05 65794

Libertad y Orden

REPÚBLICA DE COLOMBIA

DIVISIÓN DE PROPIEDAD INDUSTRIAL

PATENTE DE INVENCIÓN PCT

Industria y Comercio
SUPERINTENDENCIA

05-65794

TITULO: DERIVADOS DE DIAZOPINOINDOL COMO INHIBIDORES DE QUINAZA

SOLICITANTE: PFIZER INC.

CLASIFICACION INTERNACIONAL: A61K31/55 ; A61P35/00

DIRECCIÓN 235 East 42nd Street, New York, NY 10017 E.U.A.

APODERADO CARLOS R. OLARTE

SS

BOGOTÁ, Julio 05 de 2005

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA Y COMERCIO
Radicacion : 05065794 00000000 Folios: 758
Fecha (MM/): 2005-07-05 16:56:37
Tramite : 011 PCT-PATENTE 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 09-08-05

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** PFIZER INC **Dirección:** 235 East 42nd Street, New York, NY 10017 E.U.A. **Nacionalidad o Domicilio:** ESTADOUNIDENSE **Lugar de Constitución:** Delaware, Estados Unidos de América. **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10 **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [X] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79782747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA. **Dirección:** VER PAGINA ADJUNTA. **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA.	

(5) **PCT (86)**

Solicitud Internacional No. PCT/IB2004/000026 Fecha Enero 5, 2004

Publicación Internacional No. WO 2004/063198 Fecha Julio 29, 2004

(6) **Título (54)** **DERIVADOS DE DIAZOPINOINDOL COMO INHIBIDORES DE QUINAZA**

Clasificación Internacional (51) **C07D 487/06 ; A61P 35/00 ; A61K 31/55**

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Enero 9, 2003	60/439,396

(9) **Comprobante de pago No.** 48,920 **Fecha** Junio 30, 2005

(0) **ANEXOS**

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

(1) **FIGURA CARACTERÍSTICA:**

(2) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

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4

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05055731 00000000
Fecha (ORD): 2005-07-05 16:56:37 Folios: 758
Tramite : 011 PCI-PATENT 3/3 FASE/ANCI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 48,920
FECHA : JUNIO 30 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	35420630	30/06/2005	1,999,000.00

***** 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	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercia funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE



1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular.de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

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Power of Attorney

The undersigned,

Pfizer Inc.

domiciled in

235 East 42nd Street, New York, NY 10017 USA

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

Pfizer Inc.

domiciliado en

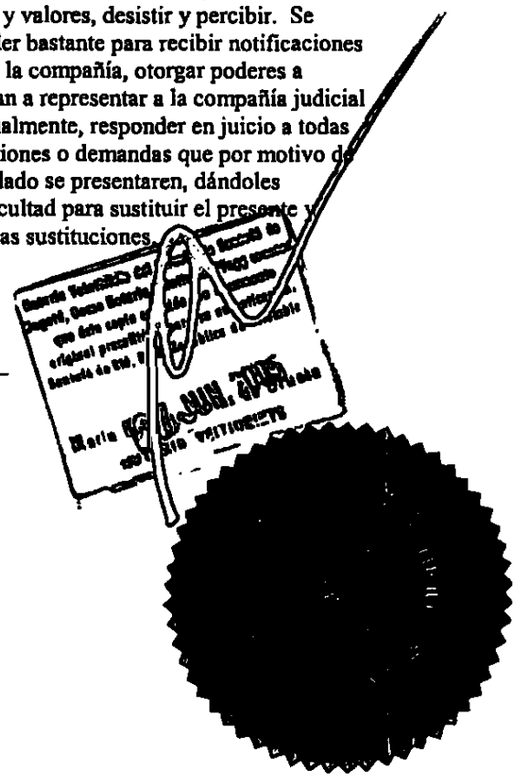
235 East 42nd Street, New York, NY 10017 USA

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA



OLARTE RAISBECK

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FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb
of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in
New York, New York, U.S.A.
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el [illegible] documento en su carácter de [illegible] de

4. Que
con sede principal ubicada en [illegible]

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by **K Greenwood**
   a été signé par

3. Acting in the capacity of **Notary Public**
   agissant en qualité de

4. Bears the seal/stamp of **The Said Notary Public**
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres
6. the/le **17 July 2003**

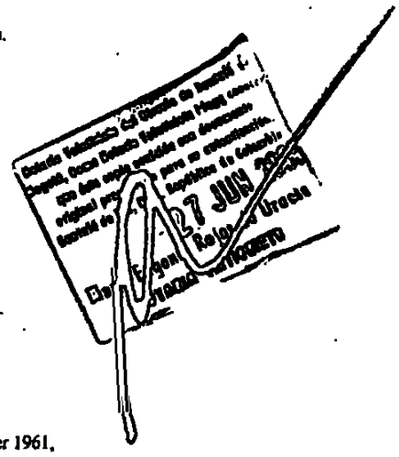
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G210434**

9. Stamp:
   timbre:

10. Signature: **R. Bawden**





For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

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

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(72) Inventors; and

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(74) Agents: LUMB, J., Trevor et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ07950 (US).

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

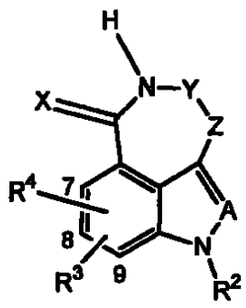
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, 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*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/063198 A1

(54) Title: DIAZEPINOINDOLE DERIVATIVES AS KINASE INHIBITORS



(I)

(57) Abstract: Protein kinase, such as CHK-1, inhibiting tricyclic compounds of the following formula (wherein R^2, R^3 and R^4 are as defined in the specification) pharmaceutical compositions containing effective amounts of said compounds or their salts are useful as a single agent or in combination with an anti-neoplastic agent or therapeutic radiation having an anti-neoplastic effect for treating diseases or conditions, such as cancers.

TRICYCLIC COMPOUNDS PROTEIN KINASE INHIBITORS FOR ENHANCING THE EFFICACY OF ANTI-NEOPLASTIC AGENTS AND RADIATION THERAPY

Field of The Invention

This invention relates to novel tricyclic compounds of formula I that inhibit protein kinases, preferably CHK-1. The invention further relates to pharmaceutical compositions containing such compounds, and to methods for the treatment of a condition which can be treated by the inhibition of protein kinases, preferably CHK-1, in a mammal by administering effective amounts of such compounds in conjunction with an anti-neoplastic agent, a radiation therapy, or as a single agent.

Background of The Invention

A eukaryotic cell cycle has a carefully regulated progression of phases: initial gap (G_1), DNA synthesis (S), secondary gap (G_2), and mitosis (M). G_1, S and G_2 are known as interphase. In G_1, the cell, whose biosynthetic pathways were slowed during mitosis, resumes a high rate of RNA and protein biosynthesis. The S phase begins when DNA synthesis starts and ends when the DNA content of the nucleus has been replicated. The cell then enters G_2 where again RNA and protein biosynthesis occur. Following G_2, the cell enters M phase that begins with nuclear division and ends with the complete division of the cytoplasm into two daughter cells. This marks the beginning of interphase for the new cells. Non-dividing cells exist at G_0, a time following mitosis and before DNA synthesis.

Checkpoint enzymes, such as the serine/threonine protein kinase called checkpoint kinase 1 (CHK-1 or p56CHK-1), are responsible for maintaining the order and fidelity of events in the cell cycle. CHK-1 transduces signals from the DNA damage sensory complex to inhibit activation of Cdc2-cyclin B complex which promotes mitotic entry (*Science*, **277**, 1501-1505 (1997); *Science*, 277, 1497-1501 ((1997)). In eukaryotes, Cdc2 is known as Cdk1 (cyclin-dependent kinase 1). CHK-1 regulates Cdc25, a dual specificity phosphatase that activates Cdc2. Thus, CHK-1 serves as the direct link between the G_2 checkpoint and the negative regulation of Cdc2.

Healthy cells have both the G_1 and G_2 checkpoints and their associated repair processes to ensure viability after treatment of DNA damage (chemotherapy and/or radiation). Cancer cells, however, rely exclusively on the G_2 checkpoint and its associated repair processes in order to remain viable and to continue replication. Abrogation of the G_2 checkpoint would leave cancer cells with no means to delay progression into mitosis following DNA damage. Inactivation of CHK-1 has been shown to abrogate G_2 arrest induced by DNA damage inflicted by either anticancer agents or endogenous DNA damage. In addition, inactivation of CHK-1 results in preferential killing of the resulting DNA damaged, checkpoint defective cells (*Cell*, **91**, 865-867 (1997); *Science*, 277, 1450-1451 (1997); *Nature*, 363, 368-371 (1993); *Molec. Biol. Cell*, **5**, 147-160 (1994)). Therefore there is a need for small molecule inhibitors of CHK-1 to preferentially

abrogate the G_2 checkpoint over G_1 and to effectively remove the only checkpoint control found in many types of cancers. When administered during the course of a DNA damaging event, such as chemotherapy employing anti-neoplastic agents, radiation therapy, immunotherapies and antiangiogenic therapies, a CHK-1 inhibitor can sensitize cancer cells thereby triggering damage-mediated apoptosis. Therefore there is a need for a combination therapy involving CHK-1 inhibitor in the course of a DNA damaging event.

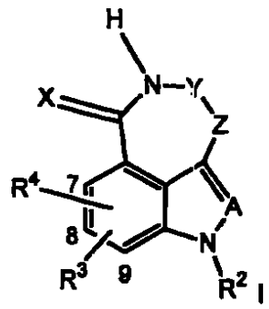
Since protein kinases are ubiquitous and interrelated, selective modulation of a single kinase, such as CHK-1, or family of kinases may not result in an effective therapeutic treatment. There is therefore a need for small molecule inhibitors to influence one or more targeted protein kinases whose inhibition, taken as a whole, would produce the desired therapeutic treatment. Although kinase selectivity and its relation to generalized toxicity are important, therapeutic efficacy may rely on the inhibition of more than one protein kinase. Chemical core structures that can be suitably appended to interact selectively and potently with targeted protein kinases represent a valuable tool for drug discovery and scientific research. Therefore there is a need for such a core structure as an inhibitor of one or more protein kinases. Whether administered as a single agent or as co-therapy, the protein kinase inhibitors, such as CHK-1 inihibitors, of the present invention could prove beneficial in the treatment of a number of human diseases, such as cancer.

Certain CHK-1 inhibitors have been proposed for cancer therapy (see Sanchez, Y. et.al. (1997) Science 277: 1497-1501 and Flaggs, G. et. al. (1997) Current Biology 7:977-986; U.S. Patent Nos. 6,413,755, 6,383,744, and 6,211,164; and International Publication Nos. WO 01/16306, WO 01/21771, WO 00/16781, and WO 02/070494).

SUMMARY OF THE INVENTION

An object of the invention is to provide compounds that inhibit the activity of one or more protein kinases, such as CHK-1.

In a general aspect, the invention relates to a protein kinase inhibitor, preferably CHK-1 inhibitor, tricyclic compounds of the Formula I:



I

wherein:

X is =O or =S;

A is $=CR^1-$ or =N-;

The group -Y-Z- has the formula $-O-CH_2-$ or -N=CH-;

R^1 is:

(a) (C_1-C_8)alkyl;

(b) $-C(=O)-R^5$;

(c) $-C(=O)-NR^6R^7$; or

(d) R^{35}, or R^{36}, (C_2-C_8)alkenyl, or (C_2-C_8)alkynyl {wherein each of said (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of F, Cl, OH, $-NH_2$, R^{40}, and R^{42}};

R^2 is

(a) H, OH, or (C_1-C_8)alkyl;

(b) $-C(=O)-R^8$;

(c) $-(C=S)-R^9$ or $-(C=S)-NR^{10}R^{11}$; or

(d) R^{38} or R^{39};

R^3 is

(a) (C_1-C_8)alkyl;

(b) $-C(=O)-R^{12}$;

(c) $-C(=O)-NR^{13}R^{14}$;

(d) $-NR^{15}-C(=O)-R^{16}$;

(e) $-NR^{17}-SO_2R^{18}$;

(f) $-NR^{19}-SO_n-NR^{20}R^{21}$ {wherein n is 1 or 2};

(g) $-NR^{22}-(C=S)-R^{23}$ or $-NR^{22}-(C=S)-NR^{23}R^{24}$;

(h) R^{36}, (C_2-C_8)alkenyl, or (C_2-C_8)alkynyl {wherein each of said R^3 (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, R^{40}, R^{41}, and R^{42}};

(i) R^{37}, $-NH_2$, $-NH((C_2-C_8)$alkenyl), $-NH((C_2-C_8)$alkynyl), $-N((C_1-C_8)$alkyl)$((C_2-C_8)$alkenyl), or $-N((C_1-C_8)$alkyl)$((C_2-C_8)$alkynyl) {wherein each of said R^{28} (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{40}, R^{41}, and R^{42}}; or

(j) R^{38};

R^4 is selected from the group consisting of H, F, Br, Cl, and (C_1-C_8)alkyl;

R^5 is selected from the group consisting of H, (C_1-C_8)alkyl, (C_1-C_8)alkyl-O-, and R^{36};

Each R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_8)alkyl, and R^{36};

R^8 is selected from the group consisting of (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $-NH_2$, R^{36}, and R^{37};

Each of R^9, R^{10} and R^{11} are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, and R^{36};

R^{12} is selected from the group consisting of H, OH, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkyl-O-, and R^{35};

R^{13} is H or $(C_1$-$C_8)$alkyl;

R^{14} is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $-CH_2$-$(C=O)$-O-$(C_1$-$C_8)$alkyl, and R^{35};

R^{15} is H or $(C_1$-$C_8)$alkyl;

R^{16} is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $-NH_2$, R^{35}, and R^{37};

wherein each of said R^{15} and R^{16} $(C_2$-$C_8)$alkenyl or $(C_2$-$C_8)$alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{40}, R^{41}, and R^{42};

R^{17} is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, and R^{36};

R^{18} is $(C_1$-$C_8)$alkyl or R^{35};

R^{19}, R^{20}, and R^{21} are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, and R^{36};

R^{22}, R^{23} and R^{24} are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, and R^{36};

R^{25} is H or $(C_1$-$C_8)$alkyl;

R^{26} is selected from the group consisting of $-C(=O)$-O-$C(CH_3)_3$, $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, $(C_2$-$C_{10})$heterocyclyl, $(C_6$-$C_{10})$aryl, and $(C_1$-$C_{10})$heteroaryl;

or R^{25} and R^{26} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{27} is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, $(C_2$-$C_{10})$heterocyclyl, $(C_6$-$C_{10})$aryl, and $(C_1$-$C_{10})$heteroaryl;

R^{28} is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, $(C_2$-$C_{10})$heterocyclyl, $(C_6$-$C_{10})$aryl, and $(C_1$-$C_{10})$heteroaryl;

R^{29} is H or $(C_1$-$C_8)$alkyl;

R^{30} is $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, $(C_2$-$C_{10})$heterocyclyl, $(C_6$-$C_{10})$aryl, or $(C_1$-$C_{10})$heteroaryl;

or R^{29} and R^{30} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{31} is H or $(C_1$-$C_8)$alkyl;

R^{32} is independently selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_3$-$C_{10})$cycloalkyl, $(C_2$-$C_{10})$heterocyclyl, $(C_6$-$C_{10})$aryl, and $(C_1$-$C_{10})$heteroaryl;

or R^{31} and R^{32} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{33} is (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl;

R^{34} is (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl;

Each R^{35} is independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-NH-C(=O)-O-C(CH_3)_3$, and CF_3;

Each R^{36} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

Each R^{37} is independently selected from the group consisting of:

(a) $-NR^{25}R^{26}$; and

(b) $R^{27}-O-$;

R^{38} is $R^{28}-SO_n-$; wherein n is 0,1, or 2 when $-SO_n-$ is bonded to R^{28} via an R^{28} carbon atom, or wherein n is 1 or 2 when $-SO_n-$ is bonded to R^{28} via an R^{28} ring nitrogen atom;

R^{39} is $R^{29}R^{30}N-SO_n-$; wherein n is 1 or 2;

wherein each of said (C_1-C_8)alkyl, wherever it occurs in any of said R^1(a)-(d), R^2(a)-(d), R^3(a)-(j), R^4, R^{37}, R^{38}, or R^{39}, is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_2-C_8)alkenyl, R^{40}, R^{41}, and R^{42};

wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in said R^{36}, R^{37}, R^{38}, or R^{39}, is independently unsubstituted or substituted with one to four substituents independently selected from R^{40};

R^{40} is selected from the group consisting of (C_1-C_8)alkyl, R^{41}, R^{42}, and R^{43};

Each R^{41} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-NH-C(=O)-O-C(CH_3)_3$, COOH, $-C(=O)(C_1-C_8)$alkyl, $-C(=O)-O-(C_1-C_8)$alkyl, $-NH-SO_2-(C_1-C_8)$alkyl, $-NH-SO_2-(C_6-C_{10})$aryl, and CF_3;

Each R^{42} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

Each R^{43} is independently selected from the group consisting of:

(a) $-NR^{31}R^{32}$;

(b) $R^{33}-O-$; and

(c) $R^{34}-SO_n-$; wherein n is 0,1, or 2 when $-SO_n-$ is bonded to R^{34} via an R^{34} carbon atom, or wherein n is 1 or 2 when $-SO_n-$ is bonded to R^{34} via an R^{34} ring nitrogen atom;

wherein each of said (C_1-C_8)alkyl, wherever it occurs in any of R^{40} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{44} and R^{45};

wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in any of said R^{42} or R^{43}, is independently unsubstituted or

substituted with one to four substituents independently selected from the group consisting of R^{47} selected from the group consisting of (C_1-C_8)alkyl, R^{44}, and R^{45};

Each R^{44} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-CF_3$, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-(C=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N<[(C_1-C_8)\text{alkyl}]_2$, $-NH-(C=O)-(C_1-C_8)$alkyl, R^{37}, and R^{38};

Each R^{45} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

wherein each of said (C_1-C_8)alkyl wherever it occurs in any of said R^{44} or R^{45} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{46} and R^{47};

wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in any of said R^{43} or R^{44} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, R^{46} and R^{47};

Each R^{46} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-(C=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N<[(C_1-C_8)\text{alkyl}]_2$, $-NH-(C=O)-(C_1-C_8)$alkyl, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-(C=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N>[(C_1-C_8)\text{alkyl}]_2$, $-NH-(C=O)-(C_1-C_8)$alkyl, R^{37}, and R^{38}; and

Each R^{47} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl; (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

or a pharmaceutically acceptable salt thereof.

The invention is also directed to pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of the compounds of Formula I. Pharmaceutically acceptable salts of such active metabolites are also provided. Advantageous methods of making the compounds of the Formula I are also described.

The compounds of this invention include all stereoisomers (*e.g.*, cis and trans isomers) and all optical isomers of compounds of the Formula I (*e.g.*, R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

The compounds of the invention may also exist in different tautomeric forms. This invention relates to all tautomers of Formula I.

The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

In one embodiment, the invention relates to compounds of the Formula I wherein R^3 is (C_1-C_8)alkyl substituted with one to four substituents independently selected from the group consisting of F, OH, $-NH_2$, (C_1-C_8)alkyl-NH-, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_6-C_{10})heteroaryl.

In another embodiment, the invention relates to compounds of the Formula I wherein R^3 is selected from the group consisting of (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_2-C_{10})heterocyclyl, phenyl, and (C_1-C_{10})heteroaryl; wherein each of said (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to three substituents independently selected from the group consisting of F, OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl; and wherein each of said (C_3-C_8)cycloalkyl, (C_2-C_{10})heterocyclyl, phenyl, or (C_1-C_{10})heteroaryl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl.

In a preferred embodiment, the invention relates to compounds of the Formula I wherein R^3 is $-C(=O)-NR^{13}R^{14}$ {wherein R^{13} is H or (C_1-C_8)alkyl}, wherein said R^{13} (C_1-C_4)alkyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of F, OH, $-NH_2$, R^{41}, and R^{42}; wherein each of said R^{36} is unsubstituted or substituted with one or two substituents independently selected from the group consisting of (C_6-C_{10})aryl, (C_1-C_{10})heteroaryl, (C_2-C_{10})heterocyclyl, (C_1-C_8)alkyl-NH-, and $[(C_1-C_8)alkyl]_2>N-$; and wherein each of said (C_6-C_{10})aryl substituent is unsubstituted or substituted with one to three substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, Cl, $-CF_3$, and OH.

In another embodiment, the invention relates to compounds of the Formula I wherein R^{15} is (C_1-C_8)alkyl unsubstituted or substituted with one to four substituents independently selected from the group consisting of OH, CN, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, $[(C_1-C_8)alkyl][(C_3-C_{10})cycloalkyl]>N-$, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl; wherein said (C_6-C_{10})aryl substituent is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, Cl, Br, CN, OH, and CF_3; and wherein said (C_2-C_{10})heterocyclyl substituent is unsubstituted or substituted with one or two substituents independently selected from the group consisting of (C_1-C_8)alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-S-(C_1-C_8)$alkyl, F, Br, OH, and CF_3.

In another embodiment, the invention relates to compounds of the Formula I wherein R^3 is $-NR^{15}-C(=O)-R^{16}$; wherein R^{16} is (C_2-C_8)alkenyl unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl; wherein said (C_6-C_{10})aryl substituent is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, Cl, Br, CN, OH, and CF_3; and wherein said (C_2-C_{10})heterocyclyl

substituent is unsubstituted or substituted with one or two substituents independently selected from the group consisting of (C_1-C_8)alkyl, -(C=O)-(C_1-C_8)alkyl, -(C=O)-O-(C_1-C_8)alkyl, -S-(C_1-C_8)alkyl, F, Br, OH, and CF_3.

In a preferred embodiment, the invention relates to compounds of the Formula I wherein R^3 is $-NR^{15}-C(=O)-R^{16}$; wherein R^{16} is (C_1-C_{10})heteroaryl unsubstituted or substituted with one or two substituents independently selected from the group consisting of (C_1-C_8)alkyl, -(C=O)-(C_1-C_8)alkyl, -S-(C_1-C_8)alkyl, F, Cl, CN, OH, and CF_3. More preferably the R^{16} (C_1-C_{10})heteroaryl is pyridinyl.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein R^3 is $-NR^{15}-C(=O)-R^{16}$; wherein R^{16} is (C_3-C_{10})cycloalkyl unsubstituted or substituted with one or two substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, Cl, CN, OH, NH_2, CF_3, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl; wherein said (C_6-C_{10})aryl substituent is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, Cl, Br, CN, OH, and CF_3; and wherein said (C_2-C_{10})heterocyclyl substituent is unsubstituted or substituted with one or two substituents independently selected from the group consisting of (C_1-C_8)alkyl, -(C=O)-(C_1-C_8)alkyl, -(C=O)-O-(C_1-C_8)alkyl, -S-(C_1-C_8)alkyl, F, Br, OH, and CF_3. More preferably said R^{16} (C_3-C_{10})cycloalkyl is selected from the group consisting of cyclopropyl and cyclohexyl. More preferably said (C_6-C_{10})aryl substituents is unsubstituted.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein R^3 is $-NR^{15}-C(=O)-R^{16}$; wherein R^{16} is (C_2-C_{10})heterocyclyl unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, -(C=O)-(C_1-C_8)alkyl, -(C=O)-O-(C_1-C_8)alkyl, F, Cl, CN, OH, and CF_3. More preferably said R^{16} (C_2-C_{10})heterocyclyl is selected from the group consisting of piperazinyl, piperidinyl, pyrrolidinyl, pyrrolidinonyl, thiadiazolyl, tetrahydroisoquinolinyl, tetrahydronaphthalenyl, and indanyl.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein R^3 is $-NR^{15}-C(=O)-R^{16}$; wherein R^{16} is phenyl unsubstituted or substituted with one to three substituents independently selected from the group consisting of (C_1-C_8)alkyl, (C_1-C_8)alkyl-O-, F, Cl, Br, CN, OH, and CF_3.

In another embodiment, the invention relates to compounds of the Formula I wherein R^1 is (C_1-C_8)alkyl substituted with one to two substituents independently selected from the group consisting of F, Cl, -OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, and (C_1-C_8)alkyl-O-; wherein each of said (C_1-C_8)alkyl substituent, wherever it occurs, is independently unsubstituted or substituted with one to three substituents independently selected from the group consisting of -NH_2, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, -O-(C=O)-(C_1-C_8)alkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl.

In another embodiment, the invention relates to compounds of the Formula I wherein R^1 is unsubstituted (C_1-C_8)alkyl; such as methyl or ethyl.

In another embodiment, the invention relates to compounds of the Formula I wherein R^1 is (C_2-C_8)alkenyl or (C_2-C_8)alkynyl; wherein each of said (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to two substituents independently selected from the group consisting of $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, (C_2-C_{10})heterocyclyl, and (C_1-C_{10})heteroaryl; wherein each of said (C_1-C_8)alkyl substituent, wherever it occurs, is independently unsubstituted or substituted with one to three substituents independently selected from the group consisting of $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, $-O-(C=O)-(C_1-C_8)$alkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein R^1 is R^{36} selected from the group consisting of H, Cl, and Br.

In another embodiment, the invention relates to compounds of the Formula I wherein R^1 is selected from the group consisting of (C_3-C_8)cycloalkyl, (C_2-C_{10})heterocyclyl, phenyl, and (C_1-C_{10})heteroaryl; wherein each of said (C_2-C_{10})heterocyclyl, phenyl, or (C_1-C_{10})heteroaryl is unsubstituted or substituted with one to three substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, Cl, $-NH_2$, -OH, (C_1-C_8)alkyl-NH-, and $[(C_1-C_8)alkyl]_2>N-$; wherein each of said (C_1-C_8)alkyl substituent, wherever it occurs, is unsubstituted or substituted with one to three substituents selected from $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, $-O-(C=O)-(C_1-C_8)$alkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl. Within this embodiment, preferably R^1 is phenyl, tetrahydropyridinyl, piperidinyl or pyridinyl.

In another embodiment, the invention relates to compounds of the Formula I wherein R^1 is $-C(=O)-R^5$, and R^5 is (C_1-C_8)alkyl-O- or (C_2-C_{10})heterocyclyl, such as morpholinyl; wherein said R^5 (C_2-C_{10})heterocyclyl is unsubstituted or substituted with (C_1-C_8)alkyl, such as methyl or ethyl.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein R^1 is $-C(=O)-NR^6R^7$; wherein each of said R^6 and R^7 are independently H or (C_1-C_8)alkyl; and wherein each of said R^6 and R^7 (C_1-C_8)alkyl are unsubstituted or substituted with one to three substituents independently selected from the group consisting of OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, (C_2-C_{10})heterocyclyl, and (C_1-C_{10})heteroaryl.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein R^2 is H or (C_1-C_8)alkyl unsubstituted or substituted with one to four substituents independently selected from the group consisting of OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, (C_2-C_{10})heterocyclyl, and (C_1-C_{10})heteroaryl.

In another embodiment, the invention relates to compounds of the Formula I wherein A is =N-.

In another embodiment, the invention relates to compounds of the Formula I wherein R^2 is $-C(=O)-R^8$, wherein R^8 is selected from the group consisting of (C_1-C_8)alkyl, (C_2-C_8)alkenyl, $(C_2-$

C_8)alkynyl, $-NH_2$, and R^{37} selected from the group consisting of (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, and (C_1-C_8)alkyl-O-; wherein each of said R^8 and R^{37} (C_1-C_8)alkyl, wherever it occurs, is independently unsubstituted or substituted with one to four substituents independently selected from R^{40} selected from the group consisting of F, OH, $-NH_2$, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, (C_1-C_{10})heteroaryl; (C_1-C_8)alkyl-NH- and $[(C_1-C_8)alkyl]_2>N-$;

wherein each of said R^{40} (C_1-C_8)alkyl, wherever it occurs, is independently unsubstituted or substituted with one to four substituents independently selected from R^{44} independently selected from the group consisting of OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, and (C_3-C_{10})cycloalkyl-NH-;

wherein each of said each of said R^{40} (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs, is independently unsubstituted or substituted with one to four substituents independently selected from R^{47} selected from the group consisting of (C_1-C_8)alkyl, OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, and (C_3-C_{10})cycloalkyl-NH-; and

wherein each of said R^{47} (C_1-C_8)alkyl, wherever it occurs, is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, and (C_3-C_{10})cycloalkyl-NH.

In another embodiment, the invention relates to compounds of the Formula I wherein R^2 is $-C(=O)-R^8$, wherein R^8 is selected from the group consisting of (C_3-C_8)cycloalkyl, (C_2-C_{10})heterocyclyl, phenyl, or (C_1-C_{10})heteroaryl; wherein each of said R^8 (C_3-C_8)cycloalkyl, (C_2-C_{10})heterocyclyl, phenyl, or (C_1-C_{10})heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^{40} selected from the group consisting of (C_1-C_8)alkyl, F, OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl; wherein each of said R^{40} (C_1-C_8)alkyl, wherever it occurs, is independently unsubstituted or substituted with one to four substituents independently selected from R^{44} independently selected from the group consisting OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, and (C_3-C_{10})cycloalkyl-NH-; wherein each of said R^{40} (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^{47} selected from the group consisting of (C_1-C_8)alkyl, OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, and (C_3-C_{10})cycloalkyl-NH-; wherein each of said R^{47} (C_1-C_8)alkyl, wherever it occurs, is unsubstituted or substituted with one to four substituents independently selected from the group consisting of OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, and (C_3-C_{10})cycloalkyl-NH.

In another embodiment, the invention relates to compounds of the Formula I wherein said R^3 is on any one of position 7, 8, or 9 of said compound of the formula I. Preferably, the invention relates to compounds of the Formula I wherein said R^3 is on position 8 of said compound of the formula I.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein said R^4 is on position 7 of said compound of the formula I. More preferably, said R^3 is on position 8 of said compound of the formula I and said R^4 is on position 7 of said compound of the formula I.

In another embodiment, the invention relates to compounds of the Formula I wherein said R^4 is Cl or Br on position 7 of said compound of the formula I.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein said R^4 is H on position 7 of said compound of the formula I.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein X is O.

In another preferred embodiment, the invention relates to compounds of the Formula I wherein the group -Y-Z- has the formula -N=CH-.

Preferably the invention relates to compounds of the Formula I selected from the group

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenyl-acetamide;

2-Cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-phenyl-butyramide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide;

3-Fluoro-2-methyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide;

2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-trifluoromethyl-benzamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-(3-Chlorophenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide;

1-Acetyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)piperidine-4-carboxamide;

3-(2-Methylphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide;

(2S)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-phenyl-butyramide compound with trifluoro-acetic acid;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide trifluoroacetate;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-Ethylsulfanyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-nicotinamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

N-[2-(3-Dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-fluoro-3-trifluoromethyl-benzamide;

6-Oxo-2-phenyl-*N*-(2-phenylcyclopropyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

N-[1-(4-Fluorophenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt);

Acetic acid 3-[6-oxo-8-[((1R, 2R)-2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-benzyl ester;

(1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-hydroxymethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide (hydrochloric salt);

N-[1-(4-Hydroxyphenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

2,3-Difluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

N-(4-Fluorobenzyl)-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-cyclobutylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide(hydrochloric salt);

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-ylmethyl-phenyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide(hydrochloric salt);

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-[6-(trifluoromethyl)pyridin-3-yl]cyclopropanecarboxamide trifluoroacetate;

(2R)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenyl-acetamide (hydrochloric salt);

(2R)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide(hydrochloric salt);

(3E)-4-Phenyl-but-3-enoic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-Indan-2-yl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

(1,2-*trans*)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt);

(1,2-*trans*)-2-(3-Methoxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-Indan-2-yl-(6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

(2*R*)-2-Hydroxy-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylethanamide;

(1,2-*trans*)-2-Pyridin-2-yl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide acetic acid;

(1,2-*trans*)-2-(1*H*-Imidazol-4-yl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide acetic acid;

(2R)-Piperidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt);

(2S)- 2-Amino-3-cyano-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-propionamide acetic acid;

(2R)-2-amino-3-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide (hydrochloric salt);

(1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester;

(2R)-3-(4-Hydroxyphenyl)-2-(methylamino)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide (hydrochloric salt);

(2R)-2-Amino-3-(4-fluorophenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide (hydrochloric salt);

(1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methylamide;

(1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide;

(1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide;

(2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide (hydrochloric salt);

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1,2-*trans*)-2-(3-Bromo-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1,2-*trans*)-2-(3-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-bromo-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt);

(1R,2R)-*N*-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide;

N-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-pyridin-3-ylcyclopropanecarboxamide;

N-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-pyridin-3-ylcyclopropanecarboxamide;

(1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-propyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-propenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt);

(1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (dihydrochloric salt);

(2R)-2-Amino-2-cyclohexyl-*N*-[2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide (dihydrochloric salt);

(1,2-*trans*)-*N*-[1-(2-Hydroxyethyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-phenylcyclopropanecarboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-dimethylaminomethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [1-(2-amino-ethyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-morpholin-4-yl-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-yl-prop-1-ynyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide; and

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [1-(2-amino-ethyl)-2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(1*H*-imidazol-2-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-cyano-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; and

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(1*H*-imidazol-2-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide; or

the pharmaceutically acceptable salts or solvates thereof.

Other preferred compounds are selected from the group consisting of:

3-Fluoro-2-methyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide;

2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

Acetic acid 3-[6-oxo-8-[((1R, 2R)-2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-benzyl ester;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-hydroxymethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-cyclobutylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-ylmethyl-phenyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

2-Indan-2-yl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

(1,2-*trans*)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(2*R*)-2-Amino-3-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methylamide;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1H-[1,2]diazepino[4,5,6-cd]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1H-[1,2]diazepino[4,5,6-cd]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide;

(2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide;

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide;

(1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-propenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(2R)-2-Amino-2-cyclohexyl-*N*-[2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamidede;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-hydroxymethyl-6-oxo-5,6-dihydro-1*H*-[1,2-*cd*]diazepino[4,5,6]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-yl-prop-1-ynyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(1*H*-imidazol-2-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-cyano-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; and

(2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide hydrochloride; or

the pharmaceutically acceptable salts or solvates thereof.

Other preferred compounds of formula I are selected from the group consisting of:

2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide;

(1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-hydroxymethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide(hydrochloride);

6-Oxo-2-phenyl-*N*-[(1*R*)-1-phenylethyl]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(2*R*)-2-Hydroxy-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylethanamide;

(1,2-*trans*)-2-Pyridin-2-yl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (acetic acid salt);

(1,2-*trans*)-2-(1*H*-Imidazol-4-yl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (acetic acid salt);

(2R)-Piperidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt);

(2*R*)-2-Amino-3-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide;

Example 182: (1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-*N*-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide; and

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [1-(2-amino-ethyl)-2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide; or

the pharmaceutically acceptable salts or solvates thereof.

In another embodiment, the invention also relates to compounds of the Formula I that are selective for CHK-1 over CHK-2 with selectivity ratio between about 5 folds and about 5000 folds; preferably between about 50 folds and about 1000 folds; and more preferably between about 70 folds and about 830 folds. Within this embodiment, the more preferred compounds are selected from the group consisting of:

2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide;

N-[2-(3-Dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-fluoro-3-trifluoromethyl-benzamide;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide(hydrochloride);

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide;

(2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide hydrochloride;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide; and

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; or

the pharmaceutically acceptable salts or solvates thereof.

Another object of the invention is to provide a composition for the treatment of neoplasms, and for enhancing the antineoplastic effects of anti-neoplastic agents and therapeutic radiation.

In an embodiment, the invention relates to a composition containing a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof and an anti-neoplastic agent as a combined preparation for the simultaneous, separate or sequential use in treating a neoplasm.

In another embodiment, the invention relates to a composition containing a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof and an anti-neoplastic agent as a combined preparation for the simultaneous, separate or sequential use in treating a neoplasm wherein the anti-neoplastic agent is selected from the group consisting of alkylating agents, antibiotics and plant alkaloids, hormones and steroids, synthetic agents having anti-neoplastic activity, antimetabolites and biological molecules having anti-neoplastic activity.

In another embodiment, the invention relates to a composition containing a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof and an anti-neoplastic agent as a combined preparation for the simultaneous, separate or sequential use in treating a neoplasm wherein the anti-neoplastic agent is selected from the group consisting of

Ara-c, VP-16, cis-platin, adriamycin, 2-chloro-2-deoxyadenosine, 9- (3-D-arabinosyl-2-fluoroadenine, carboplatin, gemcitabine, camptothecin, paclitaxel, BCNU, 5-fluorouracil, irinotecan, and doxorubicin.

Another object of the invention is to provide a method for the treatment of neoplasms.

In an embodiment, the invention relates to a method for treating a neoplasm which comprises administering to a mammal in need thereof, an anti-neoplastic agent in combination with a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In another embodiment, the invention relates to a method for treating a neoplasm which comprises administering to a mammal in need thereof, an anti-neoplastic agent in combination with a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein the anti-neoplastic agent is selected from the group consisting of Ara-c, VP-16, cis-platin, adriamycin, 2-chloro-2-deoxyadenosine, 9-β-D-arabinosyl-2-fluoroadenine, carboplatin, gemcitabine, camptothecin, paclitaxel, BCNU, 5-fluorouracil, irinotecan, and doxorubicin. In another embodiment, more than one anti-neoplastic agents may be used in combination with a compound of the Formula I, the pharmaceutically acceptable salts, solvates, or prodrugs thereof.

Another object of the invention is to provide methods for enhancing the anti-neoplastic effect of therapeutic radiation.

In an embodiment, the invention relates to a method for treating a neoplasm which comprises administering to a mammal in need thereof, therapeutic radiation having an anti-neoplastic effect in combination with a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Another object of the invention is to provide methods for enhancing the antineoplastic effect of an anti-neoplastic agent.

In an embodiment, the invention relates to a method for enhancing the anti-neoplastic effect of an anti-neoplastic agent in a mammal which comprises administering to a mammal in need thereof, a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof, in combination with an antineoplastic agent. The antineoplastic agents include alkylating agents, antibiotics and plant alkaloids, hormones and steroids, synthetic agents having anti-neoplastic activity, antimetabolites and biological molecules having anti-neoplastic activity. Specific antineoplastic agents include Ara-c, VP-16, cis-platin, adriamycin, 2-chloro-2-deoxyadenosine, 9-β-D-arabinosyl-2-fluoroadenine, carboplatin, gemcitabine, camptothecin, paclitaxel, BCNU, 5-fluorouracil, irinotecan, and doxorubicin.

In another embodiment, the invention relates to a method for enhancing the anti-neoplastic effect of therapeutic radiation in a mammal which comprises administering to a mammal in need thereof, a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof, in combination with therapeutic radiation having an anti-neoplastic effect.

Another object of the invention is to provide a method for the treatment of a condition which can be treated by the inhibition of protein kinases. In one embodiment of the invention, the protein kinases are selected from the group consisting of *Checkpoint kinase 1* (CHK-1), *Checkpoint kinase 2* (CHK-2), *Cyclin dependent kinase 1* (CDK1), *Serum and glucocorticoid regulated kinase* (SGK), *Adenosine 5'-monophosphate (AMP)-activated protein kinase* (AMPK), *Lymphoid T cell tyrosine kinase* (LCK), *Mitogen activated protein kinase-2* (MAPK-2), *Mitogen- and stress-activated protein kinase 1* (MSK1), *Rho kinase* (ROCK-II), *P70 S6 kinase* (p70S6K), *cAMP (adenosine 3',5' cyclic monophosphate)-dependent protein kinase* (PKA), *Mitogen activated protein kinase* (MAPK), *Mitogen activated protein kinase-1* (MAPK-1), *Protein kinase C-related kinase 2* (PRK2), *3'-Phosphoinositide dependent kinase 1* (PDK1), *Fyn kinase* (FYN), *Protein kinase C* (PKC), *Protein Kinase C Beta 2* (PKCβII), *Protein Kinase C Gamma* (PKCγ), *Vascular endothelial growth factor receptor 2* (VEGFR-2), *Fibroblast growth factor receptor* (FGFR), *Phosphorylase kinase* (PHK), *Wee1 kinase* (Wee1), and *Protein Kinase B* (PKB). Preferably, the protein kinases are selected from the group consisting of *Checkpoint kinase 1* (CHK-1), *Checkpoint kinase 2* (CHK-2), *Mitogen activated protein kinase* (MAPK), *Mitogen activated protein kinase-1* (MAPK-1), *Mitogen activated protein kinase-2* (MAPK-2), *Vascular endothelial growth factor receptor 2* (VEGFR-2), *Fibroblast growth factor receptor* (FGFR), *Phosphorylase kinase* (PHK), *Protein Kinase B alpha* (PKBα), and *Wee1 kinase* (Wee1).

In an embodiment, the invention relates to a method for the treatment of a condition which can be treated by the inhibition of protein kinases in a mammal, including a human, comprising administering to a mammal in need thereof, a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In another embodiment, said condition which can be treated by the inhibition of protein kinases is selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers.

Other aspects, advantages, and preferred features of the invention will become apparent from the detailed description below.

Detailed Description And Preferred Embodiments of The Invention

For purposes of the present invention, as disclosed and claimed herein, the following terms and abbreviations are defined as follows:

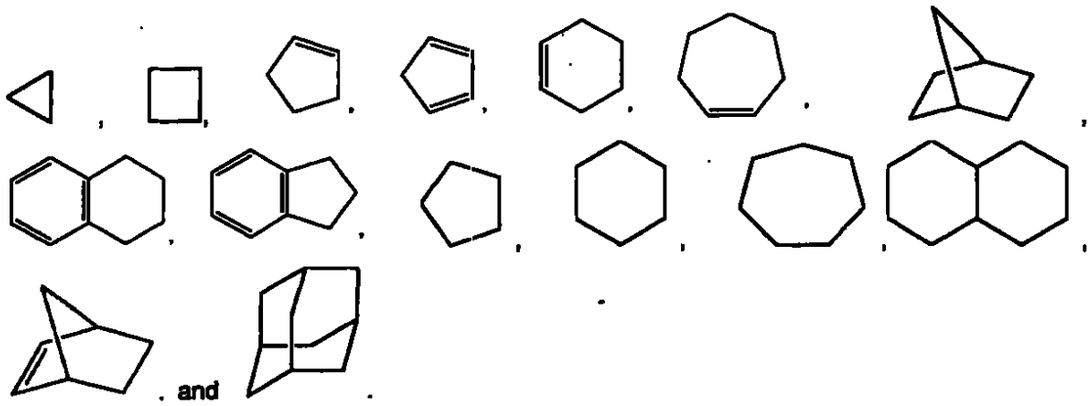
Unless otherwise indicated, the term "wherever it occurs" refers to any occurrence of any functional groups (such as R^1, R^2 or any substituents thereof), including any occurrence of any component of any functional groups referred to herein (*e.g.*, the "$(C_1$-$C_8)$alkyl component of $(C_1$-$C_8)$alkyl-O-).

Unless otherwise indicated, the term "(C_1-C_8)alkyl" as well as the (C_1-C_8)alkyl component of other terms referred to herein (*e.g.*, the "(C_1-C_8)alkyl component of (C_1-C_8)alkyl-O-), may be linear or branched (such as methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl).

Unless otherwise indicated, the term "(C_2-C_8)alkenyl" means straight or branched hydrocarbon radical, substituent, moiety, or sub-moiety referred to herein having 2 to 8 carbon atoms having at least one double bond including, but not limited to ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, or 2-butenyl.

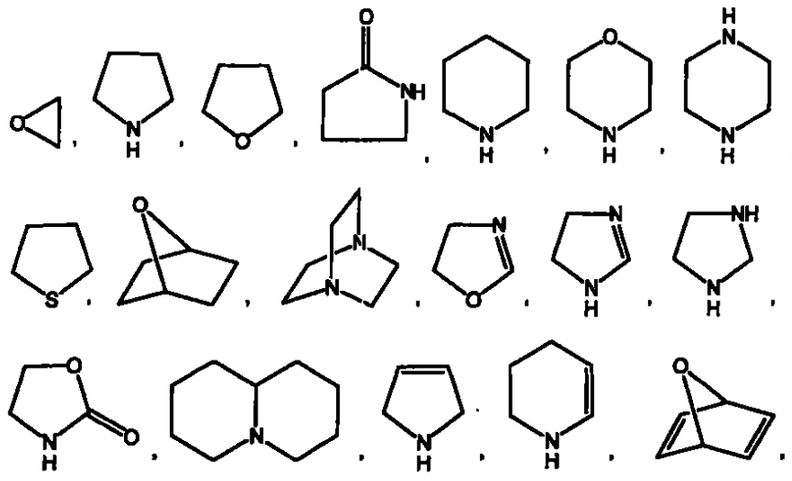
Unless otherwise indicated, the term "(C_2-C_8)alkynyl" is used herein to mean straight or branched hydrocarbon radical, substituent, moiety, or sub-moiety referred to herein having 2 to 8 carbon atoms having one triple bond including, but not limited to, ethynyl (-C≡C-H), propynyl (-CH_2-C≡C-H or -C≡C-CH_3), or butynyl (-CH_2-CH_2-C≡C-H, or -CH_2-C≡C-CH_3, or -C≡C-CH_2CH_3).

Unless otherwise indicated, the term "(C_3-C_{10})cycloalkyl" refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon radical, substituent, moiety, or sub-moiety referred to herein containing a total of from 3 to 10 carbon atoms, preferably 5-8 ring carbon atoms. Exemplary (C_3-C_{10})cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Illustrative examples of (C_3-C_{10})cycloalkyl are derived from, but not limited to, the following:

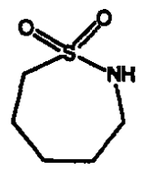


Unless otherwise indicated, the term "(C_2-C_{10})heterocyclyl" refers to a non-aromatic, saturated or partially saturated, monovalent, monocyclic or fused, spiro or unfused bicyclic or tricyclic radical, substituent, moiety, or sub-moiety referred to herein containing a total of from 2 to 10 ring carbon atoms and 1 to 5 ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of (C_2-C_{10})heterocyclyl include azetidinyl, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, chromenyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl, dihydrofuryl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.1]nonyl, azabicylo[4.3.0]nonyl,

oxabicyclo[2.2.1]heptyl, 1,5,9-triazacyclododecyl, and the like. Additional illustrative examples of (C_2-C_{10})heterocyclyl are derived from, but not limited to, the following:



and



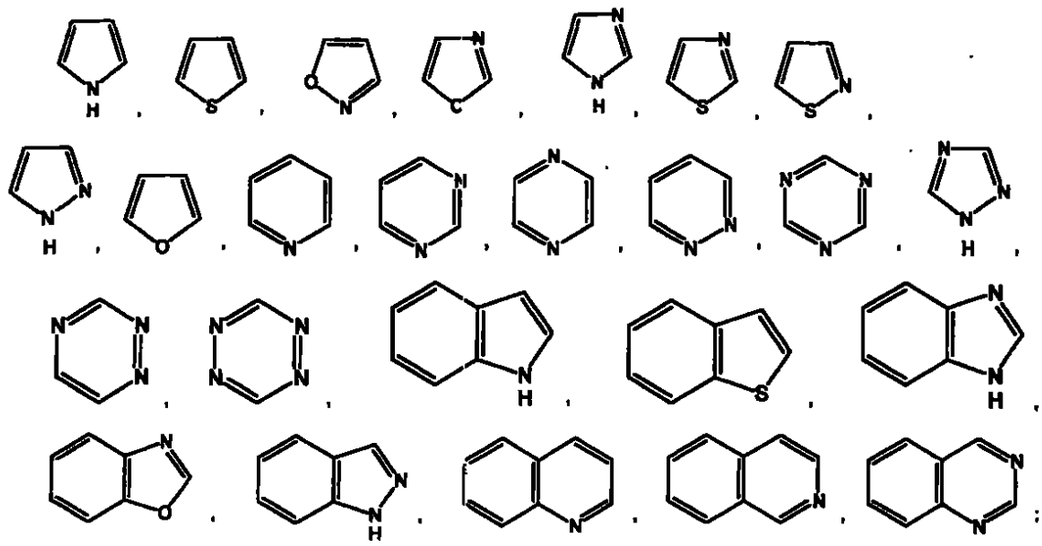
unless otherwise indicated, the foregoing (C_2-C_{10})heterocyclyl can be C-attached or N-attached where such is possible. For instance, piperidyl can be piperid-1-yl (N-attached) or piperid-2-yl (C-attached).

Unless otherwise indicated, the term "(C_6-C_{10})aryl" refers to an aromatic, monovalent, monocyclic or fused or unfused bicyclic or tricyclic radical, substituent, moiety, or sub-moiety referred to herein containing a total of from 6 to 10 ring carbon atoms. Illustrative examples of (C_6-C_{10})aryl are derived from, but not limited to, the following:



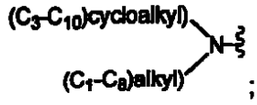
Unless otherwise indicated, the term "(C_1-C_{10})heteroaryl" refers to an aromatic, monovalent monocyclic, fused or unfused bicyclic or tricyclic radical, substituent, moiety, or sub-

moiety referred to herein containing a total of from 1 to 10 ring carbon atoms and 1 to 5 ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of (C_1-C_{10})heteroaryl include, but not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxyalinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, and phenoxazinyl. Further examples of (C_1-C_{10})heteroaryl are derived from, but not limited to, the following:



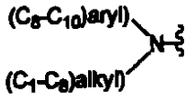
unless otherwise indicated, the foregoing (C_1-C_{10})heteroaryl can be C-attached or N-attached where such is possible. For instance, pyridyl can be pyrid-1-yl (N-attached) or pyrid-3-yl (C-attached).

Unless otherwise indicated, the term "((C_3-C_{10})cycloalkyl)((C_1-C_8)alkyl)>N-" refers to a radical, substituent, moiety, or sub-moiety referred to herein having the formula:



; wherein the terms "(C_3-C_{10})cycloalkyl" and "(C_1-C_8)alkyl" are as defined above.

Unless otherwise indicated, the term "((C_6-C_{10})aryl)((C_1-C_8)alkyl)>N-" refers to a radical, substituent, moiety, or sub-moiety referred to herein having the formula:



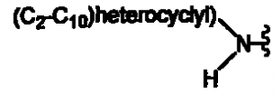
; wherein the terms "(C_6-C_{10})aryl" and "(C_1-C_8)alkyl" are as defined above.

Unless otherwise indicated, the term "(C_1-C_{10})heteroaryl-NH-" refers to a radical, substituent, moiety, or sub-moiety referred to herein having the formula:



; wherein the term "(C_1-C_{10})heteroaryl" is as defined above and wherein said (C_1-C_{10})heteroaryl is bonded to the –NH- via a ring (C_1-C_{10})heteroaryl carbon atom.

Unless otherwise indicated, the term "(C_2-C_{10})heterocyclyl-NH-" refers to a radical, substituent, moiety, or sub-moiety referred to herein having the formula:



; wherein the term "(C_2-C_{10})heterocyclyl" is as defined above and wherein said (C_2-C_{10})heterocyclyl is bonded to the –NH- via a ring (C_2-C_{10})heterocyclyl carbon atom.

The term "a pharmaceutically acceptable salt" refers to a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

The term "prodrug", as used herein, refers to a metabolic precursor of a compound of the Formula I (or a salt thereof) that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject but is converted *in vivo* to an active compound of the Formula I. The term "active metabolite", as used herein, refers to a metabolic product of a compound of the Formula I that is pharmaceutically acceptable and effective. Prodrugs and active metabolites of compounds of the Formula I may be determined using techniques known in the art. Prodrugs and active metabolites of a compound may be identified using routine techniques known in the art. See, e.g., Bertolini et al., *J. Med. Chem.*, 40, 2011-2016 (1997); Shan, et al., *J. Pharm. Sci.*, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.*, 34, 220-230 (1995); Bodor, *Advances in Drug Res.*, 13,

224-331 (1984); Bundgaard, Design of Prodrugs (Elsevier Press 1985); and Larsen, Design and Application of Prodrugs. Drug Design and Development (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

The CHK-1 inhibitor of the present invention may be administered in combination with other anti-neoplasm therapies including anti-neoplastic agents and radiation therapy.

The term "in combination with" means that the compound of Formula I may be administered shortly before, shortly after, concurrently, or any combination of before, after, or concurrently, with such other anti-neoplasm therapies. Thus, the compound and the anti-neoplastic agent may be administered simultaneously as either as a single composition or as two separate compositions or sequentially as two separate compositions. Likewise, the compound and radiation therapy may be administered simultaneously, separately or sequentially. The compound may be administered in combination with more than one anti-neoplasm therapy. In a preferred embodiment, the compound may be administered from 2 weeks to 1 day before any chemotherapy, or 2 weeks to 1 day before any radiation therapy. In another preferred embodiment, the CHK-1 inhibitor may be administered during anti-neoplastic chemotherapies and radiation therapies. If administered following such chemotherapy or radiation therapy, the CHK-1 inhibitor may be given within 1 to 14 days following the primary treatments. The CHK-1 inhibitor may also be administered chronically or semi-chronically, over a period of from about 2 weeks to about 5 years. One skilled in the art will recognize that the amount of CHK-1 inhibitor to be administered in accordance with the present invention in combination with other antineoplastic agents or therapies is that amount sufficient to enhance the anti-neoplasm effects of anti-neoplastic agents or radiation therapies or that amount sufficient to induce apoptosis or cell death along with the anti-neoplastic or radiation therapy and/or to maintain an antianglogenic effect. Such amount may vary, among other factors, depending upon the size and the type of neoplasia, the concentration of the compound in the therapeutic formulation, the specific anti-neoplasm agents used, the timing of the administration of the CHK-1 inhibitors relative to the other therapies, and the age, size and condition of the patient.

The term "protein kinases", as used herein, refers to enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differentiation and proliferation, i.e., virtually all aspects of cell life in one way or another depend on the protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer). The protein kinases can be conveniently broken down into two major classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs). In addition, a third class of dual specificity kinases which can phosphorylate both tyrosine and serine-threonine residues is known. Examples of protein kinases and their isoforms

contemplated within this invention include, but are not limited to, *Checkpoint kinase 1* (CHK-1), *Checkpoint kinase 2* (CHK-2), *Cyclin dependent kinase 1* (CDK1), *Serum and glucocorticoid regulated kinase* (SGK), *Adenosine 5'-monophosphate (AMP)-activated protein kinase* (AMPK), *Lymphoid T cell tyrosine kinase* (LCK), *Mitogen activated protein kinase-2* (MAPK-2), *Mitogen- and stress-activated protein kinase 1* (MSK1), *Protein Kinase B* (PKB), *Protein Kinase B alpha* (PKBα), *Rho kinase* (ROCK-II), *P70 S6 kinase* (p70S6K), *cAMP (adenosine 3',5' cyclic monophosphate)-dependent protein kinase* (PKA), *Mitogen activated protein kinase-1* (MAPK-1), *Protein kinase C-related kinase 2* (PRK2), *3'-Phosphoinositide dependent kinase 1* (PDK1), *Fyn kinase* (FYN), *Protein kinase C* (PKC), *Protein Kinase C Beta 2* (PKCβII), *Protein Kinase C Gamma* (PKCγ), *Vascular endothelial growth factor receptor 2* (VEGFR-2), *Fibroblast growth factor receptor* (FGFR), *Phosphorylase kinase* (PHK), *Wee1 kinase* (Wee1), and *Protein Kinase B* (PKB).

Checkpoint kinase 2 (CHK-2) acts as a cell cycle checkpoint controller in response to DNA damage. CHK-2 is a downstream effector of ATM which phosphorylates p53 protein and affects cell cycle progreesion from G_1 to the S phase. CHK-2 activation also affects S phase progression. In addition along with CHK-1, CHK-2 influences G_2/M transition and plays a role in apoptosis if the damage cannot be repaired. CHK-2 could play a role in sensitizing cancer cells to DNA-damaging therapies. CHK-2 may also play a role as a tumor suppressor. Bartek, J. et. al. (2001) *Nature Reviews, Molecular Cell biology* 2:877-886.

Cyclin dependent kinase 1 (CDK1) is also known as Cdc2 in yeast cells. The cell cycle directs specific events that control growth and proliferation of cells. The cyclin B/Cdk1 complex promotes entry into mitosis. Cyclin B1 overexpression has been found in 90% of colorectal carcinomas Since the cell cycle is dysregulated in human cancers, modulation of CDK activity is a possible therapy. Olomoucine, a CDK inhibitor, has been shown to inhibit cellular proliferation in human cancer cells. In lymphoma cells, olomoucine arrests the cell cycle in both the G_1 and G_2 phases by inhibiting cyclin E/CDK2 and cyclin B/CDK1. Buolamwini, J.K. (2000) *Current Pharmaceutical Design* 6:379-392; Fan, S. et. al. (1999) *Chemotherapy* 45:437-445.

Serum and glucocorticoid regulated kinase (SGK) is rapidly and highly regulated by corticosteroids in A6 cells at the mRNA and protein levels. SGK is also induced by aldosterone in the kidney of adrenalectomized rats. SGK is activated by 3'-phosphoinositide dependent kinase 1 (PDK1). SGK might play a critical role in aldosterone target cells and may be physiologically important in the early response to aldosterone. Aldosterone receptor antagonists have recently shown great promise in clinical trials for patients with heart failure. The ability to mediate the physiological responses to aldosterone may like-wise prove beneficial. See Leslie, N. R. et. al. (2001) *Chemical Reviews* 101(8):2365-2380; Funder, J. W. (1999) *Molecular and Cellular Endocrinology* 151(1-2):1-3; Verrey, F. et. al. (2000) *Kidney International* 57(4):1277-1282.

Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) isoform α2 (AMPK α2) is present in high concentrations in skeletal muscle, heart, and liver while the α1 isoform is widely distributed. AMPK, probably the α2 isoform, phosphorylates acetyl-CoA carboxylase β isoform (ACCβ) and inactivates it under conditions electrical stimulation or exercise. In rat skeletal muscle, malonyl-CoA is regulated by ACCβis and involved in the regulatory mechanism of transferring long chain fatty acids into the mitochondria where they are oxidized. AMPK could therefore be linked to obesity and/or insulin resistance, and modulation of AMPK could be potentially beneficial in the treatment of these diseases. AMPK inhibits enzymes involved in glycogen and cholesterol synthesis. It is a possible regulatory enzyme that in response to adenosine 5'-triphosphate (ATP) depletion, reduces further ATP consumption by initiating cellular adjustments that are directed toward maintaining ATP levels. In addition, AMPK has been linked to transcription , regulation of creatinine kinase, apoptosis, and glucose transport. See Kemp, B. E. et. al. (1999) *Trends in Biochemical Sciences* 24(1):22-25; Friedman, J. (2002) *Nature* 415(6869):268-269; Ruderman, N. B. et. al. (1999) *American Journal of Physiology* 276(1, Pt. 1):E1-E18.

Lymphoid T cell tyrosine kinase (LCK) is a cytosolic non-receptor tyrosine kinase and a T-lymphocyte member of the Src family. LCK has been implicated in early phase T-cell receptor activation by antigens and plays a critical role in T-cell mediated immune responses. Upon activation by autophosphorylation, LCK phosphorylates T-cell receptor ξ–chains which can then recruit a second cytoplasmic protein-tyrosine kinase ZAP-70 to promote T-cell activation. Inhibitors could be used for the treatment of rheumatoid arthritis, diseases related to immune response and T-cell based leukemias and lymphomas. See Garcia-Echeverria, C. (2001) Current *Medicinal Chemistry* 8(13):1589-1604; Majolini, M. B. et. al. (1999) *Leukemia & Lymphoma* 35(3/4):245-254.

Mitogen- and stress-activated protein kinase 1 (MSK1) is activated on stimulation of the Ras-mitogen activated protein kinase (MAPK) pathway and also by the p38 stress kinase pathway. Both pathways are implicated in tumorigenesis. Stimulation of the Ras-MAPK signal transduction pathway by growth factors or phorbol esters results in phosphorylation of histone H3. MSK1 has been shown to mediate epidermal growth factor (EGF) or TPA (12-O-tetradecanoylphorbol-13-acetate, a phorbol ester) induced phosphorylation of H3. There is evidence that persistent activation of Ras-MAPK pathway and MSK1 resulting in elevated phosphorylated H3 levels may contribute to aberrant gene expression observed in oncogene-transformed cells. Inhibition of MSK1 suppressed the induction of c-fos (proto-oncogene) and uPA genes in parental and oncogene-transformed cells. Both c-fos and uPA are involved in tumor invasion and metastasis. See Strelkov, I. et. al. (2002) *Cancer Research* 62(1):75-78; Zhong, S. et. al. (2001) *Journal of Biological Chemistry* 276(35):33213-33219; Nomura, M. et. al. (2001) *Journal of Biological Chemistry* 276(27);25558-25567.

Rho kinase (ROCK-II) is also known as ROKα. By inhibiting ROCK-II, one could potentially influence Rho GTPases which act as molecular controls that regulate many essential cellular processes, including actin dynamics, cell-cycle progression, and cell adhesion. The *in vitro* and *in vivo* biological effects of Y-27632, a specific inhibitor of ROCK, have been described in the literature and include lowering blood pressure in hypertensive rats, inhibition of Rho-induced formation of stress fibers and focal adhesions, and inhibition of tumor growth. See Narumiya, S. et. al(2000) *Methods in Enzymology* 325 (Regulators and Effectors of Small GTPases, Part D): 273-284 (and associated references listed therein); Bishop, et al. (2000) *Biochem. J.* 348: 241-255.

P70 S6 kinase ($p70^{S6K}$) is found as two isoforms-one cytoplasmic and the other in the nucleus. They are similar except for N-terminus, and both are called $p70^{S6K}$ or S6K1. A second functional homologue S6K2 was also identified. $P70^{S6K}$ is a downstream target of the lipid kinase phosphoinositide 3-OH kinase (PI(3)K). $P70^{S6K}$ is implicated in cell cycle control and neuronal cell differentiation. $P70^{S6K}$ may also function in regulating cell motility which could influence tumor metastases, the immune response, and tissue repair. Along with PKB/Akt, $p70^{S6K}$ is a crucial effector in oncogenic protein-tyrosine kinase (PTK) signaling. $P70^{S6K}$ may be a more potent kinase for BAD than PKB/Akt (see above) in response to insulin growth factor 1 (IGF-1) stimulation. $P70^{S6K}$ may therefore play an important antiapoptotic role. See Blume-Jensen, P. et. al. (2001) *Nature* 411(6835):355-365; Accili, D. (2001) *Journal of Clinical Investigation* 108(11):1575-1576; Hidalgo, M. et al. (2000) *Oncogene* 19(56):6680-6686; Berven, L. et. al. (2000) *Immunology and Cell Biology* 78(4):447-451.

cAMP (adenosine 3',5' cyclic monophosphate)-dependent protein kinase (PKA) is involved in a wide range of physiological responses following interaction with cAMP. cAMP is a second messenger that regulates many different cellular activities such as gene transcription, cell growth and differentiation, ion channel conductivity, and release of neurotransmitters. The cAMP/PKA interaction acts as a major regulatory mechanism in mammals, and PKA has been shown phosphorylate a myriad of physiolcgical substrates. PKA has two major isoforms- PKAI and PKAII. PKAI inhibitors have shown enhancing effects when used in combination certain cytotoxic cancer therapies. Antisense oligonucleotides targeting the PKAI subunit RIα have shown enhanced anti-tumor effects when combined with Taxol. Glucagon activates PKA and PKA may influence insulin response along with calmodulin-dependent protein kinase and protein kinase C. PKA is involved in regulating cardiac L-type calcium channels, and modulation of the implicated regulatory pathways may prove useful in the treatment of heart disease. In addition, dysfunctional T-cells isolated from HIV patients have been restored by the addition of PKAI antagonists. See Skalhegg, B.S. et. al. (2000) *Frontiers In Bioscience* [Electronic Publication] 5:D678-D693; *Brandon*, E. P. et. al. (1997) *Current Opinion in Neurobiology* 7(3):397-*403; Nesher, R. et. al.(2002) Diabetes 51(Suppl. 1): S68-S73; Shabb, J. B. (2001) Chemical* Reviews 101(8):2381-

2411; Kamp, T.J. et. al. (2000) *Circulation Research* 87(12);1095-1102; Tortora, G. et.al. (2002) *Clinical Cancer Research* 8:303-304; Tortora, G. et.al. (2000) *Clinical Cancer Research* 6:2506-2512.

