 (s, 1 H) 3,51 (s, 1 H) 3,60 - 3,91 (m, 7 H) 3,93 (s, 3 H) 4,24 (s, 0,6 H) 4,47 - 4,68 (m, 2 H) 4,84 (d, *J*=13,43 Hz, 1 H) 6,86 - 6,98 (m, 1 H) 7,07 - 7,17 (m, 1 H) 7,53 (d, *J*=8,55 Hz, 1 H) 7,58 - 7,84 (m, 2 H) 7,93 (d, *J*=7,93 Hz, 1 H) 10,07 (s, 1 H).

Tiempo de retención LC-MS 1,56 min; 739m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

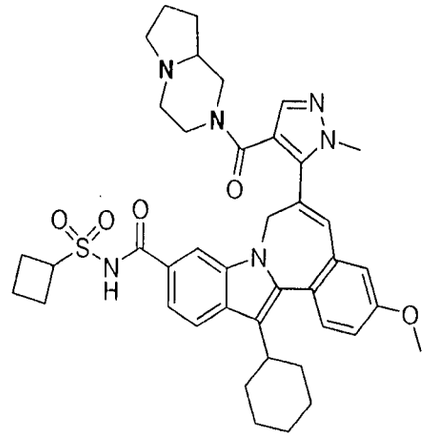
Procedimiento HPLC: La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La mezcla de reacción se diluyó hasta 4 ml usando acetonitrilo y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 50% de disolvente A / 50% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 20 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El compuesto se purificó como dos inyecciones de 2 ml.

Los volátiles de las fracciones de producto se eliminaron a vacío usando

un SpeedVac durante la noche con calentamiento. Las fracciones de producto se reunieron usando diclorometano y el disolvente se eliminó a vacío dando 35,4 mg (71%) del compuesto del epígrafe como un sólido amorfo amarillo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,22 (m, 1 H) 1,33 - 1,55 (m, 3 H) 1,79 (d, *J*=10,68 Hz, 2 H) 1,91 - 2,21 (m, 7 H) 2,37 (d, *J*=29,60 Hz, 3 H) 2,56 - 2,79 (m, 4 H) 2,78 - 2,96 (m, 4 H) 3,12 (s, 3 H) 3,90 (s, 3 H) 3,94 (s, 3 H) 4,53 - 4,65 (m, 2 H) 4,89 (d, *J*=14,95 Hz, 1 H) 6,86 (s, 1 H) 6,95 (d, *J*=2,44 Hz, 1 H) 7,12 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,57 (d, *J*=8,85 Hz, 1 H) 7,59 (d, *J*=8,55 Hz, 1 H) 7,67 (s, 1 H) 7,69 (s, 1 H) 7,93 (d, *J*=8,54 Hz, 1 H) 10,24 (s, 1 H).

LCMS para 74814-024-a: Tiempo de retención LC-MS 1,61min; 696 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

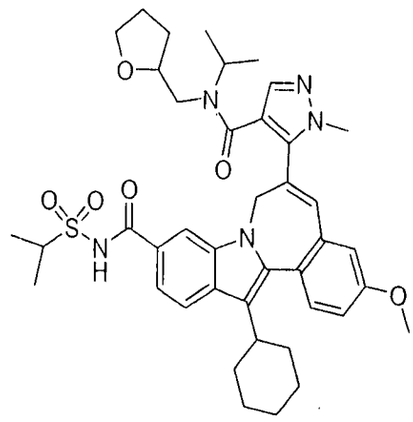
Procedimiento HPLC: La muestra se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La reacción se diluyó hasta 4 ml usando acetonitrilo y trazas de metanol y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto =5,72 minutos.

El compuesto se purificó como dos inyecciones de 2 ml. Los volátiles se eliminaron de las fracciones de producto a vacío durante la noche usando un

SpeedVac en posición de calentamiento medio.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,24 (s, 1 H) 1,30 - 1,45 (m, 2 H) 1,31 - 1,45 (m, 2 H) 1,58 (ninguno, 2 H) 1,73 (s, 4 H) 1,88 - 2,24 (m, 9 H) 2,34 (s, 2 H) 2,65 (s, 3 H) 2,74 - 3,18 (m, 3 H) 3,18 - 3,87 (m, 9 H) 3,89 - 3,96 (m, 3 H) 3,96 - 4,35 (m, 3 H) 4,45 - 4,68 (m, 2 H) 4,76 - 5,00 (m, 1 H) 6,80 - 6,95 (m, 1 H) 6,96 (s, 1 H) 7,05 - 7,15 (m, *J*=8,24 Hz, 1 H) 7,47 - 7,68 (m, 3 H) 7,68 - 7,81 (m, 1 H) 7,88 (s, 1 H) 9,94 (s, 1 H) 12,54 (s, 1 H).

Tiempo de retención LC-MS 1,61 min; 735 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[[(1-metiletil)[(tetrahidro-2-furanil)metil]amino]carbonil]-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

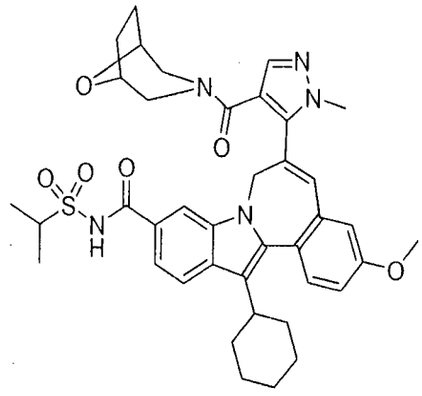
En un vial de 2 dram se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (51,1mg, 0,083 mmol) en DMF (329 µl) y se añadió a la reacción HATU (66,3 mg, 0,174 mmol). La reacción se agitó en una atmósfera de nitrógeno durante 1,2 horas a temperatura ambiente. Se añadió DMAP (41,5 mg, 0,340 mmol) a la reacción y se agitó hasta disolución, a continuación se añadió el reactivo amina, isopropil-(tetrahidro-furan-2-ilmetil)-amina (36 µl, 0,251 mmol) y la reacción se tapó en nitrógeno y se agitó a temperatura ambiente durante 17 horas. Nota: se supone que la densidad del reactivo amina es 1 g/cc, aspecto importante ya que no es estequiometría exacta porque hay presente exceso de amina. El producto se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo / DMF (1:1) (2 ml) y se purificó usando una columna de 5 um 19mm x 100 mm Waters

Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto es 13,3 minutos. Se toma la fracción de producto y se eliminan los volátiles a vacío usando un evaporador rotatorio. El compuesto del epígrafe se aisló (47,4mg, 77%) como un sólido amarillo amorfo. El espectro de RMN de protón presenta características de rotación limitada (picos ancho y rotómeros).

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,61 (s, 1,6 H) 0,80 - 1,11 (m, 5,1 H) 1,23 (s, 2,7 H) 1,31 - 1,57 (m, 10,7 H) 1,76 (s, 4,0 H) 1,87 - 2,13 (m, 5,9 H) 2,20 (s, 2,4 H) 2,38 - 2,75 (m, 0,7 H) 2,78 - 2,92 (m, 1,2 H) 3,06-3,25 (m, 1,3 H) 3,37 - 3,82 (m, 6,9 H) 3,91 (s, 3,9 H) 3,97 - 4,27 (m, 2,0 H) 4,56 (d, *J*=12,82 Hz, 0,9 H) 4,93 - 5,23 (m, 0,9 H) 6,87 (s, 1,0 H) 6,94 (d, *J*=2,44 Hz, 1,0 H) 7,07 (d, *J*=7,93 Hz, 1,0 H) 7,51 (d, *J*=7,93 Hz, 1,1 H) 7,57 (s, 2,2 H) 7,81 - 8,01 (m, 2,1 H) 9,48 - 9,81 (m, 0,6 H) 9,96 (s, 0,5 H).

Tiempo de relención LC-MS 1,76 min; 740 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Waters Xterra MS 7u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de

disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-ilcarbonil)-1H-pirazol-5-il]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En un vial de 2 dram, se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico (50,8 mg, 0,082 mmol) en DMF (824 µl) y se añadió HATU (72,2 mg, 0,190 mmol) y la reacción se agitó en una atmósfera de nitrógeno durante 1 hora a temperatura ambiente. Se añadió DMAP (41,8mg, 0,342 mmol) a la reacción y se agitó hasta disolución, a continuación se añadió el reactivo amina, clorhidrato de 8-oxa-3-azabiciclo[3.2.1]octano (30,6 mg, 0,205 mmol). La reacción se tapó en nitrógeno y se agitó a temperatura ambiente

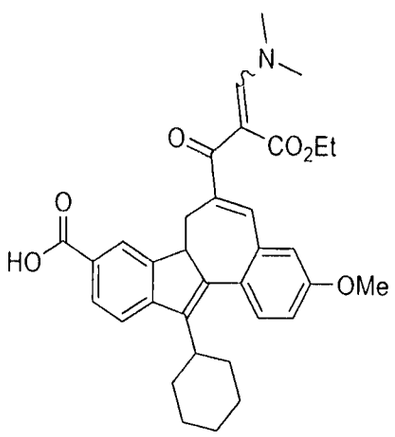
durante la noche. El producto se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La reacción se acidificó con ácido acético acuoso y luego se diluyó hasta 2 ml con acetonitrilo y se filtró usando un filtro de jeringa de 0,45 uM. El filtrado se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 20 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El producto se recogió como una única fracción desde 13,99 a 14,70 minutos. Los volátiles de la fracción producto se eliminaron a vacío usando un SpeedVac en una posición de calentamiento medio.

El compuesto del epígrafe se aisló (46,0 mg, 73% de rendimiento) como un sólido amorfo amarillo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,26 - 1,05 (m, 1,2 H) 1,14 - 1,32 (m, 1,9 H) 1,33 - 1,45 (m, 2,3 H) 1,49 (dd, *J*=14,04, 6,71 Hz, 7,1 H) 1,53 - 1,72 (m, 3,4 H) 1,79 (d, *J*=9,77 Hz, 2,2 H) 1,97 (d, *J*=10,99 Hz, 1,2 H) 2,02 - 2,15 (m, 3,1 H) 2,27 (d, *J*=11,29 Hz, 0,7 H) 2,86 (t, *J*=11,60 Hz, 1,6 H) 3,02 (d, *J*=8,85 Hz, 1,5 H) 3,16 (s, 3,9 H) 3,32 (d, *J*=11,60 Hz, 1,1 H) 3,73 - 3,87 (m, 2,1 H) 3,90 (s, 2,8 H) 3,92 - 3,97 (m, 3,4 H) 4,00 - 4,11 (m, 1,4 H) 4,59 (d, *J*=15,26 Hz, 1,0 H) 4,86 (d, *J*=14,34 Hz, 0,8 H) 5,04 (s, 0,3 H) 6,86 (s, 1,0 H)

6,95 (s, 1,0 H) 7,11 (dd, *J*=8,55, 2,44 Hz, 1,0 H) 7,54 (d, *J*=8,85 Hz, 1,2 H) 7,57 - 7,77 (m, 2,7 H) 7,80 - 8,02 (m, 1,3 H) 9,74 (s, 0,2 H) 10,11 (s, 0,7 H).

Tiempo de retención LC-MS 1,61 min; 710 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



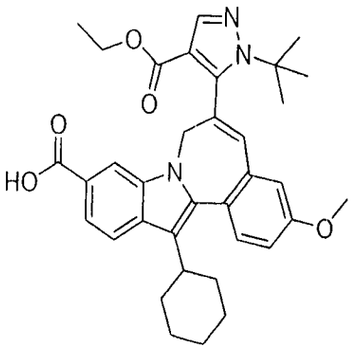
ácido 13-ciclohexil-6-((2E,Z)-3-(dimetilamino)-2-(etoxicarbonil)-2-propenoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico

En un matraz de fondo redondo de 50 ml se disuelve 13-ciclohexil-6-((2E,Z)-3-(dimetilamino)-2-(etoxicarbonil)-2-propenoil)-3-metoxi-7H-indolo[2,1-

a][2]benzazepin-10-carboxilato de terc-butilo (538mg, 0,879 mmol) en 1,2-dicloroetano (5 ml) y luego se añade TFA (5 ml). La mezcla de reacción vira a un color rojizo más oscuro tras la adición de TFA. Se coloca la reacción en una atmósfera de nitrógeno y se agita a temperatura ambiente durante 2,25 horas. Se eliminan los volátiles a vacío usando un evaporador rotatorio, se disuelve el residuo rojo oleoso en diclorometano/benceno y los volátiles se eliminan a vacío en un evaporador rotatorio. Se toma el aceite rojo resultante disuelto en acetato de etilo y se lava con ácido clorhídrico acuoso 1,0N. Se volvió a extraer la fase acuosa con acetato de etilo. Las fases orgánicas se reunieron y se lavaron secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y los disolvente se eliminaron a vacío dando un aceite rojizo-naranja que se disolvió en benceno y se eliminaron los volátiles a vacío proporcionando 519 mg del compuesto del epígrafe como una espuma rojo-naranja. El compuesto se usó sin purificación posterior.

Tiempo de retención LC-MS 1,86 min; 555 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo

electronebulización.



ácido 13-ciclohexil-6-[1-(1,1-dimetiletil)-4-(etoxicarbonil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico

Se disolvió ácido 13-ciclohexil-6-[(2*E*,*Z*)-3-(dimetilamino)-2-[[(2*R*,6*S*)-2,6-dimetil-4-morfolinil]carbonil]-1-oxo-2-propenil]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (101 mg, 0,181 mmol) en etanol (726 µl) y dioxano (181 µl). Se añadió trietilamina (59 µl, 0,423 mmol) a la reacción seguido por el reactivo hidrazina, clorhidrato de terc-butilhidrazina (23,6 mg, 0,189 mmol). La reacción se tapó en una atmósfera de nitrógeno y se calentó en un microondas hasta 160°C durante 45 minutos. La reacción se concentró a vacío usando un evaporador rotatorio y el residuo se disolvió en acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y luego salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminaron los volátiles a vacío dando 91 mg de un sólido amorfo amarillo. El producto se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La

muestra se disolvió en una mezcla acetonitrilo / DMF (1:1) y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 20 minutos con un tiempo de ejecución de 30 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente.

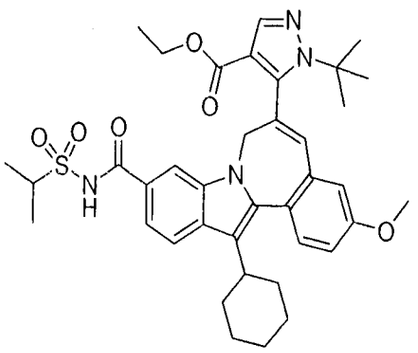
El tiempo de retención del producto mayoritario isomérico anterior fue 18,54 minutos. El pirazol alquilado isomérico minoritario se recogió con un tiempo de retención de 20,54 minutos.

Los volátiles se eliminaron de las fracciones de producto a vacío obteniendo 29,8 mg del compuesto del epígrafe como un sólido amorfo amarillo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,09 (s, 9 H) 1,18 - 1,56 (m, 8 H) 1,63 (d, 1 H) 1,78 (d, *J*=3,55 Hz, 2 H) 1,88 - 2,22 (m, 5 H) 2,89 (t, *J*=11,75 Hz, 1 H) 3,89 (s, 3 H) 4,27 (s, 2 H) 4,84 (d, *J*=14,65 Hz, 1 H) 4,96 (d, *J*=14,95 Hz, 1 H) 6,81 (s, 1 H) 6,90 (d, *J*=2,14 Hz, 1 H) 7,05 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,52 (d, *J*=8,54 Hz, 1 H) 7,76 (dd, *J*=8,55, 1,22 Hz, 1 H) 7,83 (d, *J*=8,55 Hz, 1 H) 7,92 (s, 1 H) 8,01 (s, 1 H).

Tiempo de retención LC-MS 2,20 min; 550 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las

condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



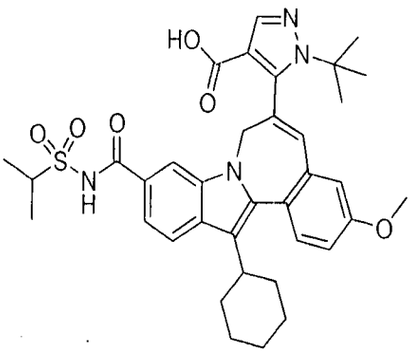
éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(1,1-dimetiletil)-1H-pirazol-4-carboxílico

En un vial de 2 dram se disolvió ácido 13-ciclohexil-6-[1-(1,1-dimetiletil)-4-(etoxicarbonil)-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (139 mg, 0,239 mmol) en diclorometano (2,4ml) y se añadieron propano-2-sulfonamida (98 mg, 0,796 mmol) y DMAP (90 mg, 0,737 mmol) a la reacción seguido por EDC (70,3 mg, 0,367 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18 horas. La

reacción se controló por HPLC y luego se dejó continuar agitando en una atmósfera de nitrógeno a temperatura ambiente durante 24 horas.

El posterior análisis HPLC no reveló cambio discernible en la composición de reacción durante las últimas 24 horas. Los volátiles se eliminaron de la reacción a vacío usando un evaporador rotatorio y el residuo de reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N, NaH_2PO_4 acuoso 0,1M y ácido clorhídrico acuoso 1,0N y luego salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminó el disolvente a vacío. El producto se secó a vacío a temperatura ambiente dando 165 mg de producto como un sólido amarillo amorfo. El producto se usó sin ninguna purificación posterior.

Tiempo de retención LC-MS 2,03min; 685m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

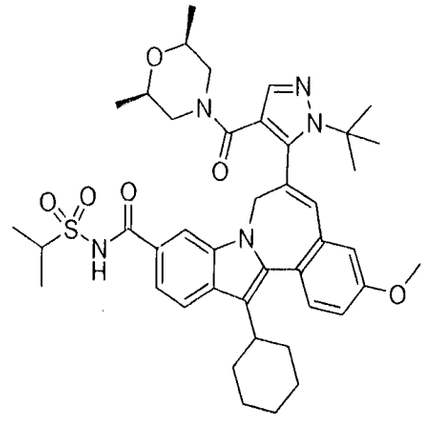


ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(1,1-dimetiletil)-1H-pirazol-4-carboxílico

Se disolvió éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-(1,1-dimetiletil)-1*H*-pirazol-4-carboxílico (164 mg, 0,239 mmol) en THF (3 ml) y metanol (3,00 ml) y luego se añadió hidróxido sódico acuoso 1,0 N (3,00 ml) a la reacción y la reacción se colocó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 25 horas. La reacción se concentró a vacío usando un evaporador rotatorio sin calentamiento y luego se repartió entre acetato de etilo y ácido clorhídrico acuoso 1,0 N. Se lavó el acetato de etilo con ácido clorhídrico acuoso 1N, se reunieron las fases orgánicas y se volvieron a extraer con acetato de etilo. Las fases orgánicas se reunieron y se lavaron con salmuera, se secaron sobre sulfato de magnesio y se eliminó el disolvente a vacío usando un evaporador rotatorio. El producto se secó a vacío a temperatura ambiente dando 158,1 mg como un sólido amorfo amarillo. El producto se usó sin ninguna purificación posterior.

Tiempo de retención LC-MS 1,54 min; 657 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un

detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-6-[1-(1,1-dimetiletil)-4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

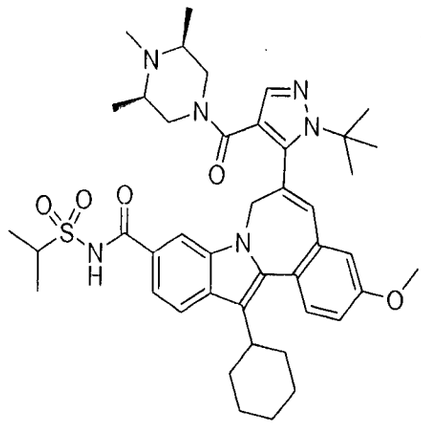
Se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-(1,1-dimetiletil)-1*H*-pirazol-4-carboxílico (60mg, 0,091 mmol) en DMF (911 µl). Se añadió HATU (81,5 mg, 0,214 mmol) a la reacción y la reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 1,25 horas.

Se añadió DMAP (45,9 mg, 0,376 mmol) a la reacción seguida por el reactivo amina, (2R,6S)-2,6-dimetilmorfolina (34 µl, 0,275 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18 horas. El producto se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La reacción se diluyó hasta 2 ml usando acetonitrilo y un par de gotas de ácido acético acuoso y luego se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 20 minutos con un tiempo de ejecución de 30 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto fue 18,5 minutos. Las fracciones de producto se reunieron y los volátiles se eliminaron a vacío usando un evaporador rotatorio. La muestra se secó a vacío a temperatura ambiente dando 32,5 mg como una película amarilla amorfa. Los resultados de la RMN de ^{1}H son característicos de rotación limitada con ensanchamiento y división de los picos.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,66 (d, *J*=6,10 Hz, 2,4 H) 0,71 (d, *J*=6,10 Hz, 2,3 H) 0,78 (dd, *J*=11,29, 6,10 Hz, 1,8 H) 1,10 (s, 1,2 H) 1,25 (dd, *J*=13,73, 6,71 Hz, 3,0 H) 1,35 - 1,44 (m, 2,5 H) 1,46 (t, *J*=7,02 Hz, 4,7 H) 1,54 (d, *J*=6,71 Hz, 3,7 H) 1,67 (s, 0,6 H) 1,71 (s, 6,8 H) 1,72 - 1,75 (m, 2,7

H) 1,79 (d, *J*=11,90 Hz, 2,5 H) 1,83 - 1,92 (m, 1,0 H) 1,98 (d, *J*=12,51 Hz, 2,2 H) 2,02 - 2,21 (m, 7,9 H) 2,21 - 2,30 (m, 1,4 H) 2,80 - 2,95 (m, 2,3 H) 3,04 (d, *J*=42,42 Hz, 0,6 H) 3,23 (d, *J*=13,73 Hz, 0,3 H) 3,34 (d, *J*=12,82 Hz, 0,8 H) 3,92 (d, *J*=4,88 Hz, 0,5 H) 3,95 (s, 3,0 H) 4,04 - 4,13 (m, 1,1 H) 4,49 - 4,58 (m, 1,0 H) 4,79 (d, *J*=14,65 Hz, 0,3 H) 4,86 (d, *J*=15,26 Hz, 0,7 H) 6,78 (s, 0,8 H) 6,85 (s, 0,3 H) 6,87 (d, *J*=2,75 Hz, 0,8 H) 6,91 (s, 0,3 H) 7,14 (dd, *J*=8,55, 2,44 Hz, 1,0 H) 7,55 - 7,60 (m, 0,9 H) 7,60 - 7,64 (m, 2,3 H) 7,64 - 7,68 (m, 1,0 H) 7,83 - 7,95 (m, 1,3 H) 10,32 (s, 0,3 H) 10,60 (s, 0,7 H).

Tiempo de retención LC-MS 2,10 min; 754m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-6-[1-(1,1-dimetiletil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

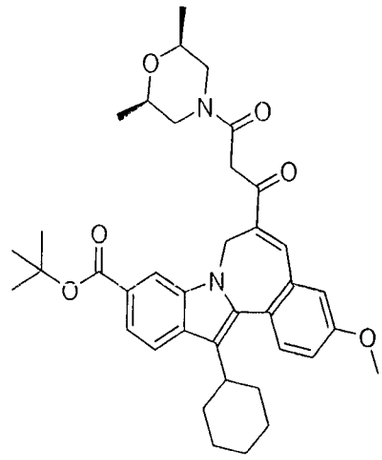
Se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-(1,1-dimetiletil)-1*H*-pirazol-4-carboxílico (48,8 mg, 0,074 mmol) en DMF (741 µl). Se añadió HATU (65,3 mg, 0,172 mmol) a la reacción y la reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 1 horas. Se añadió DMAP (53,8 mg, 0,440 mmol) a la reacción seguido por el reactivo amina, diclorhidrato de (2R,6S)-1,2,6-trimetilpiperazina (34,5 mg, 0,172 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18 horas. El producto se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La reacción se acidificó con unas pocas gotas de ácido acético acuoso y se diluyó hasta 2 ml con acetonitrilo, luego se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud

de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 25 ml / min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 20 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. Se recogió producto a partir de 8,14 minutos hasta 9,45 minutos. Los volátiles se eliminaron a vacío desde las fracciones de producto reunidas dando finalmente 11,1 mg del compuesto del epígrafe como una película amorfa amarilla.

PMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,93 - 1,34 (m, 9,7 H) 1,37 - 1,52 (m, 9,5 H) 1,56 - 1,68 (m, 1,6 H) 1,68 - 1,83 (m, 9,2 H) 1,87 - 2,20 (m, 5,4 H) 2,28 - 2,52 (m, 2,0 H) 2,55 - 3,01 (m, 9,4 H) 3,19 (d, *J*=40,59 Hz, 0,8 H) 3,63 (d, *J*=134,23 Hz, 2,4 H) 3,83 - 4,04 (m, 4,0 H) 4,54 (d, *J*=14,65 Hz, 0,8 H) 4,76 (d, *J*=14,34 Hz, 0,8 H) 6,72 - 6,97 (m, 2,0 H) 7,08 (d, *J*=7,32 Hz, 1,0 H) 7,36 - 7,76 (m, 3,4 H) 7,88 (s, 1,2 H) 10,86 (s, 0,5 H) 11,26 (s, 0,4 H).

Tiempo de retención LC-MS 1,81min; 767 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se

determinaron usando una plataforma Micromass para LC en modo electronebulización.



éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[3-[(2R,6S)-2,6-dimetil-4-morfolinil]-1,3-dioxopropil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico

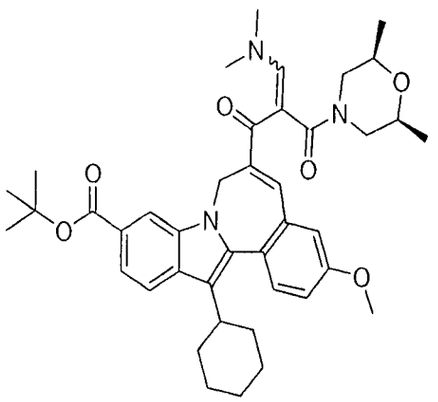
En un matraz de fondo redondo de 250 ml se disuelve 13-ciclohexil-6-(3-etoxi-3-oxopropanoil)-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxilato de terc-butilo (3,13 g, 5,61 mmol) en tolueno (56 ml) y se añade cis-2,6-dimetilmorfolina (2,6 ml, 20,99 mmol) a la reacción. Se coloca la reacción en una atmósfera de nitrógeno y se calienta hasta reflujo durante 9 horas. La reacción se repartió entre acetato de etilo y ácido cítrico acuoso 1,0M. La fase orgánica se lavó secuencialmente con ácido cítrico acuoso 1,0M, NaH_2PO_4 0,1M y salmuera. Se seca la fase orgánica sobre sulfato de magnesio, se filtra y se elimina el disolvente a vacío dando 3,01g de producto bruto como una espuma naranja-ámbar. Se disuelve el producto bruto en diclorometano y se adsorbe sobre 8,2 g de gel de sílice. Se somete el producto bruto a

cromatografía en 90 g de suspensión de gel de sílice rellenada en acetato de etilo al 5% en diclorometano, se eluye con un gradiente de 5% de acetato de etilo en diclorometano hasta 10% de acetato de etilo en diclorometano. Las fracciones de producto puras se reunieron el disolvente se eliminó a vacío usando un evaporador rotatorio proporcionando un sólido amorfo amarillo que se secó seguidamente a vacío a temperatura ambiente proporcionando 1,23 g del compuesto del epígrafe. Las fracciones menos puras produjeron otros 0,48 g de producto. El análisis LCMS dio dos picos de masa equivalente a la del producto deseado. La resolución de los dos picos por HPLC Prep en las siguientes condiciones proporcionó picos que interconvertían cuando se analizaban después de la resolución: Sistema de cromatografía líquida de alta presión Shimadzu usando software Discovery SP conectado con un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra 76816-035-a (63 mg) se disolvió en mezcla acetonitrilo / DMF (2:1, 2ml) purificada usando una columna Phenonmenex Luna C18 30 x 100mm 10u y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda de detector de 220 nm. Las condiciones de elución emplearon un caudal de 40 ml/min, un gradiente de 60% de disolvente A / 40% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un Tiempo de gradiente de 15 minutos con un tiempo de ejecución de 25 minutos usando %A= Acetato Amónico 10mM en Agua/Acetonitrilo 95:5 %B= Acetato Amónico 10mM en Agua/Acetonitrilo 5:95 como sistema disolvente. Se aislaron dos picos de la muestra: Primer pico a TR= 16,3 minutos. Ambas muestras presentaron espectros HPLC idénticos después de aislamiento que indica interconversión.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,89 (s, 2,0 H) 1,01 (s,

3,3 H) 1,19 (d, *J*=26,25 Hz, 3,5 H) 1,30 - 1,47 (m, 4,5 H) 1,55 (s, 4,2 H) 1,60 (s, 3,6 H) 1,63 (s, 9,0 H) 1,76 (d, *J*=8,24 Hz, 3,1 H) 1,93 (d, *J*=9,46 Hz, 1,9 H) 1,98 - 2,15 (m, 4,2 H) 2,23 (s, 1,2 H) 2,39 (s, 0,4 H) 2,56 - 2,72 (m, 1,6 H) 2,74 - 2,86 (m, 1,6 H) 2,91 (s, 0,3 H) 3,47 - 3,65 (m, 2,3 H) 3,74 - 3,85 (m, 1,6 H) 3,90 (s, 1,4 H) 3,91 (s, 3,1 H) 3,93 - 4,04 (m, 1,8 H) 4,19 (d, *J*=12,82 Hz, 0,5 H) 4,26 (d, *J*=14,65 Hz,0,5 H) 4,39 (s, 0,5 H) 4,47 (d, *J*=11,29 Hz, 0,4 H) 5,18 (s, 0,3 H) 5,71 - 5,92 (m, 1,1 H) 7,01 (d, *J*=2,75 Hz, 0,4 H) 7,03 - 7,06 (m, 1,4 H) 7,11 (dd, *J*=8,70, 2,59 Hz, 1,0 H) 7,47 - 7,51 (m, 0,9 H) 7,52 (s, 0,5 H) 7,57 (s, 0,4 H) 7,65 (d, *J*=1,53 Hz, 0,2 H) 7,68 (dd, *J*=8,55, 1,22 Hz, 1,2 H) 7,80 (s, 0,6 H) 7,80 - 7,82 (m, 0,7 H) 7,84 (s, 0,2 H) 7,91 (s, 0,4 H) 8,04 (s, 0,5 H) 8,19 (s, 0,3 H) 8,21 (d, *J*=1,22 Hz, 1,0 H) 15,15 (d, *J*=23,80 Hz, 0,4 H).