Mitogen activated protein kinase (MAPK) is also known as ERK. In tumorigenesis, ras oncogenes transmit extracellular growth signals. The MAPK pathway is an important signaling route between membrane-bound ras and the nucleus. A phosphorylation cascade involving three key kinases is involved. They are Raf, MEK (MAP kinase kinase) and MAPK/ERK. Raf isoforms phosphorylate and activate isoforms MEK1 and MEK2. MEK1 and 2 are dual specificity kinases that in turn phosphorylate and activate the MAPK isoforms MAPK1/ERK1 and MAPK2/ERK2. In fibroblasts, MAPK1/ERK1 and MAPK2/ERK2 are both strongly activated by growth factors and by tumor-promoting phorbol esters. MAPK1/ERK1 and MAPK2/ERK2 are also involved with glucose regulation, neurotransmitter regulation, and secetagogue regulation (in endocrine tissues). The MAPK pathway has also been linked to the induction of cyclin D1 mRNA and thus linked to G1 phase of cell cycle. See Webb, C.P. et. al. (2000) *Cancer Research* 60(2), 342-349; Roovers, K. et. al. (2000) *BioEssays* 22(9):818-826; Chen, Z. et. al. (2001) *Chemical Reviews* 101(8):2449-2476; Lee, J. C. et. al. (2000) *Immunopharmacology* 47(2-3):185-201, Sebolt-Leopold J.S. (2000) Oncogene 19:6594-6599; Cheng, F.Y. et. al. (2001) *Journal of Biological Chemistry* 276(35):32552-32558; Cobb, M.H.et. al. (2000) Trends in Biochemical Sciences 25(1):7-9; Cobb, M.H.et. al. (1995) *Journal of Biological Chemistry* 270(25):14843-14846; Deak, M. et. al. (1998) *EMBO Journal* 17(15):4426-4441; Davis, J.D. (1993) *Journal of Biological Chemistry* 268(20):14553-14556.

cSrc (also known as p60 c-src) is cytosolic, non-receptor tyrosine kinase. c-Src is involved in the transduction of mitogenic signals from a number of polypeptide growth factors such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF). c-Src is over expressed in mammary cancers, pancreatic cancers, neuroblastomas, and others. Mutant c-Src has been identified in human colon cancer. c-Src phosphorylates a number of proteins that are involved in regulating cross-talk between the extracellular matrix and the cytoplasmic actin cytoskeleton. Modulation cSrc activity could have implications in diseases relating to cell proliferation, differentiation and death. See Bjorge, J.D. et. al. (2000) *Oncogene* 19(49):5620-5635; Halpern, M. S. et. al. (1996) *Proc. Natl. Acad. Sci. U. S. A.* 93(2), 824-7; Belsches, A.P. et. al. (1997) *Frontiers in Bioscience* [Electronic Publication] 2:D501-D518; Zhan, X. et. al (2001) *Chemical Reviews* 101:2477-2496; Haskell, M.D. et. al. (2001) *Chemical Reviews* 101:2425-2440;

Protein kinase C-related kinase 2 (PRK2) is regulated by the G-protein Rho. PRK2 is found in regions of large actin turnover. Endogenous PRK2 kinase activity increases with keratinocyte differentiation and is associated with keratinocyte cell-cell adhesion and Fyn kinase activation. See Gross, C., et. al. (2001) *FEBS Letters* 496(2,3):101-104; Calautti, E. et. al. (2002) *Journal of Cell Biology* 156(1):137-148.

3'-Phosphoinositide dependent kinase 1 (PDK1) phosphorylates and activates members of the AGC (cAMP-dependent, cGMP-dependent, and protein kinase C) kinase family that are activated downstream of phosphoinositide 3-kinase (PI3K). PI3K becomes active through insulin stimulation. PDK1 activates a number of protein kinases and therefore can be connected to the regulation of a number of insulin specific events. PDK1 phosphorylation and activation of PKCζ is necessary for insulin-dependent GLUT4 translocation. Insulin-induced GLUT4 translocation is physiologically related to the actin-based cytoskeleton. Disturbances in actin filaments have been linked to loss of insulin effect on glucose transport and decreased translocation of GLUT4. See Wick, K. L. et. al. (2001) *Current Drug Targets: Immune, Endocrine and Metabolic Disorders* 1(3):209-221; Peterson, R. T. et. al. (1999) *Current Biology* 9(14):R521-R524; Toker, A. et al. (2000) *Cell* 103(2):185-188; Leslie, N.R. (2001) *Chem. Rev.* 101: 2365-2380.

Fyn kinase (FYN) is a member of the Src family of tyrosine kinases. Fyn has been implicated in positive control of keratinocyte cell-cell adhesion. Adhesion plays a crucial function in establishment and maintenance of organized tissues. Fyn knockout and transgenic mice established that Fyn participates in T cell receptor (TCR) signaling. Overexpression of the fyn(T) transgene produces T cells with enhanced responsiveness to TCR signaling. Conversely, expression of an inactive kinase form is inhibitory. Fyn may be an appropriate target for treatment of autoimmune diseases. Fyn -/- mice are hypersensitive to alcohol which suggests that Fyn might be a target for the treatment of alcoholism. Alteration of Fyn levels may also aid in the treatment of skin disorders. Fyn has been implicated in the regulation of programmed cell death, and Fyn-/- mice exhibit reduced apoptosis. See also PRK2. See Calautti, E. et. al. (2002) *Journal of Cell Biology* 156(1):137-148; Resh, M. D. (1998) *Journal of Biochemistry & Cell Biology* 30(11):1159-1162.

Vascular endothelial growth factor receptor 2 (VEGFR-2) is also known as FLK-1 and as KDR (kinase insert domain receptor). Other VEGF receptor tyrosine kinases include VEGFR-1(Flt-1) and VEGFR-3 (Flt-4). Angiogenesis or the development of new vasculature is central to the process by which solid tumors grow. The degree of vasculaturization has been linked with increased potential for metastasis. VEGFR-2, expressed only on endothelial cells, binds the potent angiogenic growth factor VEGF and mediates the subsequent signal transduction. Inhibition of VEGF-R2 activity has resulted in decreased angiogenesis and tumor growth in *in vivo* models, and inhibitors of VEGFR-1 are currently in clinical trials for the treatment of cancer. See Strawn et al.,(1996) *Cancer Research* 56:3540-3545; Millauer et al.,(1996) *Cancer Research* 56:1615-1620; Sakamoto, K. M. (2001) *IDrugs* 4(9):1061-1067; Ellis, L. M. et.al. (2000) *Oncologist* 5(Suppl. 1):11-15; Mendel, D.B. et. al (2000) *Anti-Cancer Drug Design* 15:29-41; Kumar, C.C. et.al. (2001) *Expert Opin. Emerging Drugs* 6(2):303-315; Vajkoczy, P. et. al (1999) *Neoplasia* 1(1):31-41.

Fibroblast growth factor receptor (FGFR) binds the angiogenic growth factors aFGF and bFGF and mediates subsequent intracellular signal transduction. Growth factors such as bFGF may play a critical role in inducing angiogenesis in solid tumors that have reached a certain size. FGFR is expressed in a number of different cell types throughout the body and may or may not play important roles in normal physiological processes in adult humans. Systemic administration of a small-molecule inhibitor of FGFR has been reported to block bFGF-induced angiogenesis in mice. See Yoshiji et al., (1997) *Cancer Research* 57: 3924-3928; Mohammad et al., (1998) *EMBO Journal* 17:5996-5904.

Phosphorylase kinase (PHK) activates glycogen phosphorylase. The primary consequence of this activation is to release glucose 1-phosphate from glycogen. Conversion to glycogen is the major means by which glucose is stored in mammals. Intracellular glycogen stores are used to maintain blood-glucose homeostasis during fasting and are a source of energy for muscle contraction. *In Vivo*, PHK is phosphorylated by cAMP-dependent protein kinase (PKA) which increases the specific activity of PHK. Both Type 1 and 2 diabetics show reduced glycogen levels in liver and muscle cells. Glycogen levels are tightly regulated by hormones and metabolic signaling. Kinase inhibitors that could augment intracellular glycogen levels may prove beneficial in the treatment of diabetes. See Brushia, R.J. et.al. (1999) *Frontiers in Bioscience* [Electronic Publication] 4:D618-D641; Newgard, C.B. et. al. (2000) *Diabetes* 49:1967-1977; Venien-Bryan, C. et. al. (2002) *Structure* 10:33-41; Graves, D. et. al. (1999) *Pharmacol. Ther.* 82:(2-3)143-155; Kilimann, M.W. (1997) Protein Dysfunction and Human Genetic Disease Chapter 4:57-75.

Wee1 kinase (Wee1) along with Mik1 kinase has been shown to phosphorylate Cdc2. Phosphorylation of Cdc2 has been shown to prevent mitotic entry. Wee1 may play an important role the normal growth cycle of cells and may be implicated in cell-cycle checkpoint control. Rhind, N. et. al. (2001) *Molecular and Cellular Biology* 21(5):1499-1508.

Protein Kinase B (PKB) is also known as Akt. There are three very similar isoforms known as PKB α, β, and γ (or Akt 1, 2, and 3). Ultraviolet irradiation in the 290-320nM range has been associated with the harmful effects of sunlight. This irradiation causes activation of PKB/Akt and may be implicated in tumorigenesis. Over expressed PKB/Akt has been shown in ovarian, prostate, breast & pancreatic cancers. PKB/Akt is also involved in cell cycle progression. PKB/Akt promotes cell survival in a number of ways. It phosphorylates the proapoptotic protein, BAD, so that it is unable to bind and inactivate the antiapoptotic protein Bcl-xl. PKB/Akt also serves to inhibit apoptosis by inhibiting caspase 9 and forkhead transcription factor and by activating IkB kinase. See Barber, A.J. (2001) *Journal of Biological Chemistry* 276(35):32814-32821; Medema, R.H. et al. (2000) *Nature* 404:782-787; Muise-Helmericks, R.C. et. al (1998) *Journal of Biological Chemistry* 273(45): 29864-29872; Nomura, M. et. al. (2001) *Journal of Biological Chemistry* 276(27): 2558-25567; Nicholson, K. M. et.al. (2002) Cellular Signaling 14(5): 381-395; Brazil,

D.P. et. al. (2001) *Trends in Biochemical Sciences* 26(11): 657-664. Leslie, N.R. (2001) *Chem Rev* 101: 2365-2380.

Protein kinase C (PKC) classical isoforms are designated α,β1, β2 and γ and all are Ca^{2+} dependent. PKC isoforms are involved in signal transduction pathways linked to a number of physiological responses including membrane transport, cellular differentiation and proliferation, organization of cytoskeletal proteins and gene expression. Tumor promoting phorbol esters activate classical PKC isoforms and antisense oligonucleotides can block this activation. PKC isoforms are often over expressed in various cancers. PKC inhibitors have been shown to reverse p-glycoprotein-mediated multi-drug resistance and can increase intracellular concentrations of other anti-cancer agents. In myocytes, PKC isoforms have been implicated in certain cardiac pathologies. PKC–γ is highly expressed in brain and spinal cord and is primarily localized in dendrites and neuron cell bodies. PKC–β2 is involved in cell proliferation and overexpression increases sensitivity to cancer. PKCβ inhibitors are a potential new therapy for diabetic retinopathy with clinical trials ongoing. See Magnelli, L. et. al. (1997) Journal of Cancer Research and Clinical *Oncology* 123(7):365-369; Clerk, A. et. al (2001) *Circulation Research* 89(10): 847-849; Carter, C. (2000) Current Drug Targets1(2):163-183; Greenberg, S. et. al. (1998) *Alcohol* 16(2);167-175; Rosenzweig, T. et. al. (2002) Diabetes51(6):1921-1930; Deucher, A. et. al. (2002) *Journal of Biological Chemistry* 277(19):17032-17040; Frank, R.N. (2002) *American Journal of Ophthalmology* 133(5):693-698; Parekh, D. et. al. (2000) *EMBO Journal* 19(4):496-503; Newton, A.C. (2001) *Chem. Rev.*101:2353-2364.

The term "treating" or "treated", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

"Connective tissue disorders" as used herein refers to disorders such as degenerative cartilage loss following traumatic joint injury, osteoarthritis, osteoporosis, Paget's disease, loosening of artificial joint implants, periodontal disease and gingivitis.

"Destruction of articular cartilage" as used herein refers to connective tissue disorders resulting in articular cartilage destruction, preferably joint injury, reactive arthritis, acute pyrophosphate arthritis (pseudogout), psoriatic arthritis, or juvenile rheumatoid arthritis, more preferably osteoarthritis.

"Inflammatory disorders" as used herein refers to disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, chondrocalcinosis, gout, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibromyalgia, and cachexia.

"Immunology/allergy disorders" as used herein refers to disorders such as organ transplant toxicity, allergic reactions, allergic contact hypersensitivity, autoimmune disorders such

as those disorders associated with granulomatous inflammation/tissue remodeling (such as asthma), immunosuppression and sarcoid.

"Infectious diseases," including those mediated by viruses, bacteria, fungi or mycobacterial infection, as used herein refers to disorders such as septic arthritis, AIDS, fever; Prion diseases, myasthenia gravis, Malaria, sepsis, hemodynamic shock and septic shock.

"Respiratory diseases" as used herein refers to disorders such as chronic obstructive pulmonary disease (including emphysema), acute respiratory distress syndrome, asthma, hyperoxic alveolar injury and idiopathic pulmonary fibrosis and other fibrotic lung diseases.

"Cardiovascular diseases" as used herein refers to disorders such as atherosclerosis including atherosclerotic plaque rupture; aortic aneurysm including abdominal aortic aneurysm and brain aortic aneurysm; congestive heart failure; myocardial and cerebral infarction; stroke; cerebral ischemia; coagulation and acute phase response; left ventricular dilation; post ischemic reperfusion injury; angiofibromas; hemangiomas; and restenosis.

"Eye diseases" as used herein refers to disorders such as aberrant angiogenesis, ocular angiogenesis, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, corneal graft rejection, corneal injury, neovascular glaucoma, corneal ulceration, corneal scarring, macular degeneration (including "Age Related Macular Degeneration (ARMD) including both wet and dry forms), proliferative vitreoretinopathy and retinopathy of prematurity.

"Metabolic diseases" as used herein refers to disorders such as diabetes (including non-insulin dependent diabetes mellitus, diabetic retinopathy, insulin resistance, diabetic ulceration).

"Central Nervous System" (CNS) disorders as used herein refers to disorders such as head trauma, spinal cord injury, Inflammatory diseases of the central nervous system, neuro-degenerative disorders (acute and chronic), Alzheimer's disease, demyelinating diseases of the nervous system, Huntington's disease, Parkinson's disease, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, migraine, depression and anorexia.

"Liver/Kidney diseases" as used herein refers to disorders such as nephrotic syndromes such as glomerulonephritis and glomerular disease of the kidney, proteinuria, cirrhosis of the liver and interstitial nephritis.

"Reproductive Health disorders" as used herein refers to disorders such as endometriosis, contraception (male/female), dysmenorrhea, dysfunctional uterine bleeding, premature rupture of fetal membranes and abortifactant.

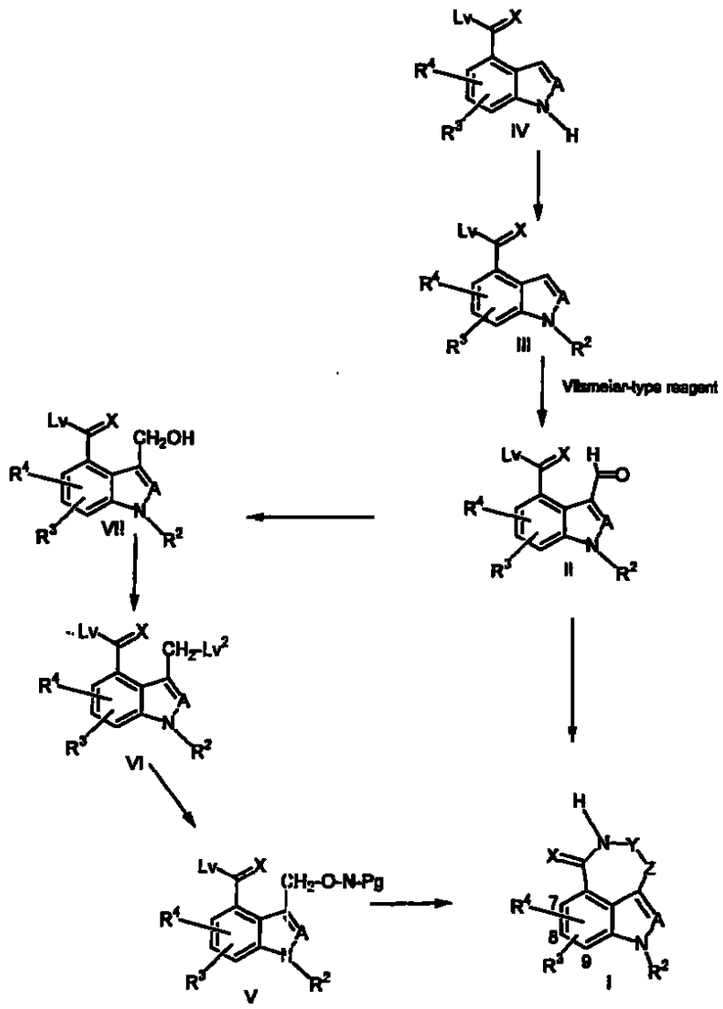
"Gastric disorders" as used herein refers to disorders such as colonic anastomosis and gastric ulcers.

"Skin disorders" as used herein refers to disorders such as skin aging, pressure sores, psoriasis, eczema, dermatitis, radiation damage, tissue ulceration, decubital ulcers, epidermolysis bullosa, abnormal wound healing (topical and oral formulations), burns and scleritis.

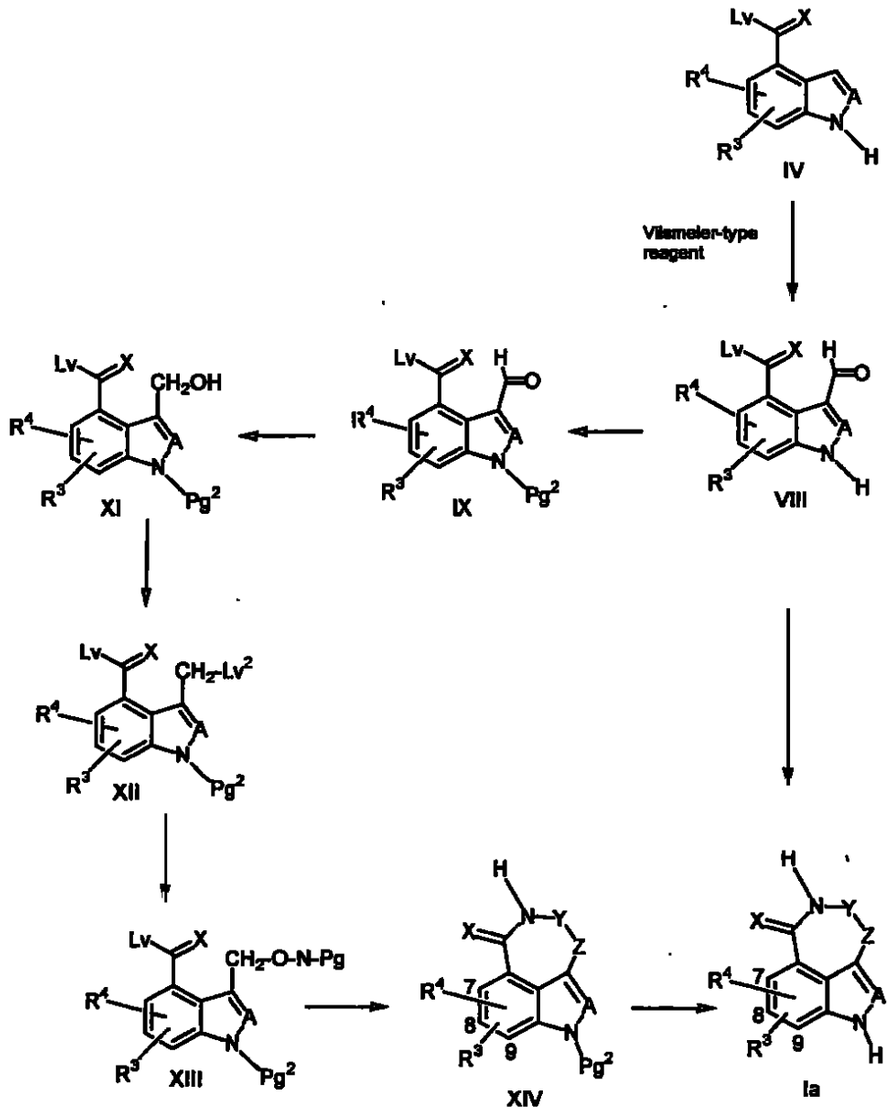
"Cancers" as used herein refers to disorders such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer, tumor invasion, tumor growth tumor metastasis, cancers of the oral cavity and pharynx (lip, tongue, mouth, pharynx), esophagus, stomach, small intestine, large intestine, rectum, liver and bliary passages, pancreas, larynx, lung, bone, connective tissue, skin, cervix uteri, corpus endometrium, ovary, testis, bladder, kidney and other urinary tissues, eye brain and central nervous system, thyroid and other endocrine gland, Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma and hematopoietic malignancies including leukemias and lymphomas including lymphocytic, granulocytic and monocytic.

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated each of A, the group -Y-Z-, X, R^1, R^2, R^3, and R^4 in the reaction Schemes and the discussion that follows are defined as above.

SCHEME 1



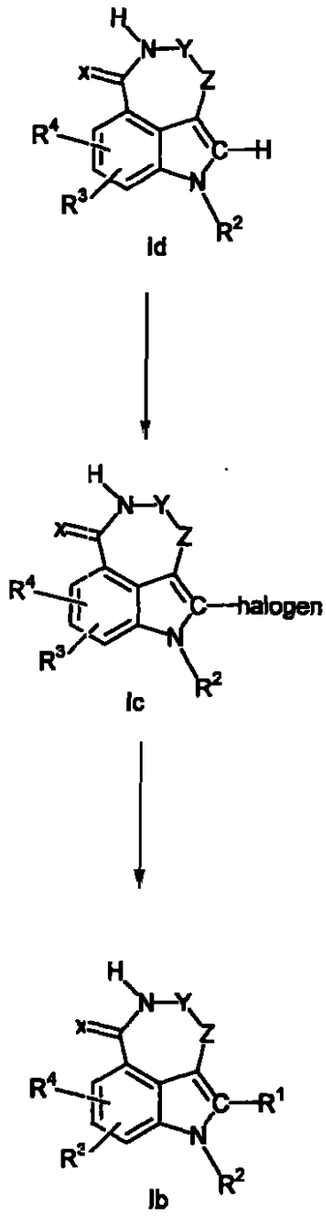
SCHEME 2


Lv
X
R4
R3
A
N
H
IV
Vilsmeier-type reagent
H
O
VIII
IX
CH2OH
XI
CH2-Lv2
XII
CH2-O-N-Pg
XIII
Pg2
XIV
Y
Z
7
8
9
Ia

5

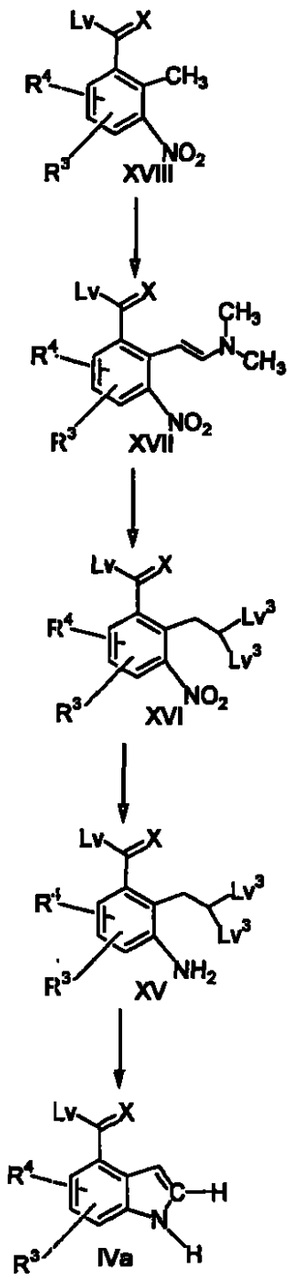
10

SCHEME 3

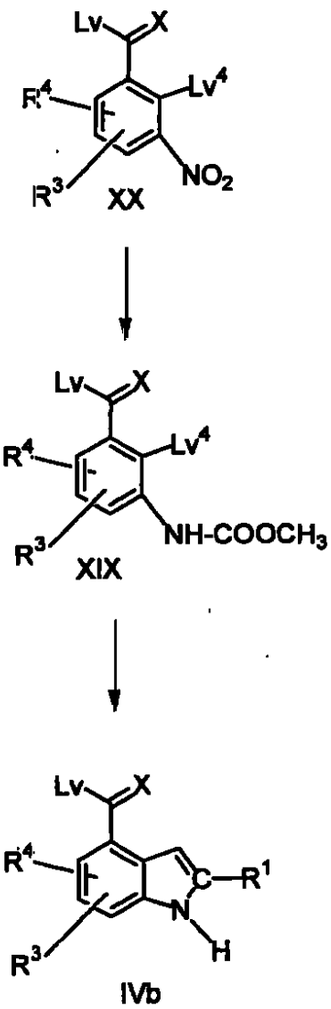

H
N
Y
Z
X
R4
C
H
R3
N
R2
Id
H
N
Y
Z
X
R4
C
halogen
R3
N
R2
Ic
H
N
Y
Z
X
R4
C
R1
R3
N
R2
Ib

5

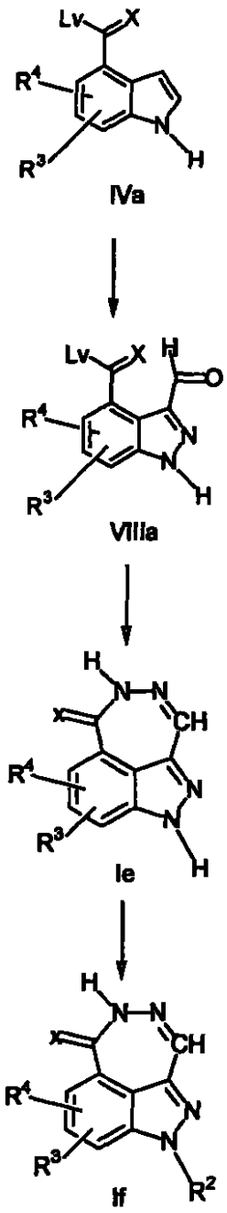
SCHEME 4



SCHEME 5



SCHEME 6


Lv
X
R4
R3
N
H
IVa
Lv
X
H
O
R4
R3
N
N
H
VIIIa
H
N
N
X
CH
R4
R3
N
N
H
Ie
H
N
N
X
CH
R4
R3
N
N
R2
If

Scheme 1 refers to the preparation of compounds of the formula I. Referring to Scheme 1, a compound of formula I, wherein the group -Y-Z- has the formula -N=CH- and R^2 is other than hydrogen, can be prepared by reacting a compound of the formula II, wherein R^2 is other than hydrogen and wherein Lv is a leaving group, with hydrazine in a solvent. Suitable Lv leaving groups include methoxy, ethoxy, or benzyloxy, preferably methoxy. Suitable solvents include alcohols (such as ethanol), preferably methanol. The aforesaid reaction can be conducted at a temperature of about 25 °C to about 90°C, preferably about 65°C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 0.5 hour.

Compounds of formula II, wherein R^2 is other than hydrogen and wherein Lv is as described above, can be prepared by reacting a compound of the formula III, wherein R^2 is other than hydrogen and wherein Lv is as described above, with a Vilsmeier-type formylating reagent in a solvent. Suitable Vilsmeier-type formylating reagents include $POCl_3$ and DMF or $(CF_3SO_2)_2O$ and DMF; preferably $POCl_3$ and DMF. Suitable solvents include chloroform, dioxane, tetrahydrofuran, dimethylformamide, or methylene chloride; preferably methylene chloride. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 25 °C, preferably about 0 °C during the reagent addition then allowing the reaction mixture to warm to 23 °C over about 0.5 hour. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 0.5 hour.

Compounds of formula III, wherein R^2 is other than hydrogen and wherein Lv is as described above, can be prepared reacting a compound of formula IV, wherein Lv is as described above, with a compound of formula:

R^2-Lv^1

wherein Lv^1 is a leaving group, such as halo, preferably bromo or chloro, in the presence of a suitable base in a polar solvent. Suitable bases include alkoxide bases (such as sodium methoxide, sodium ethoxide, or potassium *tert*-butoxide); hydride bases (such as sodium hydride); or carbonate bases (such as potassium carbonate or cesium carbonate); preferably potassium carbonate. Suitable polar solvents include tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, or alcohols (such as ethanol), preferably dimethylformamide. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 100 °C, preferably about 80 °C. The aforesaid reaction can be conducted for a time period of about 0.5 hour to about 72 hours, preferably about 24 hours.

A compound of formula I, wherein the group -Y-Z- is -O-CH_2- and wherein R^2 is other than hydrogen, can be prepared by reacting a compound of formula V, wherein R^2 is other than hydrogen, wherein Pg is a protecting group, and Lv is as described above, with a Pg deprotecting agent. Suitable Pg includes phthaloyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, or ethoxycarbonyl; preferably phthaloyl. Suitable Pg deprotecting agents include hydrazine, trifluoroacetic acid, hydrochloric acid, hydrogen chloride, hydrogen bromide in acetic acid, or hydrogen gas and Pd

catalyst; preferably hydrazine. Acidic reactions can be neutralized after deprotection with a suitable base including tertiary amines (such as triethylamine or diisopropylethylamine) or carbonate bases (such as potassium carbonate); preferably triethylamine. Suitable solvents include dimethylformamide, methylene chloride, chloroform, or alcohol, (such as methanol), preferably methanol. The aforesaid reaction can be conducted at a temperature of about 20 °C to about 130 °C, preferably about 65 °C. The aforesaid reaction can be conducted for a time period of about 0.5 hours to about 48 hours, preferably about 2 hours.

A compound of formula V, wherein R^2 is other than hydrogen, wherein Pg is a protecting group, and Lv is as described above, can be prepared by reacting a compound of formula VI, wherein R^2 is other than hydrogen, Lv^2 is a leaving group and Lv is as described above, with a compound of formula

Pg-N-OH

in the presence of a base in a solvent. Suitable Lv^2 leaving groups include halo, toluenesulfonyl, methanesulfonyl, trifluoromethanesulfonyl, or Mitsunobu-type reaction adducts. Suitable compounds of formula Pg-N-OH include *N*-hydroxyphthalimide, tert-butyl *N*-hydroxylcarbamate, *N*-hydroxyurethane, or benzyl *N*-hydroxycarbamate. Suitable bases include sodium hydride, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, tertiary amines (such as diisopropylethylamine or triethylamine) or carbonate bases (such as sodium carbonate); preferably sodium carbonate. Suitable solvents include dimethylformamide, dimethylsulfoxide, tetrahydrofuran, methylene chloride, chloroform, or alcohol (such as methanol); preferably dimethylsulfoxide. The aforesaid reaction can be conducted at a temperature of about –25 °C to about 80 °C, preferably about 23 °C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 48 hours, preferably about 20 hours.

A compound of formula VI, wherein R^2 is other than hydrogen and Lv^2 and Lv are as described above, can be prepared by reacting a compound of formula VII, wherein R^2 is other than hydrogen and Lv is as described above, with an Lv^2 producing agent, in a solvent. Suitable Lv^2 producing agents include $(C_6H_5)_3P$ and CCl_4; $(C_6H_5)_3P$ and PBr_3; para-$CH_3C_6H_4SO_2Cl$; CH_3SO_2Cl; $(CF_3SO_2)_2O$; or Mitsunobu-type reagents (such as diethyl azodicarboxylate and $(C_6H_5)_3P$); preferably $(C_6H_5)_3P$ and CCl_4. Suitable solvents include methylene chloride, chloroform, tetrahydrofuran, carbon tetrachloride, benzene, or toluene; preferably methylene chloride. The aforesaid reaction can be conducted at a temperature of about –25 °C to about 80 °C, preferably about 23 °C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 20 hours.

A compound of formula VII, wherein R^2 is other than hydrogen and Lv is as described above, can be prepared by reacting a compound of formula II, wherein R^2 is other than hydrogen and Lv is as described above, with a reducing agent in a solvent. Suitable reducing agents include sodium borohydride, lithium borohydride, zinc borohydride, diborane, borane complexes,

triacetoxyborohydride, sodium cyanoborohydride, or lithium cyanoborohydride; preferably sodium borohydride. Suitable solvents include alcohol (such as methanol), tetrahydrofuran, a mixture of methanol and anhydrous HCl, or a mixture of methanol and acetic acid; preferably methanol. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 50 °C, preferably about 23°C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 15 minutes.

Scheme 2 refers to the preparation of compounds of the formula Ia, which is a compound of formula I wherein R^2 is hydrogen. Referring to Scheme 2, a compound of formula Ia, wherein the group -Y-Z- has the formula -N=CH-, can be prepared by reacting a compound of the formula VIII, wherein Lv is a leaving group, as described above, with hydrazine in a solvent. The reaction condition is as described above in the description for Scheme 1 for the preparation of a compound of formula I from a compound of formula II.

Compounds of formula VIII, wherein Lv is as described above, can be prepared by reacting a compound of the formula IV, wherein Lv is as described above, with a Vilsmeier reagent in a solvent. The reaction condition is as described above in the description for Scheme 1 for the preparation of compounds of formula II from a compound of formula III.

A compound of formula Ia, wherein the group -Y-Z- is $-O-CH_2-$, can be prepared by reacting a compound of formula XIV, wherein Pg^2 is a protecting group, with a Pg^2 deprotecting agent in a solvent. Suitable Pg^2 protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, or 2-(trimethylsilyl)ethoxymethyl; preferably *tert*-butoxycarbonyl. Suitable Pg^2 deprotecting agents include trifluoroacetic acid, hydrochloric acid, hydrogen chloride, hydrogen bromide in acetic acid, hydrogen gas and Pd catalyst, or tetrabutylammonium fluoride; preferably trifluoroacetic acid. Suitable solvents include methylene chloride, chloroform, dioxane, dimethylformamide, or alcohol (such as methanol); preferably methylene chloride. The aforesaid reaction can be conducted at a temperature of about 20 °C to about 80 °C, preferably about 23 °C. The aforesaid reaction can be conducted for a time period of about 15 minutes to about 48 hours, preferably about 2 hours.

A compound of formula XIV, wherein Pg^2 is as described above, can be prepared by reacting a compound of formula XIII, wherein Pg is a protecting group as described in the compound of formula V of Scheme 1, and Pg^2 and Lv are as described above, with a Pg deprotecting agent. The reaction condition is as described above in the description for Scheme 1 for the preparation of a compound of formula I from a compound of formula V.

A compound of formula XIII, wherein Pg^2, Lv and Lv^2 are as described above, can be prepared by reacting a compound of formula XII, wherein Pg^2, Lv and Lv^2 are as described above, with a compound of formula

Pg-N-OH

wherein Pg is as described above, in the presence of a base in a solvent, The reaction condition is as described above in the description for Scheme 1 for the preparation of a compound of formula V from a compound of formula VI.

A compound of formula XII, wherein Pg^2, Lv^2 and Lv are as described above, can be prepared by reacting a compound of formula XI, wherein Pg^2 and Lv are as described above, with an Lv^2 producing agent, in a solvent. The reaction condition is as described above in the description for Scheme 1 for the preparation of a compound of formula VI from a compound of formula VII.

A compound of formula XI, wherein Pg^2 and Lv are as described above, can be prepared by reacting a compound of formula IX, wherein Pg^2 and Lv are as described above, with a reducing agent in a solvent. The reaction condition is as described above in the description for Scheme 1 for the preparation of a compound of formula VII from a compound of formula II.

A compound of formula IX, wherein Pg^2 and Lv are as described above, can be prepared by reacting a compound of formula VIII, wherein Lv is as described above, with a Pg^2 protecting agent in the presence of a suitable base in a solvent. Suitable Pg^2 protecting agents include di-*tert*-butyl dicarbonate, benzyl chloroformate, or 2-(trimethylsilyl)ethoxymethyl chloride; preferably di-*tert*-butyl dicarbonate. Suitable bases include hydride bases (such as sodium hydride, lithium hydride, or potassium hydride); preferably sodium hydride. Suitable solvents include tetrahydrofuran or dimethylformamide; preferably tetrahydrofuran. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 60 °C, preferably about 23 °C. The aforesaid reaction can be conducted for a time period of about 15 minutes to about 24 hours, preferably about 1 hour.

Scheme 3 refers to the preparation of a compound of the formula Ib, which is a compound of the formula I wherein A is $=CR^1-$. Referring to Scheme 3, a compound of formula Ib, can be prepared by reacting a compound of the formula Ic, wherein halogen is selected from bromo or iodo, with a coupling reagent of the formula:

R^1-M

wherein M is a H or metal, in the presence of palladium and copper catalysts in a solvent. Suitable metals include boron and tin, preferably boron. Suitable coupling reagents include Stille coupling reagent (see Chamoin, S., Houldsworth, S., Snieckus, V. *Tetrahedron Lett.*1998, *39*, 4175-4178 incorporated herein by reference), Suzuki coupling reagent (see Littke, A.F., Chaoyang, D., Fu, G.C. *J.Am. Chem. Soc.* 2000, *122*, 4020-4028 incorporated herein by reference), or Sonogashira coupling reagent (see Sonogashira, K., Tohda, Y., Hagihara, N. *Tetrahedron Lett.* 1975, *16*, 44467-4470 incorporated herein by reference); preferably Suzuki coupling reagent or Stille coupling reagent. Suitable palladium and copper catalysts include $Pd(C_6H_5)_3P)_4$, $Pd(dba)_2$, $Pd(P(C_6H_5)_3)Cl_2$ and CuI. Suitable solvents include dimethylformamide or tetrahydrofuran; preferably dimethylformamide. The aforesaid reaction can be conducted at a temperature of about

22 °C to about 110 °C, preferably about 90 °C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 48 hours, preferably about 2 hours.

Some compounds of the formula Ib, such as those wherein R^1 is a substituted alkyne (for example methylaminopropynyl) may need additional steps requiring the use of a protecting group (for example tert-butoxycarbonyl). These protection groups and their removal processes are well known in the art and can be found in Greene and Wuts, "Protecting Groups in Organic Synthesis," (John Wiley & Sons, 2nd Ed). Furthermore, compounds of the Ib, such as those wherein R^1, R^2 or R^3 is a substituted alkyl, alkynyl, aromatic or vinyl are subjected to additional standard chemical transformations (for example catalytic hydrogenation, OsO_4/NMMO/$NaIO_4$ oxidative cleavage, mesylation/displacement, reductions and reductive amination). These processes are also well known in the art and can be found in Larock, R.C., "Comprehensive Organic Transformations" (Wiley-VCH, 2nd Ed.).

A compound of formula Ib, wherein A is $=CR^1-$ and R^1 is $-(C=O)-O-(C_1-C_6)$alkyl, can be prepared by reacting a compound of the formula Ic, wherein halogen is selected from bromo or iodo, with carbon monoxide in the presence of a palladium catalyst, a base, and a compound of the formula H-O-(C_1-C_6)alkyl (depending on the -(C_1-C_6)alkyl part of the desired R^1) in a solvent. Suitable palladium catalysts include $Pd(dppf)Cl_2$. Suitable bases include tertiary amine bases such as triethylamine. Suitable compounds of the formula H-O-(C_1-C_6)alkyl include methanol, ethanol, or propanol. Suitable solvents include dimethylformamide or tetrahydrofuran; preferably dimethylformamide. The aforesaid reaction can be conducted at a temperature of about 22 °C to about 110 °C, preferably about 85 °C. The aforesaid reaction can be conducted for a time period of about 30 minutes to about 48 hours, preferably about 16 hours.

A compound of formula Ib, wherein A is $=CR^1-$ and R^1 is -(C=O)-NH-(C_1-C_6)alkyl or -(C=O)-NH-(C_1-C_6)alkyl-OH or -(C=O)-NH-(C_1-C_6)alkyl-$N(CH_3)_2$ or -(C=O)-1-(4-*N*-methylpiperazine) can be prepared by reacting a compound of the formula Ic, wherein halogen is selected from bromo or iodo, with carbon monoxide in the presence of a palladium catalyst, a base, and a compound of the formula H_2N-(C_1-C_6)alkyl or H_2N-(C_1-C_6)alkyl-OH or H_2N-(C_1-C_6)alkyl-$N(CH_3)_2$ or *N*-methylpiperazine (depending on the -(C_1-C_6)alkyl part of the desired R^1) in a solvent. Suitable palladium catalysts include $Pd(dppf)Cl_2$. Suitable bases include tertiary amine bases such as triethylamine. Suitable compounds of the formulas H_2N-(C_1-C_6)alkyl or H_2N-(C_1-C_6)alkyl-OH or H_2N-(C_1-C_6)alkyl-$N(CH_3)_2$ or *N*-methylpiperazine include 2-aminoethanol, *N,N*-dimethylethylenediamine, methylamine *N*-methylpiperazine Suitable solvents include dimethylformamide or toluene; preferably dimethylformamide. The aforesaid reaction can be conducted at a temperature of about 22 °C to about 110 °C, preferably about 85 °C. The aforesaid reaction can be conducted for a time period of about 30 minutes to about 48 hours, preferably about 16 hours.

A compound of formula Ic, wherein halogen is bromo or iodo, can be prepared by reacting a compound of formula Id with a suitable halogenating agent in a solvent. Suitable halogenating agents include *N*-bromosuccinimide or *N*-iodosuccinimide; preferably *N*-bromosuccinimide. Suitable solvents include tetrahydrofuran or dimethylformamide, preferably dimethylformamide. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 75 °C, preferably about 22 °C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 1 hour.

A compound of formula Ic, wherein halogen is chloro, can be prepared by reacting a compound of formula Id with a suitable chlorinating agent in a solvent. Suitable chlorinating agents include *N*-chlorosuccinimide Suitable solvents include tetrahydrofuran or dimethylformamide; preferably dimethylformamide. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 75 °C, preferably about 45 °C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 1 hour.

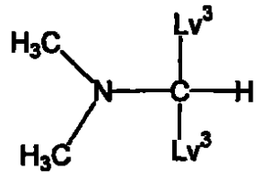
Scheme 4 refers to the preparation of a compound of the formula IVa, which is a compound of formula IV of Scheme 1, wherein A is =CH-. Referring to Scheme 4, a compound of formula IVa, wherein Lv is as described above, can be prepared by reacting a compound of formula XV, wherein Lv is as described above and each of Lv^3 is a leaving group, with a suitable acid in a polar protic solvent (see Coe, J.W., Vetelino, M.G., Bradlee, M.J. *Tetrahedron Lett.* 1996, *37*, 6045-6047 incorporated herein by reference). Suitable Lv^3 leaving groups include methoxy or ethoxy, preferably methoxy. Suitable acids include HCl, H_2SO_4, *para* toluenesulfonic acid, camphorsulfonic acid, or Lewis acids; preferably HCl. Suitable polar protic solvents include alcohols (such as methanol or ethanol), preferably methanol. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 100 °C, preferably about 65 °C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 1 hour.

A compound of formula XV, wherein Lv and Lv^3 are as described above, can be prepared by reacting a compound of formula XVI, wherein Lv and Lv^3 are as described above, with a reducing agent in a polar solvent. Suitable reducing agents include catalytic transfer reagents such as hydrazine hydrate, ammonium formate, ammonium chloride, cyclohexene, or hydrogen gas in the presence of catalysts [such as Pd on carbon (see Coe, J.W., Vetelino, M.G., Bradlee, M.J. *Tetrahedron Lett.* 1996, *37*, 6045-6047 incorporated herein by reference), Ru, Rh, Raney nickel, or Pt]; HCl or acetic acid in the presence of In, Fe, Sn, or Zn; $HCl/SnCl_2$;$SnCl_2.2H_2O$; $Bu_3SnH/AIBN$; or $Fe_3(CO)_{12}$; preferably $SnCl_2.2H_2O$ or hydrogen gas in the presence of Pd on carbon or Raney nickel. Suitable polar solvents include alcohols (such as methanol or ethanol), preferably methanol. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 100 °C, preferably about 23 °C. Where hydrogen gas is used the reaction pressure can be

1 to 4 atm, preferably 1 atm. The aforesaid reaction can be conducted for a time period of about 2 hours to about 48 hours, preferably about 24 hours.

A compound of formula XVI, wherein Lv and Lv^3 are as described above, can be prepared by reacting a compound of formula XVII, wherein Lv is as described above, with a suitable acid in an anhydrous polar protic solvent of formula Lv^3-H. Suitable acids include HCl, H_2SO_4, or *para* toluenesulfonic acid, preferably HCl. Alternatively, HCl can be generated *in situ* by using an HCl generating agent such as TMS-Cl or acetyl chloride, preferably TMS-Cl, in an anhydrous polar protic solvent such as methanol. Suitable anhydrous polar protic solvents of formula Lv^3-H include anhydrous alcohols (such as methanol or ethanol), preferably anhydrous methanol. The aforesaid reaction can be conducted at a temperature of about 23 °C to about 78 °C, preferably about 65 °C. The aforesaid reaction can be conducted for a time period of about 30 minutes to about 48 hours, preferably about 24 hours.

A compound of formula XVII, wherein Lv is as described above, can be prepared by reacting a compound of formula XVIII, wherein Lv is as described above, with a compound of formula



wherein each of Lv^3 is as described above, in a polar solvent. Suitable compounds of formula $(CH_3)_2$-N-CH-$(Lv^3)_2$ include dimethylformamide-dimethylacetal. Suitable polar solvents include dimethylformamide, toluene, or alcohol (such as ethanol), preferably dimethylformamide. The aforesaid reaction can be conducted at a temperature of about 22 °C to about 150 °C, preferably about 110 °C. The aforesaid reaction can be conducted for a time period of about 15 minutes to about 24 hours, preferably about 6 hours.

Compounds of formula $(CH_3)_2$-N-CH-$(Lv^3)_2$ are commercially available.

Compounds of the formula XVII, wherein Lv is as described above, are commercially available or alternatively can be made by methods well known to those skilled in the art.

Scheme 5 refers to preparation of a compound of the formula IVb, which is a compound of formula IV of Scheme 1, wherein A is $=CR^1$-. Referring to Scheme 5, a compound of formula IVb can be prepared by reacting a compound of the formula XIX, wherein Lv is as described above and Lv^4 is a leaving group, with a suitable substituted alkyne of formula

M^1-C≡C-R^1

wherein M^1 is H or metal (such as Sn or Si), preferably H or Sn, in the presence of a metal catalyst in a polar solvent. Suitable Lv^4 leaving groups include halo preferably bromo or iodo. Suitable metal catalysts include palladium or copper catalysts (See Fagnola, M.C. et al. *Tetrahedron*

*Lett.*1997, *38*, 2307-2310 incorporated herein by reference). Suitable polar solvents include dimethylformamide, dioxane, dimethylsulfoxide, or mixtures thereof, preferably a mixture of dimethylformamide and dioxane. The aforesaid reaction can be conducted at a temperature of about 22 °C to about 120 °C, preferably about 90 °C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 8 hours.

Compounds of formula M^1-C≡C-R^1 are commercially available or can be made by methods well known to those skilled in the art.

A compound of formula XIX, wherein Lv and Lv^4 are as described above, can be prepared by reacting a compound of formula XX, wherein Lv and Lv^4 are as described above, with a reducing agent in the presence of $(CH_3CO)_2O$ in a polar solvent. Suitable reducing agents include hydrogen gas in the presence of catalysts such as Pd/C (see Coe, J.W., Vetelino, M.G., Bradlee, M.J. *Tetrahedron Lett.*1996, *37*, 6045-6047 incorporated herein by reference), Rd, Raney nickel, or Pt; acetic acid in the presence of In, Fe, or Zn; $SnCl_2$; or $Fe_3(CO)_{12}$; preferably hydrogen gas in the presence of Pd/C; or acetic acid in the presence of Fe. Suitable polar solvents include dimethylformamide, methanol, ethanol, or acetic acid; preferably methanol or acetic acid. The aforesaid reaction can be conducted at a temperature of about 20 °C to about 100 °C, preferably about 22 °C. Where hydrogen gas is used the reaction pressure can be 1 to 4 atm, preferably 1 atm. The aforesaid reaction can be conducted for a time period of about 2 hours to about 48 hours, preferably about 24 hours.

Compounds of the formula XX are commercially available or can be made by methods well known to those skilled in the art.

Scheme 6 refers to preparation of a compound of the formula If, which is a compound of formula I of Scheme 1, wherein the group -Y-Z- has the formula -N=CH-, A is =N-, and R^2 is other than hydrogen. Referring to Scheme 6, a compound of formula If can be prepared by reacting a compound of the formula Ie, which is a compound of formula I of Scheme 1, wherein the group -Y-Z- has the formula -N=CH-, A is =N-, and R^2 is hydrogen, with a compound of formula

$$R^2\text{-}Lv^1$$

wherein Lv^1 is a leaving group, such as halo, preferably bromo or chloro, in the presence of a suitable base in a polar solvent. The reaction condition is as described above in the description for Scheme 1 for the preparation of compounds of formula III from a compound of formula IV.

Compounds of formula Ie can be prepared by reacting a compound of the formula VIIIa, which is a compound of formula VIII of Scheme 2, wherein A is =N- and Lv is as described above, with hydrazine in a solvent. The reaction condition is as described above in the description for Scheme 1 for the preparation of a compound of formula I from a compound of formula II.

Compounds of formula VIIIa can be prepared by reacting a compound of the formula IVa, which is a product of Scheme 4, with a nitrous acid producing agent in the presence of an acid in a solvent. Suitable nitrous acid producing agents include $NaNO_2$, KNO_2, isoamyl nitrite, or *tert*-

butyl nitrite; preferably $NaNO_2$. Suitable acids include acetic acid or aqueous HCl; preferably acetic acid. Suitable solvents include acetic acid, benzene, dimethylformamide, toluene, or alcohols (such as methanol), preferably acetic acid. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 30 °C, preferably about 0 °C warming to 23 °C. The aforesaid reaction can be conducted for a time period of about 5 minutes to about 24 hours, preferably about 1 hour.

Within the invention it is understood that a compound of Formula I may exhibit the phenomenon of tautomerism and that the formula drawings within this specification represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which modulates and/or inhibits kinase activity and is not to be limited merely to any one tautomeric form utilized within the formula drawings.

Some of the inventive compounds may exist as single stereoisomers (*i.e.*, essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Preferably, the inventive compounds that are optically active are used in optically pure form.

As generally understood by those skilled in the art, an optically pure compound having one chiral center (*i.e.*, one asymmetric carbon atom) is one that consists essentially of one of the two possible enantiomers (*i.e.*, is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. Preferably, the compounds of the present invention are used in a form that is at least 90% optically pure, that is, a form that contains at least 90% of a single isomer (80% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), more preferably at least 95% (90% e.e. or d.e.), even more preferably at least 97.5% (95% e.e. or d.e.), and most preferably at least 99% (98% e.e. or d.e.).

Additionally, Formula I is intended to cover solvated as well as unsolvated forms of the identified structures. For example, Formula I include compounds of the indicated structure in both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyrovic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic

acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

The pharmaceutically acceptable salts of the compound of Formula I can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

The compound of Formula I may be used in combination with conventional antineoplasm therapies to treat mammals, especially humans, with neoplasia. The procedures for conventional anti-neoplasm therapies, including chemotherapies using anti-neoplastic agents and therapeutic radiation, are readily available, and routinely practiced in the art, e.g., see Harrison's PRINCIPLES OF INTERNAL MEDICINE 11th edition, McGraw-Hill Book Company.

Neoplasia is characterized by abnormal growth of cells which often results in the invasion of normal tissues, e. g., primary tumors or the spread to distant organs, e. g., metastasis. The treatment of any neoplasia by conventional non-surgical anti-neoplasm therapies may be enhanced by the present invention. Such neoplastic growth includes but not limited to primary tumors, primary tumors that are incompletely removed by surgical techniques, primary tumors which have been adequately treated but which are at high risk to develop a metastatic disease subsequently, and an established metastatic disease.

Specifically, the CHK-1 inhibitor of Formula I above may enhance the anti-neoplasm effects of an anti-neoplastic agent. The wide variety of available anti-neoplastic agents are contemplated for combination therapy in accordance with present invention. In a preferred embodiment, anti-neoplastic agents that assert their cytotoxic effects by activating programmed cell death or apoptosis may be used in combination with the described CHK-1 inhibitor. The anti-neoplastic agents contemplated in accordance with the present invention include, but are not limited to alkylating agents, including busulfan, chlorambucil, cyclophosphamide, iphosphamide,

melphalan, nitrogen mustard, streptozocin, thiotepa, uracil nitrogen mustard, triethylenemelamine, temozolomide, and SARCnu; antibiotics and plant alkaloids including actinomycin-D, bleomycin, cryptophycins, daunorubicin, doxorubicin, idarubicin, Irinotecan, L-asparaginase, mitomycin-C, mitramycin, navelbine, paclitaxel, docetaxel, topotecan, vinblastine, vincristine, VM-26, and VP-16-213; hormones and steroids including 5α-reductase inhibitor, aminoglutethimide, anastrozole, bicalutamide, chlorotrianisene, DES, dromostanolone, estramustine, ethinyl estradiol, flutamide, fluoxymesterone, goserelin, hydroxyprogesterone, letrozole, leuprolide, medroxyprogesterone acetate, megestrol acetate, methyl prednisolone, methyltestosterone, mitotane, nilutamide, prednisolone,
SERM3, tamoxifen, testolactone, testosterone, triamicnolone, and zoladex; synthetics including all-trans retinoic acid, BCNU (carmustine), CBDCA carboplatin (paraplatin), CCNU (lomustine), cis-diaminedichloroplatinum (cisplatin), dacarbazine, gliadel, hexamethylmelamine, hydroxyurea, levamisole, mitoxantrone, o, p'-DDD (lysodren, mitotane), oxaliplatin, porfimer sodium, procarbazine, GleeVec; antimetabolites including chlorodeoxyadenosine, cytosine arabinoside, 2'-deoxycoformycin, fludarabine phosphate, 5-fluorouracil, 5-FUDR, gemcitabine, camptothecin, 6-mercaptopurine, methotrexate, MTA, and thioguanine; and biologics including alpha interferon, BCG, G-CSF, GM-CSF, interleukin-2, herceptin; and the like.

In a preferred embodiment of the invention, the anti-neoplastic agent is selected from the group consisting of alkylating agents, antibiotics and plant alkaloids, hormones and steroids, synthetic agents having anti-neoplastic activity, antimetabolites and biological molecules having anti-neoplastic activity.

In a preferred embodiment of the invention the antineoplastic agent is selected from the group consisting of Ara-c, VP-16, cis-platin, adriamycin, 2-chloro-2-deoxyadenosine, 9-β-D-arabinosyl-2-fluoroadenine, carboplatin, gemcitabine, camptothecin, paclitaxel, BCNU, 5-fluorouracil, irinotecan, and doxorubicin; more preferably gemcitabine.

All the neoplastic conditions treatable with such anti-neoplastic agents may be treated in accordance with the present invention by using a combination of the compound of Formula I with one or more anti-neoplastic agents. The anti-neoplastic agents assert their cytotoxicity or anti-neoplasm effects in a variety of specific neoplastic conditions. For example, Ara-c is normally used for treatment of childhood-null acute lymphoid leukemia (ALL), thymic ALL, B-cell ALL, acute myeloid leukemia, acute granulocytic leukemia and its variants, non-Hodgkins lymphoma, myelomonocytoid leukemia, acute megakaryocytoid leukemia and Burkitt's lymphoma, Adult-B-ALL, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, and T cell leukemia. VP-16 is normally used for treatment of testicular carcinoma, small and large non-small cell lung carcinoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, choriocarcinoma, Ewing's

sarcoma, and acute granulocytic leukemia. Cis-platin can be employed for treatment of testicular carcinoma, germ cell tumors, ovarian carcinomas, prostate cancer, lung cancer, sarcomas, cervical cancer, endometrial cancer, gastric cancer, breast cancer, and cancer of the head and neck. 2-Chloro-2-deoxyadenosine and 9-β-D-arabinosyl-2-fluoroadenine can be used to treat chronic lymphoid leukemia, lymphomas and hairy cell leukemia. Doxorubicin can be used to treat acute granulocytic leukemia and its variants, ALL, breast cancer, bladder cancer, ovarian cancer, thyroid cancer, lung cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, sarcomas, gastric carcinoma, prostate cancer, endometrial cancer, Wilm's tumor and neuroblastoma.

Clinical effects of anti-neoplastic agents in all neoplastic conditions treatable with antineoplastic agents including the ones discussed above may be potentiated by use of a combination therapy with the identified CHK-1 inhibitor in accordance with the present invention.

The CHK-1 inhibitor identified in the present invention may also enhance the antineoplasm effects of radiation therapy. Usually, radiation can be used to treat the site of a solid tumor directly or administered by brachytherapy implants. The various types of therapeutic radiation which are contemplated for combination therapy in accordance with the present invention may be those used in the treatment of cancer which include, but are not limited to X-rays, gamma radiation, high energy electrons and High LET (Linear Energy Transfer) radiation such as protons, neutrons, and alpha particles. The ionizing radiation may be employed by techniques well known to those skilled in the art. For example, X-rays and gamma rays are applied by external and/or interstitial means from linear accelerators or radioactive sources. High-energy electrons may be produced by linear accelerators. High LET radiation is also applied from radioactive sources implanted interstitially.

The specific dosage amount of a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof being administered to obtain therapeutic or inhibitory effects may be determined in a manner known in the art according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. An exemplary total daily dose of a compound of the Formula I, which may be administered in single or multiple doses, contains a dosage level of from about 0.01mg/kg body weight to about 50 mg/kg body weight.

The compounds of the Formula I of the invention may be administered by any of a variety of suitable routes, such as orally, rectally, transdermally, subcutaneously, intravenously, intramuscularly, or intranasally. The compounds of the Formula I are preferably formulated into compositions suitable for the desired routes before being administered.

A pharmaceutical composition or preparation according to the invention comprises an effective amount of a compound of the Formula I, optionally one or more other active agents, and a pharmaceutically acceptable carrier, such as a diluent or excipient for the agent; when the

carrier serves as a diluent, it may be a solid, semi-solid, or liquid material acting as a vehicle, excipient, or medium for the active ingredient(s). Compositions according to the invention may be made by admixing the active ingredient(s) with a carrier, or diluting it with a carrier, or enclosing or encapsulating it within a carrier, which may be in the form of a capsule, sachet, paper container, or the like. Exemplary ingredients, in addition to one or more compounds of the Formula I and any other active ingredients, include Avicel (microcrystalline cellulose), starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid, peanut oil, olive oil, glyceryl monostearate, Tween 80 (polysorbate 80), 1,3-butanediol, cocoa butter, beeswax, polyethylene glycol, propylene glycol, sorbitan monostearate, polysorbate 60, 2-octyldodecanol, benzyl alcohol, glycine, sorbic acid, potassium sorbate, disodium hydrogen phosphate, sodium chloride, and water.

The compositions may be prepared in any of a variety of forms suitable for the desired mode of administration. For example, pharmaceutical compositions may be prepared in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as solids or in liquid media), ointments (*e.g.*, containing up to 10% by weight of a compound of the Formula I), soft-gel and hard-gel capsules, suppositories, sterile injectable solutions, sterile packaged powders, and the like.

Similarly, the carrier or diluent may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like.

A variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation can be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension.

To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of an inventive agent is dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, gylcerin and the like in concentrations ranging from 0-60% of the total volume. A compound of Formula I may be dissolved in DMSO and diluted with water. The composition may also be in the form of a solution of a salt form of the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

The compositions of the invention may be manufactured in manners generally known for preparing pharmaceutical compositions, *e.g.*, using conventional techniques such as mixing,

dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing. Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers, which may be selected from excipients and auxiliaries that facilitate processing of the active compounds into preparations which can be used pharmaceutically.

Proper formulation is dependent upon the route of administration chosen. For injection, the agents of the invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, methyl cellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration intranasally or by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

For administration to the eye, the active agent is delivered in a pharmaceutically acceptable ophthalmic vehicle such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, including, for example, the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera. The pharmaceutically acceptable ophthalmic vehicle may be an ointment, vegetable oil, or an encapsulating material. A compound of the invention may also be injected directly into the vitreous and aqueous humor.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an

acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.* polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Some of the compounds of the invention may be provided as salts with pharmaceutically compatible counter ions. Pharmaceutically compatible salts may be formed with many acids, including hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free-base forms.

The compounds of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof are useful as anti-angiogenesis agents and as agents for modulating and/or inhibiting the activity of protein kinases, thus providing treatments for cancer or other diseases associated with cellular proliferation mediated by protein kinases.

Therapeutically effective amounts of the agents of the invention may be used to treat diseases mediated by modulation or regulation of protein kinases. An "effective amount" is intended to mean that amount of an agent that, when administered to a mammal in need of such treatment, is sufficient to effect treatment for a disease mediated by the activity of one or more kinases. Thus, *e.g.*, a therapeutically effective amount of a compound of the Formula I, a pharmaceutically acceptable salt, solvate, or prodrug thereof is a quantity sufficient to modulate, regulate, or inhibit the activity of one or more kinases such that a disease condition which is mediated by that activity is reduced or alleviated.

BIOCHEMICAL AND BIOLOGICAL EVALUATION

Enzyme Assays

CHK-1 Construct for Assay

As previously detailed in European Patent Application No. 1 096 014 A2 (filed October 31, 2000), the C-terminally His-tagged kinase domain of human CHK-1 (KH289), amino acid residues 1-289, can be expressed using the baculovirus/insect cell system. This construct has been shown to possess catalytic activity approximately 10-fold greater than full length CHK-1. The Bac-to-Bac system (Life Technologies) can be used to generate recombinant baculovirus for the expression of KH289 as per instructions. Recombinant viruses can be confirmed by PCR for the presence of CHK-1 cDNA insertion. Protein expression can be confirmed by SDS-PAGE or Western blot with CHK-1 polyclonal antibodies. Sf9 insect cells (Invitrogen, Carlsbad, CA, USA) can be used for initial amplification of recombinant virus stock. High titer stocks of recombinant viruses can be generated by 2 to 3 rounds of amplification using Sf21 insect cells. Hi-S insect cells (Invitrogen, Carlsbad, CA, USA) can be used for protein production. Both Sf9 and Hi-S cell lines can be adapted to grow in insect medium containing 1% Fetal Bovine Serum (Life Technologies, Grand Island, NY, USA). The viral stock was stored at 10°C and used for large-scale protein production within 2 months to avoid viral instability. For protein production, infected HI-S cells can be harvested by centrifugation and stored at -80°C. From these cells, 6X-His tagged KH289 (identified by SDS-PAGE) can be obtained after purification and can be flash-frozen in liquid N_2 and stored at -80°C. Maintaining salt concentration around 500 mM NaCl including 5% glycerol was found to be crucial for preventing aggregation of CHK-1 proteins during purification and storage.

CHK-1 Assay

As previously detailed in European Patent Application No. 1 096 014 A2 (filed October 31, 2000), the enzymatic activity of a kinase can be measured by its ability to catalyze the transfer of a phosphate residue from a nucleoside triphosphate to an amino acid side chain in a selected protein target. The conversion of ATP to ADP generally accompanies the catalytic reaction. Herein, a synthetic substrate peptide, Syntide-2, having amino acid sequence PLARTLSVAGLPGKK can be utilized. The production of ADP from ATP that accompanies

phosphoryl transfer to the substrate can be coupled to oxidation of NADH using phosphoenolpyruvate (PEP) through the actions of pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH can be monitored by following the decrease of absorbance at 340 nm (e340=6.22 cm-1 mM-1) using a HP8452 spectrophotometer. Typical reaction solutions contained: 4 mM PEP, 0.15 mM NADH, 28 units of LDH/mL, 16 units of PK/mL, 3 mM DTT, 0. 125 mM Syntide-2, 0.15 mM ATP and 25 mM MgCl2 in 50 mM TRIS pH 7.5; 400 mM NaCl. Assays can be initiated with 10 nM of kinase domain of CHK-1, KH289. Ki values can be determined by measuring initial enzyme activity in the presence of varying concentrations of inhibitors. The data can be analyzed using Enzyme Kinetic and Kaleidagraph software.

VEGF-R2 Construct for Assay

This construct determines the ability of a test compound to inhibit tyrosine kinase activity. A construct (VEGF-R2Δ50) of the cytosolic domain of (human) vascular endothelial growth factor receptor 2 (VEGF-R2) lacking the 50 central residues of the 68 residues of the kinase insert domain can be expressed in a baculovirus/insect cell system. Of the 1356 residues of full-length VEGF-R2, VEGF-R2Δ50 contains residues 806-939 and 990-1171, and also one point mutation (E990V) within the kinase insert domain relative to wild-type VEGF-R2. Autophosphorylation of the purified construct can be performed by incubation of the enzyme at a concentration of 4 μM in the presence of 3 mM ATP and 40 mM $MgCl_2$ in 100 mM HEPES, pH 7.5, containing 5% glycerol and 5 mM DTT, at 4 °C for 2 hours. After autophosphorylation, this construct has been shown to possess catalytic activity essentially equivalent to the wild-type autophosphorylated kinase domain construct. See Parast et al. (1998) Biochemistry 37:16788-16801.

VEGF-R2 Assay

Coupled Spectrophotometric (FLVK-P) Assay

The production of ADP from ATP that accompanies phosphoryl transfer can be coupled to oxidation of NADH using phosphoenolpyruvate (PEP) and a system having pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH can be monitored by following the decrease of absorbance at 340 nm (e_{340} = 6.22 cm^{-1} mM^{-1}) using a Beckman DU 650 spectrophotometer. Assay conditions for phosphorylated VEGF-R2Δ50 can be the following: 1 mM PEP; 250 μM NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 5.1 mM poly(E_4Y_1); 1 mM ATP; and 25 mM $MgCl_2$ in 200 mM HEPES, pH 7.5. Assay conditions for unphosphorylated VEGF-R2Δ50 can be the following: 1 mM PEP; 250 μM NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 20 mM poly(E_4Y_1); 3 mM ATP; and 60 mM $MgCl_2$ and 2 mM $MnCl_2$ in 200 mM HEPES, pH 7.5. Assays can be initiated with 5 to 40 nM of enzyme. Enzyme percentage inhibition values can be determined by measuring enzyme activity in the presence of 0.05μM test compound. The data can be analyzed using Enzyme Kinetic and Kaleidagraph software.