Tiempo de retención LC-MS 4,21 min (88%); 625m/z (MH-) y 5,23min (12%); 625m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 4,6x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 70% de disolvente A / 30% de disolvente B hasta 2% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de 0 min y un tiempo de análisis de 5 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización

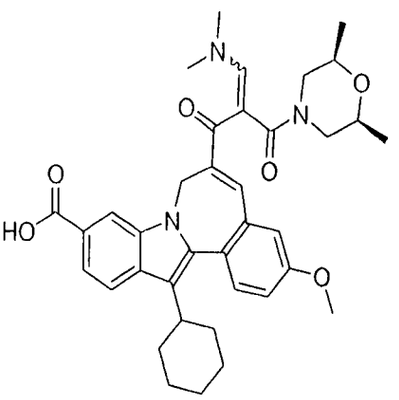


éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[(2E,Z)-3-(dimetilamino)-2-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-oxo-2-propenil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico

Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[3-[(2*R*,6*S*)-2,6-dimetil-4-morfolinil]-1,3-dioxopropil]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico en N,N-dimetilformamida dimetil acetal (10 ml,). Se ajustó un condensador a la reacción y se colocó en una atmósfera de nitrógeno. La reacción se calentó hasta reflujo durante 3 horas, luego se eliminaron los volátiles a vacío usando un evaporador rotatorio, luego se secó a vacío a temperatura ambiente obteniendo el producto como un sólido naranja amorfo (517 mg, 86%).

Tiempo de retención LC-MS 4,60 min; 682 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 4,6x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de

2 min y un tiempo de análisis de 7 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización. El intermedio se usó sin purificación posterior

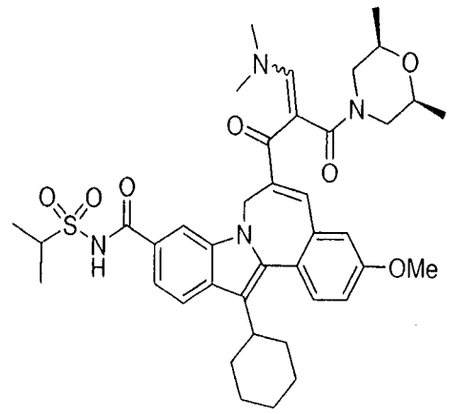


ácido 13-ciclohexil-6-[(2E,Z)-3-(dimetilamino)-2-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-oxo-2-propenil]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico

Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[(2*E*,Z)-3-(dimetilamino)-2-[[(2*R*,6*S*)-2,6-dimetil-4-morfolinil]carbonil]-1-oxo-2-propenil]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico en 1,2-dicloroetano (5 ml) y se añadió TFA (5 ml) a la reacción. La reacción se colocó en una atmósfera de nitrógeno y se agitó durante 2,5 horas. Los volátiles se eliminaron a vacío de la reacción usando un evaporador rotatorio dando un aceite rojizo. El producto se disolvió en benceno/diclorometano y se eliminaron de nuevo los volátiles a vacío dando una espuma roja. El producto se disolvió en acetato de etilo y se lavó con ácido clorhídrico acuoso 1,0N. Se volvió a extraer la fase acuosa con

acetato de etilo. Los extractos orgánicos se reunieron, se lavaron con salmuera y se secaron sobre sulfato de magnesio. La solución orgánica se filtró y los volátiles se eliminaron a vacío usando un evaporador rotatorio dando una espuma ámbar-naranja. El producto se secó a vacío a temperatura ambiente dando 388 mg de sólido ámbar-naranja amorfo.

Tiempo de retención LC-MS 2,83 min; 624 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 4,6x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de 2 min y un tiempo de análisis de 7 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-6-[(2E,Z)-3-(dimetilamino)-2-[[(2R,6S)-2,6-dimetil-4-

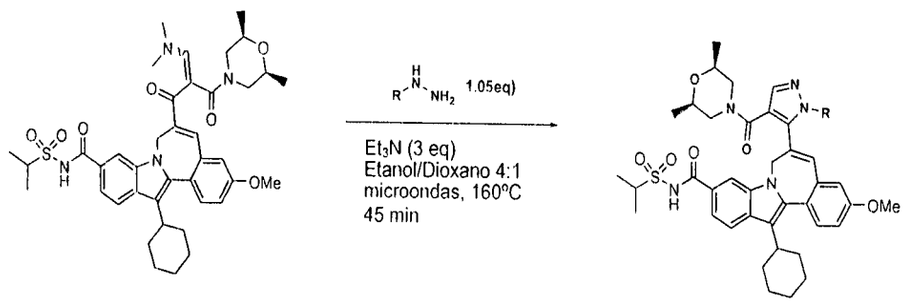
morfolinil]carbonil]-1-oxo-2-propenil]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

En un matraz de fondo redondo de 25 ml se disuelve ácido 13-ciclohexil-6-[(2*E*,*Z*)-3-(dimetilamino)-2-[[(2*R*,6*S*)-2,6-dimetil-4-morfolinil]carbonil]-1-oxo-2-propenil]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (385 mg, 0,616 mmol) en diclorometano (6,2 ml), se añade propano-2-sulfonamida (233 mg, 1,892 mmol) y DMAP (230 mg, 1,880 mmol) a la reacción seguido por EDC (177 mg, 0,924 mmol). La reacción se colocó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18,5 horas. La reacción se diluyó con acetato de etilo y se lavó con ácido clorhídrico acuoso 1,0N. Las fases orgánicas se reunieron y se volvieron a extraer con acetato de etilo. Las fases orgánicas se reunieron y se lavaron secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La solución orgánica se secó sobre sulfato de magnesio, se filtró y el disolvente se eliminó a vacío usando un evaporador rotatorio dando un sólido naranja amorfo/espuma que se secó a vacío dando 415 mg de producto bruto.

Tiempo de retención LC-MS 3,00 min; 729m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 4,6x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 7 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 5min, un tiempo de mantenimiento de 2 min y un tiempo de análisis de 5 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de

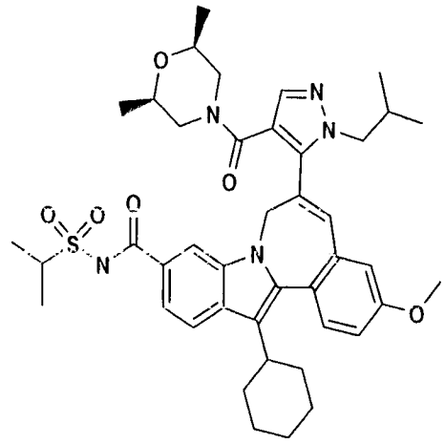
H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

El producto bruto se usó sin purificación posterior en la siguiente síntesis de pirazol.



El siguiente análogo se puede preparar usando la metodología general descrita a continuación.

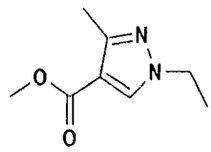
13-ciclohexil-6-[(2*E*,*Z*)-3-(dimetilamino)-2-[[(2*R*,6*S*)-2,6-dimetil-4-morfolinil]carbonil]-1-oxo-2-propenil]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxamida (100 mg, 0,137 mmol) en etanol (547 µl) y dioxano (137 µl). Se añadió el reactivo hidrazina (0,146 mmol) seguido por TEA (58,2 µl, 0,417 mmol) a la reacción en un recipiente de reacción de microondas de 0,5-2 ml. Se tapó el recipiente en una atmósfera de nitrógeno y se calentó a 160°C durante 45 minutos. La reacción se diluyó en DMF/Acetonitrilo el compuesto producto se purificó por HPLC de fase inversa.

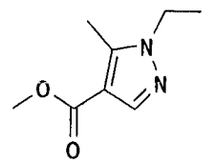


13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-(2-metilpropil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

Este compuesto se aisló usando HPLC de fase inversa con la instrumentación enumerada a continuación usando el procedimiento de gradiente Bin nº 16. Dionex APS-3000: Software de LC Chromeleon 6,70 sp1; Software de MS Thermo-Finnigan Xcalibur; Bomba binaria Dionex P680 para analítica; bomba binaria prep Dionex PP150; espectrómetro UV Dionex UVD340U; detector ELS Polymer Labs PL-ELS 1000; espectrómetro de masas Thermo-Finnigen MSQ Surveyor Plus. Condiciones de LC: Columna; Waters Xbridge 19x200mm 5 um C18; Columna auxiliar; Waters Xbridge 19x10mm 5 um C18; Fase móvil; A = Agua, NH_4OH 20 mM; B = CAN. Tiempo de retención LC-MS 5,47 min; 756,87 m/z (MH+). Los datos LC se registraron usando Masslynx 4,0 SP4 con un sistema equipado con: Muestreador automático CTC-Leap HTS-PAL con módulo de inyección de 4 orificios Harney, bomba binaria Waters 1525, detector UV Waters 2488 a 220 nm, detector ELS Polymer Lab

1000 (T evap. =90ºC, T Nebuliz.= 80C) y un espectrómetro de masas Waters LCT con una fuente MUX de 4 vías. La muestra se analizó usando una columna Ascentis 4,6x50mm 5uM C18. Las condiciones de elución emplearon un caudal de 2 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 9 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Ionización MS usando un espectrómetro de masas Waters LCT en modo positivo de ESI.





1-Etil-3-metil-1H-pirazol-4-carboxilato de metilo y 1-etil-5-metil-1H-pirazol-4-carboxilato de metilo

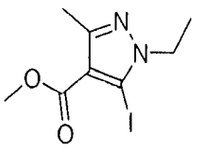
Se suspendió 2-((dimetilamino)metilen)-3-oxobutanoato de metilo (1,712 g, 10 mmol) en éter dietílico (50 ml) en una atmósfera de nitrógeno hasta 0ºC. Se añadieron entonces oxalato de etilhidrazina (1,651 g, 11 mmol) en éter dietílico (13 ml), trietilamina (7,0 ml, 50,2 mmol) y etanol (6 ml). La mezcla resultante se volvió lentamente más homogénea y se continuó agitando a 0ºC durante 40 minutos, después de lo cual se retiró el baño de hielo y se agitó la mezcla durante otras 1,5 horas. La reacción se repartió entonces entre acetato de etilo y ácido clorhídrico acuoso 1,0N. Se extrajo la fase acuosa con acetato

de etilo. Se reunieron las fases orgánicas y se lavaron secuencialmente con ácido clorhídrico acuoso 1,0N, bicarbonato sódico acuoso saturado y salmuera. Se secó la fase orgánica sobre sulfato de magnesio, se filtró y se eliminaron los volátiles a vacío proporcionando un aceite amarillo, se traspasó a un matraz pequeño en forma de pera en benceno, se eliminaron los volátiles a vacío usando evaporador rotatorio. La muestra se secó rápidamente a vacío en un evaporador rotatorio proporcionando 1,549 g de un líquido/aceite amarillo.

El análisis RMN de ^{1}H indicó una mezcla de isómeros de relación 53:46.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,40 (t, *J*=7,32 Hz, 3,01 H) 1,46 (t, *J*=7,32 Hz, 3,56 H) 2,44 (s, 3,45 H) 2,52 (s, 2,99 H) 3,79 (s, 3,49 H) 3,79 (s, 2,79 H) 4,05 - 4,13 (m, 4,44 H) 7,80 (s, 1,09 H) 7,82 (s, 0,86 H).

Tiempo de retención LC-MS 0,80min; 169m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



1-Etil-5-yodo-3-metil-1H-pirazol-4-carboxilato de metilo

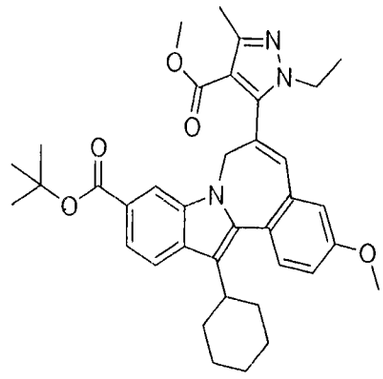
Se disolvió en un matraz de fondo redondo de 100 ml una mezcla de 1-etil-3-metil-1H-pirazol-4-carboxilato de metilo y 1-etil-5-metil-1H-pirazol-4-carboxilato de metilo (1,539 g, 9,15 mmol) en THF anhidro (44 ml). La reacción se colocó en una atmósfera de nitrógeno y se enfrió hasta -78°C, luego se añadió gota a gota n-butil litio (5,49 ml, 10,98 mmol) 2,0M en pentano. La solución naranja a -78°C se sumergió entonces en un baño de acetonitrilo/CO_2 a -44°C y se agitó durante 1 hora. La reacción se enfrió hasta -78°C y se añadió una solución de yodo (2,55 g, 10,07 mmol) en tetrahidrofurano (10 ml) mediante cánula durante aproximadamente 10 minutos. La reacción se agitó a -78°C durante 10 minutos después de la adición de yodo y luego se retiró el baño de enfriamiento y se dejó calentar la reacción hasta temperatura ambiente durante 1 hora. La reacción se inactivó con una solución acuosa saturada de cloruro amónico y se extrajo en acetato de etilo. La reacción se repartió entre acetato de etilo y cloruro amónico acuoso saturado, se lavó con sulfito sódico acuoso y de nuevo con cloruro amónico acuoso saturado y salmuera. La solución de producto se secó sobre sulfato de magnesio y los volátiles se eliminaron a vacío usando evaporador rotatorio. El producto bruto se aisló como un aceite ámbar (aproximadamente 2,1 g). El compuesto del epígrafe se aisló por cromatografía sobre gel de sílice (Pf=0,66 en acetato de etilo al 50% /

hexanos en placa TLC de 250 micrómetros GHLF de gel de sílice Analtech Uniplate). La reacción bruta se adsorbió sobre 5,5 g de gel de sílice usando diclorometano y se sometió a cromatografía en 55,9 g de suspensión de sílice rellenada en una columna usando acetato de etilo al 10% en hexanos. La elución con acetato de etilo al 10% en hexanos y luego un gradiente de etapas de acetato de etilo al 15%, 20%, 25%, 30%, 40%, 50% y finalmente hasta 70% en hexanos proporcionó el producto purificado y la separación de los componentes de reacción brutos.

El compuesto del epígrafe (424 mg, 30%) se aisló como un sólido casi incoloro.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 1,40 (t, *J*=7,17 Hz, 3 H) 2,45 (s, 3 H) 3,84 (s, 3 H) 4,24 (c, *J*=7,32 Hz, 2 H).

Tiempo de retención LC-MS 1,19 min; 295 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[1-etil-4-(metoxicarbonil)-3-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico

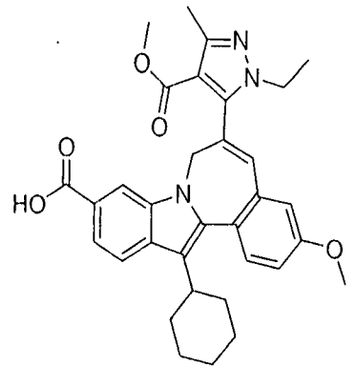
En un recipiente de microondas de 20 ml se cargó éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-(tributilestannil)-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (300 mg, 0,409 mmol), 1-etil-5-yodo-3-metil-1H-pirazol-4-carboxilato de metilo (169 mg, 0,573 mmol), dicloruro de bis(trifenilfosfina)paladio(II) (29,6 mg, 0,042 mmol) y 1 g de tamices moleculares activados de 3A. Se tapó el recipiente de reacción y se llenó con nitrógeno durante tres ciclos. Se añadió dioxano a la reacción y los reactivos se disolvieron a temperatura ambiente. La reacción sellada se calentó a 120°C durante 17 horas. Se añadió acetato de etilo a la reacción y ésta se filtró a través de un filtro autovial Whatman de 0,45 um. Se aclaró la torta del filtro con acetato de etilo y se eliminaron los volátiles del filtrado a vacío dando 508 mg de aceite amarillo. El producto bruto con olor a estaño se disolvió en 13 ml de dioxano y se agitó durante 2 horas con una solución acuosa de fluoruro potásico. Un intento de filtrar la solución no funcionó y se vertió la suspensión acuosa/orgánica en un embudo de separación y se añadió acetato de etilo y se extrajo la fase acuosa con acetato de etilo. La fase orgánica se lavó con

salmuera y se secó sobre sulfato de magnesio, se filtró y se eliminaron los volátiles a vacío obteniendo 446 mg de aceite ámbar que todavía olía a estaño. El producto bruto se adsorbió sobre 1,1 g de gel de sílice usando diclorometano y se purificó en 15,0 g de suspensión de gel de sílice en columna cargada en diclorometano. La columna eluyó con un gradiente de etapas de diclorometano hasta acetato de etilo al 2% en diclorometano y finalmente se llenó con acetato de etilo al 5% en diclorometano. La fracción de producto se reunió y se eliminó el disolvente a vacío dando el compuesto del epígrafe (152 mg, 61%) como un sólido amarillo amorfo. El compuesto tenía un olor apagado indicando que cantidades minoritarias de estaño pueden estar presentes. El producto se usó en posteriores etapas sin purificación adicional.

La RMN de ^{1}H indica que la muestra contiene probablemente una impureza de butil estaño. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,64 (s, 3 H) 0,81 - 0,89 (m, 2 H) 0,91 (t, *J*=7,32 Hz, 2,5 H, compuesto de Sn?) 1,20 - 1,31 (m, 7 H) 1,31 - 1,41 (m, 3 H) 1,43 - 1,55 (m, 3 H) 1,56 (s, 5 H) 1,58 (s, 8 H) 1,60 - 1,68 (m, 2 H) 1,77 (d, *J*=9,46 Hz, 2 H) 1,94 (d, *J*=7,63 Hz, 1 H) 2,03 (s, 0,9 H, EtOAc) 2,07 (s, 2 H) 2,45 (s, 0,4 H) 2,47 (s, 3 H) 2,53 (s, 0,3 H) 2,85 (t, *J*=11,90 Hz, 1 H) 3,50 (d, *J*=54,93 Hz, 3 H) 3,73 - 3,85 (m, 3 H) 3,90 (s, 3 H) 4,08 - 4,14 (m, 0,8 H, EtOAc e impureza) 4,59 (c, *J*=7,22 Hz, 1 H) 4,66 (d, *J*=13,43 Hz, 1 H) 4,95 (d, *J*=14,04 Hz, 1 H) 6,72 (s, 1 H) 6,92 (d, *J*=2,44 Hz, 1 H) 7,05 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,51 (d, *J*=8,54 Hz, 1 H) 7,63 (dd, *J*=8,55, 1,53 Hz, 1 H) 7,78 - 7,83 (m, 1 H) 7,85 (s, 1 H).

Tiempo de retención LC-MS 2,74 min; 610 m/z (MH+). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado

con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



ácido 13-ciclohexil-6-[1-etil-4-(metoxicarbonil)-3-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico

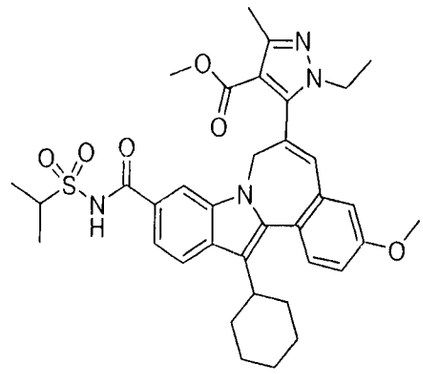
Se disolvió éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[1-etil-4-(metoxicarbonil)-3-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-*a*][2]benzazepin-10-carboxílico (151mg, 0,248 mmol) en 1,2-dicloroetano (2ml) y se añadió TFA (2,000 ml). La reacción se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 2,5 horas. Los volátiles de la

reacción se eliminaron a vacío usando un evaporador rotatorio dando un aceite naranja/ámbar. El producto oleoso se disolvió en una mezcla de diclorometano y benceno y los volátiles se eliminaron a vacío obteniendo un sólido amorfo amarillo. El sólido se suspendió en benceno-diclorometano y de nuevo se eliminaron los volátiles a vacío. El producto se secó a vacío a temperatura ambiente dando 151 mg de un sólido amarillo con un ligero olor a estaño. El producto se trituró con la adición de 1,5 a 2 ml de diclorometano y varios mililitros de hexanos. La suspensión se calentó hasta reflujo y luego se dejó enfriar. El producto se filtró como un sólido amarillo amorfo y se aclaró con hexanos y se secó a vacío a temperatura ambiente proporcionando 114,7mg del compuesto del epígrafe.

PMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,60 (s, 3 H) 0,88 (t, *J*=7,02 Hz, 1 H) 1,19 - 1,33 (m, 3 H) 1,34 - 1,58 (m, 3 H) 1,79 (d, *J*=3,85 Hz, 2 H) 1,96 (s, 1 H) 2,08 (s, 3 H) 2,51 (s, 3 H) 2,86 (t, *J*=11,60 Hz, 1 H) 3,41 - 3,71 (m, 3 H) 3,73 - 3,89 (m, 2 H) 3,91 (s, 3 H) 4,49 (s, 6 H) 4,70 (d, *J*=12,21 Hz, 1 H) 4,96 (d, *J*=12,21 Hz, 1 H) 6,76 (s, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,03 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,54 (d, *J*=8,54 Hz, 1 H) 7,76 (dd, *J*=8,39, 1,37 Hz, 1 H) 7,89 (d, *J*=8,54 Hz, 1 H) 7,95 (s, 1 H).

Tiempo de retención LC-MS1,87 min; 552 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de

1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-etil-3-metil-1H-pirazol-4-carboxílico

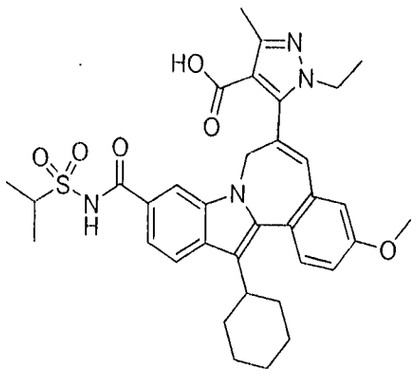
Se suspendió ácido 13-ciclohexil-6-[1-etil-4-(metoxicarbonil)-3-metil-1H-pirazol-5-il]-3-metoxi-7H-indolo[2,1-a][2]benzazepin-10-carboxílico (109,4 mg, 0,198 mmol) en diclorometano (2ml) y se añadieron a la reacción propano-2-sulfonamida (82 mg, 0,666 mmol) y DMAP (77,8 mg, 0,637 mmol). Tras la adición de DMAP la reacción se convirtió en una solución amarilla homogénea. Se añadió EDC (57,7 mg, 0,301 mmol) a la reacción y la reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 2 días. La reacción se diluyó con acetato de etilo y se lavó secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se eliminó el disolvente a vacío obteniendo 128 mg de producto como

una espuma amarilla.

El análisis RMN de ^1H mostró la presencia de acetato de etilo y aproximadamente 0,24 equivalentes de reactivo propano-2-sulfonamida. El material se usó sin purificación posterior.

Tiempo de retención LC-MS 1,34 min; 657 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.

RMN de ^1H (500 MHz, CLOROFORMO-D) δ ppm 0,66 (s, 2 H) 0,79 - 0,94 (m, 2 H) 1,28 - 1,39 (m, 2 H) 1,45 - 1,49 (m, 6 H) 1,50 - 1,56 (m, 1 H) 1,79 (d, *J*=8,85 Hz, 2 H) 1,96 (s, 2 H) 2,05 - 2,11 (m, 2 H) 2,26 (s, 7 H, pico H_2O) 2,49 (s, 3 H) 2,81 - 2,91 (m, 1 H) 3,38 - 3,71 (m, 4 H) 3,74 - 3,88 (m, 2 H) 3,91 (s, 3 H) 4,01 - 4,08 (m, 1 H) 4,69 (d, *J*=15,26 Hz, 1 H) 4,94 (d, *J*=12,51 Hz, 1 H) 6,76 (s, 1 H) 6,94 (d, *J*=2,75 Hz, 1 H) 7,08 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,33 (d, *J*=8,55 Hz, 1 H) 7,53 (d, *J*=8,55 Hz, 1 H) 7,76 (s, 1 H) 7,89 (d, *J*=8,54 Hz, 1 H) 8,30 (s, 1 H).



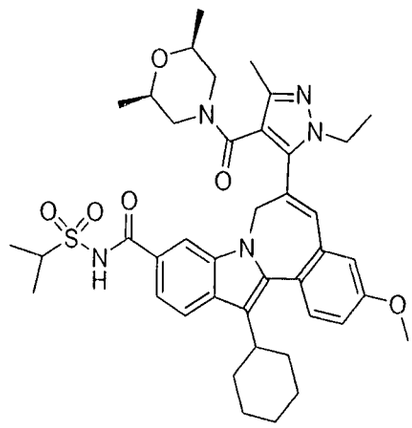
ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-etil-3-metil-1H-pirazol-4-carboxílico

Se disolvió éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-etil-3-metil-1*H*-pirazol-4-carboxílico (127mg, 0,193 mmol) en THF (3ml) y se añadió a la solución metanol (3 ml). Se añadió hidróxido sódico (3 ml, 3,00 mmol, solución acuosa 1,0N) a la solución amarillo homogénea. La reacción viró a un color turbio rosa-rojizo después de completarse la adición de solución de hidróxido sódico. La reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno y finalmente se convirtió en una solución color rosa transparente. La reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno. El análisis HPLC después de 40 horas mostró una conversión del 78% en producto. Se añadió hidróxido sódico (1,0 ml, 1,00 mmol, solución acuosa 1,0N) a la reacción y la reacción se agitó en una atmósfera de nitrógeno durante otras 24 horas más. La reacción se concentró hasta sequedad a vacío usando un evaporador rotatorio con un baño a temperatura ambiente. El residuo sólido rosa se repartió entre acetato de etilo y ácido clorhídrico acuoso 1,0N. La fase acuosa orgánica se extrajo con acetato de

etilo y las fases orgánicas se reunieron y se lavaron secuencialmente con ácido clorhídrico acuoso 1,0N y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se eliminaron los disolventes a vacío dando un sólido amarillo que se secó a vacío a temperatura ambiente dando 108 mg del compuesto del epígrafe como un sólido amarillo amorfo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,71 (s, 3 H) 0,81 - 0,94 (m, 2 H) 0,96 - 1,20 (m, 3 H) 1,23 - 1,27 (m, 3 H) 1,27 - 1,37 (m, 3 H) 1,41 (t, *J*=7,17 Hz, 6 H) 1,45 - 1,53 (m, 2 H) 1,60 - 1,73 (m, 1 H) 1,77 (d, *J*=11,90 Hz, 2 H) 1,86 - 2,02 (m, 2 H) 2,04 - 2,08 (m, 1 H) 2,47 (s, 2 H) 2,77 - 2,89 (m, 1 H) 3,43 - 3,69 (m, 4 H) 3,70 - 3,86 (m, 2 H) 3,99 - 4,06 (m, 2 H) 4,61 (d, *J*=10,07 Hz, 1 H) 4,95 (d, *J*=13,73 Hz, 1 H) 6,75 (s, 1 H) 6,94 (d, *J*=2,44 Hz, 1 H) 7,03 - 7,10 (m, 1 H) 7,42 (d, *J*=8,24 Hz, 1 H) 7,47 - 7,54 (m, 1 H) 7,79 - 7,91 (m, 2 H) 8,76 (s, 1 H).

Tiempo de retención LC-MS 1,50 min; 643 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-etil-3-metil-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

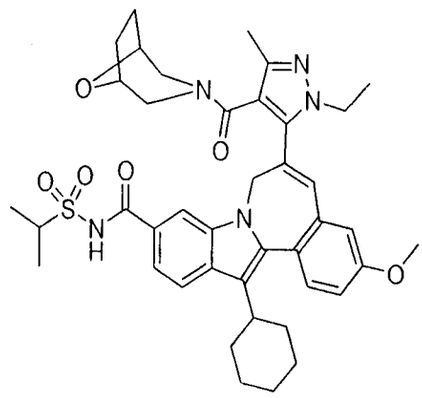
Se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-etil-3-metil-1*H*-pirazol-4-carboxílico (61,1 mg, 0,095 mmol) en DMF (948 µl) y se añadió a la reacción HATU (80 mg, 0,210 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 1 hora. Se añadió a la reacción DMAP (36,7 mg, 0,300 mmol) seguido por el reactivo amina, (2R,6S)-2,6-dimetilmorfolina (35,2 µl, 0,284 mmol). La solución de reacción amarillo transparente se tapó en una atmósfera de nitrógeno y la reacción se agitó a temperatura ambiente durante 42 horas. El compuesto del epígrafe se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La muestra se disolvió en acetonitrilo y DMF y se purificó usando una columna de 5 um 19mm x 100 mm Waters Sunfire Prep C18 OBD y se controló usando un

detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 30 ml / min, un gradiente de 50% de disolvente A / 50% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 25 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto fue de 16,16 a 17,47 minutos. Las fracciones de producto se reunieron y los volátiles se eliminaron a vacío usando un evaporador rotatorio. El compuesto del epígrafe se secó a vacío a temperatura ambiente proporcionando 36,3 mg de un sólido amorfo amarillo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,68 (s, 4 H) 0,75 - 0,93 (m, 2 H) 1,05 (s, 1 H) 1,30 - 1,45 (m, 6 H) 1,51 (dd, *J*=21,82, 6,26 Hz, 7 H) 1,79 (d, *J*=10,68 Hz, 2 H) 1,89 - 2,02 (m, 3 H) 2,03 - 2,16 (m, 3 H) 2,26 (s, 12 H) 2,88 (t, *J*=10,68 Hz, 1 H) 2,95 - 3,31 (m, 3 H) 3,34 - 3,75 (m, 1 H) 3,94 (s, 3 H) 4,03 - 4,11 (m, 1 H) 4,17 (s, 2 H) 4,57 (d, *J*=14,65 Hz, 1 H) 4,87 (d, *J*=15,56 Hz, 1 H) 6,74 - 6,86 (m, 1 H) 6,93 (s, 1 H) 7,12 (d, *J*=7,02 Hz, 1 H) 7,58 (d, *J*=8,54 Hz, 1 H) 7,66 (s, 1 H) 7,73 (s, 1 H) 7,90 (d, *J*=8,24 Hz, 1 H) 10,66 (s, 1 H).