FGFR

FGF-R1 Construct for Assay

The intracellular kinase domain of (human) FGF-R1 can be expressed using the baculovirus vector expression system starting from the endogenous methionine residue 456 to glutamate 766, according to the residue numbering system of Mohammadi et al. (1996) Mol. Cell. Biol.16:977-989. In addition, the construct also has the following 3 amino acid substitutions: L457V, C488A, and C584S.

FGF-R Assay

The spectrophotometric assay can be carried out as described above for VEGF-R2, except for the following changes in concentration: FGF-R = 50 nM, ATP = 2 mM, and poly(E4Y1) = 15 mM. K_i values can be determined by measuring enzyme activity in the presence of varying concentrations of test compounds.

PHK

Phosphorylase Kinase Construct for Assay.

The truncated catalytic subunit (gamma subunit) of phosphorylase kinase (amino acids 1-298) can be expressed in E.coli and isolated from inclusion bodies. Phosphorylase kinase can then be refolded and stored in glycerol at –20 °C.

Phosphorylase Kinase Assay.

In the assay, the purified catalytic subunit can be used to phosphorylate phosphorylase b using radiolabled ATP. Briefly, 1.5 mg/ml of phosphorylase b can be incubated with 10 nM phosphorylase kinase in 10 mM $MgCl_2$, 50 mM Hepes pH 7.4, at 37 °C. The reaction can be started with the addition of ATP to 100 uM and incubated for 15 min at 25 °C or 37 °C. The reaction can be terminated and proteins can be precipitated by the addition of TCA to 10% final concentration. The precipitated proteins can be isolated on a 96 well Millipore MADP NOB filter plate. The filter plate can be extensively washed with 20% TCA, and dried. Scintilation fluid can be then added to the plate and incorporated radiolabel can be counted on a Wallac microbeta counter. The % inhibition of phosphoryl transfer from ATP to phosphorylase b in the presence of 10 μM of compound can then be measured.

CHK-2 Assay

CHK-2 enzyme can be obtained from Upstate Group, Inc. and is an N-terminal, GST-tagged and C-terminal His-tagged fusion protein corresponding to amino acids 5-543 of human CHK-2 as confirmed by mass tryptic fingerprinting, expressed in E. coli; Mr~87kDa. The assay condition for CHK-2 can be as described above for CHK-1, except that the enzyme CHK2 (0.059μM) can be utilized in place of KH289. Further, no NaCl can be added.

CDK-1 Assay

CDK-1/cyclin B, active complex can be obtained from Upstate Group, Inc. and is a C-terminal, His-tagged CDK-1 and an N-terminal GST-tagged-cyclin B as confirmed by mass tryptic fingerprinting and protein sequencing, produced individually in Sf21 cells and then complexed *in vitro*. The assay condition for CDK-1 can be as described above for CHK-1, except that the

enzyme complex CDK-1/cyclin B (0.2μM) can be utilized in place of KH289, and Histone-H1 (Upstate USA, Inc.) (0.059μM) can be utilized as a substrate in place of Syntide-2. Further, no NaCl can be added.

WEE-1 assay

Delfia (R) Assay Protocol for WEE-1

WEE-1 enzyme can be obtained from Upstate Group, Inc. and is an N-terminal, GST-tagged fusion protein to full length rat WEE-1, expressed in E. coli; Mr~100kDa. This kinase assay can be carried out on coated poly (Glu-Tyr) 4:1 (random copolymer) 96-well filter plates (NoAb Diagnostics). The assay volume can be 100μl per well plus 2μl DMSO (control) or 2μl of compound in DMSO. Buffer A can be 10% glycerol, 20mM TRIS (pH7.5), 10mM $MgCl_2$, 50mM NaCl and 5mM DTT. The plates can be prepared by automation.

To an appropriate well can be added either 2μl of DMSO (control) or 2μl of compound in DMSO. To the positive control wells can be added 30μl of 0.5M EDTA. To each well can be added 50μl ATP in Buffer A such that the ATP assay concentration can be 33μM. To start the reaction, 50μl Wee1 in Buffer A can be added to each well such that the Wee1 assay concentration can be 0.1ng/μl. The plate can be can be mixed by shaking and then allowed to remain at room temperature for 30 minutes. To stop the reaction, the plate can be washed once with Delfia Wash on an EL405 plate washer. To each well can be added 100μl of EuPY in Delfia(R) assay buffer such that the EuPY assay concentration can be 0.0149 ng/μl. The plate can be allowed to sit for 1 hours or overnight. The plate can be washed once again with Delfia(R) Wash (EL405 plate washer), and allowed to dry. To each well can be added 100μl of Delfia (R) Enhancement solution and the plate can be allowed to sit for 10 minutes. The plate can be read on Wallac's Victor fluorescence reader (Europium Protocol). K_i values can be determined by measuring enzyme activity in the presence of varying concentrations of test compounds.

SGK Assay

SGK (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 30μM Crosstide, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 50mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compounds.

AMPK Assay

AMPK (rat) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 50mM Hepes pH7.4, 1mM DTT, 0.02% Brij35, 200μM AMP, 200μM AMARAASAAALARRR, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

LCK Assay

LCK (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 50mM Tris pH7.5, 0.1mM EGTA, 0.1mM NaVanadate, 250□M KVEKIGEGTYGVVYK (CDC2 peptide), 10mM MgAcetate and [γ^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

MAPK2 Assay

MAPK2 (mouse) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 25mM Tris pH 7.5, 0.02mM EGTA, 0.33mg/ml myelin basic protein, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

MSK1 Assay

MSK1 (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 30pM Crosstide, 10mM MgAcetate and [γ-^{33}P-ATP]

(Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25µl. Compounds can be tested at 1µM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10µM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5µl of a 3% phosphoric acid solution. 10µl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 50mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

PKBα Assay

PKBα (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 30µM Crosstide, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25µl. Compounds can be tested at 1µM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10µM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5µl of a 3% phosphoric acid solution. 10µl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 50mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

ROCKII Assay

ROCKII (rat) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 50mM Tris pH7.5, 0.1mM EGTA, 30□M KEAKEKRQEQIAKRRRLSSLRASTSKSGGSQK, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25µl. Compounds can be tested at 1µM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10µM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5µl of a 3% phosphoric acid solution. 10µl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

p70 S6K Assay

p70S6K (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 100µM KKRNRTLTV, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25µl. Compounds can be tested at 1µM. The reaction can be initiated by the addition of

Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

PKA Assay

PKA (bovine) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 30μM LRRASLG (Kemptide), 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 50mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

MAPK1 Assay

MAPK1 (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 25mM Tris pH7.5, 0.02mM EGTA, 1mM synthetic peptide, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

cSRC Assay

cSRC (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 250μM KVEKIGEGTYGVVYK (CDC2 peptide), 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution, 10μl of the reaction can then be spotted onto a P30 filtermat and

washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

PRK2 Assay

PRK2 (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 50mM Tris pH7.5, 0.1mM EGTA, 0.1% β-mercaptoethanol, 30μM AKRRRLSSLRA, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

PDK1 Assay

PDK1 (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 50mM Tris pH7.5, 100μM KTFCGTPEYLAPEVRREPRILSEEEQEMFRDFDYIADWC (PDKtide), 0.1% β-mercaptoethanol, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

FYN Assay

FYN (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 50mM Tris pH7.5, 0.1mM EGTA, 0.1mM NaVanadate, 250μM KVEKIOEGTYGVVYK (CDC2 peptide), 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two

experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

PKCβII (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 20mM Hepes pH7.4, 0.03% Triton X-100, 0.1mM $CaCl_2$, 0.1mg/ml phosphatidylserine, 10μg/ml diacylglycerol, 0.1mg/ml histone H1, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

PKCγ Assay

PKCγ (human) (Upstate Group, Inc., KINASEPROFILER™) (5-10mU) can be incubated with 20mM Hepes pH7.4, 0.03% Triton X-100, 0.1mM $CaCl_2$, 0.1mg/ml phosphatidylserine, 10μg/ml diacylglycerol, 0.1mg/ml histone H1, 10mM MgAcetate and [γ-^{33}P-ATP] (Specific activity approximately 500cpm/pmol, concentration as required) to form a final reaction volume of 25μl. Compounds can be tested at 1μM. The reaction can be initiated by the addition of Mg^{2+}[γ-^{33}P-ATP]. The ATP concentration can be 10μM. After incubation for 40 minutes at room temperature, the reaction can be stopped by the addition of 5γl of a 3% phosphoric acid solution. 10μl of the reaction can then be spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. Results represent an average of two experiments and enzymatic activity can be expressed as a percentage of that in control incubations without test compound.

Whole Cell Checkpoint Abrogation Assay

Chk1 Mitotic Index ELISA Assay

To examine the in vitro effects of Chk1 inhibitory compounds, an ELISA assay can be designed to monitor the abrogation of DNA damage-induced checkpoint control. The assay can be based on the trapping and detection of mitotic cells following DNA damage-induced arrest. Phosphorylation of Histone H3 on serine 10 has been shown to correlate with mitosis and therefore can be required for chromosome condensation; consequently a mitosis specific phospho-epitope on Histone H3 can be used as a signal for checkpoint abrogation.

CA-46 (lymphoma) cells can be treated with a DNA damaging agent, such as camptothecin (Sigma), at 50nM for 8 hours to induce DNA damage. The control compound or Chk1 inhibitor can be then added at increasing concentrations with Nocodazole (Sigma) at

0.1μg/ml and plates can be incubated for 16 hours. Control cells, where only Chk1 inhibitors can be added, can be prepared as well to assure that the inhibitors alone have no effect on the cell cycle. The cells can be then harvested, washed with PBS, and crude acid extraction can be performed. Pellets can be resuspended in 80μl of Acid Extraction Buffer (10mM Hepes pH 7.9, 1.5mM $MgCl_2$, 10mM KCl, 0.5mM DTT, 1.5mM PMSF, 0.4N sulfuric acid), vortexed briefly, and incubated for 30 minutes on ice. Samples can be then centrifuged and 75μl of the supernatant can be transferred to a 96 well flat-bottom plate (VWR 3596). Next 15μl Neutralizing Cocktail (# of samples x (10μl 10N NaOH + 5μl 1M Tris Base) can be added to each well, and after mixing, 5μl of this can be transferred to another 96 well plate with 100μl 50mM Tris base (pH 9.6) in each well. Samples can be dried overnight. The wells can be then washed with 200μl ELISA wash buffer (PBS with 20mM Tris pH 7.5, 0.05% Tween 20) 5 times and blocked with 200μl blocking buffer (PBS with 20mM Tris pH 7.5, 0.05% Tween 20, 3.5% Dry milk, 1.5% BSA. pH to 7.5 after preparation) for 1 hour at room temperature. Following wash and block, anti-phospho Histone H3 antibodies (Upstate USA, Inc., rabbit polyclonal) can be added at 0.5μg/ml in block (100μl per well) and incubated for 2 hours at room temperature. Wells can be washed again to remove unbound primary antibody and 100μl alkaline phosphatase conjugated secondary antibodies at 0.3mg/ml (Pierce, goat anti-rabbit IgG (HOURS+L)) in block can be added for 1 hour at room temp. Wells can be washed 5 times to remove unbound secondary antibody, and washed again 3 times with PBS alone to remove detergents. Then 100μl alkaline phosphatase substrate (Pierce 1-Step pNPP) can be added to wells. Plates can be protected from light and incubated at room temp for 1 hour. The OD can be read on Molecular Devices Vmax Kinetic Microplate Reader at 405nm. The ratio of the OD (optical density) of a compound treated sample to the Nocodazole only treated sample (about 100% mitotic or abrogation) can be expressed in a percentage, and quantifies the percent abrogation of the checkpoint. The concentration at which a compound causes 50% abrogation of the checkpoint can be called the EC_{50}. The raw OD values can be graphed in Excel, and an EC_{50} value can be generated using Kaleidograph software. Strong signal results from Nocodazole only treated cells, and equals 100% mitosis in this assay. Camptothecin + Nocodazole treated control samples have low signal, signifying no mitosis and therefore, no checkpoint abrogation. When potent Chk1 inhibitors are added to Camptothecin treated cells with Nocodazole, a high signal can be generated (generally in a dose dependent manner), due to the checkpoint abrogation activity caused by the combination treatment.

The examples above illustrate compounds according to Formula I and assays that may readily be performed to determine their activity levels against the various kinase complexes. It will be apparent that such assays or other suitable assays known in the art may be used to select an inhibitor having a desired level of activity against a selected target.

The exemplary compounds described above may be formulated into pharmaceutical compositions according to the following general examples.

Parenteral Composition

To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula I or II may be dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture may be incorporated into a dosage unit form suitable for administration by injection.

Oral Composition

To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula I or II may be mixed with 750 mg of lactose. The mixture may be incorporated into an oral dosage unit for, such as a hard gelatin capsule, which may be suitable for oral administration.

The starting materials used in the examples are commercially available and/or can be prepared by techniques known in the art. Freebases and salts of prepared starting materials and intermediates were used interchangeably and are indicated. Freebases were prepared by addition of a tertiary base to the salt followed by silica gel chromatograpy of the resulting freebase if necessary. Salts were prepared by adding an equivalent amount of the appropriate acid to the freebase in a slurry or solution.

The preparation of specific preferred compounds of the invention is described in detail in the following examples. The artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other kinase inhibitors of the invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company or Lancaster Synthesis Ltd. and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF) distilled from calcium hydride and N, N-dimethylformamide (DMF) were purchased from Aldrich in Sure seal bottles and used as received. All solvents were purified using standard methods readily known to those skilled in the art, unless otherwise indicated.

The reactions set forth below were done generally under a positive pressure of argon or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed on glass-backed silica gel 60 F 254 plates Analtech (0.25 mm) and eluted with the

appropriate solvent ratios (v/v), and are denoted where appropriate. The reactions were assayed by TLC and terminated as judged by the consumption of starting material.

Visualization of the TLC plates was done with an iodine chamber, UV, p-anisaldehyde spray reagent or phosphomolybdic acid reagent (Aldrich Chemical 20 wt% in ethanol), ninhydrin reagent, and activated with heat. Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions *using 25% by volume of the extraction volume unless otherwise indicated.* Product solutions were dried over anhydrous Na_2SO_4 or $MgSO_4$ prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacuo.* Flash column chromatography (Still et al., *J. Org. Chem.*, 43, 2923 (1978)) was done using Baker grade flash silica gel (47-61 μm) and a silica gel: crude material ratio of about 20:1 to 50:1 unless otherwise stated. Hydrogenation was done at the pressure indicated in the examples or at atmospheric pressure.

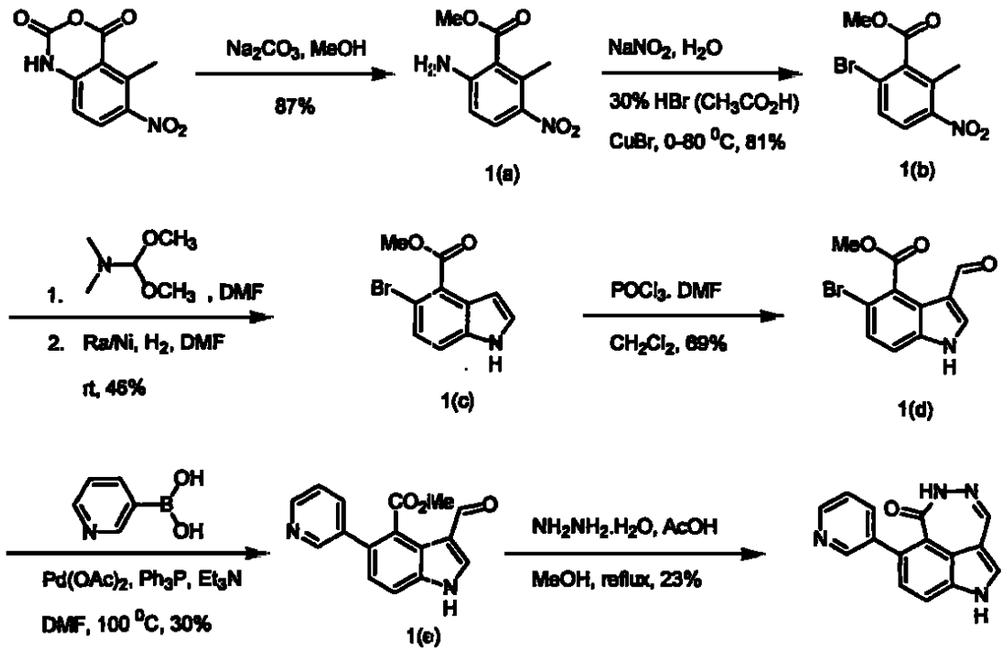
^{1}H-NMR spectra were recorded on a Bruker instrument operating at 300 M Hz, 400 M Hz or 500 M Hz and ^{13}C-NMR spectra were recorded operating at 75 M Hz. NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or DMSO-D_6 (2.50 ppm and 39.51 ppm) or or CD_3OD (3.4 ppm and 4.8 ppm and 49.3 ppm), or internal tetramethylsilane (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

The starting materials used in the examples are commercially available and/or can be prepared by techniques known in the art. Freebases and salts of prepared starting materials and intermediates were used interchangeably and are indicated. Freebases were prepared by addition of a tertiary base to the salt followed by silica gel chromatograpy of the resulting freebase if necessary. Salts were prepared by adding an equivalent amount of the appropriate acid to the freebase in a slurry or solution.

The following abbreviations may be used herein: Et_2O (diethyl ether); DMF (*N,N*-dimethylformamide); DMSO (dimethylsulfoxide); MeOH (methanol); EtOH (ethanol); EtOAc (ethyl acetate); THF (tetrahydrofuran); Ac (acetyl); Me (methyl); Et (ethyl); and Ph (phenyl).

EXAMPLES:

Example 1: 7-Pyridin-3-yl-1,5-dihydro-[1,2]diazepino[4,5,6-cd]indol-6-one



Step 1. Preparation of 6-Amino-2-methyl-3-nitro-benzoic acid methyl ester 1(a)

5-Methyl-6-nitro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (8 g, 36.0 mmol,) prepared from 2-Amino-6-methyl-benzoic acid (Aldrich) as described by Abood, N.A., et al. (1997) Bioorganic & Med. Chem. Lett. 7: 2105-2108 and sodium carbonate (3.82, 36.0 mmol) were stirred in methanol (180 mL, 0.1 M) at 0 °C for 0.5 hours and then at ambient temperature for 3 hours. Strongly acidic ion-exchange resin (Dowex® 50 WX4-200) was added until neutral pH and the solution was filtered. The solvent was removed under reduced pressure and silica gel chromatography (60:40 hexane/ethyl acetate) afforded intermediate 1(a) (6.59 g) in 87% yield.

^{1}H-NMR (d_6-DMSO): δ 7.88 (d, 1H, *J* = 9.1 Hz), 6.65 (d, 1H, *J* = 9.2 Hz), 6.55 (s, 2H), 3.86 (s, 3H), 2.38 (s, 3H).

LCMS: ($M-H^+$) 209.1

Step 2. Preparation of 6-Bromo-2-methyl-3-nitro-benzoic acid methyl ester 1(b)

Intermediate 1(a) (0.29 g, 1.38 mmol) was added to an ice-cold solution of HBr (30% in acetic acid, 1.6 mL) and water (3.0 mL). Sodium nitrite (0.103 g, 1.5 mmol) in water (2.0 mL) was added dropwise and the mixture stirred at 0 °C for 0.5 hours. Excess nitric acid was destroyed by the addition of urea. The diazonium salt solution was added to a mixture of CuBr (0.6 g, 4.18 mmol), HBr (30% in acetic acid, 3.5 mL) and water (5.0 mL) at 35 °C and the reaction mixture was heated at 80 °C for 1.5 hours. The resulting precipitate was filtered and washed with water to afford Intermediate 1(b) (0.307 g) in 81% yield.

^{1}H-NMR (d_6-DMSO): δ 7.99 (d, 1H, *J* = 8.8 Hz), 7.85 (d, 1H, *J* = 8.8 Hz), 3.94 (s, 3H), 2.39 (s, 3H).

Step 3. Preparation of 5-Bromo-1*H*-indole-4-carboxylic acid methyl ester 1(c)

Intermediate 1(b) (2.6 g, 9.5 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (0.5 M, 20 mL). *N,N*-Dimethylformamide dimethyl acetal (3.0 eq, 3.8 mL, 28.5 mmol) was added under an argon atmosphere at ambient temperature with stirring. The mixture was heated at 130 °C for 5 hours and cooled to ambient temperature. *N,N*-Dimethylformamide and the unreacted *N,N*-dimethylformamide dimethyl acetal was removed under reduced pressure (35 °C, c.a. 5 mm Hg). Toluene (~50 mL) was added and the volatiles removed under vacuum. The crude enamine was dissolved in *N,N*-dimethylformamide (0.2 M, 50 mL) followed by the addition of Ra/Ni (~300 mg). The reaction mixture was stirred under hydrogen atmosphere for 7 hours, filtered over celite and concentrated. Silica gel chromatography (80:20 hexane/ethyl acetate) afforded Intermediate 1(c) (1.1 g) in 46% yield.

^{1}H-NMR (d_6-DMSO): δ 11.54 (s, 1H), 7.51 (d, 1H, J = 1.8 Hz), 7.49 (dd, 1H, J = 8.5, 0.8 Hz), 7.33 (dd, 1H, J = 8.7 Hz), 6.50-6.47 (m, 1H), 3.92 (s, 3H).

LCMS: ($M+H^+$) 252.1

Step 4. Preparation of 5-Bromo-3-formyl-1*H*-indole-4-carboxylic acid methyl ester 1(d)

A premixed Vilsmeier reagent consisting of $POCl_3$ (0.53 mL, 5.7 mmol) in *N,N*-dimethylformamide (1.2 mL, 15.6 mmol) was added dropwise at 0 °C, to Intermediate 1(c) (0.66 g, 2.6 mmol) in anhydrous CH_2Cl_2 (13 mL, 0.2 M) with vigorous stirring. The mixture was stirred for 0.5 hours at ambient temperature, quenched with aqueous sodium acetate (2.0 M, 10 ml) and neutralized with solid Na_2CO_3. The mixture was partitioned between ethyl acetate (50 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (1 X 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated to give Intermediate 1(d) (0.51 g) in 69% yield.

^{1}H-NMR (d_6-DMSO): δ 12.54 (s, 1H), 9.80 (s, 1H), 8.43 (s, 1H), 7.59-7.48 (m, 2H), 3.91 (s, 3H).

LCMS: ($M+H^+$) 306.0

Step 5. Preparation of 3-Formyl-5-pyridin-3-yl-1*H*-indole-4-carboxylic acid methyl ester 1(e)

A solution of Intermediate 1(d) (0.05 g, 0.18 mmol), 3-boronic acid pyridine (0.034 g, 0.27 mmol), palladium (II) acetate (0.004 g, 0.0018 mmol), triphenylphosphine (0.009 g, 0.035 mmol) and triethylamine (0.08 mL, 0.55 mmol) in *N,N*-dimethylformamide (0.7 mL, 0.25 M) was heated at 100 °C for 96 hours. The reaction mixture was cooled and filtered through celite, providing after column chromatography Intermediate 1(e) (0.015 g) in 30% yield.

LCMS: ($M+H^+$) 281.1

Step 6. Preparation of Title Compound: 7-Pyridin-3-yl-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one

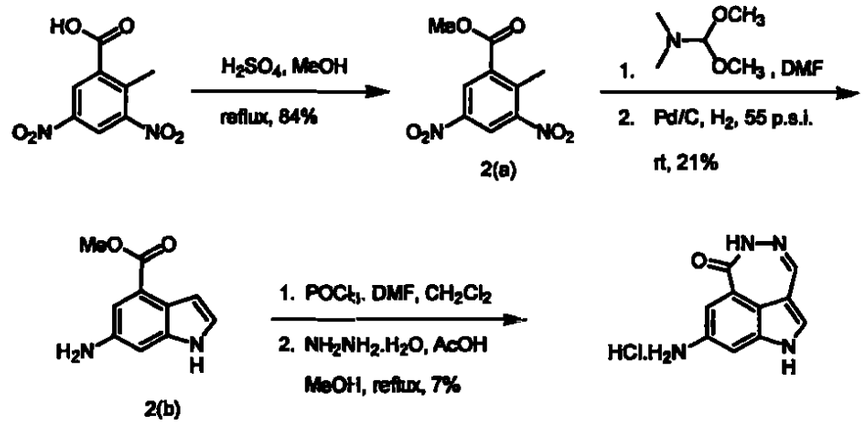
A solution of Intermediate 1(e) (0.015 g, 0.054 mmol), hydrazine (0.008 mL, 0.135 mmol) and acetic acid (0.020 mL, 2%) in anhydrous methanol (1.0 mL, 0,05 M) was heated at 80 °C for 24

hours. The reaction mixture was cooled at ambient temperature and the title compound (0.0035 g) was obtained after a preparative HPLC purification in 23% yield.

^{1}H-NMR (d_6-DMSO): δ 12.03 (s, 1H), 9.97 (s, 1H), 8.69 (s, 1H), 8.65 (d, 1H, J = 4.6 Hz), 8.09 (d, 1H, J = 8.3 Hz), 7.77 (d, 1H, J = 2.7 Hz), 7.76-7.68 (m, 1H), 7.61 (d, 1H, J = 8.4 Hz), 7.54 (s, 1H), 7.01 (d, 1H, J = 8.4 Hz).

LCMS: ($M+H^+$) 263.1

Example 2: 8-Amino-1,5-dihydro-[1,2]diazepino[4,5,6-cd]indol-6-one (hydrochloric salt)



Step 1. Preparation of 2-Methyl-3,5-dinitro-benzoic acid methyl ester 2(a)

Concentrated sulfuric acid (0.5 mL) was added slowly at ambient temperature with stirring to 2-methyl-3,5-dinitro-benzoic acid (5.22 g, 23.06 mmol) in anhydrous methanol (200 mL). After refluxing overnight under an argon atmosphere, the reaction was determined to be about 50% complete. Toluene (100 mL) was used to azeotrope the H_2O generated from the reaction, and fresh anhydrous methanol (300 mL) and H_2SO_4 (0.5 mL) were added and the mixture was again refluxed overnight under an argon atmosphere at which point the volatile components were reduced *in vacuo*. Ethyl acetate and 5% aqueous NaOH were added with stirring, and the product was extracted into the ethyl acetate. The ethyl acetate was then washed twice each with 5% aqueous NaOH and saturated aqueous $NaHCO_3$, once with brine and dried with Na_2SO_4 to give Intermediate 2(a) (4.65 g, 19.37 mmol) as a white solid in 84% yield.

Step 2. Preparation of 6-Amino-1*H*-indole-4-carboxylic acid methyl ester 2(b)

Using a modification of the procedure described by Coe, J.W., et. al. (1996) Tetrahedron Letters 37(34):6045-6048, Intermediate 2(a) (268 mg, 1.12 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (0.56 mL) and *N,N*-dimethylformamide dimethyl acetal (0.445 mL, 3.35 mmol) was added under an Ar atmosphere with stirring. The mixture was heated at 120 °C overnight at which point the unreacted *N,N*-dimethylformamide dimethyl acetal was removed under vacuum (35-40 °C, c.a. 5 mm Hg). To the resulting red enamine was added anhydrous *N,N*-dimethylformamide (c.a. 10 mL) and 10% palladium on carbon (230 mg) and the mixture was hydrogenated at 55 p.s.i. for 5 hours. The Pd catalyst was filtered through diatomaceous earth

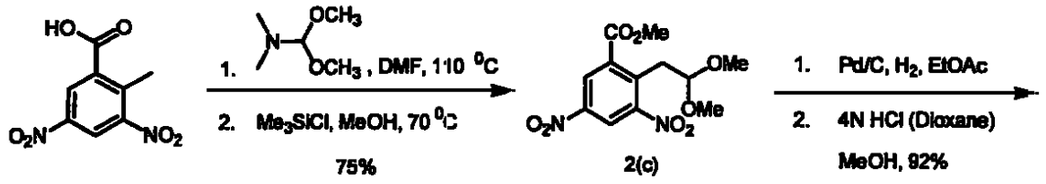
and H_2O was added to the filtrate. The aqueous component was then extracted multiple times with ethyl acetate and the combined extracts were dried with Na_2SO_4, filtered, and the volatile components were removed *in vacuo* to give the crude Intermediate 2(90 mg) as a brown glass. Purification was carried out by eluting through a silica plug with 20% ethyl acetate and 20% ethanol in hexane giving Intermediate 2(b) (45 mg, 0.24 mmol) as a brown solid in 21% yield.

Step 3. Preparation of Title Compound: 8-Amino-1,5-dihydro-[1,2]diazepino[4,5,6-cd]indol-6-one (hydrochloric salt)

With ice bath cooling under argon, to Intermediate 2(b) (45 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was added dropwise a premixed Vilsmeier reagent (0.1 mL) consisting of $POCl_3$ (0.47 mL) in *N,N*-dimethylformamide (0.77 mL). After removing the ice bath, the mixture was stirred for 0.5 hours at which point the reaction was again cooled in an ice bath and an additional Vilsmeier reagent (0.1 mL) was added. Following removal of the ice bath, the reaction was stirred 0.5 hours and then poured onto ice. Ethyl acetate was added followed by aqueous saturated $NaHCO_3$. The product was then extracted into ethyl acetate, washed with brine, dried with Na_2SO_4, and filtered to give (by LCMS) di-*N*-formylated 3-formyl-1*H*-indole-4-carboxylic acid methyl ester (37 mg, 0.13 mmol) as a brown glass which was then dissolved in anhydrous methanol (2.2 mL). Acetic acid (0.022, 0.384 mmol) and $H_2NNH_2.H_2O$ (0.038 mL, 0.78 mmol) were added, and the mixture was refluxed for 2 hours. After removing the volatile components *in vacuo*, the crude product was dissolved in H_2O and filtered, the water was lyophilized and the resulting yellow glass (36 mg) was chromatographed on silica gel eluting with 10% methanol in CH_2Cl_2. Fractions judged pure were pooled, and the product in methanol was acidified with 1M HCl. The volatile components were removed *in vacuo* using acetonitrile to azeotrope remaining water affording the title compound (4 mg, 0.016 mmol) as a brown solid in 7% yield.

^1H NMR (d_6-DMSO): δ 11.99 (s, 1H), 10.40 (s, 1H), 7.70 (s, 1H), 7.55 (s, 1H), 7.52-7.41 (m, 2H). HRMS (MALDI M+H$^+$) Calcd for $C_{10}H_8N_4O$: 201.0771. Found: 201.0776.

Altenative Method for the Preparation of Intermediate 2(b) hydrochloride:





2(b) hydrochloride

Step 4. Preparation of 2-(2,2-Dimethoxy-ethyl)-3,5-dinitro-benzoic acid methyl ester 2(c)

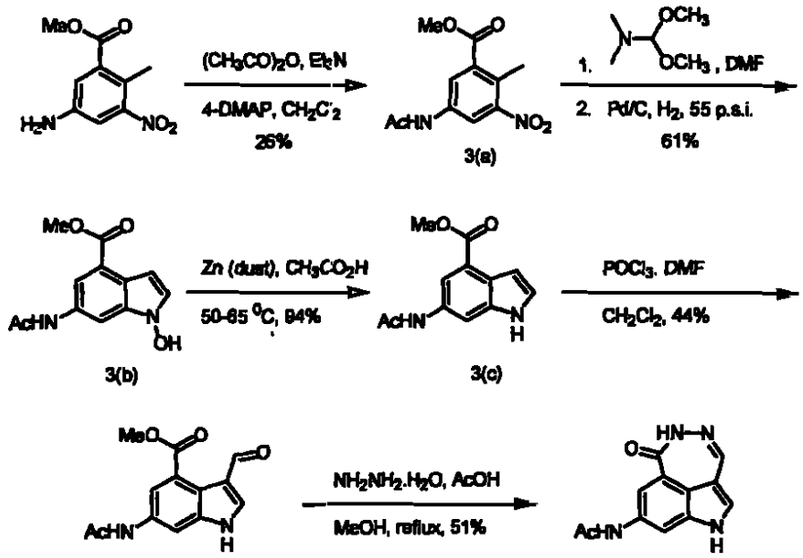
[Attn; 2-(2-Dimethylamino-vinyl)-3,5-dinitro-benzoic acid methyl ester generated during (first step of Step 4) enamine formation could lead to explosive decomposition!]

2-Methyl-3,5-dinitro-benzoic acid (100 g, 0.442 mol) was dissolved in anhydrous *N,N*-dimethylformamide (1 M, 400 mL). *N,N*-Dimethylformamide dimethyl acetal (188 mL, 1.33 mol) was added under an argon atmosphere over 10 min at ambient temperature with stirring. The mixture was heated at 110 °C for 5 hours behind a shield, and cooled at ambient temperature. *N,N*-Dimethylformamide and the unreacted *N,N*-dimethylformamide dimethyl acetal were removed under reduced pressure (35 °C, c.a. 5 mm Hg). Toluene (~50 mL) was added and the volatiles removed under vacuum. 2-(2-Dimethylamino-vinyl)-3,5-dinitro-benzoic acid methyl ester, isolated as a dark red solid, was mixed with anhydrous methanol (880 mL) and chlorotrimethylsilane (140 mL, 1.10 mol) was added over 10 min. The solution was heated at reflux (oil bath 67-70 °C) under argon for 20 hours, cooled to ambient temperature, and the volume of the mixture was reduced under vaccuum to approximately 100 mL. The precipitated solid was collected by filtration and washed with cold methanol (100 mL). The dark brown solid was dried under vacuum, triturated with acetone (100 mL), again collected by filtration and washed with diethyl ether (150 mL) to afford Intermediate 2(c) (79 g). The mother liquor from the first precipitation and the various triturations were combined and concentrated. Additional Intermediate 2(c) (21 g) was then recrystallized from cyclohexane/ethyl acetate (9:1) providing a second batch. Again the resulting mother liquor was reduced *in vacuo* and a third batch of Intermediate 2(c) (4 g) was recrystallized from acetone/H_2O (6:4). The combined yield for all three batches of Intermediate 2(c) (104 g) was 75%.

Step 5. Preparation of 6-Amino-1*H*-indole-4-carboxylic acid methyl ester hydrochloride 2(b)

Intermediate 2(c) (20 g, 63.6 mmol) was dissolved in anhydrous ethyl acetate (350 mL) and 10% palladium on carbon (7.4 g, 6.36 mmol) was added under argon. The mixture was hydrogenated at 1 atm until the reaction was judged complete by LCMS. The Pd catalyst was removed by filtering through diatomaceous earth, and the filtrate was reduced *in vacuo*. The crude 3,5-diamino-2-(2,2-dimethoxy-ethyl)-benzoic acid methyl ester was dissolved in anhydrous methanol (40 ml), and 4.0 M HCl in dioxane (160 mL) was added. The mixture was stirred at ambient temperature for one hour. The precipitated solid was collected by filtration and washed with CH_2Cl_2 and diethyl ether and dried under vacuum to produce Intermediate 2(b) (hydrochloride) (11.85 g) as a gray solid. The filtrate was concentrated and more Intermediate 2(b) hydrochloride (1.48 g) was precipitated. The combined yield for both batches of Intermediate 2(b) (13.33 g) was 92%

Example 3: *N*-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide



Step 1. Preparation of 5-Acetylamino-2-methyl-3-nitro-benzoic acid methyl ester 3(a)

To 5-amino-2-methyl-3-nitro-benzoic acid methyl ester (428 mg, 2.04 mmol), prepared as described by Cannon et. al. (1984) J. Med. Chem. 27:386-389, in CH_2Cl_2 (4 mL) was added triethylamine (1.71 mL, 12.2 mmol), acetic anhydride (0.77 mL, 8.14 mmol) and 4-(dimethylamino)pyridine (30mg, 0.25 mmol) with stirring at ambient temperature. After stirring overnight, LCMS indicated a mixture of mono and diacetylated products. Saturated aqueous $NaHCO_3$ was added, and the mixture was again allowed to stir overnight. Additional CH_2Cl_2 was added, and the layers were separated. The organic layer was reduced and ethyl acetate was added. The organic layer was washed with saturated aqueous $NaHCO_3$, with H_2O, with saturated aqueous $KHSO_4$, with brine, dried (Na_2SO_4), filtered and evaporated to an oil which was then re-dissolved in a minimal amount of ethyl acetate. Hexane was added and the resulting precipitate

was isolated as tan solids (469 mg) which were then purified on silica gel, eluting with 1:2 ethyl acetate:hexane followed by 1:1 ethyl acetate:hexane, to afford Intermediate 3(a) (133 mg, 0.53 mmol) as a cream solid in 26% yield. (5-diacetylamino-2-methyl-3-nitro-benzoic acid methyl ester (248 mg, 0.84 mmol) was also isolated.)

^{1}H NMR (d_6-DMSO): δ 10.46 (br s, 1H, exchanges), 8.34 (s, 1H), 8.14 (s, 1H), 3.89 (s, 3H), 2.43 (s, 3H), 2.08 (s, 3H).

LCMS: $(M-H)^-$ 251.3.

Step 2. Preparation of 6-Acetylamino-1-hydroxy-1*H*-indole-4-carboxylic acid methyl ester 3(b)

To Intermediate 3(a) (117 mg, 0.46 mmol) in anhydrous *N,N*-dimethylformamide (0.5 mL) was added, under an Ar atmosphere with stirring, *N,N*-dimethylformamide dimethyl acetal (0.185 mL, 1.39 mmol). The mixture was heated at 120 °C for 5-6 hours at which point the unreacted *N,N*-dimethylformamide dimethyl acetal was removed under vacuum (35-40 °C, c.a. 5 mm Hg). To the resulting red enamine was added anhydrous *N,N*-dimethylformamide (c.a. 20 mL), ethyl acetate (10 mL) and 10% palladium on carbon (150 mg). The mixture was hydrogenated at 55 p.s.i. for 4 hours at which point the *N,N*-dimethylformamide was removed *in vacuo*, methanol was added, and the Pd catalyst was removed by filtration. Again the volatile components were removed *in vacuo*. Following diethyl ether trituration, the triturate was evaporated to afford crude Intermediate 3(b) (70 mg, 0.28 mmol) as tan solids in 61% yield which were carried forward without further purification.

LCMS: $(M-H)^-$ 247.3.

Step 3. Preparation of 6-Acetylamino-1*H*-indole-4-carboxylic acid methyl ester 3(c)

To Intermediate 3(b) (39 mg, 0.16 mmol) in acetic acid (1 mL) was added zinc dust (206 mg, 3.15 mmol) with stirring. The mixture was heated at 50 °C for 0.5 hours and then 65 °C for 0.5 hours during which time the mixture turns green. After cooling to room temperature methanol is added and the mixture is filtered though diatomaceous earth rinsing several times with methanol. Following evaporation the resulting tan solids are triturated with methanol and the volatile components of the triturate are remove *in vacuo* to afford crude Intermediate 3(c) (35 mg, 0.15 mmol) as tan solids in 94% crude yield which were then carried on without further purification.

LCMS: $(M-H)^-$ 231.2.

Step 4. Preparation of 6-Acetylamino-3-formyl-1*H*-indole-4-carboxylic acid methyl ester 3(d)

With ice bath cooling under argon, 0.2 mL of a premixed Vilsmeier reagent consisting of $POCl_3$ (0.47 mL) in *N,N*-dimethylformamide (0.77 mL) was added in two equal portions to Intermediate 3(c) (35 mg, 0.15 mmol) in 1:1 CH_2Cl_2: *N,N*-dimethylformamide (1 mL). After 0.5 hours the reaction was quenched with water and extracted with ethyl acetate. The aqueous layer was then basified to about pH 8 with 5% aqueous NaOH and extracted again with ethyl acetate. The combined ethyl acetate extracts were dried with Na_2SO_4, filtered and evaporated to give

Intermediate 3(d) (19 mg, 0.07 mmol) as yellow solids in 44% crude yield which were then carried on without further purification.

LCMS: $(M-H)^-$ 259.3.

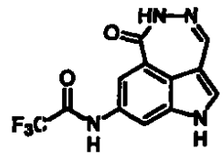
Step 5. Preparation of Title Compound: *N*-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide

To Intermediate 3(d) (19 mg, 0.07 mmol) in anhydrous methanol (2.0 mL) was added acetic acid (0.006 mL, 0.1 mmol) and $H_2NNH_2 \cdot H_2O$ (11 mg, 0.22 mmol) and the mixture was refluxed for about 1 hour after which the volatile components were removed *in vacuo* and the resulting yellow glass was redissolved in methanol. Following recrystallization from methanol/diethyl ether, the title compound (9 mg, 0.04 mmol) was obtained as a yellow powder in 51% yield.

^{1}H NMR (d_6-DMSO): δ 11.60 (br s, 1H, exchanges), 10.10 (s, 1H, exchanges), 9.90 (s, 1H, exchanges), 8.00 (s, 1H), 7.45 (br s, 2H), 7.30 (s, 1H), 1.90 (s, 3H).

LCMS: $(M+H^+)$ 243.1, $(M+Na^+)$ 265.1.

Example 4: 2,2,2-Trifluoro-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide

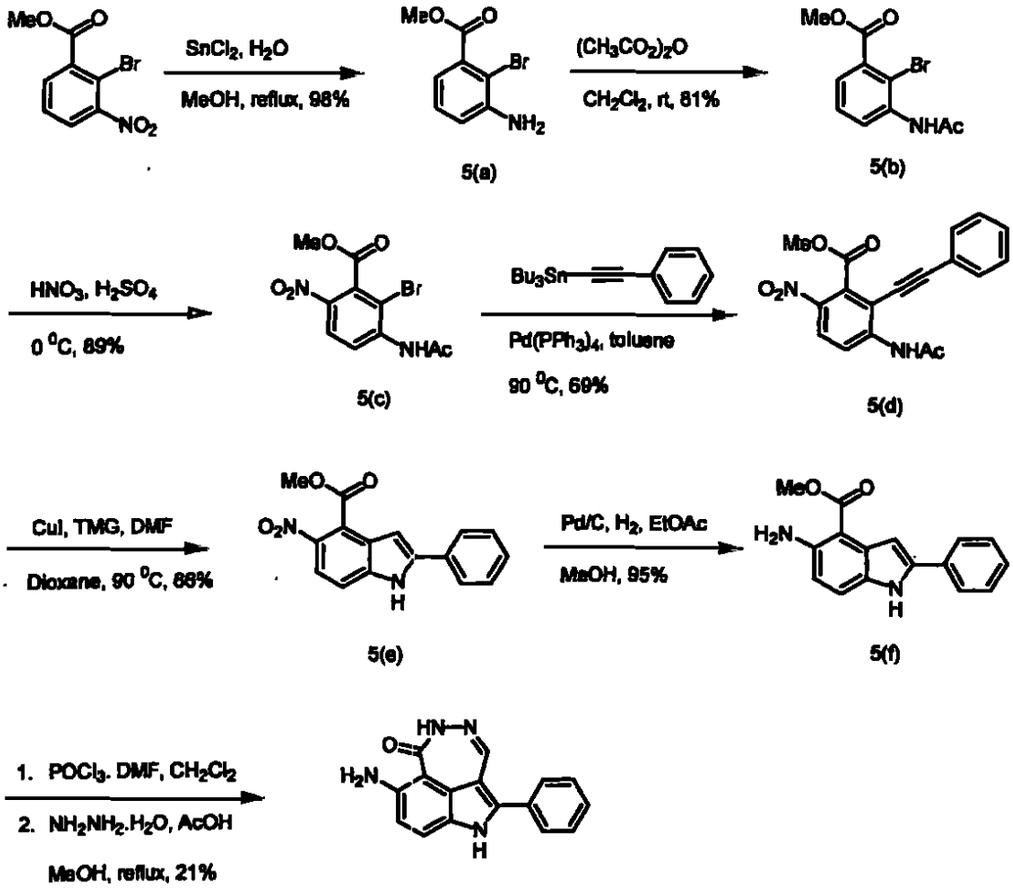


With stirring, trifluoroacetic anhydride (0.032 mL, 0.23 mmol) was added dropwise to triethylamine (0.088 mL, 0.63 mmol) and the title compound of Example 2 (freebase) (43 mg, 0.21 mmol) in *N,N*-dimethylformamide (2 mL). After 2.5 hours, additional trifluoroacetic anhydride (0.032 mL, 0.23 mmol) was added to drive the reaction to completion at which point diethyl ether was added to precipitate brown solids (25 mg), which were discarded. The triturate was reduced in volume and subjected to preparative HPLC (MetaChem Metasil AQ C18 reverse-phase 10μm, 120A, 250x21.2 mm column eluting with CH_3CN/0.1%TFA in H_2O at a flowrate of 20 mL/min using a gradient of 5-95% CH_3CN over 20 min) affording, after isolation, the title compound (3.7 mg, 0.01 mmol) as a brown solid in 6% yield.

^{1}H NMR (d_6-DMSO): δ 12.01 (s, 1H), 11.41 (s, 1H), 10.40 (s, 1H), 8.15 (s, 1H), 7.91 (s, 1H), 7.78 (s, 1H), 7.61 (s, 1H)

LCMS: $(M-H)^-$ 295.2.

Example 5: 7-Amino-2-phenyl-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one



Step 1. Preparation of 3-Amino-2-bromo-benzoic acid methyl ester 5(a)

2-Bromo-3-nitro-benzoic acid methyl ester (12.9 g, 49.5 mmol) (prepared from 2-amino-3-nitro-benzoic acid as described by Webber E. S. et al., see patent application number **WO 01/16136 A2**) and $SnCl_2$ (42 g, 223 mmol) were refluxed in methanol (225 mL, 0.2 M) and H_2O (5.3 g, 243 mmol) for 2 hours. After cooling at ambient temperature, diatomaceous earth (20 g) and dichloromethane (1 L) were added followed with 3N aqueous sodium hydroxide (150 mL) with vigorous stirring. The mixture was filtered and the organic phase was washed with saturated aqueous sodium chloride. The organic solution was dried over sodium sulfate, filtered and all volatiles were removed under reduced pressure to afford Intermediate 5(a) (11.4 g) in 98% yield.
^{1}H-NMR (d_6-DMSO): δ 7.12 (dd, 1H, J = 8.1, 7.5 Hz), 6.93 (dd, 1H, J = 8.1, 1.6 Hz), 6.80 (dd, 1H, J = 7.4, 1.6 Hz), 5.57 (s, 2H), 3.81 (s, 3H).

Step 2. Preparation of 3-Acetylamino-2-bromo-benzoic acid methyl ester 5(b)

Intermediate 5(a) (2.21 g, 9.6 mmol) and acetic anhydride (1.82 mL, 19.2 mmol) were stirred in CH_2Cl_2 (100 mL, 0.1 M) at 22 °C for 24 hours. Volatiles were removed in vacuo and silica gel chromatography afforded Intermediate 5(b) (2.08 g) in 79% yield.

^{1}H-NMR (d_6-DMSO): δ 9.58 (s, 1H), 7.70 (dd, 1H, *J* = 6.9, 2.7 Hz), 7.50-7.41 (m, 2H), 3.86 (s, 3H), 2.09 (s, 3H).

LCMS: ($M+H^+$) 272.0, 274.0

Step 3. Preparation of 3-Acetylamino-2-bromo-6-nitro-benzoic acid methyl ester 5(c)

Intermediate 5(b) (1.0 g, 3.7 mmol) was nitrated in a manner analogous to step 1 of Example 2. Intermediate 5(c) (1.0 g, 89%) was obtained after silica gel chromatography.

^{1}H-NMR (d_6-DMSO): δ 9.83 (s, 1H), 8.3 (d, 1H, *J* = 9.0 Hz), 8.15 (d, 1H, *J* = 9.0 Hz), 3.93 (s, 3H), 2.20 (s, 3H).

LCMS: ($M+H^+$) 315.0, 317.0

Step 4. Preparation of 3-Acetylamino-6-nitro-2-phenylethynyl-benzoic acid methyl ester 5(d)

Intermediate 5(c) (0.85 g, 2.7 mmol) was acetylated in a manner analogous to step 3 of Example 6 to afford Intermediate 5(d) (0.4 g, 44%) after silica gel chromatography.

^{1}H-NMR (d_6-DMSO): δ 9.93 (s, 1H), 8.32-8.25 (m, 2H), 7.65-7.59 (m, 2H), 7.53-7.47 (m, 3H), 3.97 (s, 3H), 2.25 (s, 3H).

LCMS: ($M-H^+$) 337.1

Step 5. Preparation of 5-Nitro-2-phenyl-1*H*-indole-4-carboxylic acid methyl ester 5(e)

Intermediate 5(d) (0.096 g, 0.28 mmol), copper iodide (0.076 g, 0.4 mmol), *N,N,N,N*-tetramethylguanidine (0.36 mL, 2.8 mmol) were stirred in a mixture of dimethylformamide/dioxane (1:4, 2 mL, 0.15 M) at 90 °C for 2 hours. The reaction mixture was cooled to ambient temperature and poured into ethyl acetate (30 mL). The organic layer was washed subsequently with a saturated ammonium chloride solution (3 X 5 mL), H_2O (2 X 5 mL), saturated aqueous sodium chloride solution (2 X 5 mL), dried over sodium sulfate, filtered and volatiles removed in vacuo. Silica gel chromatography afforded Intermediate 5(e) (0.073 g) in 86% yield.

^{1}H-NMR (d_6-DMSO): δ 12.50 (s, 1H), 7.98-7.88 (m, 3H), 7.69-7.40 (m, 4H), 7.13 (broad s, 1H), 3.97 (s, 3H).

LCMS: ($M-H^+$) 295.1

Step 6. Preparation of 5-Amino-2-phenyl-1*H*-indole-4-carboxylic acid methyl ester 5(f)

In an analogous manner to that of the preparation of Example 2 (step 5), Intermediate 5(e) (0.072 g, 0.24 mmol) was hydrogenated to afford Intermediate 5(f) (0.06 g, 95%).

^{1}H-NMR (d_6-DMSO): δ 11.68 (s, 1H), 7.86 (d, 2H, *J* = 7.4 Hz), 7.52-7.43 (m, 3H), 7.31 (dd, 1H, *J* = 7.4, 7.2 Hz), 7.20 (s, 1H), 6.83 (d, 1H, *J* = 8.5 Hz), 3.94 (s, 3H).

LCMS: ($M+H^+$) 235.1

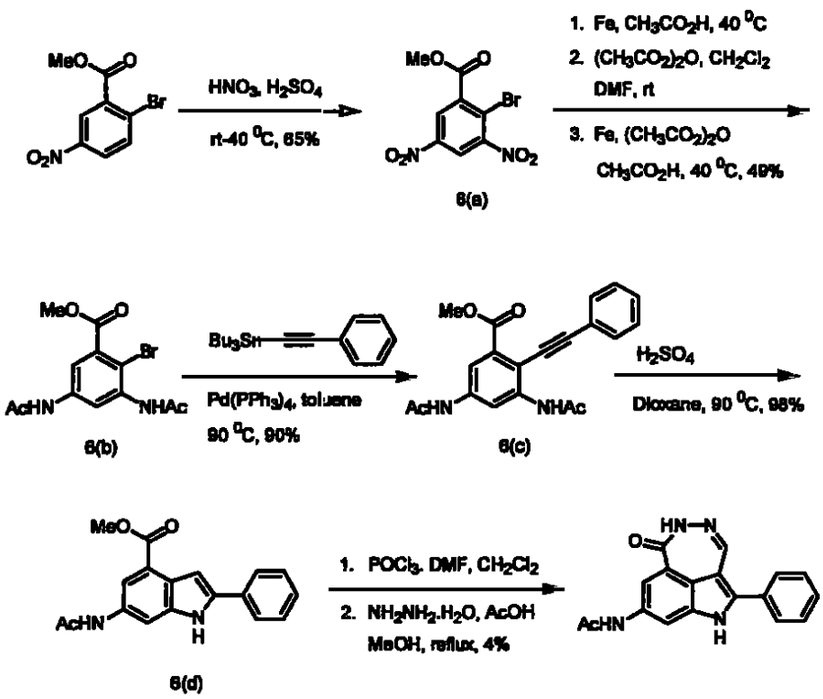
Step 7. Preparation of Title Compound: 7-Amino-2-phenyl-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one

Carried out analogously to steps 4 and 5 of Example 3, Intermediate 5(f) (0.055g, 0.21 mmol) was formylated and cyclized to provide the title compound (0.012g, 21%).

^{1}H-NMR (d_6-DMSO): δ 12.17 (s, 1H), 8.32 (s, 1H), 7.95-7.84 (m, 3H), 7.74 (d, 1H, *J* = 1.8 Hz), 7.55-7.47 (m, 2H), 7.42 (d, 1H, *J* = 8.6 Hz), 7.37 (dd, 1H, *J* = 7.4, 7.3 Hz), 5.91 (s, 2H).

LCMS: $(M+H^+)$ 277.1

Example 6: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl-acetamide



Step 1. Preparation of 2-Bromo-3,5-dinitro-benzoic acid methyl ester 6(a)

Concentrated sulfuric acid (20 mL) was slowly added to 2-bromo-5-nitro-benzoic acid methyl ester (20.52 g, 78.91 mmol) with stirring. After a few minutes, fuming nitric acid (20 mL) was added and the mixture was capped and heated at 40°C for approximately 60 hours at which point the flask was cooled to ambient temperature, carefully opened, and the reaction was poured onto ice water and ethyl acetate. The product was extracted into ethyl acetate and washed twice with H_2O, twice with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and filtered to afford Intermediate 6(a) (15.64 g, 51.26 mmol) as a cream solid in 65% yield.

^{1}H NMR (d_6-DMSO): δ 9.07 (s, 1H), 8.73 (s, 1H), 3.98 (s, 3H).

LCMS: $(M-CO_2CH_3)^-$ 245.1, 247.1.

Step 2. Preparation of 3,5-Bis-acetylamino-2-bromo-benzoic acid methyl ester 6(b)

To acetic acid (250 mL) at room temperature was added Intermediate 6(a) (15.49 g, 50.79 mmol). The mixture was placed in an oil bath at 40 °C for c.a. 10 min and stirred vigorously under an Ar atmosphere until the soution went clear. Iron powder (25.34 g, 453.72 mmol) was added and the mixture was heated at 40 °C for c.a. 6 hours. The mixture was filtered through diatomaceous earth, rinsing with methanol. The combined filtrate and rinses were evaporated to give orange solids, which were determined to be a mixture of products (13.2 g) resulting from incomplete reduction of the nitro groups. This mixture (13.1 g) in CH_2Cl_2 (48 mL) and *N,N*-dimethylformamide (5 mL) was then treated with acetic anhydride (36 mL, 382 mmol) and stirred overnight under an Ar atmosphere. The CH_2Cl_2 was evaporated and the mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ .The aqueous layer was extracted twice with ethyl acetate and the combined extracts were washed successively with 1:1 H_2O:saturated aqueous $NaHCO_3$ (multiple washings), 0.5 M aqueous HCl (X2), saturated aqueous $NaHCO_3$ (X2) and brine. The ethyl acetate solution was then dried (Na_2SO_4), filtered and evaporated to give yellow solids, which were then triturated with diethyl ether (c.a. 75 mL) to give a mixture of acetylated products (11.4 g) as a yellow solids. A portion of this mixture of acetylated products (5.5 g) in acetic acid (17.4 mL) was then treated with acetic anhydride (16.5 mL, 174 mmol) and iron powder (9.74 g, 174 mmol) and heated at 40°C under an Ar atmosphere overnight. Methanol was then added and the reaction was stirred at room temperature for c.a. 1.5 hours. Then 9:1 CH_2Cl_2:methanol was added, and the mixture was filtered through diatomaceous earth, rinsing with 9:1 CH_2Cl_2:methanol. The combined filtrate and rinses were evaporated and again methanol was added and the mixture was stirred c.a. 0.5 hours after which the methanol was evaporated. Ethyl acetate was added followed by hexane to precipitate orange solids (6.9 g) which were collected. Silica gel chromatography eluting with 1:1 acetone:hexane which afforded, after isolation, Intermediate 6(b) (4.1 g, 12.46 mmol) as a cream solid in 49% yield.

Step 3. Preparation of 3,5-Bis-acetylamino-2-phenylethynyl-benzoic acid methyl ester 6(c)

With stirring, argon was bubbled into anhydrous toluene (18 mL) containing Intermediate 6(b) (1.08 g, 3.29 mmol). Tributyl-phenylethynyl-stannane (1.73 mL, 4.94 mmol) and tetrakis(triphenylphosphine) palladium(0) (310 mg, 0.28 mmol) were added sequentially and more Ar was bubbled into the reaction. After capping tightly, the mixture was heated at 90 °C overnight under an argon atmosphere. After cooling to ambient temperature, H_2O, and saturated aqueous $KHSO_4$ were added and the product was extracted into ethyl acetate and isolated. Following silica gel chromatography eluting with 2:3 acetone:hexane, fractions judged pure were pooled. Intermediate 6(c) (1.14 g, 3.25 mmol) was isolated, found to be contaminated by approximately 5-10% triphenylphosphine oxide, and carried on to the next step without further purification.

^{1}H NMR (d_6-DMSO): δ 10.30 (s, 1H), 9.50 (s, 1H), 8.23 (s, 1H), 8.08 s, 1H), 7.63-7.51 (m, 2H, contaminated by Ph_3PO), 7.50-7.38 (m, 3H, contaminated by Ph_3PO), 3.90 (s, 3H), 2.17 (s, 3H), 2.05 (s, 3H).

LCMS: $(M+H^+)$ 351.1, $(M+Na^+)$ 373.1, $(M-H^-)$ 349.1.

Step 4. Preparation of 6-Acetylamino-2-phenyl-1*H*-indole-4-carboxylic acid methyl ester 6(d)

To the impure Intermediate 6(c) (853 mg, 2.4 mmol) is added concentrated sulfuric acid (15 mL). After stirring 0.5 hours, the mixture is carefully poured onto methanol (30 mL) with vigorous swirling. Ethyl acetate (c.a. 300 mL) and H_2O (c.a.100 mL) are added. The aqueous layer is extracted three times with ethyl acetate, and the combined extracts are washed with saturated aqueous $NaHCO_3$ until the evolution of CO_2 ceases. The product in ethyl acetate is then washed with brine, dried (Na_2SO_4), filtered and volatile components evaporated to afford crude Intermediate 6(d) (790 mg, c.a. 2.4 mmol) as a yellow powder which was carried on without further purification.

^{1}H NMR (d_6-DMSO): δ 11.75 (s, 1H, exchanges), 10.07 (s, 1H, exchanges), 8.33 (s, 1H), 7.90-7.80 (m, 3H), 7.66-7.23 (m, 4H, partially obscured), 3.93 (s, 3H), 2.07 (s, 3H).

LCMS: $(M+H^+)$ 309.1, $(M+Na^+)$ 331.1, $(M-H)^-$ 307.1.

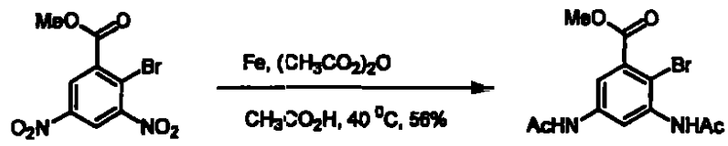
Step 5. Preparation of Title Compound: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl-acetamide

Crude Intermediate 6(d) (312 mg, c.a. 1 mmol) in *N,N*-dimethylformamide (2 mL) and CH_2Cl_2 (5 mL) was treated with Vilsmeier reagent (0.9 mL) in a manner similar to that described for Example 3, step 4. After removal of the CH_2Cl_2, adjusting the pH to c.a. 8 with 1N NaOH and removal of the volatile components *in vacuo*, the yellow solids were triturated with ethyl acetate and methanol. The triturate was evaporated to afford the crude 6-acetylamino-3-formyl-2-phenyl-1*H*-indole-4-carboxylic acid methyl ester (405 mg) as a yellow solid contaminated with salts from the aqueous quench. In a procedure similar to that described for Example 3, step 5, anhydrous methanol (15 mL), acetic acid (0.084 mL, 1.47 mmol) and $H_2NNH_2{\cdot}H_2O$ (0.147 mL, 3.03 mmol) were then added and the mixture was refluxed for 2 hours. The volatile components were evaporated and the resulting solids were triturated with methanol to dissolve the product while leaving behind most of the insoluble solids. The triturate was evaporated, and this process was repeated. The second triturate was evaporated to give yellow solids (70 mg) enriched in product which were then subjected to silica gel chromatography eluting with hexane:ethyl acetate:ethanol (4:1:1) to give the title compound (12 mg, 0.04 mmol) after isolation as a yellow powder in approximately 4% overall yield.

^{1}H NMR (d_6-DMSO): δ 12.10 (s, 1H, exchanges), 10.33(s, 1H, exchanges), 10.06(s, 1H, exchanges), 8.17 (s, 1H), 7.70-7.43 (m, 7H), 2.05 (s, 3H).

LCMS: $(M+H^+)$ 319.1, $(M+Na^+)$ 341.1, $(M-H)^-$ 317.

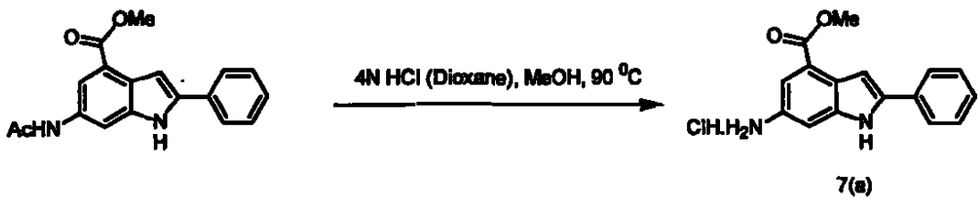
Alternative Method for the Preparation of Intermediate 6(b).



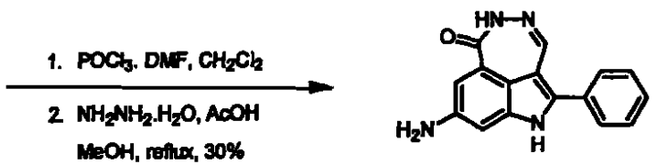
(b)

To acetic acid (10 mL) at room temperature was added acetic anhydride (10.0 mL, 106 mmol), iron powder (5.5 g, 98 mmol) and Intermediate 6(a) (3.0 g, 9.8 mmol). The mixture was placed in an oil bath at 43 °C and stirred vigorously under argon for 48 hours. The thick slurry goes from orange to tan in color. Additional acetic acid (2 mL), acetic anhydride (2 mL, 21.2 mmol), and iron powder (1.0 g, 17.9 mmol) were added, and the mixture was stirred at 43 °C for an additional 24 hours whereupon the mixture was poured into 10% methanol in CH_2Cl_2 (300 mL) and filtered though diatomaceous earth. The filtrate was concentrated and ethyl acetate (300 mL) and H_2O (300 mL) were added. The product was extracted into ethyl acetate and washed twice with H_2O, twice with brine, dried ($MgSO_4$), and filtered. Following recrystallization from hot ethyl acetate (10 mL), collection by filtration and subsequent washing of the solids with CH_2Cl_2 (5 mL) and diethyl ether (30 mL), Intermediate 6(b) (1.8 g, 5.47 mmol) was obtained as a white solid in 56% yield.

Example 7: 8-Amino-2-phenyl-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one



7(a)



Step 1. Preparation of 6-Amino-2-phenyl-1*H*-indole-4-carboxylic acid methyl ester (hydrochloric salt) salt 7(a)

Intermediate 6(d) of Example 6 (9.3 g, 30.2 mmol) and anhydrous 4M HCl in dioxane (160 mL, 604 mmol) were heated in anhydrous methanol (160 mL) at reflux for 3 hours, cooled to ambient temperature and volatiles removed *in vacuo*. The resulting solid was triturated with ethyl acetate/CH_2Cl_2 (1:1, 50 mL) and dried to afford Intermediate 7(a) (8.7 g) in 95% yield.

^{1}H-NMR (d_6-DMSO): δ 12.26 (s, 1H), 10.10 (broad, 1H), 7.93 (d, 2H, *J* = 7.7 Hz), 7.71 (d, 2H, *J* = 12.2 Hz), 7.52 (dd, 2H, *J* = 7.7, 7.6 Hz), 7.43-7.36 (m, 2H), 3.96 (s, 3H).

LCMS: ($M+H^+$) 267.2.

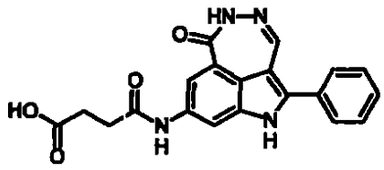
Step 2. Preparation of Title Compound: 8-Amino-2-phenyl-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one

In two steps, analogous to steps 4 and 5 of Example 3, Intermediate 7(a) (8.7 g, 28.7 mmol) was cyclized to afford the title compound (5.47 g, 69%).

^{1}H-NMR (d_6-DMSO): δ 11.53 (s, 1H), 10.15 (s, 1H), 7.62-7.40 (m, 6H), 6.98 (d, 1H, *J* = 1.8 Hz), 6.65 (d, 1H, *J* = 1.8 Hz), 5.21 (s, 2H).

LCMS: ($M+H^+$) 277.2.

Example 8: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-succinamic acid

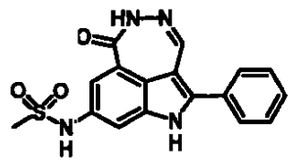


Succinic anhydride (3 eq, 0.022 g) was added to a solution of the title compound of Example 7 (0.02 g, 0.072 mmol) in *N,N*-dimethylformamide (0.7 M, 1 mL) and methanol (2.5 M, 0.3 mL). The reaction mixture was stirred at 22 °C for 24 hours and concentrated under reduced pressure. The yellow solid was triturated with methanol (1.0 mL) and collected by filtration. Following washes with methanol (4 mL) and diethyl ether (5.0 mL), the title compound (21 mg) was obtained in 77% yield.

^{1}H-NMR (d_6-DMSO): δ 12.03 (s, 1H), 10.31 (s, 1H), 10.09 (s, 1H), 8.12 (s, 1H), 7.68-7.45 (m, 7H), 2.60-2.53 (m, 4H).

LCMS: ($M+H^+$) 377.1.

Example 9: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-methanesulfonamide

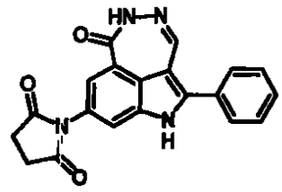


Methanesulfonyl Chloride (1.5 eq, 0.003 g) was added to a solution of the title compound of Example 7 (0.005 g, 0.018 mmol) in CH_2Cl_2 (0.045 M, 0.4 mL) and pyridine (0.045 M, 0.4 mL). The mixture was stirred at 22 °C for 24 hours and concentrated under reduced pressure. Silica gel chromatography (triethylamine/methanol/ CH_2Cl_2; 1:5:94) afforded the title compound (1.7 mg) in 30% yield.

^{1}H-NMR (d_6-DMSO): δ 12.15 (s, 1H), 10.40 (s, 1H), 9.71 (s, 1H), 7.70-7.43 (m, 8H), 2.30 (m, 3H).

LCMS: $(M+H^+)$ 355.1.

Example 10: 1-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-pyrrolidine-2,5-dione

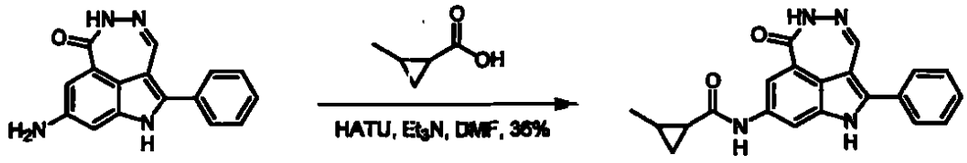


Triethylamine (0.18 mmol, 0.025 mL) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.04 mmol, 0.013 g) were added to a solution of the title compound of Example 8 (0.013 g, 0.036 mmol) in *N,N*-dimethylformamide (0.05 M, 0.75 mL). The reaction mixture was stirred at 22 °C for 12 hours and concentrated under reduced pressure. The yellow solid was triturated with methanol (3.0 mL), collected by filtration, and washed with methanol (4.0 mL) and diethyl ether (5.0 mL) to afford the title compound (5.8 mg) in 47% yield.

^{1}H-NMR (d_6-DMSO): δ 12.38 (s, 1H), 10.44 (s, 1H), 9.71 (s, 1H), 7.74-7.42 (m, 8H), 2.79 (m, 3H).

LCMS: $(M+H^+)$ 359.1.

Example 11: 2-Methyl-cyclopropanecarboxylic acid(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

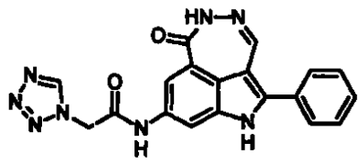


Triethylamine (0.030 mL, 0.22 mmol), the title compound of Example 7 (15mg, 0.054 mmol) and 2-methyl-cyclopropanecarboxylic acid (6 mg, 0.062 mmol) were stirred in *N,N*-dimethylformamide (1.0 mL). O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) was added and the reaction was stirred overnight at which point the volatile components were removed under vacuum. The resulting mixture was purified on silica gel, eluting with 3:2 hexane:ethyl acetate. The purest fractions were combined and after solvent removal, the resulting solids were triturated with diethyl ether to give the title compound (7 mg, 0.020 mmol) as yellow powder in 36% yield.

^{1}H-NMR (d_6-DMSO): δ 12.03 (s, 1H), 10.32 (s, 1H), 10.27 (s, 1H), 8.13 (s, 1H), 7.67-7.48 (m, 7H), 1.54 (m, 1H), 1.11(s, 1H), 1.09 (d, 3H), 1.07 (m, 1H), 1.03 (m, 1H).

LCMS: $(M+H^+)$ 359.1, $(M+Na^+)$ 381.1.

Example 12: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-tetrazol-1-yl-acetamide

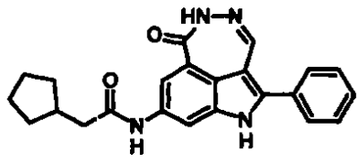


Preparation of example 12 from the title compound of Example 7 (15 mg, 0.054 mmol), tetrazol-1-yl-acetic acid (8 mg, 0.062 mmol), triethylamine (0.030 mL, 0.22 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example 11. Additional tetrazol-1-yl-acetic acid acid (1.0 mg, 0.008 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (3.0 mg, 0.008 mmol) were added after c.a. 18 hours to drive the reaction to completion. Filtration, concentration and recrystallization afforded the title compound (12 mg, 0.031 mmol) as a yellow powder in 58% yield.

^{1}H-NMR (d_6-DMSO): δ 12.13 (s, 1H), 10.71 (s, 1H), 10.39 (s, 1H), 9.44 (s, 1H), 8.07 (m, 1H), 7.68-7.47 (m, 7H), 5.05 (s, 2H).

LCMS: ($M+H^+$) 387.2, ($M+Na^+$) 409.1.

Example 13: 2-Cyclopentyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide

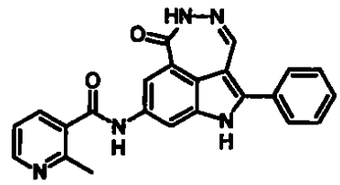


Preparation of example 13 from the title compound of Example 7 (15 mg, 0.054 mmol), cyclopentyl-acetic acid (8 mg, 0.062 mmol), triethylamine (0.030 mL, 0.22 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) in dimethylformamide (1.0 mL) was carried out analogously to Example 11. Silica gel chromatography (1:1 ethyl acetate:hexane), also in an analogous manner, followed by diethyl ether trituration afforded the title compound (3 mg, 0.008 mmol) as a yellow powder in 14% yield.

^{1}H-NMR (d_6-DMSO): δ 12.03 (s, 1H), 10.32 (s, 1H), 9.99 (s, 1H), 8.17 (s, 1H), 7.67-7.49 (m, 7H), 2.33-2.26 (m, 3H), 1.78 (m, 2H), 1.65-1.53 (m, 4H), 1.22 (m, 2H).

LCMS: ($M+H^+$) 387.2, ($M+Na^+$) 409.2.

Example 14: 2-Methyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-nicotinamide

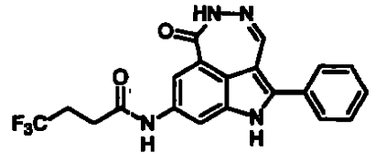


Preparation of example 14 from the title compound of Example 7 (15 mg, 0.054 mmol), 2-methyl-nicotinic acid (9 mg, 0.062 mmol), triethylamine (0.030 mL, 0.22 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example 11. Silica gel chromatography (ethyl acetate), also in an analogous manner, followed by diethyl ether trituration afforded the title compound (7 mg, 0.018 mmol) as a yellow powder in 33% yield.

^{1}H-NMR (d_6-DMSO): δ 12.13 (s, 1H), 10.57 (s, 1H), 10.36 (s, 1H), 8.57 (m, 1H), 8.25 (s, 1H), 7.90 (m, 1H), 7.84 (m, 1H), 7.68 (m, 2H), 7.61-7.50 (m, 4H), 7.34 (m, 1H), 2.60 (s, 3H).

LCMS: (M+H$^+$) 396.2, (M+Na$^+$) 418.1.

Example 15: 4,4,4-Trifluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-butyramide

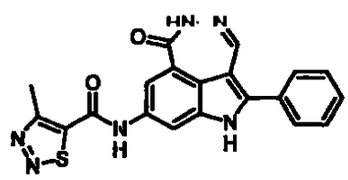


Preparation of example 15 from the title compound of Example 7 (15 mg, 0.054 mmol), 4,4,4-trifluorobutyric acid (9 mg, 0.062 mmol), triethylamine (0.030 mL, 0.22 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example 11. Silica gel chromatography (1:1 ethyl acetate:hexane), also in an analogous manner, followed by diethyl ether trituration afforded the title compound (7 mg, 0.017 mmol) as a yellow powder in 32% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.34 (s, 1H), 10.22 (s, 1H), 8.14 (s, 1H), 7.68-7.50 (m, 7H), 2.62 (m, 4H).

LCMS: (M+H$^+$) 401.1, (M+Na$^+$) 423.0.

Example 16: 4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

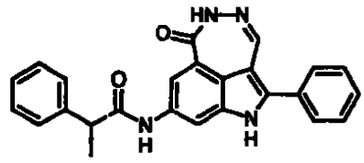


Preparation of example 16 from the title compound of Example 7 (15 mg, 0.054 mmol), 4-methyl-[1,2,3]thiadiazole-5-carboxylic acid (8 mg, 0.062 mmol), triethylamine (0.030 mL, 0.22 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example 11. Additional 4-methyl-[1,2,3]thiadiazole-5-carboxylic acid (1.0 mg, 0.006 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (2.0 mg, 0.006 mmol) were added after c.a. 18 hours to drive the reaction to completion. Silica gel chromatography, also in an analogous manner, followed by diethyl ether trituration afforded the title compound (7 mg, 0.017 mmol) as a yellow powder in 32% yield.

^{1}H-NMR (d_6-DMSO): δ 12.21 (s, 1H), 10.85 (s, 1H), 10.41 (s, 1H), 8.18 (s, 1H), 7.81 (m, 1H), 7.69 (m, 2H), 7.61-7.51 (m, 4H), 2.85 (s, 3H).

LCMS: $(M+H^+)$ 403.1, $(M+Na^+)$ 425.0.

Example 17: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenyl-propionamide

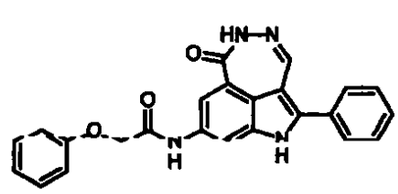


Preparation of example 17 from the title compound of Example 7 (15 mg, 0.054 mmol), 2-phenyl-propionic acid (9 mg, 0.062 mmol), triethylamine (0.030 mL, 0.22 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example 11. Silica gel chromatography (1:1 ethyl acetate:hexane), also in an analogous manner, followed by diethyl ether trituration afforded the title compound (7 mg, 0.017 mmol) as a yellow powder in 32% yield.

^{1}H-NMR (d_6-DMSO): δ 12.08 (s, 1H), 10.33 (s, 1H), 10.21 (s, 1H), 8.16 (s, 1H), 7.64 (m, 3H), 7.59 (m, 2H), 7.55 (m, 2H), 7.43 (m, 2H), 7.37 (m, 2H), 7.32 (m, 1H), 3.31 (quart., 1H), 1.45 (d, 3H).

LCMS: $(M+H^+)$ 409.1, $(M+Na^+)$ 431.1.

Example 18: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenoxy-acetamide



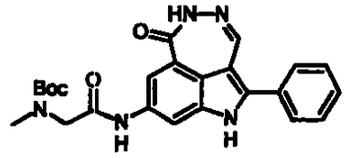
Preparation of example 18 from the title compound of Example 7 (15 mg, 0.054 mmol), phenoxy-acetic acid (9 mg, 0.062 mmol), triethylamine (0.030 mL, 0.22 mmol), and O-(7-azabenzotriazol-1-

yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **11**. Silica gel chromatography (1:1 ethyl acetate:hexane increasing to 100% ethyl acetate), also in an analogous manner, followed by diethyl ether trituration afforded the title compound (4.5 mg, 0.011 mmol) as a yellow powder in 20% yield.

^{1}H-NMR (d_6-DMSO): δ 12.13 (s, 1H), 10.36 (s, 1H), 10.26 (s, 1H), 8.16 (s, 1H), 7.73 (m, 1H), 7.66 (m, 2H), 7.57 (m, 2H), 7.51 (m, 2H), 7.31 (m, 2H), 7.03 (m, 3H), 4.71 (s., 2H).

LCMS: ($M+H^+$) 411.0, ($M+Na^+$) 433.1.

Example 19: Methyl-[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester

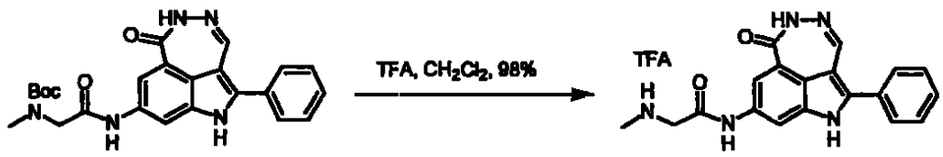


Preparation of example 19 from the title compound of Example **7** (hydrochloride) (18 mg, 0.065 mmol), (*tert*-butoxycarbonyl-methyl-amino)-acetic acid (12 mg, 0.065 mmol), triethylamine (0.012 mL, 0.085 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (27 mg, 0.072 mmol) in CH_2Cl_2 (0.5 mL) and *N,N*-dimethylformamide (0.5 mL) was carried out analogously to Example **11**. Silica gel chromatography (10:9:1 hexane:CH_2Cl_2:methanol), also in an analogous manner, followed by diethyl ether trituration afforded the title compound (28 mg, 0.063 mmol) as a yellow powder in 96% yield.

^{1}H NMR ($CDCl_3$): δ 9.11 (br s, 1H), 8.38 (br s, 2H), 7.62-7.46 (m, 7 H), 7.43 (s, 1H), 4.02 (s, 2H), 3.03 (s, 3H), 1.50 (s, 9H).

LCMS: ($M+H^+$) 448.1, ($M+Na^+$) 470, ($M-H^-$) 446.1.

Example 20: 2-Methylamino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-methyl]-acetamide: compound with trifluoro-acetic acid

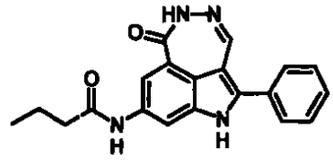


The title compound of Example **19** (19 mg, 0.042 mmol) in CH_2Cl_2 (0.65 mL) was treated with trifluoroacetic acid (0.45 mL) and allowed to stir for 0.5 hours. The volatile components were removed under vacuum, and diethyl ether was added and evaporated three times to give the title compound (19 mg, 0.041 mmol) as a yellow, orange powder in 98% yield.

^{1}H NMR (d_4-methanol): δ 8.15 (s, partially exchanged), 7.68-7.52 (m, 8H), 4.00 (s, 2H), 2.80 (s, 3H).

LCMS: ($M+H^+$) 348.2.

Example 21: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-butyramide

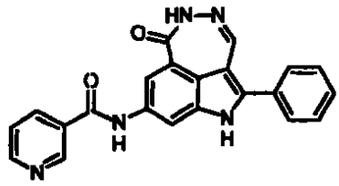


Preparation of example 21 from the title compound of Example 7 (hydrochloride) (22 mg, 0.080 mmol), n-butyric acid (0.007 mL, 0.080 mmol), triethylamine (0.014 mL, 0.10 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (32 mg, 0.084 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (10:9:1 hexane:CH_2Cl_2:methanol followed by 9:5:1 $CH2Cl_2$:hexane:methanol), also in an analogous manner, afforded the title compound (14 mg, 0.04 mmol) as a yellow powder in 50% yield.

^{1}H NMR (d_6-DMSO): δ 12.05 (s, 1H, exchanges), 10.22 (s, 1H, exchanges), 10.00 (s, 1H, exchanges), 8.15 (s, 1H), 7.39-7.71 (m, 7H), 2.30 (m, 2H)[1], 1.67 (m, 2H)[2], 0.95 (m, 3H)[1]. [1] Becomes triplet upon DCl addition, [2] Becomes quartet upon DCl addition.

LCMS: ($M+H^+$) 347.1, ($M+Na^+$) 369.1.

Example 22: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-nicotinamide



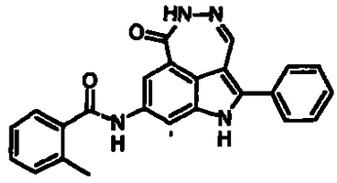
Preparation of example 22 from the title compound of Example 7 (hydrochloride) (21 mg, 0.076 mmol), nicotinic acid (7 mg, 0.076 mmol), triethylamine (0.014 mL, 0.10 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (32 mg, 0.084 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (9:1 CH_2Cl_2:methanol), also in an analogous manner, afforded the title compound (20 mg, 0.052 mmol) as a yellow powder in 69% yield.

^{1}H NMR (d_6-DMSO): δ 12.18 (s, 1H, exchanges), 10.59 (s, 1H, exchanges), 10.38 (s, 1H, exchanges), 9.17(s, 1H), 8.80 (s, 1H, partially obscurred, with fine splitting), 8.40-8.26 (m, 2H), 7.91 (s, 1H), 7.73-7.65 (m, 2H), 7.62-7.47 (m, 5H).

^{1}H NMR (d_6-DMSO/DCl): δ 9.44 (s, 1H), 9.10 (d, 1H, *J* = 5.0 Hz), 9.00 (d, 1H, *J* = 9.5), 8.32 (s, 1H), 8.15 (dd, 1H, *J* = 7.0, 7.5 Hz), 7.92 (s, 1H), 7.73 (s, 1H, overlapping), 7.68 (s, 1H, overlapping), 7.64-7.50 (m, 4H).

LCMS: ($M+H^+$) 382.1, ($M+Na^+$) 404.1.

Example 23: 2-Methyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide

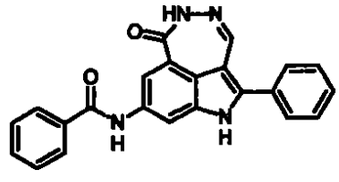


Preparation of example 23 from the title compound of Example 7 (hydrochloride) (22 mg, 0.08 mmol), 2-methyl-benzoic acid (11 mg, 0.08 mmol), triethylamine (0.014 mL, 0.10 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (33 mg, 0.088 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (8:5:2 CH_2Cl_2:hexane:methanol), also in an analogous manner, afforded the title compound (23 mg, 0.058 mmol) as a yellow powder in 73% yield.

^{1}H NMR (d_6-DMSO): δ 12.11 (s, 1H, exchanges), 10.42 (s, 1H, exchanges), 10.34 (s, 1H, exchanges), 8.24 (s, 1H), 7.88 (s, 1H), 7.71-7.65 (m, 2H), 7.63-7.45 (m, 3H), 7.43-7.35 (m, 2H), 7.34-7.25 (m, 3H), 2.4 (s, 3H).

LCMS: $(M+H^+)$ 395.1, $(M+Na^+)$ 417.0.

Example 24: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide



Preparation of example 24 from the title compound of Example 7 (hydrochloride) (23 mg, 0.082 mmol), benzoic acid (11 mg, 0.09 mmol), triethylamine (0.016 mL, 0.115 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (34 mg, 0.090 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (10:9:1 hexane:CH_2Cl_2:methanol followed by 8:5:2 CH_2Cl_2:hexane:methanol), also in an analogous manner, afforded the title compound (20 mg, 0.053 mmol) as a yellow powder in 64% yield.

^{1}H NMR (d_6-DMSO): δ 12.13 (s, 1H), 10.41 (s, 1H), 10.35 (s, 1H), 8.32 (s, 1H), 8.03 (d, 2H, J = 8 Hz), 7.94 (s, 1H), 7.70 (s, 1H, overlapping), 7.67 (s, 1H, overlapping), 7.63-7.48 (m, 7H).

LCMS: $(M+H^+)$ 381.1, $(M+Na^+)$ 403.1.

Example 25: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenyl-acetamide

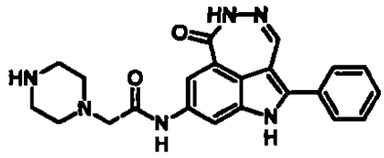


Preparation of example 25 from the title compound of Example 7 (hydrochloride) (20 mg, 0.072 mmol), phenyl-acetic acid (11 mg, 0.08 mmol), triethylamine (0.014 mL, 0.10 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (30 mg, 0.080 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (8:5:2 CH_2Cl_2:hexane:methanol), also in an analogous manner, afforded the title compound (27 mg, 0.068 mmol) as a yellow powder in 95% yield.

^{1}H NMR (d_6-DMSO): δ 12.08 (s, 1H, exchanges), 10.31 (s, 2H, exchanges), 8.18 (s, 1H), 7.72-7.62 (m, 3H), 7.60-7.45 (m, 4H), 7.41-7.21 (m, 5H), 3.68 (s, 2H).

LCMS: $(M+H^+)$ 395.1, $(M+Na^+)$ 417.1.

Example 26: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-piperazin-1-yl-acetamide *Di*-trifluoroacetic acid Salt



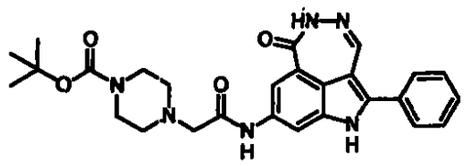
2X TFA

To a suspension of the title compound of Example 27 in dichloromethane (0.3 M, 0.6 mL), was added trifluoroacetic acid (0.3 M, 0.6 mL). The reaction mixture was stirred at 22 °C for 0.5 hours and concentrated under reduced pressure. The solid was triturated with dichloromethane (3.0 mL), collected by filtration, and washed with diethyl ether (5.0 mL) to afford the title compound (9.8 mg) in 95% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.36 (s, 1H), 9.98 (s, 1H), 8.53 (bs, 2H), 8.16 (d, 1H, J = 1.6 Hz), 7.66 (m, 2H), 7.69-7.48 (m, 7H), 3.32 (s, 2H), 3.20 (m, 4H), 2.82 (m, 4H).

HRMS: $(M+H^+)$ calcd for $C_{22}H_{23}N_6O_2$, 403.1882, found 403.1902.

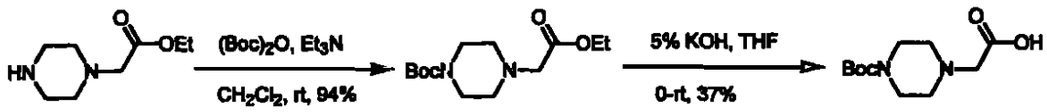
Example 27: 4-[(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-methyl]-piperazine-1-carboxylic acid *tert*-butyl ester



Preparation of example 27 from the title compound of Example 7 (0.025g, 0.09 mmol), 4-carboxymethyl-piperazine-1-carboxylic acid *tert*-butyl ester (0.044 g, 0.18 mmol), triethylamine (0.05 mL, 0.4 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (38 mg, 0.1 mmol) and *N,N*-dimethylformamide (0.05 M, 1.8 mL) was carried out analogously to Example **11**. Silica gel chromatography (95:5 CH_2Cl_2/methanol), also in an analogous manner, afforded the title compound (15 mg) as a yellow powder in 33% yield.

^{1}H-NMR (d_6-DMSO): δ 12.07 (s, 1H), 10.34 (s, 1H), 9.92 (s, 1H), 8.17 (s, 1H), 7.69-7.64 (m, 3H), 7.61-7.54 (m, 2H), 7.52-7.47 (m, 2H), 3.40 (m, 4H), 3.29 (m buried, 4H), 3.18 (s, 2H).
HRMS: ($M+H^+$) calcd for $C_{29}H_{31}N_6O_4$, 503.2407, found 503.2407.

The starting material 4-Carboxymethyl-piperazine-1-carboxylic acid *tert*-butyl ester was prepared as follow:



27(a) 27(b)

Step 1. Preparation of 4-Methoxycarbonylmethyl-piperazine-1-carboxylic acid *tert*-butyl ester 27(a)

Piperazin-1-yl-acetic acid ethyl ester (2.84 g, 15.7 mmol), triethylamine (7.6 mL, 55.0 mmol) and di-*tert*-butyl dicarbonate (4.45 g, 20.4 mmol) were stirred in CH_2Cl_2 (0.3 M, 55 mL) at 22 °C for 24 hours. The volatiles were removed *in vacuo* and silica gel chromatography (60:40 ethyl acetate/hexanes), afforded Intermediate 27(a) (4.01 g) in 94% yield.

^{1}H-NMR (d_6-DMSO): δ 4.08 (q, 2H, J = 7.1 Hz), 3.35-3.21 (m, 6H), 2.52-2.41 (m, 4H), 1.39 (s, 9H), 1.18 (t, 7.1 Hz).

^{13}C-NMR (d_6-DMSO): δ 170.2, 154.2, 79.1, 60.2, 58.6, 52.0, 28.4, 14.5.

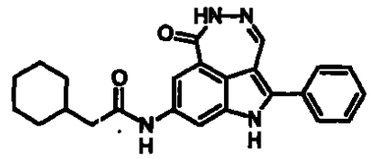
Step 2. Preparation of 4-Carboxymethyl-piperazine-1-carboxylic acid *tert*-butyl ester 27(b)

Intermediate 27(a) (3.6 g, 13.2 mmol) and a 5% aqueous KOH solution (90 mL, 80.0 mmol) were stirred in tetrahydrofuran (30 mL, 0.44 M) at 22 °C for 2 hours. The volatiles were removed *in vacuo* and treatment with strongly acidic Dowex-50™ (WX8-200), elution with ammonium

hydroxide (1.0 N), and treatment with Amberlite™ CG-50 afforded Intermediate 27(b) (1.2 g) in 37% yield.

^{1}H-NMR (d_6-DMSO): δ 3.35-3.31 (m, 4H), 3.21 (s, 2H), 2.52-2.41 (m, 4H), 1.39 (s, 9H).

Example 28: 2-Cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide

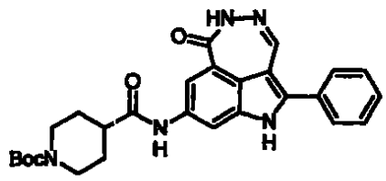


Preparation of example 28 from the title compound of Example 7 (0.025g, 0.09 mmol), Cyclohexyl-acetic acid (0.015g, 0.11 mmol), triethylamine (0.05 mL, 0.4 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (38 mg, 0.1 mmol) and *N,N*-dimethylformamide (0.05 M, 1.8 mL) was carried out analogously to Example 11. Silica gel chromatography (95:5 CH_2Cl_2/methanol) also in an analogous manner followed by diethyl ether trituration afforded the title compound (13 mg) as a yellow powder in 36% yield.

^{1}H-NMR (d_6-DMSO): δ 12.03 (s, 1H), 10.32 (s, 1H), 9.99 (s, 1H), 8.17 (s, 1H), 7.68-7.45 (m, 7H), 2.20 (d, 2H, J = 7.0 Hz), 1.86-1.58 (m, 6H), 1.31-1.10 (m, 3H), 1.10-0.91 (m, 2H).

HRMS: (M+H$^+$) calcd for $C_{24}H_{25}N_4O_2$, 401.1978, found 401.1987.

Example 29: 4-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

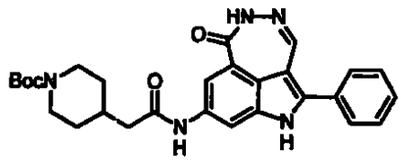


Preparation of example 29 from the title compound of Example 7 (hydrochloride) (22 mg, 0.07 mmol), piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester (19 mg, 0.084 mmol), triethylamine (0.015 mL, 0.105 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (32 mg, 0.084 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (8:5:2 CH_2Cl_2:hexane:methanol), also in an analogous manner, afforded the title compound (24 mg, 0.049 mmol) as a yellow powder in 70% yield.

^{1}H NMR (d_6-DMSO): 12.09 (s, 1H), 10.38 (s, 1H), 10.12 (s, 1H), 8.17 (s, 1H), 7.70-7.64 (m, 3H), 7.62-7.54 (m, 2H), 7.53-7.49 (m, 2H), 4.01 (br d, 2H, J = 12.06 Hz), 2.86-2.72 (m, 2H), 1.81 (br d, 2H, J = 13.00 Hz), 1.58-1.44 (m, 2H), 1.42 (s, 9H), 1.40 (m, 1H, partially obscured).

LCMS: (M-H)$^-$ 486.2.

Example 30: 4-[(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester

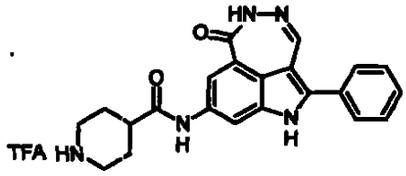


Preparation of example 30 from the title compound of Example 7 (hydrochloride) (22 mg, 0.07 mmol), 4-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (20 mg, 0.084 mmol), triethylamine (0.015 mL, 0.105 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (32 mg, 0.084 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (8:5:2 CH_2Cl_2:hexane:methanol), also in an analogous manner, afforded the title compound (35 mg, 0.070 mmol) as a yellow powder in 100% yield.

^{1}H NMR (d_6-DMSO): 12.08 (s, 1H), 10.38 (s, 1H), 10.09 (s, 1H), 8.19 (s, 1H), 7.70-7.46 (m, 7H), 3.93 (br d, 2H, J = 12.24 Hz), 2.81-2.66 (m, 2H), 2.27 (d, 2H, J = 7.16 Hz), 1.96 (br s, 1H), 1.67 (br d, 2H, J = 13.94 Hz), 1.40 (s, 9H), 1.17-1.01 (m, 2H).

LCMS: $(M+Na^+)$ 524.2, $(M-H)^-$ 500.1.

Example 31: Piperidine-4-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide: compound with trifluoro-acetic acid

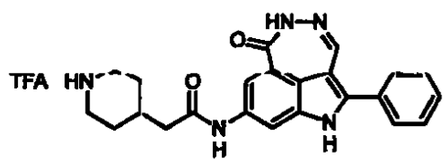


Preparation of example 31 from the title compound of Example 29 (20 mg, 0.041 mmol) and 45% TFA in CH_2Cl_2 (1 mL) was carried out analogously to Example 20. Isolation, also in an analogous manner, afforded the title compound (20 mg, 0.040 mmol) as a yellow powder in 97% yield.

^{1}H NMR (d_4-methanol): 8.03 (s, 1H), 7.56-7.31 (m, 7H), 3.43-3.32 (m, 2H), 3.01-2.90 (m, 2H), 2.61 (m, 1H), 2.04 -1.78 (m, 4H).

LCMS: $(M+H^+)$ 388.1

Example 32: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-piperidin-4-yl-acetamide: compound with trifluoro-acetic acid

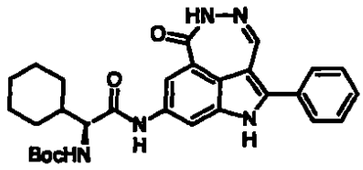


Preparation of example 32 from the title compound of Example **30** (31 mg, 0.062 mmol) and 45% TFA in CH_2Cl_2 (1 mL) was carried out analogously to Example **20**. Isolation, also in an analogous manner, afforded the title compound (29 mg, 0.056 mmol) as a yellow powder in 91% yield.

^{1}H NMR (d_4-methanol): δ 8.20 (s, 1H), 7.70-7.50 (m, 7H), 3.50-3.40 (m, 2H, partially obscurred), 3.10 (dd, 2H, *J* = 9.0, 9.2 Hz), 2.45 (d, 2H, *J* = 7.2 Hz), 2.25 (br m, 1H), 2.0-2.11 (m, 2H), 1.68-1.45 (m, 2H).

LCMS: $(M+H^+)$ 402.2

Example 33: *tert*-butyl (1*S*)-1-cyclohexyl-2-oxo-2-[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]ethylcarbamate

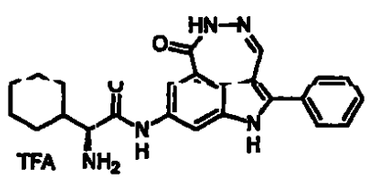


Preparation of example 33 from the title compound of Example **7** (35 mg, 0.13 mmol), (2*S*)-[(*tert*-butoxycarbonyl)amino](cyclohexyl)ethanoic acid (39 mg, 0.15 mmol), triethylamine (0.073 mL, 0.52 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (58 mg, 0.15 mmol) in *N,N*-dimethylformamide (2.0 mL) was carried out analogously to Example **11** except that after 24 hours additional (2*S*)-[(*tert*-butoxycarbonyl)amino](cyclohexyl)ethanoic acid (17 mg, 0.065 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.065 mmol) were added to drive the reaction to completion. Silica gel chromatography (1:1 ethyl acetate:hexane), also in an analogous manner, followed by diethyl ether trituration afforded the title compound (45 mg, 0.087 mmol) as a yellow powder in 67% yield.

^{1}H-NMR (d_6-DMSO): δ 12.08 (s, 1H), 10.38 (s, 1H), 10.13 (s, 1H), 8.14 (s, 1H), 7.71-7.44 (m, 6H), 6.90 (m, 1H), 3.95 (m, 1H), 1.78-1.44 (m, 5H), 1.43-1.24 (m, 10H, contains singlet at 1.39), 1.23-1.02 (m, 5H).

LCMS: $(M+H)^+$ 514.1.

Example 34: (2*S*)-2-amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide trifluoroacetate

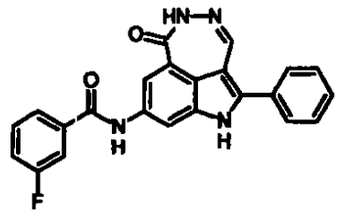


Preparation of example 34 from the title compound of Example 33 (40 mg, 0.078 mmol), and 1:1 TFA/CH_2Cl_2 (5 mL) was carried out analogously to Example 20. Isolation, also in an analogous manner, included a further trituration with methanol/diethyl ether and afforded the title compound (10 mg, 0.019 mmol) as an orange/yellow powder in 24% yield.

^{1}H NMR (d_6-DMSO): δ 12.19 (s, 1H), 10.60 (s, 1H), 10.44 (s, 1H), 8.25 (br s, 3H), 8.11 (s, 1H), 7.71-7.46 (m, 7H), 3.69 (m, 1H), 1.93-1.52 (m, 6H), 1.29 -0.97 (m, 5H).

LCMS: ($M+H^+$) 415.1.

Example 35: 3-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide

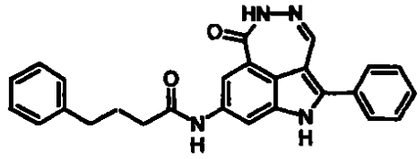


Preparation of example 35 from the title compound of Example 7 (0.025g, 0.09 mmol), 3-Fluoro-benzoic acid (0.015g, 0.11 mmol), triethylamine (0.05 mL, 0.4 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (38 mg, 0.1 mmol) and *N,N*-dimethylformamide (0.05 M, 1.8 mL) was carried out analogously to Example 11. Silica gel chromatography (95:5 CH_2Cl_2/methanol), also in an analogous manner, afforded the title compound (15 mg) as a yellow powder in 42% yield.

^{1}H-NMR (d_6-DMSO): δ 12.18 (s, 1H), 10.47 (s, 1H), 10.40 (s, 1H), 8.31 (d, 1H, J = 1.3 Hz), 7.92 (d, 1H, J = 1.5 Hz), 7.90-7.81 (m, 2H), 7.72-7.41 (m, 8H).

HRMS: ($M+H^+$) calcd for $C_{23}H_{16}N_4O_2F$, 399.1257, found 399.1257.

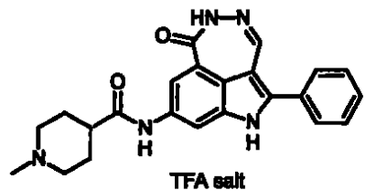
Example 36: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-phenyl-butyramide



Preparation of example 36 from the title compound of Example 7 (0.030g, 0.11 mmol), 4-Phenyl-butyric acid (0.027g, 0.16 mmol), triethylamine (0.077 mL, 0.44 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (63 mg, 0.16 mmol) and *N,N*-dimethylformamide (0.05 M, 2.0 mL) was carried out analogously to Example 11. Silica gel chromatography (95:5 CH_2Cl_2/methanol) afforded the title compound (15 mg) as a yellow powder in 33% yield.

^{1}H-NMR (d_6-DMSO): δ 12.06 (s, 1H), 10.35 (s, 1H), 10.06 (s, 1H), 8.18 (d, 1H, *J* = 1.5 Hz), 7.69-7.46 (m, 7H), 7.33-7.16 (m, 5H), 2.64 (dd, 2H, *J* = 7.4, 7.0 Hz), 2.35 (m, 5H), 1.97-1.86 (m, 2H).
HRMS: (M+H$^+$) calcd for $C_{28}H_{23}N_4O_2$, 423.1821, found 423.1826.
Anal. Calcd. for $C_{28}H_{22}N_4O_2 \cdot 0.2\ H_2O$: C, 73.29; H, 5.30; N, 13.15. Found: C, 73.33; H, 5.28; N, 13.23.

Example 37: 1-Methyl-piperidine-4-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; 2,2,2-trifluoro-acetic acid salt

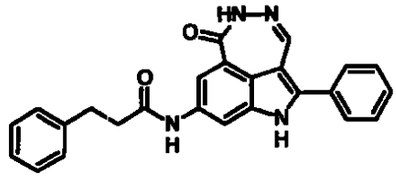


TFA salt

Preparation of example 37 from the title compound of Example 7 (0.030g, 0.11 mmol), 1-Methyl-piperidine-4-carboxylic acid (0.023g, 0.16 mmol), triethylamine (0.077 mL, 0.44 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (63 mg, 0.16 mmol) and *N,N*-dimethylformamide (0.05 M, 2.0 mL) was carried out analogously to Example 11. HPLC purification afforded the title compound (23 mg) as a yellow powder in 41% yield.

^{1}H-NMR (d_6-DMSO): δ 12.10 (s, 1H), 10.39 (s, 1H), 10.23 (s, 1H), 9.17 (bs, 1H), 8.12 (d, 1H, *J* = 1.5 Hz), 7.69-7.47 (m, 7H), 3.05-2.93 (m, 2H), 2.80 (d, 3H), 2.65-2.48 (buried m, 1H), 2.10-2.01 (m, 2H), 1.92-1.80 (m, 2H).
HRMS: (M+H$^+$) calcd for $C_{23}H_{24}N_5O_2$, 402.1930, found 402.1937.

Example 38: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide

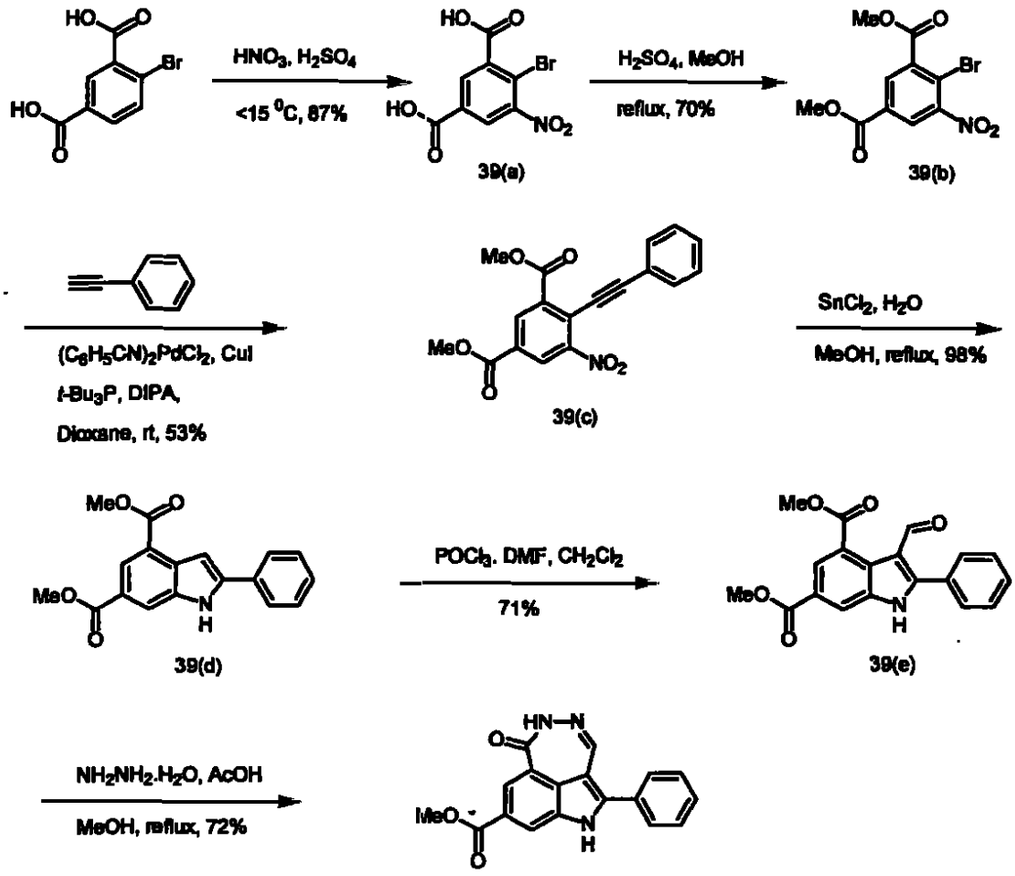


Preparation of example 38 from the title compound of Example 7 (0.030g, 0.11 mmol), 3-Phenyl-propionic acid (0.025g, 0.16 mmol), triethylamine (0.077 mL, 0.44 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (63 mg, 0.16 mmol) and *N,N*-dimethylformamide (0.05 M, 2.0 mL) was carried out analogously to Example 11. Silica gel chromatography (95:5 CH_2Cl_2/methanol) afforded the title compound (15 mg) as a yellow powder in 34% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.38 (s, 1H), 10.36 (s, 1H), 10.13 (s, 1H), 8.15 (d, 1H, J = 1.5 Hz), 7.68-7.46 (m, 11H), 7.31 (d, 2H, J = 8.4 Hz), 7.24 (d, 1H, J = 8.2 Hz), 3.65 (s, 2H), 3.45 (s, 2H).

HRMS: ($M+H^+$) calcd for $C_{25}H_{21}N_4O_2$, 409.1665, found 409.1683.

Example 39: 6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxylic acid methyl ester



Step 1. Preparation of 4-bromo-5-nitroisophthalic acid 39(a)

To a 3-L 4-neck round-bottomed flask equipped with a mechanical stirrer, thermometer, 250-mL addition funnel and charged with concentrated H_2SO_4 (577 mL), was added 4-bromoisophthalic acid (75.0 g, 306 mmol). The white suspension was cooled to ice-bath temperature and a nitrating reagent (pre-prepared by the careful addition of H_2SO_4 (169 mL) to HNO_3 (107 mL)) was slowly added while maintaining an internal reaction temperature of less than 15 °C. When addition was complete, the ice-bath was removed and the suspension stirred overnight at room temperature. After approximately 14 hours, the flask was placed in an ice-bath and crushed ice was added to quench the excess nitrating reagent while maintaining an internal temperature less than 40 °C. The cream-colored suspension was filtered, and the solids were collected by filtration and washed

with a small volume of ice-cold water. The solids were dissolved in methanol and the volatile components were evaporated. The resulting solids were dried at 60 °C in a vacuum oven overnight to afford Intermediate 39(a) (79.6 g) in 87% yield.

^{1}H NMR (d_4-methanol): δ 8.47 (d, 1H, J = 1.8 Hz), 8.39 (d, 1H, J = 1.8 Hz).

LCMS: (M-H) 289.

Step 2. Preparation of Dimethyl 4-bromo-5-nitroisophthalate 39(b)

To a solution of Intermediate 39(a) (77.6 g, 267 mmol) in methanol (500 mL) was added concentrated H_2SO_4 (10 mL). The reaction flask was heated in an oil bath at reflux with stirring for approximately 8 hours at which point LC/MS analysis indicated consumption of starting material. The mixture was allowed to cool to room temperature and white solids began to crystallize in the flask. After sitting overnight, the crystals were collected by filtration and washed with water until the pH of the filtrate was neutral. The crystals (51.9 g) were dried in an Abderhalden drying apparatus over refluxing acetone. The mother liquor was concentrated to provide a second crop (7.58 g) which was combined with the first to afford Intermediate 39(b) (59.4 g) in 70% yield.

^{1}H NMR (d_6-DMSO): δ 8.62 (s, 1H), 8.45 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H).

Step 3. Preparation of Dimethyl 5-nitro-4-(phenylethynyl)isophthalate 39(c)

A flask containing 1,4-dioxane (16 mL) was purged with nitrogen. CuI (0.12 g, 0.628 mmol) and bis(benzonitrile)dichloropalladium(II) (0.361 g, 0.942 mmol) were added in portions. Tri-*tert*-butylphosphine (7.83 mL, 1.88 mmol) was added as a 0.24 M solution in 1,4-dioxane *via* syringe. The solution was allowed to stir for approximately 5 min at which point diisopropylamine (2.65 mL, 18.9 mmol) was added *via* syringe. Intermediate 39(b) (5.00 g, 15.7 mmol) was added in one solid portion followed by phenylacetylene (2.08 mL, 18.9 mmol). A precipitate formed immediately. The reaction was capped and stirred at room temperature overnight. The mixture was filtered through diatomaceous earth which was subsequently washed with ethyl acetate to recover any trapped product. The combined filtrate and washings were concentrated and dissolved in a minimal amount of hot ethyl acetate. Hexane was added to recrystallize brown needles which were collected by filtration and further washed with hexane. The needles (4.5 g) were dried in a vacuum oven at 60 °C overnight. The mother liquor was concentrated and subjected to silica gel chromatography (10-30% ethyl acetate/hexanes) to yield an additional 1.2 g of a dark brown solid which was combined with the first batch to afford Intermediate 39(c) (5.7 g) in 53% yield.

^{1}H NMR ($CDCl_3$): δ 8.73 (d, 1H, J = 1.5 Hz), 8.65 (d, 1H, J = 1.8 Hz), 7.61-7.64 (m, 2H), 7.37-7.46 (m, 3H), 4.03 (s, 3H), 4.00 (s, 3H).

LCMS: (M+H) 340.

Step 4. Preparation of Dimethyl 2-phenyl-1*H*-indole-4,6-dicarboxylate 39(d)

To Intermediate 39(c) (6.37 g, 18.8 mmol) was added anhydrous methanol (120 mL). To the resulting slurry was added Tin(II) chloride (35.6 g, 188 mmol), and the reaction flask was refluxed for 55 hours. Methanol was removed under reduced pressure and the resulting residue was

suspended in a small volume of ethyl acetate. Dichloromethane was then added such that the resulting concentration was approximately 95% dichloromethane : 5% ethyl acetate. This suspension was then filtered through a short silica gel plug. The filtrate was concentrated and purified twice by flash silica gel chromatography (5-40% ethyl acetate/dichloromethane) to obtain 3.1 g of Intermediate 39(d) in 53% yield.

^{1}H NMR (d_6-DMSO): δ 12.35 (s, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.98-8.00 (m, 2H), 7.47-7.60 (m, 4H), 3.99 (s, 3H), 3.93 (s, 3H).

LCMS: (M+H) 310.

Step 5. Preparation of Dimethyl 3-formyl-2-phenyl-1*H*-indole-4,6-dicarboxylate 39(e)

To a solution of Intermediate 39(d) (0.052 g, 0.17 mmol) in anhydrous *N,N*-dimethylformamide (2 mL) at room temperature was added $POCl_3$ (0.2 mL, 2.1 mmol). The resulting violet solution was stirred for 1 hour at room temperature. The mixture was poured into saturated aqueous sodium carbonate (15 mL) and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated, and purified by silica gel chromatography (33% ethyl acetate/hexanes) to give Intermediate 39(e) (0.0404 g) in 71% yield.

^{1}H NMR (d_6-DMSO): δ 13.00 (s, 1H), 9.95 (s, 1H), 8.21 (s, 1H), 7.94 (s, 1H), 7.85-7.75(m, 2H), 7.70-7.55 (m, 3H), 3.90 (s, 3H), 3.86 (s, 3H).

LCMS: (M+H) 338, (M-H) 336.

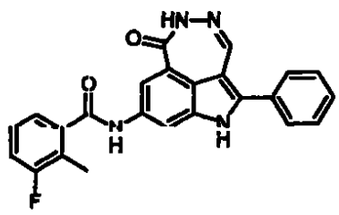
Step 6. Preparation of Title Compound: 6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxylic acid methyl ester

To a solution of Intermediate 39(e) (1.39 g, 4.12 mmol) in anhydrous methanol (70 mL) was added anhydrous hydrazine (0.19 mL, 6.18 mmol). The mixture was refluxed overnight. After cooling, the yellow precipitate was collected by filtration and washed with ice-cold methanol. After drying under vacuum at 60 °C overnight, the title compound (1.06 g) was obtained as a bright yellow solid in 72% yield.

^{1}H-NMR (d_6-DMSO): δ 12.58 (s, 1H), 10.54 (s, 1H), 8.13 (d, 1H, *J* = 1.3 Hz), 8.07 (d, 1H, *J* = 1.3 Hz), 7.77-7.67(m, 2H), 7.65-7.54 (m, 3H), 7.52 (s, 1H), 3.88 (s, 3H).

LCMS: ($M+H^+$) 320.3

Example 40: 3-Fluoro-2-methyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide

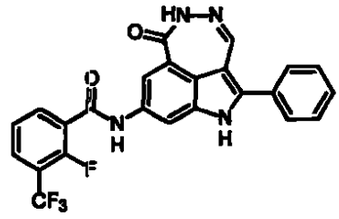


Preparation of example 40 from the title compound of Example 7 (0.030g, 0.11 mmol), 3-Fluoro-2-methyl-benzoic acid (0.025g, 0.16 mmol), triethylamine (0.077 mL, 0.44 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (63 mg, 0.16 mmol) and *N,N*-dimethylformamide (0.05 M, 2.0 mL) was carried out analogously to Example 11. Silica gel chromatography (95:5 CH_2Cl_2/methanol) afforded the title compound (14 mg) as a yellow powder in 33% yield.

^{1}H-NMR (d_6-DMSO): δ 12.15 (s, 1H), 10.55 (s, 1H), 10.39 (s, 1H), 8.23 (d, 1H, *J* = 1.5 Hz), 7.84 (d, 1H, *J* = 1.4 Hz), 7.72-7.48 (m, 6H), 7.39-7.27 (m, 3H), 2.31 (s, 3H).

LCMS: ($M-H^+$) 411.0.

Example 41: 2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide



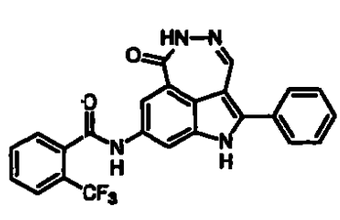
Preparation of example 41 from the title compound of Example 7 (0.1 g, 0.36 mmol), 2-Fluoro-3-trifluoromethyl-benzoic acid (0.113 g, 0.54 mmol), triethylamine (0.2 mL, 1.45 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.207 g, 0.54 mmol) and *N,N*-dimethylformamide (0.1 M, 3.6 mL) was carried out analogously to Example 11. Silica gel chromatography (95:5 CH_2Cl_2/methanol) afforded the title compound (0.147 g) as a yellow powder in 87% yield.

^{1}H-NMR (d_6-DMSO): δ 12.20 (s, 1H), 10.81 (s, 1H), 10.43 (s, 1H), 8.24 (d, 1H, *J* = 1.5 Hz), 8.05-7.93 (m, 2H), 7.79 (d, 1H, *J* = 1.4 Hz), 7.72-7.67 (m, 2H), 7.62-7.49 (m, 5H).

HRMS: ($M+H^+$) calcd for $C_{24}H_{15}N_4O_2F_4$, 467.1131, found 467.1119.

Anal. Calcd. for $C_{24}H_{14}N_4O_2F_4 \cdot 0.2\ H_2O$: C, 61.33; H, 3.09; N, 11.92; F, 16.17. Found: C, 61.17; H, 3.09; N, 11.93; F, 16.65.

Example 42: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-trifluoromethyl-benzamide



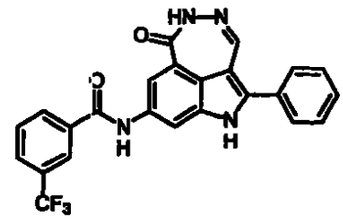
Preparation of example 42 from the title compound of Example 7 (0.1 g, 0.36 mmol), 2-Trifluoromethyl-benzoic acid (0.103g, 0.54 mmol), triethylamine (0.2 mL, 1.45 mmol), O-(7-

azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.207 g, 0.54 mmol) and *N,N*-dimethylformamide (0.1 M, 3.6 mL) was carried out analogously to Example **11**. Silica gel chromatography (95:5 CH_2Cl_2/methanol) afforded the title compound (0.075 g) as a yellow powder in 46% yield.

^{1}H-NMR (d_6-DMSO): δ 12.14 (s, 1H), 10.71 (s, 1H), 10.40 (s, 1H), 8.17 (d, 1H, *J* = 1.4 Hz), 7.89-7.66 (m, 7H), 7.62-7.49 (m, 4H).

HRMS: ($M+H^+$) calcd for $C_{24}H_{16}N_4O_2F_3$, 449.1225, found 449.1223.

Example 43: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide

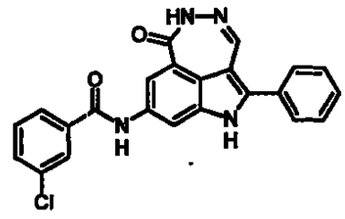


Preparation of example 43 from the title compound of Example **7** (0.03 g, 0.11 mmol), 3-Trifluoromethyl-benzoic acid (0.031 g, 0.16 mmol), triethylamine (0.078 mL, 0.43 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.062 g, 0.11 mmol) and *N,N*-dimethylformamide (0.05 M, 2.0 mL) was carried out analogously to Example **11**. Silica gel chromatography (95:5 CH_2Cl_2/methanol) afforded the title compound (0.030 g) as a yellow powder in 61% yield.

^{1}H-NMR (d_6-DMSO): δ 12.20 (s, 1H), 10.62 (s, 1H), 10.42 (s, 1H), 8.39-8.30 (m, 3H), 7.98 (d, 1H, *J* = 7.4 Hz), 7.91 (d, 1H, *J* = 1.6 Hz), 7.80 (dd, 1H, *J* = 7.7, 7.5 Hz), 7.69 (d, 2H, *J* = 7.2 Hz), 7.62-7.48 (m, 4H).

HRMS: ($M+H^+$) calcd for $C_{24}H_{16}N_4O_2F_3$, 449.1225, found 449.1229.

Example 44: 3-Chloro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide



Preparation of example 44 from the title compound of Example **7** (0.03 g, 0.11 mmol), 3-Chloromethyl-benzoic acid (0.025 g, 0.16 mmol), triethylamine (0.078 mL, 0.43 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.062 g, 0.11 mmol) and *N,N*-dimethylformamide (0.05 M, 2.0 mL) was carried out analogously to Example **11**. Silica

gel chromatography (95:5 CH_2Cl_2/methanol) afforded the title compound (0.015 g) as a yellow powder in 33% yield.

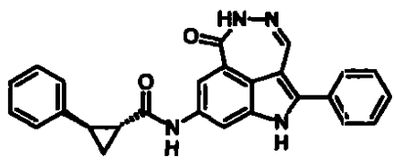
^{1}H-NMR (d_6-DMSO): δ 12.18 (s, 1H), 10.50 (s, 1H), 10.41 (s, 1H), 8.32 (d, 1H, *J* = 1.5 Hz), 8.09 (s, 1H), 7.98 (d, 1H, *J* = 7.8 Hz), 7.91 (d, 1H, *J* = 1.6 Hz), 7.72-7.65 (m, 3H), 7.62-7.47 (m, 5H).

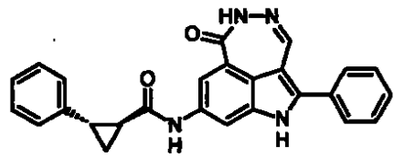
HRMS: $(M+H^+)$ calcd for $C_{23}H_{16}N_4O_2Cl$, 415.0962, found 415.0981.

Example 45:

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; and

(1S,2S)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



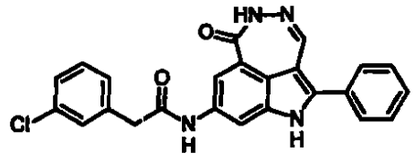


Preparation of example 45 from the title compound of Example 7 (30 mg, 0.11 mmol), ± trans-2-phenyl-1-cyclopropanecarboxylic acid (26 mg, 0.16 mmol), triethylamine (0.076 mL, 0.55 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (62 mg, 0.16 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example 11. Silica gel chromatography (1:1 ethyl acetate:hexane), also in an analogous manner, followed by trituration with ethyl acetate / diethyl ether afforded the title compound (6.5 mg, 0.015 mmol) (mixture of trans diastereomers) as a yellow powder in 14% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.44 (s, 1H), 10.37 (s, 1H), 8.17 (s, 1H), 7.71-7.44 (m, 7H), 7.35-7.25 (m, 2H), 7.24-7.10 (m, 3H), 2.39 (m, 1H), 2.10 (m, 1H), 1.52 (m, 1H), 1.38 (m, 1H).

LCMS: $(M+H)^-$ 419.1.

Example 46: 2-(3-Chlorophenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide



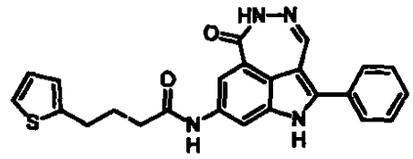
Preparation of example 46 from the title compound of Example 7 (30 mg, 0.11 mmol), (3-chlorophenyl)acetic acid (28 mg, 0.16 mmol), triethylamine (0.076 mL, 0.55 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (62 mg, 0.16 mmol) in *N,N*-dimethylformamide (1.5 mL) was carried out analogously to Example 11. Silica gel

chromatography (1:1 ethyl acetate:hexane), also in an analogous manner, followed by methanol trituration afforded the title compound (6.5 mg, 0.015 mmol) as a yellow powder in 14% yield.

^{1}H-NMR (d_6-DMSO): δ 12.10 (s, 1H), 10.39 (s, 1H), 10.17 (s, 1H), 8.16 (s, 1H), 7.70 -7.18 (m, 11H), 3.69 (s, 1H), 3.50 (s, 1H).

LCMS: $(M+H)^+$ 427.1.

Example 47: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide

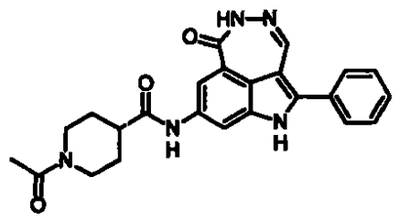


Preparation of example 47 from the title compound of Example 7 (30 mg, 0.11 mmol), 4-thien-2-ylbutanoic acid (24 mg, 0.16 mmol), triethylamine (0.076 mL, 0.55 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (62 mg, 0.16 mmol) in *N,N*-dimethylformamide (1.5 mL) was carried out analogously to Example 11. Silica gel chromatography (3% methanol in CH_2Cl_2 increasing to 6% methanol in CH_2Cl_2), also in an analogous manner, followed by methanol trituration afforded the title compound (6.5 mg, 0.015 mmol) as a yellow powder in 14% yield.

^{1}H-NMR (d_6-DMSO): δ 12.07 (s, 1H), 10.38 (s, 1H), 10.09 (s, 1H), 8.18 (s, 1H), 7.69-7.61 (m, 3H), 7.60-7.53 (m, 2H), 7.52-7.45 (m, 2H), 7.33 (m, 1H), 6.96 (m, 1H), 6.89 (m, 1H), 2.86 (t, 2H, J = 7.53 Hz), 2.40 (t, 2H, J = 7.35 Hz), 2.02 -1.89 (m, 2H).

LCMS: $(M+H)^+$ 427.1.

Example 48: 1-Acetyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)piperidine-4-carboxamide



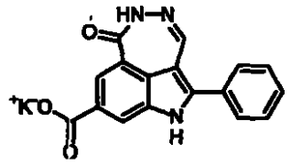
Preparation of example 48 from the title compound of Example 7 (30 mg, 0.11 mmol), 1-acetylpiperidine-4-carboxylic acid (28 mg, 0.16 mmol), triethylamine (0.076 mL, 0.55 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (62 mg, 0.16 mmol) in *N,N*-dimethylformamide (1.5 mL) was carried out analogously to Example 11. Silica gel chromatography (3% methanol in CH_2Cl_2 increasing to 6% methanol in CH_2Cl_2), also in an

analogous manner, followed by methanol trituration afforded the title compound (12 mg, 0.028 mmol) as a yellow powder in 25% yield.

^{1}H-NMR (d_6-DMSO): δ 12.07 (s, 1H), 10.37 (s, 1H), 10.10, s, 1H), 8.17 (s, 1H), 7.72-7.43 (m, 7H), 4.41 (d, 1H, J = 15.07 Hz), 3.87 (d, 1H, J = 14.13 Hz), 3.07 (t, 1H, J = 12.81 Hz), 2.65-2.53 (m, 2H, partially obscured), 2.02 (s, 3H), 1.76-1.90 (m, 2H), 1.70-1.37 (m, 2H).

LCMS: $(M+H^+)$ 430.1, $(M+Na^+)$ 452.1.

Example 49: 6-Oxo-2-phenyl-5,6-dihydro-1H-[1,2]diazepino[4,5,6-cd]indole-8-carboxylic acid, potassium salt

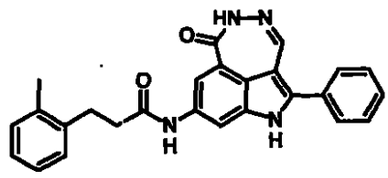


To the title compound of Example 39 (3.0 g, 9.39 mmol) was added DMSO (20 mL). To this semi-suspension was added 2N KOH (19 mL, 37.8 mmol). The solution turned a deep red color and was stirred for approximately 1.5 hours at room temperature. The reaction was purified by preparative HPLC (5-60% CH_3CN/H_2O) over 60 minutes. Fractions containing the product were lyophilized to afford the title compound (0.8 g) as an orange solid in 25% yield.

^{1}H-NMR (d_6-DMSO): δ 12.21 (s, 1H), 10.12 (s, 1H), 8.16 (d, 1H, J = 1.0 Hz), 8.01 (d, 1H, J = 1.0 Hz), 7.73-7.65 (m, 2H), 7.62-7.46 (m, 3H), 7.44 (s, 1H).

LCMS: $(M+H^+)$ 306.1

Example 50: 3-(2-Methylphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide

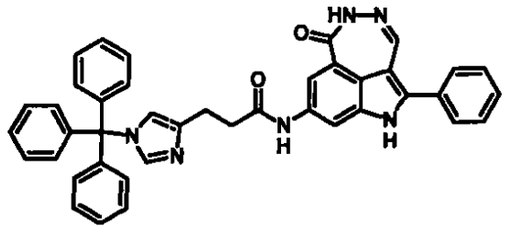


Preparation of example 50 from the title compound of Example 7 (30 mg, 0.11 mmol), 3-(2-methylphenyl)propanoic acid (27 mg, 0.16 mmol), triethylamine (0.076 mL, 0.55 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (62 mg, 0.16 mmol) in *N,N*-dimethylformamide (1.5 mL) was carried out analogously to Example 11. Silica gel chromatography (3% methanol in CH_2Cl_2 increasing to 5% methanol in CH_2Cl_2), also in an analogous manner, followed by methanol trituration afforded the title compound (6 mg, 0.014 mmol) as a yellow powder in 13% yield.

^{1}H-NMR (d_6-DMSO): δ 12.08 (s, 1H), 10.37 (s, 1H), 10.10 (s, 1H), 8.20 (s, 1H), 7.72-7.42 (m, 7H), 7.26-7.05 (m, 4H), 2.96-2.87 (m, 2H), 2.64-2.55 (m, 2H, partially obscured), 2.32 (s, 3H).

LCMS: $(M+H)^+$ 421.1.

Example 51: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-(1-trityl-1*H*-imidazol-4-yl)-propionamide

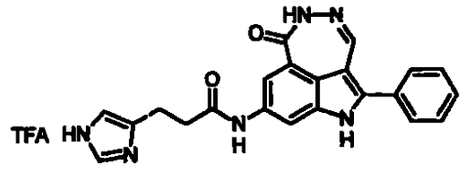


Preparation of example 51 from the title compound of Example 7 (hydrochloride) (31 mg, 0.10 mmol), 3-(1-Trityl-1H-imidazol-4-yl)-propionic acid (46 mg, 0.12 mmol), triethylamine (0.021 mL, 0.15 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (3% triethylamine in 5:4:1 hexane:CH_2Cl_2:methanol), also in an analogous manner, afforded the title compound (40 mg, 0.062 mmol) as a yellow powder in 62% yield.