LC-MS tiempo de retención 1,93 min; 740m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0x50mm Phenomenex-Luna 10u C18 usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de

acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



13-ciclohexil-6-[1-etil-3-metil-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-ilcarbonil)-1H-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7H-indolo[2,1-a][2]benzazepin-10-carboxamida

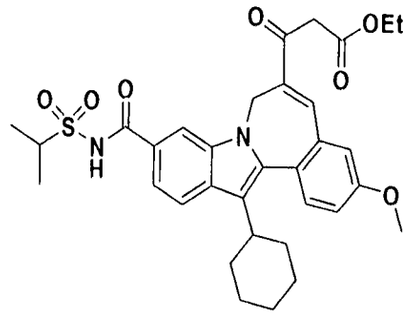
Se disolvió ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-*a*][2]benzazepin-6-il]-1-etil-3-metil-1*H*-pirazol-4-carboxílico (45,8 mg, 0,071 mmol) en DMF (710 µl) y se añadió a la reacción HATU (62,7 mg, 0,165 mmol). La reacción se tapó en una atmósfera de nitrógeno y se agitó durante 1 hora a temperatura ambiente. Se añadió a la reacción DMAP (37,1 mg, 0,304 mmol) seguido por el reactivo amina, clorhidrato de 8-oxa-3-azabiciclo[3.2.1]octano (23,3 mg, 0,156 mmol). La reacción se tapó de nuevo en una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 42 horas. El producto se purificó en un sistema de cromatografía líquida de alta presión Shimadzu que emplea software

Discovery VP conectado a un controlador SCL-10A, muestreador automático SIL-10A y recolector de fracciones FRC-10A. La reacción se diluyó hasta 2 ml con acetonitrilo purificado usando una columna de 5 um 19mm x 150 mm Waters Sunfire Prep C18 OBD y se controló usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 35 ml / min, un gradiente de 50% de disolvente A / 50% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 25 minutos con un tiempo de ejecución de 25 minutos usando %A= 10% de acetonitrilo, 90% de agua, 0,1% de TFA; %B= 90% de acetonitrilo, 10% de agua, 0,1% de TFA como sistema disolvente. El tiempo de retención del producto fue de 14,77 a 15,57 minutos. Los volátiles se eliminaron de la fracción de producto a vacío usando un evaporador rotatorio. El compuesto del epígrafe se secó a vacío a temperatura ambiente proporcionando 28,2 mg de un sólido amorfo amarillo.

RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 0,68 (s, 1 H) 1,14 - 1,30 (m, 2 H) 1,32 - 1,55 (m, 11 H) 1,55 - 1,72 (m, 3 H) 1,80 (t, *J*=10,68 Hz, 2 H) 1,90 - 2,02 (m, 2 H) 2,11 (s, 12 H) 2,19 - 2,34 (m, 4 H) 2,85 (t, *J*=11,75 Hz, 1 H) 2,98 (d, *J*=11,90 Hz, 1 H) 3,13 (s, 1 H) 3,25 - 3,68 (m, 2 H) 3,74 - 3,91 (m, 2 H) 3,94 (s, 3 H) 4,00 - 4,10 (m, 1 H) 4,19 (d, *J*=27,77 Hz, 2 H) 4,55 (d, *J*=14,95 Hz, 1 H) 4,80 (d, *J*=14,65 Hz, 1 H) 5,03 (s, 0,15 H) 6,82 (s, 1 H) 6,93 (s, 1 H) 7,11 (dd, *J*=8,70, 2,59 Hz, 1 H) 7,54 (d, *J*=8,55 Hz, 1 H) 7,62 (d, *J*=7,63 Hz, 2 H) 7,81 - 8,01 (m, 1 H) 10,51 (s, 1 H).

Tiempo de retención LC-MS 1,79 min; 738 m/z (MH-). Los datos de LC se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna de 3,0:50mm Phenomenex-Luna 10u C18 usando un

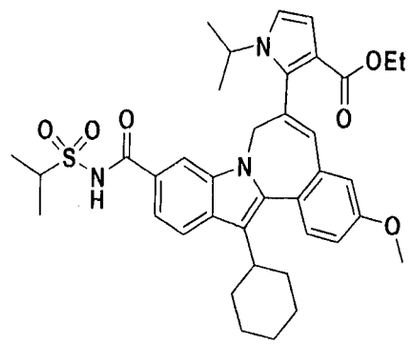
detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nm. Las condiciones de elución emplearon un caudal de 5 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 min, un tiempo de mantenimiento de 1 min y un tiempo de análisis de 4 min en el que el disolvente A fue 5% de acetonitrilo / 95% de H_2O / acetato amónico 10 mM y el disolvente B fue 5% de H_2O / 95% de acetonitrilo / acetato amónico 10 mM. Los datos de MS se determinaron usando una plataforma Micromass para LC en modo electronebulización.



éster etílico del ácido 13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-beta-oxo-7H-indolo[2,1-a][2]benzazepin-6-propanoico.

A una solución agitada de ácido 13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-carboxílico (4 g, 7,45 mmol) en THF (20 ml) se añadió CDI (1,151 g, 7,10 mmol) y la mezcla se calentó a 45ºC durante 0,5 horas y se enfrió la mezcla de reacción y se traspasó a una suspensión de cloruro de magnesio (1,419 g, 14,91 mmol) y etilmalonato polásico (2,54 g, 14,91 mmol) en THF (15 ml). Se añadió más THF

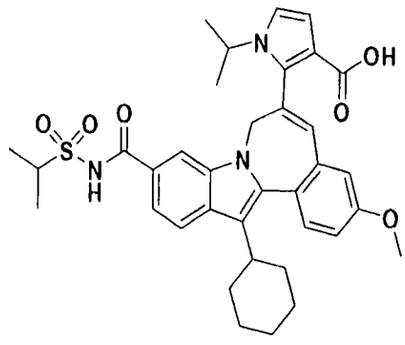
(40 ml) para disolver el precipitado originado. La mezcla de reacción se agitó durante 0,5 horas a TA y luego se calentó a 60ºC durante la noche. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con EtOAc, se lavó con HCl 1N, salmuera y se secó (Mg_2SO_4). El producto bruto se purificó en una columna Thomson de 160 g (MeOH/DCM: 0 hasta 25%) proporcionando el producto como un sólido rojizo (3,5 g, 84%). Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm 3S. LC/MS: tiempo de retención 3,418 min, m/z 607 (MH^+).



éster etílico del ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(1-metiletil)-1H-pirrol-3-carboxílico.

A una solución de éster etílico del ácido 13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-beta-oxo-7H-indolo[2,1-a][2]benzazepin-6-propanoico (0,8 g, 1,055 mmol) en THF (3 ml) se añadió propan-2-amina (0,624 g, 10,55 mmol) y ácido tósico (10,03 mg, 0,053 mmol). La mezcla se agitó a TA durante 0,5 horas y se añadió acetato de 1,2-dibromoetilo (0,337 g, 1,371

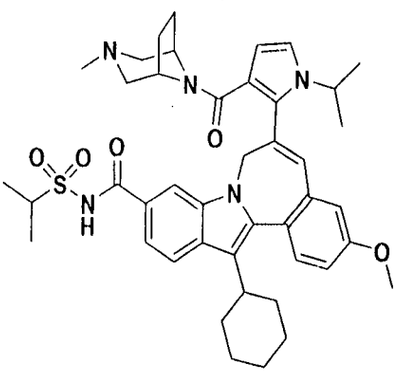
mmol) a 0°C. La mezcla de reacción se agitó a TA durante 0,5 h y luego se añadió hidruro sódico (0,051 g, 2,110 mmol) y se agitó durante 10 min a ta. La mezcla se calentó a 60° C durante 3 h y se enfrió hasta temperatura ambiente, se diluyó con EtOAc y se lavó con HCl 0,5 N enfriado en hielo (1N), salmuera y se secó ($MgSO_4$). El producto bruto se purificó en una columna Biotage 25M, (EtOAc/hexano: 5-100%) proporcionando el compuesto como una espuma beige (0,26 g, 35%). Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,631 min, m/z 672 (MH^+).



Ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]-carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(metiletil)-1H-pirrol-3-carboxílico.

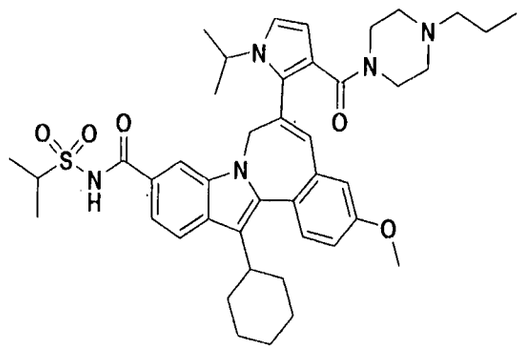
A una solución de éster etílico del ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1-(1-metiletil)-1H-pirrol-3-carboxílico (80 mg, 0,119 mmol) en THF (2 ml) se añadió trimetilsilanolato potásico (45,8 mg, 0,357 mmol). La mezcla se agitó en nitrógeno durante 30 min y se añadió otra porción de trimetilsilanolato potásico

(100 mg). La mezcla de reacción se agitó a temperatura ambiente durante 2 días y se diluyó con EtOAc, se lavó con HCl 1N frío, salmuera, se secó (MgSO4) y se eliminó el disolvente proporcionando el ácido como un sólido beige (71 mg, 88%). RMN de ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 8,80 (1 H, s ancho), 7,81 - 7,89 (1 H, m), 7,76 (1 H, s), 7,45 - 7,52 (1 H, m), 7,42 (1 H, d, *J*=6,29 Hz), 7,03 (1 H, dd, *J*=8,69, 2,64 Hz), 6,93 (1 H, d, *J*=2,27 Hz), 6,47 - 6,76 (3 H, m), 4,98 (1 H, d, *J*=13,85 Hz), 4,61 (1 H, d, *J*=14,60 Hz), 3,97 - 4,07 (1 H, m), 3,89 (1 H, s), 3,34 - 3,52 (1 H, m), 2,73 - 2,89 (1 H, m), 1,87 - 2,12 (4 H, m), 1,66 - 1,84 (2 H, m), 0,81 - 1,55 (19 H, m). Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,503 min, m/z 644 (MH^+).



13-Ciclohexil-6-(1-isopropil-3-(3-metil-3,8-diazabiciclo[3.2.1]octano-8-carbonil)-1H-pirrol-2-il)-3-metoxi-N-(isopropilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

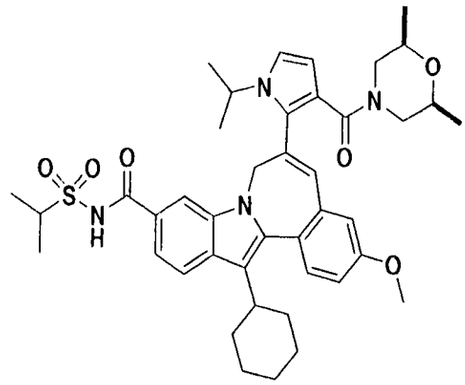
RMN de ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7,87 (1 H, d, *J*=8,56 Hz), 7,78 (1 H, s), 7,66 (1 H, d, *J*=8,06 Hz), 7,54 (1 H, d, *J*=8,31 Hz), 7,02 - 7,09 (1 H, m), 6,89 (1 H, d, *J*=2,77 Hz), 6,83 (1 H, s ancho), 6,69 (1 H, s ancho), 6,48 (1 H, s ancho), 4,91 (1 H, d, *J*=15,36 Hz), 4,55 (1 H, d, *J*=15,61 Hz), 4,48 (1 H, s ancho), 4,01 - 4,13 (1 H, m), 3,93 (3 H, s), 3,58 (1 H, s ancho), 3,12 (1 H, s ancho), 2,78 - 2,92 (1 H, m), 1,70 - 2,34 (14 H, m), 1,13 - 1,63 (16 H, m), 1,05 (1 H, s ancho), 0,52 (1 H, s ancho), -0,30 (1 H, s ancho). Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,331 min, m/z 752 (MH^+).



13-Ciclohexil-6-(1-isopropil-3-(4-propilpiperazin-1-carbonil)-1H-pirrol-2-il)-3-metoxi-N-(isopropilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

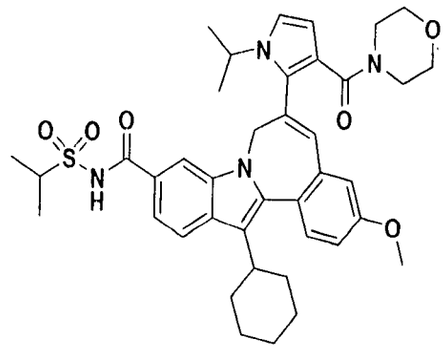
RMN de ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 7,87 (1 H, d, *J*=8,56 Hz), 7,79 (1 H, s), 7,59 (1 H, d, *J*=8,31 Hz), 7,53 (1 H, d, *J*=8,56 Hz), 7,05 (1 H, dd, *J*=8,69, 2,64 Hz), 6,90 (1 H, d, *J*=2,52 Hz), 6,78 (1 H, s ancho), 6,63 (1 H, s),

6,32 (1 H, d, *J*=2,27 Hz), 4,91 (1 H, d, *J*=14,60 Hz), 4,55 (2 H, d, *J*=14,86 Hz), 3,99 - 4,50 (2 H, m), 3,95 - 4,32 (1 H, m), 3,92 (3 H, s), 2,70 - 3,19 (5 H, m), 1,86 - 2,16 (8 H, m), 1,67 - 1,84 (2 H, m), 1,09 - 1,64 (18 H, m), 0,65 - 0,83 (3 H, m). Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: YBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,330 min, m/z 754 (MH^+).

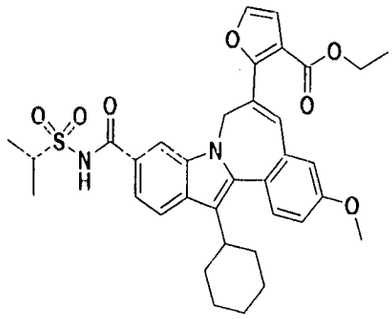


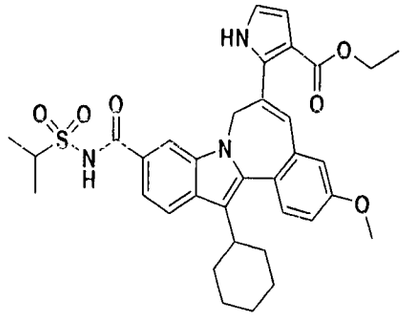
13-Ciclohexil-6-(3-((2S,6R)-2,6-dimetilmorfolin-4-carbonil)-1-isopropil-1H-pirrol-2-il)-3-meloxi-N-(isopropilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. RMN de ^1H (400 MHz, CLOROFORMO-d) δ ppm 7,87 - 7,93 (1 H, m), 7,75 (1 H, s ancho), 7,44 - 7,66 (2 H, m), 7,01 - 7,12 (1 H, m), 6,90 (1 H, s ancho), 6,83 (1 H, s ancho), 6,64 (1 H, s ancho), 6,37 (1 H, s ancho), 4,90 (0 H, d, *J*=14,86 Hz), 4,57 (1 H, s), 4,31 - 4,50 (1 H, m), 4,05 - 4,16 (1 H, m), 3,94 (3 H, s), 3,85 - 3,92 (1 H, m), 2,70 - 3,74 (5 H, m), 1,84 - 2,25 (7 H, m), 1,66 - 1,84 (2 H, m), 0,97 - 1,66 (20 H, m), 0,53 - 0,93 (5 H, m); Procedimiento LC/MS:

% B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,550 min, m/z 741 (MH^+).



13-Ciclohexil-6-(1-isopropil-3-(morfolin-4-carbonil)-1H-pirrol-2-il)-3-metoxi-N-(isopropilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. RMN de ^1H (400 MHz, CLOROFORMO-d) δ ppm 10,21 (1 H, s ancho), 7,92 (1 H, d, *J*=8,56 Hz), 7,84 (1 H, s), 7,61 (1 H, d, *J*=8,31 Hz), 7,56 (1 H, d, *J*=8,81 Hz), 7,09 (1 H, dd, *J*=8,69, 2,64 Hz), 6,90 (1 H, d, *J*=2,77 Hz), 6,82 (1 H, s ancho), 6,69 (1 H, s), 6,36 (1 H, d, *J*=2,52 Hz), 4,94 (1 H, d, *J*=14,86 Hz), 4,56 (1 H, d, *J*=15,11 Hz), 4,38 (1 H, s ancho), 4,02 - 4,12 (1 H, m), 3,94 (3 H, s), 3,58 - 4,14 (2 H, m), 2,53 - 3,28 (6 H, m), 1,95 (1 H, s ancho), 1,88 - 2,30 (4 H, m), 1,72 - 1,85 (2 H, m), 1,08 - 1,64 (16 H, m).



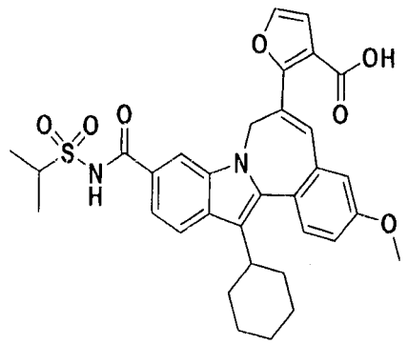


Éster etílico del ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-3-furancarboxílico.

éster etílico del ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-1H-pirrol-3-carboxílico

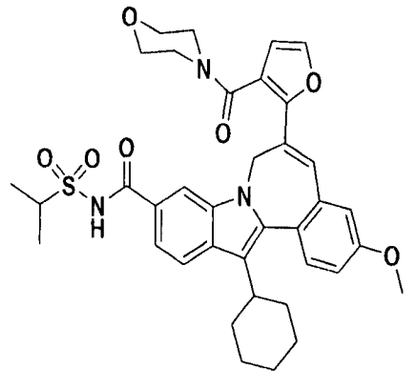
Se añadió acetalo de 1,2-dibromoacetilo en THF (0,26 M, 9,13 ml, 2,373 mmol) a una solución del éster etílico del ácido 13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-beta-oxo-7H-indolo[2,1-a][2]benzazepin-6-propanoico de partida (1,200 g, 1,978 mmol) en THF (20 ml). Se burbujeó entonces NH_3 a través de la mezcla durante 10 minutos y se mantuvo la reacción en amoníaco (1 atmósfera) durante la noche. La mezcla se calentó entonces a 60° C durante 2 h y luego se enfrió hasta temperatura ambiente, se diluyó con EtOAc y se lavó con HCl 0,5 N frío (3x) y salmuera. La fase orgánica se secó entonces ($MgSO_4$) y se filtró y el filtrado se evaporó a presión reducida. El producto bruto se purificó en una columna Biotage 40M (EtOAc/hexano 0% a 100%) proporcionando un sólido amarillo que se purificó seguidamente por HPLC prep proporcionando el furano del epígrafe (65 mg, 5%) y el pirrol del

epígrafe (145 mg, 11%). Producto furano: RMN de ^{1}H (400 MHz, *METANOL-d_4*) δ ppm 8,10 (1 H, s), 7,90 (1 H, d, *J*=8,56 Hz), 7,81 (1 H, s), 7,49 - 7,63 (3 H, m), 7,05 - 7,18 (2 H, m), 6,56 (1 H, d, *J*=2,01 Hz), 5,93 (1 H, d, *J*=14,35 Hz), 4,28 - 4,47 (3 H, m), 3,94 - 4,02 (1 H, m), 3,92 (3 H, s), 2,79 - 2,96 (1 H, m), 1,86 - 2,23 (4 H, m), 1,69 - 1,84 (2 H, m), 1,44 (6 H, d, *J*=6,80 Hz), 1,35 (3 H, t, *J*=7,05 Hz), 1,27 - 1,60 (4 H, m). Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,736 min, m/z 631 (MH^+). Producto pirrol: RMN de ^{1}H (400 MHz, *MeOD*) δ ppm 11,02 (1 H, s ancho), 8,03 (1 H, s ancho), 7,84 (1 H, d, *J*=8,56 Hz), 7,31 (1 H, s), 7,47 - 7,56 (2 H, m), 7,01 - 7,11 (2 H, m), 6,90 (1 H, s), 6,58 - 6,64 (2 H, m), 5,44 (1 H, d, *J*=17,63 Hz), 4,51 (1 H, d, *J*=14,10 Hz), 4,18 - 4,35 (2 H, m), 3,87 (3 H, s), 3,81 - 3,97 (1 H, m), 2,82 - 2,95 (1 H, m), 1,86 - 2,20 (4 H, m), 1,68 - 1,84 (2 H, m), 1,12 - 1,55 (13 H, m). Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,475 min, m/z 630 (MH^+).



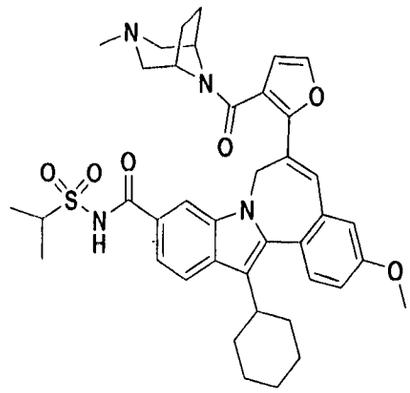
Ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-3-furancarboxílico.

A una mezcla de éster etílico del ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7H-indolo[2,1-a][2]benzazepin-6-il]-3-furancarboxílico (63 mg, 0,100 mmol) y trimetilsilanolato potásico (128 mg, 0,999 mmol) se añadió THF (2 ml). La mezcla se agitó a ta en nitrógeno durante 2 horas. Se diluyó con EtOAc y se lavó con HCl 1N frío y se secó ($MgSO_4$), se eliminaron los disolventes proporcionando el ácido (48 mg, 80%). Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,553 min, m/z 603 (MH^+).

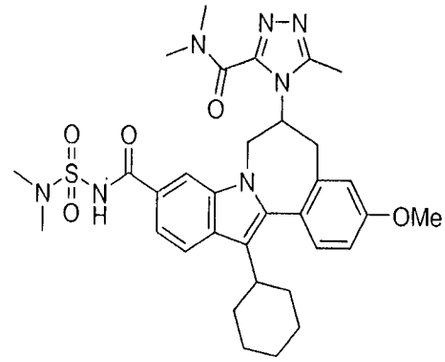


13-ciclohexil-6-(3-(morfolina-4-carbonil)furan-2-il)-3-metoxi-N-(isopropilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida.

RMN de ^{1}H (400 MHz, CLOROFORMO-d) δ ppm 8,08 (1 H, d, *J*=1,01 Hz), 7,86 (1 H, d, *J*=8,56 Hz), 7,66 (1 H, dd, *J*=8,44, 1,38 Hz), 7,49 (1 H, d, *J*=8,56 Hz), 7,40 (1 H, d, *J*=1,76 Hz), 7,33 (1 H, s), 7,04 (1 H, dd, *J*=8,56, 2,77 Hz), 6,96 (1 H, d, *J*=2,52 Hz), 6,48 (1 H, d), 5,23 (1 H, d), 4,40 (1 H, d), 3,99 - 4,18 (2 H, m), 3,90 (3 H, s), 3,79 - 3,95 (1 H, m), 3,67 - 3,78 (2 H, m), 3,42 - 3,51 (2 H, m), 3,33 - 3,41 (1 H, m), 3,19 - 3,31 (1 H, m), 2,75 - 2,88 (1 H, m), 1,86 - 2,13 (4 H, m), 1,14 - 1,83 (12 H, m); Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,276 min, m/z 711 (MH^+).



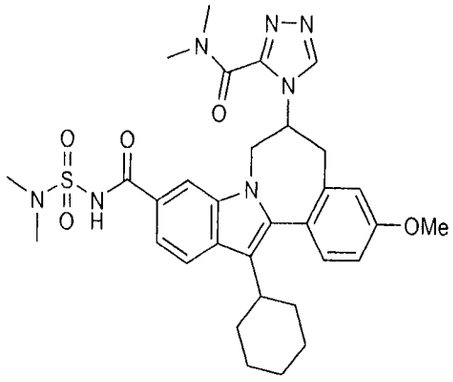
13-ciclohexil-6-(3-(3-metil-3,8-diazabiciclo[3.2.1]octano-3-carbonil)furan-2-il)-1H-pirrol-2-il)-3-metoxi-N-(isopropilsulfonil)-7H-indolo[2,1-a][2]benzazepin-10-carboxamida. Procedimiento LC/MS: % B inicial: 0; % B final: 100; Tiempo de gradiente: 3 min; Tiempo de parada: 4 min; Caudal: 4 ml/min; Longitud de onda: 220 Disolvente A: 10% de MeOH / 90% de H_2O / 0,1% de ácido trifluoracético; Disolvente B: 10% de H_2O / 90% de MeOH / 0,1% de ácido trifluoracético; Columna: XBridge 4,6 x 50 mm S5. LC/MS: tiempo de retención 3,503 min, m/z 644 (MH^+).



13-ciclohexil-6-[3-[(dimetilamino)carbonil]-5-metil-4H-1,2,4-triazol-4-il]-N-[(dimetilamino)sulfonil]-6,7-dihidro-3-metoxi-5H-indolo[2,1-a][2]benzazepin-10-carboxamida. A una mezcla de *N*-[13-ciclohexil-10-

[[[(dimetilamino)sulfonil]amino]carbonil]-6,7-dihidro-3-metoxi-5*H*-indolo[2,1-a][2]benzazepin-6-il]-*N*,*N*-dimetil-etanodiamina (19,9 mg, 0,033 mmol) en CH_2Cl_2 (1 ml) a 0ºC en N_2 se añadió pentacloruro de fósforo (20,4 mg, 0,098 mmol). La mezcla se agitó a 0ºC durante 2 horas y luego se añadió acetilhidrazina (7,25 mg, 0,098 mmol). La mezcla se agitó a 0ºC durante 1 hora y luego a TA durante 21 horas. Se añadieron a la mezcla otros 14,5 mg (0,196 mmol) de acetilhidrazina, se evaporó hasta sequedad, se añadió $PhCH_3$ (1 ml), y luego se agitó a 120ºC durante 6 horas. La mezcla se enfrió entonces hasta temperatura ambiente y luego se evaporó. El residuo se diluyó con MeOH y se purificó usando HPLC de fase inversa preparativa Shimadzu-VP obteniendo la sal TFA del producto usando el procedimiento de separación: Disolvente A= 10% de MeOH–90% de H_2O–0,1% de TFA, Disolvente B= 90% de MeOH–10% de H_2O–0,1% de TFA, % B inicial= 60, % B final= 90, Tiempo de gradiente = 10 min, Tiempo de parada= 12 min, Caudal = 30 ml/min, Columna: Xterra Prep MS C18 5u 30x50mm, Recolección de fracciones: 7,02 – 7,62 min. (Detección UV a 220 nm). La LS/MS se llevó a cabo usando instrumentación Shimadzu-VP con detección UV a 220 nm y Waters Micromass. Procedimiento HPLC: Disolvente A= 10% de MeOH–90% de H_2O–0,1% de TFA, Disolvente B= 90% de MeOH–10% de H_2O–0,1% de TFA, % B inicial= 0, % B final= 100, Tiempo de gradiente = 2 min, Tiempo de parada= 3 min, Caudal = 5 ml/min, Columna: Xterra MS C18 S7 3,0 x 50mm; (ES+) m/z $(M+H)^+$ = 648,41, HPLC R_t = 1,787 min. Procedimiento HPLC: Disolvente A= 5% de MeCN–95% de H_2O–10 mM NH_4OAc, Disolvente B= 95% de MeCN–5% de H_2O–10 mM NH_4OAc, % B inicial= 0, % B final= 100, Tiempo de gradiente = 2 min, Tiempo de parada= 3 min, Caudal = 5 ml/min, Columna: Phenomenex Lina C18 5um 3,0 x 50mm;

(ES+) m/z $(M+H)^+$ = 648,38, HPLC R_t = 1,260 min. La HPLC analítica se llevó a cabo usando instrumentación Shimadzu-VP con detección UV a 254 nm y 256 nm. Procedimiento de HPLC analítica: Disolvente A= 5% de MeCN–95% de H_2O–0,1% de TFA, Disolvente B= 95% de MeCN–5% de H_2O–0,1% de TFA, % B inicial= 10, % B final= 100, Tiempo de gradiente = 10 min, Tiempo de parada= 20 min, Caudal = 1 ml/min, Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 um; R_t = 10,46 min; Columna: Waters Xbridge Fenil 4,6 x 150 mm, 3,5 um; R_t = 9,42 min.