^{1}H NMR ($CDCl_3$/d_4-methanol): δ 8.21 (s, 1H), 7.65-7.25 (m, 15H, partially obscurred), 7.10-7.02 (m, 8H), 6.65 (s, 1H), 2.99-2.89 (m, 2H), 2.71-2.62 (m, 2H).

LCMS: $(M+H^+)$ 641.2.

Example 52: 3-(1*H*-Imidazol-4-yl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-propionamide: compound with trifluoro-acetic acid

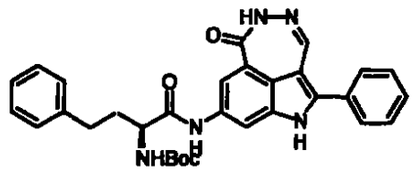


Preparation of example 52 from the title compound of Example 51 (32 mg, 0.050 mmol) and 45% TFA in CH_2Cl_2 (1 mL) was carried out analogously to Example 20. (Deprotection of trityl group was effected using the same conditions as for *tert*-butoxycarbonyl deprotection.) Isolation, also in an analogous manner, additionally included recrystallization from methanol/ethyl acetate and diethyl ether to afford the title compound (16 mg, 0.031 mmol) as a yellow powder in 62% yield.

^{1}H NMR (d_6-DMSO): 13.95 (br s, 1H), 12.10 (s, 1H), 10.40 (s, 1H), 10.20 (s, 1H), 8.83 (s, 1H), 8.13 (s, 1H), 7.70-7.63 (m, 3H), 7.62-7.47 (m, 5H), 7.38 (s, 1H), 3.02 -2.93 (m, 2H), 2.78-2.70 (m, 2H).

LCMS: $(M+H^+)$ 399.2.

Example 53: [(S)-1-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-3-phenyl-propyl]-carbamic acid *tert*-butyl ester

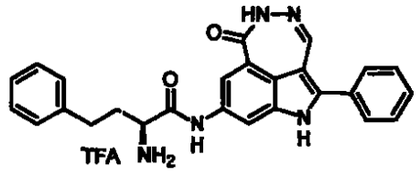


Preparation of example 53 from the title compound of Example 7 (hydrochloride) (31 mg, 0.10 mmol), (S)-2-*tert*-Butoxycarbonylamino-4-phenyl-butyric acid (34 mg, 0.12 mmol), triethylamine (0.021 mL, 0.15 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography, (5:4:1 hexane:CH_2Cl_2:methanol), also in an analogous manner, afforded the title compound (40 mg, 0.074 mmol) as a yellow powder in 74% yield.

^{1}H NMR (d_6-DMSO): 12.11 (s, 1H), 10.40 (s, 1H), 10.17 (s, 1H), 8.40 (br s, 1H), 8.16 (s, 1H), 7.71-7.45 (m, 6H), 7.35-7.15 (m, 6H), 4.06 (m, 1H), 2.77-2.53 (m, 2H, partially obscured), 1.92 (m, 2H), 1.42 (s, 9 H).

LCMS: $(M+H^+)$ 538.1, $(M+Na^+)$ 560.2, $(M-H)^-$ 536.0.

Example 54: (2S)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-phenyl-butyramide: compound with trifluoro-acetic acid

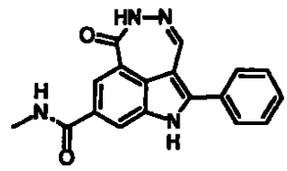


Preparation of example 54 from the title compound of Example 53 (30 mg, 0.056 mmol) and 45% TFA in CH_2Cl_2 (1 mL) was carried out analogously to Example 20. Isolation, also in an analogous manner, afforded the title compound (26 mg, 0.047 mmol) as a yellow powder in 84% yield.

^{1}H NMR (d_6-DMSO): δ 12.22 (s, 1H), 10.71 (s, 1H), 10.47 (s, 1H), 8.38 (br s, 3H), 8.13 (s, 1H), 7.72-7.66 (m, 2H), 7.64-7.49 (m, 4H), 7.36-7.28 (m, 2H), 7.27-7.19 (m, 4H), 4.05 (br s, 1H), 2.77-2.65 (m, 2H), 2.21-2.09 (m, 2H).

LCMS: $(M+H^+)$ 438.2, $(M+Na^+)$ 460.1, $(M-H)^-$ 436.1.

Example 55: *N*-Methyl-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

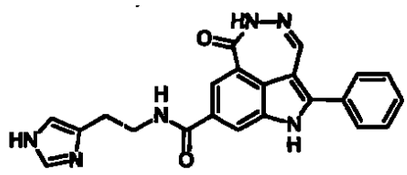


To a solution of the title compound of Example 49 (0.058 g, 0.17 mmol) in DMSO (4 mL) was added triethylamine (0.069 mL, 0.5 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.084 g, 0.22 mmol). After approximately 5 min, 2.0 M methylamine in tetrahydrofuran (0.5 mL, 0.25 mmol) was added and the solution was stirred for 2 hours. The mixture was purified using preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% HOAc). The pure fractions were combined and lyophilized to afford the title compound (0.0036 g) in 6.7% yield.

^{1}H-NMR (d_6-DMSO): δ 12.46 (s, 1H), 10.45 (s, 1H), 8.58 (s, 1H), 8.20-7.90(m, 2H), 7.85-7.35 (m, 6H), 2.79 (s, 3H).

LCMS: ($M+H^+$) 319.1.

Example 56: *N*-[2-(1*H*-Imidazol-4-yl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide



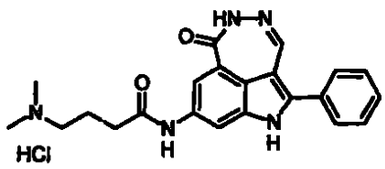
Preparation of example 56 from the title compound of Example 49 (0.0956 g, 0.28 mmol), 2-(1*H*-imidazol-4-yl)ethylamine dihydrochloride (0.0618 g, 0.34 mmol), triethylamine (0.2 mL, 1.4 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.129 g, 0.34 mmol) in DMSO (6 mL) was carried out analogously to Example 58. Preparative HPLC (10-80% CH_3CN/H_2O), also in an analogous manner, afforded the title compound (0.0021 g) in 18% yield.

^{1}H-NMR (d_6-DMSO): δ 12.48 (s, 1H), 10.49 (s, 1H), 8.77 (t, 1H, J = 5.7 Hz), 8.08 (s, 1H), 8.01 (s, 1H), 7.75-7.66(m, 2H), 7.64-7.54 (m, 5H), 7.51 (s, 1H), 6.85 (s, 1H), 3.55-3.45 (m, 2H), 2.84-2.73 (t, 2H, J = 7.2 Hz).

LCMS: ($M+H^+$) 399.1

Anal. Calcd. for $C_{22}H_{18}N_6O_2 \cdot 0.60$ HCl $\cdot$ 0.75 H_2O: C, 60.91; H, 4.67; N, 19.37. Found: C, 60.74; H, 4.74; N, 19.48.

Example 57: 4-Dimethylamino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-butyramide (hydrochloric salt)

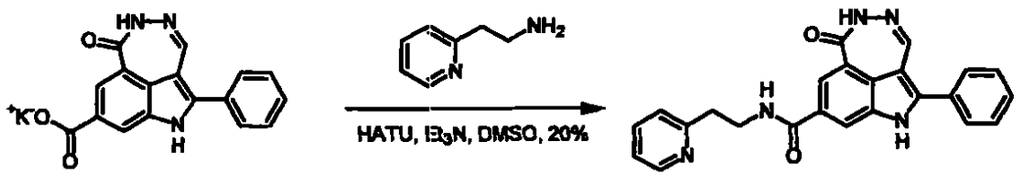


Preparation of example 57 from the title compound of Example 7 (hydrochloride) (27 mg, 0.086 mmol), 4-dimethylamino-butyric acid(hydrochloride)(17 mg, 0.104 mmol), triethylamine (0.036 mL, 0.258 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (40 mg, 0.104 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (2% triethylamine in 9:1 CH_2Cl_2:methanol) of the freebase afforded, after acidification with HCl, the title compound (18 mg, 0.042 mmol) as a yellow powder in 49% yield.

^{1}H NMR (d_6-DMSO): δ 12.10 (s, 1H), 10.39 (s, 1H), 10.21 (s, 1H), 9.60 (br s, 1H, HCl), 8.13 (s, 1H), 7.69-7.46 (m, 7H), 3.15-3.04 (m, 2H), 2.80 (s, 6H, with fine splitting), 2.45 (t, 2H, partially obscurred), 2.02-1.90 (m, 2H).

LCMS: ($M+H^+$) 390.2.

Example 58: 6-Oxo-2-phenyl-*N*-(2-pyridin-2-ylethyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

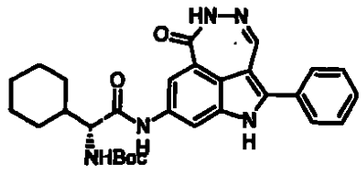


To a solution of the title compound of Example 49 (0.0548 g, 0.16 mmol) in DMSO (1.8 mL) was added triethylamine (0.0268 mL, 0.192 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.0669 g, 0.176 mmol). After approximately 5 min, 2-pyridin-2-ylethylamine (0.0215 g, 0.176 mmol) was added and the solution was allowed to stir overnight. The product was purified using preparative HPLC (5-35% CH_3CN/H_2O). The pure fractions were combined and lyophilized to afford the title compound (0.013 g) as a yellow powder in 20% yield.

^{1}H NMR (d_6-DMSO): δ 10.37 (s, 1H), 8.74 (s, 1H), 8.51 (d, 1H, *J* = 3.0 Hz), 8.01 (d, 2H, *J* = 11 Hz), 7.49-7.71 (m, 7H), 7.20-7.29 (m, 2H), 3.62 (d, 1H, *J* = 4.9 Hz), 3.02 (t, 1H, *J* = 6.4 Hz).

LCMS: (M+H) 410.

Example 59: *tert*-Butyl (1R)-1-cyclohexyl-2-oxo-2-[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]ethylcarbamate



Preparation of example 59 from the title compound of Example 7 (70 mg, 0.25 mmol), (2*R*)-[(*tert*-butoxycarbonyl)amino](cyclohexyl)ethanoic acid (98 mg, 0.38 mmol), triethylamine (0.139 mL, 1.0 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (144 mg, 0.38 mmol) in *N,N*-dimethylformamide (2.0 mL) was carried out analogously to Example 11 except that after 24 hours additional (2*R*)-[(*tert*-butoxycarbonyl)amino](cyclohexyl)ethanoic acid (32 mg, 0.13 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (48 mg, 0.13 mmol) were added to drive the reaction to completion. Silica gel chromatography (1:1 ethyl acetate:hexane), also in an analogous manner, followed by diethyl ether trituration afforded the title compound (90 mg, 0.17 mmol) as a yellow powder in 70% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 11.43 (s, 1H), 10.39 (s, 1H), 10.14 (s, 1H), 8.16 (s, 1H), 7.70-7.64 (m, 3H), 7.61-7.54 (m, 2H), 7.53-7.46 (m, 2H), 3.96 (m, 1H), 1.79-1.49 (m, 6H), 1.41-1.29 (m, 14H, contains singlet at 1.38).

LCMS: $(M+H)^+$ 514.2.

Example 60: (2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide trifluoroacetate

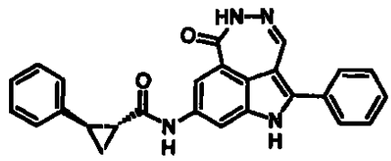


Preparation of example 60 from the title compound of Example 59 (90 mg, 0.17 mmol), and 1:1 TFA/CH_2Cl_2 (5 mL) was carried out analogously to Example 20. Isolation, also in an analogous manner, included a further trituration with methanol/diethyl ether and afforded the title compound (70 mg, 0.013 mmol) as an orange/yellow powder in 78% yield.

^{1}H-NMR (d_6-DMSO): δ 12.22 (s, 1H), 10.63 (s, 1H), 10.47 (s, 1H), 8.22 (br s, 2H), 8.14 (s, 1H), 7.72-7.66 (m, 3H), 7.64-7.49 (m, 4H), 3.72 (m, 1H), 1.91-1.59 (m, 6H), 1.29-1.14 (m, 5H, partially obscured by diethyl ether).

LCMS: $(M+H^+)$ 416.2, $(M+Na^+)$ 438.2.

Example 61: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

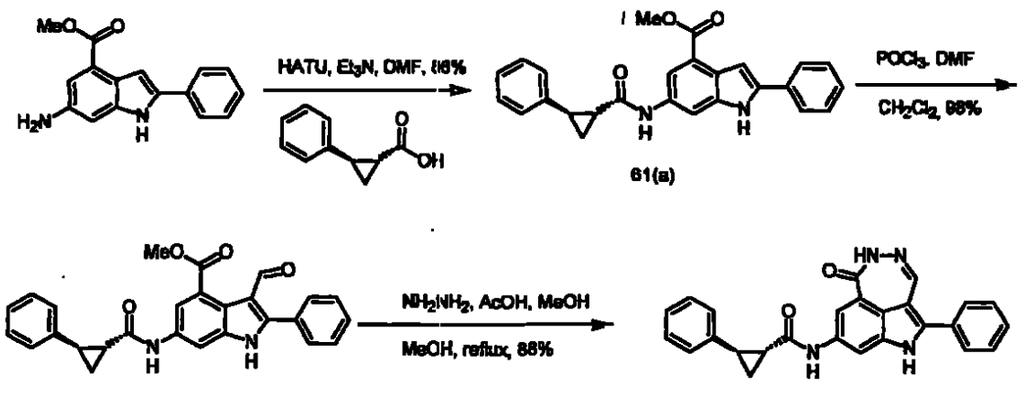


Preparation of example 61 from the title compound of Example 7 (198 mg, 0.72 mmol), (1*R*,2*R*)-2-phenylcyclopropanecarboxylic acid (175 mg, 1.08 mmol; as described by A. Thurkauf, et al., *J. Med. Chem. 43*, 3923-3932, (2000)), triethylamine (0.401 mL, 2.88 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (411 mg, 1.08 mmol) in *N,N*-dimethylformamide (10.0 mL) was carried out analogously to Example 11. Silica gel chromatography (3% methanol in CH_2Cl_2), also in an analogous manner, followed by collection on a frit and subsequent washing with diethyl ether afforded the title compound (86 mg, 0.20 mmol) as a yellow powder in 28% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.44 (s, 1H), 10.37 (s, 1H), 8.16 (d, 1H, *J* = 1.6 Hz), 7.69-7.63 (m, 3H), 7.60-7.46 (m, 4H), 7.34-7.17 (m, 5H), 2.44-2.35 (m, 1H), 2.13-2.05 (m, 1H), 1.55-1.46 (m, 1H), 1.42-1.34 (m, 1H).

LCMS: ($M+H^+$) 421.1.

Alternative Method for the Preparation of Example 61



Step 1. Preparation of 2-Phenyl-6-[((1R,2R)-2-phenyl-cyclopropanecarbonyl)-amino]-1*H*-Indole-4-carboxylic acid methyl ester 61(a)

Preparation from Intermediate 7(a) (3.83 g, 12.64 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (2.27 mg, 13.97 mmol), triethylamine (3.52 mL, 25.28 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (5.31g, 13.97 mmol) in CH_2Cl_2 (6.5 mL) and *N,N*-dimethylformamide (6.5 mL) was carried out analogously to Example

11. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ afforded the crude product as an oil in *N,N*-dimethylformamide. Diethyl ether (c.a. 500 mL) and CH_2Cl_2 (80 mL) were added and the mixture was capped and stirred vigorously overnight whereupon the oil was converted to greenish tan solids which were collected by filtration and washed with diethyl ether, methanol, and water. The filtrate was evaporated to an oil and water was added to precipitate a second batch of solids which was also collected by filtration and also washed with methanol and water. Both batches of precipitated and washed solids were combined to give 4.18 g of desired product. In addition, the final filtrate was evaporated and subjected to silica gel chromatography eluting with 1:1 hexane:acetone to give a small amount of additional product (0.275 mg).The combined batches afforded Intermediate 61(a) (4.46 g, 10.86 mmol) as a tan solid in 86% yield.

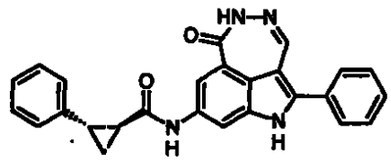
Step 2. Preparation of 3-formyl-2-phenyl-6-[((1R,2R)-2-phenyl-cyclopropanecarbonyl)-amino]-1*H*-indole-4-carboxylic acid methyl ester 61(b)

Intermediate 61(a) (4.02 g, 9.79 mmol) was dissolved in CH_2Cl_2 (80 mL) and treated with Vilsmeier reagent (2.94 mL) in a manner similar to that described in step 4 of Example 3. After c.a. 10 min stirring at ice bath temperature followed by 10 min at room tempeature, the volume of CH_2Cl_2 was reduced under vacuum. With ice bath cooling and stirring, Na_2CO_3 (c.a. 1.2 g) in H_2O (10 mL) was added as a paste to the reaction. Additional H_2O (20 mL) was then added to the still cool reaction. Methanol (c.a. 100 mL) was added and the reaction was allowed to warm to room temperature, still stirring, whereup the slow evolution of gas was observed. After 4 hours, the volume of the mixture was reduced under vacuum, and CH_2Cl_2 was added to adjust the solvent composition to approximately 4:1 CH_2Cl_2:methanol. Precipitated Na_2CO_3 was then removed by filtration, and the volume of filtrate was reduced under vacuum leaving mostly methanol as the solvent. Ethyl acetate was added and mixture was then dried (Na_2SO_4) and filtered and evaporated to give yellow solids. Silica gel chromatography (eluting with 4:1 hexane:acetone increasing to 1:1 hexane:acetone) afforded Intermediate 61(b) (4.2 g, 9.64 mmol) as a yellow powder in c.a. 98% yield.

Step 3. Preparation of Title Compound: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

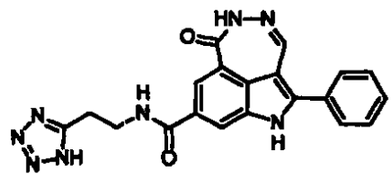
Intermediate 61(b) (4.1 g, 9.41 mmol) acetic acid (0.78 mL, 13.63 mmol) and $H_2NNH_2 \cdot H_2O$ (1.37 mL, 28.23 mmol) in anhydrous methanol (100 mL) were refluxed in manner similar to that described for Example 3, step 5. The resulting precipitate was collected by filtration and washed with a minimum amount of methanol affording the title compound (3.5 g, 8.28 mmol) as a yellow powder in 88% yield.

Example 62: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



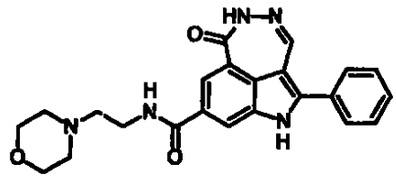
Preparation of example 62 from the title compound of Example 7 (79 mg, 0.28 mmol), (1S,2S)-2-phenylcyclopropanecarboxylic acid (60 mg, 0.37 mmol; as described by A. Thurkauf, et al., *J. Med. Chem.* *43*, 3923-3932, (2000)), triethylamine (0.160 mL, 1.14 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (141 mg, 0.37 mmol) in *N,N*-dimethylformamide (10.0 mL) was carried out analogously to Example 11. Silica gel chromatography (5% methanol in CH_2Cl_2), also in an analogous manner, followed by trituration with methanol afforded the title compound (26 mg, 0.06 mmol) as a yellow powder in 22% yield. ^{1}H-NMR (d_6-DMSO): δ 12.10 (s, 1H), 10.44 (s, 1H), 10.37 (s, 1H), 8.17 (s, 1H), 7.72-7.43 (m, 7H), 7.35-7.26 (m, 2H), 7.24-7.17 (m, 3H), 2.40 (m, 1H), 2.10 (m, 1H), 1.52 (m, 1H), 1.38 (m, 1H). LCMS: ($M+H^+$) 421.3, ($M+Na^+$) 423.2.

Example 63: 6-Oxo-2-phenyl-*N*-[2-(1*H*-tetraazol-5-yl)ethyl]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide



Preparation of example 63 from the title compound of Example 49 (0.0989 g, 0.288 mmol), 2-(1*H*-tetraazol-5-yl)ethylamine (0.072 g, 0.317 mmol), triethylamine (0.0883 mL, 0.634 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.121 g, 0.317 mmol) in DMSO (2 mL) was carried out analogously to Example 58. Preparative HPLC (25-80% CH_3CN/H_2O), also in an analogous manner, afforded the title compound (0.002 g) in 1.7% yield. ^{1}H NMR (d_6-DMSO): δ 12.50 (s, 1H), 10.49 (s, 1H), 8.83 (t, 1H, *J* = 4.9 Hz), 8.05 (s, 1H), 7.98 (s, 1H), 7.70 (d, 2H, *J* = 7.6 Hz), 7.51-7.62 (m, 4H), 3.64 (q, 2H, *J* = 6.1 Hz), 3.14 (t, 2H, *J* = 6.8 Hz). HRMS calculated for $C_{20}H_{17}N_8O_2$ 401.1474 (M+H), found 401.1476.

Example 64: *N*-[2-(4-Morpholinyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

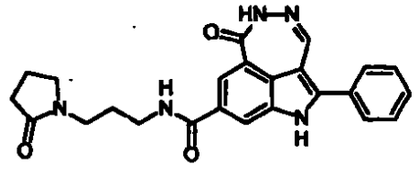


Preparation of example 64 from the title compound of Example 49 (0.0991 g, 0.289 mmol), 2-morpholin-4-ylethylamine (0.041 g, 0.317 mmol), triethylamine (0.0483 mL, 0.347 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.121 g, 0.317 mmol) in DMSO (2 mL) was carried out analogously to Example 58. Preparative HPLC (10-80% CH_3CN/H_2O), also in an analogous manner, afforded the title compound (0.018 g) in 15% yield.

^1H NMR (d_6-DMSO): δ 12.48 (s, 1H), 10.49 (s, 1H), 8.62 (t, 1H, J = 5.3 Hz), 8.07 (s, 1H), 8.00 (s, 1H), 7.70 (d, 2H, J = 6.8 Hz), 7.51-7.62 (m, 4H), 3.57 (t, 4H, J = 4.3 Hz), 3.37-3.43 (m, 2H), 2.41 (br s, 6H).

HRMS calculated for $C_{23}H_{24}N_5O_3$ 418.1879 (M+H), found 418.1858.

Example 65: 6-Oxo-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

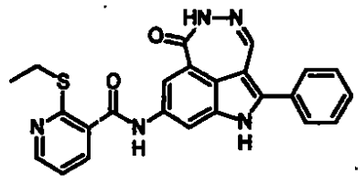


Preparation of example 65 from the title compound of Example 49 (0.109 g, 0.319 mmol), 1-(3-aminopropyl)pyrrolidin-2-one (0.05 g, 0.351 mmol), triethylamine (0.0534 mL, 0.383 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.133 g, 0.351 mmol) in DMSO (2 mL) was carried out analogously to Example 58. Preparative HPLC (10-80% CH_3CN/H_2O), also in an analogous manner, afforded the title compound (0.035 g) in 26% yield.

^1H NMR (d_6-DMSO): δ 12.54 (s, 1H), 10.51 (s, 1H), 8.66 (s, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 7.70 (d, 2H, J = 7.2 Hz), 7.53-7.62 (m, 4H), 3.23-3.37 (m, 6H), 2.21 (t, 2H, J = 7.9 Hz), 1.89-1.96 (m, 2H), 1.72 (t, 2H, J = 6.8 Hz).

HRMS calculated for $C_{24}H_{24}N_5O_3$ 430.1879 (M+H), found 430.1899.

Example 66: 2-Ethylsulfanyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-nicotinamide



Preparation of example 66 from the title compound of Example 7 (hydrochloride) (30 mg, 0.096 mmol), 2-ethylsulfanyl-nicotinic acid (22 mg, 0.12 mmol), triethylamine (0.020 mL, 0.14 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (pre-rinsed silica with 3% triethylamine in ethyl acetate, eluted with 3% triethylamine in 19:6:1 ethyl acetate:hexane:methanol), also in an analogous manner, afforded the title compound (7 mg, 0.016 mmol) as a yellow powder in 17% yield.

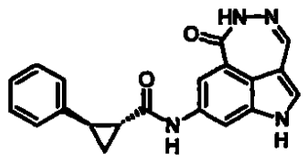
^{1}H NMR (d_6-DMSO): δ 12.15 (s, 1H), 10.60 (s, 1H), 10.39 (s, 1H), 8.59 (s, 1H, with fine splitting), 8.22 (s, 1H), 7.95 (m,1H), 7.82 (s, 1H), 7.72-7.48 (m, 6H), 7.25 (m,1H), 3.21-3.10 (m, 2H, partially obscured), 1.35-1.23 (m, 3H).

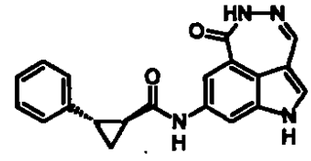
LCMS: $(M+H^+)$ 442.3, $(M+Na^+)$ 464.1.

Example 67:

(1*R*,2*R*)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; and

(1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



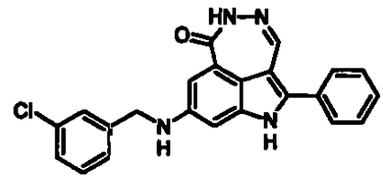


Preparation of example 67 from the title compound of Example 2 (freebase) (21 mg, 0.105 mmol), ± trans-2-phenyl-1-cyclopropanecarboxylic acid (20 mg, 0.126 mmol), triethylamine (0.044 mL, 0.315 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (48 mg, 0.126 mmol) in CH_2Cl_2 (0.3 mL) and *N,N*-dimethylformamide (0.3 mL) was carried out analogously to Example 11. Silica gel chromatography (5:4:1 hexane:CH_2Cl_2:methanol followed by 9:1 CH_2Cl_2:methanol), also in an analogous manner, afforded the title compound (20 mg, 0.058 mmol) (mixture of trans diastereomers) as a yellow powder in 55% yield.

^{1}H NMR (d_6-DMSO): δ 11.72 (s, 1H), 10.38 (s, 1H), 10.25 (s, 1H), 8.13 (s, 1H), 7.56 (s, 1H, overlapping), 7.55 (s, 1H, overlapping), 7.46 (s, 1H), 7.37-7.13 (m, 5H), 2.39 (m, 1H), 2.10 (m, 1H), 1.51 (m, 1H), 1.39 (m, 1H).

LCMS: ($M+H^+$) 345.4, ($M+Na^+$) 367.3.

Example 68: 8-(3-Chloro-benzylamino)-2-phenyl-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one



To the title compound of Example 7 (hydrochloride) (40 mg, 0.13 mmol), and triethylamine (0.053 mL, 0.38 mmol) in *N,N*-dimethylformamide (0.9 mL) was added 1-bromomethyl-3-chloro-benzene (0.17 mL, 0.13 mmol) dropwise with stirring. After stirring overnight, the mixture was chromatographed on silica eluting with 2:1 hexane:ethyl acetate to afford, after isolation, the title compound (36 mg, 0.090 mmol) as a yellow powder in 71% yield.

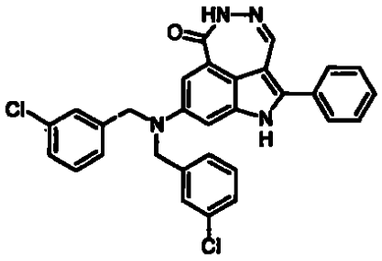
^{1}H NMR (d_6-DMSO): δ 11.59 (s, 1H, exchanges), 10.22 (s, 1H, exchanges), 7.60-7.27 (m, 10H), 7.08 (s, 1H), 6.60 (t, 1H, J = 4.9 Hz, exchanges), 6.45 (s, 1H), 4.36 (m, 2H).

LCMS: ($M+H^+$) 401.3, 403.3.

Anal. Calcd. for $C_{23}H_{17}N_4OCl \cdot 0.3\ H_2O$: C, 67.99; H, 4.37; N, 13.79.

Found: C, 67.98; H, 4.35; N, 13.58.

Example 69: 8-[Bis-(3-chloro-benzyl)-amino]-2-phenyl-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one

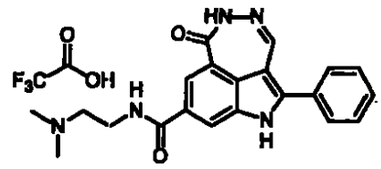


The title compound (7 mg, 0.013 mmol) was isolated as a yellow powder in 10% yield as a by-product from the synthesis outlined in Example 68.

^{1}H NMR (d_4-methanol): δ 7.51-7.31 (m, 6H), 7.25-7.10 (m, 9H), 6.64 (s, 1H), 4.64 (s, 4H).

LCMS: ($M+H^+$) 525.3.

Example 70: *N*-[2-(Dimethylamino)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide trifluoroacetate



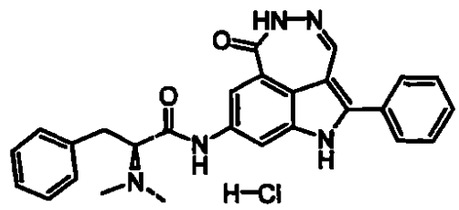
Preparation of example 70 from the title compound of Example **49** (0.08 g, 0.23 mmol), *N*,*N*-dimethylethane-1,2-diamine (0.0247 g, 0.28 mmol), triethylamine (0.17 mL, 1.2 mmol), and O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (0.106 g, 0.28 mmol) in DMSO (6 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid) also in an analogous manner afforded the title compound (0.0076 g) in 6.8% yield.

^1H NMR (d_6-DMSO): δ 12.53 (s, 1H), 10.54 (s, 1H), 9.30 (s, 1H), 8.84 (t, 1H, *J* = 5.5 Hz), 8.12 (s, 1H), 8.04 (s, 1H), 7.75-7.67(m, 2H), 7.66-7.53 (m, 3H), 7.52 (s, 1H), 3.62 (m, 2H), 3.39 (m, 2H), 2.86 (s, 6H).

LCMS: $(M+H^+)$ 376.1

HRMS: $C_{21}H_{21}N_5O_2$ • H: 376.1774. Found: 376.1785.

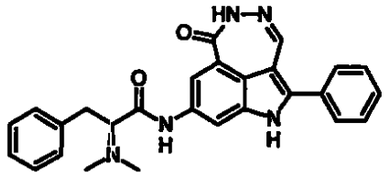
Example 71a: (S)-2-Dimethylamino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide (hydrochloric salt)



Preparation from the title compound of Example **7** (hydrochloride) (40 mg, 0.128 mmol), (S)-2-Dimethylamino-3-phenyl-propionic acid (30 mg, 0.154 mmol), triethylamine (0.071 mL, 0.512 mmol), and O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (59 mg, 0.154 mmol) in CH_2Cl_2 (0.4 mL) and *N*,*N*-dimethylformamide (0.4 mL) was carried out analogously to Example **11**. Silica gel chromatography (elute with 1.5% triethylamine in CH_2Cl_2 followed by 1.5% triethylamine in 9:1 CH_2Cl_2:methanol), also in an analogous manner, afforded the freebase of the title compound (46 mg, 0.10 mmol) in three separate batches for a combined 80% yield. Two of the batches were carried on to Examples 71b and 71c respectively. To the third batch (8 mg, 0.018 mmol) was added tetrahydrofuran and 1.2 equivalents of HCl in dioxane (from a 4M stock solution). After evaporation, trituration with diethyl ether and 1:1 CH_2Cl_2:hexane gave the title compound (6 mg, 0.012 mmol) as a yellow powder in 67% yield for the salt formation.

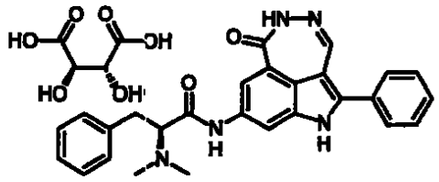
^{1}H NMR (d_6-DMSO): δ 12.25 (s, 1H, exchanges), 10.76 (br s, 2H, exchanges), 10.42 (s, 1H, exchanges), 7.95 (s, 1H), 7.72-7.45 (m, 7H), 7.35-7.16 (m,5H), 4.28 (m, 1H), 3.05 -2.90 (m, 6H).
LCMS (freebase): ($M+H^+$) 452.3, ($M+Na^+$) 474.3.

Example 71b: (S)-2-Dimethylamino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide



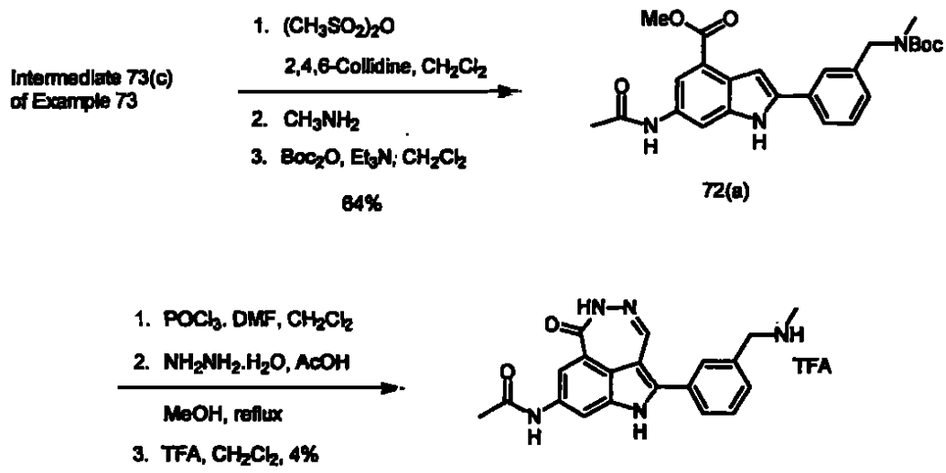
One batch of freebase (S)-2-Dimethylamino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide (13 mg, 0.029 mmol) from Example 71a was triturated with 1:1 diethyl ether:hexane to give the purified title compound (12 mg, 0.027 mmol) as a yellow powder in 93% yield for the trituration.

Example 71c: (S)-2-Dimethylamino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide: compound with (2R,3R)-2,3-dihydroxy-succinic acid



One batch of freebase (S)-2-Dimethylamino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide (22 mg, 0.049 mmol) from Example 71a was triturated with 1:1 diethyl ether:hexane giving purified material (20 mg, 0.044 mmol). A portion (10 mg, 0.022 mmol) was then dissolved in a small amount of c.a. 1:1 tetrahydrofuran:methanol and treated with L-tartaric acid (3.3 mg, 0.022 mmol). The volatile components of the resulting clear solution were removed under a stream of argon. To the resulting yellow oil was added diethyl ether plus one drop of methanol giving a fine yellow precipitate which was isolated by decanting most of the liquid and subsequent high vacuum removal of the remaining volatile components to afford the title compound as a tartrate salt (13 mg, 0.022 mmol) in quantitative yield.

Example 72: *N*-(2-{4-[(methylamino)methyl]phenyl}-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide trifluoroacetate



Step 1. Preparation of Methyl 6-(acetylamino)-2-(3-[[{[(1,1-dimethylethyl)oxy]carbonyl}(methyl)amino] methyl}phenyl)-1*H*-indole-4-carboxylate 72(a)

With stirring, to Intermediate 73(c) of Example **73** (54 mg, 0.16 mmol) in CH_2Cl_2 (2.5 mL) is added 2,4,6-trimethylpyridine (0.11 mL, 0.80 mmol) followed by methanesulfonic anhydride (42 mg, 0.23 mmol). After 3.5 hours, additional methanesulfonic anhydride (7 mg, 0.04 mmol) is added, and the mixture is stirred for an additional 1 hour whereupon methylamine in tetrahydrofuran (2.0 mL, 2.0 M) is added, and the reaction is stirred overnight at room temperature. Following evaporation of the volatile components, CH_2Cl_2 (2.0 mL), triethylamine (0.064 mL, 0.46 mmol), and di-*tert*-butyl dicarbonate (50 mg, 0.23 mmol) are added and the reaction is stirred for 2.5 hours whereupon, after removal of the volatile components, the crude product was purified by silica gel chromatography eluting with 1:1 ethyl acetate:hexane to afford Intermediate 72(a) (46 mg, 0.10 mmol) in 64% yield.

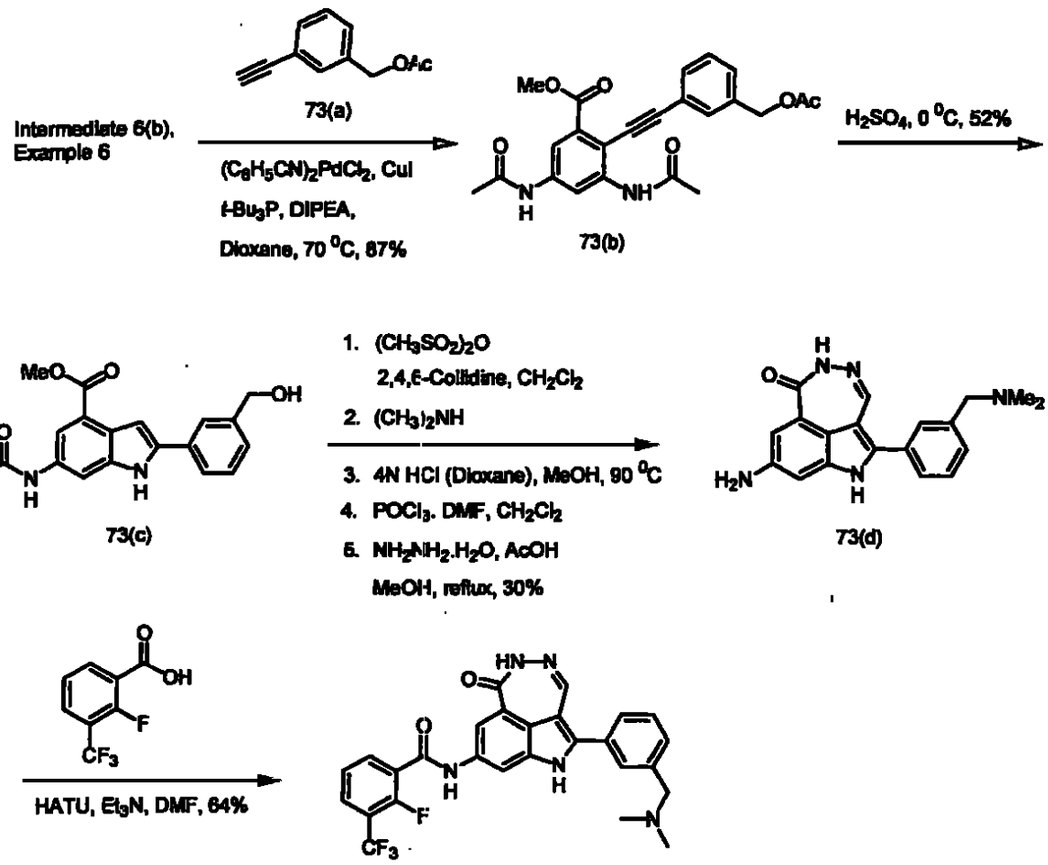
Step 2. Preparation of Title Compound: *N*-(2-{4-[(Methylamino)methyl]phenyl}-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide trifluoroacetate

In a manner similar to that described for Example **3**, step 4, Intermediate 72(a) (45 mg, 0.10 mmole), in CH_2Cl_2 (1.5 mL) was treated with a premixed Vilsmeier reagent consisting of $POCl_3$ (0.021 mL, 0.23 mmol) and *N,N*-dimethylformamide (0.05 mL, 0.65 mmol). After 2 h, 2 N sodium acetate in water was added, and the crude 3-formylated product was isolated by extractive work up using ethyl acetate. After evaporation of the volatile components, methanol (1.5 mL), $H_2NNH_2 . H_2O$ (0.015 mL, 0.31 mmol) and acetic acid (0.010 mL, 0.17 mmol) were added, and the mixture was heated in a 70 °C oil bath for 45 min. Purification was effected using silica gel chromatography eluting with 3:2 ethyl acetate:hexane. The protected intermediate, 1,1-dimethylethyl {4-[8-(acetylamino)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-

yl]phenyl}methyl(methyl)carbamate, was treated with 1:1 TFA/CH_2Cl_2 (5 mL) analogously to Example **20**. Isolation afforded the title compound (2 mg, 0.004 mmol) in 4% yield.

LCMS: ($M+H^+$) 362.3.

Example 73: *N*-[2-(3-Dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-fluoro-3-trifluoromethyl-benzamide



Step 1. Preparation of 2-(3-Acetoxymethyl-phenylethynyl)-3,5-bis-acetylamino-benzoic acid methyl ester 73(b)

A mixture of $(C_6H_5CN)_2PdCl_2$ (0.8 g, 2 mmol), CuI (0.267 g, 1.4 mmol), and tri-*tert*-butyl-phosphane (1.05 mL, 4 mmol) in dioxane (35 mL, 2.0 M) was stirred at 22 °C for 0.25 hours. Diisopropylamine (17.1 mL, 122 mmol), Intermediate 6(b) of Example 6 (23 g, 69.9 mmol), acetic acid 3-ethynyl-benzyl ester (17 g, 98.0 mmol) (see below for preparation) and *N,N*-dimethylformamide (35 mL, 2.0 M) were added sequentially. The reaction mixture stirred at 70 °C for 16 hours. Ethyl acetate (300 mL) was added and the salts were filtered through diatomaceous

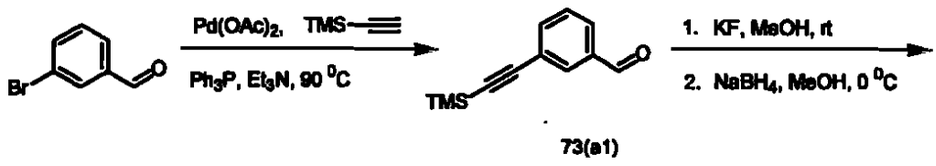
earth. The solvent was removed under reduced pressure, and the resulting solid was triturated with ethyl acetate (25 mL), dichloromethane (50 mL) and diethyl ether (25 mL). The precipitate was collected by filtration and washed with 5% dichloromethane in diethyl ether (100 mL) to afford, after drying, Intermediate 73(b) (25.7 g) in 87% yield as a white powder.

^{1}H-NMR (d_6-DMSO): δ 10.35 (s, 1H), 9.54 (s, 1H), 8.21 (d, 1H, J = 2.1 Hz), 8.08 (d, 1H, J = 2.1 Hz), 7.58-7.38 (m, 4H), 5.12 (s, 2H), 3.90 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H).

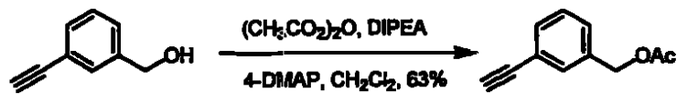
LCMS: (M-H$^+$) 421.3

For step 1, compound 73(a) (acetic acid 3-ethynyl-benzyl ester) was prepared as follows:

Step 1a – 1c.



73(a1)



73(a2) 73(a)

Step 1a: Preparation of crude 3-trimethylsilanylethynyl-benzaldehyde 73(a1)

3-Bromobenzaldehyde (30 g, 162 mmol), ethynyl-trimethyl-silane (30 mL, 211 mmol), triphenylphosphine (2.13 g, 8 mmol), palladium (II) acetate (0.91 g, 4 mmol) and triethylamine (540 mL, 0.3 M) were heated at 90 °C for 5 hours, after cooling to ambient temperature, the mixture was filtered. The filtrate was evaporated, and the residue was subjected to silica gel chromatography (hexane to 4:96 diethyl ether/hexane) to afford 3-trimethylsilanylethynyl-benzaldehyde 73(a1).

Step 1b: Preparation of crude (3-ethynyl-phenyl)-methanol 73(a2)

To 3-trimethylsilanylethynyl-benzaldehyde 73(a1) from step 1a in methanol (540 mL, 0.3 M) was added KF (18.8 g, 324 mmol), and the resulting mixture stirred at 22 °C for 6 hours. After cooling to 0 °C, $NaBH_4$ (6.13 g, 162 mmol) was carefully added over 0.5 hours. Aqueous saturated NH_4Cl was carefully added and the volatiles were removed *in vacuo*. Ethyl acetate (200 mL) was added, and the organic phase was washed with water and a saturated aqueous NaCl solution, dried over $MgSO_4$ and filtered. The volatiles were removed *in vacuo* to afford crude (3-ethynyl-phenyl)-methanol 73(a2).

Step 1c: Preparation of acetic acid 3-ethynyl-benzyl 73(a)

Crude (3-ethynyl-phenyl)-methanol 73(a2) from step 1b, acetic anhydride (20 mL, 21 mmol), diisopropylethylamine (85 mL, 486 mmol) and 4-dimethylamino-pyridine (0.3963.2 mmol) were

stirred in CH_2Cl_2 (540 mL, 0.3 M) for 0.5 hours. Aqueous saturated NH_4Cl (100 mL) was carefully added and the organic phase washed with brine, dried over $MgSO_4$ and filtered. The volatiles were removed *in vacuo* to afford, after silica gel chromatography (hexanes to 12:88 diethyl ether/hexanes), acetic acid 3-ethynyl-benzyl (a) (17.83 g) in 63% yield.

^{1}H-NMR (d_6-DMSO): δ 7.32-7.01 (m, 4H), 4.85 (s, 2H), 4.01 (s, 1H), 1.89 (s, 3H).

Step 2. Preparation of 6-Acetylamino-2-(3-hydroxymethyl-phenyl)-1*H*-indole-4-carboxylic acid methyl ester 73(c)

In a manner analogous to Step 4 of Example 6, Intermediate 73(b) (24 g, 56.8 mmol) was cyclized to Intermediate 73(c) (10.1 g) in 52% yield.

^{1}H-NMR (d_6-DMSO): δ 11.89 (s, 1H), 10.16 (s, 1H), 8.35 (s, 1H), 7.89 (bs, 2H), 7.51 (d, 1H, J = 7.9 Hz), 7.49 (dd, 1H, J = 7.7, 7.5 Hz), 7.33 (bs, 2H), 5.37 (dd, 1H, J = 5.8, 5.7 Hz), 4.64 (d, 2H, J = 5.65 Hz), 3.99 (s, 3H), 2.13 (s, 3H).
LCMS: ($M+H^+$) 339.0

Step 3. Preparation of 8-Amino-2-(3-dimethylaminomethyl-phenyl)-1,5-dihydro-[1,2]diazepino [4,5,6-*cd*]indol-6-one 73(d)

To a solution of Intermediate 73(c) (1 g, 3 mmol) in dichloromethane (0.1 M, 30 mL) was added 2,4,6-Collidine (1.56 mL, 12 mmol) followed by $(CH_3SO_2)_2O$ (0.62 g, 3.6 mmoL). After stirring for 2 hours, dimethylamine (5.6 M solution in ethanol, 2.6 mL, 15 mmol) was added and the reaction mixture stirred for 24 hours at 22 °C. The volatiles were removed *in vacuo*, and the crude mixture was dissolved in methanol (15 mL). Anhydrous 4M HCl in dioxane (15 mL, 60 mmol) was carefully added, and the solution heated at 90 °C for 2.5 hours. After cooling at 22 °C, the volatiles were removed *in vacuo* and the crude 6-amino-2-(3-dimethylaminomethyl-phenyl)-1*H*-indole-4-carboxylic acid methyl ester was formylated and cyclized in a manner analogous to steps 4 and 5 of Example 3. Silica gel chromatography (90:10 to 75:25 CH_2Cl_2/ 2M ammonia in isopropyl alcohol) provided Intermediate 73(d) (0.3 g, 0.9 mmol) in 30% yield.

^{1}H-NMR (d_6-DMSO): δ 11.54 (s, 1H), 10.15 (s, 1H), 7.55-7.32 (m, 5H), 6.98 (d, 1H, J = 1.3 Hz), 6.65 (d, 1H, J = 1.4 Hz), 5.2 (bs, 2H), 3.49 (b, 2H), 2.20 (bs, 6H).
LCMS: ($M+H^+$) 334.2

Step 4. Preparation of Title Compound: *N*-[2-(3-Dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-fluoro-3-trifluoromethyl-benzamide

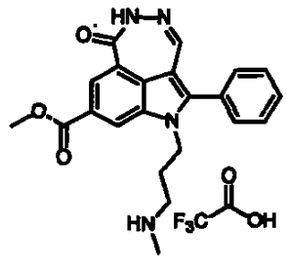
Preparation from Intermediate 73(d) (0.11 g, 0.4 mmol), 2-Fluoro-3-trifluoromethyl-benzoic acid (0.103 g, 0.6 mmol), triethylamine (0.183 mL, 1.6 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.188 g, 0.6 mmol) and *N,N*-dimethylformamide (0.2 M, 1.7 mL) was carried out analogously to Example 11. Silica gel chromatography (90:10 to 80:20

CH_2Cl_2/ 2M ammonia in isopropyl alcohol) afforded the title compound (0.11 g) as a yellow powder in 64% yield.

^{1}H-NMR (d_6-DMSO): δ 12.26 (s, 1H), 10.84 (s, 1H), 10.51 (s, 1H), 9.62 (b, 1H), 8.29 (d, 1H, J = 1.4 Hz), 8.08-7.94 (m, 2H), 7.85-7.53 (m, 7H), 4.39 (s, 2H), 2.73 (s, 6H).

LCMS: ($M+H^+$) 524.2.

Example 74: Methyl 1-[3-(methylamino)propyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxylate trifluoroacetate



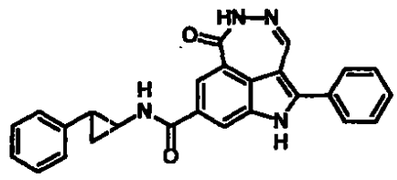
To a solution of the title compound from Example **39** (0.32 g, 1 mmol) in anhydrous DMSO (10 mL) was added NaH (60% suspension in mineral oil) (0.088 g, 2.2 mmol). The mixture was allowed to stir for 5 min whereupon 1,2-dibromopropane (0.24 g, 1.2 mmol) was added. The mixture was allowed to stir overnight at room temperature at which point a 2M solution of methylamine in methanol (4 mL, 8 mmol) was added. The mixture was subjected to preparative HPLC (20-50% CH_3CN/H_2O containing 0.1% trifluoroacetic acid). The purest fractions were combined and lyophilized to afford the title compound (0.0209 g) in 4.1% yield.

^{1}H NMR (d_6-DMSO): δ 10.61 (s, 1H), 8.39 (d, 1H, J = 1.0 Hz), 8.22 (d, 1H, J = 1.0 Hz), 7.70-7.55(m, 5H), 7.07 (s, 1H), 4.41 (t, 2H, J = 7.2 Hz), 3.92 (s, 3H), 2.80-2.60 (broad, 2H), 2.43 (s, 3H), 1.95-1.75 (m, 2H).

LCMS: ($M+H^+$) 391.2

HRMS: $C_{22}H_{22}N_4O3$ • H: 391.1770. Found: 391.1768.

Example 75: 6-Oxo-2-phenyl-*N*-((1,2-*trans*)-2-phenylcyclopropyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide



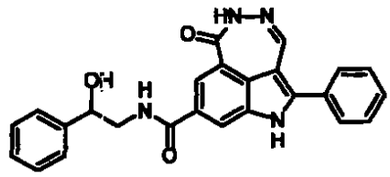
Preparation of example 75 from the title compound of Example **49** (0.34 g, 1 mmol), ±(1,2-*trans*)-2-phenylcyclopropylamine hydrochloride (0.2 g, 1.2 mmol), triethylamine (0.28 mL, 2 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.46 g, 1.2 mmol)

in DMSO (10 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0145 g) in 3.5% yield.

^1H NMR (d_6-DMSO): δ 12.46 (s, 1H), 10.47 (s, 1H), 8.88 (d, 1H, J = 4.4 Hz), 8.10 (d, 1H, J = 1.4 Hz), 8.02 (d, 1H, J = 1.4 Hz), 7.75-7.63(m, 2H), 7.64-7.53 (m, 3H), 7.51 (s, 1H), 7.32-7.25 (m, 2H), 7.23-7.10 (m, 3H), 3.08 (m, 1H), 2.11 (m, 1H), 1.41 (m, 1H), 1.23 (m, 1H).

LCMS: ($M+H^+$) 421.1.

Example 76: *N*-(2-Hydroxy-2-phenylethyl)-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

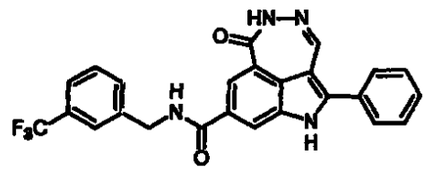


To a solution of the title compound of Example 49 (0.105 g, 0.306 mmol) in DMSO (2 mL) was added triethylamine (0.085 mL, 0.612 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.232 g, 0.612 mmol). After approximately 5 min, 2-amino-1-phenylethanol (0.084 g, 0.612 mmol) was added, and the mixture was stirred overnight. The mixture was subjected to preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), and the purest fractions were combined and lyophilized to afford the title compound (0.018 g) as a yellow powder in 14% yield.

^1H NMR (d_6-DMSO): δ 12.47 (s, 1H), 10.45 (s, 1H), 8.68 (t, 1H, J = 4.5 Hz), 8.09 (s, 1H), 8.01 (s, 1H), 7.71 (d, 2H, J = 6.8 Hz), 7.51-7.62 (m, 4H), 7.24-7.41 (m, 5H), 4.80-4.84 (m, 1H), 3.46-3.54 (m, 2H).

HRMS calculated for $C_{25}H_{21}N_4O_3$ 425.1614 (M+H), found 425.1633.

Example 77: 6-Oxo-2-phenyl-*N*-[3-(trifluoromethyl)benzyl]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide



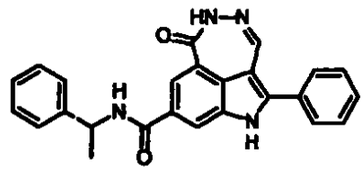
Preparation of example 77 from the title compound of Example 49 (0.1 g, 0.291 mmol), 3-(trifluoromethyl)benzylamine (0.102 g, 0.582 mmol), triethylamine (0.081 mL, 0.582 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.221 g, 0.582

mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.024 g) as a yellow powder in 18% yield.

^1H NMR (d_6-DMSO): δ 12.49 (s, 1H), 10.48 (s, 1H), 9.33 (t, 1H, J = 6.0 Hz), 8.14 (s, 1H), 8.06 (s, 1H), 7.52-7.72 (m, 10H), 4.58 (d, 3H, J = 5.7 Hz).

HRMS calculated for $C_{25}H_{18}N_4O_2F_3$ 463.1382 (M+H), found 463.1391.

Example 78: 6-Oxo-2-phenyl-*N*-(1-phenylethyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

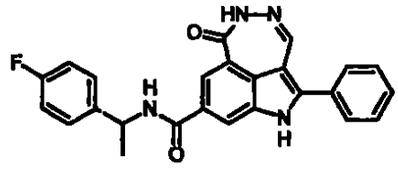


Preparation of example 78 from the title compound of Example 49 (0.103 g, 0.3 mmol), 1-phenylethylamine (0.0727 g, 0.6 mmol), triethylamine (0.084 mL, 0.6 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.228 g, 0.6 mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0081 g) as a yellow powder in 6.6% yield.

^1H NMR (d_6-DMSO): δ 12.44 (s, 1H), 10.46 (s, 1H), 9.03 (d, 1H, J = 7.9 Hz), 8.14 (s, 1H), 8.03 (s, 1H), 7.71 (d, 2H, J = 7.2 Hz), 7.51-7.62 (m, 4H), 7.41 (d, 2H, J = 7.6 Hz), 7.32 (t, 2H, J = 7.6 Hz), 7.22 (t, 1H, J = 7.2 Hz), 5.16-5.25 (m, 1H), 1.51 (d, 3H, J = 6.8 Hz).

HRMS calculated for $C_{25}H_{21}N_4O_2$ 409.1665 (M+H), found 409.1679.

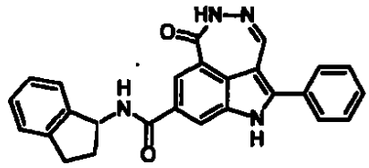
Example 79: *N*-[1-(4-Fluorophenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide



Preparation of example 79 from the title compound of Example 49 (0.0979 g, 0.285 mmol), 1-(4-fluorophenyl)ethylamine (0.0793 g, 0.57 mmol), triethylamine (0.079 mL, 0.57 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.217 g, 0.57 mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0043 g) as a yellow powder in 3.5% yield.

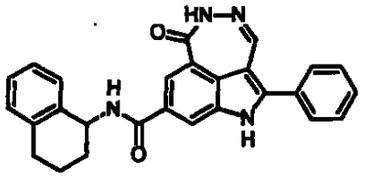
^{1}H NMR (d_6-DMSO): δ 12.44 (s, 1H), 10.47 (s, 1H), 9.03 (d, 1H, *J* = 7.9 Hz), 8.13 (s, 1H), 8.02 (s, 1H), 7.71 (d, 2H, *J* = 6.8 Hz), 7.51-7.62 (m, 4H), 7.42-7.47 (m, 2H), 7.12-7.18 (m, 2H), 5.15-5.24 (m, 1H), 1.50 (d, 3H, *J* = 7.2 Hz).
HRMS calculated for $C_{25}H_{20}N_4O_2F$ 427.1570 (M+H), found 427.1584.

Example 80: *N*-(2,3-Dihydro-1*H*-inden-1-yl)-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide



Preparation of example 80 from the title compound of Example 49 (0.1 g, 0.291 mmol), 2,3-dihydro-1*H*-inden-1-ylamine (0.0775 g, 0.582 mmol), triethylamine (0.081 mL, 0.582 mmol), and O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (0.221 g, 0.582 mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0045 g) as a yellow powder in 3.7% yield.
^{1}H NMR (d_6-DMSO): δ 12.45 (s, 1H), 10.45 (s, 1H), 9.01 (d, 1H, *J* = 8.3 Hz), 8.15 (s, 1H), 8.09 (s, 1H), 7.71 (d, 2H, *J* = 6.8 Hz), 7.51-7.62 (m, 4H), 7.18-7.28 (m, 4H), 5.56-5.64 (m, 1H), 2.79-3.06 (m, 2H), 1.98-2.46 (m, 2H).
HRMS calculated for $C_{25}H_{20}N_4O_2F$ 427.1570 (M+H), found 427.1584.

Example 81: 6-Oxo-2-phenyl-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

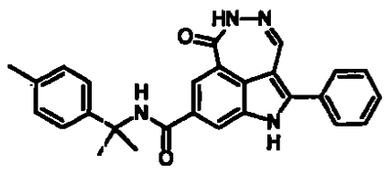


Preparation of example 81 from the title compound of Example 49 (0.103 g, 0.3 mmol), 1,2,3,4-tetrahydronaphthalen-1-ylamine (0.0883 g, 0.6 mmol), triethylamine (0.084 mL, 0.6 mmol), and O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (0.228 g, 0.6 mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0136 g) as a yellow powder in 10% yield.

^{1}H NMR (d_6-DMSO): δ 12.44 (s, 1H), 10.44 (s, 1H), 9.01 (d, 1H, *J* = 8.7 Hz), 8.15 (s, 1H), 8.09 (s, 1H), 7.71 (d, 2H, *J* = 6.8 Hz), 7.51-7.62 (m, 4H), 7.10-7.23 (m, 4H), 5.23-5.30 (m, 1H), 2.75-2.81 (m, 2H), 1.96-2.01 (m, 2H), 1.74-1.90 (m, 2H).

HRMS calculated for $C_{27}H_{23}N_4O_2$ 435.1821 (M+H), found 435.1810.

Example 82: *N*-[1-Methyl-1-(4-methylphenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

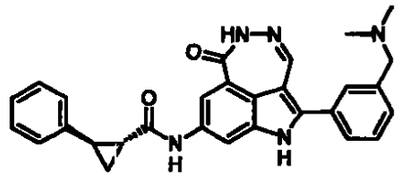


Preparation of example 82 from the title compound of Example 49 (0.103 g, 0.3 mmol), 1-methyl-1-(4-methylphenyl)ethylamine (0.0885 g, 0.6 mmol), triethylamine (0.084 mL, 0.6 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.228 g, 0.6 mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0304 g) as a yellow powder in 23% yield.

^{1}H NMR (d_6-DMSO): δ 12.41 (s, 1H), 10.45 (s, 1H), 8.60 (s, 1H), 8.05 (s, 1H), 7.94 (s, 1H), 7.70 (d, 2H, *J* = 6.80 Hz), 7.51-7.62 (m, 4H), 7.26 (d, 2H, *J* = 8.3 Hz), 7.08 (d, 2H, *J* = 7.9 Hz), 2.25 (s, 3H), 1.67 (s, 6H).

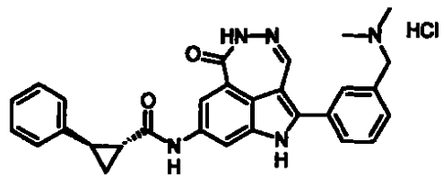
HRMS calculated for $C_{27}H_{25}N_4O_2$ 437.1978 (M+H), found 437.1987.

Example 83a: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide



Preparation of example 83a from Intermediate 73(d) of Example 73 (0.11 g, 0.33 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (0.08 g, 0.5 mmol), triethylamine (0.183 mL, 1.32 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.188 g, 0.5 mmol) and *N,N*-dimethylformamide (0.2 M, 1.7 mL) was carried out analogously to Example 11. Silica gel chromatography (90:10 to 80:20 CH_2Cl_2/ 2M ammonia in isopropyl alcohol) afforded the title compound (0.12 g) as a yellow powder in 76% yield.

Example 83b: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide HCl Salt

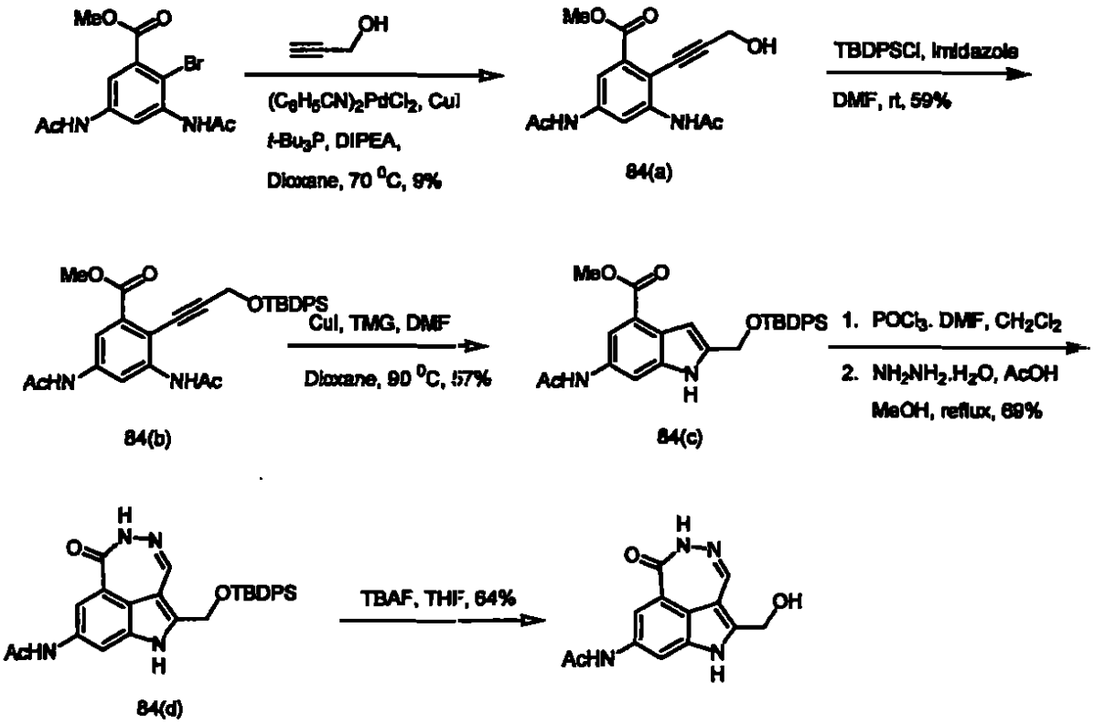


The title compound of Example **83a** (0.075 g, 0.16 mmol) in dichloromethane (1.0 mL) was treated with 4M HCl in dioxane (0.043 mL, 0.17 mmol). After concentrating to dryness, the title compound (0.08 g) was obtained in quantitative yield.

^{1}H-NMR (d_6-DMSO): δ 12.19 (s, 1H), 10.48 (s, 1H), 10.44 (s, 1H), 10.02 (b, 1H), 8.20 (d, 1H, *J* = 1.5 Hz), 7.84 (s, 1H), 7.76 (d, 1H, *J* = 7.4 Hz), 7.71-7.59 (m, 4H), 7.34-7.17 (m, 5H), 4.38 (d, 1H, *J* = 5.0 Hz), 2.78 (d, 6H, *J* = 4.6 Hz), 2.45-2.37 (m, 1H), 2.14-2.07 (m, 1H), 1.56-1.47 (m, 1H), 1.42-1.35 (m, 1H).