13-ciclohexil-6-[3-[(dimetilamino)carbonil]-4H-1,2,4-triazol-4-il]-N-[(dimetilamino)sulfonil]-6,7-dihidro-3-metoxi-5H-indolo[2,1-a][2]benzazepin-10-carboxamida. Este ejemplo se preparó de una forma similar a la descrita usando formilhidrazina como pareja de acoplamiento. Purificación por HPLC de fase inversa preparativa Shimadzu-VP obteniendo la sal TFA del producto usando el procedimiento de separación: Disolvente A= 10% de MeOH–90% de H_2O–0,1% de TFA, Disolvente B= 90% de MeOH–10% de H_2O–0,1% de TFA, % B inicial= 40, % B final= 90, Tiempo de gradiente = 10 min, Tiempo de parada= 12 min, Caudal = 30 ml/min, Columna: Xterra Prep MS C18 5u 30x50mm, Recolección de fracciones: 9,57 – 9,99 min. (Detección UV a 220

nm). La LS/MS se llevó a cabo usando instrumentación Shimadzu-VP con detección UV a 220 nm y Waters Micromass. Procedimiento HPLC: Disolvente A= 10% de MeOH–90% de H_2O–0,1% de TFA, Disolvente B= 90% de MeOH–10% de H_2O–0,1% de TFA, % B inicial= 0, % B final= 100, Tiempo de gradiente = 2 min, Tiempo de parada= 3 min, Caudal = 5 ml/min, Columna: Xterra MS C18 S7 3,0 x 50mm; (ES+) m/z $(M+H)^+$ = 634,45, HPLC R_t = 1,785 min. La HPLC analítica se llevó a cabo usando instrumentación Shimadzu-VP con detección UV a 254 nm y 256 nm. Procedimiento de HPLC analítica: Disolvente A= 5% de MeCN–95% de H_2O–0,1% de TFA, Disolvente B= 95% de MeCN–5% de H_2O–0,1% de TFA, % B inicial= 10, % B final= 100, Tiempo de gradiente = 10 min, Tiempo de parada= 20 min, Caudal = 1 ml/min, Columna: Waters Sunfire C-18, 4,6 x 150 mm, 3,5 um; R_t = 10,33 min; Columna: Waters Xbridge Fenil 4,6 x 150 mm, 3,5 um; R_t = 9,44 min.

Procedimientos biológicos

Los compuestos demostraron actividad contra NS5B de VHC como se determina en los siguientes ensayos de RdRp (ARN polimerasa dependiente de ARN) en VHC.

Clonación, expresión y purificación de NS5B RdRp de VHC. Se clonó en el vector de expresión pET21 el ADNc que codifica la proteína NS5B de VHC, genotipo 1b. La proteína se expresó con un truncamiento en el extremo C-terminal de 18 aminoácidos para potenciar la solubilidad. Se usó la línea celular competente en E. coli BL21(DE3) para la expresión de la proteína. Los cultivos

se reprodujeron a 37°C durante ~ 4 horas hasta que los cultivos alcanzaron una densidad óptica de 2,0 a 600 nm. Los cultivos se enfriaron hasta 20°C y se indujeron con IPTG 1 mM. Se añadió ampicilina nueva hasta una concentración final de 50 µg/ml y se reprodujeron las células durante la noche a 20°C.

Se lisaron los sedimentos celulares (3 l) para la purificación proporcionando 15-24 mg de NS5B purificada. El tampón de lisis estaba constituido por Tris-HCl 20 mM, pH 7,4, NaCl 500 mM, Triton X-100 al 0,5%, DTT 1 mM, EDTA 1mM, glicerol al 20%, 0,5 mg/ml de lisozima, $MgCl_2$ 10 mM, 15 ug/ml de desoxirribonucleasa I y comprimidos de inhibidor de proteasa TM completo (Roche). Después de la adición del tampón de lisis, se volvieron a suspender los sedimentos celulares congelados usando un homogeneizador de tejidos. Para reducir la viscosidad de la muestra se sometieron alícuotas del lisado a ultrasonidos en hielo usando una micropunta unida a un sonicador Branson. Se centrifugó el lisado sonicado a 100,000 x g durante 1 hora a 4°C y se filtró a través de una unidad de filtro de 0,2 µm (Corning).

La proteína se purificó usando tres etapas cromatográficas secuenciales: Heparin sepharose CL-6B, polyU sepharose 4B y Hitrap SP sepharose (Pharmacia). Los tampones de cromatografía fueron idénticos al tampón de lisis pero no contenían lisozima, desoxirribonucleasa I, $MgCl_2$ o inhibidor de proteasa y la concentración de NaCl del tampón se ajustó de acuerdo con las necesidades de carga de la proteína en la columna. Cada columna se eluyó con un gradiente de NaCl que variaba desde 5-50 volúmenes de columna

dependiendo del tipo de columna. Después de la etapa final de cromatografía, la pureza resultante de la enzima es >90% en base a un análisis de SDS-PAGE. La enzima se separó en alícuotas y se almacenó a -80°C.

Ensayo de enzima NS5B RdRp de VHC convencional. Se realizaron ensayos RdRp del genotipo 1b de VHC en un volumen final 60 µl en placas de 96 pocillos (Costar 3912). El tampón de ensayo estaba constituido por Hepes 20 mM, pH 7,5, KCl 2,5 mM, MgCl2 2,5 mM, DTT 1 mM, 1,6 U de inhibidor de ARNasa (Promega N2515), 0,1 mg/ml de BSA (Promega R3961) y 2% de glicerol. Todos los compuestos se diluyeron en serie (a la tercera parte) en DMSO y se diluyeron adicionalmente en agua tal que la concentración final de DMSO en el ensayo fue del 2%. Se usó la enzima RdRp para VHC genotipo 1b en una concentración final de 28 nM. Se usó un molde polyA a 6 nM y se usó un cebador oligo-dT12 biotinilado a 150 nM de concentración final. El molde se obtuvo comercialmente (Amersham 27-4110). El cebador biotinilado se preparó por Sigma Genosys. Se usó 3H-UTP a 0,6 µCi (UTP total 0,29 µM). Las reacciones se iniciaron mediante adición de enzima, se incubaron a 30°C durante 60 min y se detuvieron añadiendo microesferas SPA que contenían 25 µl de EDTA 50 mM (4 µg/µl, Amersham RPNQ 0007). Las placas se leyeron en un Packard Top Count NXT después de más de una hora de incubación a temperatura ambiente.

Ensayo de enzima NS5B RdRp de VHC modificado. Se llevó a cabo un ensayo de enzima modificado básicamente como se describe para el ensayo convencional salvo por lo siguiente: Se precapturó el cebador oligo dT12

biotinilado sobre microesferas de SPA revestidas de estreptavidina mezclando el cebador y las microesferas en tampón de ensayo e incubando a temperatura ambiente durante una hora. Se separó el cebador no ligado después de centrifugar. Las microesferas ligadas al cebador se volvieron a suspender en tampón Hepes 20 mM Hepes, pH 7,5 y se usaron en el ensayo en concentraciones finales de cebador 20 nM y 0,67 µg/µl de microesferas. Orden de adición en el ensayo: se añadió enzima (14 nM) al compuesto diluido seguido por la adición de una mezcla de molde (0,2 nM), 3H-UTP (0,6 µCi, 0,29 µM) y microesferas ligadas a cebador para iniciar la reacción; las concentraciones dadas son finales. Las reacciones se dejaron transcurrir durante 4 horas a 30 °C.

Se determinaron valores de CI_{50} para los compuestos usando siete [I]. Los valores de CI_{50} se calcularon a partir de la inhibición usando la fórmula y = A+((B-A)/(1+((C/x)^D))).

Preparación del ensayo FRET. Para llevar a cabo el ensayo de rastreo en VHC, se usaron placas de cultivo celular de 96 pocillos. El péptido FRET (Anaspec, Inc.) (Taliani et al., *Anal. Biochem.* **1996**, *240*, 60-67) contiene un donante de fluorescencia, EDANS, cerca de un extremo del péptido y un aceptor, DABCYL, cerca del otro extremo. La fluorescencia del péptido se extingue por transferencia de energía de resonancia intermolecular (RET) entre el donante y el aceptor, pero cuando la proteasa de NS3 corta el péptido los productos se libran de la extinción por RET y se hace aparente la fluorescencia del donante. El reactivo de ensayo se preparó como sigue: se diluye reactivo

de lisis de cultivo celular Luciferasa de Promega (#E153A) con células a 5X hasta 1X con dH_2O, se añade NaCl hasta 150 mM final, el péptido FRET se diluye hasta una concentración final 20 µM de una solución madre 2 mM.

Para preparar las placas, se tripsinizaron células de replicón del VHC, con o sin el gen informador de luciferasa Renilla y se colocan en cada uno de los pocillos de una placa de 96 pocillos con compuestos de ensayo tritiado añadidos en las columnas 3 a 12; las columnas 1 y 2 contenían un compuesto control (inhibidor de proteasa del VHC) y la fila de abajo contenía células sin compuesto. Las placas se colocan entonces en un incubador con CO_2 a 37ºC.

Ensayos. Después de la adición de los compuestos de ensayo descrita antes (Preparación de Ensayo FRET), en varios puntos, se retiró la placa y se añadió solución de azul Alamar (Trek Diagnostics, #00-100) por pocillo como medida de la toxicidad celular. Después de leer en un aparato Cytoflour 4000 (PE Biosystems), las placas se lavaron con PBS y luego se usaron para el ensayo FRET mediante la adición de 30 ul del reactivo de ensayo de péptido FRET descrito antes (Preparación de Ensayo FRET) por pocillo. La placa se colocó entonces en el aparato Cytoflour 4000 que se había ajustado a 340 de excitación/490 de emisión, modo automático para 20 ciclos y se leyó la placa en un modo cinético. De forma típica, la relación señal a ruido usando un análisis del resultado después de las lecturas fue de al menos la tercera parte. Como alternativa, después de la lectura con azul Alamar, las placas se lavaron con PBS, se añadieron 50 ul de DMEM (rico en glucosa) sin rojo fenol y se usaron entonces las placas para el ensayo de luciferasa usando el Sistema de

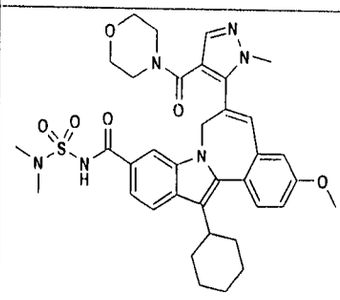
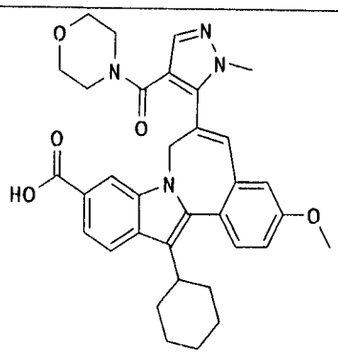
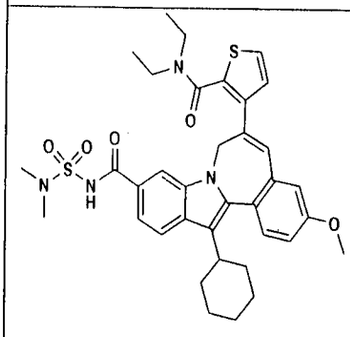
Ensayo de Luciferasa Dual-Glo de Promega.

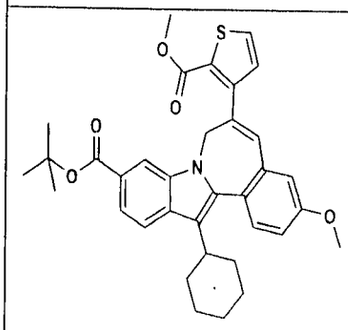
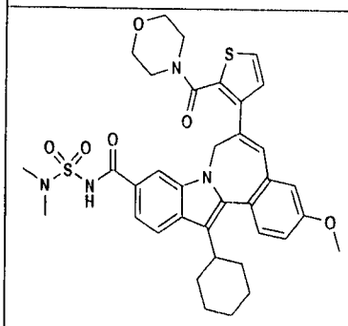
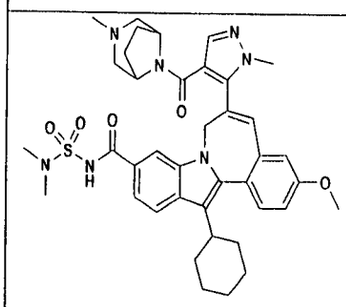
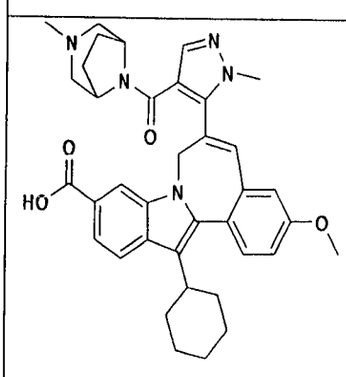
El análisis del compuesto se determinó por cuantificación de la inhibición relativa del replicón del VHC y los valores de toxicidad relativa. Para calcular los valores de toxicidad, se fijaron como 100% no tóxicos las señales de fluorescencia con azul Alamar de los pocillos control. Las señales individuales de cada uno de los pocillos de compuesto de ensayo se dividieron entonces por la señal control promedio y se multiplicaron por 100% para determinar la citotoxicidad porcentual. Para calcular los valores de inhibición del replicón del VHC se obtuvo un valor de referencia de los dos pocillos que contenían la mayor cantidad de inhibidor de proteasa del VHC al finalizar el período de ensayo. Estos valores fueron similares a los obtenidos de células Huh-7 no tratadas.

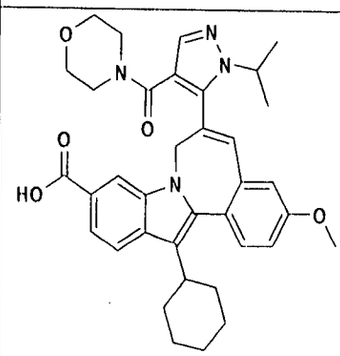
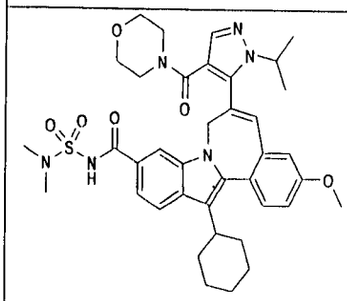
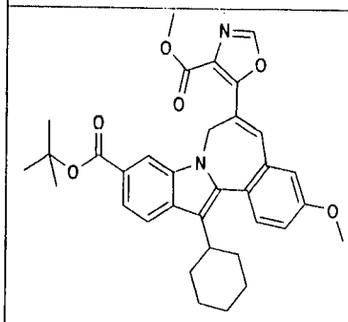
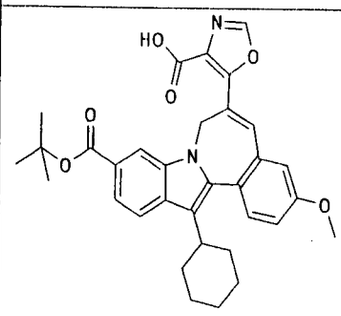
Los valores de referencia se restaron entonces de la señal promedio obtenida de los pocillos control y se usó este número como actividad 100%. Las señales individuales en cada uno de los pocillos de compuesto de ensayo se dividieron entonces por los valores control promedio después de restar el valor de referencia y se multiplicaron por 100% para determinar la actividad porcentual. Los valores de CE_{50} para la valoración del inhibidor de proteasa se calcularon como la concentración que causa una reducción del 50% en la actividad de FRET o luciferasa. Los dos valores generados para la placa de compuesto, citotoxicidad porcentual y actividad porcentual se usaron para determinar los compuestos de interés para posteriores análisis.

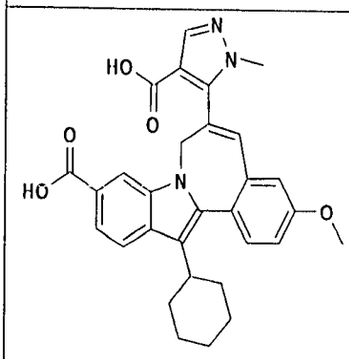
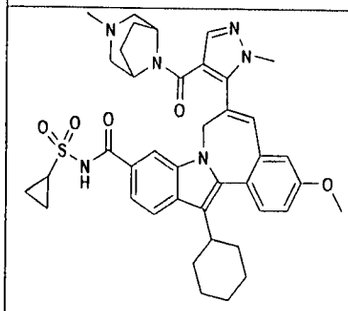
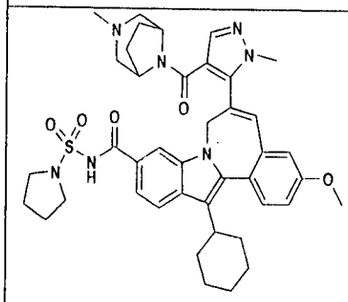
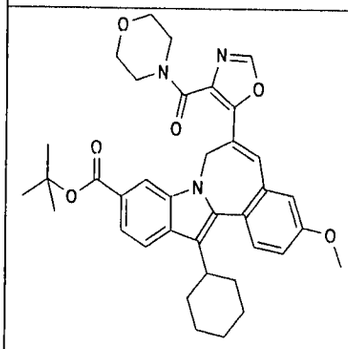
Los datos representativos para algunos compuestos se presentan en la Tabla 1.

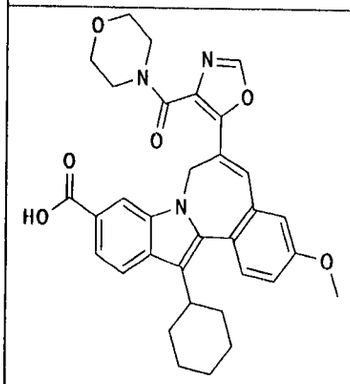
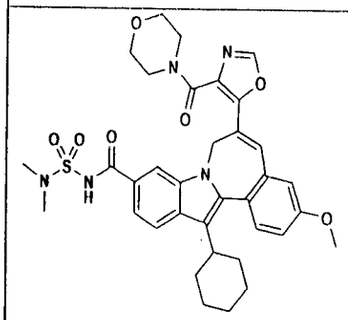
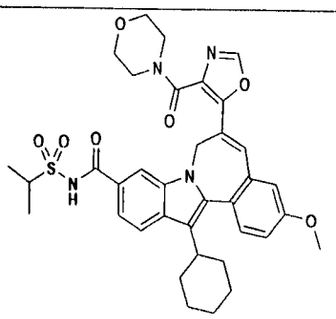
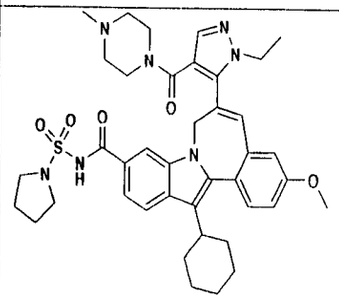
Tabla 1.

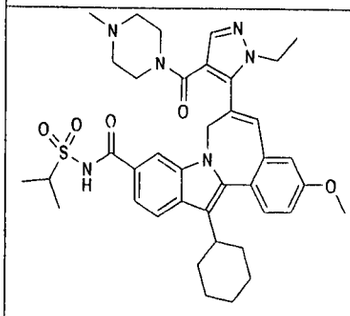
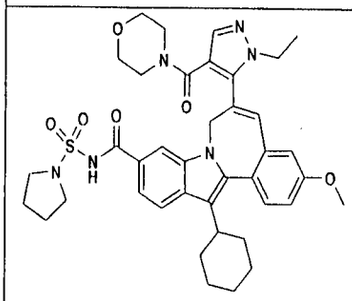
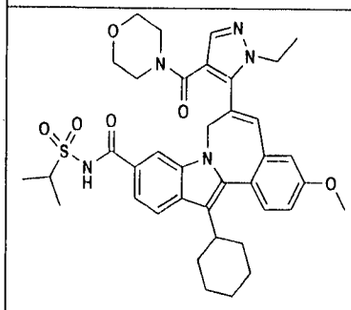
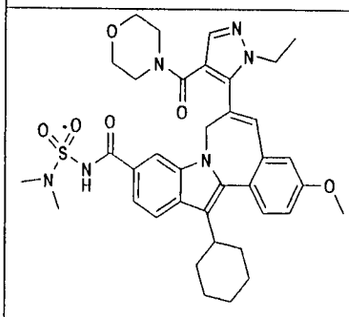
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B

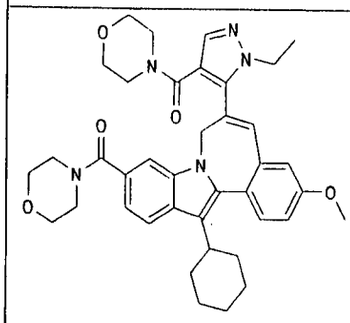
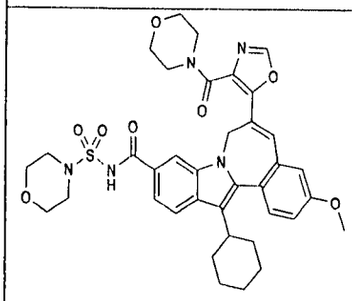
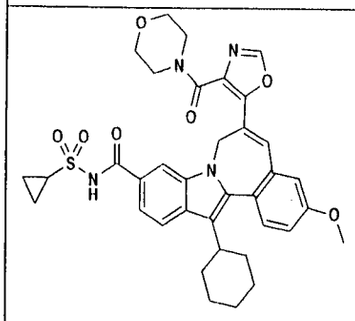
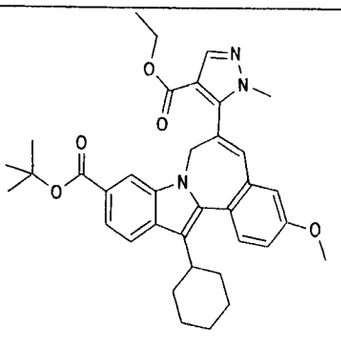
Estructura	CI_{50} (μM)	CE_{50} (μM)
		
	B	B
	B	B
	A	B

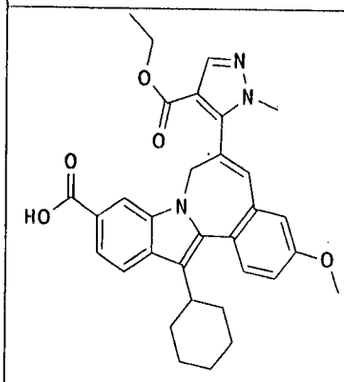
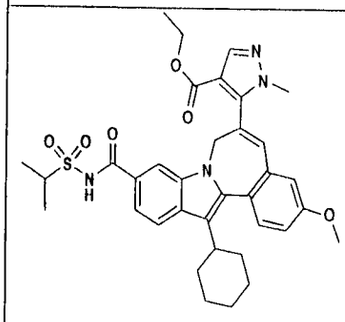
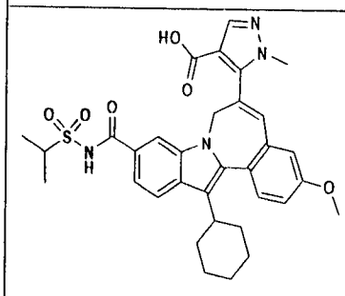
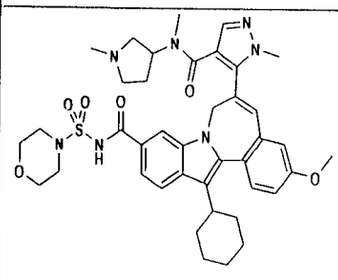
Estructura	CI_{50} (µM)	CE_{50} (µM)
	B	B
	B	B
	D	D
	D	D

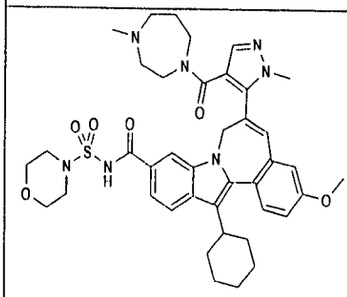
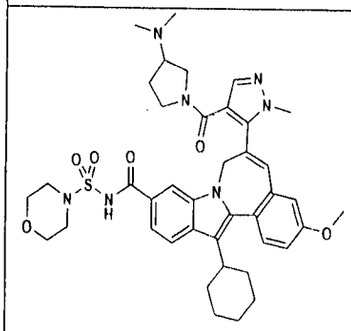
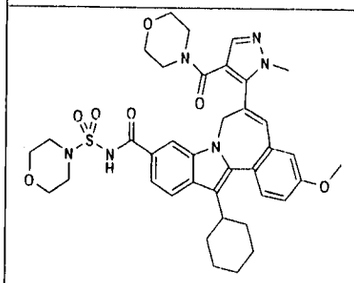
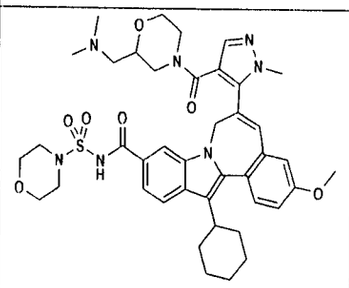
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	D
	B	B
	B	B
	D	D

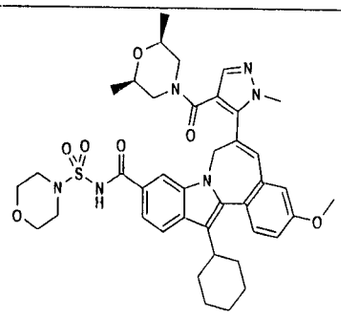
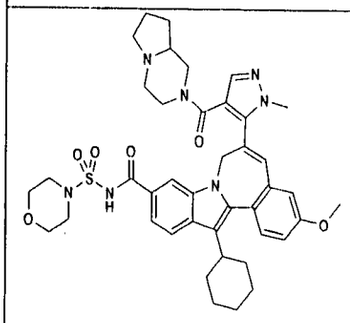
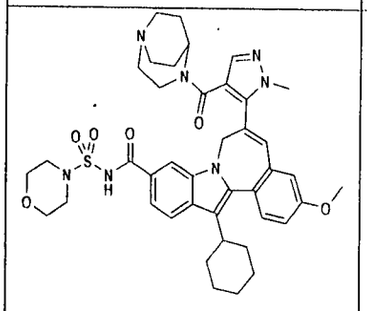
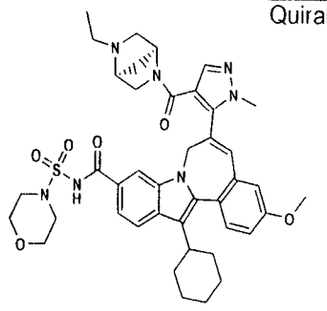
Estructura	CI_{50} (µM)	CE_{50} (µM)
	B	B
	B	B
	B	B
	B	B

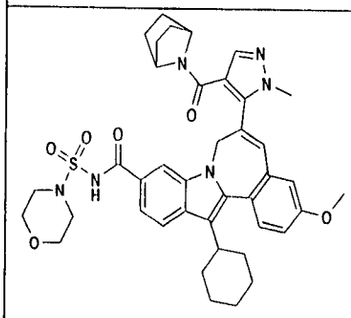
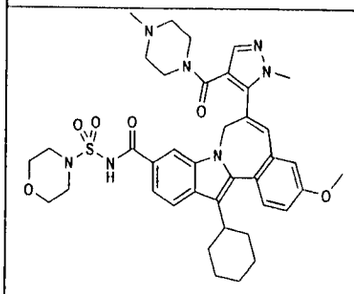
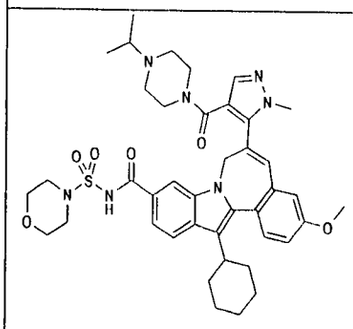
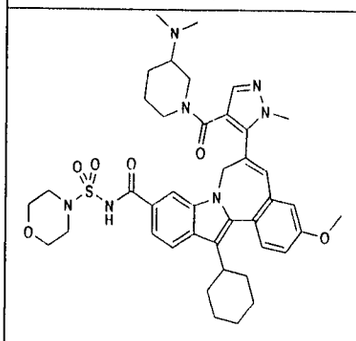
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
	B	B

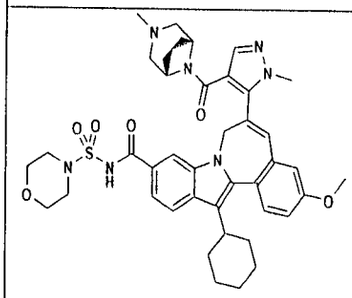
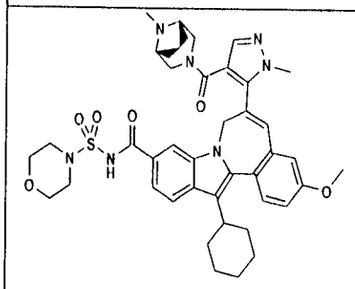
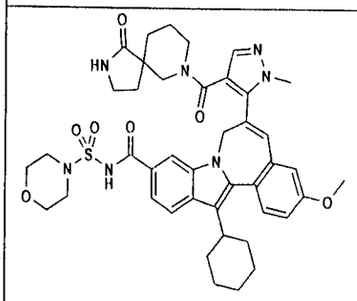
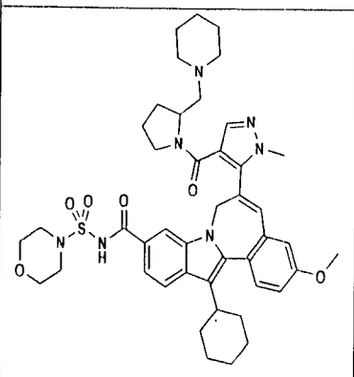
Estructura	CI_{50} (μM)	CE_{50} (μM)
	A	B
	B	B
	B	B
	D	B

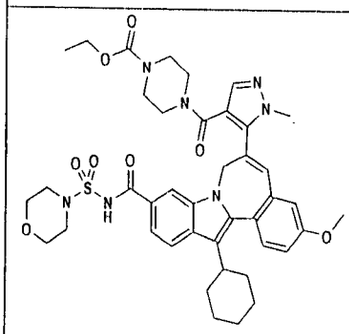
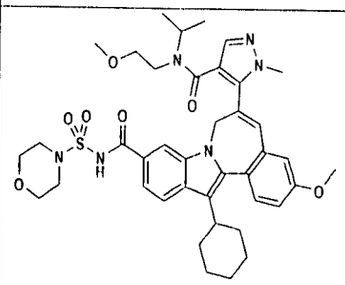
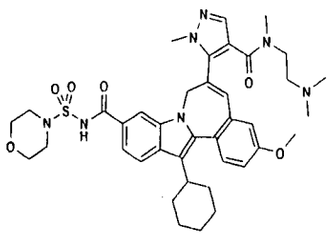
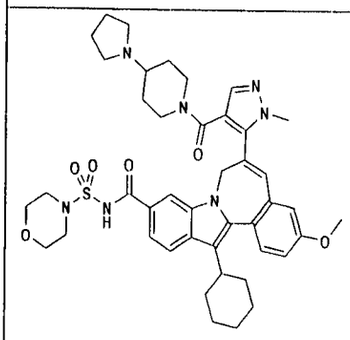
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	
	B	B

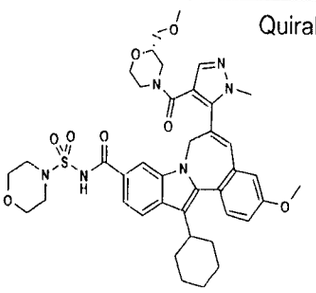
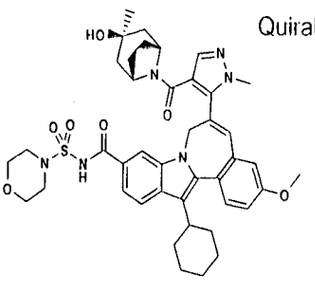
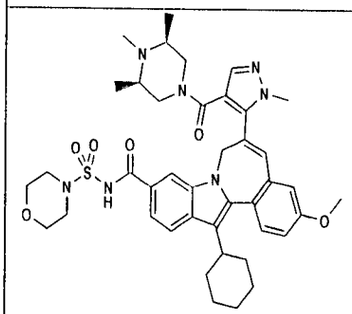
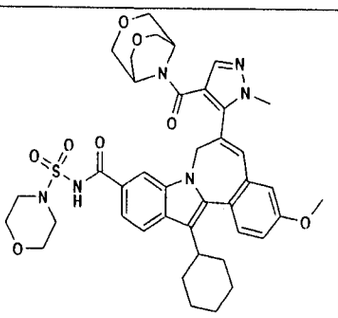
Estructura	CI_{50} (μM)	CE_{50} (μM)
	C	B
	B	B
	C	B
	B	B

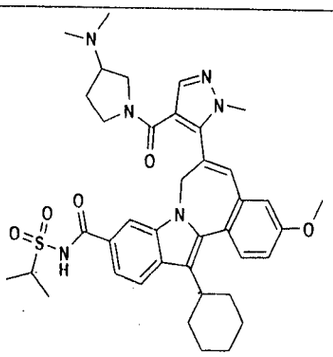
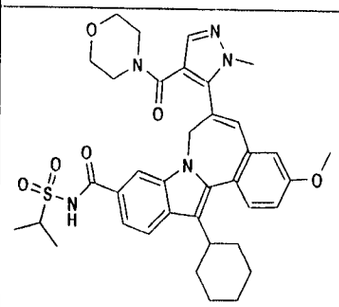
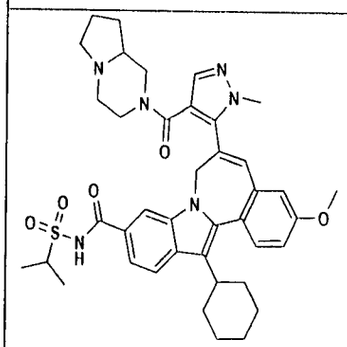
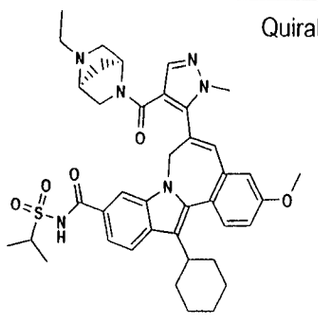
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
Quiral 	B	B

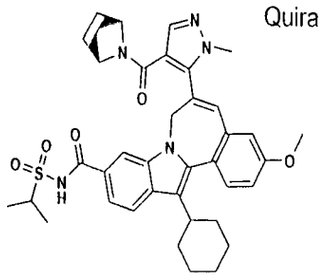
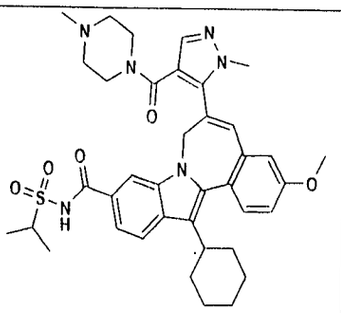
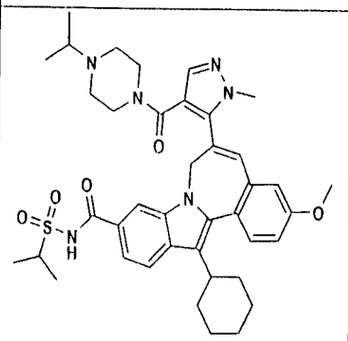
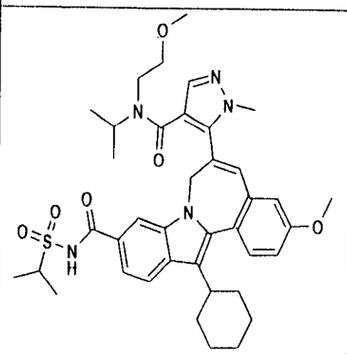
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
	B	B

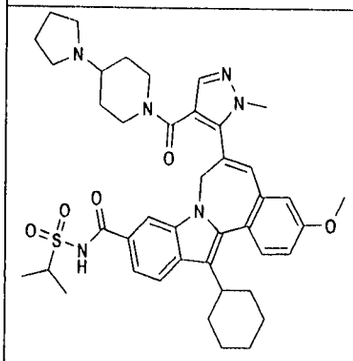
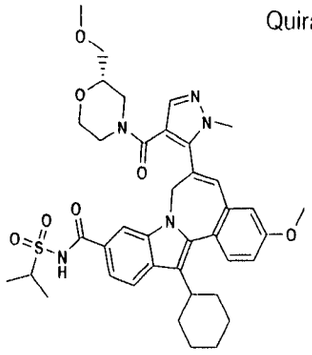
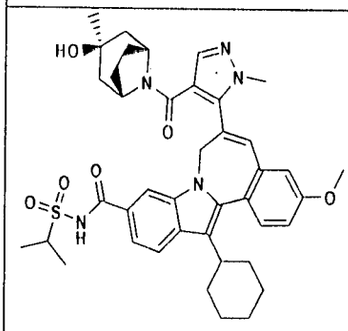
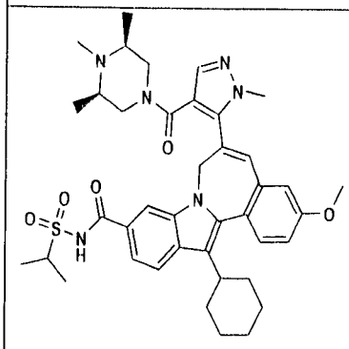
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
	B	B

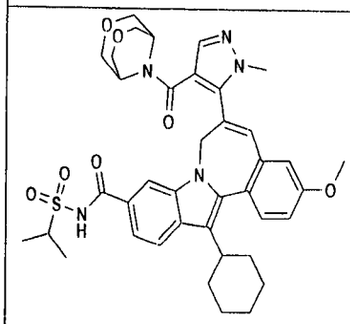
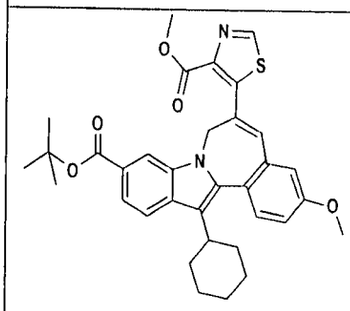
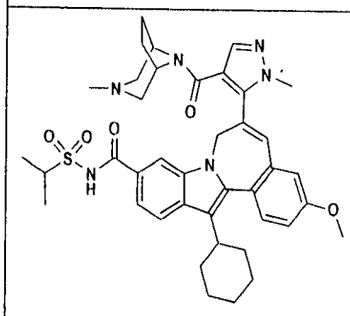
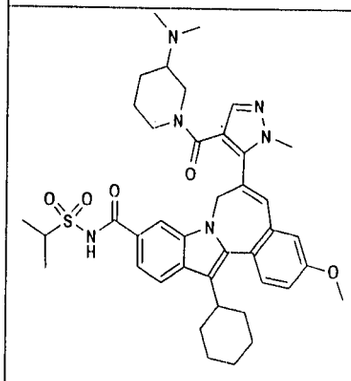
Estructura	CI_{50} (µM)	CE_{50} (µM)
	B	B
	B	B
	B	B
	B	A

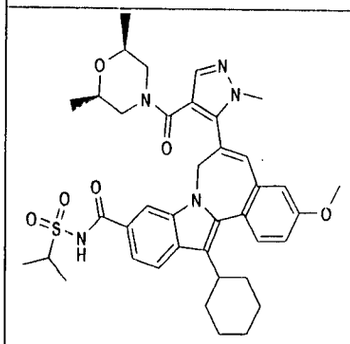
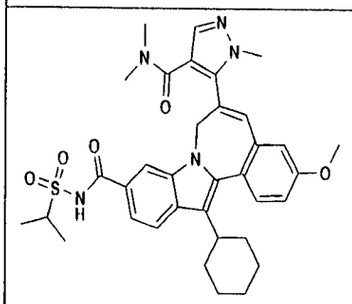
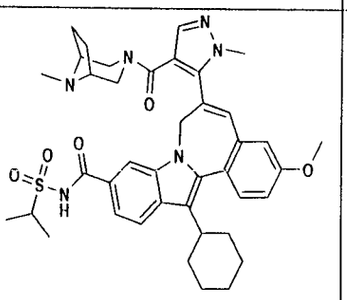
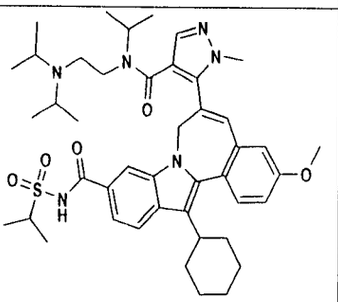
Estructura	CI_{50} (μM)	CE_{50} (μM)
 Quiral	B	B
 Quiral	B	B
	B	B
	B	B

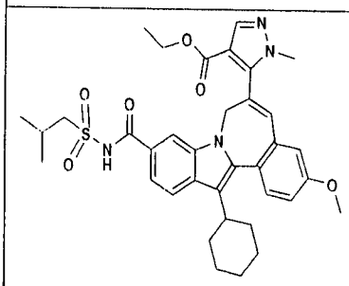
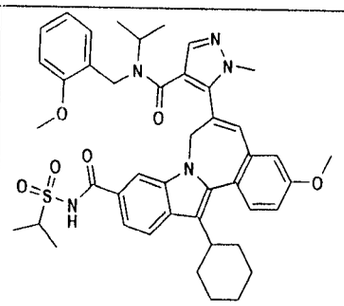
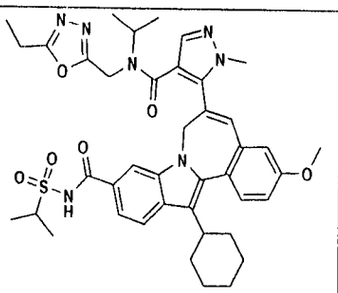
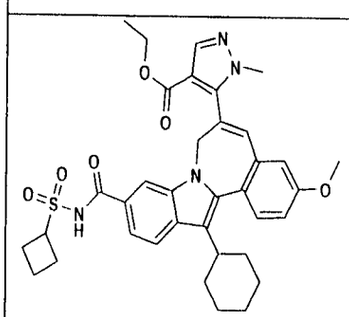
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
Quiral 	B	B

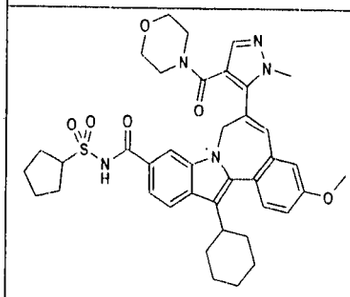
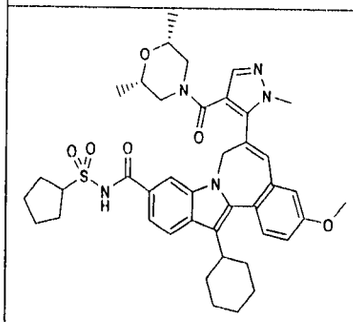
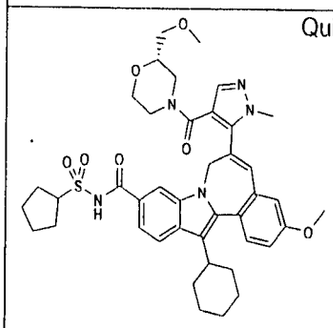
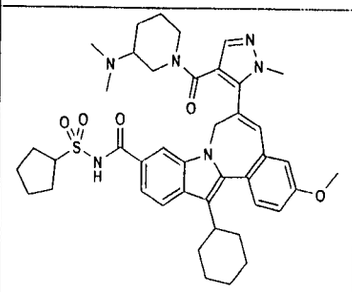
Estructura	CI_{50} (μM)	CE_{50} (μM)
Quiral 	B	B
	B	B
	B	B
	B	B

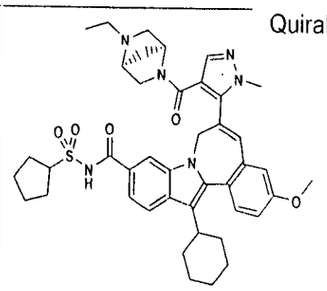
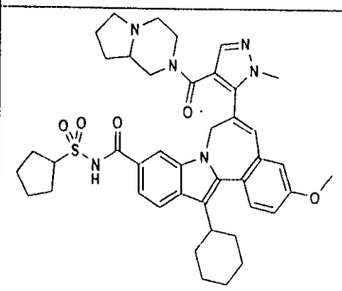
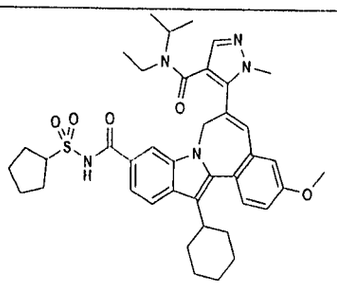
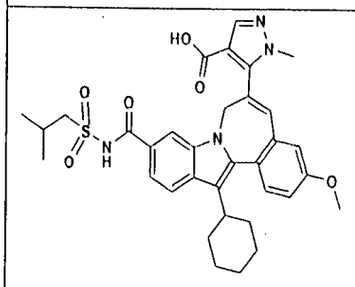
Estructura	CI_{50} (µM)	CE_{50} (µM)
	B	B
Quiral 	B	B
	B	B
	B	B

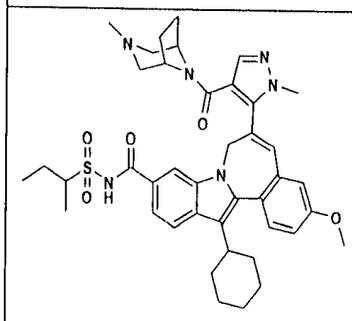
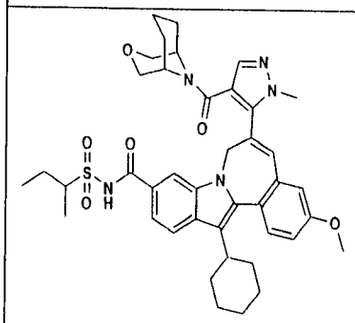
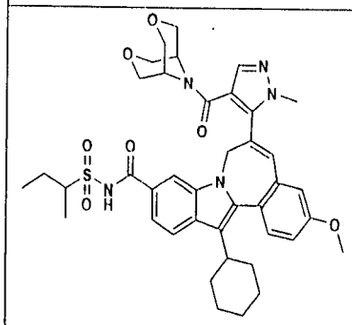
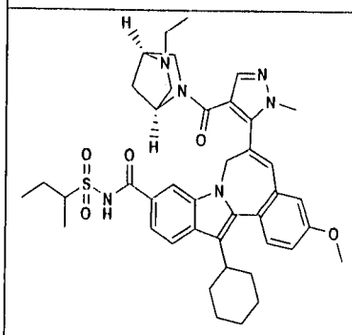
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
		
	B	B
	B	B

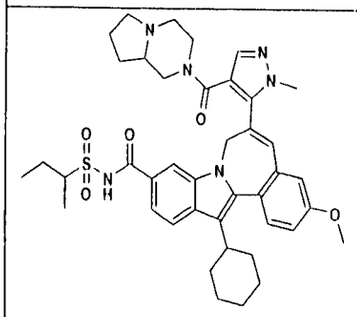
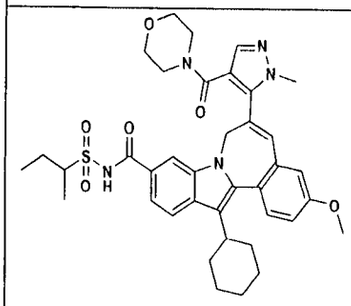
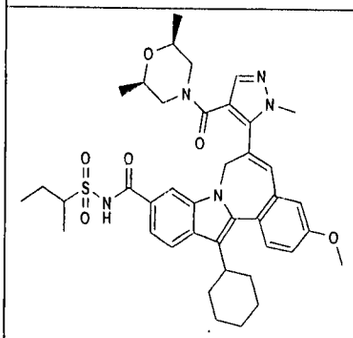
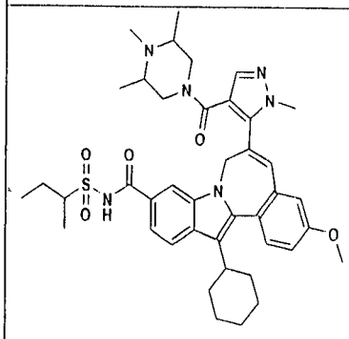
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
	B	B

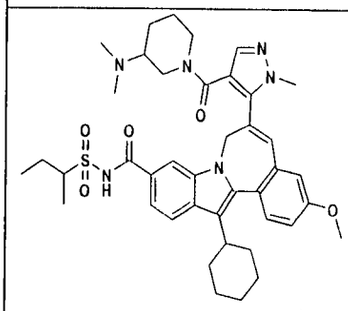
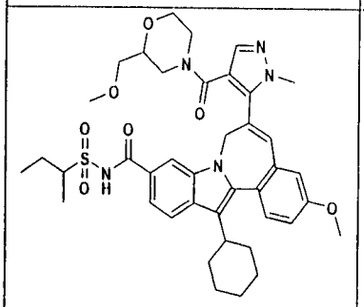
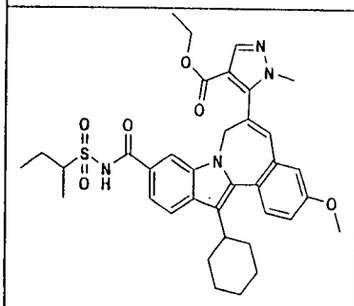
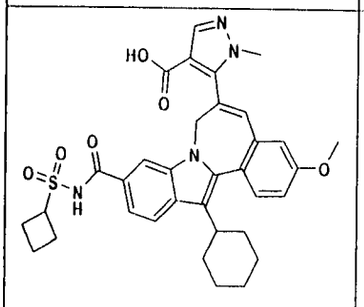
Estructura	CI_{50} (µM)	CE_{50} (µM)
	B	
	B	
	B	
	B	

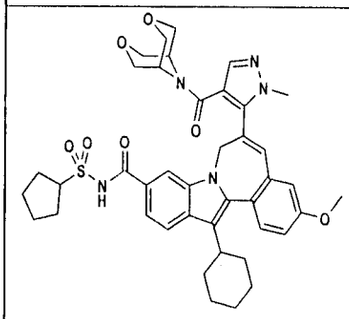
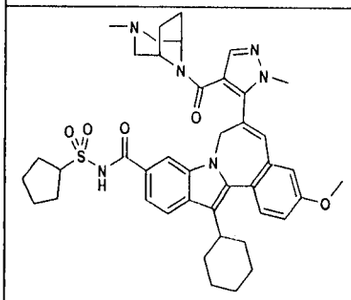
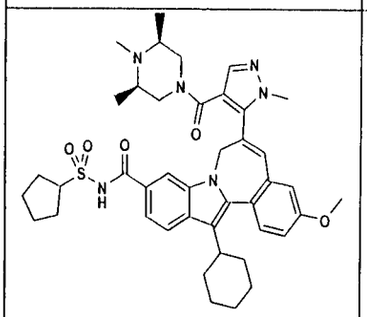
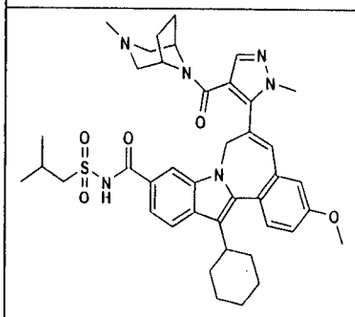
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	
Quiral 	B	B
	B	

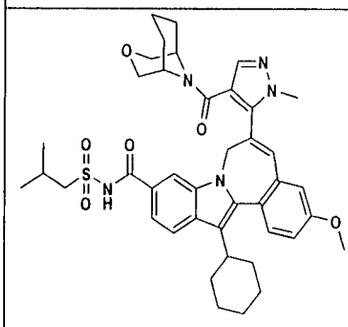
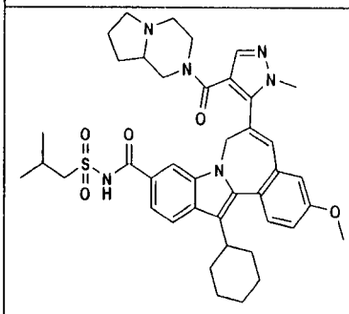
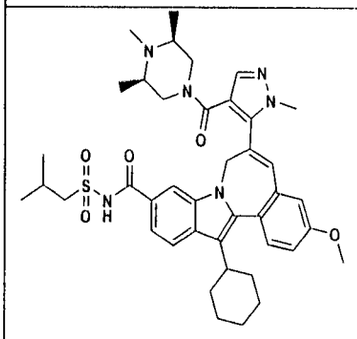
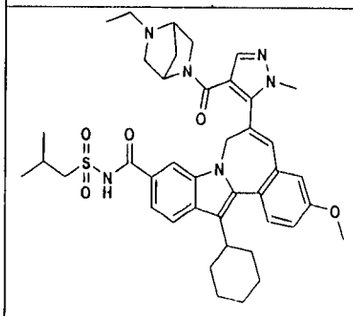
Estructura	CI_{50} (μM)	CE_{50} (μM)
Quiral 	B	
	B	
	B	
		

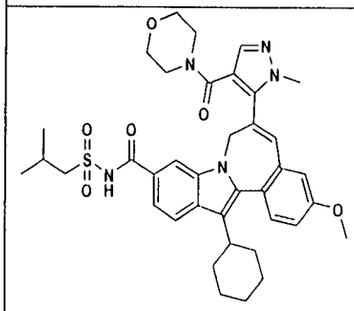
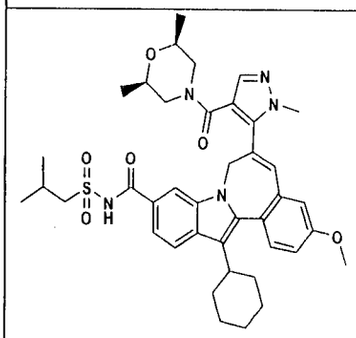
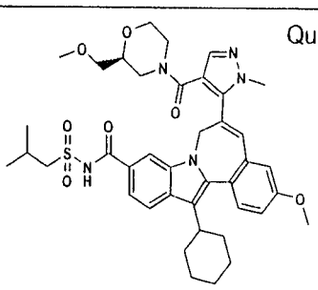
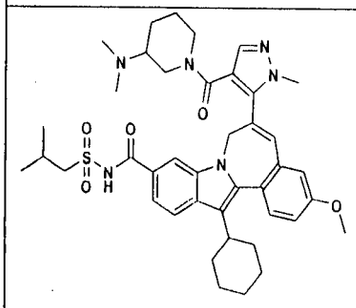
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
	B	

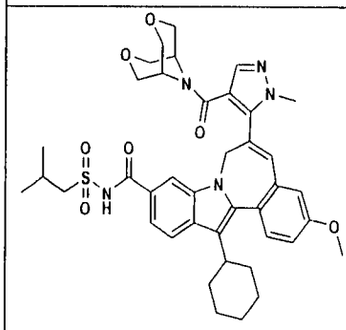
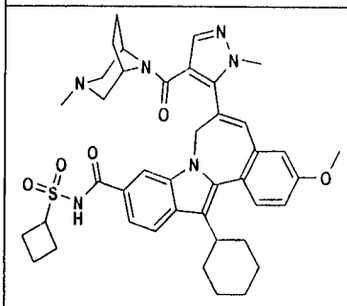
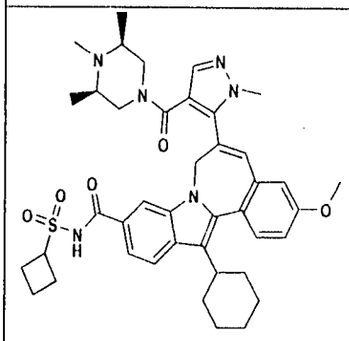
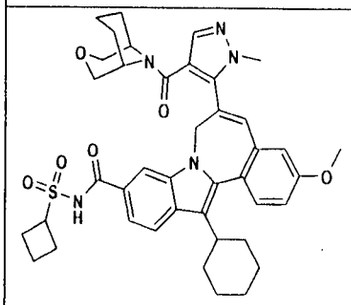
Estructura	CI_{50} (µM)	CE_{50} (µM)
	B	
	B	B
	B	B
	B	B

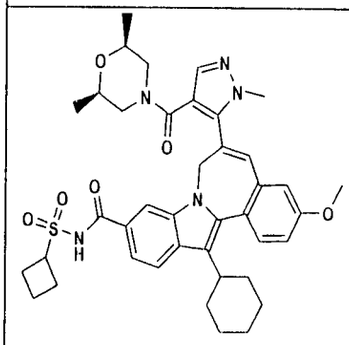
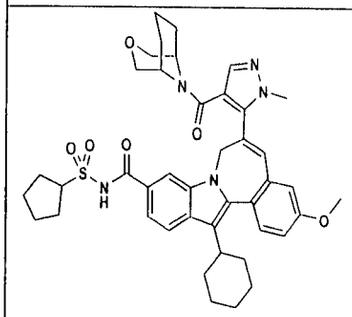
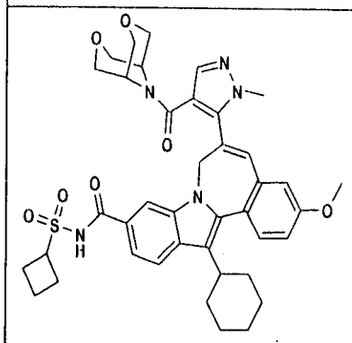
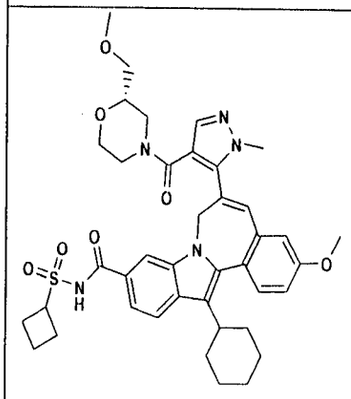
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	
	B	

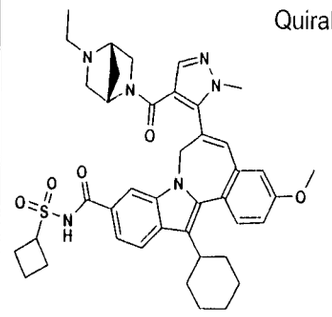
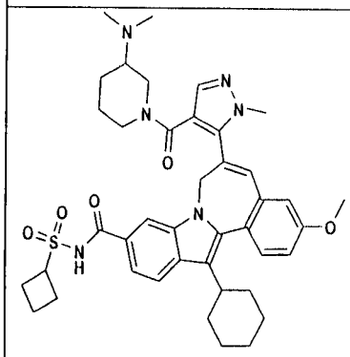
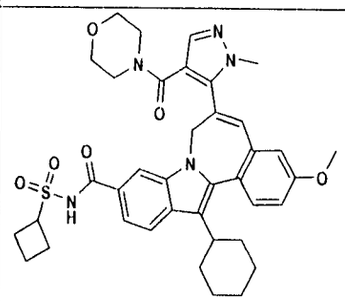
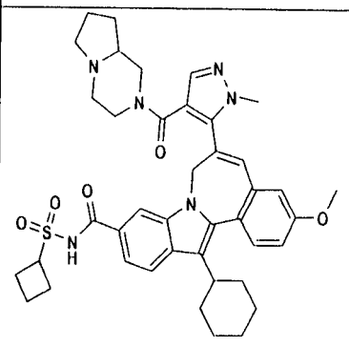
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	
	B	B

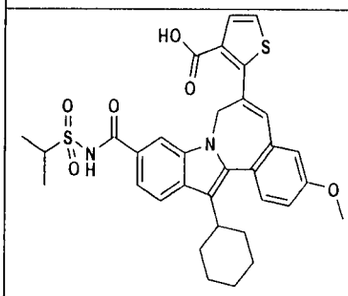
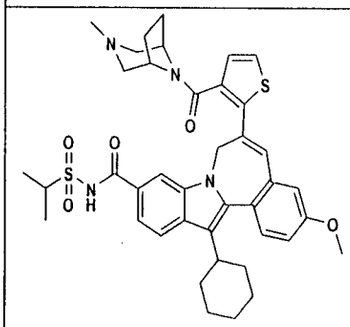
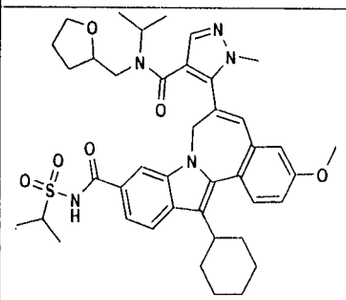
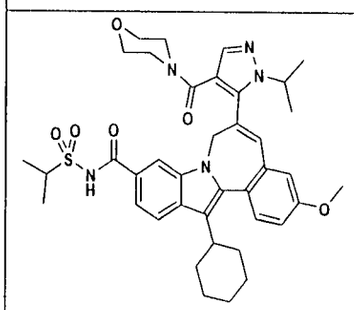
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	
	B	
	B	