HRMS: ($M+H^+$) calcd for $C_{29}H_{28}N_5O_2$, 478.2243, found 478.2261.

Example 84: *N*-(2-Hydroxymethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide



Step 1. Preparation of 3,5-Bis-acetylamino-2-(3-hydroxy-prop-1-ynyl)-benzoic acid methyl ester 84(a)

Intermediate 6(b) (10 g, 30.4 mmol) of Example 6 and propargyl alcohol were reacted in a manner analogous to step 1 of Example 73. Intermediate 84(a) (0.85 g) was obtained in 9% yield.

^{1}H-NMR (d_6-DMSO): δ 10.29 (s, 1H), 9.11 (s, 1H), 8.30 (s, 1H), 8.00 (s, 1H), 5.34 (t, 1H, *J* = 5.84 Hz), 4.38 (d, 2H, *J* = 5.84 Hz), 3.83 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H).

Step 2. Preparation of 3,5-Bis-acetylamino-2-[3-(*tert*-butyl-diphenyl-silanyloxy)-prop-1-ynyl]-benzoic acid methyl ester 84(b)

Chloro-*tert*-butyl-diphenyl-silane (1.3 g, 2 mmol), imidazole (0.54 g, 7.9 mmol) and Intermediate 84(a) (0.48 g, 1.6 mmol) were stirred in *N,N*-dimethylformamide (0.2 M, 15 mL) for 0.5 hours at 22 °C. Methanol was added, the volatiles removed *in vacuo*, and ethyl acetate (50 mL) was added. The organic phase was washed with 1N aqueous HCl, brine, dried over $MgSO_4$, filtered, and the volatiles removed *in vacuo*. Silica gel chromatography (80:20 ethyl acetate/hexanes) afforded Intermediate 84(b) (0.5 g) in 59% yield.

^{1}H-NMR (d_6-DMSO): δ 10.31 (s, 1H), 9.18 (s, 1H), 8.25 (d, 1H, *J* = 1.8 Hz), 8.00 (d, 1H, *J* = 1.8 Hz), 7.74-7.68 (m, 4H), 7.50-7.41 (m, 6H), 4.67 (s, 2H), 3.81 (s, 3H), 2.05 (s, 6H), 1.01 (s, 9H).
LCMS: ($M-H^+$) 541.1

Step 3. Preparation of 6-Acetylamino-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-1*H*-indole-4-carboxylic acid methyl ester 84(c)

In a manner analogous to step 5 of Example 5, from Intermediate 84(b) (0.46 g, 0.84 mmol) was reacted to provide Intermediate 84(c) (0.24 g) in 57% yield.

^{1}H-NMR (d_6-DMSO): δ 11.36 (s, 1H), 10.04 (s, 1H), 8.25 (s, 1H), 7.78 (d, 1H, *J* = 1.5 Hz), 7.74-7.66 (m, 4H), 7.50-7.41 (m, 6H), 6.72 (s, 1H), 4.85 (s, 2H), 3.87 (s, 3H), 2.06 (s, 3H), 1.03 (s, 9H).
LCMS: ($M-H^+$) 499.1

Step 4. Preparation of *N*-[2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide 84(d)

In a manner analogous to steps 4 and 5 of Example 3, Intermediate 84(c) (0.2 g, 0.4 mmol) was formylated and cyclized to provide Intermediate 84(d) (0.14 g) in 69% yield.

LCMS: ($M-H^+$) 509.1.

Step 5. Preparation of Title Compound: *N*-(2-Hydroxymethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide

To a solution of Intermediate 84(d) (0.085 g, 0.17 mmol) in tetrahydrofuran (0.1 M, 1.6 mL) was added a 1M solution of *tetra*-butyl ammonium fluoride in tetrahydrofuran (0.184 mL, 0.18 mmol). The mixture was stirred at 22 °C for 2 hours, and the yellow solid was collected by filtration and

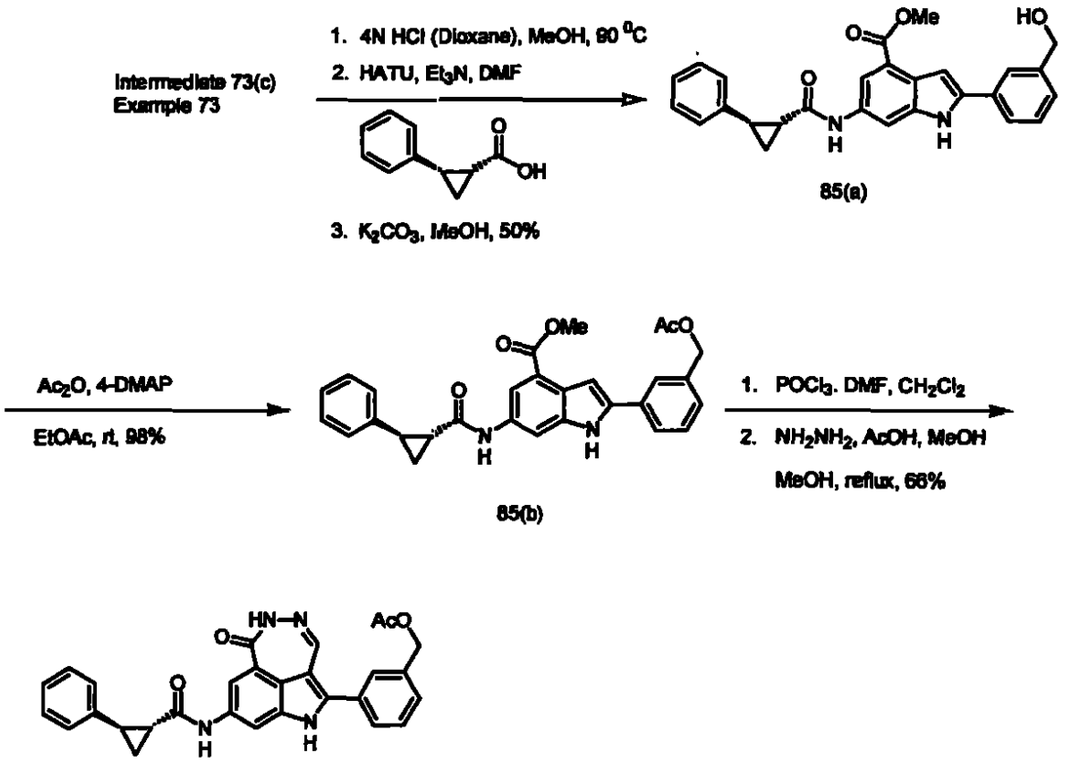
washed with methanol (5.0 mL) and diethyl ether (5.0 mL) to afford the title compound (0.029 g) in 64% yield.

^{1}H-NMR (d_6-DMSO): δ 11.74 (s, 1H), 10.17 (s, 1H), 10.02 (s, 1H), 8.04 (d, 1H, J = 1.3 Hz), 7.54 (s, 1H), 7.53 (s, 1H), 5.47 (dd, 1H, J = 5.5, 5.5 Hz), 4.68 (d, 2H, J = 5.4 Hz).

LCMS: ($M+H^+$) 273.1.

HRMS: ($M+H^+$) calcd for $C_{13}H_{13}N_4O_3$, 273.1001, found 273.0988.

Example 85: Acetic acid 3-[6-oxo-8-[((1R, 2R)-2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-benzyl ester



Step 1. Preparation of 2-(3-Hydroxymethyl-phenyl)-6-[(1R,2R)-(2-phenyl-cyclopropanecarbonyl)-amino]-1*H*-indole-4-carboxylic acid methyl ester 85(a)

Intermediate 73(c) from Example **73** (1.8 g, 5 mmol) was dissolved in methanol (22 mL). 4M HCl in dioxane (22 mL, 75 mmol) was carefully added, and the solution was heated at 90 °C for 1 hour. After cooling to 22 °C, the volatiles were removed *in vacuo* giving 6-amino-2-(3-hydroxymethyl-phenyl)-1*H*-indole-4-carboxylic acid methyl ester which was then combined with (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (2 g, 12.5 mmol), triethylamine (3.5 mL, 25 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (4.7 g, 12.5 mmol) in *N,N*-dimethylformamide (0.2 M, 25 mL) and stirred at 22 °C for 12 hours. Volatiles were removed *in vacuo* and the crude mixture dissolved in methanol (25 mL, 0.2 M) was treated with K_2CO_3 (1.38 g, 10 mmol) for 1 hour at 22 °C. Excess K_2CO_3 was removed by filtration, and acetic

acid (2 drops) was added to the filtrate. Following filtrate evaporation, the residue was subjected to silica gel chromatography (90:10 to 100:0 ethyl acetate/hexane) which provided Intermediate 85(a) (1.1 g, 2.5 mmol) in 50% yield.

^{1}H-NMR (d_6-DMSO): δ 11.83 (s, 1H), 10.41 (s, 1H), 8.25 (s, 1H), 7.90 (s, 1H), 7.84 (s, 1H), 7.75 (d, 1H, *J* = 7.9 Hz), 7.43 (dd, 1H, *J* = 7.7, 7.5 Hz), 7.35-7.17 (m, 7H), 5.30 (dd, 1H, *J* = 5.8, 5.6 Hz), 4.59 (d, 2H, *J* = 5.4 Hz), 2.45-2.36 (m, 1H), 2.14-2.07 (m, 1H), 1.58-1.47 (m, 1H), 1.42-1.34 (m, 1H).

HRMS: (M+H$^+$) calcd for $C_{27}H_{25}N_2O_4$, 441.1828, found 441.1814.

Step 2. Preparation of 2-(3-Acetoxymethyl-phenyl)-6-[(1R,2R)-(2-phenyl-cyclopropanecarbonyl)-amino]-1*H*-indole-4-carboxylic acid methyl ester 85(b)

To a suspension of Intermediate 85(a) (1.1 g, 2.3 mmol) in ethyl acetate (22 mL, 0.1 M) was added 4-(dimethylamino)-pyridine (0.28 g, 2.3 mmol) and acetic anhydride (0.47 g, 4.6 mmol). The mixture was stirred at 22 °C for 1 h, and the volatiles were removed *in vacuo*. Silica gel chromatography (70:30 to 100:0 ethyl acetate/Hexanes) provided Intermediate 85(b) (1.1 g, 2.3 mmol) in quantitative yield.

^{1}H-NMR (d_6-DMSO): δ 11.85 (s, 1H), 10.43 (s, 1H), 8.26 (s, 1H), 7.92-7.81 (m, 3H), 7.49 (dd, 1H, *J* = 7.7, 7.6 Hz), 7.37-7.13 (m, 7H), 5.15 (s, 2H), 3.92 (s, 3H), 2.45-2.36 (m, 1H), 2.14-2.07 (m, 1H), 1.58-1.47 (m, 1H), 1.42-1.34 (m, 1H).

HRMS: (M+H$^+$) calcd for $C_{29}H_{27}N_2O_5$, 483.1920, found 483.1945.

Step 3. Preparation of Title Compound: Acetic acid 3-{6-oxo-8-[((1R, 2R)-2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl}-benzyl ester

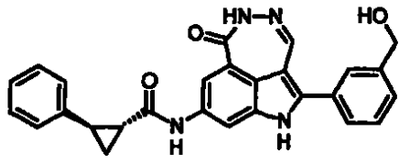
In a manner analogous to steps 4 and 5 of Example 3, Intermediate 85(b) (0.75 g, 1.56 mmol) was formylated and cyclized. Purification by silica gel chromatography (40:60 to 100:0 ethyl acetate/ Hexanes) afforded the title compound (0.505 g, 1.03 mmol) as a yellow powder in 66% yield.

^{1}H-NMR (d_6-DMSO): δ 12.13 (s, 1H), 10.44 (s, 1H), 10.39 (s, 1H), 8.16 (d, 1H, *J* = 1.5 Hz), 7.68-7.45 (m, 6H), 7.34-7.17 (m, 5H), 5.18 (s, 2H), 2.50-2.34 (m, 1H), 2.14-2.07 (m, 4H), 1.58-1.47 (m, 1H), 1.43-1.35 (m, 1H).

HRMS: (M+H$^+$) calcd for $C_{29}H_{25}N_4O_4$, 493.1876, found 493.1882.

Anal. Calcd. for $C_{29}H_{24}N_4O_4 \cdot 0.4\ H_2O$: C, 69.70; H, 5.00; N, 11.21. Found: C, 69.71; H, 5.03; N, 11.33.

Example 86: (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-hydroxymethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide



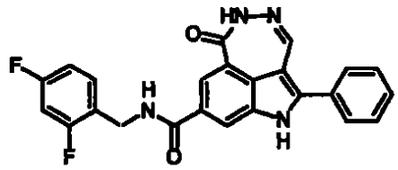
The title compound of Example **85** (0.288 g, 0.58 mmol) and K_2CO_3 (0.161 g, 1.17 mmol) were stirred in methanol (0.2 M, 1.7 mL) and tetrahydrofuran (0.2 M, 1.7 mL) for 1.5 hours at 22 °C. After the solution was filtered and acidified with two drops of glacial acetic acid, the volatiles were removed *in vacuo*. Silica gel chromatography (40:60 to 0:100 hexane/ethyl acetate) afforded the title compound (0.26 g) as a yellow powder in 95% yield.

^{1}H-NMR (d_6-DMSO): δ 12.11 (s, 1H), 10.43 (s, 1H), 10.36 (s, 1H), 8.15 (d, 1H, *J* = 1.0 Hz), 7.64 (d, 1H, *J* = 1.0 Hz), 7.61 (s, 1H), 7.55-7.17 (m, 9H), 5.35 (dd, 1H, *J* = 5.8, 5.6 Hz), 4.60 (d, 2H, *J* = 5.6 Hz), 2.45-2.36 (m, 1H), 2.14-2.07 (m, 1H), 1.58-1.47 (m, 1H), 1.42-1.34 (m, 1H).

LCMS: ($M-H^+$) 449.1.

Anal. Calcd. for $C_{27}H_{22}N_4O_3 \cdot 0.1\ CH_2Cl_2 \cdot 0.1\ C_2H_5O_2CCH_3$: C, 70.61; H, 4.96; N, 11.98. Found: C, 70.01; H, 4.95; N, 11.95.

Example 87: *N*-(2,4-Difluorobenzyl)-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

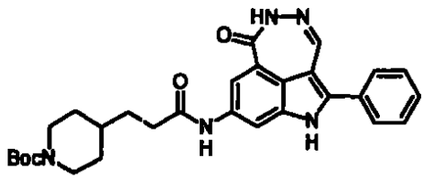


Preparation of example 87 from the title compound of Example **49** (0.102 g, 0.297 mmol), 2,4-difluorobenzylamine (0.085 g, 0.594 mmol), triethylamine (0.083 mL, 0.594 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.226 g, 0.594 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0044 g) as a yellow powder in 3.4% yield.

^{1}H NMR (d_6-DMSO): δ 12.48 (s, 1H), 10.48 (s, 1H), 9.20 (t, 1H, *J* = 5.5 Hz), 8.13 (s, 1H), 8.05 (s, 1H), 7.71 (d, 2H, *J* = 7.2 Hz), 7.52-7.62 (m, 4H), 7.40-7.47 (m, 1H), 7.16-7.25 (m, 1H), 7.03-7.10 (m, 1H), 4.49 (d, 2H, *J* = 5.3 Hz).

HRMS calculated for $C_{24}H_{17}N_4O_2F_2$ 431.1320 (M+H), found 431.1324.

Example 88: 4-[2-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester

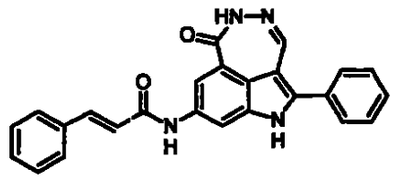


Preparation of example 88 from the title compound of Example 7 (hydrochloride) (44 mg, 0.141 mmol), 4-(2-carboxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (43 mg, 0.169 mmol), triethylamine (0.059 mL, 0.423 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (64 mg, 0.169 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 8:5:2 CH_2Cl_2:hexane:methanol), also in an analogous manner, afforded the title compound (62 mg, 0.120 mmol) as a yellow powder in 85% yield.

^{1}H NMR (d_6-DMSO): δ 12.15 (s, 1H), 10.37 (s, 1H), 10.06 (s, 1H), 8.20 (s, 1H), 7.70-7.46 (m, 7H), 3.96-3.87 (m, 2H), 2.75-2.63 (m, 2H), 2.42-2.34 (m, 2H), 1.72-1.55 (m, 5H), 1.40 (s, 9H), 1.06-0.98 (m, 2H).

LCMS: $(M+H^+)$ 416.3, $(M+Na^+)$ 538.3.

Example 89: (E)-*N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-acrylamide



Preparation of example 89 from the title compound of Example 7 (hydrochloride) (40 mg, 0.128 mmol), (*E*)-3-phenyl-acrylic acid (23 mg, 0.154 mmol), triethylamine (0.054 mL, 0.384 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (59 mg, 0.154 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 2:1 hexane:acetone), also in an analogous manner, after a final trituration with methanol afforded the title compound (47 mg, 0.116 mmol) as a yellow powder in 90% yield.

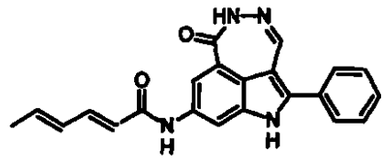
^{1}H NMR (d_6-DMSO): δ 12.14 (s, 1H), 10.43 (s, 1H), 10.40 (s, 1H), 8.38 (s, 1H), 7.71-7.40 (m, 13H), 6.87 (d, 1H, J = 16.2 Hz).

LCMS: $(M+H^+)$ 407.1, $(M+Na^+)$ 429.0, $(M-H^-)$ 405.2.

Anal. Calcd. for $C_{25}H_{18}N_4O_2 \cdot 2.7\ H_2O$: C, 65.98; H, 5.18; N, 12.31.

Found: C, 65.62; H, 4.63; N, 12.10.

Example 90: (2E,4E)-Hexa-2,4-dienoic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

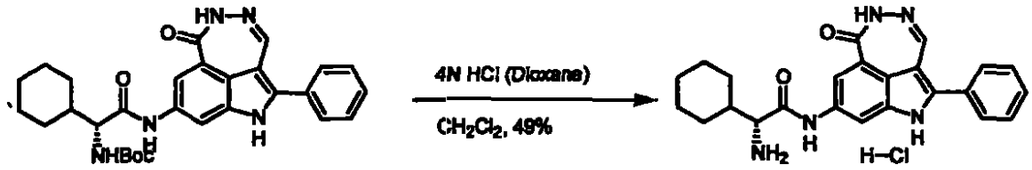


Preparation of example 90 from the title compound of Example 7 (hydrochloride) (41 mg, 0.131 mmol), (2E,4E)-hexa-2,4-dienoic acid (18 mg, 0.157 mmol), triethylamine (0.055 mL, 0.393 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (60 mg, 0.157 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 2:1 hexane:acetone), also in an analogous manner, after a final trituration with methanol afforded the title compound (8 mg, 0.022 mmol) as a yellow powder in 16% yield.

^{1}H NMR (d_6-DMSO): δ 12.13 (s, 1H), 10.38 (s, 1H), 10.21 (s, 1H), 8.30 (s, 1H), 7.71-7.48 (m, 7H), 7.15 (m, 1H), 6.38-6.07 (m, 3H), 1.84 (d, 3H, J = 5.8 Hz).

LCMS: ($M+H^+$) 371.1, ($M+Na^+$) 393.0.

Example 91: (2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide(hydrochloride)



The title compound of Example 59 (210mg, 0.41 mmol) was treated with 4M HCl in dioxane and allowed to stir tightly capped as a slurry for about 4 hours after which the volatile components were evaporated and diethyl ether was added and evaporated several times. The resulting solids were dissolved in methanol, precipitated with diethyl ether, and collected to afford the title compound (161 mg, 0.36 mmol) as a yellow powder in 87% yield.

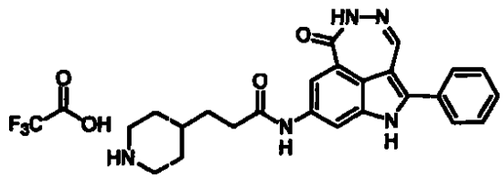
^{1}H NMR (d_6-DMSO): δ 12.27 (s, 1H), 10.83 (s, 1H), 10.44 (s, 1H), 8.36 (br s, 2H), 8.13 (s, 1H), 7.78-7.64 (m, 3H), 7.63-7.48 (m, 4H), 3.81 (br s, 1H), 1.91-1.58 (m, 6H), 1.31-1.00 (m, 5H).

LCMS: ($M+H^+$) 416.1,($M+Na^+$) 438.2.

Anal. Calcd. for $C_{24}H_{25}N_5O_2 \cdot 1.5\ HCl \cdot 2.0\ H_2O$: C, 56.94; H, 6.07; N, 13.84.

Found: C, 57.20; H, 6.01; N, 13.57.

Example 92: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-piperidin-4-yl-propionamide: compound with trifluoro-acetic acid

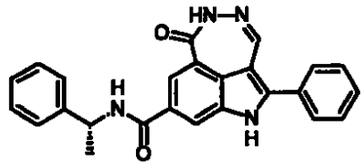


Preparation of example 92 from title compound of Example **88** (52 mg, 0.101 mmol) and 45% TFA in CH_2Cl_2 (1 mL) was carried out analogously to Example **20**. Isolation, also in an analogous manner, afforded the title compound (50 mg, 0.084 mmol) as a yellow powder in 82% yield.

^{1}H NMR (d_6-DMSO): δ 12.07 (s, 1H), 10.38 (s, 1H), 10.09 (s, 1H), 8.45 (br s, 1H), 8.17 (s, 1H), 7.70-7.44 (m, 7H), 3.31-3.20 (m, 2H, partially obscurred), 2.93-2.76 (m, 2H), 2.41-2.31 (m, 2H), 1.91-1.76 (m, 2H), 1.64-1.49 (m, 3H), 1.38-1.19 (m, 2H).

Anal. Calcd. for $C_{24}H_{25}N_5O_2 \cdot 1.5\ TFA \cdot 0.8\ H_2O$: C, 53.64; H, 4.75; N, 11.58.
Found: C, 53.59; H, 4.74; N, 11.55.

Example 93: 6-Oxo-2-phenyl-*N*-[(1*R*)-1-phenylethyl]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

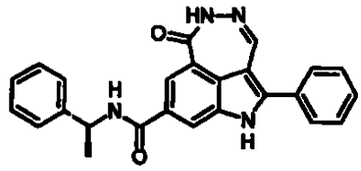


Preparation of example 93 from the title compound of Example **49** (0.105 g, 0.306 mmol), (1*R*)-1-phenylethylamine (0.0742 g, 0.612 mmol), triethylamine (0.085 mL, 0.612 mmol), and O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (0.233 g, 0.612 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0235 g) as a yellow powder in 19% yield.

^{1}H NMR (d_6-DMSO): δ 12.44 (s, 1H), 10.46 (s, 1H), 9.03 (d, 1H, *J* = 7.9 Hz), 8.14 (s, 1H), 8.04 (s, 1H), 7.70 (d, 2H, *J* = 6.8 Hz), 7.51-7.62 (m, 4H), 7.42 (d, 2H, *J* = 7.2 Hz), 7.30-7.36 (m, 2H), 7.20-7.24 (m, 1H), 5.16-5.25 (m, 1H), 1.50 (d, 3H, *J* = 7.2 Hz).

HRMS calculated for $C_{25}H_{21}N_4O_2$ 409.1665 (M+H), found 409.1666.

Example 94: 6-Oxo-2-phenyl-*N*-[(1*S*)-1-phenylethyl]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

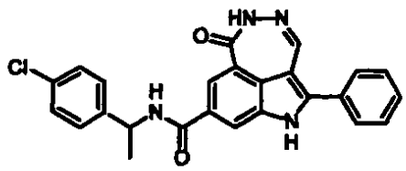


Preparation of example 94 from the title compound of Example 49 (0.0976 g, 0.284 mmol), (1*S*)-1-phenylethylamine (0.0688 g, 0.568 mmol), triethylamine (0.079 mL, 0.568 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.216 g, 0.568 mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0197 g) as a yellow powder in 17% yield.

^1H NMR (d_6-DMSO): δ 12.44 (s, 1H), 10.46 (s, 1H), 9.04 (d, 1H, *J* = 7.9 Hz), 8.14 (s, 1H), 8.03 (s, 1H), 7.70 (d, 2H, *J* = 8.3 Hz), 7.51-7.62 (m, 4H), 7.42 (d, 2H, *J* = 7.2 Hz), 7.30-7.36 (m, 2H), 7.20-7.24 (m, 1H), 5.16-5.25 (m, 1H), 1.50 (d, 3H, *J* = 7.2 Hz).

HRMS calculated for $C_{25}H_{21}N_4O_2$ 409.1665 (M+H), found 409.1666.

Example 95: *N*-[1-(4-Chlorophenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

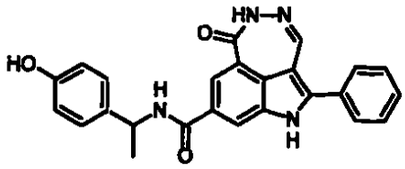


Preparation of example 95 from the title compound of Example 49 (0.104 g, 0.303 mmol), 1-(4-chlorophenyl)ethylamine (0.0943 g, 0.606 mmol), triethylamine (0.084 mL, 0.606 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.606 mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0025 g) as a yellow powder in 1.9% yield.

^1H NMR (d_6-DMSO): δ 12.45 (s, 1H), 10.47 (s, 1H), 9.06 (d, 1H, *J* = 7.9 Hz), 8.14 (s, 1H), 8.03 (s, 1H), 7.70 (d, 2H, *J* = 7.9 Hz), 7.51-7.62 (m, 4H), 7.38-7.44 (m, 4H), 5.13-5.22 (m, 1H), 1.49 (d, 3H, *J* = 7.2 Hz).

HRMS calculated for $C_{25}H_{20}N_4O_2Cl$ 443.1275 (M+H), found 443.1265.

Example 96: *N*-[1-(4-Hydroxyphenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

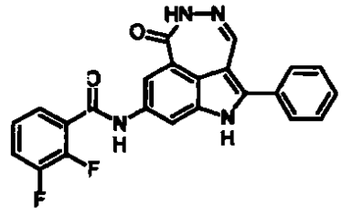


Preparation of example 96 from the title compound of Example 49 (0.104 g, 0.303 mmol), 1-(4-hydroxyphenyl)ethylamine (0.0831 g, 0.606 mmol), triethylamine (0.084 mL, 0.606 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.606 mmol) in DMSO (2 mL) was carried out analogously to Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0205 g) as a yellow powder in 16% yield.

^1H NMR (d_6-DMSO): δ 12.42 (s, 1H), 10.45 (s, 1H), 9.21 (br s, 1H), 8.91 (d, 1H, J = 8.3 Hz), 8.11 (s, 1H), 8.02 (s, 1H), 7.70 (d, 2H, J = 6.8 Hz), 7.51-7.61 (m, 4H), 7.21 (d, 2H, J = 8.3 Hz), 6.71 (d, 2H, J = 8.3 Hz), 5.08-5.16 (m, 1H), 1.46 (d, 3H, J = 7.2 Hz).

HRMS calculated for $C_{25}H_{21}N_4O_3$ 425.1614 (M+H), found 425.1626.

Example 97: 2,3-Difluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide

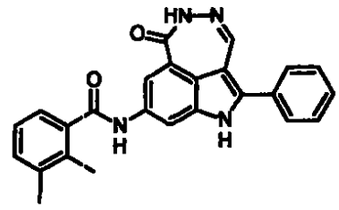


Preparation of example 97 from the title compound of Example 7 (hydrochloride) (40 mg, 0.128 mmol), 2,3-difluoro-benzoic acid (24 mg, 0.154 mmol), triethylamine (0.054 mL, 0.384 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (59 mg, 0.154 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 2:1 hexane:acetone increasing to 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (24 mg, 0.058 mmol) as a yellow powder in 45% yield.

^1H NMR (d_6-DMSO): δ 12.20 (s, 1H), 10.72 (s, 1H), 10.42 (s, 1H), 8.24 (s, 1H), 7.81 (s, 1H), 7.72-7.45 (m, 8H), 7.37 (m, 1H).

LCMS: ($M+H^+$) 417.0, ($M+Na^+$) 439.1.

Example 98: 2,3-Dimethyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide

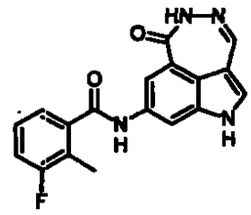


Preparation of example 98 from the title compound of Example 7 (hydrochloride) (42 mg, 0.134 mmol), 2,3-dimethyl-benzoic acid (24 mg, 0.161 mmol), triethylamine (0.056 mL, 0.402 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (61 mg, 0.161 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. The mixture was stirred as a thick slurry and additional 2,3-dimethyl-benzoic acid (12 mg, 0.08 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (30 mg, 0.08 mmol) were added after 48 hours to drive the reaction to completion. The mixture was filtered to collect the solids which were then washed with methanol. After drying the solids under high vacuum, the title compound (32 mg, 0.078 mmol) was obtained as a yellow powder in 58% yield.

^{1}H NMR (d_6-DMSO): δ 12.14 (s, 1H), 10.47 (s, 1H), 10.39 (s, 1H), 8.25 (s, 1H), 7.86 (m, 1H), 7.72-7.66 (m, 2H), 7.63-7.49 (m, 4H), 7.33-7.25 (m, 2H), 7.21 (m, 1H), 2.31 (s, 3H), 2.29 (s, 3H).

LCMS: ($M+H^+$) 409.1, ($M+Na^+$) 431.1.

Example 99: 3-Fluoro-2-methyl-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide



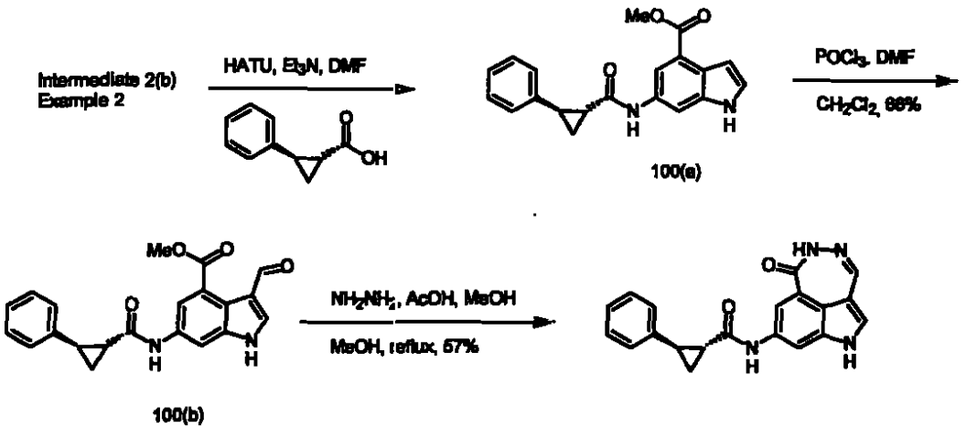
Preparation of example 99 from title compound of Example 2 (21 mg, 0.105 mmol), 3-fluoro-2-methyl-benzoic acid (19 mg, 0.126 mmol), triethylamine (0.044 mL, 0.315 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (48 mg, 0.126 mmol) in CH_2Cl_2 (0.2 mL) and *N,N*-dimethylformamide (0.2 mL) was carried out analogously to Example 11. The mixture was stirred as a thick slurry and additional 3-fluoro-2-methyl-benzoic acid (11 mg, 0.07 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (27 mg, 0.07 mmol) were added after 24 hours to drive the reaction to completion. Purification, also in an analogous manner, except that it required two successive silica gel chromatographies

(both eluted with 2:1 hexane:acetone increasing to 1:1 hexane:acetone) afforded the title compound (14 mg, 0.042 mmol) as a yellow powder in 40% yield.

^{1}H NMR (d_6-DMSO): δ 11.79 (s, 1H), 10.50 (s, 1H), 10.25 (s, 1H), 8.20 (s, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.49 (s, 1H), 7.46-7.17 (m, 3H), 2.30 (s, 3H).

LCMS: ($M+H^+$) 337.1, ($M+Na^+$) 359.1.

Example 100: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1. Preparation of 6-[((1R,2R)-2-Phenyl-cyclopropanecarbonyl)-amino]-1*H*-indole-4-carboxylic acid methyl ester 100(a)

Preparation of intermediate 100(a) from Intermediate 2(b) of Example 2 (111 mg, 0.49 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (119 mg, 0.73 mmol), triethylamine (0.273 mL, 1.96 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (278 mg, 0.73 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ afforded crude Intermediate 100(a) (222 mg) as a tan solid which was carried on without purification.

Step 2. Preparation of 3-Formyl-6-[((1R,2R)-2-phenyl-cyclopropanecarbonyl)-amino]-1*H*-indole-4-carboxylic acid methyl ester 100(b)

Intermediate 100(a) (214 mg) was dissolved in CH_2Cl_2 (3 mL) and *N,N*-dimethylformamide (0.2 mL) and treated with Vilsmeier reagent (0.147 mL) in a manner similar to that described for Example 3, Step 4. Upon addition, an immediate precipitate formed causing a thick slurry. Additional CH_2Cl_2 (5.0 mL) and *N,N*-dimethylformamide (0.2 mL) was added to facilitate stirring. Additional Vilsmeier reagent (0.147 mL) was also added. After c.a. 10 min, hexane was added, and the solids were allowed to settle. After decanting the supernatant, additional hexane was added and the trituration was repeated- discarding both triturates. To the remaining solids, methanol (8 mL) was added along with K_2CO_3 (750 mg, 5.43 mmol) and H_2O (4 mL), and the

mixture was allowed to stir. After c.a. 30 min, ethyl acetate was added and the K_2CO_3/H_2O aggregates were removed by decanting the product away in solution. The solvents were then reduced in volume, additional ethyl acetate was added, and the product was subjected to extractive work-up to afford Intemediate 100(b) (117 mg, 0.32 mmol) as a brownish powder in about a 66% combined, crude yield over steps 1 and 2.

Step 3. Preparation of Title Compound: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

Intermediate 100(b) (105 mg), acetic acid (0.048 mL, 0.84 mmol) and $H_2NNH_2 \cdot H_2O$ (0.084 mL, 1.74 mmol) in anhydrous methanol (4.4 mL) were refluxed in manner similar to that described for Example 3, Step 5. The crude product was purified on silica gel eluting with 2:1 then 1:1 hexane:acetone to afford the title compound (61 mg, 0.17 mmol) in about a 57% yield for the last step.

^{1}H NMR (d_6-DMSO): δ 11.74 (s, 1H), 10.38 (s, 1H), 10.23 (s, 1H), 8.13 (s, 1H), 7.60-7.53 (m, 2H), 7.46 (s, 1H), 7.35-7.26 (m, 2H), 7.24-7.15 (m, 3H), 2.38 (m, 1H), 2.08 (m, 1H), 1.50 (m, 1H), 1.36 (m, 1H).

LCMS: ($M+H^+$) 345.2, ($M+Na^+$) 367.1.

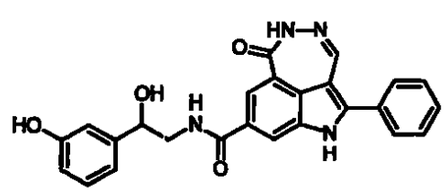
Anal. Calcd. for $C_{20}H_{16}N_4O_2 \cdot 0.6\ H_2O \cdot 0.1$ methanol $\cdot 0.1\ CH_2Cl_2$: C, 66.13; H, 4.89; N, 15.27.

Found: C, 66.19; H, 5.03; N, 15.07.

Altenative Method for the Preparation of Example 100.

Preparation of example 100 from the title compound of Example 2 (3.0 g, 12.7 mmol), (1*R*,2*R*)-2-phenylcyclopropanecarboxylic acid (2.36 g, 14.6 mmol) (prepared as described by A. Thurkauf, et al. (2000) J. Med. Chem. 43:3923-3932), triethylamine (8.8 mL, 63.4 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (5.3 g, 14.5 mmol) in *N,N*-dimethylformamide (30.0 mL, 0.4 M) was carried out analogously to Example 11. Silica gel chromatography (5:50:45 methanol/ethyl acetate/CH_2Cl_2), also in an analogous manner, afforded the title compound (3.67 g, 10.7 mmol) as a yellow powder in 84% yield.

Example 101: *N*-[2-Hydroxy-2-(3-hydroxyphenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide



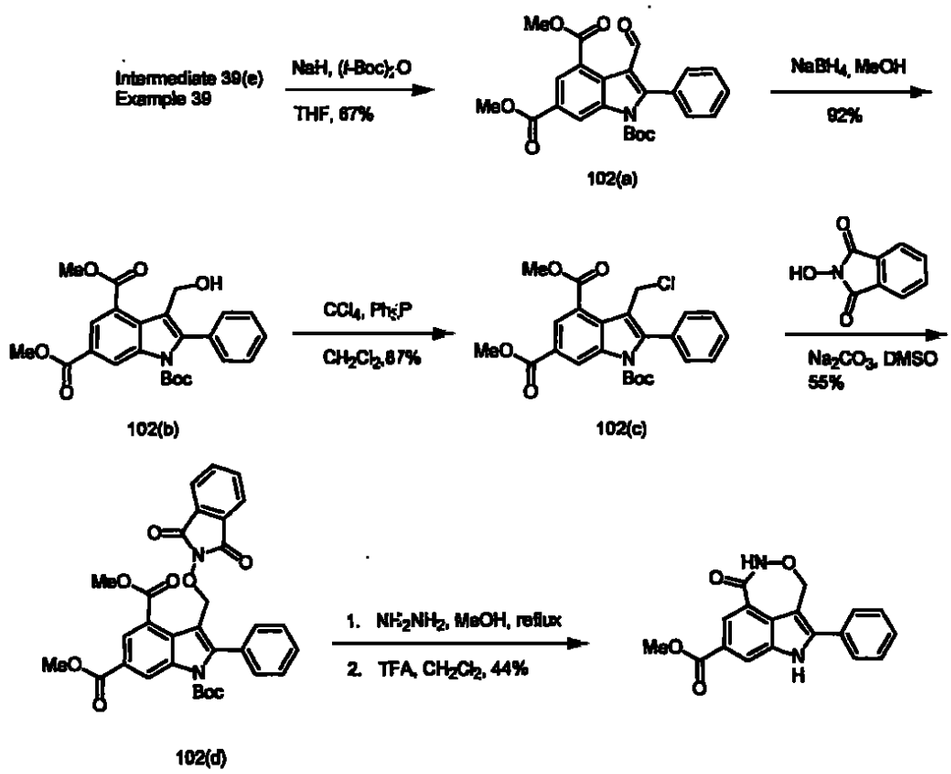
Preparation of example 101 from the title compound of Example 49 (0.238 g, 0.693 mmol), 2-hydroxy-2-(3-hydroxyphenyl)ethylamine hydrochloride (0.264 g, 1.39 mmol), triethylamine (0.29

mL, 2.08 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.528 g, 1.39 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0414 g) as a yellow powder in 14% yield.

^{1}H NMR (d_6-DMSO): δ 12.47 (s, 1H), 10.45 (s, 1H), 9.27 (br s, 1H), 8.68 (t, 1H, *J* = 5.7 Hz), 8.10 (s, 1H), 8.02 (s, 1H), 7.71 (d, 2H, *J* = 7.2 Hz), 7.51-7.62 (m, 4H), 7.08-7.13 (m, 1H), 6.76-6.81 (m, 2H), 6.61-6.64 (m, 1H), 4.70-4.74 (m, 1H).

HRMS calculated for $C_{25}H_{21}N_4O_4$ 441.1563 (M+H), found 441.1543.

Example 102: Methyl-6-oxo-2-phenyl-1,3,5,6-tetrahydro[1,2]oxazepino[6,5,4-*cd*]indole-8-carboxylate



Step 1. Preparation of 1-*tert*-butyl-4,6-dimethyl-3-formyl-2-phenyl-1*H*-indole-1,4,6-tricarboxylate 102(a)

To a solution of Intermediate 39(e) of Example 39 (2.25 g, 6.7 mmol), and di-*tert*-butyl dicarbonate (11.68 g, 54 mmol) in 150 ml of tetrahydrofuran was added a 60% suspension of NaH in mineral oil (1.60 g, 40 mmol). The reaction mixture was stirred at room temperature for 1 hour. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ followed by silica gel chromatography afforded Intermediate 102(a) (1.97 g), in 67% yield.

^{1}H NMR (d_6-DMSO): δ 9.56 (s, 1H), 8.96 (s, 1H), 8.08 (s, 1H), 7.70-7.50 (m, 5H), 3.93 (s, 3H), 3.83 (s, 3H), 1.20 (s, 9H).

Step 2. Preparation of 1-(*tert*-Butoxycarbonyl)-3-(hydroxymethyl)-6-(methoxycarbonyl)-2-phenyl-1*H*-indole-4-carboxylic acid 102(b)

Intermediate 102(a) (1.95 g) was dissolved in methanol (200 mL) and $NaBH_4$ (1.70 g) was added and stirred for 15 min. After removing solvent, silica gel chromatography afforded Intermediate 102(b) (1.81 g) in 92% yield.

^{1}H NMR (d_6-DMSO): δ 8.97 (d, 1H, *J* = 1.5 Hz), 8.10 (d, 1H, H=1.5 Hz), 7.35-7.55 (m, 5H), 4.61 (t, 1H, *J* = 5.1 Hz), 4.41 (d, 2H, *J* = 5.0 Hz), 3.92 (s, 3H), 3.87 (s, 3H), 1.16 (s, 9H).

Step 3. Preparation of 1-*tert*-Butyl-4,6-dimethyl-3-(chloromethyl)-2-phenyl-1*H*-indole-1,4,6-tricarboxylate 102(c)

To a solution of Intermediate 102(b) (1.88 g, 3.8 mmol) and CCl_4 (3.50 g, 23 mmol) in 20 ml of dichloromethane was added Ph_3P (2.42 g, 9.2 mmol). The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated, and residue was purified using silica gel chromatography to afford Intermediate 102(c) (1.53 g) in 87% yield.

^{1}H NMR (d_6-DMSO): δ 8.97 (d, 1H, *J* = 1.5 Hz), 8.10 (d, 1H, *J* = 1.5 Hz), 7.35-7.55 (m, 5H), 4.61 (t, 1H, *J* = 5.1 Hz), 4.41 (d, 2H, *J* = 5.0 Hz), 3.92 (s, 3H), 3.87 (s, 3H), 1.16 (s, 9H).

Step 4. Preparation of 1-*tert*-Butyl 4,6-dimethyl 3-{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-2-phenyl-1*H*-indole-1,4,6-tricarboxylate 102(d)

A mixture of Intermediate 102(c) (0.23 g, 0.5 mmol), *N*-hydroxyphthalimide (0.24 g, 1.5 mmol) and Na_2CO_3 (0.32 g, 3 mmol) was stirred in anhydrous DMSO (10 mL) at room temperature overnight. Extractive work-up from ethyl acetate, followed by silica gel chromatography afforded Intermediate 102(d) (0.16 g) in 55% yield.

^{1}H NMR (d_6-DMSO): δ 9.02 (d, 1H, *J* = 1.1 Hz), 8.31 (d, 1H, H=1.1 Hz), 7.75-7.82 (m, 2H), 7.64-7.71(m, 2H), 7.39 (t, 1H, *J* = 7.6 Hz), 7.26 (t, 2H, *J* = 7.6), 7.18 (d, 2H, *J* = 7.8 Hz), 5.32 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 1.11 (s, 9H).

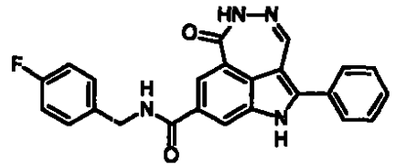
Step 5. Preparation of Title Compound Methyl-6-oxo-2-phenyl-1,3,5,6-tetrahydro[1,2]oxazepino[6,5,4-*cd*]indole-8-carboxylate

A mixture of Intermediate 102(d) (0.15 g, 0.26 mmol) and hydrazine (0.20 g, 6.3 mmol) in methanol (15 mL) was refluxed for 2 hours. After solvent evaporation, the residue was mixed with CH_2Cl_2 (15 ml) and trifluoroacetic acid (7.5 ml) and stirred for 2 hours. After solvent removal, the residue was subjected to reverse-phase preparative HPLC affording the title compound (34.8 mg) in 42% yield.

^{1}H NMR (d_6-DMSO): δ 12.20 (s, 1H), 11.23 (s, 1H), 8.30 (d, 1H, *J* = 1.2 Hz), 8.21 (d, 1H, H=1.2 Hz), 7.40-7.75 (m, 5H), 5.44 (d, 1H, *J* = 14.7 Hz), 5.22 (d, 1H, *J* = 14.7 Hz), 3.92 (s, 3H).

LCMS (M^++1): 323.0

Example 103: *N*-(4-Fluorobenzyl)-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

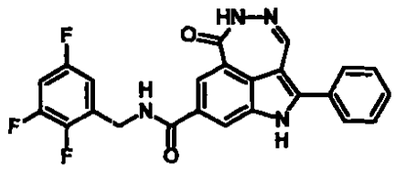


Preparation of example 103 from the title compound of Example **49** (0.108 g, 0.314 mmol), 4-fluorobenzylamine (0.079 g, 0.628 mmol), triethylamine (0.088 mL, 0.628 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.239 g, 0.628 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0121 g) as a yellow powder in 9.3% yield.

^1H NMR (d_6-DMSO): δ 12.47 (s, 1H), 10.47 (s, 1H), 9.23 (t, 1H, J = 5.9 Hz), 8.13 (s, 1H), 8.05 (s, 1H), 7.71 (d, 2H, J = 6.8 Hz), 7.51-7.63 (m, 4H), 7.35-7.40 (m, 2H), 7.12-7.18 (m, 2H), 4.46 (d, 2H, J = 5.7 Hz).

HRMS calculated for $C_{24}H_{18}N_4O_2F$ 413.1414 (M+H), found 413.1394.

Example 104: 6-Oxo-2-phenyl-*N*-(2,3,5-trifluorobenzyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

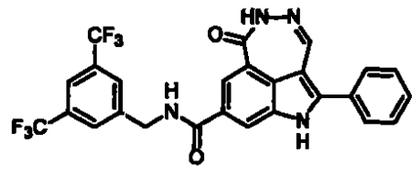


Preparation of example 104 from the title compound of Example **49** (0.101 g, 0.294 mmol), 2,3,5-trifluorobenzylamine (0.0947 g, 0.588 mmol), triethylamine (0.082 mL, 0.588 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.224 g, 0.588 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.006 g) as a yellow powder in 4.5% yield.

^1H NMR (d_6-DMSO): δ 12.50 (s, 1H), 10.49 (s, 1H), 9.27 (t, 1H, J = 5.9 Hz), 8.13 (s, 1H), 8.05 (s, 1H), 7.71 (d, 2H, J = 6.8 Hz), 7.52-7.62 (m, 4H), 7.40-7.48 (m, 1H), 7.05-7.08 (m, 1H), 4.56 (d, 2H, J = 4.9 Hz).

HRMS calculated for $C_{24}H_{16}N_4O_2F_3$ 449.1225 (M+H), found 449.1209.

Example 105: *N*-[3,5-Bis(trifluoromethyl)benzyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

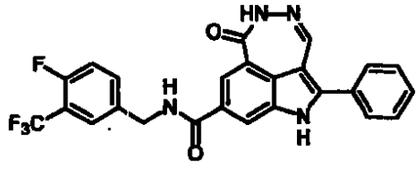


Preparation of example 105 from the title compound of Example **49** (0.101 g, 0.294 mmol), 3,5-bis(trifluoromethyl)benzylamine (0.143 g, 0.588 mmol), triethylamine (0.082 mL, 0.588 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.224 g, 0.588 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.004 g) as a yellow powder in 2.6% yield.

^1H NMR (d_6-DMSO): δ 12.50 (s, 1H), 10.50 (s, 1H), 9.37 (t, 1H, J = 5.9 Hz), 8.14 (s, 1H), 8.05 (m, 3H), 8.00 (s, 1H), 7.71 (d, 2H, J = 8.3 Hz), 7.52-7.62 (m, 4H), 4.67 (d, 2H, J = 5.7 Hz).

HRMS calculated for $C_{26}H_{17}N_4O_2F_6$ 531.1256 (M+H), found 531.1272.

Example 106: *N*-[4-Fluoro-3-(trifluoromethyl)benzyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

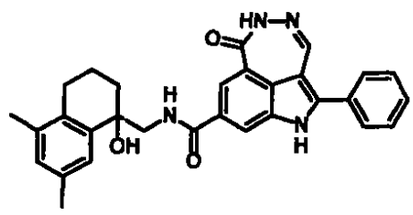


Preparation of example 106 from the title compound of Example **49** (0.105 g, 0.306 mmol), 4-fluoro-3- (trifluoromethyl)benzylamine (0.118 g, 0.612 mmol), triethylamine (0.085 mL, 0.612 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.233 g, 0.612 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0205 g) as a yellow powder in 14% yield.

^1H NMR (d_6-DMSO): δ 12.49 (s, 1H), 10.48 (s, 1H), 9.30 (t, 1H, J = 5.9 Hz), 8.13 (s, 1H), 8.05 (m, 3H), 7.69-7.75 (m, 4H), 7.45-7.63 (m, 5H), 4.53 (d, 2H, J = 5.7 Hz).

HRMS calculated for $C_{25}H_{17}N_4O_2F_4$ 481.1287 (M+H), found 481.1291.

Example 107: *N*-[(1-Hydroxy-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

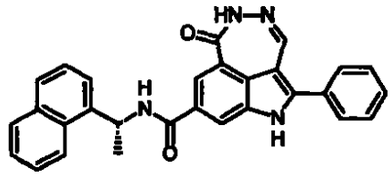


Preparation of example 107 from the title compound of Example **49** (0.104 g, 0.303 mmol), 1-(aminomethyl)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (0.124 g, 0.606 mmol), triethylamine (0.084 mL, 0.606 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.606 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid) also in an analogous manner afforded the title compound (0.0145 g) as a yellow powder in 9.7% yield.

^1H NMR (d_6-DMSO): δ 12.47 (s, 1H), 10.48 (s, 1H), 8.48-8.52 (m, 1H), 8.10 (s, 1H), 8.03 (s, 1H), 7.70-7.73 (m, 2H), 7.52-7.62 (m, 4H), 7.25 (s, 1H), 6.86 (s, 1H), 3.66-3.73 (m, 2H), 2.55-2.63 (m, 2H), 2.22 (s, 3H), 2.14 (s, 3H), 1.81-1.98 (m, 4H).

HRMS calculated for $C_{30}H_{29}N_4O_3$ 493.2240 (M+H), found 493.2252.

Example 108: *N*-[(1R)-1-(1-Naphthyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide

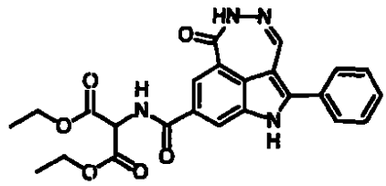


Preparation of example 108 from the title compound of Example **49** (0.105 g, 0.306 mmol), 1-(1-naphthyl)ethylamine (0.105 g, 0.612 mmol), triethylamine (0.085 mL, 0.612 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.233 g, 0.612 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0161 g) as a yellow powder in 12% yield.

^1H NMR (d_6-DMSO): δ 12.44 (s, 1H), 10.46 (s, 1H), 9.14 (d, 1H, J = 7.9 Hz), 8.17 (s, 1H), 8.05 (s, 1H), 7.87-7.90 (m, 4H), 7.69-7.72 (m, 2H), 7.46-7.63 (m, 7H), 5.34-5.140 (m, 1H), 1.61 (d, 3H, J = 6.8 Hz).

HRMS calculated for $C_{29}H_{23}N_4O_2$ 459.1821 (M+H), found 459.1795.

Example 109: Diethyl 2-[[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)carbonyl]amino]malonate

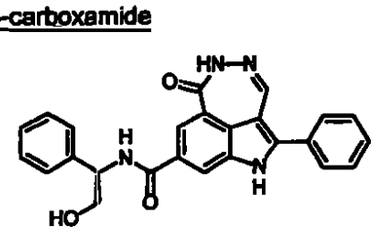


Preparation of example 109 from the title compound of Example **49** (0.106 g, 0.309 mmol), diethyl 2-aminomalonate hydrochloride (0.131 g, 0.618 mmol), triethylamine (0.129 mL, 0.926 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.235 g, 0.618 mmol) in DMSO (2 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0064 g) as a yellow powder in 4.5% yield.

^1H NMR (d_6-DMSO): δ 12.53 (s, 1H), 10.50 (s, 1H), 9.55 (t, 1H, J = 7.6 Hz), 8.14 (s, 1H), 8.07 (s, 1H), 7.71-7.73 (m, 2H), 7.52-7.62 (m, 4H), 5.29-5.32 (m, 2H), 4.15-4.25 (m, 4H), 1.23 (t, 6H, J = 7.2 Hz).

HRMS calculated for $C_{24}H_{23}N_4O_6$ 463.1618 (M+H), found 463.1606.

Example 110: *N*-[(1R)-2-Hydroxy-1-phenylethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide



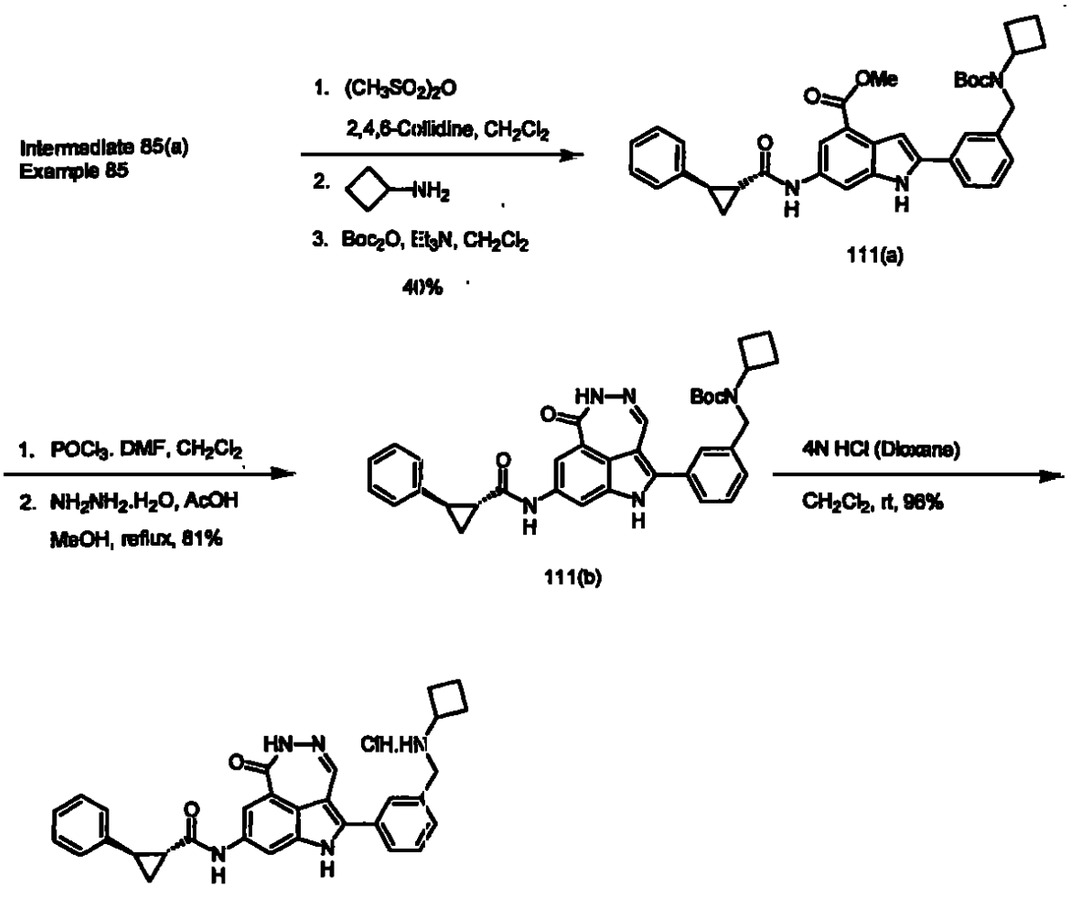
Preparation of example 110 from the title compound of Example **49** (0.17 g, 0.5 mmol), (2*R*)-2-amino-2-phenylethanol (0.0822 g, 0.6 mmol), triethylamine (0.14 mL, 1 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.6 mmol) in DMSO (8 mL) was carried out analogously to Example **76**. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.0351 g) in 17% yield.

^1H NMR (d_6-DMSO): δ 12.45 (s, 1H), 10.47 (s, 1H), 8.92 (d, 1H, J = 7.9 Hz), 8.17 (s, 1H), 8.04 (s, 1H), 7.75-7.65 (m, 2H), 7.65-7.50 (m, 4H), 7.45-7.37 (m, 2H), 7.37-7.27 (m, 2H), 7.27-7.15 (m, 1H), 5.18-5.01 (m, 1H), 3.83-3.60 (m, 2H).

LCMS: $(M+H^+)$ 425.1

Anal. Calcd. for $C_{25}H_{20}N_4O_3$ • 0.2 trifluoroacetic acid • 1.68 H_2O: C, 63.88; H, 4.97; N, 11.73. Found: C, 63.86; H, 4.97; N, 11.66.

Example 111: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-cyclobutylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt)



Step 1. Preparation of (1R,2R)- 2-[3-[(*tert*-Butoxycarbonyl-cyclobutyl-amino)-methyl]-phenyl]-6-[(2-phenyl-cyclopropanecarbonyl)-amino]-1*H*-indole-4-carboxylic acid methyl ester 111(a)

To a suspension of Intermediate 85(a) of Example 85 (0.260 g, 0.6 mmol) in dichloromethane (6.0 mL, 0.1 M) was added 2,4,6-Collidine (0.312 mL, 2.4 mmol) followed by $(CH_3SO_2)_2O$ (0.123 g, 0.7 mmol). After stirring for 1 hour, cyclobutylamine (0.252 mL, 3.0 mmol) was added, and the reaction mixture stirred for 24 hours at 22 °C. The volatiles were removed *in vacuo* and dichloromethane (6.0 mL), triethylamine (3 mmol) and di-*tert*-butyl dicarbonate (1.2 mmol) were added. The mixture was stirred at 22 °C for 12 hours and volatiles were removed *in vacuo*. Silica gel chromatography provided Intermediate 111(a) (0.14 g, 0.24 mmol) in 40% yield.

^{1}H-NMR (d_6-DMSO): δ 11.82 (s, 1H), 10.42 (s, 1H), 8.27 (s, 1H), 7.89 (d, 1H, J = 1.6 Hz), 7.72 (d, 1H, J = 8.1 Hz), 7.67 (s, 1H), 7.44 (dd, 1H, J = 7.7, 7.6 Hz), 7.36-7.08 (m, 7H), 4.51 (s, 2H), 3.91 (s, 3H), 2.45-2.37 (m, 1H), 2.14-1.95 (m, 5H), 1.62-1.22 (m, 14H).

Step 2. Preparation of (1R,2R)-Cyclobutyl-(3-{6-oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl}-benzyl)-carbamic acid *tert*-butyl ester 111(b)

In a manner analogous to steps 4 and 5 of Example 3, Intermediate 111(a) (0.13 g, 0.22 mmol) was formylated and cyclized. After silica gel chromatography, Intermediate 111(b) (0.107 g, 0.18 mmol) was obtained as a yellow powder in 81% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.43 (s, 1H), 10.37 (s, 1H), 8.16 (d, 1H, *J* = 1.2 Hz), 7.63 (d, 1H, *J* = 1.4 Hz), 7.55-7.42 (m, 4H), 7.35-7.16 (m, 6H), 4.53 (s, 2H), 2.45-2.37 (m, 1H), 2.14-1.95 (m, 5H), 1.60-1.23 (m, 14H).

LCMS: ($M-H^+$) 602.2.

Step 3. Preparation of Title Compound: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-cyclobutylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt)

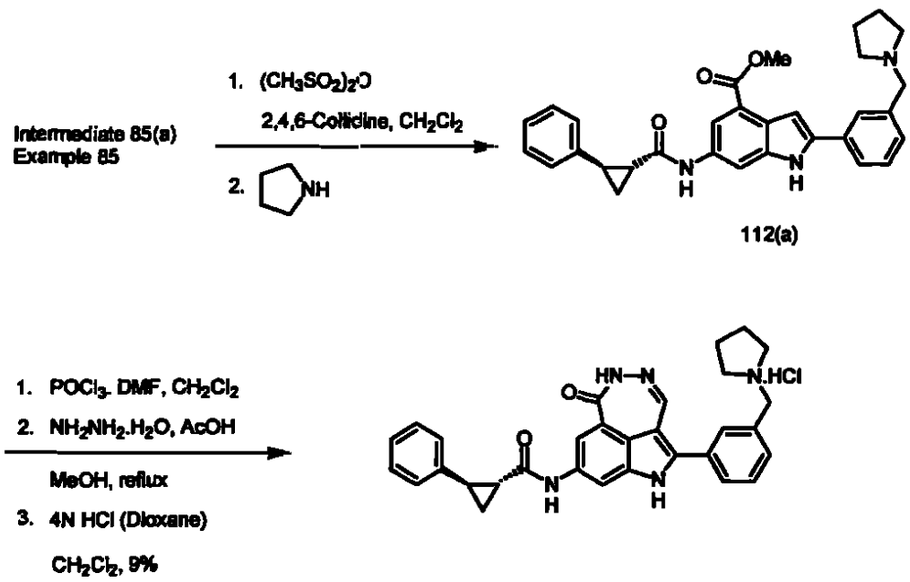
Preparation from Intermediate 111(b) (0.105 g, 0.17 mmol) and 4M HCl in dioxane (1.7 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2/diethyl ether and afforded the title compound (0.09 g, 0.17 mmol) as an orange/yellow powder in 96% yield.

^{1}H-NMR (d_6-DMSO): δ 12.20 (s, 1H), 10.49 (s, 1H), 10.43 (s, 1H), 9.32 (b, 1H), 8.18 (d, 1H, *J* = 1.4 Hz), 7.83 (s, 1H), 7.75-7.58 (m, 5H), 7.35-7.15 (m, 5H), 4.13 (s, 2H), 3.80-3.50 (buried m, 1H), 2.45-2.35 (m, 1H), 2.28-2.08 (m, 5H), 1.88-1.75 (m, 2H), 1.55-1.47 (m, 1H), 1.42-1.34 (m, 1H).

LCMS: ($M+H^+$) 504.2.

HRMS: ($M+H^+$) calcd for $C_{31}H_{30}N_5O_2$, 504.2400, found 504.2378.

Example 112: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-ylmethyl-phenyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt)



Step 1. Preparation of (1R,2R) 6-[(2-Phenyl-cyclopropanecarbonyl)-amino]-2-(3-pyrrolidin-1-ylmethyl-phenyl)-1*H*-indole-4-carboxylic acid methyl ester 112(a)

To a suspension of Intermediate 85(a) of Example **85** (0.260 g, 0.6 mmol) in dichloromethane (6.0 mL, 0.1 M) was added 2,4,6-Collidine (0.312 mL, 2.4 mmol) followed by $(CH_3SO_2)_2O$ (0.123 g, 0.7 mmol). After stirring for 1 hour, pyrrolidine (0.252 mL, 3.0 mmol) was added and the reaction mixture stirred for 24 hours at 22 °C. Volatiles were removed *in vacuo*, and the crude Intermediate 112(a) was carried on directly to the next step.

Step 2. Preparation of Title Compound: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-ylmethyl-phenyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt)

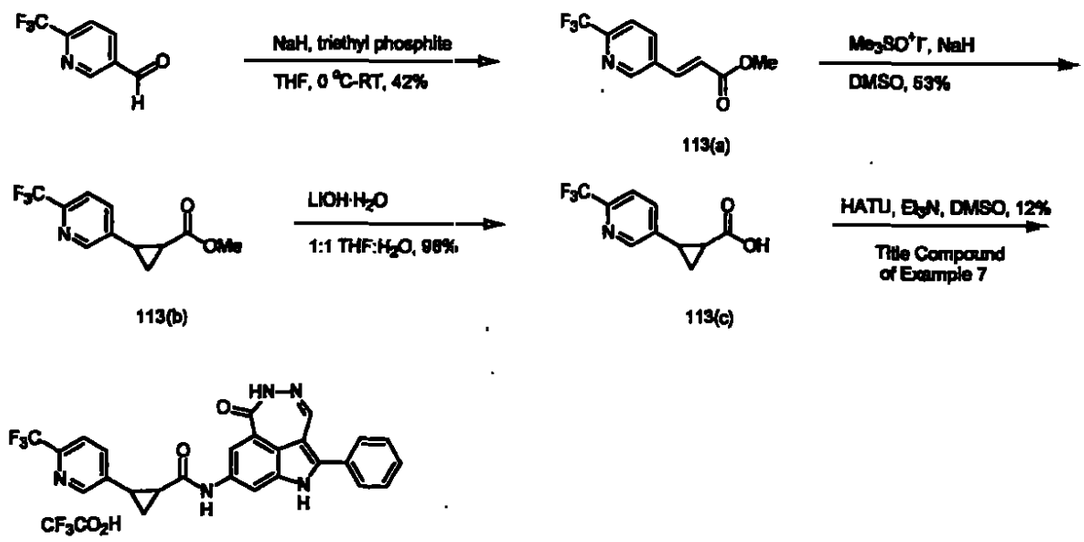
In a manner analogous to steps 4 and 5 of Example **3**, Intermediate 112(a) (0.42g, 0.85 mmol) was formylated and cyclized. Silica gel chromatography (90:10:0 to 70:20:10 CH_2Cl_2/2.0 M ammonia in isopropyl alcohol/methyl alcohol) and conversion to the HCl salt (4M HCl in dioxane) afforded the title compound (0.04 g, 0.18 mmol) as a yellow-orange powder in 9% yield.