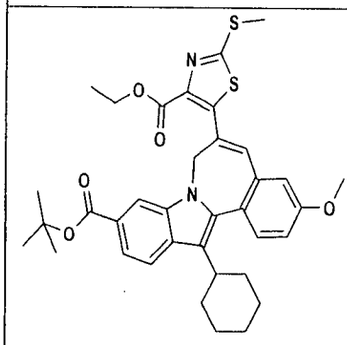
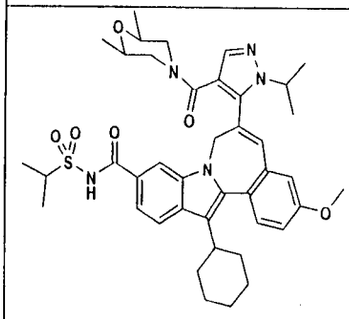
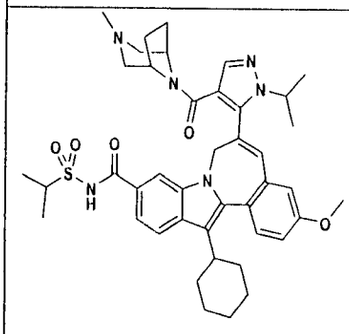
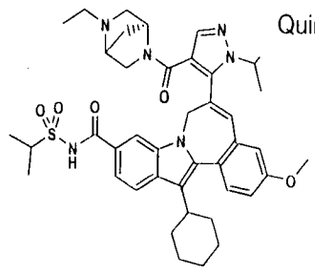
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
Quiral 	B	B
	B	

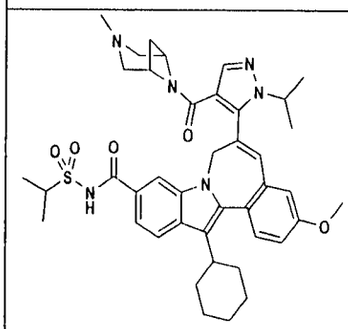
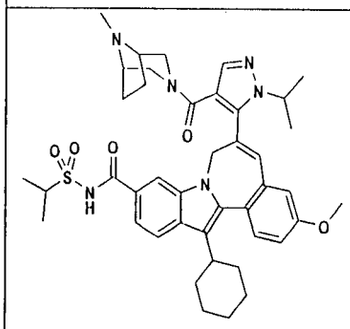
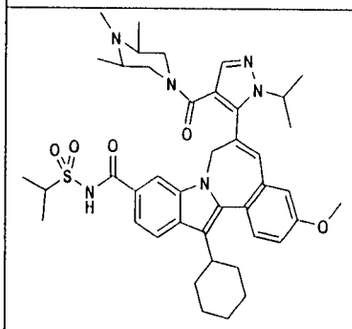
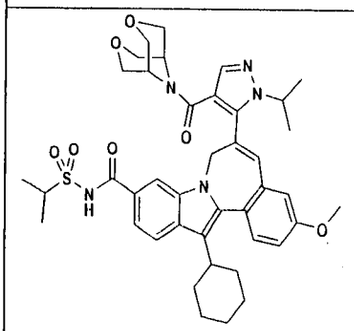
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	
	B	B

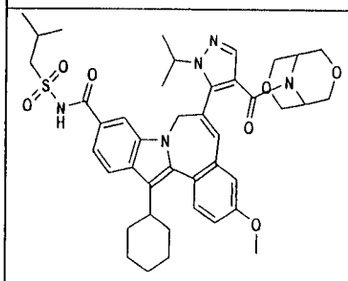
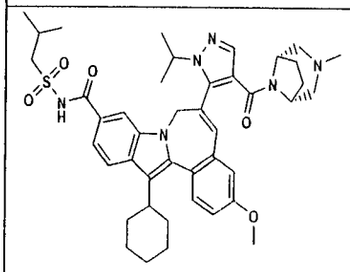
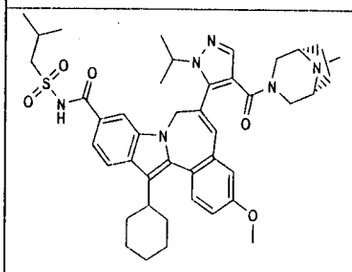
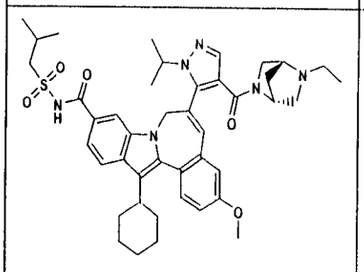
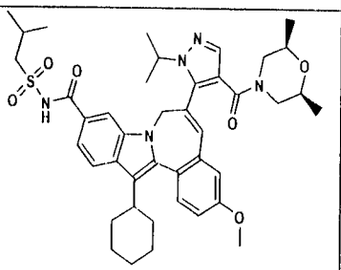
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	
	B	B
	B	B
	B	B

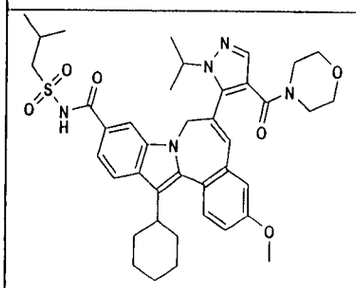
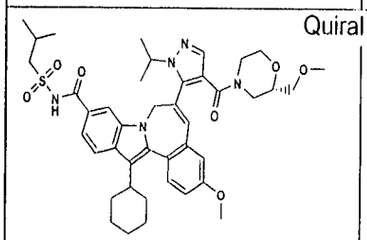
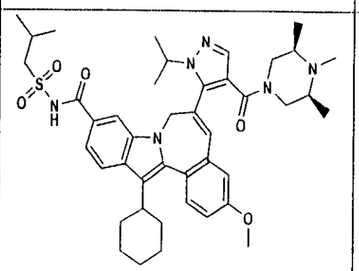
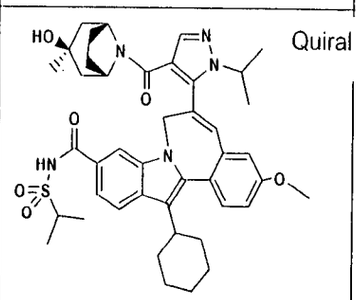
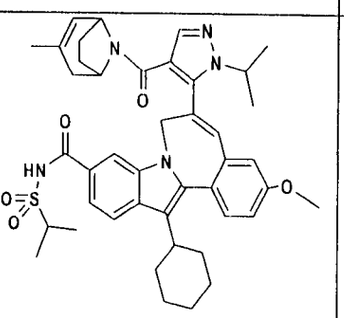
Estructura	CI_{50} (μM)	CE_{50} (μM)
Quiral 	B	B
	B	B
	B	B
	B	B

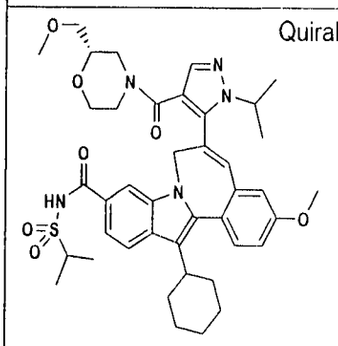
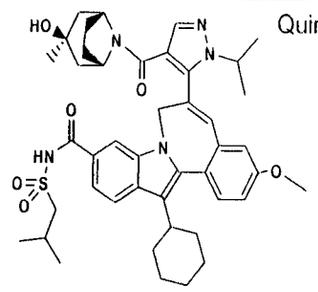
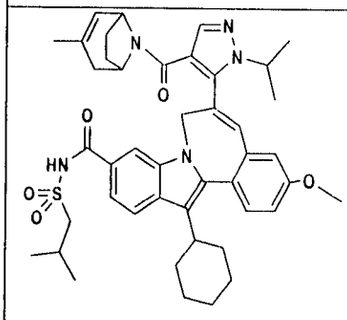
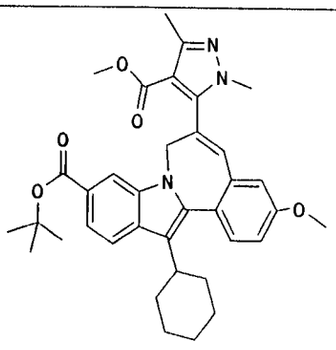
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	D
	B	B
	B	B
	B	B

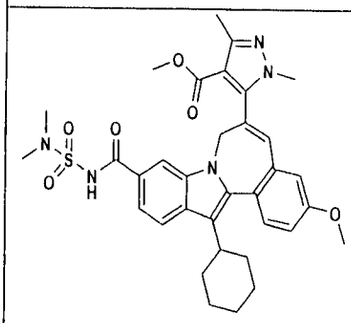
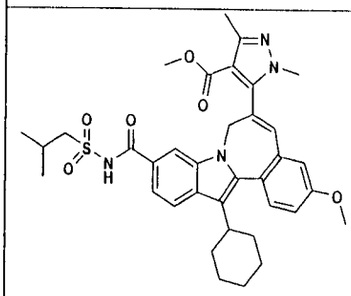
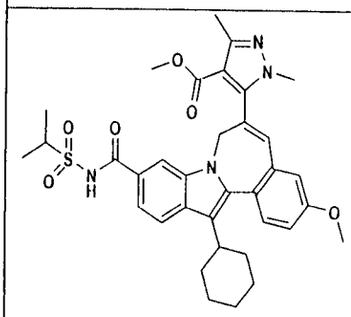
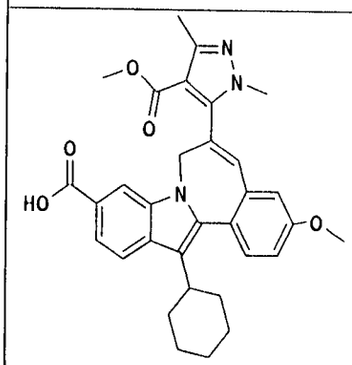
Estructura	CI_{50} (μM)	CE_{50} (μM)
		
	B	B
	B	B
Quiral 	B	B

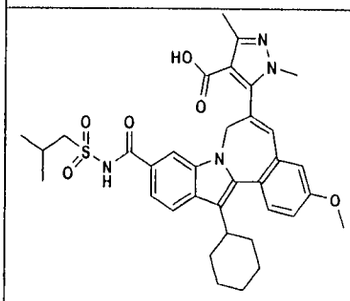
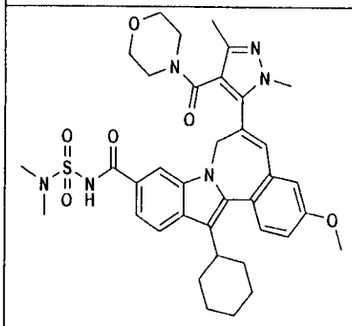
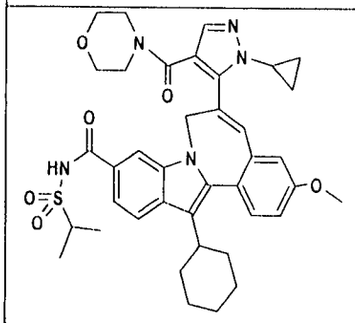
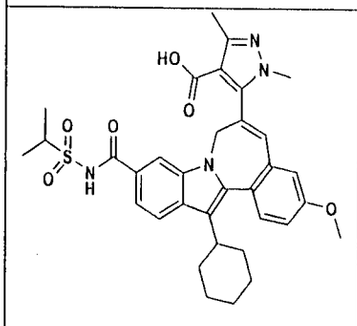
Estructura	CI_{50} (µM)	CE_{50} (µM)
	B	B
	B	B
	B	B
	B	B

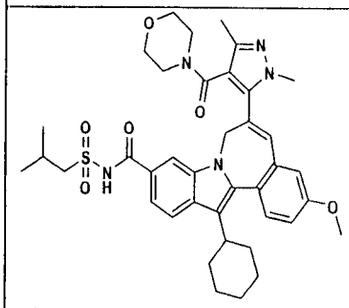
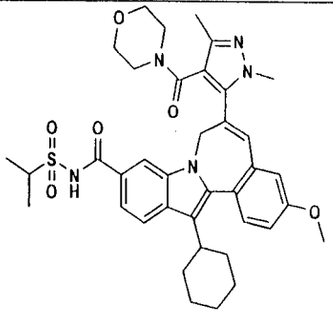
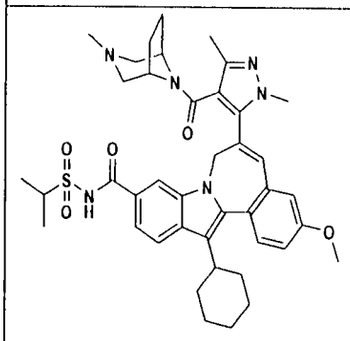
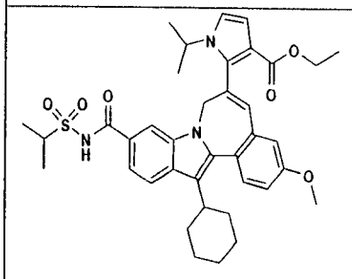
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
	B	B
	B	B

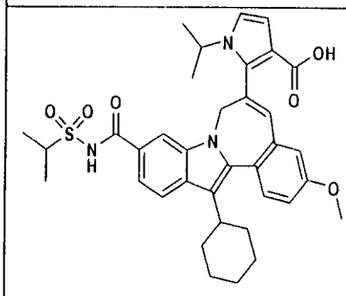
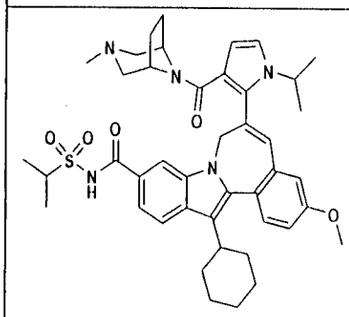
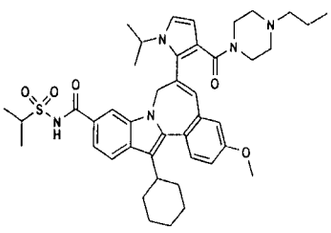
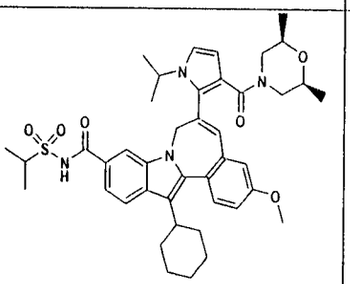
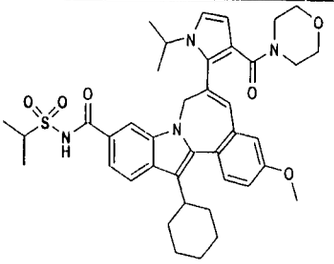
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
Quiral 	B	B
	B	B
Quiral 	B	B
	B	B

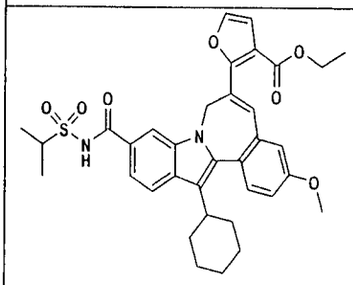
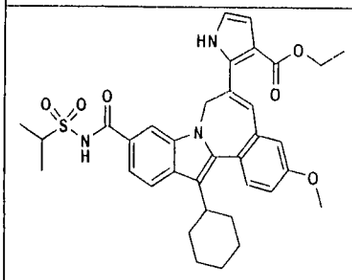
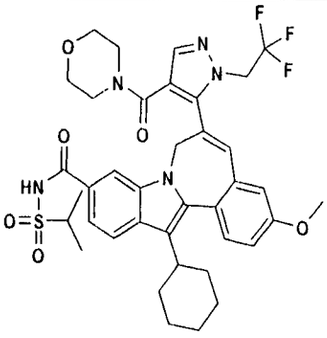
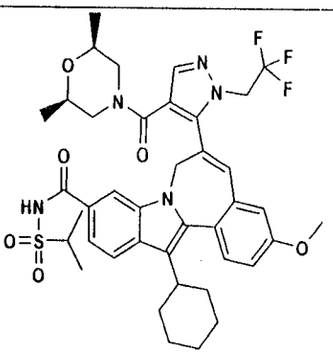
Estructura	CI_{50} (μM)	CE_{50} (μM)
 Quiral	B	B
 Quiral	B	B
	B	B
		

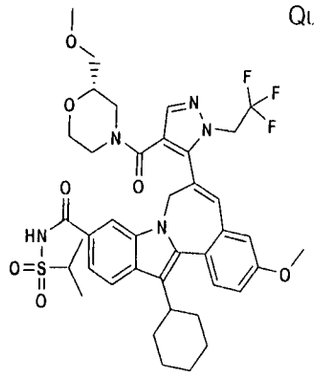
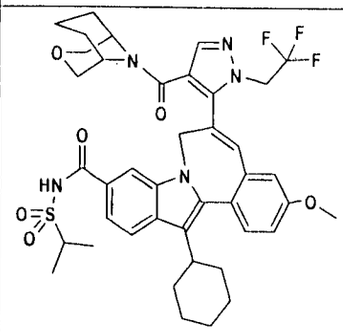
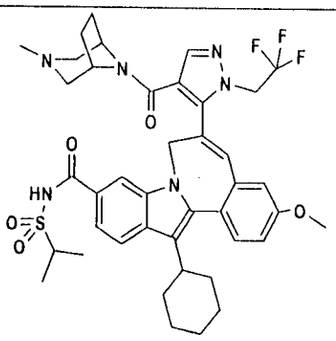
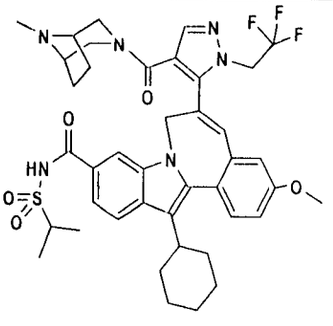
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	
	B	
		
	B	B

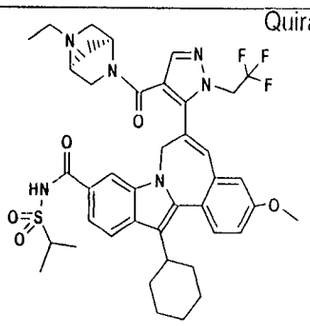
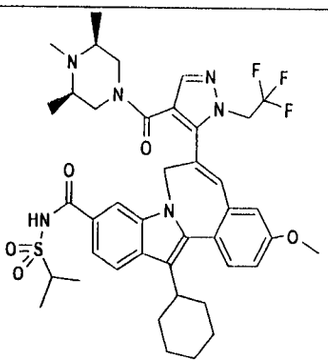
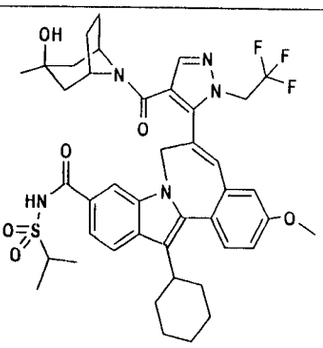
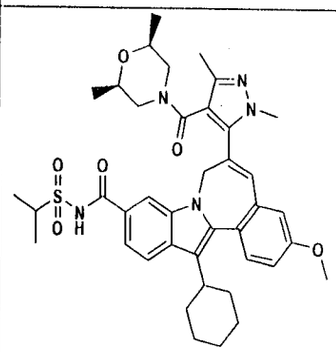
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	D
	B	B
	B	B
	B	A

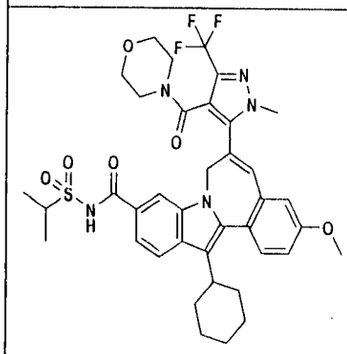
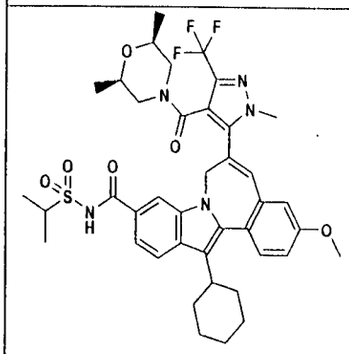
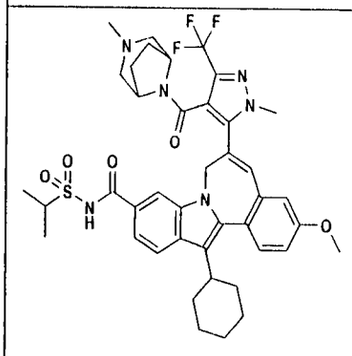
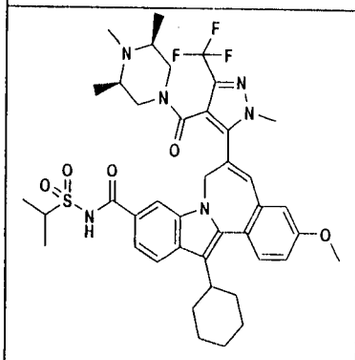
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
		

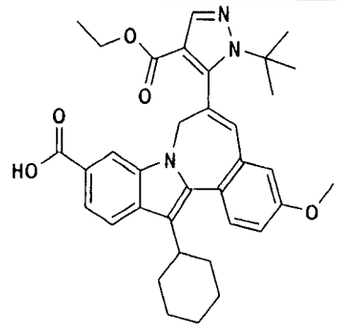
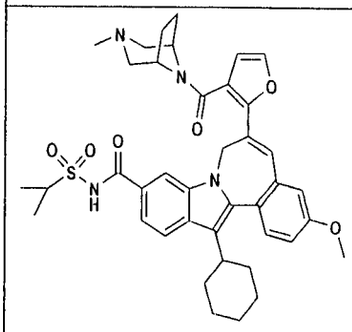
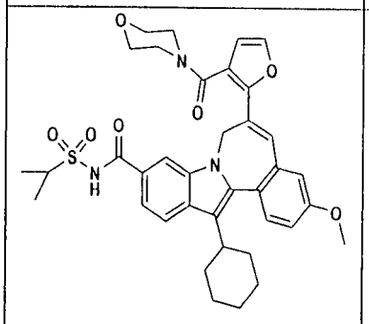
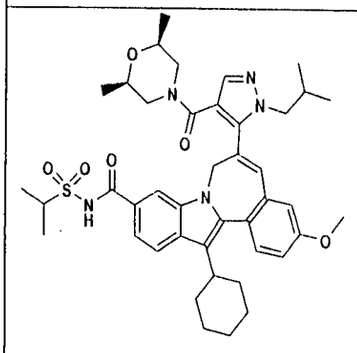
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	A
	B	B
	B	B
	B	B
	B	B

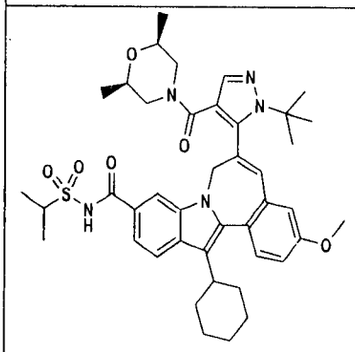
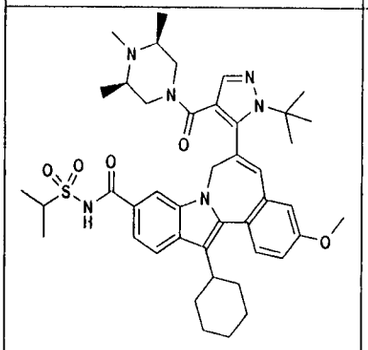
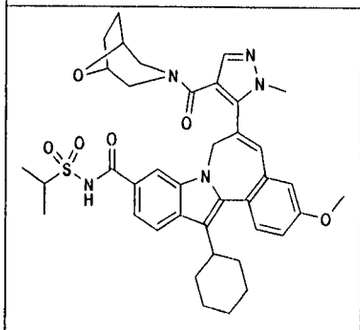
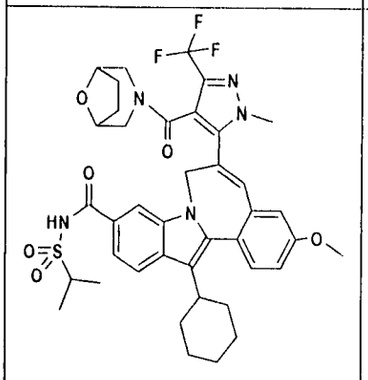
Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	A
	B	B
	B	B
	B	B

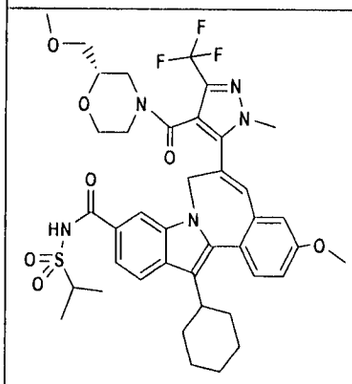
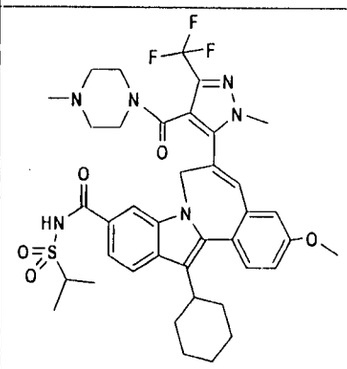
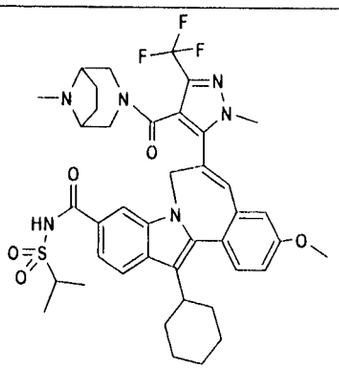
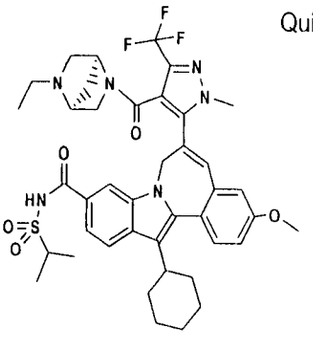
Estructura	CI_{50} (μM)	CE_{50} (μM)
Quiral 	B	B
	B	B
	B	B
	B	B

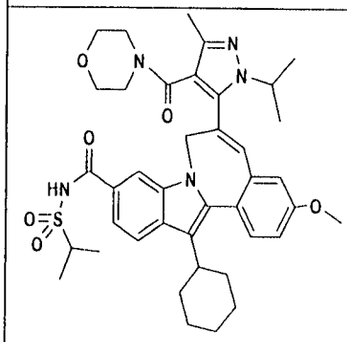
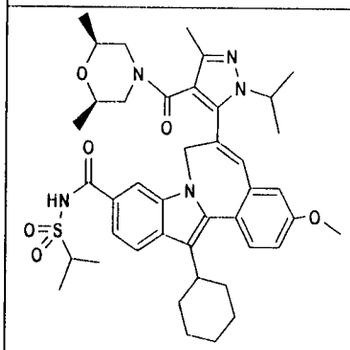
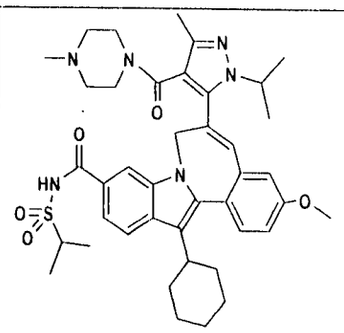
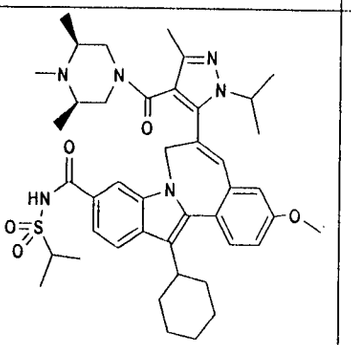
Estructura	CI_{50} (μM)	CE_{50} (μM)
Quiral 	B	B
	B	B
	B	B
	B	B

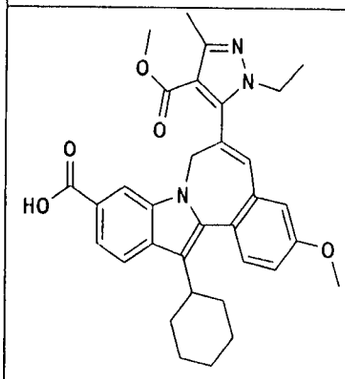
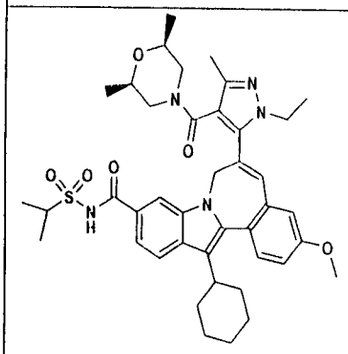
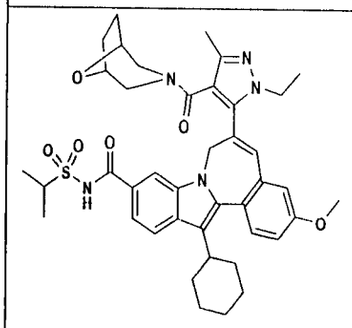
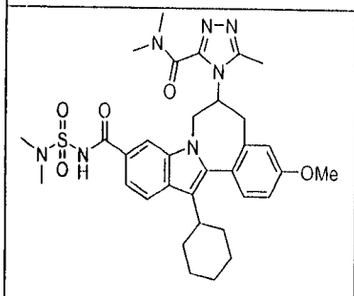
Estructura	CI_{50} (μM)	CE_{50} (μM)
	C	B
	C	B
	B	B
	B	B

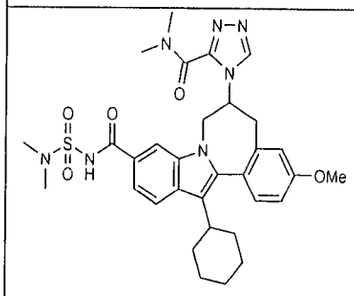
Estructura	CI_{50} (μM)	CE_{50} (μM)
		
	B	B
	B	B
	B	B

Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	C	B
	B	B

Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
Quiral 	B	B

Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B
	B	B
	B	B
	B	B

Estructura	CI_{50} (μM)	CE_{50} (μM)
		
		
		
	B	B

Estructura	CI_{50} (μM)	CE_{50} (μM)
	B	B

A>0,5 μM; B 0,001 μM – 0,5 μM; C <0,02 μM pero no se determinó un valor exacto; D>0,04 μM; pero no se determinó un valor exacto.

Composiciones farmacéuticas y procedimientos de tratamiento

Los compuestos demuestran actividad contra NS5B de VHC y pueden ser útiles para tratar VHC e 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 comprende además un compuesto que tiene actividad contra VIH.

Otro aspecto de la invención es una composición en la que el compuesto que tiene actividad contra VIH es un interferón. Otro aspecto de la invención es cuando el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón consenso, interferón alfa 2A e interferón linfoblastoide tau.

Otro aspecto de la invención es una composición en la que el compuesto

que tiene actividad contra VIH es una ciclosporina. Otro aspecto de la invención es cuando la ciclosporina es ciclosporina A.

Otro aspecto de la invención es una composición en la que el compuesto que tiene actividad contra VIH se selecciona del grupo constituido por interleuquina 2, interleuquina 6, interleuquina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T auxiliares tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

Otro aspecto de la invención es una composición en la que el compuesto que tiene actividad contra VIH es eficaz para inhibir la fusión de una diana seleccionada de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamblaje del VHC, salida del HCV, proteína NS5A del VHC, IMPDH y un análogo nucleósido 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 farmacéuticamente aceptable, un interferón y ribavirina.

Otro aspecto de la invención es un procedimiento para inhibir la función del replicón del VHC que comprende poner en contacto el replicón del VHC con un compuesto o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un procedimiento para inhibir la función de la proteína NS5B de VHC que comprende poner en contacto la proteína NX5B del VHC con un compuesto o una de sus sales farmacéuticamente aceptables.

Otro aspecto de la invención es un procedimiento para 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 aceptable. En otra realización, el compuesto es eficaz para inhibir la función del replicón del VHC. En otra realización, el compuesto es eficaz para inhibir la función de la proteína NS5B del VHC.

Otro aspecto de la invención es un procedimiento para 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 aceptable, en combinación con (antes de, después o a la vez) de otro compuesto que tiene actividad contra el VHC.

Otro aspecto de la invención es el procedimiento en el que el compuesto que tiene actividad contra el VHC es un interferón.

Otro aspecto de la invención es el procedimiento en el que el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón consenso, interferón alfa 2A e interferón linfoblastoide tau.

Otro aspecto de la invención es el procedimiento en el que el otro compuesto que tiene actividad contra el VHC es una ciclosporina.

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 el VHC se selecciona de interleuquina 2, interleuquina 6, interleuquina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T auxiliares tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina

Otro aspecto de la invención es el procedimiento en el que el otro compuesto que tiene actividad contra el VHC es eficaz para inhibir la función de una diana seleccionada de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B de VHC, entrada del VHC, ensamblaje del VHC, salida del VHC, proteína NS5A de VHC, IMPDH y un análogo nucleósido 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 el VHC es eficaz para inhibir la función de una diana en el ciclo de vida del VHC distinto de la proteína NS5B del VHC.

"Terapéuticamente eficaz" se refiere a la cantidad de agente requerida

para proporcionar un beneficio significativo al paciente tal como es conocido por los expertos en el campo de la hepatitis e infección por VHC.

"Paciente" se refiere a una persona infectada con el virus VHC y adecuado para tratamiento tal como es conocido por los expertos en el campo de la hepatitis e infección por VHC.

"Tratamiento", "terapia", "pauta", "infección por VHC" y términos relacionados se usan tal como es conocido por los expertos en el campo de la hepatitis e infección por VHC.

Los compuestos de esta invención se administran generalmente como composiciones farmacéuticas formadas por una cantidad terapéuticamente eficaz de un compuesto o su sal farmacéuticamente aceptable y un vehículo farmacéuticamente aceptable y pueden contener excipientes convencionales. Una cantidad terapéutica es aquella que se necesita para proporcionar un beneficio significativo al paciente. Vehículos farmacéuticamente aceptables son aquellos vehículos conocidos convencionalmente que tienen perfiles de seguridad aceptables. Las composiciones incluyen todas las formas sólidas y líquidas habituales que incluyen cápsulas, comprimidos, pastillas y polvos, así como suspensiones líquidas, jarabes, elixires y soluciones. Las composiciones se preparan usando técnicas convencionales de formulación y por lo general para las composiciones se usan excipientes convencionales (tales como agentes ligantes y humectantes) y vehículos (tales como agua y alcoholes).

Las composiciones sólidas se formulan normalmente en dosis unitarias y se prefieren composiciones que proporcionan de aproximadamente 1 a 1000 mg de ingrediente activo por dosis. Algunos ejemplos de dosificación son1 mg, 10 mg, 100 mg, 250 mg, 500 mg y 1000 mg. Por lo general, otros agentes estarán presentes en un intervalo de dosis unitaria similar a los agentes de la clase usada clínicamente. De forma típica esto es 0,25-1000 mg/unidad.

Las composiciones líquidas están normalmente en intervalos de dosis unitaria. Por lo general, la composición líquida estará en un intervalo de dosis unitaria 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. Por lo general, otros agentes estarán presentes en un intervalo de dosis unitaria similar a los agentes de la clase usada clínicamente. De forma típica esto es 1-100 mg/ml.

La invención comprende todos los modos de administración convencionales; se prefieren procedimientos orales y parenterales. Por lo general, la pauta de dosificación será similar a la de otros agentes usados clínicamente. De forma típica, la dosis diaria variará de 1-100 mg/kg de peso corporal. Por lo general, se requiere más compuesto por vía oral y menos por vía parenteral. Sin embargo, la pauta de dosificación específica, se determinará por un médico usando el criterio médico habitual.

La invención también comprende procedimientos en los que el compuesto se administra en un tratamiento de combinación. Es decir, el compuesto se puede usar en combinación con, pero de forma separada de,

otros agentes útiles en el tratamiento de hepatitis e infección por VHC. En estos procedimientos de combinación, el compuesto se administrará por lo general en una dosis diaria de 1-100 mg/kg de peso corporal por día en combinación con otros agentes. Los otros agentes se administrarán por lo general en las cantidades usadas terapéuticamente. Sin embargo, la pauta de dosificación específica, se determinará por un médico usando el criterio médico habitual.

En la Tabla 2 se presentan algunos ejemplos de compuestos adecuados para composiciones y procedimientos.

Tabla 2.

Nombre comercial	**Tipo de Inhibidor o Diana**	**Empresa comercializadora**
Omega IFN	IFN-ω	Intarcia Therapeutics
BILN-2061	inhibidor de serina proteasa	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
Summetrel	antivírico	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
Roferon A	IFN-α2a	F. Hoffmann-La Roche LTD, Basilea, Suiza

Nombre comercial	Tipo de Inhibidor o Diana	Empresa comercializadora
Pegasys	IFN-α2a PEGilado	F. Hoffmann-La Roche LTD, Basilea, Suiza
Pegasys y Ribavirin	IFN-α2a PEGilado/ribavirina	F. Hoffmann-La Roche LTD, Basilea, Suiza
CellCept	inmunosupresor de IgG de VHC	F. Hoffmann-La Roche LTD, Basilea, Suiza
Wellferon	IFN-αn1 linfoblastoide	GlaxoSmithKline plc, Uxbridge, UK
Albuferon - α	IFN-α2b de albúmina	Human Genome Sciences Inc., Rockville, MD
Levovirin	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	Empresa comercializadora
Infergen A	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
ISIS 14803	antisentido	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., Nueva York, NY
JTK-003	inhibidor de RdRp	Japan Tobacco Inc., Tokio, Japón
Pegasys y Ceplene	IFN-α2a PEGilado Modulador inmune	Maxim Pharmaceuticals Inc., San Diego, CA
Ceplene	Modulador inmune	Maxim Pharmaceuticals Inc., San Diego, CA
Civacir	inmunosupresor de IgG de VHC	Nabi Biopharmaceuticals Inc., Boca Raton, FL

Nombre comercial	Tipo de Inhibidor o Diana	Empresa comercializadora
Intron A y Zadaxin	IFN-α2b/α1-timosina	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Levovirin	inhibidor de IMPDH	Ribapharm Inc., Costa Mesa, CA
Viramidine	Ribavirina Profármaco	Ribapharm Inc., Costa Mesa, CA
Heptazyme	ribozima	Ribozyme Pharmaceuticals Inc., Boulder, CO
Intron A	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron	IFN-α2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ
Rebetron	IFN-α2b/ribavirina	Schering-Plough Corporation, Kenilworth, NJ

Nombre comercial	Tipo de Inhibidor o Diana	Empresa comercializadora
Ribavirin	ribavirina	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	IFN-α2b PEGilado/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Zadazim	Modulador inmune	SciClone Pharmaceuticals Inc., San Mateo, CA
Rebif	IFN-β1a	Serono, Ginebra, Suiza
IFN-β y EMZ701	IFN-β y EMZ701	Transition Therapeutics Inc., Ontario, Canada
Batabulin (T67)	inhibidor de β-tubulina	Tularik Inc., South San Francisco, CA
Merimepodib (VX-497)	inhibidor de IMPDH	Vertex Pharmaceuticals Inc., Cambridge, MA

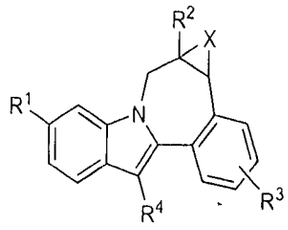
Nombre comercial	Tipo de Inhibidor o Diana	Empresa comercializadora
Telaprevir (VX-950, LY-570310)	inhibidor de serina proteasa de NS3	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
Omniferon	IFN-α natural	Viragen Inc., Plantation, FL
XTL-6865 (XTL-002)	anticuerpo monoclonal	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
HCV-796	inhibidor de replicasa de NS5B	Wyeth / Viropharma
NM-283	inhibidor de replicasa de NS5B	Idenix / Novartis
GL-59728	inhibidor de replicasa de NS5B	Gene Labs / Novartis
GL-60667	inhibidor de replicasa de NS5B	Gene Labs / Novartis
2'C MeA	inhibidor de replicasa de NS5B	Gilead
PSI 6130	inhibidor de replicasa de NS5B	Roche

Nombre comercial	Tipo de Inhibidor o Diana	Empresa comercializadora
R1626	inhibidor de replicasa de NS5B	Roche
SCH 503034	inhibidor de serina proteasa	Schering Plough
NIM811	Inhibidor de ciclofilina	Novartis
Suvus	Azul de metileno	Bioenvision
Multiferon	IFN de larga duración	Viragen/Valentis
Actilon (CPG10101)	agonista de TLR9	Coley
Interferon-β	Interferon-β-1a	Serono
Zadaxin	Immunomodulador	Sciclone
Compuestos y sales de pirazolopirimidina del documento WO-2005047288 26 de mayo de 2005	inhibidores de HCV	Arrow Therapeutics Ltd.
2'C Metil adenosine	inhibidor de replicasa de NS5B	Merck
GS-9132 (ACH-806)	inhibidor de HCV	Achillion / Gilead

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de fórmula I



I

en la que:

R^1 es CO_2R^5 o $CONR^6R^7$;

R^2 es furanilo, pirrolilo, tienilo, pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, triazolilo o tetrazolilo, y está sustituido con 0-2 sustituyentes seleccionados de oxo, amino, alquiltio, alquilo y haloalquilo, y 1 sustituyente seleccionado de CO_2R^5, $CON(R^{12})_2$ y COR^{13};

R^3 es hidrógeno, halo, alquilo, alquenilo, hidroxi, benciloxi o alcoxi;

R^4 es cicloalquilo;

R^5 es hidrógeno o alquilo;

R^6 es hidrógeno, alquilo, alquilSO_2, cicloalquilSO_2, haloalquilSO_2, $(R^9)(R^{10})NSO_2$ o $(R^{11})SO_2$;

R^7 es hidrógeno o alquilo;

R^8 es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, alquilcarbonilo, cicloalquilcarbonilo, haloalquilcarbonilo, alcoxicarbonilo, alquilSO_2, cicloalquilSO_2, haloalquilSO_2, aminocarbonilo, (alquilamino)carbonilo, (dialquilamino)carbonilo, bencilo, benciloxicarbonilo o piridinilo;

R^9 es hidrógeno o alquilo;

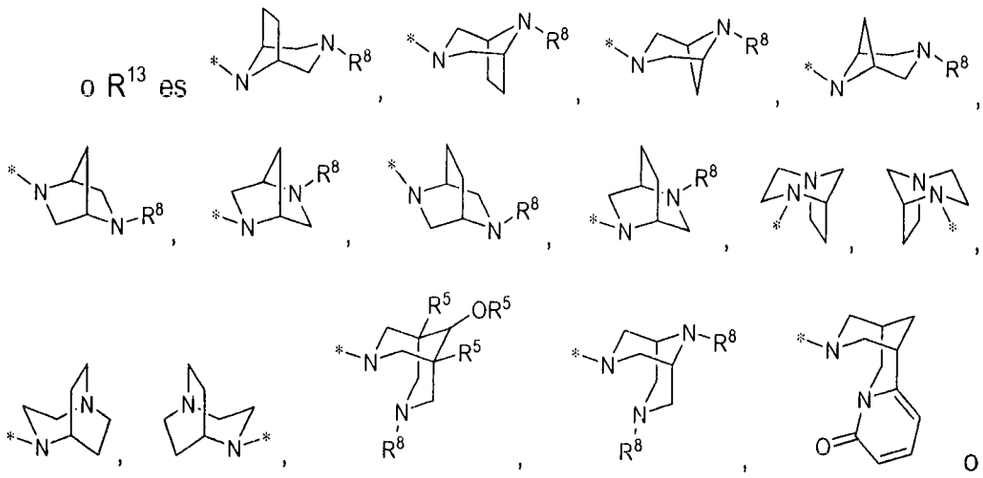
R^{10} es hidrógeno o alquilo;

R^{11} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-1 sustituyentes alquilo;

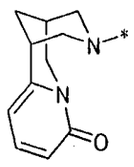
R^{12} es hidrógeno, alquilo, alcoxialquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o (R^{11})alquilo;

R^{13} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-3 sustituyentes seleccionados de alquilo, alcoxialquilo, amino, alquilamino, dialquilamino, R^{11}, aminoalquilo, (alquilamino)alquilo,

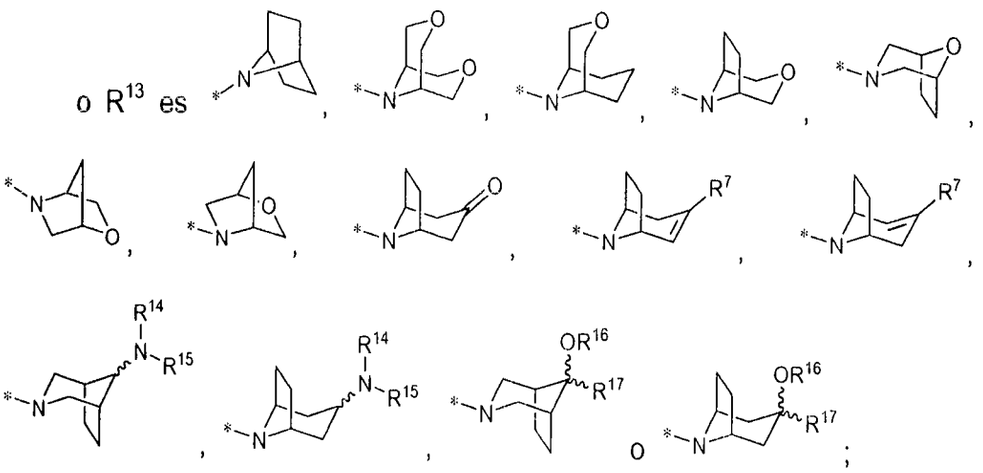
(dialquilamino)alquilo, (R^{11})alquilo o CO_2R^5;

o R^{13} es 

o

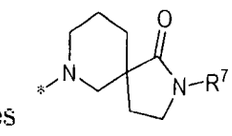
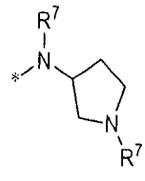
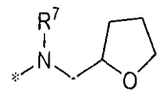
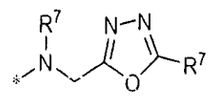
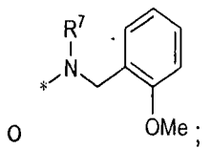


;

o R^{13} es 

;

o R^{13} es una diamina bicíclica [4.3.0] o [3.3.0] unida al carbonilo a través de un nitrógeno, y está sustituido con 0-2 sustituyentes R^8;

o R^{13} es  ,  ,  ,  ,  ;

R^{14} es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o bencilo;

R^{15} es hidrógeno, alquilo, cicloalquilo, (cicloalquil)alquilo, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o bencilo;

o $NR^{14}R^{15}$ tomados conjuntamente es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-(alquil)piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo o homomorfolinilo;

R^{16} es hidrógeno o alquilo;

R^{17} es hidrógeno, alquilo o cicloalquilo; y

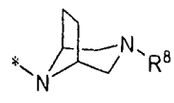
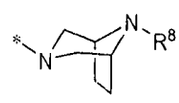
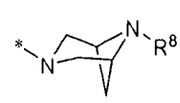
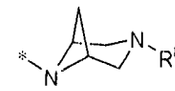
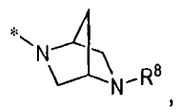
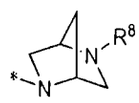
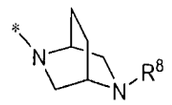
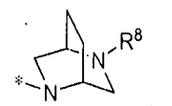
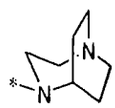
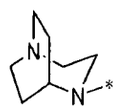
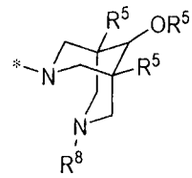
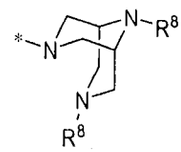
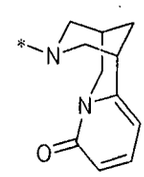
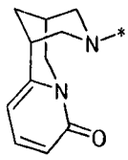
X es metileno, un enlace o no está presente;

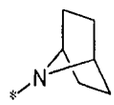
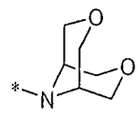
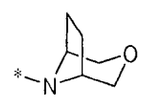
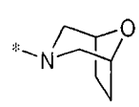
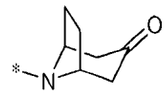
o una de sus sales farmacéuticamente aceptables.

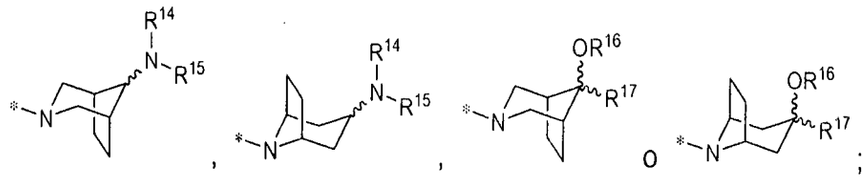
2. Un compuesto según la reivindicación 1, en el que:

R^2 es furanilo, pirrolilo, tienilo, pirazolilo, isoxazolilo, isotiazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, triazolilo o tetrazolilo, y está sustituido con 0-2 sustituyentes seleccionados de oxo, amino, alquilo y haloalquilo, y 1 sustituyente seleccionado de CO_2R^5, $CON(R^{12})_2$ y COR^{13}; y

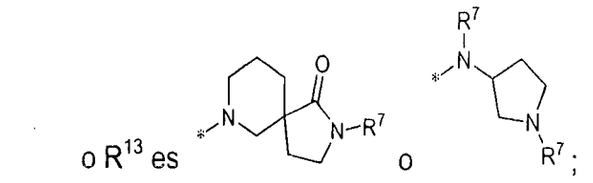
R^{13} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-3 sustituyentes seleccionados de alquilo, alcoxialquilo, amino, alquilamino, dialquilamino, R^{11}, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo, (R^{11})alquilo o CO_2R^5;

o R^{13} es  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , o  ;

o R^{13} es  ,  ,  ,  ,  ,



o R^{13} es una diamina bicíclica [4.3.0] o [3.3.0] unida al carbonilo a través de un nitrógeno, y está sustituido con 0-2 sustituyentes R^8;



o una de sus sales farmacéuticamente aceptables.

3. Un compuesto según la reivindicación 1, en el que:

R^2 es furanilo, pirrolilo, tienilo, pirazolilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo o tetrazolilo, y está sustituido con 0-2 sustituyentes seleccionados de oxo, amino y alquilo, y 1 sustituyente seleccionado de CO_2R^5, $CON(R^{12})_2$ y COR^{13};

R^{11} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, N-alquilpiperazinilo, morfolinilo, tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo; y

R^{13} es azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo,

tiomorfolinilo, homopiperidinilo, homopiperazinilo o homomorfolinilo, y está sustituido con 0-3 sustituyentes seleccionados de alquilo, amino, alquilamino, dialquilamino, R^{11}, aminoalquilo, (alquilamino)alquilo, (dialquilamino)alquilo o (R^{11})alquilo;

o una de sus sales farmacéuticamente aceptables.

4. Un compuesto según la reivindicación 1, en el que R^1 es $CONR^6R^7$; R^6 es alquilSO_2, cicloalquilSO_2, haloalquilSO_2, $(R^9)_2NSO_2$ o (R^{10})SO_2; y R^7 es hidrógeno.

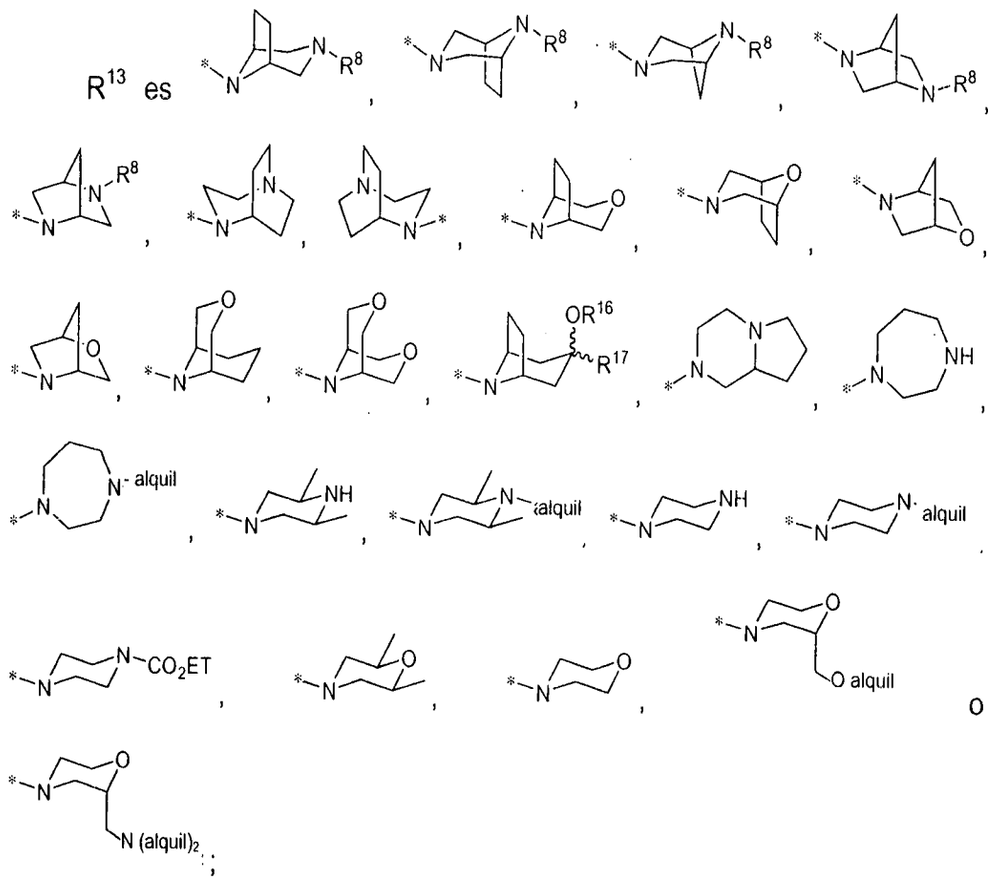
5. Un compuesto según la reivindicación 1, en el que R^3 es hidrógeno.

6. Un compuesto según la reivindicación 1, en el que R^3 es metoxi.

7. Un compuesto según la reivindicación 1, en el que R^4 es ciclohexilo.

8. Un compuesto según la reivindicación 1, en el que R^6 es alquilSO_2, cicloalquilSO_2, (R^9)(R^{10})NSO_2 o (R^{11})SO_2.

9. Un compuesto según la reivindicación 1, en el que R^2 es pirazolilo sustituido con 2 sustituyentes seleccionados de alquilo y haloalquilo y 1 sustituyente COR^{13};

R^{13} es 

R^8 es hidrógeno o alquilo;

R^{16} es hidrógeno o alquilo; y

R^{17} es alquilo;

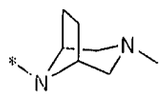
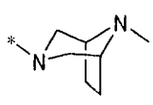
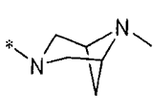
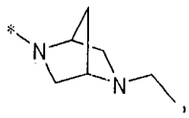
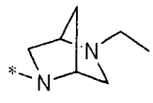
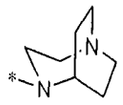
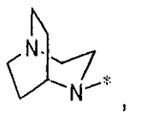
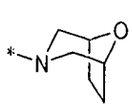
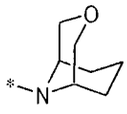
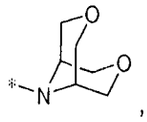
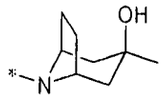
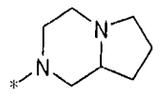
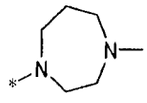
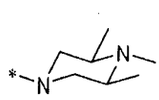
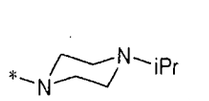
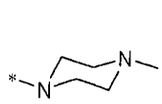
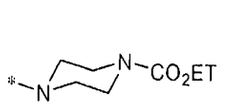
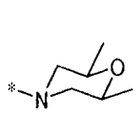
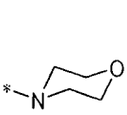
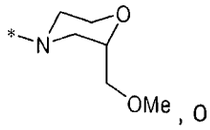
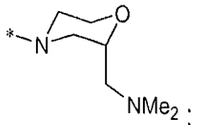
o una de sus sales farmacéuticamente aceptables.

10. Un compuesto según la reivindicación 1, en el que X es metileno.

11. Un compuesto según la reivindicación 1, en el que X no está presente.

12. Un compuesto según la reivindicación 1, en el que X es un enlace.

13. Un compuesto según la reivindicación 12, en el que R^1 es $CONR^6R^7$;

R^2 es pirazolilo sustituido con 2 sustituyentes seleccionados de alquilo y haloalquilo y 1 sustituyente COR^{13}, en el que R^{13} es  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ;

R^3 es hidrógeno o metoxi;

R^4 es ciclohexilo;

R^6 es alquilSO_2, cicloalquilSO_2, haloalquilSO_2, $(R^9)_2NSO_2$, o $(R^{10})SO_2$;

y R^7 es hidrógeno;

o una de sus sales farmacéuticamente aceptables.