^{1}H-NMR (d_6-DMSO): δ 12.20 (s, 1H), 10.55 (s, 1H), 10.49 (s, 1H), 10.43 (b, 1H), 8.19 (d, 1H, *J* = 1.3 Hz), 8.13 (s, 1H), 7.76-7.62 (m, 5H), 7.34-7.16 (m, 5H), 4.45 (d, 2H, *J* = 5.5 Hz), 3.45-3.35 (m, 2H), 3.19-3.07 (m, 2H), 2.45-2.35 (m, 1H), 2.14-1.85 (m, 5H), 1.55-1.47 (m, 1H), 1.42-1.34 (m, 1H).

LCMS: ($M+H^+$) 504.2.

HRMS: ($M+H^+$) calcd for $C_{31}H_{30}N_5O_2$, 504.2400, found 504.2404.

Example 113: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-[6-(trifluoromethyl)pyridin-3-yl]cyclopropanecarboxamide trifluoroacetate



Step 1. Preparation of 3-(6-Trifluoromethyl-pyridin-3-yl)-acrylic acid methyl ester 113(a)

To a solution of triethyl phosphite in anhydrous tetrahydrofuran (25 mL) cooled to 0 °C was added a 60% suspension of sodium hydride in mineral oil (472 mg, 19.7 mmol) in small portions. This mixture was allowed to stir for 30 min at the same low temperature at which point the cooling bath was removed, and the mixture was allowed to warm to room temperature over 60 min. The mixture was cooled again to 0 °C and a solution of 6-trifluoromethyl-3-pyridine carboxaldehyde in anhydrous tetrahydrofuran (20 mL) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature overnight. After 19 hours, the reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were dried over anhydrous magnesium sulfate and concentrated to a pale green oil. Purification was carried out using flash silica gel chromatography eluting with 5:95 then 1:9 ethyl acetate:hexane. Pure fractions were combined and concentrated to afford Intermediate 113(a) (1.68 g, 6.85 mmol) as a white solid in 42% yield.

Step 2. Preparation of (1,2-*trans*)-2-(6-Trifluoromethyl-pyridin-3-yl)-cyclopropanecarboxylic acid 113(b)

Trimethylsulfoxonium iodide (574 mg, 2.61 mmol) was added to 60% NaH in mineral oil (63 mg, 2.61 mmol), and the flask was purged with nitrogen. Methyl sulfoxide (10 mL) was added slowly over 20 minutes until evolution of hydrogen ceased. To this milky solution was added Intermediate 113(a) (493 mg, 2.01 mmol) in methyl sulfoxide (15 mL) dropwise. The solution was allowed to stir at room temperature overnight. After 26 hours the excess NaH was carefully quenched with water (100 mL). Ethyl ether (100 mL) was added and the layers separated. The aqueous layer was extracted with fresh ethyl ether (3 x 50 mL). The combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. Flash silica gel

chromatography of the crude residue eluting with 1:9 then 1:4 ethyl acetate:hexane gave two pure fractions that upon combining and concentrating under reduced pressure yielded Intermediate 113(b) (275 mg, 1.06 mmol) as white feathers in 53% yield.

Step 3. Preparation of (1,2-*trans*)-2-[6-(Trifluoromethyl)pyridin-3-yl]cyclopropanecarboxylic acid 113(c)

To a solution of Intermediate 113(b) (275 mg, 1.06 mmol) in a 1:1 mixture of tetrahydrofuran:water (4 mL) was added lithium hydroxide monohydrate (133 mg, 3.18 mmol). The semi-suspension was allowed to stir at room temperature over 2 days. The reaction mixture was acidified with 2M aqueous hydrochloric acid (c.a. 2 mL). The reaction mixture was then concentrated and lyophilized to obtain Intermediate 113(c) as a white powder containing lithium chloride which was carried on directly without further purification.

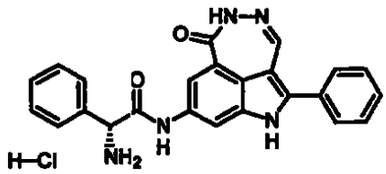
Step 4. Preparation of Title Compound: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-[6-(trifluoromethyl)pyridin-3-yl]cyclopropanecarboxamide trifluoroacetate

To a solution of Intermediate 113(c) (85 mg, 0.368 mmol) in methyl sulfoxide (2 mL) was added triethylamine (0.056 mL, 0.405 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (154 mg, 0.405 mmol). After c.a. 10 min, the title compound of Example 7 (0.102 g, 0.368 mmol) was added. The reaction was capped and stirred overnight at room temperature. The mixture was subjected to preparative HPLC (20-100% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were combined and lyophilized to afford the title compound (27 mg, 0.045 mmol) as an orange powder in 12% yield.

^{1}H-NMR (d_6-DMSO): δ 12.11 (b, 1H), 10.50 (b, 1H), 10.39 (b, 1H), 8.71 (b, 1H), 8.15 (b, 2H), 7.90-7.80 (m, 2H), 7.70-7.45 (m, 6H), 2.65-2.55 (m, 1H), 2.27-2.18 (m, 1H), 1.67-1.51 (m, 2H).

LCMS: (M+H$^+$) 490.1.

Example 114: (2R)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenyl-acetamide (hydrochloric salt)



Preparation of example 114 from the impure title compound of Example 117 (90 mg, 0.18 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example 91. Isolation, also in an analogous manner, afforded the title compound (65 mg, 0.10 mmol) as a yellow powder in 71% yield over two steps (including Example 117).

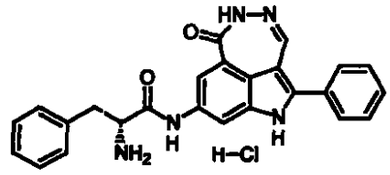
^{1}H NMR (d_6-DMSO): δ 12.26 (s, 1H, exchanges), 11.08 (s, 1H, exchanges), 10.42 (s, 1H, exchanges), 8.86 (br s, 3H, exchanges), 8.07 (s, 1H), 7.72-7.63 (m, 5H), 7.62-7.41 (m, 7H), 5.22 (m, 1H).

LCMS: ($M+H^+$) 410.1, ($M+Na^+$) 432.0.

Anal. Calcd. for $C_{24}H_{19}N_5O_2 \cdot 5.6$ HCl · 0.2 diethyl ether: C, 47.40; H, 4.27; N, 11.14.

Found: C, 47.64; H, 4.21; N, 10.91.

Example 115: (2R)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide (hydrochloric salt)



Preparation of example 115 from the title compound of Example **118** (71 mg, 0.136 mmol) and 4M HCl in dioxane (20 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (66 mg, 0.12 mmol) as a yellow powder in 87% yield over two steps (from Example 118).

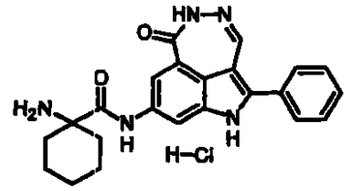
^{1}H NMR (d_6-DMSO): δ 12.20 (s, 1H, exchanges), 10.66 (s, 1H, exchanges), 10.44 (s, 1H, exchanges), 8.39 (br s, 3H, exchanges), 8.05 (s, 1H), 7.73-7.46 (m, 7H), 7.39-7.22 (m, 5H), 4.19 (m, 1H), 3.21-3.06 (m, 2H, partially obscured).

LCMS: ($M+H^+$) 424.1.

Anal. Calcd. for $C_{25}H_{21}N_5O_2 \cdot 2.8$ HCl · 0.1 diethyl ether · 0.2 dioxane: C, 57.15; H, 4.83; N, 12.72.

Found: C, 57.33; H, 5.01; N, 12.56.

Example 116: 1-Amino-cyclohexanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)



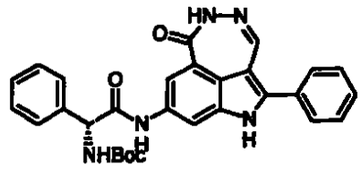
Preparation of example 116 from the title compound of Example **119** (311 mg, 0.062 mmol) and 4M HCl in dioxane (5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2/hexane and afforded the title compound (29 mg, 0.053 mmol) as an orange/yellow powder in 85% yield.

^{1}H NMR (d_6-DMSO): δ 12.29 (s, 1H, exchanges), 10.44 (s, 1H, exchanges), 10.28 (s, 1H, exchanges), 8.36 (br s, 3H, exchanges), 8.11 (s, 1H), 7.81 (s, 1H), 7.74-7.46 (m, 6H), 2.37-2.14 (m, 2H), 1.96-1.35 (m, 8H).

LCMS: $(M+H^+)$ 402.2, $(M+Na^+)$ 424.1.

Anal. Calcd. for $C_{23}H_{23}N_5O_2 \cdot 3.1\ HCl \cdot 0.1$ diethyl ether $\cdot 0.3$ dioxane: C, 53.88; H, 5.42; N, 12.77. Found: C, 53.86; H, 5.60; N, 12.70.

Example 117: [(R)-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-phenyl-methyl]-carbamic acid *tert*-butyl ester

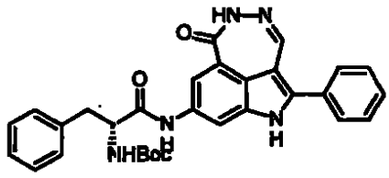


Preparation of example 117 from the the title compound of Example 7 (hydrochloride) (44 mg, 0.141 mmol), (R)-*tert*-butoxycarbonylamino-phenyl-acetic acid (42 mg, 0.169 mmol), triethylamine (0.059 mL, 0.423 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (64 mg, 0.169 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (102 mg) as a yellow powder contaminated with an unknown impurity. The compound was an intermediate and carried on without further purification to Example 91.

^1H NMR (d_6-DMSO): δ 12.12 (s, 1H), 10.41 (s, 2H), 8,12 (s, 1H), 7.69-7.48 (m, 10H), 7.42-7.27 (m, 3H), 5.36 (d, 1H, J = 8.67 Hz), 1.41 (s, 9H).

LCMS: $(M-H^-)$ 508.1, $(M+H^+)$ 510.2, $(M+Na^+)$ 532.2.

Example 118: [(R)-1-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-2-phenyl-ethyl]-carbamic acid *tert*-butyl ester

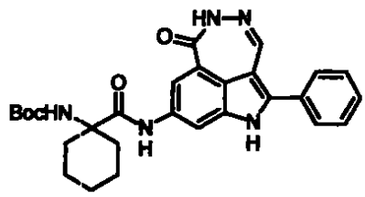


Preparation of example 118 from the title compound of Example 7 (hydrochloride) (43 mg, 0.138 mmol), (R)-*tert*-butoxycarbonylamino-3-phenyl-propionic acid (44 mg, 0.166 mmol), triethylamine (0.058 mL, 0.414 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (63 mg, 0.166 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (80 mg) as a yellow powder contaminated with an unknown impurity. The compound was carried on without further purification to Example 115.

^{1}H NMR (d_6-DMSO): δ 12.12 (1H), 10.41 (s, 1H), 10.25 (s, 1H), 8.18 (s, 1H), 7.71-7.48 (m, 7H), 7.38-7.11 (m, 6H), 4.34 (br s, 1H), 3.02 (m, 1H), 2.87 (m, 1H, partially obscured by *N,N*-dimethylformamide singlet), 1.34 (s, 9H).

LCMS: $(M+H^+)$ 524.2, $(M+Na^+)$ 546.2.

Example 119: [1-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-cyclohexyl]-carbamic acid *tert*-butyl ester

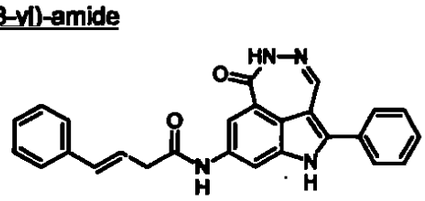


Preparation of example 119 from the title compound of Example 7 (hydrochloride) (45 mg, 0.142 mmol), 1-*tert*-butoxycarbonylamino-cyclohexanecarboxylic acid (42 mg, 0.171 mmol), triethylamine (0.059 mL, 0.426 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (65 mg, 0.171 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (38 mg, 0.076 mmol) as a yellow powder in 53% yield.

^{1}H NMR (d_6-DMSO): δ 12.08 (s, 1H), 10.37 (s, 1H), 9.59 (s, 1H), 8.14 (s, 1H), 7.70-7.48 (m, 8H), 2.03-1.92 (m, 2H), 1.81-1.71 (m, 2H), 1.47 (m, 5H), 1.40-1.31 (m, 10H).

LCMS: $(M+H^+)$ 502.1, $(M+Na^+)$ 524.1.

Example 120: (3E)-4-Phenyl-but-3-enoic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Preparation of example 120 from the title compound of Example 7 (hydrochloride) (44 mg, 0.141 mmol), (E)-4-phenyl-but-3-enoic acid (27 mg, 0.169 mmol), triethylamine (0.059 mL, 0.423 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (64 mg, 0.169 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. When the reaction was judged complete, the mixture was filtered to collect the solids which were then washed with methanol. After drying under vacuum, the title compound (41 mg, 0.0.095 mmol) was obtained as a yellow powder in 68% yield.

^{1}H NMR (d_6-DMSO): δ 12.10, (s, 1H, exchanges), 10.38 (s, 1H, exchanges), 10.22 (s, 1H, exchanges), 8.21 (s, 1H), 7.77-7.63 (m, 3H), 7.60-7.53 (m, 2H), 7.53-7.42 (m, 4H), 7.38-7.30 (m, 2H), 7.24 (m, 1H), 6.57 (d, 1H, J = 16.01 Hz), 6.45 (m, 1H).

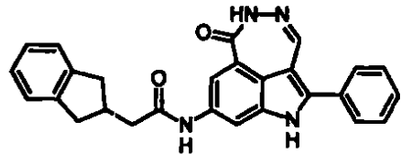
^{1}H NMR (d_6-DMSO/DCl): δ 8.20 (s, 1H), 7.75 (s, 1H), 7.71-7.65 (m, 2H), 7.60-7.47 (m, 4H), 7.43-7.37 (m, 2H), 7.38-7.29 (m, 2H), 7.22 (m, 1H), 6.55 (d, 1H, *J* = 16.23 Hz), 6.44 (m, 1H), 3.33 (d, 2H, *J* = 9.09 Hz).

LCMS: $(M+H^+)$ 421.1, $(M+Na^+)$ 443.1.

Anal. Calcd. for $C_{28}H_{20}N_4O_2 \cdot 0.1\ H_2O \cdot 0.1$ *N,N*-dimethylformamide: C, 73.53; H, 4.90; N, 13.37.

Found: C, 73.26; H, 4.50; N, 13.61.

Example 121: 2-Indan-2-yl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide



Preparation of example 121 from the title compound of Example 7 (hydrochloride) (41 mg, 0.131 mmol), indan-2-yl-acetic acid (28 mg, 0.157 mmol), triethylamine (0.055 mL, 0.393 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (60 mg, 0.157 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. When the reaction was judged complete, the mixture was filtered to collect the solids, which were then washed with methanol. After drying under vacuum, the title compound (45 mg, 0.101 mmol) was obtained as a yellow powder in 77% yield.

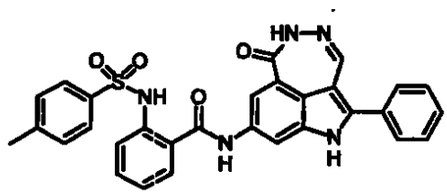
^{1}H NMR (d_6-DMSO): δ 12.08, (s, 1H, exchanges), 10.37 (s, 1H, exchanges), 10.11 (s, 1H, exchanges), 8.20 (s, 1H), 7.70-7.45 (m, 7H), 7.26-7.18 (m, 2H), 7.16-7.08 (m, 2H), 3.07 (dd, 2H, *J* = 7.72, 15.83 Hz), 2.87 (m, 1H), 2.65 (dd, 2H, *J* = 6.59, 15.26 Hz).

LCMS: $(M+H^+)$ 435.2, $(M+Na^+)$ 457.1.

Anal. Calcd. for $C_{27}H_{22}N_4O_2 \cdot 0.5\ H_2O$: C, 73.12; H, 5.23; N, 12.63.

Found: C, 72.84; H, 4.99; N, 12.99.

Example 122: *N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-(toluene-4-sulfonylamino)-benzamide



Preparation of example 122 from the title compound of Example 7 (100 mg, 0.362 mmol), 2-(toluene-4-sulfonylamino)-benzoic acid (158 mg, 0.542 mmol), triethylamine (0.201 mL, 1.446 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (206 mg, 0.542 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example 11. When the reaction was judged complete, *N,N*-dimethylformamide was evaporated and methanol

was added. The mixture was filtered and the solids collected and washed with methanol, dichloromethane and diethyl ether. After drying under vacuum, the title compound (121 mg, 0.220 mmol) was obtained as a yellow powder in 61% yield.

^{1}H NMR (d_6-DMSO): δ 12.19 (s, 1H), 10.63 (s, 1H), 10.45 (s, 1H), 10.42 (s, 1H), 8.12 (s, 1H), 7.85-7.78 (m, 2H), 7.74-7.67 (m, 2H), 7.64-7.56 (m, 4H), 7.56-7.42 (m, 4H), 7.29-7.20 (m, 3H), 2.27 (s, 3H).

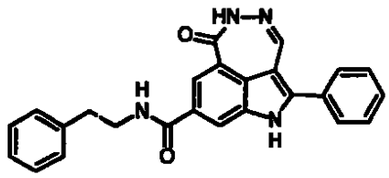
LCMS: $(M+H^+)$ 550.1; $(M-H)^-$ 548.2.

HRMS: $(M+H^+)$ calcd for $C_{30}H_{24}N_5O_4S$, 550.1549, found 550.1551.

Anal. Calcd. for $C_{30}H_{23}N_5O_4S \cdot 0.5\ H_2O$: C, 64.50; H, 4.33; N, 12.54.

Found: C, 64.51; H, 4.20; N, 12.71.

Example 123: 6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxylic acid phenethyl-amide

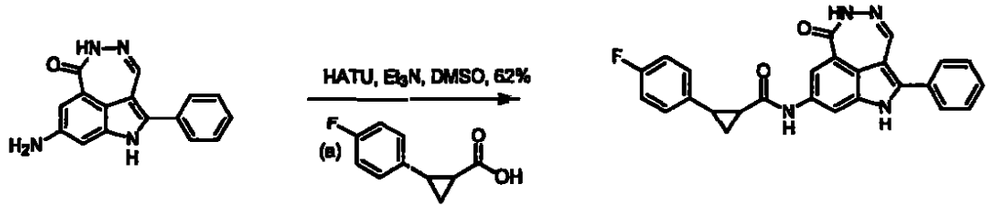


Preparation of example 123 from the title compound of Example 49 (0.17 g, 0.5 mmol), phenethylamine (73 mg, 0.6 mmol), triethylamine (100 mg, 1.0 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.6 mmol) in DMSO (8 mL) was carried out analogously to the preparation of Example 76. Preparative HPLC (20-100% CH_3CN/H_2O containing 0.1% trifluoroacetic acid), also in an analogous manner, afforded the title compound (0.021 g) as a yellow powder in 9% yield.

^{1}H NMR (d_6-DMSO): δ 12.49 (s, 1H), 10.49 (s, 1H), 8.77 (t, 1H, H=5.5 Hz), 8.07 (s, 1H), 8.00 (s, 1H), 7.10-7.80 (m, 11H), 3.48 (m, 2H), 2.86 (t, 2H, J = 7.5 Hz).

LCMS (M^++1): 409.1

Example 124: (1,2-*trans*)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-3-yl)-amide

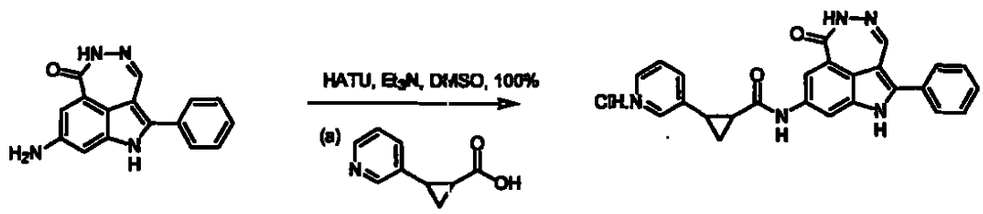


Preparation of example 124 was carried out analogously to the preparation of Example **113** except that (1,2-*trans*)-2-(4'-fluorophenyl)-cyclopropanecarboxylic acid was used instead of (1,2-*trans*)-2-(6-trifluoromethyl-pyridin-3-yl)-cyclopropanecarboxylic acid in step 4. (1,2-*trans*)-2-(4'-Fluorophenyl)-cyclopropanecarboxylic acid was prepared using procedures similar to those described in steps 1-3 of Example **113**, except that 4-fluoro-benzaldehyde was used instead of 6-trifluoromethyl-3-pyridine carboxaldehyde. Final HPLC purification, also analogous to Example **113**, afforded the title compound (100 mg, 0.228 mmol) as a yellow powder in 62% yield.

^{1}H-NMR (d_6-DMSO): δ 12.12 (b, 1H), 10.46 (b, 1H), 10.41 (b, 1H), 8.18 (b, 1H), 7.70-7.45 (m, 7H), 7.30-7.10 (m, 4H), 2.65-2.55 (m, 1H), 2.27-2.18 (m, 1H), 1.67-1.51 (m, 2H).

HRMS: $C_{21}H_{21}N_5O_2$ • H: 439.1570. Found: 439.1584.

Example 125: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)

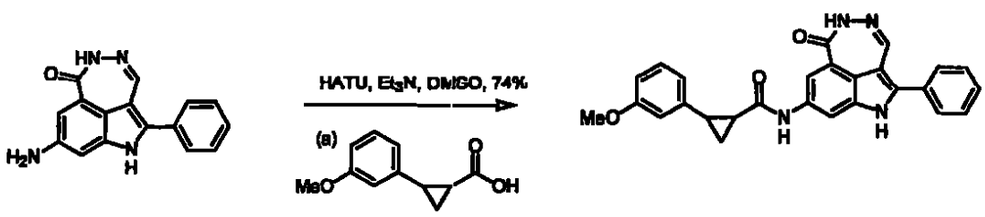


Preparation of example 125 was carried out analogously to the preparation of Example **113** except that (1,2-*trans*)-2-pyridin-3'-yl-cyclopropanecarboxylic acid was used instead of (1,2-*trans*)-2-(6-trifluoromethyl-pyridin-3-yl)-cyclopropanecarboxylic acid in step 4. (1,2-*trans*)-2-Pyridin-3'-yl-cyclopropanecarboxylic acid was prepared using procedures similar to those described in steps 1-3 of Example **113** except that pyridine-3-carbaldehyde was used instead of 6-trifluoromethyl-3-pyridine carboxaldehyde. Final HPLC purification, also analogous to Example **113**, afforded the title compound (230 mg, 0.381 mmol) as an orange fluffy solid in quantitative yield.

^{1}H-NMR (d_6-DMSO): δ 12.15 (s, 1H), 10.58 (s, 1H), 10.38 (s, 1H), 8.81 (s, 1H), 8.15 (b, 2H), 7.82-7.45 (m, 9H), 2.35-2.25 (m, 1H), 1.70-1.51 (m, 1H), 1.35-1.10 (m, 1H), 0.90-0.65 (m, 1H).

LCMS: ($M+H^+$) 422.1.

Example 126: (1,2-*trans*)-2-(3-Methoxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

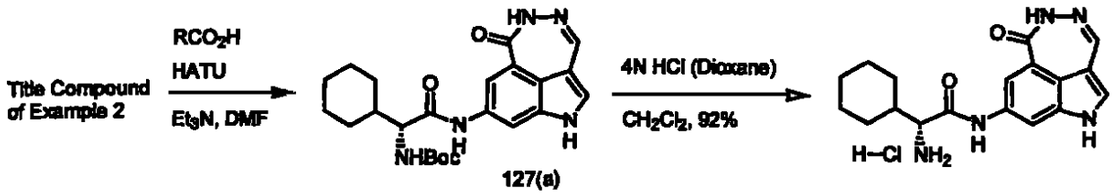


Preparation of example 126 was carried out analogously to the preparation of Example **113** except that (1,2-*trans*)-2-(3'-methoxyphenyl)-cyclopropanecarboxylic acid was used instead of (1,2-*trans*)-2-(6-trifluoromethyl-pyridin-3-yl)-cyclopropanecarboxylic acid in step 4. (1,2-*trans*)-2-(3'-Methoxyphenyl)-cyclopropanecarboxylic acid was prepared using procedures similar to those described in steps 1-3 of Example **113** except that 3-methoxy-benzaldehyde was used instead of 6-trifluoromethyl-3-pyridine carboxaldehyde. Final HPLC purification, also analogous to Example **113**, afforded the title compound (132 mg, 0.293 mmol) as a pale orange solid in 74% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.43 (s, 1H), 10.38 (s, 1H), 8.15 (s, 1H), 7.70-7.40 (m, 7H), 7.25-7.15 (m, 1H), 6.77 (b, 3H), 3.74 (s, 3H), 2.40-2.30 (m, 1H), 2.12-2.05 (m, 1H), 1.55-1.47 (m, 1H), 1.42-1.33 (m, 1H).

LCMS: $(M+H^+)$ 451.1.

Example 127: (R)-2-Amino-2-cyclohexyl-(6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide (hydrochloric salt)



Step 1. Preparation of [(R)-Cyclohexyl-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-methyl]-carbamic acid tert-butyl ester 127(a)

Preparation of Intermediate 127(a) from the title compound of Example **2** (105 mg, 0.445 mmol), (R)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (172 mg, 0.668 mmol), triethylamine (0.248 mL, 1.782 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (254 mg, 0.668 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with 1:1 hexane:ethyl acetate), also in an analogous manner, afforded Intermediate 127(a) (110 mg, 0.250 mmol) as a yellow powder in 56% yield.

^{1}H NMR (d_6-DMSO): δ 11.71 (d, 1H, J = 2.26 Hz), 10.23 (s, 1H), 10.07 (s, 1H), 8.10 (s, 1H), 7.59 (s, 1H), 7.55 (d, 1H, J = 2.45 Hz), 7.46 (s, 1H), 6.86 (d, 1H, J = 8.85 Hz), 3.92 (dd, 1H, J = 8.10, 7.91 Hz), 1.77-1.46 (m, 6H), 1.37 (s, 9H), 1.24-0.93 (m, 5H).

LCMS: $(M+H^+)$ 440.1, $(M+Na^+)$ 462.2; $(M-H)^-$ 438.2.

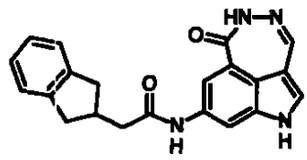
Step 2. Preparation of Title Compound: (R)-2-Amino-2-cyclohexyl-(6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide (hydrochloric salt)

Preparation of the title compound from Intermediate 127(a) (66.1 mg, 0.150 mmol) and 4.0 M HCl in dioxane (1.5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (52.0 mg, 0.138 mmol) as a yellow powder in 92% yield.

^{1}H NMR (d_6-DMSO): δ 11.86 (s, 1H), 10.69 (s, 1H), 10.31 (s, 1H), 8.29 (br s, 3H), 8.08 (s, 1H), 7.63 (s, 1H), 7.49 (s, 1H), 3.80-3.69 (*m*, 1H), 1.93-1.55 (*m*, 6H), 1.29-0.98 (*m*, 5H).

LCMS: ($M+H^+$) 340.3, ($M+Na^+$) 362.3.

Example 128: 2-Indan-2-yl-(6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide

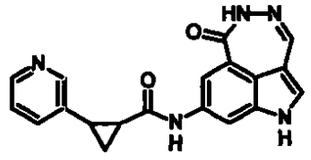


Preparation of example 128 from the title compound of Example 2 (freebase) (88.7 mg, 0.443 mmol), indan-2-yl-acetic acid (117 mg, 0.665 mmol), triethylamine (0.247 mL, 1.774 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (253 mg, 0.665 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example 11. When the reaction was judged complete, *N,N*-dimethylformamide was evaporated and methanol was added. The mixture was filtered to collect the solids, which were then washed with methanol, dichloromethane and diethyl ether. After drying under vacuum, the title compound (115 mg, 0.321 mmol) was obtained as a yellow powder in 72% yield.

^{1}H NMR (d_6-DMSO): δ 11.71 (s, 1H), 10.23 (s, 1H), 10.05 (s, 1H), 8.15 (s, 1H), 7.58(s, 1H), 7.55 (d, 1H, *J* = 2.26 Hz), 7.46 (s, 1H), 7.26-7.16 (m, 2H), 7.16-7.06 (m, 2H), 3.06 (dd, 2H, *J* = 7.54, 5.54 Hz), 2.92-2.79 (m, 1H), 2.65 (dd, 2H, *J* = 6.59, 6.78 Hz), 2.47 (d, 2H, *J* = 9.80 Hz).

LCMS: ($M+H^+$) 359.1, ($M+Na^+$) 381.0; ($M-H)^-$ 357.2.

Example 129: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Preparation of example 129 from the title compound of Example 2 (freebase) (200 mg, 1.00 mmol), (1,2-*trans*)-2-pyridin-3'-yl-cyclopropanecarboxylic acid (see Example 125 for preparation-estimated purity c.a. 75%) (240 mg, c.a.1.10 mmol), triethylamine (0.550 mL, 3.96 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (570 mg, 1.50 mmol) in *N,N*-dimethylformamide (8.0 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 100:10:1 ethyl acetate: methanol: ammonium hydroxide), also in an analogous manner, afforded the title compound (38 mg, 0.110 mmol) as a yellow powder in 11% yield.

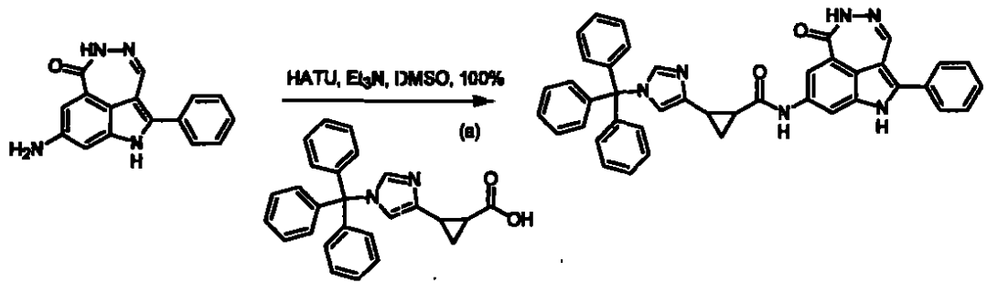
^{1}H NMR (d_6-DMSO): δ 11.73 (d, 1H, *J* = 2.26 Hz), 10.41 (s, 1H), 10.23 (s, 1H), 8.50 (d, 1H, *J* = 1.88 Hz), 8.41 (dd, 1H, *J* = 3.20, 1.51 Hz), 8.11 (d, 1H, *J* = 1.51 Hz), 7.61-7.48 (m, 3H), 7.45 (s,

1H), 7.32 (dd, 1H, *J* = 5.09, 3.20 Hz), 2.45-2.36 (m, 1H), 2.18-2.05 (m, 1H), 1.58-1.49 (m, 1H), 1.49-1.36 (m, 1H).

LCMS: $(M+H^+)$ 346.1; $(M-H)^-$ 344.1.

HRMS: $(M+H^+)$ calcd for $C_{19}H_{16}N_5O_2$, 346.1304, found 346.1316.

Example 130: (1,2-*trans*)-2-(1'-Trityl-1*H*-imidazol-4'-yl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

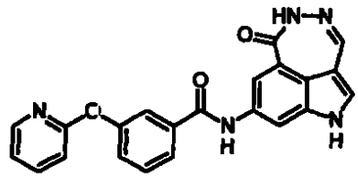


Preparation of example 130 was carried out analogously to the preparation of Example **113** except that (1,2-*trans*)-2-(1'-trityl-1*H*-imidazol-4'-yl)-cyclopropanecarboxylic acid was used instead of (1,2-*trans*)-2-(6-trifluoromethyl-pyridin-3-yl)-cyclopropanecarboxylic acid in step 4. (1,2-*trans*)-2-(1'-trityl-1*H*-imidazol-4'-yl)-cyclopropanecarboxylic acid was prepared using procedures similar to those described in steps 1-3 of Example **113** except that 1-trityl-1*H*-imidazole-4-carbaldehyde was used instead of 6-trifluoromethyl-3-pyridine carboxaldehyde. Final purification consisted of methanol trituration. The resulting solids were isolated by filtration, washed with cold methanol, and dried overnight under vacuum at room temperature to afford the title compound (263 mg, 0.366 mmol) as a yellow powder in quantitative yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.43 (s, 1H), 10.38 (s, 1H), 8.13 (s, 1H), 7.70-7.30 (m, 18H), 7.25 (s, 1H), 7.15-7.05 (m, 6H), 6.87 (s, 1H), 2.35-2.24 (m, 1H), 2.20-2.13 (m, 1H), 1.38-1.23 (m, 2H).

LCMS: $(M+H^+)$ 653.3

Example 131: (6-Oxo-5, 6-dihydro-1-[1,2]diazepino[4,5,6-]indol-8-yl)-3-(pyridin-2-yloxy)-benzamide



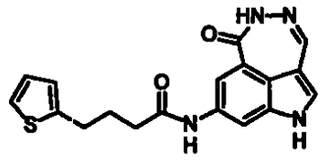
Preparation of example 131 from the title compound of Example **2** (25 mg, 0.125 mmol), 3-(pyridin-2-yloxy)-benzoic acid (88 mg, 0.348 mmol), *N,N*-diisopropylethylamine (0.19 mL, 1.04 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (159 mg, 0.42 mmol) in *N,N*-dimethylformamide (3 mL) was carried out analogously to Example **11**.

Silica gel chromatography (eluted with 2% methanol in CH_2Cl_2), also in an analogous manner, afforded the title compound (20 mg, 0.05 mmol) as a yellow powder in 40% yield.

^{1}H NMR (d_6-Acetone): δ 7.92 (s, 1H), 7.89 (s, 1H), 7.55-7.52 (m, 4H), 7.39 (s, 1H), 7.37 (s, 1H), 7.34 (m, 1H), 7.32-7.24 (m, 2H), 7.15 (m, 1H), 6.95 (m, 1H), 6.93 (m, 1H), 6.77-6.73 (m, 5H), 6.88 (m, 1H).

LCMS: ($M+H^+$) 398.1.

Example 132: *N*-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thiophen-2-yl-butyramide



Preparation of example 132 from the title compound of Example **2** (freebase) (200 mg, 1.00 mmol), 4-thiophen-2-yl-butyric acid (187 mg, 1.10 mmol), triethylamine (0.550 mL, 3.96 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (570 mg, 1.50 mmol) in *N,N*-dimethylformamide (8.0 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with ethyl acetate), also in an analogous manner, afforded the title compound (72 mg, 0.204 mmol) as a yellow powder in 20% yield.

^{1}H NMR (d_6-DMSO): δ 11.70 (d, 1H, J = 2.07 Hz), 10.22 (s, 1H), 10.03 (s, 1H), 8.13 (d, 1H, J = 1.51 Hz), 7.55 (d, 1H, J = 1.51 Hz), 7.53 (d, 1H, J = 2.45 Hz), 7.45 (s, 1H), 7.31 (dd, 1H, J = 4.33, 0.94 Hz), 6.94 (dd, 1H, J = 3.39, 1.70 Hz), 6.86 (d, 1H, J = 2.83 Hz), 3.84 (t, 2H, J = 7.54 Hz), 2.37 (t, 2H, J = 7.35 Hz), 1.93 (tt, 2H, J = 7.54, 7.35 Hz).

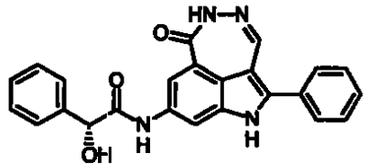
LCMS: ($M+H^+$) 353.2, ($M+Na^+$) 375.2; $(M-H)^-$ 351.2.

HRMS: ($M+H^+$) calcd for $C_{18}H_{17}N_4O_2S$, 353.1072, found 353.1056.

Anal. Calcd. for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90.

Found: C, 61.06; H, 4.52; N, 15.71.

Example 133: (2*R*)-2-Hydroxy-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylethanamide



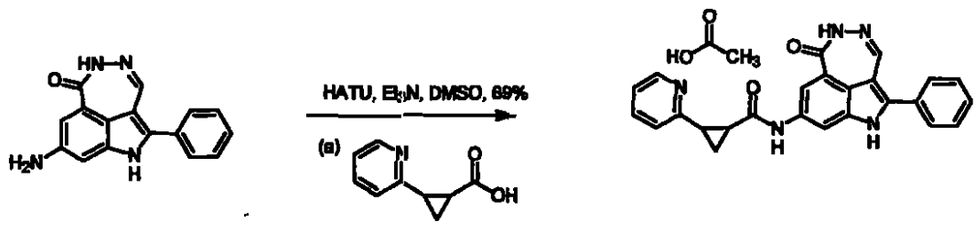
Preparation of example 133 from the title compound of Example **7** (hydrochloride) (46 mg, 0.147 mmol), (2*R*)-hydroxy(phenyl)ethanoic acid (27 mg, 0.177 mmol), triethylamine (0.061 mL, 0.44 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (67 mg, 0.177 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with 3:1:1 hexane:ethyl

acetate:ethanol), also in an analogous manner, followed by two successive triturations (ethyl acetate/diethyl ether then methanol/diethyl ether) afforded the title compound (34 mg, 0.082 mmol) as a yellow powder in 56% yield.

^{1}H NMR (d_6-DMSO): δ 12.12, (s, 1H), 10.38 (s, 1H), 10.16 (s, 1H), 8.14 (s, 1H), 7.81 (s, 1H), 7.70-7.64 (m, 2H), 7.61-7.45 (m, 6H), 7.42-7.26 (m, 3H), 6.35 (br s, 1H, partially exchanged), 5.13 (s, 1H).

LCMS: $(M-H)^-$ 409.2.

Example 134: (1,2-*trans*)-2-Pyridin-2-yl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (acetic acid salt)

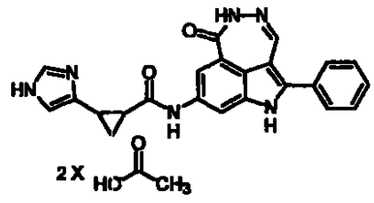


Preparation of example 134 was carried out analogously to the preparation of Example **113** except that (1,2-*trans*)-2-pyridin-2'-yl-cyclopropanecarboxylic acid was used instead of (1,2-*trans*)-2-(6-trifluoromethyl-pyridin-3-yl)-cyclopropanecarboxylic acid in step 4. (1,2-*trans*)-2-Pyridin-2'-yl-cyclopropanecarboxylic acid was prepared using procedures similar to those described in steps 1-3 of Example **113** except that pyridine-2-carbaldehyde was used instead of 6-trifluoromethyl-3-pyridine carbaldehyde. Final HPLC purification, also in an analogous manner but using 0.1% acetic acid instead of 0.1% TFA, afforded the title compound (107 mg, 0.254 mmol) as a greenish-yellow solid in 69% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.43 (s, 1H), 10.38 (s, 1H), 8.15 (s, 1H), 7.70-7.40 (m, 7H), 7.25-7.15 (m, 1H), 6.77 (b, 3H), 3.74 (s, 3H), 2.40-2.30 (m, 1H), 2.12-2.05 (m, 1H), 1.55-1.47 (m, 1H), 1.42-1.33 (m, 1H).

LCMS: $(M+H^+)$ 422.1.

Example 135: (1,2-*trans*)-2-(1*H*-Imidazol-4-yl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (acetic acid salt)



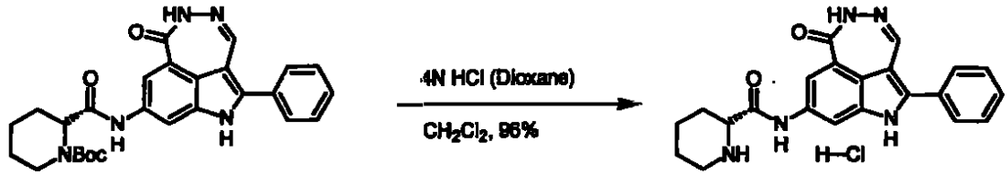
Preparation of example 135 was carried out by suspending the title compound of Example **130** (260 mg, 0.398 mmol) in anhydrous dichloromethane (5 mL) and adding anhydrous trifluoroacetic

acid (5 mL) at room temperature. After 30 minutes, the mixture was concentrated and subjected to preparative HPLC, in a manner analogous to Example **134**, to afford the title compound (72 mg, 0.175 mmol) as a fluffy yellow solid in 44% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.43 (s, 1H), 10.37 (s, 1H), 8.15 (s, 1H), 7.97 (b, 1H), 7.70-7.45 (m, 7H), 7.13 (b, 1H), 2.40-2.30 (m, 1H), 2.12-2.04 (m, 1H), 1.45-1.33 (m, 2H).

LCMS: (M+H$^+$) 422.1.

Example 136: (2R)-Piperidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)



136(a)

Step 1. Preparation of (2R)-2-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester 136(a)

Preparation of Intermediate 136(a) from the title compound of Example **7** (0.11 g, 0.4 mmol), (2R)-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.143 g, 0.6 mmol), triethylamine (0.3 mL, 2 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.63 mmol) and *N,N*-dimethylformamide (0.1 M, 5 mL) was carried out analogously to Example **11**. Silica gel chromatography afforded Intermediate 136(a) (0.21 g) as a yellow powder in 88% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.40 (s, 1H), 10.11 (s, 1H), 8.10 (s, 1H), 7.74-7.44 (m, 7H), 4.64-4.55 (m, 1H), 3.83 (d, 1H, *J* = 12.25 Hz), 3.35-3.20 (buried m, 1H), 2.20-2.05 (m, 1H), 1.80-1.50 (m, 3H), 1.45-1.25 (bs, 11H).

LCMS: (M+H$^+$) 488.2.

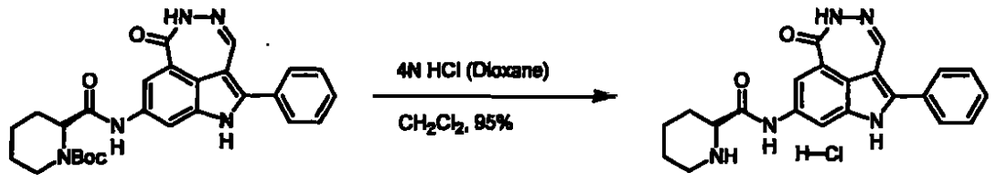
Step 2. Preparation of Title Compound: (2R)-Piperidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)

Preparation of the title compound from Intermediate 136(a) (0.16 g, 0.33 mmol) and 4M HCl in dioxane (1.6 mL, 6.6 mmol) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2/diethyl ether and afforded the title compound (0.137 g) as an orange/yellow powder in 96% yield.

^{1}H-NMR (d_6-DMSO): δ 12.31 (s, 1H), 10.90 (s, 1H), 10.45 (s, 1H), 9.26 (b, 1H), 8.80-8.76 (m, 1H), 8.11 (s, 1H), 7.76-7.46 (m, 7H), 3.95-3.81 (m, 1H), 3.35-3.25 (m, 1H), 3.10-2.92 (m, 1H), 2.36-2.26 (m, 1H), 1.76-1.51 (m, 5H).

LCMS: (M+H$^+$) 388.1.

Example 137: (2S)-Piperidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)



137(a)

Step 1. Preparation of (2S)-2-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester 137(a)

Preparation of Intermediate 137(a) from the title compound of Example 7 (0.138 g, 0.5 mmol), (2S)-Piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.143 g, 0.6 mmol), triethylamine (0.3 mL, 2 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.63 mmol) and *N,N*-dimethylformamide (0.1 M, 5 mL) was carried out analogously to Example 11. Silica gel chromatography afforded Intermediate 137(a) (0.20 g) as a yellow powder in 84% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.40 (s, 1H), 10.11 (s, 1H), 8.10 (s, 1H), 7.74-7.44 (m, 7H), 4.64-4.55 (m, 1H), 3.83 (d, 1H, *J* = 12.25 Hz), 3.35-3.20 (buried m, 1H), 2.20-2.05 (m, 1H), 1.80-1.50 (m, 3H), 1.45-1.25 (bs, 11H).

LCMS: $(M+H^+)$ 488.1.

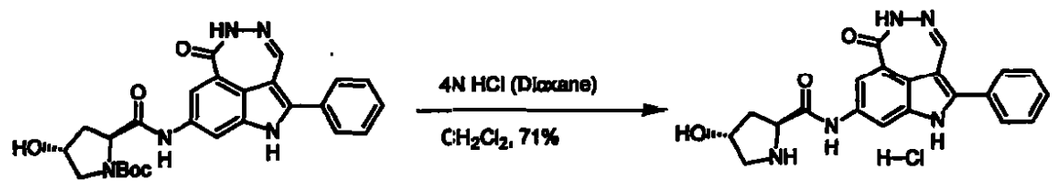
Step 2. Preparation of Title Compound: (2S)-Piperidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)

Preparation of the title compound from Intermediate 137(a) (0.16 g, 0.33 mmol) and 4M HCl in dioxane (1.6 mL, 6.6 mmol) was carried out analogously to Example 91. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2/diethyl ether and afforded the title compound (0.132 g) as an orange/yellow powder in 95% yield.

^{1}H-NMR (d_6-DMSO): δ 12.31 (s, 1H), 10.90 (s, 1H), 10.45 (s, 1H), 9.26 (b, 1H), 8.80-8.75 (m, 1H), 8.11 (s, 1H), 7.76-7.46 (m, 7H), 3.95-3.81 (m, 1H), 3.35-3.25 (m, 1H), 3.10-2.92 (m, 1H), 2.36-2.26 (m, 1H), 1.76-1.51 (m, 5H).

LCMS: $(M+H^+)$ 388.2.

Example 138: (2S,4R)-4-Hydroxy-pyrrolidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)



138(a)

Step 1. Preparation of (2S, 4R)-4-Hydroxy-2-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester 138(a)

Preparation of Intermediate 138(a) from the title compound of Example **7** (0.138 g, 0.5 mmol), (2S, 4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.144 g, 0.6 mmol), triethylamine (0.3 mL, 2 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.63 mmol) and *N,N*-dimethylformamide (0.1 M, 5 mL) was carried out analogously to Example **11**. Silica gel chromatography afforded Intermediate 138(a) (0.127 g) as a yellow powder in 52% yield.

^{1}H-NMR (d_6-DMSO): δ 12.19 (s, 1H), 10.46 (s, 1H), 10.28 (s, 1H), 8.29 (s, 0.8H, major rotamer), 8.29 (s, 0.2H, minor rotamer), 7.75-7.51 (m, 7H), 4.50-4.35 (m, 2H), 3.60-3.30 (m, 3H), 2.30-2.17 (m, 1H), 2.10-1.90 (m, 1H), 1.48 (s, 2H, minor rotamer), 1.34 (s, 2H, major rotamer).

LCMS: ($M+H^+$) 490.1.

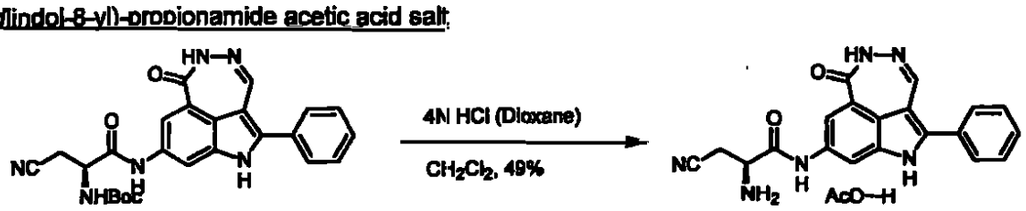
Step 2. Title Compound: (2S,4R)-4-Hydroxy-pyrrolidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)

Preparation of the title compound from Intermediate 138(a) (0.105 g, 0.21 mmol) and 4M HCl in dioxane (1 mL, 4.2 mmol) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2/diethyl ether and afforded the title compound (0.065 g) as an orange/yellow powder in 71% yield.

^{1}H-NMR (d_6-DMSO): δ 12.33 (s, 1H), 10.93 (s, 1H), 10.44 (s, 1H), 10.10-9.95 (m, 1H), 8.90-8.45 (m, 1H), 8.08 (s, 1H), 7.75-7.45 (m, 7H), 4.75-4.35 (bm, 3H), 3.45-3.30 (m, 1H), 3.20-3.10 (m, 1H), 2.50-2.35 (m, 1H), 2.10-1.95 (m, 1H).

LCMS: ($M+H^+$) 390.1.

Example 139: (2S)- 2-Amino-3-cyano-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-propionamide acetic acid salt



138(a)

Step 1. Preparation of (1S)- [2-Cyano-1-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester 139(a)

Preparation of Intermediate 139(a) from the title compound of Example **7** (0.138 g, 0.5 mmol), (2S)-2-*tert*-butoxycarbonylamino-3-cyano-propionic acid (0.134 g, 0.6 mmol), triethylamine (0.3 mL, 2 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23

g, 0.63 mmol) and *N,N*-dimethylformamide (0.1 M, 5 mL) was carried out analogously to Example **11**. Silica gel chromatography afforded Intermediate 139(a) (0.094 g) as a yellow powder in 40% yield.

^{1}H-NMR (d_6-DMSO): δ 12.15 (s, 1H), 10.42 (s, 1H), 10.37 (s, 1H), 8.11 (s, 1H), 7.75-7.48 (m, 8H), 4.55-4.40 (m, 1H), 3.02 (dd, 1H, *J* = 17.1, 4.9 Hz), 2.85 (dd, 1H, *J* = 17.0, 9.0 Hz), 1.43 (s, 9H).

LCMS: (M+H$^+$) 473.2.

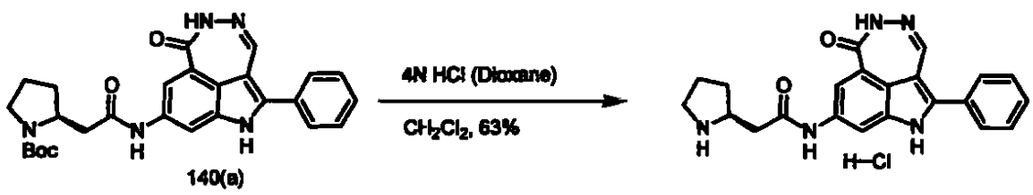
Step 2. Preparation of Title Compound: (2S)- 2-Amino-3-cyano-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-propionamide acetic acid salt

Preparation of the title compound from Intermediate 139(a) (0.084 g, 0.18 mmol) and 4M HCl in dioxane (0.9 mL, 3.6 mmol) was carried out analogously to Example **91**. A preparative HPLC afforded the title compound (0.038 g) as an orange/yellow powder in 49% yield.

^{1}H-NMR (d_6-DMSO): δ 12.31 (s, 1H), 10.50 (s, 1H), 10.35 (bs, 1H), 8.24 (s, 1H), 7.80-7.55 (m, 7H), 3.84 (dd, 1H, *J* = 7.0, 6.9 Hz), 2.99 (dd, 1H, *J* = 16.8, 5.7 Hz), 2.85 (dd, 1H, *J* = 16.6, 7.2 Hz), 2.73 (s, 6H).

LCMS: (M+H$^+$) 373.1.

Example 140: (2S)-*N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-pyrrolidin-2-yl-acetamide (hydrochloric salt)



Step 1. Preparation of (2S)-2-[(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester 140(a)

Preparation of Intermediate 140(a) from the title compound of Example 7 (0.138 g, 0.5 mmol), (2S)-2-carboxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.143 g, 0.6 mmol), triethylamine (0.3 mL, 2 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.63 mmol) and *N,N*-dimethylformamide (0.1 M, 5 mL) was carried out analogously to Example **11**. Silica gel chromatography afforded Intermediate 140(a) (0.155 g) as a yellow powder in 64% yield.

^{1}H-NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.39 (s, 1H), 10.17 and 10.10 (2s, 1H, minor and major rotamer), 8.20 (s, 1H), 7.75-7.45 (m, 7H), 4.10 (s, 1H), 4.20-4.05 (m, 1H), 3.50-3.25 (m, 2H), 2.10-1.75 (m, 4H), 1.40 and 1.29 (2s, 9H, minor and major rotamer).

LCMS: (M-Boc+H$^+$) 388.2.

Step 2. Preparation of Title Compound: (2S)-*N*-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-pyrrolidin-2-yl-acetamide (hydrochloric salt)

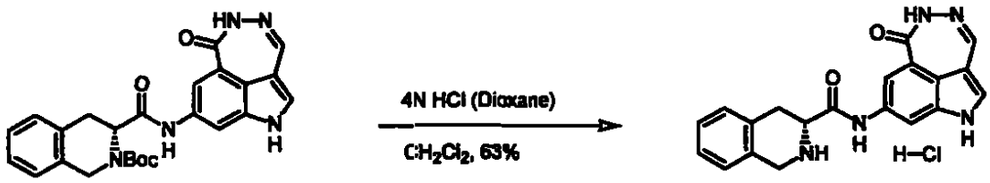
Preparation of the title compound from Intermediate 140(a) (0.1 g, 0.20 mmol) and 4M HCl in dioxane (1 mL, 4.2 mmol) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2/diethyl ether and afforded the title compound (0.055 g) as an orange/yellow powder in 63% yield.

major rotamer; ^{1}H-NMR (d_6-DMSO): δ 12.23 (s, 1H), 10.48 (s, 1H), 10.41 (s, 1H), 9.25-9.10 (m, 1H), 8.95-8.80 (m, 1H), 8.11 (s, 1H), 7.75-7.45 (m, 7H), 4.10 (buried m, 1H), 3.90-3.75 (m, 1H), 3.25-3.15 (m, 2H), 2.95-2.85 (m, 2H), 2.25-1.55 (m, 5H).

minor rotamer; ^{1}H-NMR (d_6-DMSO): δ 12.31 (s, 1H), 10.92 (s, 1H), 10.45 (s, 1H), 9.85-9.75 (m, 1H), 8.75-8.60 (m, 1H), 3.35-3.25 (m, 2H).

LCMS: ($M+H^+$) 388.2.

Example 141: (3R)-1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)



141(a)

Step 1. Preparation of (3R) 3-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester 141(a)

Preparation of intermediate 141(a) from the title compound of Example **2** (0.1 g, 0.5 mmol), (3R)-3,4-dihydro-1*H*-isoquinoline-2,3-dicarboxylic acid 2-*tert*-butyl ester (0.103 g, 0.6 mmol), triethylamine (0.3 mL, 2 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.63 mmol) and *N,N*-dimethylformamide (0.1 M, 5 mL) was carried out analogously to Example **11**. Silica gel chromatography afforded Intermediate 141(a) (0.094 g) as a yellow powder in 41% yield.

^{1}H-NMR (d_6-DMSO): δ 11.72 (bs, 1H), 10.25 (s, 1H), 10.14 (bs, 1H), 8.09 and 7.96 (2s, 1H, major and minor rotamer), 7.57 (s, 2H), 7.47 (s, 1H), 7.30-7.10 (m, 4H), 4.75-4.60 (m, 1H), 4.48-4.34 (m, 1H), 3.40-3.00 (m, 3H), 1.47 (s, 3H), 1.31(s, 6H).

LCMS: ($M-H^+$) 458.3.

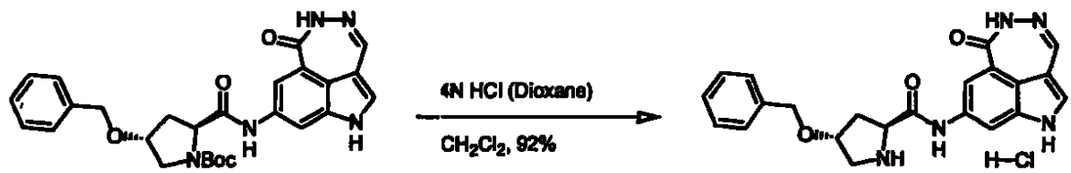
Step 2. Preparation of Title Compound: (3R)-1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)

Preparation of the title compound from Intermediate 141(a) (0.094 g, 0.20 mmol) and 4M HCl in dioxane (1 mL, 4.2 mmol) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2/diethyl ether and afforded the title compound (0.051 g) as an orange/yellow powder in 63% yield.

^{1}H-NMR (d_6-DMSO): δ 11.98 (s, 1H), 11.08 (s, 1H), 10.32 (s, 1H), 9.93 (b, 1H), 9.64 (b, 1H), 8.09 (s, 1H), 7.74 (s, 1H), 7.64 (s, 1H), 7.51 (s, 1H), 7.29 (s, 5H), 4.50-4.10 (buried m, 3H), 3.53 (dd, 1H, J = 16.4, 4.0 Hz), 3.14 (dd, 1H, J = 16.8, 12.06 Hz).

LCMS: (M+H$^+$) 360.1.

Example 142: (2S, 4R)-4-Benzyloxy-pyrrolidine-2-carboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)



142(a)

Step 1. Preparation of (2S, 4R) 4-Benzyloxy-2-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester 142(a)

Preparation of intermediate 142(a) from the title compound of Example **2** (0.1 g, 0.5 mmol), (2S, 4R)-4-benzyloxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (0.103 g, 0.6 mmol), triethylamine (0.3 mL, 2 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.63 mmol) and *N,N*-dimethylformamide (0.1 M, 5 mL) was carried out analogously to Example **11**. Silica gel chromatography afforded Intermediate 142(a) (0.126 g) as a yellow powder in 50% yield.

^{1}H-NMR (d_6-DMSO): δ 11.76 (s, 1H), 10.26 (s, 1H), 10.18 (s, 1H), 8.18 and 8.10 (s, 1H, rotamers), 7.60 (s, 1H), 7.58 (s, 1H), 7.48 (s, 1H), 7.42-7.26 (m, 5H), 4.53 (s, 2H), 4.39-4.26 (m, 1H), 4.22 (bs, 1H), 3.54 (bs, 2H), 3.32 (s, 2H), 1.27 (s, 6H).

LCMS: (M-H$^+$) 502.2.

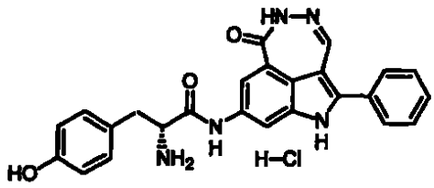
Step 2. Preparation of Title Compound: (2S, 4R)-4-Benzyloxy-pyrrolidine-2-carboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)

Preparation of the title compound from Intermediate 142(a) (0.106 g, 0.21 mmol) and 4M HCl in dioxane (1 mL, 4.2 mmol) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2/diethyl ether and afforded the title compound (0.085 g) as an orange/yellow powder in 92% yield.

^{1}H-NMR (d_6-DMSO): δ 11.96 (s, 1H), 10.94 (s, 1H), 10.33 (s, 1H), 10.12 (b, 1H), 8.89 (b, 1H), 8.06 (s, 1H), 7.70 (s, 1H), 7.64 (s, 1H), 7.51 (s, 1H), 7.45-7.28 (m, 7H), 4.40 (b, 2H), 3.47 (b, 2H), 2.80-2.65 (m, 1H), 2.15-2.01 (m, 1H).

LCMS: (M+H$^+$) 404.2.

Example 143: (2*R*)-2-Amino-3-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride

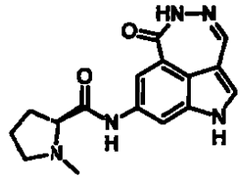


Preparation of example 143 from title compound of Example **150** (64 mg, 0.119 mmol), and 4M HCl in dioxane (5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included freebasing with triethylamine and subsequent silica gel chromatography eluting with 3:1:1 hexane:ethyl acetate:ethanol. With ice bath cooling, the purified freebase in CH_2Cl_2 (5 mL) was treated with 4M HCl in dioxane (0.1 mL). After removal of the volatile components, the title compound (32 mg, 0.067 mmol) was obtained as an orange/yellow powder in 57% yield.

^{1}H NMR (d_6-DMSO): δ 12.25 (s, 1H, exchanges), 10.71 (s, 1H, exchanges), 10.45 (s, 1H, exchanges), 9.44 (br s, 1H, exchanges), 8.45-8.31 (br m, 2H, exchanges), 8,08 (s, 1H), 7.76-7.45 (m, 7H), 7.09 (d, 2H, *J* = 8 Hz), 6.72 9d, 2H, *J* = 8 Hz), 4.13 (m, 1H), 3.19-2.97 (m, 2H).

LCMS: $(M+H^+)$ 440.0, $(M-H)^-$ 438.2.

Example 144: (*S*)-1-Methyl-pyrrolidine-2-carboxylic acid (6-oxo-5, 6-dihydro-1-[1,2]diazepino[4,5,6-*lindol*-8-yl)-amide



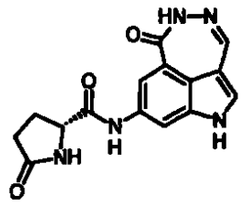
Preparation of example 144 from the title compound of Example **2** (190 mg, 0.95 mmol), *N*-methylproline (129 mg, 1.47 mmol), triethylamine (0.19 mL, 1.43 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (470 mg, 1.3 mmol) in *N,N*-dimethylformamide (5 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with 10 % methanol in CH_2Cl_2), also in an analogous manner, afforded title compound (100 mg, 0.32 mmol) as a yellow powder in 34% yield.

^{1}H NMR (d_6-DMSO): 11.83 (s, 1H), 10.33 (s, 1H), 9.96 (s, 1H), 8.24 (s, 1H), 7.73 (s, 1H), 7.65 (s, 1H), 7.55 (s, 1H), 3.20 (m, 1H), 3.03 (m, 1H), 2.63 (m, 1H), 2.23 (m, 1H), 1.91-1.88 (m, 3H).

Anal. Calcd for $C_{16}H_{17}N_5O_2 \cdot 0.2\ H_2O$: C, 61.02; H, 5.57; N, 22.24. Found: C, 60.83; H, 5.29; N, 22.23.

LCMS: $(M+H^+)$ 312.1.

Example 145: (2R)-5-Oxo-pyrrolidine-2-carboxylic acid (6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide



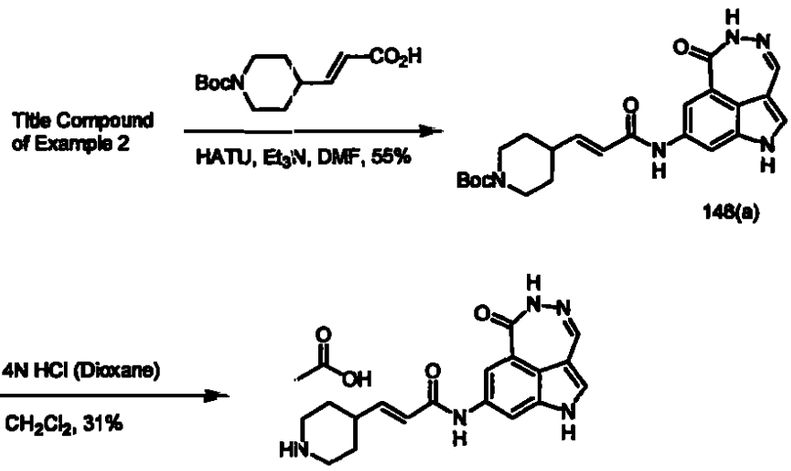
Preparation of example 145 from the title compound of Example 2 (freebase) (190 mg, 0.95 mmol), (*R*)-(+)-pyrrolidonecarboxylic acid (167 mg, 1.29 mmol), triethylamine (0.25 mL, 1.77 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (538 mg, 1.42 mmol) in *N,N*-dimethylformamide (5 mL) was carried out analogously to Example 11. The mixture was concentrated and the residue was triturated with methanol. The resulting solids were then collected by filtration and washed with methanol to give the title compound (220 mg, 0.57 mmol) as a yellow powder in 60% yield.

^{1}H NMR (d_6-DMSO): 11.79 (s, 1H), 10.27 (s, 1H), 10.20 (s, 1H), 8.11 (s, 1H), 7.91 (s, 1H), 7.62 (s, 1H), 7.59 (s, 1H), 7.49 (s, 1H), 4.21 (m, 1H), 2.36 (m, 1H), 2.24-2.16 (m, 2H), 2.03 (m, 1H).