14. Un compuesto según la reivindicación 1 seleccionado del grupo constituido por

éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[2-(metoxicarbonil)-3-tienil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

ácido 6-(4-carboxi-1-metil-1*H*-pirazol-5-il)-13-ciclohexil-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-(1,4-diazabiciclo[3.2.2]non-4-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[[(1R,5S)-8-metil-3,8-diazabiciclo[3.2.1]oct-3-

il]carbonil]-1*H*-pirazol-5-il]-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-5-tiazolil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-3-tiofencarboxílico;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-(1-metiletil)-4-[(3,4,5-trimetil-1-piperazinil)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(1R,5S)-3-metil-3,8-diazabiciclo[3.2.1]oct-8-il]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-*N*-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1,3-dimetil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-

indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico;

ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-(1-metiletil)-1*H*-pirrol-3-carboxílico;

13-ciclohexil-3-metoxi-6-[4-[(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)carbonil]-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-(4-morfolinilcarbonil)-3-(trifluorometil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(2*S*)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-3-(trifluorometil)-1*H*-pirazol-5-il]-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-[(4-metil-1-piperazinil)carbonil]-3-(trifluorometil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(1*S*,4*S*)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-3-(trifluorometil)-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[1-etil-3-metil-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-ilcarbonil)-1*H*-

pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-*N*-[(dimetilamino)sulfonil]-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[2-[(dietilamino)carbonil]-3-tienil]-*N*-[(dimetilamino)sulfonil]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-5-oxazolil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

ácido 13-ciclohexil-3-metoxi-6-[4-(4-morfolinilcarbonil)-5-oxazolil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-3-metoxi-6-[4-(4-morfolinilcarbonil)-5-oxazolil]-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[[metil(1-metil-3-pirrolidinil)amino]carbonil]-1*H*-pirazol-5-il]-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[2-[(dimetilamino)metil]-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-

carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[[(1R,5S)-3-metil-3,8-diazabiciclo[3.2.1]oct-8-il]carbonil]-1*H*-pirazol-5-il]-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-[[4-(1-metiletil)-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-[[4-(1-pirrolidinil)-1-piperidinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-N-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-N-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[1-metil-4-[(3-metil-3,8-

diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-

10-carboxamida;

13-ciclohexil-6-[1-ciclopropil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster etílico del ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1*H*-pirrol-3-carboxílico;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-3-(trifluorometil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[1-(1,1-dimetiletil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-[(dimetilamino)sulfonil]-3-metoxi-6-[2-(4-morfolinilcarbonil)-3-tienil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-[(dimetilamino)sulfonil]-6-[1-etil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

6-[4-(7-azabiciclo[2.2.1]hept-7-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-13-ciclohexil-3-metoxi-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[(4-metil-1-piperazinil)carbonil]-1*H*-pirazol-5-il]-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[3-(dimetilamino)-1-pirrolidinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

6-[4-(7-azabiciclo[2.2.1]hept-7-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-[(8-metil-3,8-diazabiciclo[3.2.1]oct-3-il)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster etílico del ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-*N*-(ciclopentilsulfonil)-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[1-metil-4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(1R,4R)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[(3-metil-8-azabiciclo[3.2.1]oct-2-en-8-il)carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster metílico del ácido 5-[13-ciclohexil-10-[[[(dimetilamino)sulfonil]amino]carbonil]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico;

ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[4-(4-morfolinilcarbonil)-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-(2,2,2-trifluoroetil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-3-metil-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-

a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[3-metil-1-(1-metiletil)-4-[(4-metil-1-piperazinil)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[3-metil-1-(1-metiletil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-etil-3-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

ácido 13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

ácido 13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-N-(1-pirrolidinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[4-(4-morfolinilcarbonil)-5-

oxazolil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-N-(1-pirrolidinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida

4-[[13-ciclohexil-6-[1-etil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-il]carbonil]-morfolina;

éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-6-[4-[(hexahidro-4-metil-1*H*-1,4-diazepin-1-il)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster etílico del ácido 4-[[5-[13-ciclohexil-3-metoxi-10-[[(4-morfolinilsulfonil)amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-il]carbonil]-1-piperazincarboxílico;

13-ciclohexil-3-metoxi-6-[1-metil-4-[[4-(1-pirrolidinil)-1-piperidinil]carbonil]-1*H*-pirazol-5-il]-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-

1*H*-pirazol-5-il]-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[[(2-metoxifenil)metil](1-metiletil)amino]carbonil]-1-metil-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1*H*-pirazol-5-il]-N-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-

carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico;

éster metílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1,3-dimetil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-6-[1,3-dimetil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[3-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-(1-metiletil)-1*H*-pirrol-2-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-3-(4-morfolinilcarbonil)-1*H*-pirrol-2-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[(3-hidroxi-3-metil-8-azabiciclo[3.2.1]oct-8-il)carbonil]-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-[(dimetilamino)sulfonil]-3-metoxi-6-[4-(4-morfolinilcarbonil)-5-oxazolil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[[2-(dimetilamino)etil]metilamino]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(2-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-6-[4-[[[(5-etil-1,3,4-oxadiazol-2-il)metil](1-metiletil)amino]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-*N*-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

ácido 5-[10-[[(ciclobutilsulfonil)amino]carbonil]-13-ciclohexil-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(2-metilpropil)sulfonil]-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[(2,6-dimetil-4-morfolinil)carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[(3-metil-8-azabiciclo[3.2.1]oct-2-en-8-il)carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[3-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1-(1-metiletil)-1*H*-pirrol-2-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-3-[(4-propil-1-piperazinil)carbonil]-1*H*-pirrol-2-il]-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster etílico del ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-3-furancarboxílico;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-3-il)carbonil]-3-(trifluorometil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-*N*-[(dimetilamino)sulfonil]-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-*N*-[(dimetilamino)sulfonil]-3-metoxi-6-[1-(1-metiletil)-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster 10-(1,1-dimetiletílico) del ácido 6-(4-carboxi-5-oxazolil)-13-ciclohexil-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-6-[1-etil-4-[(4-metil-1-piperazinil)carbonil]-1*H*-pirazol-5-il]-3-metoxi-*N*-(1-pirrolidinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[1-etil-4-[(4-metil-1-piperazinil)carbonil]-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopropilsulfonil)-3-metoxi-6-[4-(4-morfolinilcarbonil)-5-oxazolil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(3-endo)-3-hidroxi-8-metil-8-azabiciclo[3.2.1]oct-8-il]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[(4-metil-1-piperazinil)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-6-[4-[[etil(1-metiletil)amino]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1*H*-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[(5-etil-2,5-diazabiciclo[2.2.1]hept-2-il)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-[[(1-metiletil)[(tetrahidro-2-furanil)metil]amino]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(1*R*,5*S*)-3-metil-3,8-diazabiciclo[3.2.1]oct-3-il]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-*N*-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(2*S*)-2-(metoximetil)-4-morfolinil]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-*N*-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

ácido 13-ciclohexil-3-metoxi-6-[4-(metoxicarbonil)-1,3-dimetil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-6-[1,3-dimetil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-3-(trifluorometil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-3-(trifluorometil)-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopropilsulfonil)-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster 1,1-dimetiletílico del ácido 13-ciclohexil-3-metoxi-6-[4-(4-morfolinilcarbonil)-5-oxazolil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1*H*-

pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-6-[4-[[3-(dimetilamino)-1-pirrolidinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[(1-oxo-2,7-diazaspiro[4.5]dec-7-il)carbonil]-1*H*-pirazol-5-il]-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(2-metoxietil)(1-metiletil)amino]carbonil]-1-metil-1*H*-pirazol-5-il]-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-N-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[[(2-metoxietil)(1-metiletil)amino]carbonil]-1-metil-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(3-endo)-3-hidroxi-3-metil-8-azabiciclo[3.2.1]oct-8-il]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[(dimetilamino)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-[[(1S,4S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-(1-metiletil)-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[4-[(3-metil-3,6-diazabiciclo[3,1,1]hept-6-il)carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(3-endo)-3-hidroxi-3-metil-8-azabiciclo[3.2.1]oct-8-il]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(3-endo)-3-hidroxi-3-metil-8-azabiciclo[3.2.1]oct-8-il]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster etílico del ácido 2-[13-ciclohexil-3-metoxi-10-[[[(1-

metiletil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-(1-metiletil)-1*H*-pirrol-3-carboxílico;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-(2,2,2-trifluoroetil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1,3-dimetil-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[1-(1,1-dimetiletil)-4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1*H*-pirazol-5-il]-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-ilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[1-metil-4-(8-oxa-3-azabiciclo[3.2.1]oct-3-ilcarbonil)-3-(trifluorometil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-6-[3-metil-1-(1-metiletil)-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-

carboxamida;

ácido 13-ciclohexil-3-metoxi-6-[1-metil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

ácido 13-ciclohexil-6-[4-(etoxicarbonil)-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-3-metoxi-6-[1-metil-4-[[4-(1-metiletil)-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[3-(dimetilamino)-1-piperidinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-[[2-(1-piperidinilmetil)-1-pirrolidinil]carbonil]-1*H*-pirazol-5-il]-*N*-(4-morfolinilsulfonil)-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-

carboxamida;

6-[4-[[[2-[bis(1-metiletil)amino]etil](1-metiletil)amino]carbonil]-1-metil-1*H*-pirazol-5-il]-13-ciclohexil-3-metoxi-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-N-(ciclopentilsulfonil)-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-N-[(1-metilpropil)sulfonil]-6-[1-metil-4-[(3,4,5-trimetil-1-piperazinil)carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster etílico del ácido 5-[13-ciclohexil-3-metoxi-10-[[[(1-metilpropil)sulfonil]amino]carbonil]-7*H*-indolo[2,1-a][2]benzazepin-6-il]-1-metil-1*H*-pirazol-4-carboxílico;

13-ciclohexil-6-[4-[(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[1-metil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-N-[(2-metilpropil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[1-metil-4-[[(3R,5S)-3,4,5-trimetil-1-piperazinil]carbonil]-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[1-metil-4-(3-oxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-6-[4-(3,7-dioxa-9-azabiciclo[3.3.1]non-9-ilcarbonil)-1-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

N-(ciclobutilsulfonil)-13-ciclohexil-3-metoxi-6-[4-[[(2S)-2-(metoximetil)-4-morfolinil]carbonil]-1-metil-1*H*-pirazol-5-il]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-6-[3-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-2-tienil]-N-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

éster 1,1-dimetiletílico del ácido 13-ciclohexil-6-[4-(etoxicarbonil)-2-(metiltio)-5-tiazolil]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-6-[4-[[(1S)-5-etil-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil]-1-(1-metiletil)-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-*N*-[(dimetilamino)sulfonil]-6-[1,3-dimetil-4-(4-morfolinilcarbonil)-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[1,3-dimetil-4-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

ácido 13-ciclohexil-6-[1-(1,1-dimetiletil)-4-(etoxicarbonil)-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-3-metoxi-6-[3-[(3-metil-3,8-diazabiciclo[3.2.1]oct-8-il)carbonil]-2-furanil]-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-3-metoxi-*N*-[(1-metiletil)sulfonil]-6-[3-(4-morfolinilcarbonil)-2-furanil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

13-ciclohexil-6-[4-[[(2R,6S)-2,6-dimetil-4-morfolinil]carbonil]-1-(2-metilpropil)-1*H*-pirazol-5-il]-3-metoxi-*N*-[(1-metiletil)sulfonil]-7*H*-indolo[2,1-a][2]benzazepin-10-carboxamida;

ácido 13-ciclohexil-6-[1-etil-4-(metoxicarbonil)-3-metil-1*H*-pirazol-5-il]-3-metoxi-7*H*-indolo[2,1-a][2]benzazepin-10-carboxílico;

13-ciclohexil-6-[3-[(dimetilamino)carbonil]-5-metil-4*H*-1,2,4-triazol-4-il]-*N*-[(dimetilamino)sulfonil]-6,7-dihidro-3-metoxi-5*H*-indolo[2,1-*a*][2]benzazepin-10-carboxamida; y

13-ciclohexil-6-[3-[(dimetilamino)carbonil]-4*H*-1,2,4-triazol-4-il]-*N*-[(dimetilamino)sulfonil]-6,7-dihidro-3-metoxi-5*H*-indolo[2,1-*a*][2]benzazepin-10-carboxamida;

o una de sus sales farmacéuticamente aceptables.

15. Una composición que comprende un compuesto según la reivindicación 1 o una de sus sales farmacéuticamente aceptables y un vehículo farmacéuticamente aceptable.

16. Composición según la reivindicación 15, que comprende además al menos un compuesto adicional que tiene beneficios terapéuticos para el VHC, seleccionándose el compuesto del grupo constituido por interferones, ciclosporinas, interleuquinas, inhibidores de metaloproteasa del VHC, inhibidores de serina proteasa del VHC, inhibidores de polimerasa del VHC, inhibidores de helicasa del VHC, inhibidores de la proteína NS4B del VHC, inhibidores de la entrada de VHC, inhibidores del ensamblaje del VHC, inhibidores de la salida del VHC, inhibidores de la proteína NS5A del VHC,

inhibidores de la proteína NS5B del VHC e inhibidores del replicón del VHC.

17. Un procedimiento para tratar infección por hepatitis C que comprende administrar a un paciente una cantidad terapéuticamente eficaz de un compuesto según la reivindicación 1.

18. Procedimiento según la reivindicación 17, que comprende además administrar al menos un compuesto adicional que tiene beneficios terapéuticos para el VHC, seleccionándose el compuesto del grupo constituido por interferones, ciclosporinas, interleuquinas, inhibidores de metaloproteasa del VHC, inhibidores de serina proteasa del VHC, inhibidores de polimerasa del VHC, inhibidores de helicasa del VHC, inhibidores de la proteína NS4B del VHC, inhibidores de la entrada del VHC, inhibidores del ensamblaje del VHC, inhibidores de la salida del VHC, inhibidores de la proteína NS5A del VHC, inhibidores de la proteína NS5B del VHC e inhibidores del replicón del VHC.

RESUMEN

La invención incluye compuestos de fórmula I así como composiciones y procedimientos de uso de los compuestos. Los compuestos tienen actividad contra el virus de la hepatitis C (VHC) y son útiles en el tratamiento de sujetos infectados por el VHC.

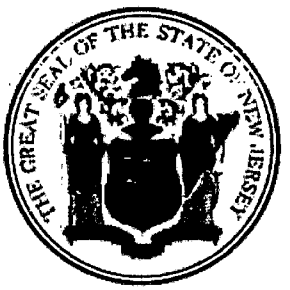
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

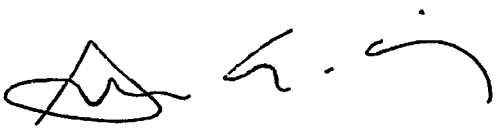
1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
   EVELYN VAZQUEZ
3. ACTING IN THE CAPACITY OF:
   NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
   EVELYN VAZQUEZ, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 22ND DAY OF JANUARY 2010
7. BY: Andrew P Sidamon-Eristoff
   Acting State Treasurer
8. NO: A384581
9. SEAL/STAMP:



10. SIGNATURE



Certificate Number: 116213462

Verify this certificate at
https://www1.state.nj.us/TYTP_StandingCert/JSP/Verify_Cert.jsp

11027-WO-PCT

AFFIDAVIT

I, Paul D. Golian, Assistant General Counsel, declare on this 15th day of January 2010, that the attached are the complete, full, true, and exact copies of the original assignments signed by the named inventors before a Notary Public.

Paul D. Golian
Assistant General Counsel
Bristol-Myers Squibb Company

STATE OF NEW JERSEY)
) ss.
COUNTY OF MERCER)

Subscribed and sworn before me in the county of Mercer and state of New Jersey, this 15th day of January 2010.

Notary Public
Evelyn Vazquez
Notary Public of New Jersey
No. 2106805
My Commission Expires December 9, 2012
Registered in Middlesex County

Worldwide
Case 11027 PSP

ASSIGNMENT

We,

Scott W. Martin, Carl P. Bergstrom, Robert G. Gentles

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

invented by us and described in the provisional United States patent application

Application No. 60/954,814, filed, August 9, 2007

including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 14th day of August, 2007 by _____
Scott W. Martin

Signed this 13th day of August, 2007 by _____
Carl P. Bergstrom

Signed this 16th day of August, 2007 by _____
Robert G. Gentles

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 14 of August, 2007, before me came **Scott W. Martin**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

_____
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 13 of August, 2007, before me came **Carl P. Bergstrom**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

Annamarie Bodicch
Notary Public

ANNAMARIE BODICCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 14 of August, 2007, before me came **Robert G. Gentles**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

[SEAL]

Annamarie Bodicch
Notary Public

ANNAMARIE BODICCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

Worldwide
Case 11027 PSP2

ASSIGNMENT

We,

Scott W. Martin, Carl P. Bergstrom, Robert G. Gentles

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Rt. 206 & Province Line Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

invented by us and described in the provisional United States patent application

Application No. 61/049,944, filed, May 2, 2008

including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 9th day of May, 2008 by _____
Scott W. Martin

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 9 of May, 2008, before me came **Scott W. Martin**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

_____
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

[SEAL]

Signed this 7th day of May, 2008 by _____
Carl P. Bergstrom

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 7 of May, 2008, before me came **Carl P. Bergstrom**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

_____
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

Signed this 6th day of May, 2008 by _____
Robert G. Gentles

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 6 of May, 2008, before me came **Robert G. Gentles**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

_____
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

Worldwide
Case 11027 NP

ASSIGNMENT

We,

Scott W. Martin, Carl P. Bergstrom, Robert G. Gentles, Kap-Sun Yeung

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Rt. 206 & Province Line Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

invented by us and described in the non-provisional United States patent application

Application No. 12/180,994, filed July 28, 2008

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 29th day of July, 2008 by Scott W. Martin
Scott W. Martin

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 29 of July, 2008, before me came **Scott W. Martin**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Annamarie Bodicch
Notary Public

ANNAMARIE BODICCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

[SEAL]

Signed this 1st day of August, 2008 by _____
Carl P. Bergstrom

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 1 of August, 2008, before me came **Carl P. Bergstrom**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

_____
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

[SEAL]

Signed this 29th day of JULY, 2008 by _____
Robert G. Gentles

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 29 of July, 2008, before me came **Robert G. Gentles**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

_____
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

Signed this 29 day of July, 2008 by _____
Kap-Sun Yeung

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On this day 29 of July, 2008, before me came **Kap-Sun Yeung**, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

_____
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

APOSTILLE
(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO FUE FIRMADO POR: EVELYN VAZQUEZ

3. ACTUANDO EN SU CALIDAD DE: NOTARIA PÚBLICA DE NEW JERSEY

4. LLEVA EL SELLO/TIMBRE DE: EVELYN VAZQUEZ, NOTARIA

CERTIFICADO

5. EN TRENTON, NEW JERSEY
6. EL 22 DE ENERO DE 2010
7. POR: Andrew P Sidamon-Eristoff TESOREPO DE NEW JERSEY INTERINO
8. NO. A384581
9. SELLO/TIMBRE
   SELLO MAYOR DEL ESTADO
   DE NEW JERSEY
10. FIRMA:
    [ILEGIBLE]

Certificado Número: 1162113462
Verifique este certificado en línea en:

https://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

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La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.

Teresa Jiménez de Montes
c.c. 41.569.149 de Bogotá
Traductora Oficial según
Resolución No.220 del
6 de febrero de 1978,
expedida por el Ministerio de Justicia.

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

TRADUCCIÓN OFICIAL Nº 0023/2010 de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor. Esta es una traducción oficial efectuada el día 30 de enero de 2010 por la señora Teresa Jiménez de Montes, con cc 41.569.149 de Bogotá, traductora oficial según Resolución Nº 220 del 6 de febrero de 1978, expedida por el Ministerio de Justicia de la República de Colombia

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10899-WO-PCT

DECLARACIÓN JURADA

Yo, Paul D. Golian Sub Asesor Jurídico, declaro hoy 15 de enero de 2010, que las copias adjuntas son copias completas, fieles y exactas de las cesiones originales firmadas por los citados inventores ante Notario Público.

[Firmado]

Paul D. Golian

Sub Asesor Jurídico

Bristol-Myers Squibb Company

Estado de New Jersey)
) suscrito y jurado
Condado de Mercer)

Suscrito y jurado ante mí en el condado de Mercer y estado de New Jersey a los 15 días del mes de enero de 2010.

Firmado, Evelyn Vazquez

Notaria Pública
Evelyn Vazquez
Notaria Pública de New Jersey
No. 2106805
Mi comisión vence el 9 de diciembre de 2012
Registrada en el Condado de Middlesex

[SELLO]
EVELYN VAZQUEZ
NOTARIA PÚBLICA
NEW JERSEY

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Mundial
Caso 11027 PSP

CESIÓN

Nosotros,

Scott W. Martin, Carl P. Bergstrom, Robert G. Gentles

conforme a las obligaciones contractuales asumidas hasta la fecha por nosotros y/o a cambio de una contraprestación válida y efectiva cuyo recibo y suficiencia acusamos por el presente documento, mediante el presente documento vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con domicilio de negocios en Lawrenceville-Princeton Road, Princeton NJ 08543-4000, a sus sucesores, causahabientes y representantes legales, la totalidad de nuestros derechos, títulos y participación, los cuales incluyen el derecho y el beneficio total sobre las prioridades que puedan otorgarse ahora o en el futuro, a nosotros, por las leyes locales o por tratados, incluida la convención internacional para la protección de propiedad industrial en y para todos los países del mundo incluidos los Estados Unidos y sus territorios y posesiones, en y sobre la invención titulada:

COMPUESTOS PARA EL TRATAMIENTO DE LA HEPATITIS C

inventada por nosotros y descrita en la solicitud de patente no provisional de los Estados Unidos

Solicitud No. 60/954,814, presentada el 9 de agosto de 2007

incluida la citada solicitud de patente provisional de los Estados Unidos y cualquier solicitud que reclame antigüedad de la citada solicitud provisional presentada en cualquier país y con respecto a cualquier patente que pueda ser emitida y/u otorgada con respecto a la misma y todas las divisiones, continuaciones, reexpediciones, certificados de re-examen, y extensiones de las mismas en todos los países, cuya participación constituye la propiedad total sobre dicha invención y sobre todas las citadas solicitudes, patentes (incluyendo reemisión de patentes) extensiones, y certificados de re-examen pertenecerán y serán disfrutados por Bristol-Myers Squibb Company y sus sucesores y causahabientes hasta el máximo de los términos para los cuales esas patentes (incluidas las reexpediciones de patentes), certificados de extensión y de re-examen puedan otorgarse y/o emitirse en su totalidad como si los mismos hubieren sido mantenidos y disfrutadas por nosotros, si esta venta, cesión y transferencia no se hubiere realizado;

Mundial
Caso 11027 PSP

Y por el presente aceptamos que se le comunique al citado cesionario o a su representante sobre cualquier hecho del que tengamos conocimiento con respecto a dicha invención, a dar testimonio en cualquier proceso legal, a firmar y/o suscribir cualquier otro documento adicional y/o instrumento que pueda ser necesario, legítimo y adecuado para la presentación y/o proceso judicial de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reemisión, certificados de extensiones y re-examen y/o el otorgamiento y/o extensión de los mismos y/o de otra manera garantizar el título de dicha invención y de todas las solicitudes, patentes (incluidas las re-emisiones de patentes, certificados de extensiones y re-examen de las mismas, en dicho cesionario y en general, a revisar todos los actos que sean

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

necesarios para colaborar con el cesionario, sus sucesores y causahabientes para obtener y hacer cumplir la adecuada protección.

Firmado hoy 14 de agosto de 2007 por [Firma ilegible]
Scott W. Martin

Firmado hoy 13 de agosto de 2007 por [Firma ilegible]
Carl P. Bergstrom

Firmado hoy 14 de agosto de 2007 por [Firma ilegible]
Robert G. Gentles

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

Hoy 14 de agosto de 2007, compareció ante mí **Scott W Martin** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

Mundial
Caso 11027 PSP

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

Hoy 13 de agosto de 2007, compareció ante mí **Carl P. Bergstrom** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

Hoy 14 de agosto de 2007, compareció ante mí **Robert G. Gentles** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Mundial
Caso 11027 PSP2

CESIÓN

Nosotros,

Scott W Martin, Carl P. Bergstrom, Robert G. Gentles

conforme a las obligaciones contractuales asumidas hasta la fecha por nosotros y/o a cambio de una contraprestación válida y efectiva cuyo recibo y suficiencia se acusan por el presente documento, mediante el presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con domicilio de negocios en Rt 206 & Province Line Road, Princeton, NJ 08543-4000, a sus sucesores, causahabientes y representantes legales, la totalidad de nuestros derechos, títulos y participación, los cuales incluyen el derecho y el beneficio total sobre las prioridades que puedan otorgarse ahora o en el futuro, a nosotros, por las leyes locales o por tratado, incluida la convención internacional para la protección de propiedad industrial en y para todos los países del mundo incluidos los Estados Unidos y sus territorios y posesiones, en y sobre la invención titulada:

COMPUESTOS PARA EL TRATAMIENTO DE LA HEPATITIS C

inventada por nosotros y descrita en la solicitud de patente provisional de los Estados Unidos

Solicitud No. 61/049,944, presentada el 2 de mayo de 2008

incluida la citada solicitud de patente provisional de los Estados Unidos y cualquier solicitud que reclame antigüedad de la citada solicitud provisional presentada en cualquier país y con respecto a cualquier patente que pueda ser emitida y/u otorgada con respecto a la misma y todas las divisiones, continuaciones, reexpediciones, certificados de re-examen, y extensiones de las mismas en todos los países, cuya participación constituye la propiedad total sobre dicha invención y sobre todas las citadas solicitudes, patentes (incluyendo reemisión de patentes) extensiones, y certificados de re-examen pertenecerán y serán disfrutados por Bristol-Myers Squibb Company y sus sucesores y causahabientes hasta el máximo de los términos para los cuales esas patentes (incluidas las reexpediciones de patentes), certificados de extensión y de re-examen puedan otorgarse y/o emitirse en su totalidad como si los mismos hubieren sido mantenidos y disfrutadas por nosotros, si esta venta, cesión y transferencia no se hubiere realizado;

Mundial
Caso 11027 PSP2

Y por el presente aceptamos que se le comunique al citado cesionario o a su representante sobre cualquier hecho del que tengamos conocimiento con respecto a dicha invención, a dar testimonio en cualquier proceso legal, a firmar y/o suscribir cualquier otro documento adicional y/o instrumento que pueda ser necesario, legítimo y adecuado para la presentación y/o proceso judicial de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reemisión, certificados de extensiones y re-examen y/o el otorgamiento y/o extensión de los mismos y/o de otra manera garantizar el título de dicha invención y de todas las solicitudes, patentes (incluidas las re-emisiones de patentes, certificados de extensiones y re-examen de las mismas, en dicho cesionario y en general, a revisar todos los actos que sean

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

necesarios para colaborar con el cesionario, sus sucesores y causahabientes para obtener y hacer cumplir la adecuada protección de la citada invención en todos los países.

Firmado hoy 9 de mayo de 2008 por Firma (ilegible)
Scott W. Martin

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

Hoy 9 de mayo de 2009, compareció ante mí **Scott W. Martin** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

Mundial
Caso 11027 PSP2

Firmado hoy 7 de mayo de 2008 por por Firma (ilegible)
Carl P. Bergstrom

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

Hoy 7 de mayo de 2008, compareció ante mí **Carl P. Bergstrom** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

Firmado hoy 6 de mayo de 2008 por por Firma (ilegible)
Robert G Gentles

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

TERESA J. DE MONTES
TRADUCTORA OFICIAL
REG. 320 MINJUSTICIA

Hoy 6 de mayo de 2008, compareció ante mí **Robert G.Gentles** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Mundial
Caso 11027 NP

CESIÓN

Nosotros,
Scott W. Martin, Carl P. Bergstrom, Robert G. Gentles, Kap-Sun Yeung

conforme a las obligaciones contractuales asumidas hasta la fecha por nosotros y/o a cambio de una contraprestación válida y efectiva cuyo recibo y suficiencia se acusan por el presente documento, mediante el presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con domicilio de negocios en Rt 206 & Province Line Road, Princeton, NJ 08543-4000, a sus sucesores, causahabientes y representantes legales, la totalidad de nuestros derechos, títulos y participación, los cuales incluyen el derecho y el beneficio total sobre las prioridades que puedan otorgarse ahora o en el futuro, a nosotros, por las leyes locales o por tratado, incluida la convención internacional para la protección de propiedad industrial en y para todos los países del mundo incluidos los Estados Unidos y sus territorios y posesiones, en y sobre la invención titulada:

COMPUESTOS PARA EL TRATAMIENTO DE LA HEPATITIS C

inventada por nosotros y descrita en la solicitud de patente no provisional de los Estados Unidos

Solicitud No. 12/180,994, presentada el 28 de julio de 2008

incluida la citada solicitud de patente no provisional de los Estados Unidos y cualquier solicitud que reclame antigüedad de la citada solicitud provisional presentada en cualquier país y con respecto a cualquier patente que pueda ser emitida y/u otorgada con respecto a la misma y todas las divisiones, continuaciones, reexpediciones, certificados de re-examen, y extensiones de las mismas en todos los países, cuya participación constituye la propiedad total sobre dicha invención y sobre todas las citadas solicitudes, patentes (incluyendo reemisión de patentes) extensiones, y certificados de re-examen pertenecerán y serán disfrutados por Bristol-Myers Squibb Company y sus sucesores y causahabientes hasta el máximo de los términos para los cuales esas patentes (incluidas las reexpediciones de patentes), certificados de extensión y de re-examen puedan otorgarse y/o emitirse en su totalidad como si los mismos hubieren sido mantenidos y disfrutadas por nosotros, si esta venta, cesión y transferencia no se hubiere realizado;

Mundial
Caso 11027 NP

Y por el presente aceptamos que se le comunique al citado cesionario o a su representante sobre cualquier hecho del que tengamos conocimiento con respecto a dicha invención, a dar testimonio en cualquier proceso legal, a firmar y/o suscribir cualquier otro documento adicional y/o instrumento que pueda ser necesario, legítimo y adecuado para la presentación y/o proceso judicial de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reemisión, certificados de extensiones y re-examen y/o el otorgamiento y/o extensión de los mismos y/o de otra manera garantizar el título de dicha invención y de todas las solicitudes, patentes (incluidas las re-emisiones de patentes, certificados de extensiones y re-examen de las mismas, en dicho cesionario y en general, a revisar todos los actos que sean

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

necesarios para colaborar con el cesionario, sus sucesores y causahabientes para obtener y hacer cumplir la adecuada protección de la citada invención en todos los países.

Firmado hoy 29 de julio de 2008 por Firma (ilegible)
Scott W. Martin

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

Hoy 29 de julio de 2008 compareció ante mí **Scott W. Martin** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

Mundial
Caso 11027 NP

Firmado hoy 1 de agosto de 2008 por Firma (ilegible)
Carl P. Bergstrom

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

Hoy 1 de agosto de 2008, compareció ante mí **Carl P. Bergstrom** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

Firmado hoy 29 de julio de 2008 por Firma (ilegible)
Robert G. Gentles

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

TERESA J. DE MONTES
TRADUCTORA OFICIAL
REG. 220 MINJUSTICIA

Hoy 29 de julio de 2008, compareció ante mí **Robert G.Gentles** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

Mundial
Caso 11027 NP

Firmado hoy 29 de julio de 2008 por Firma (ilegible)
Kap-Sun Yeung

ESTADO DE Connecticut)
) suscrito y jurado en Wallingford
CONDADO de New Haven)

Hoy 29 de julio de 2008 compareció ante mí **Kap-Sun Yeung** a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado: Annamarie Bodisch
Notaria Pública

[SELLO]
ANNAMARIE BODISCH
NOTARIA PÚBLICA
Mi comisión vence el 31 de marzo de 2010

TERESA J. DE MONTES
TRADUCTORA OFICIAL
REG. 220 MINJUSTICIA

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-011252- -00000-0000
Fecha: 2010-02-03 15:57:54 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 785

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

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

Completa ☐ Incompleta ☐

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

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

Completa ☑ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL - MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	10 11252
	Solicitud internacional	PCT/US2008/071881
	Fecha inicio fase nacional	09/03/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	No 04777

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. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

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.

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.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 09 ABR. 2010
adpa11