Anal. Calcd for $C_{15}H_{13}N_5O_3 \cdot 1\ H_2O$: C, 54.71; H, 4.59; N, 21.27. Found: C, 54.51; H, 4.68; N, 21.05.

LCMS: ($M+H^+$) 312.2.

Example 146: *N*-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-piperidin-4-yl-acrylamide acetic acid salt



Step 1. Preparation of 4-[2-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-vinyl]-piperidine-1-carboxylic acid *tert*-butyl ester 146(a)

Preparation of intermediate 146(a) from the title compound of Example 2 (freebase) (49 mg, 0.245 mmol), 4-(2-carboxy-vinyl)-piperidine-1-carboxylic acid *tert*-butyl ester (99 mg, 0.39 mmol), triethylamine (0.069 mL, 0.49 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-

tetramethyluronium hexafluorophosphate (148 mg, 0.39 mmol) in *N,N*-dimethylformamide (3 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with 10 % methanol in CH_2Cl_2), also in an analogous manner, afforded Intermediate 146(a) (58 mg, 0.13 mmol) as a yellow powder in 55% yield.

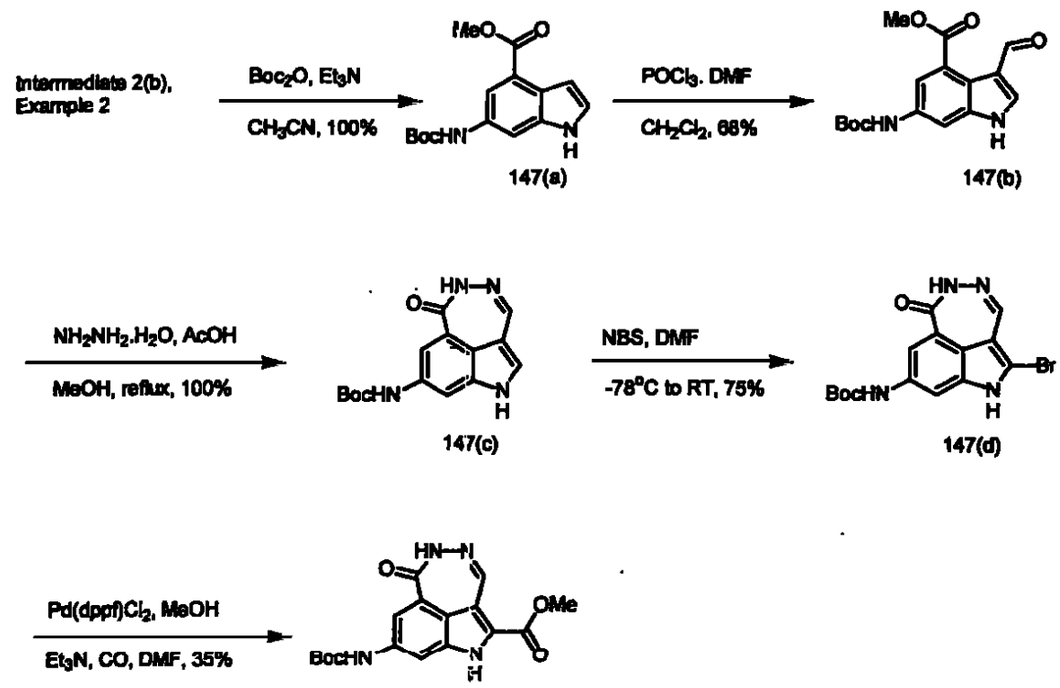
Step 2. Preparation of Title Compound: *N*-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-piperidin-4-yl-acrylamide acetic acid salt

Preparation of the title compound from Intermediate 146(a) (58 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) and 4M HCl in dioxane (2 mL) was carried out analogously to Example **91**. After concentration, the residue was purified by preparative HPLC (Peeke Scientific, HI-Q C18 reverse phase 5u, 100A, 250x21.2 mm column) eluting with CH_3CN and 0.1% acetic acid in water at a flow rate of 20 mL/min using a gradient of 5-95% CH_3CN over 40 min to give the title compound (16 mg, 0.04 mmol) as a pale yellow powder in 31% yield.

^{1}H NMR (d_6-DMSO): 11.55 (s, 1H), 10.00 (s, 1H), 9.91 (s, 1H), 8.00 (s, 1H), 7.32 (d, J = 8 Hz, 2H), 7.22 (s, 1H), 6.50 (m, 1H), 5.82 (m, 1H), 2.77-2.74 (m, 2H), 2.03 (m, 1H), 1.65-1.53 (m, 2H), 1.29-1.28 (m, 2H), 1.10-1.02 (m, 2H).

LCMS: ($M+H^+$) 337.

Example 147: 8-*tert*-Butoxycarbonylamino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester



Step 1. Preparation of 6-*tert*-Butoxycarbonylamino-1*H*-indole-4-carboxylic acid methyl ester 147(a)

Triethylamine (17.1 mL, 123 mmol) was added slowly to Intermediate 2(b) of Example 2 (hydrochloride) (27.5 g, 121 mmol) cooled to 0 °C in 400 ml anhydrous CH_3CN. After 0.5 hours, di-*tert*-butyl dicarbonate (26.76 g, 123 mmol) in anhydrous CH_3CN (50 mL) was added, and the mixture was allowed to stir at room temperature for 24 h at which point volatile components were removed *in vacuo*. Ethyl acetate (500 mL) and H_2O (500 mL) were added, and the aqueous layer was extracted with ethyl acetate (4X120 mL). The combined ethyl acetate extracts were washed with H_2O (2X170 mL) and brine (100 mL) and allowed to dry over Na_2SO_4. Following filtration, the volatile components were removed *in vacuo* to afford Intermediate 147(a) (35.1 g, 121 mmol) as a brown solid in quantitative yield.

^1H NMR (d_6-DMSO): δ 12.28 (s, 1H), 9.43 (s, 1H), 7.91 (br s, 1H), 7.89 (s, 1H), 7.42 (t, 1H, J = 2.73 Hz), 6.83 (t, 1H, J = 2.17 Hz), 3.89 (s, 3H), 1.50 (s, 9H).

LCMS: $(M+Na^+)$ 313.1; $(M-H)^-$ 289.2.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65.

Found: C, 62.08; H, 6.30; N, 9.59.

Step 2. Preparation of 6-*tert*-Butoxycarbonylamino-3-formyl-1*H*-indole-4-carboxylic acid methyl ester 147(b)

A premixed Vilsmeier reagent consisting of phosphorus oxychloride (33.67 mL, 3624 mmol) in *N,N*-dimethylformamide (81.40 mL) was added dropwise at 0 °C to Intermediate 147(a) (33.87 g, 116 mmol) stirring in anhydrous CH_2Cl_2 (584 mL). The mixture was stirred for 1 hour at room temperature, quenched with aqueous 2.0 M sodium acetate (700 ml) at 0 °C and neutralized with solid Na_2CO_3. A solid formed and the mixture was partitioned between ethyl acetate (4000 mL) and H_2O (2000 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (4 X 500 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated. Methanol (3500 mL) was added to the residue followed by K_2CO_3 (70 g). The mixture was stirred at room temperature for 16 hours at which point volatile components were removed *in vacuo*. Ethyl acetate (500 mL) and H_2O (500 mL) were added. The entire mixture was then filtered and the insoluble solids were collected and dried under vacuum to afford Intermediate 147(b) (14.35 g, 45.1 mmol) as a white solid. The aqueous layer was again extracted with ethyl acetate (4X120 mL), and the ethyl acetate extracts were combined, washed with H_2O (2X170 mL), brine and allowed to dry over Na_2SO_4. Following filtration, the volatile components were removed *in vacuo* to afford additional Intermediate 147(b) (10.74 g, 33.8 mmol) as a white solid. The combined yield for the two batches was 68%.

^1H NMR (d_6-DMSO): δ 12.28 (s, 1H), 10.09 (s, 1H), 9.60 (s, 1H), 8.23 (d, 1H, J = 3.01 Hz), 7.96 (d, 1H, J = 1.32 Hz), 7.65 (d, 1H, J = 1.88 Hz), 3.84 (s, 3H), 1.50 (s, 9H).

LCMS: $(M+H^+)$ 319, $(M+Na^+)$ 341.1; $(M-H)^-$ 317.1

Step 3. Preparation of (6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid *tert*-butyl ester 147(c)

Acetic acid (7.89 ml) was added to Intermediate 147(b) (25.1 g, 78.9 mmol) in anhydrous methanol (789 ml). The suspension was stirred at room temperature for 10 minutes and $H_2NNH_2 \cdot H_2O$ (21.43 mL, 395 mmol) was added. The mixture was stirred at room temperature for another 10 minutes, heated at 70 °C for 0.5 hours and cooled to room temperature. The volatile components were removed *in vacuo* and the residual oil was triturated with methanol and toluene to afford Intermediate 147(c) (23.6 g, 78.9 mmol) as a yellow powder in quantitative yield.

^{1}H NMR (d_6-DMSO): δ 11.63 (s, 1H), 10.19 (s, 1H), 9.45 (s, 1H), 7.76 (s, 1H), 7.62 (s, 1H), 7.51 (d, 1H, J = 2.07 Hz), 7.44 (s, 1H), 1.49 (s, 9H).

LCMS: $(M+H^+)$ 301.1, $(M+Na^+)$ 323.1; $(M-H)^-$ 299.1.

Anal. Calcd. for $C_{15}H_{16}N_4O_3 \cdot 0.5\ H_2O$: C, 59.10; H, 5.46; N, 18.38.

Found: C, 59.49; H, 5.43; N, 17.97.

Step 4. Preparation of (2-Bromo-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid *tert*-butyl ester 147(d)

Intermediate 147(c) (1.00 g, 3.33 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (15 ml) and cooled to –78 °C. N-Bromosuccinimide (0.564 g, 3.17 mmol) in anhydrous *N,N*-dimethylformamide (3.5 ml) was added dropwise over 2 min. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Additional N-bromosuccinimide (0.337 g, 2.00 mmol) in *N,N*-dimethylformamide (c.a. 1.5 mL) was then added in portions over a 0.5 hours period to drive the reaction to completion. The reaction mixture was poured into H_2O (70 mL), and a dark solid precipitated. The solid was collected by filtration and dried under vacuum to give Intermediate 147(d) (0.95 g, 2.51 mmol) as dark solid in 75% yield.

^{1}H NMR (d_6-DMSO): δ 12.54 (s, 1H), 10.47 (s, 1H), 9.57 (s, 1H), 7.77 (s, 1H), 7.71 (d, 1H, J = 1.70 Hz), 7.31 (s, 1H), 1.53 (s, 9H).

LCMS: $(M+H^+)$ 379.0, 381.0, $(M+Na^+)$ 401.0, 403.0; $(M-H)^-$ 377.1, 379.1.

Anal. Calcd. for $C_{15}H_{15}BrN_4O_3$: C, 47.51; H, 3.99; N, 14.77.

Found: C, 47.42; H, 3.99; N, 14.51.

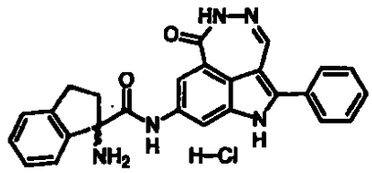
Step 5. Preparation of Title Compound: 8-*tert*-Butoxycarbonylamino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester

Intermediate 147(d) (0.200 g, 0.529 mmol), triethylamine (0.147 mL, 1.06 mmol) and anhydrous methanol (2 mL) in anhydrous *N,N*-dimethylformamide (2 ml) were purged with Ar. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) (86.4 mg, 0.106 mmol) was added and CO was bubbled into the reaction mixture for 5 minutes. The reaction was then sealed and heated at 86 °C for 16 hours. The mixture was filtered through a thin pack of diatomaceous earth and the filtrate reduced *in vacuo*. Silica gel chromatography (eluted with 1:1 ethyl acetate: hexane) afforded the title compound (66 mg, 0.184 mmol) as a yellow powder in 35% yield.

^{1}H NMR (d_6-DMSO): δ 12.42 (s, 1H), 10.80 (s, 1H), 9.69 (s, 1H), 8.14 (s, 1H) 7.91 (s, 1H), 7.76 (s, 1H), 3.92 (s, 3H), 1.49 (s, 9H).

LCMS: $(M+H^+)$ 359.1, $(M+Na^+)$ 381.2; $(M-H)^-$ 357.0.

Example 148: 1-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2,3-dihydro-1*H*-indene-1-carboxamide hydrochloride

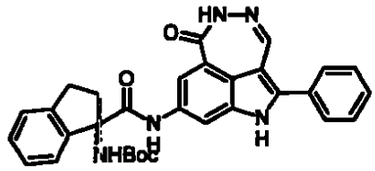


Preparation of example 148 from title compound of Example **149** (52 mg, 0.097 mmol), and 4M HCl in dioxane (5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (46 mg, 0.097 mmol) as a yellow powder in quantitative yield.

^{1}H NMR (d_6-DMSO): δ 12.42 (s, 1H), 10.60 (s, 1H), 10.20 (s, 1H), 9.05-8.86 (m, 3H), 8.23 (s, 1H), 7.90-7.73 (m, 3H), 7.72-7.57 (m, 6H), 7.55-7.41 (m 2H), 3.42 (m, 1H), 3.31 (m, 1H), 3.08 (m, 1H), 2.55 (m, 1H, partially obscured).

LCMS: $(M+H^+)$ 436.2, 419.2.

Example 149: 1,1-Dimethylethyl 1-{[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]carbonyl}-2,3-dihydro-1*H*-inden-1-ylcarbamate

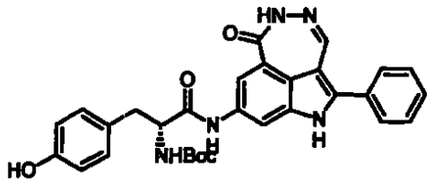


Preparation of example 149 from the title compound of Example **7** (hydrochloride) (52 mg, 0.17 mmol), 1-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2,3-dihydro-1*H*-indene-1-carboxylic acid (72 mg, 0.26 mmol), triethylamine (0.071 mL, 0.51 mmol), and O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (99 mg, 0.26 mmol) in CH_2Cl_2 (0.4 mL) and *N*,*N*-dimethylformamide (0.4 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (63 mg, 0.12 mmol) as a yellow powder in 69% yield.

^{1}H NMR (d_6-DMSO): δ 12.05 (s, 1H), 10.36 (s, 1H), 10.01 (m, 1H), 8.09 (m, 1H), 7.87-7.74 (m, 2H), 7.70-7.62 (m, 2H), 7.63-7.53 (m, 2H), 7.52-7.47 (m, 2H), 7.31-7.22 (m, 3H), 3.08-2.95 (m, 3H), 2.09 (m, 1H), 1.40 (m, 9H).

LCMS: $(M-H)^-$ 534.0.

Example 150: 1,1-Dimethylethyl (1*R*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]ethylcarbamate

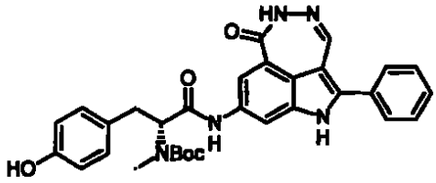


Preparation of example 150 from the title compound of Example 7 (hydrochloride) (44 mg, 0.144 mmol), (2*R*)-2-{[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-(4-hydroxyphenyl)propanoic acid (46 mg, 0.173 mmol), triethylamine (0.060 mL, 0.43 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (66 mg, 0.173 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (74 mg, 0.137 mmol) as a yellow powder in 95% yield.

^{1}H NMR (d_6-DMSO): δ 12.11 (s, 1H), 10.41 (s, 1H), 10.20 (s, 1H), 9.20 (s, 1H), 8.17 (s, 1H), 7.71-7.45 (m, 7H), 7.14 (d, 2H, *J* = 8.50 Hz), 6.68 (d, 2H, *J* = 8.40 Hz), 4.24 (m, 1H), 2.94 (m, 1H), 2.72 (m, 1H), 1.35 (s, 9H).

LCMS: $(M-H)^-$ 538.1.

Example 151: 1,1-Dimethylethyl (1*R*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]ethyl(methyl)carbamate

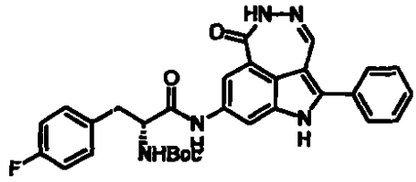


Préparation of example 151 from the title compound of Example 7 (hydrochloride) (40 mg, 0.128 mmol), (2*R*)-2-[{[(1,1-dimethylethyl)oxy]carbonyl}(methyl)amino]-3-(4-hydroxyphenyl)propanoic acid (57 mg, 0.192 mmol), triethylamine (0.054 mL, 0.384 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (73 mg, 0.192 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example **11**. Additional (2*R*)-2-[{[(1,1-dimethylethyl)oxy]carbonyl}(methyl)amino]-3-(4-hydroxyphenyl)propanoic acid (14 mg, 0.047 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (18 mg, 0.047 mmol) were added after 24 hours to drive the reaction to completion. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (55 mg, 0.099 mmol) as a yellow powder in 78% yield.

^{1}H NMR (d_6-DMSO) multiple : δ 12.10 (br s, 1H), 10.38 (br s, 1H), 9.20 (m, 1H), 8.13 (m, 1H), 7.72-7.63 (m, 3H), 7.61-7.43 (m, 4H), 7.09-7.00 (m, 2H), 6.72-6.62 (m, 2H), 4.82-4.60 (m, 1H), 3.19-3.08 (m, 1H), 2.93-2.85 (m, 1H), 2.80-2.62 (m, 3H), 1.37-1.21 (m, 9H).

LCMS: $(M+H^+)$ 554.2, $(M+Na^+)$ 576.2 $(M-H)^-$ 552.0.

Example 152: 1,1-Dimethylethyl (1*R*)-1-[(4-fluorophenyl)methyl]-2-oxo-2-[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl)amino]ethylcarbamate

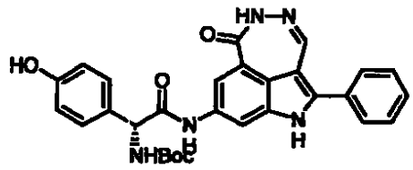


Preparation of example 152 from the title compound of Example 7 (hydrochloride) (40 mg, 0.128 mmol), (2*R*)-2-{[[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-(4-fluorophenyl)propanoic acid (54 mg, 0.192 mmol), triethylamine (0.054 mL, 0.384 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (73 mg, 0.192 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (61 mg, 0.113 mmol) as a yellow powder in 88% yield.

^{1}H NMR (d_6-DMSO): δ 12.12 (s, 1H), 10.42 (s, 1H), 10.25 (s, 1H), 8.18 (s, 1H), 7.71-7.46 (m, 7H), 7.42-7.34 (m, 2H), 7.21-7.09 (m, 3H), 4.41 (m, 1H), 3.03 (m, 1H), 2.85 (m 1H), 1.34 (s, 9H).

LCMS: $(M-H)^-$ 540.2.

Example 153: 1,1-Dimethylethyl (1*R*)-1-(4-hydroxyphenyl)-2-oxo-2-[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl)amino]ethylcarbamate

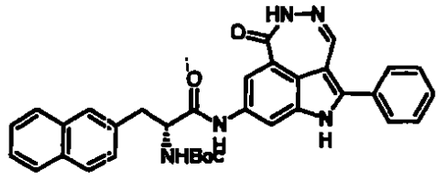


Preparation of example 153 from the title compound of Example 7 (hydrochloride) (42 mg, 0.134 mmol), (2*R*)-({[(1,1-dimethylethyl)oxy]carbonyl}amino)(4-hydroxyphenyl)ethanoic acid (54 mg, 0.202 mmol), triethylamine (0.056 mL, 0.402 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (77 mg, 0.202 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Additional (2*R*)-({[(1,1-dimethylethyl)oxy]carbonyl}amino)(4-hydroxyphenyl)ethanoic acid (27 mg, 0.10 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (39 mg, 0.10 mmol) were added after 24 hours to drive the reaction to completion. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (48 mg, 0.091 mmol) as a yellow powder in 68% yield.

^{1}H NMR (d_6-DMSO): δ 12.11 (s, 1H), 10.40 (s, 1H), 10.30 (s, 1H), 9.46 (s, 1H), 8.12 (s, 1H), 7.71-7.48 (m, 7H), 7.33-7.27 (m, 2H), 6.80-6.69 (m, 2H), 5.22 (m, 1H), 1.41 (s, 1H).

LCMS: $(M+H^+)$ 526.2.

Example 154: 1,1-Dimethylethyl (1*R*)-1-(naphthalen-2-ylmethyl)-2-oxo-2-[(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]ethylcarbamate

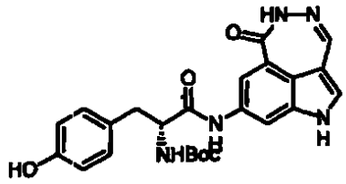


Preparation of example 154 from the title compound of Example 7 (hydrochloride) (40 mg, 0.128 mmol), (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-naphthalen-2-ylpropanoic acid (58 mg, 0.192 mmol), triethylamine (0.054 mL, 0.384 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (73 mg, 0.192 mmol) in CH_2Cl_2 (0.4 mL) and *N,N*-dimethylformamide (0.4 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 1:1 hexane:acetone), also in an analogous manner, afforded the title compound (69 mg, 0.120 mmol) as a yellow powder in 94% yield.

^{1}H NMR (d_6-DMSO): δ 12.12 (s, 1H), 10.41 (s, 1H), 10.31 (s, 1H), 8.18 (s, 1H), 7.90-7.81 (m, 4H), 7.71-7.66 (m, 3H), 7.62-7.56 (m, 3H), 7.54-7.46 (m, 4H), 7.23 (d, 1H, *J* = 8.1 Hz), 4.46 (m, 1H), 3.23 (m, 1H), 3.02 (m, 1H), 1.30 (s, 9H).

LCMS: $(M-H)^-$ 572.2.

Example 155: 1,1-Dimethylethyl (1*R*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]ethylcarbamate

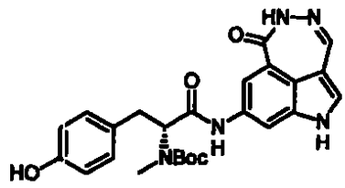


Preparation of example 155 from the title compound of Example 2 (71 mg, 0.30 mmol), (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-(4-hydroxyphenyl)propanoic acid (121 mg, 0.45 mmol), triethylamine (0.125 mL, 0.9 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (171 mg, 0.45 mmol) in CH_2Cl_2 (0.5 mL) and *N,N*-dimethylformamide (0.5 mL) was carried out analogously to Example 11. Purification, also in an analogous manner (eluted with 1:1 hexane:acetone) afforded the title compound (100 mg, 0.22 mmol) as a yellow powder in 72% yield.

^{1}H NMR (d_6-DMSO): δ 11.75 (s, 1H), 10.26 (s, 1H), 10.13 (s, 1H), 9.19 (s, 1H), 8.16 (s, 1H), 7.61-7.56 (m, 2H), 7.14 (d, 2H, *J* = 8.10 Hz), 7.04 (d, 1H, *J* = 8.48 Hz), 6.66 (d, 2H, *J* = 8.10 Hz), 4.22 (m, 1H), 3.08 (m, 1H), 2.87 (m, 1H), 1.34 (s, 9H).

LCMS: $(M+H^+)$ 464.2, $(M+Na^+)$ 486.2.

Example 156: 1,1-Dimethylethyl (1*R*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl)amino]ethyl(methyl)carbamate

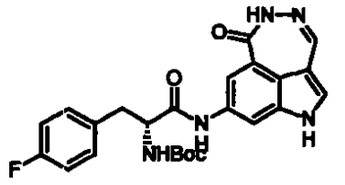


Preparation of example 156 from the title compound of Example **2** (74 mg, 0.31 mmol), (2*R*)-2-[{[(1,1-dimethylethyl)oxy]carbonyl}(methyl)amino]-3-(4-hydroxyphenyl)propanoic acid (138 mg, 0.47 mmol), triethylamine (0.130 mL, 0.93 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (179 mg, 0.47 mmol) in CH_2Cl_2 (0.5 mL) and *N,N*-dimethylformamide (0.5 mL) was carried out analogously to Example **11**. Purification, also in an analogous manner (eluted with 1:1 hexane:acetone) afforded the title compound (131 mg, 0.27 mmol) as a yellow powder in 88% yield.

^{1}H NMR (d_6-DMSO): δ 11.77 (s, 1H), 10.26 (s, 1H), 9.21 (s, 1H), 8.12 (m, 1H), 7.65 (d, 1H, *J* = 1.32 Hz), 7.58 (d, 1H), *J* = 2.26 Hz), 7.48 (s, 1H), 7.07 (d, 2H, *J* = 8.29 Hz), 6.73-6.64 (m, 2H), 4.75 (m, 1H), 3.12 (m, 1H), 2.86-2.65 (m, 4 H, partially obscurred by *N,N*-dimethylformamide), 1.35-1.25 (m, 9H).

LCMS: $(M+H^+)$ 478.3, $(M+Na^+)$ 500.3.

Example 157: 1,1-Dimethylethyl (1*R*)-1-[(4-fluorophenyl)methyl]-2-oxo-2-[(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl)amino]ethylcarbamate

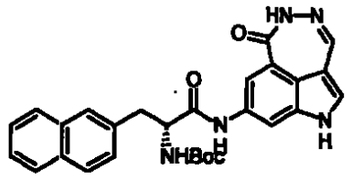


Preparation of example 157 from the title compound of Example **2** (80 mg, 0.34 mmol), (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-(4-fluorophenyl)propanoic acid (145 mg, 0.51 mmol), triethylamine (0.142 mL, 1.02 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (193 mg, 0.51 mmol) in CH_2Cl_2 (0.5 mL) and *N,N*-dimethylformamide (0.5 mL) was carried out analogously to Example **11**. Purification, also in an analogous manner (eluted with 1:1 hexane:acetone) afforded the title compound (56 mg, 0.12 mmol) as a yellow powder in 35% yield.

^{1}H NMR (d_6-DMSO): δ 11.73 (s, 1H), 10.24 (s, 1H), 10.16 (s, 1H), 8.10 (s, 1H), 7.55 (s, 1H with fine splitting), 7.45 (s, 1H), (7.38-7.29 (m, 2H), 7.16-7.04 (m, 3H), 4.25 (m, 1H), 2.97 (m, 1H), 2.79 (m, 1H), 1.30 (s, 9H).

LCMS: $(M+H^+)$ 466.2, $(M+Na^+)$ 488.3.

Example 158: 1,1-Dimethylethyl (1*R*)-1-(naphthalen-2-ylmethyl)-2-oxo-2-[(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]ethylcarbamate

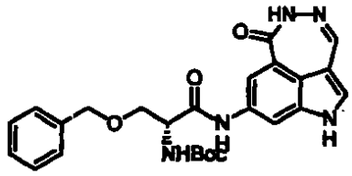


Preparation of example 158 from the title compound of Example 2 (76 mg, 0.32 mmol), (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-naphthalen-2-ylpropanoic acid (145 mg, 0.48 mmol), triethylamine (0.134 mL, 0.96 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (182 mg, 0.48 mmol) in CH_2Cl_2 (0.5 mL) and *N,N*-dimethylformamide (0.5 mL) was carried out analogously to Example 11. Purification, also in an analogous manner (eluted with 1:1 hexane:acetone) afforded the title compound (67 mg, 0.13 mmol) as a yellow powder in 42% yield.

^{1}H NMR (d_6-DMSO): δ 11.76 (br s, 1H), 10.27 (s, 1H), 10.27 (br s, 1H), 8.15 (s, 1H), 7.90-7.79 (m, 4H), 7.62-7.42 (m, 5H), 7.21 (d, 1H, *J* = 7.73 Hz), 4.43 (m, 1H), 3.18 (m, 1H), 3.02 (m, 1H), 1.29 (s, 9H).

LCMS: ($M+H^+$) 498.2, ($M+Na^+$) 520.2.

Example 159: 1,1-Dimethylethyl (1*R*)-2-oxo-2-[(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)amino]-1-{[(phenylmethyl)oxy]methyl}ethylcarbamate

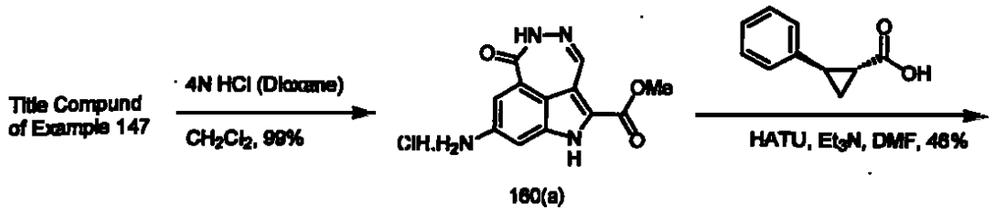


Preparation of example 159 from the title compound of Example 2 (97 mg, 0.41 mmol), (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-[(phenylmethyl)oxy]propanoic acid (182 mg, 0.62 mmol), triethylamine (0.171 mL, 1.23 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (236 mg, 0.62 mmol) in CH_2Cl_2 (0.5 mL) and *N,N*-dimethylformamide (0.5 mL) was carried out analogously to Example 11. Purification, also in an analogous manner (eluted with 1:1 hexane:acetone) afforded the title compound (40 mg, 0.083 mmol) as a yellow powder in 20% yield.

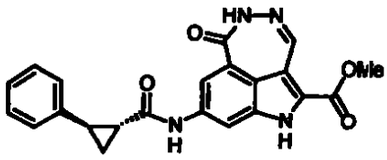
^{1}H NMR (d_6-DMSO): δ 11.78 (br s, 1H), 10.29 (s, 1H), 10.22 (s, 1H), 8.14 (s, 1H), 7.65 (s, 1H), 7.61 (s, 1H, with fine splitting), 7.75 (s, 1H), 7.38-7.26 (m, 4H), 7.08 (d, 1H, *J* = 6.02 Hz), 4.54 (s, 2H), 4.42 (m, 1H), 3.74-3.63 (m, 2H), 1.42 (s, 9H).

LCMS: ($M+H^+$) 478.3, ($M+Na^+$) 500.2.

Example 160: (1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester



160(a)



Step 1. Preparation of 8-Amino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester (hydrochloric salt) 160(a)

Preparation of intermediate 160(a) from the title compound of Example **147** (45.0 mg, 0.125 mmol) and 4.0 M HCl in dioxane (0.32 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded intermediate 160(a) (36.9 mg, 0.125 mmol) as a yellow powder in 99% yield.

Step 2. Preparation of Title Compound: (1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester

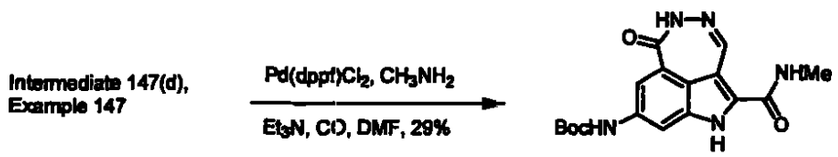
Preparation of the title compound from intermediate 160(a) (36.9 mg, 0.125 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (22.0 mg, 0.136 mmol), triethylamine (0.175 mL, 1.26 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (72.0 mg, 0.189 mmol) in *N,N*-dimethylformamide (2.0 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with 1:1 ethyl acetate: hexane), also in an analogous manner, included a further trituration with methanol and ether and afforded the title compound (23 mg, 0.0572 mmol) as a yellow powder in 46% yield.

^{1}H NMR (d_6-DMSO): δ 12.53 (s, 1H), 10.83 (s, 1H), 10.58 (s, 1H), 8.23 (d, 1H, *J* = 1.51 Hz), 8.15 (s, 1H), 7.76 (d, 1H, *J* = 1.51 Hz), 7.37-7.25 (m, 2H), 7.25-7.14 (m, 3H), 3.93 (s, 3H), 2.45-2.35 (m, 1H), 2.15-2.05 (m, 1H), 1.58-1.47 (m, 1H), 1.45-1.33 (m, 1H).

LCMS: $(M+H^+)$ 403.3, $(M+Na^+)$ 425.1; $(M-H)^-$ 401.0.

HRMS: $(M+H^+)$ calcd for $C_{22}H_{19}N_4O_4$, 403.1406, found 403.1413.

Example 161: (2-Methylcarbamoyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid *tert*-butyl ester

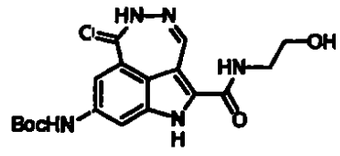


Preparation of example 161 was carried out in a manner analogous to step 5 of Example 147, except that methylamine hydrochloride was substituted for methanol. Thus CO was bubbled through a mixture of Intermediate 147(d) from Example 147 (200 mg, 0.529 mmol), triethylamine (0.29 mL, 2.11 mmol), methylamine hydrochloride (71 mg, 1.06 mmol), and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) (86 mg, 0.106mmol). Reaction conditions, work up and silica gel chromatography (eluted with 46:4:25 dichloromethane: methanol: ethyl acetate) were also carried out in an analogous manner and afforded the title compound (55 mg, 0.154 mmol) in 29% yield.

^{1}H NMR (d_6-DMSO): δ 12.01 (s, 1H), 10.55 (s, 1H), 9.58 (s, 1H), 8.33-8.25 (m, 1H) 7.98 (s, 1H), 7.80 (s, 1H), 7.71 (d, 1H, J = 1.51 Hz), 2.81 (d, 3H, J = 4.52 Hz), 1.48 (s, 9H).

LCMS: (M+H$^+$) 358.3, (M+Na$^+$) 380.1; (M-H$^-$) 356.1.

Example 162: [2-(2-Hydroxy-ethylcarbamoyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-carbamic acid *tert*-butyl ester

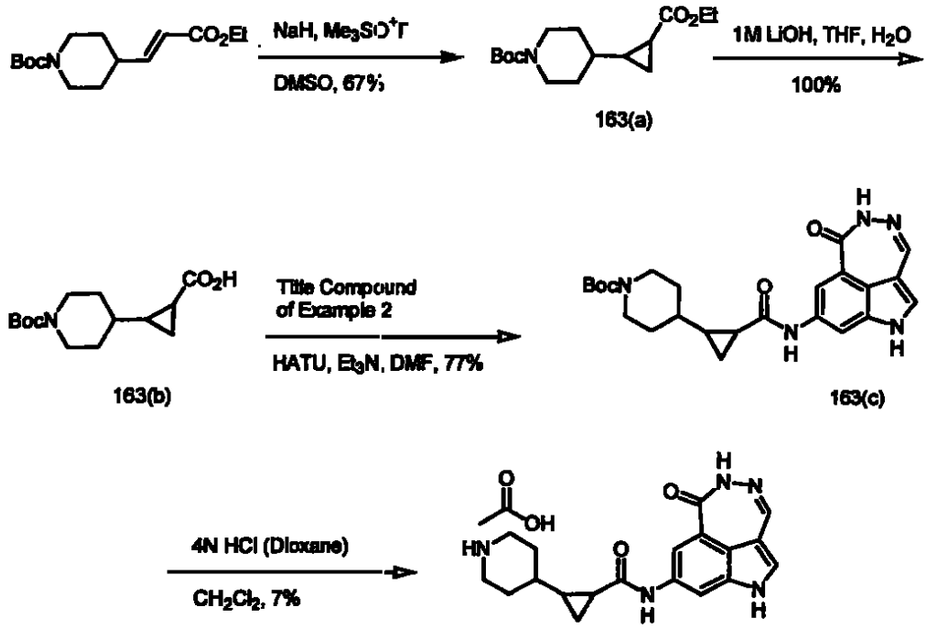


Preparation of example 162 was carried out in a manner analogous to step 5 of Example 147, except that 2-aminoethanol was substituted for methanol, and chromatography was not required. Thus CO was bubbled through a mixture of Intermediate 147(d) from Example 147 (60 mg, 0.16 mmol), triethylamine (0.044 mL, 0.32 mmol), 2-aminoethanol (19 mg, 0.32 mmol), and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) (26 mg, 0.032 mmol) in *N*, *N*-dimethylformamide (3.0 mL). After the reaction was complete, the mixture was filtered through diatomaceous earth. The filtrate was concentrated, and methanol was added. The resulting solids were collected by filtration and washed with methanol, dichloromethane and diethyl ether. After drying under vacuum, the title compound (24 mg, 0.062 mmol) was obtained as a yellow powder in 39% yield.

^{1}H NMR (d_6-DMSO): δ 12.08 (s, 1H), 10.56 (s, 1H), 9.58 (s, 1H), 8.30 (t, 1H, J = 5.84 Hz) 8.06 (s, 1H), 7.79 (s, 1H), 7.74 (s, 1H), 4.80 (br s, 1H), 3.60-3.48 (m, 2H), 3.38 (m, 2H, partially obscured), 1.48 (s, 9H).

LCMS: (M+H$^+$) 388.1, (M+Na$^+$) 410.1.

Example 163: (1,2-*trans*)-2-Piperidin-4-yl-cyclopropanecarboxylic acid (6-oxo-5, 6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (acetic acid salt)



Step 1. Preparation of 4-((1,2-*trans*)-2-Ethoxycarbonyl-cyclopropyl)-piperidine-1-carboxylic acid *tert*-butyl ester 163(a)

To a mixture of NaH (303 mg, 7.57 mmol) and trimethylsulfoxonium iodide (1.67 g, 7.57 mmol) was added dimethyl sulfoxide (10 mL). After stirring for 30 min, a solution of 4-(2-ethoxycarbonyl-vinyl)-piperidine-1-carboxylic acid *tert*-butyl ester in dimethyl sufoxide (5 mL) was added dropwise. After stirring overnight, ethyl acetate and water were added to the mixture. The aqueous layer was extracted with ethyl acetate several times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 10% ethyl acetate/hexane to give Intermediate 163(a)(1.16 g, 67%).

Step 2. Preparation of 4-((1,2-*trans*)-2-Carboxy-cyclopropyl)-piperidine-1-carboxylic acid *tert*-butyl ester 163(b)

To a mixture of Intermediate 163(a) (555 mg, 1.87 mmol) in 3:1 tetrahydrofuran-H_2O (12 mL) was added aqueous 1M LiOH (5.61 mL). The resulting mixture was stirred overnight. The mixture was then acidified with 1M HCl to pH 1 and extracted with several times with ethyl acetate. The combined organic layers was then washed with brine and concentrated to give Intermediate 163(b) (515 mg, 1.87 mmol) in quantitative yield which was carried on without further purification.

Step 3. Preparation of 4-[(1,2-*trans*)-2-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-cd]indol-8-ylcarbamoyl)-cyclopropyl]-piperidine-1-carboxylic acid *tert*-butyl ester 163(c)

Preparation of Intermediate 163(c) from the title compound of Example **2** (freebase) (374 mg, 1.87 mmol), Intermediate 163(b) (500 mg, 1.87 mmol), triethylamine (0.31 mL, 2.24 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (782 mg, 2.06 mmol) in *N,N*-dimethylformamide (10 mL) was carried out analogously to Example **11**. Silica gel chromatography (eluted with 40% acetone in hexane), also in an analogous manner, afforded Intermediate 163(c) as a yellow powder (649 mg, 1.44 mmol) in 77% yield.

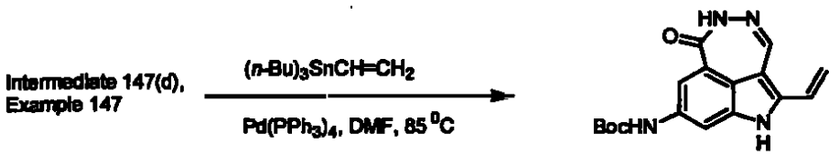
Step 4. Preparation of Title Compound: (1,2-*trans*)-2-Piperidin-4-yl-cyclopropanecarboxylic acid (6-oxo-5, 6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide (acetic acid salt)

Preparation of the title compound from Intermediate 163(c) (603 mg, 1.34 mmol) in CH_2Cl_2 (10 mL) and 4M HCl in dioxane (10 mL) was carried out analogously to Example **91**. After concentration, the crude product was purified by preparative HPLC in a manner analogous to Example **146**, Step 2, to give the title compound as a pale yellow powder (37 mg, 0.09 mmol) in 7% yield.

^{1}H NMR (d_6-DMSO): 11.71 (s, 1H), 10.26 (s, 1H), 10.23 (s, 1H), 8.11 (s, 1H), 7.55 (d, J = 8 Hz, 2H), 7.46 (s, 1H), 3.05-3.03 (m, 2H), 2.51 (m, 1H), 1.65-1.53 (m, 3H), 1.29-1.28 (m, 2H), 1.10 (m, 1H), 0.99 (m, 1H), 0.96 (m, 1H), 0.73 (m, 1H).

LCMS: ($M+H^+$) 352.

Example 164: (6-Oxo-2-vinyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid *tert*-butyl ester



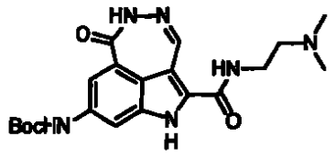
99%

Under an argon atmosphere, Intermediate 147(d) of Example **147** (0.250 g, 0.661 mmol), tributyl-vinyl-tin (0.420 g, 1.32 mmol) and tetrakis(triphenylphosphine)palladium(0) (38 mg, 0.033 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) were heated at 85 °C for 16 hours. The reaction was filtered through a thin pack of diatomaceous earth, and the filtrate concentrated *in vacuo*. Silica gel chromatography (eluted with 1:4 ethyl acetate: dichloromethane) afforded the title compound (0.18 g, 0.552 mmol) as a yellow powder in 84% yield.

^{1}H NMR (d_6-DMSO): δ 11.80 (s, 1H), 10.32 (s, 1H), 9.51 (s, 1H), 7.72-7.62 (m, 3H), 7.05 (dd, 1H, J = 11.87, 6.59 Hz), 5.89 (d, 1H, J = 17.33 Hz), 5.43 (d, 1H, J = 11.11 Hz), 1.49 (s, 9H).

LCMS: ($M+H^+$) 327.2, ($M+Na^+$) 349.1.

Example 165: [2-(2-Dimethylamino-ethylcarbamoyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-carbamic acid *tert*-butyl ester

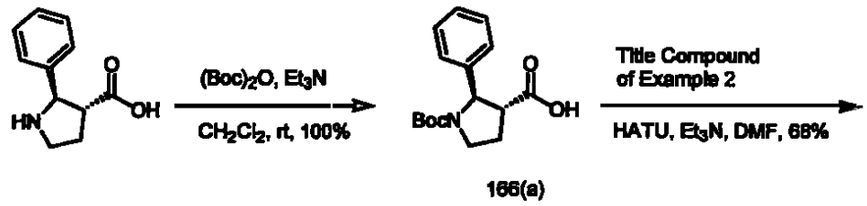


Preparation of example 165 was carried out in a manner analogous to step 5 of Example 147, except that *N,N*-dimethylethylenediamine was substituted for methanol. Thus CO was bubbled through a mixture of Intermediate 147(d) from Example 147 (1.5 g, 3.97 mmol), triethylamine (1.1 mL, 7.92 mmol), *N,N*-dimethylethylenediamine (0.7 g, 7.94 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) (0.65 g, 0.796 mmol) in *N,N*-dimethylformamide (30.0 mL). Reaction conditions, work up and silica gel chromatography (eluted with 46:4:25 dichloromethane: methanol: ethyl acetate) were also carried out in an analogous manner and afforded the title compound (1.25 g, 3.02 mmol) in 76% yield.

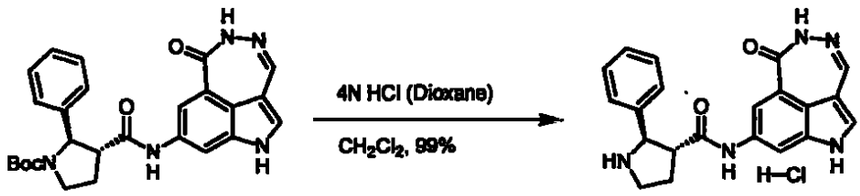
^{1}H NMR (d_6-DMSO): δ 10.55 (s, 1H), 9.59 (s, 1H), 8.25 (t, 1H, *J* = 5.65, 4.71 Hz) 8.06 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 3.45-3.37 (m, 2H, partially obscured), 2.42 (t, 2H, *J* = 6.59, 6.41 Hz), 2.20 (s, 6H), 1.49 (s, 9H).

LCMS: $(M+H^+)$ 415.3, $(M+Na^+)$ 437.1; $(M-H)^-$ 413.1.

Example 166: (2R,3R)-2-Phenyl-pyrrolidine-3-carboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)



166(a)



166(b)

Step 1. Preparation of 2-Phenyl-pyrrolidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 166(a)

To a suspension of (2R,3R)-3-phenylpyrrolidine-2-carboxylic acid (100 mg, 0.556 mmol) in dioxane (2 mL) and H_2O (2 mL) was added triethylamine followed by di-*tert*-butyl dicarbonate (127 mg, 0.583 mmol). The resulting mixture was stirred overnight. The mixture was then partitioned between ethyl acetate and 0.1 M HCl. The combined organic layers were dried over anhydrous

Na_2SO_4, filtered, and concentrated to give Intermediate 166(a) (162 mg, 0.56mmol) in 100% yield which was carried on without purification.

Step 2. Preparation of 3-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-2-phenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester 166(b)

Preparation of intermediate 166(b) from the title compound of Example 2 (300 mg, 1.0 mmol), Intermediate 166(a) (162 mg, 0.56 mmol), triethylamine (0.15 mL, 1.1 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (254 mg, 0.667 mmol) in *N,N*-dimethylformamide (10 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 40% acetone in hexane), also in an analogous manner, afforded intermediate 166(b) as a yellow powder (180 mg, 0.38 mmol) in 68% yield.

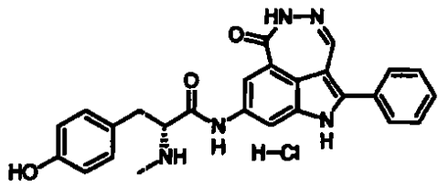
Step 3. Preparation of Title Compound: (2R,3R)-2-Phenyl-pyrrolidine-3-carboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-cd]indol-8-yl)-amide (hydrochloric salt)

Preparation of the title compound from Intermediate 166(b) (180 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) and 4M HCl in dioxane (5 mL) was carried out analogously to Example 91. The solids were collected by filtration and washed with diethyl ether to give the title compound as a pale yellow powder (154 mg, 0.37 mmol) in 99% yield.

^{1}H NMR (d_6-DMSO): 12.03 (s, 1H), 10.72 (s, 1H), 10.46 (s, 1H), 10.20 (br s, 1H), 9.24 (brs, 1H), 8.17 (s, 1H), 7.79 (d, J = 4.0 Hz, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.58-7.52 (m, 5H), 7.48 (m, 1H), 4.43 (m, 1H), 3.77 (q, J = 8.0 Hz, 1H), 3.75 (m, 1H), 3.59 (m, 1H), 2.66 (m, 1H), 2.62 (m, 1H).

LCMS: ($M+H^+$) 374.2.

Example 167: (2R)-3-(4-Hydroxyphenyl)-2-(methylamino)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride



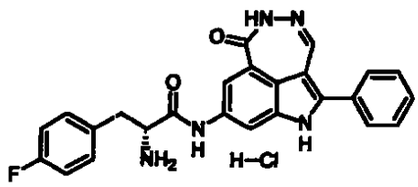
Preparation of example 167 from the title compound of Example 151 (47 mg, 0.085 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example 91. Isolation, also in an analogous manner, included freebasing with triethylamine and subsequent silica gel chromatography eluting with 3:1:1 hexane:ethyl acetate:ethanol. With ice bath cooling, the purified freebase in CH_2Cl_2 (10 mL) was treated with 4M HCl in dioxane (0.1 mL). After removal of the volatile components, the title compound (20 mg, 0.041 mmol) was obtained as an orange/yellow powder in 48% yield.

^{1}H NMR (d_6-DMSO): δ 12.21 (s, 1H), 10.70 (s, 1H), 10.43 (s, 1H), 9.44-9.06 (m, 1H), 8.02 (s, 1H), 7.72-7.64 (m, 2H), 7.61-7.54 (m, 3H), 7.53-7.47 (m, 2H) 7.05 (d, 2H, J = 8.0 Hz), 6.65 (d, 2H, J =

8.0 Hz), 4.09 (m, 1H), 3.40-3.31 (m, 2H), 3.16 (dd, 1H, *J* = 6.07, 13.90 Hz), 3.07 (dd, 1H, *J* = 7.58, 13.89 Hz), 2.55 (s, 3H).

LCMS: $(M+H^+)$ 454.1, $(M+Na^+)$ 476.1.

Example 168: (2R)-2-Amino-3-(4-fluorophenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride

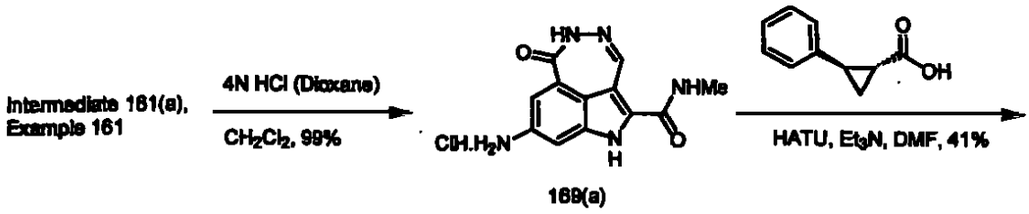


Preparation of example 168 from the title compound of Example **152** (49 mg, 0.091 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included freebasing with triethylamine and subsequent silica gel chromatography eluting with 3:1:1 hexane:ethyl acetate:ethanol. With ice bath cooling, the purified freebase in CH_2Cl_2 (10 mL) was treated with 4M HCl in dioxane (0.1 mL). After removal of the volatile components, the title compound (21 mg, 0.044 mmol) was obtained as an orange/yellow powder in 49% yield.

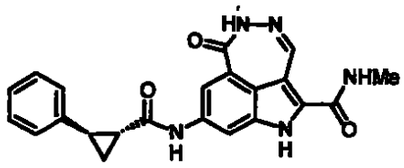
^1H NMR (d_6-DMSO): δ 12.26 (s, 1H), 10.83 (s, 1H), 10.46 (s, 1H), 8.48 (br s, 3H), 8.08 (s, 1H), 7.73-7.48 (m, 7H), 7.40-7.30 (m, 2H), 7.24-7.13 (m, 2H), 4.22 (m, 1H), 3.24 (m, 1H), 3.13 (m, 1H).

LCMS: $(M+H^+)$ 442.1, $(M+Na^+)$ 464.1.

Example 169: (1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methylamide



169(a)



Step 1. Preparation of 8-Amino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methylamide (hydrochloric salt) 169(a)

Preparation of intermediate 169(a) from 161(a) of Example **161** (55.0 mg, 0.154 mmol) and 4.0 M HCl in dioxane (0.77 mL) was carried out analogously to Example **91**. Isolation, also in an

analogous manner, afforded Intermediate 169(a) (45.0 mg, 0.154 mmol) as a yellow powder in 99% yield.

^{1}H NMR (d_6-DMSO): δ 12.46 (s, 1H), 10.71 (s, 1H), 8.54 (m, 1H), 8.05 (s, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 2.81 (s, 3H).

LCMS: $(M+H^+)$ 258.1; $(M-H)^-$ 256.1.

Step 2. Preparation of Title Compound: (1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methylamide

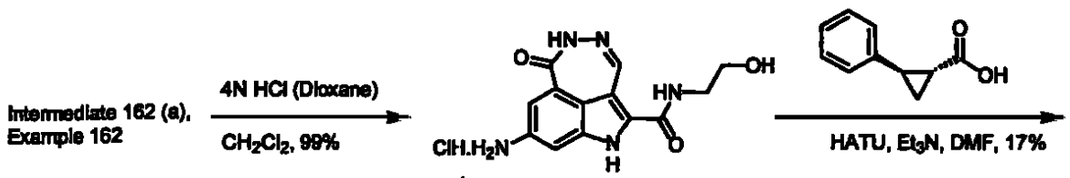
Preparation of the title compound from Intermediate 169(a) (45.0 mg, 0.154 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (59.4 mg, 0.231 mmol), triethylamine (0.086 mL, 0.616 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (87.8 mg, 0.231 mmol) in *N,N*-dimethylformamide (2.0 mL) was carried out analogously to Example **11**. When the reaction was judged complete, *N,N*-dimethylformamide was evaporated and methanol was added. The mixture was filtered to collect the solids, which were washed with methanol and diethyl ether. After drying under vacuum, the title compound (25.0 mg, 0.0623 mmol) was obtained as a yellow powder in 41% yield.

^{1}H NMR (d_6-DMSO): δ 12.13 (s, 1H), 10.60 (s, 1H), 10.51 (s, 1H), 8.36 (d, 1H, J = 4.52 Hz), 8.17 (s, 1H), 8.01 (s, 1H), 7.70 (s, 1H), 7.37-7.25 (m, 2H), 7.25-7.14 (m, 3H), 2.83 (d, 3H, J = 4.52 Hz), 2.45-2.35 (m, 1H), 2.14-2.04 (m, 1H), 1.57-1.47 (m, 1H), 1.45-1.33 (m, 1H).

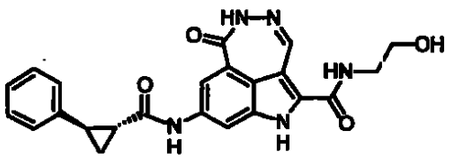
LCMS: $(M+H^+)$ 402.1, $(M+Na^+)$ 424.1.

HRMS: $(M+H^+)$ calcd for $C_{22}H_{20}N_5O_3$, 402.1566, found 402.1551.

Example 170: (1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1H-[1,2]diazepino[4,5,6-cd]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide



170(a)



Step 1. Preparation of 8-Amino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide (hydrochloric salt) 170(a)

Preparation of intermediate 170(a) from intermediate 162(a) of Example **162** (80.0 mg, 0.206 mmol) and 4.0 M HCl in dioxane (1.10 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded Intermediate 170(a) (66.7 mg, 0.206 mmol) as a yellow powder in 99% yield.

LCMS: $(M+H^+)$ 288.2.

Step 2. Preparation of Title Compound: (1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide

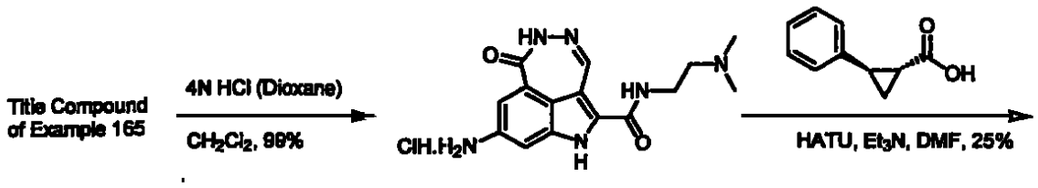
Preparation of the title compound from Intermediate 170(a) (66.7 mg, 0.206 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (46.0 mg, 0.284 mmol), triethylamine (0.143 mL, 1.03 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (147 mg, 0.387 mmol) in *N,N*-dimethylformamide (2.0 mL) was carried out analogously to Example **11**. The reaction mixture was reduced in volume and subjected to preparative HPLC (H1-Q C18 reverse-phase 5 uM, 100A, 150x20 column eluting with CH_3CN/0.1% acetic acid in H_2O at a flowrate of 20 mL/min using a gradient of 20-60% CH_3CN over 30 min) to afford the title compound (15 mg, 0.0348 mmol) as a yellow powder in 17% yield.

^1H NMR (d_6-DMSO): δ 12.19 (s, 1H), 10.31 (s, 1H), 10.52 (s, 1H), 8.36 (t, 1H, *J* = 5.65 Hz), 8.18 (d, 1H, *J* = 1.70 Hz), 8.09 (s, 1H), 7.70 (d, 1H, *J* = 1.70 Hz), 7.35-7.26 (m, 2H), 7.25-7.16 (m, 3H), 4.82 (t, 1H, *J* = 5.46 Hz), 3.54 (dd, 2H, *J* = 5.84, 5.65 Hz), 3.43-3.32 (m, 2H), 2.45-2.35 (m, 1H), 2.14-2.04 (m, 1H), 1.57-1.47 (m, 1H), 1.44-1.33 (m, 1H).

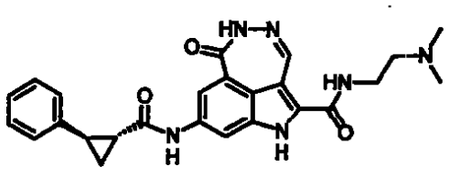
LCMS: $(M+H^+)$ 432.0, $(M+Na^+)$ 454.0.

HRMS: $(M+H^+)$ calcd for $C_{23}H_{22}N_5O_4$, 432.1672, found 432.1648.

Example 171: (1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide



171(a)



Step 1. Preparation of 8-Amino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide; dihydrochloride 171(a)

Preparation of intermediate 171(a) from the title compound of Example **165** (55.0 mg, 0.133 mmol) and 4.0 M HCl in dioxane (0.66 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded Intermediate 171(a) (51.3 mg, 0.132 mmol) as a yellow powder in 99% yield.

LCMS: $(M+H^+)$ 315.2.

Step 2. Preparation of Title Compound: (1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide

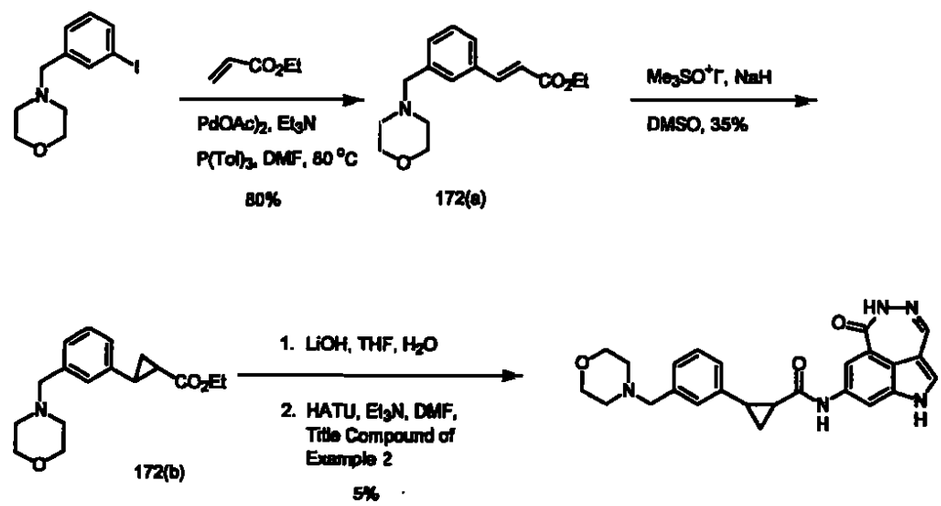
Preparation of the title compound from Intermediate 171(a) (51.3 mg, 0.132 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (24.0 mg, 0.148 mmol), triethylamine (0.074 mL, 0.535 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (76.0 mg, 0.200 mmol) in *N,N*-dimethylformamide (2.0 mL) was carried out analogously to Example **11**. The reaction mixture was reduced in volume and subjected to preparative HPLC (H1-Q C18 reverse-phase 5uM, 100A, 150x20 column eluting with CH_3CN/0.1% acetic acid in H_2O at a flowrate of 20 mL/min using a gradient of 20-60% CH_3CN over 30 min) to afford the title compound (15 mg, 0.0328 mmol) as a yellow-green powder in 25% yield.

^1H NMR (d_6-DMSO): δ 10.63 (s, 1H), 10.53 (s, 1H), 8.71 (br s, 1H), 8.20 (d, 1H, J = 1.13 Hz), 8.06 (s, 1H), 7.70 (d, 1H, J = 0.94 Hz), 7.37-7.26 (m, 2H), 7.26-7.15 (m, 3H), 3.70-3.60 (m, 2H), 3.22-3.11 (m, 2H), 2.76 (s, 6H), 2.42-2.32 (m, 1H), 2.16-2.04 (m, 1H), 1.58-1.46 (m, 1H), 1.46-1.33 (m, 1H).

LCMS: $(M+H^+)$ 459.1, $(M+Na^+)$ 481.1.

HRMS: $(M+H^+)$ calcd for $C_{25}H_{27}N_6O_3$, 459.2145, found 459.2151.

Example 172: (1.2-*trans*)-2-(3-Morpholin-4-ylmethyl-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1-[1.2]diazepino[4.5.6]indol-8-yl)-amide



Step 1. Preparation of 3-(3-Morpholin-4-ylmethyl-phenyl)-acrylic acid ethyl ester 172(a)

To a solution of 4-(3-iodo-benzyl)-morpholine (3.44 g, 11.4 mmol) in *N,N*-dimethylformamide (20 mL) was added triethylamine (1.7 mL, 12.5 mmol), ethyl acrylate (4.1 mL, 45.4 mmol), tri-o-tolylphosphine (346 mg, 1.14 mmol) and palladium (II) acetate (127 mg, 0.57 mmol). The mixture was heated at 80 °C overnight. After concentration, the mixture was chromatographed on silica gel to afford Intermediate 172(a) as a colorless oil (2.37 g, 9.1 mmol) in 80% yield.

Step 2. Preparation of (1,2-*trans*)-2-(3-Morpholin-4-ylmethyl-phenyl)-cyclopropanecarboxylic acid ethyl ester 172(b)

Preparation of intermediate 172(b) from Intermediate 172(a) (472 mg, 1.81 mmol), NaH (94 mg, 2.35 mmol) and trimethylsulfoxonium iodide (517 mg, 2.35 mmol) was carried out analogously to step 1 of Example **181**. After workup, the residue was purified by silica gel chromatography, eluting with 40% ethylacetate/hexane, to give Intermediate 172(b) as a colorless oil (175 mg, 0.64 mmol) in 35 % yield.

Step 3. Preparation of Title compound (1,2-*trans*)-2-(3-Morpholin-4-ylmethyl-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

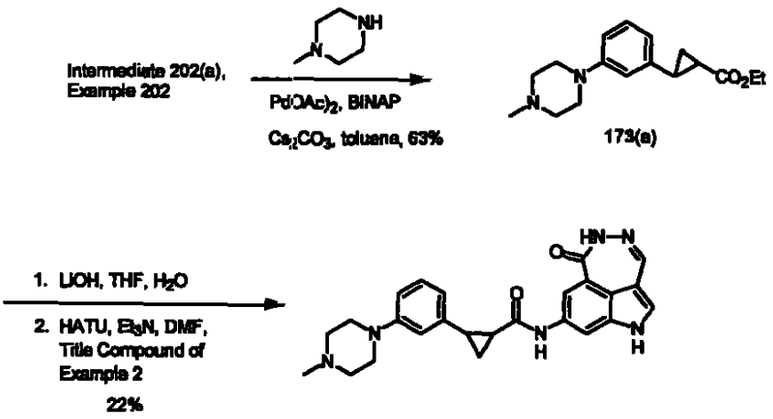
To a solution of Intermediate 172(b) (175 mg, 0.64 mmol) in tetrahydrofuran (2 mL) was added 1 M aqueous LiOH (3.8 mL, 3.8 mmol). The resulting mixture was stirred overnight whereupon mixture was acidified to pH 2 and extracted with ethyl acetate. Concentration of the organic layer gave crude 2-(3-morpholin-4-ylmethyl-phenyl)-cyclopropanecarboxylic acid which was combined with the title compound from Example 2 (227 mg, 0.756 mmol), triethylamine (0.32 mL, 2.27 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (345 mg, 0.907 mmol) in *N,N*-dimethylformamide (5 mL). After was stirring overnight, the volatile

components were removed under vacuum, and the residue was purified by silica gel chromatography to give the title compound as yellow solid (15 mg, 0.03 mmol) in 5% yield.

^{1}H NMR (CD_3OD): δ 8.30 (s, 1H), 7.69 (s, 1H), 7.61 (s, 2H), 7.51-7.28 (m, 4H), 3.84 (s, 4H), 3.66 (s, 2H), 2.61 (s, 4H), 2.45 (m, 1H), 2.21 (m, 1H), 1.76 (m, 1H), 1.53 (m, 1H).

LCMS: ($M+H^+$) 444.2

Example 173: (1,2-*trans*)-2-[3-(4-Methyl-piperazin-1-yl)-phenyl]-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1. Preparation of 2-[3-(4-Methyl-piperazin-1-yl)-phenyl]-cyclopropanecarboxylic acid ethyl ester 173(a)

To a solution of Intermediate 202(a) of Example **202** (165 mg, 0.616 mmol) in toluene (4 mL) was added 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (34.5 mg, 0.055 mmol), 4-methylpiperazine (0.082 mL, 0.74 mmol), Cs_2CO_3 (281 mg, 0.862 mmol) and $Pd(OAc)_2$ (8.3 mg, 0.037 mmol). The mixture was refluxed overnight. The brown mixture was then filtered and the filter cake was washed with ethyl acetate. After concentrating the filtrate, the residue was purified by silica gel chromatography, eluting with 2-5% MeOH/CH_2Cl_2 to afford Intermediate 173(a) as a colorless oil (111 mg, 0.39 mmol) in 63% yield.

Step 2. Preparation of Title compound: (1,2-*trans*)-2-[3-(4-Methyl-piperazin-1-yl)-phenyl]-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

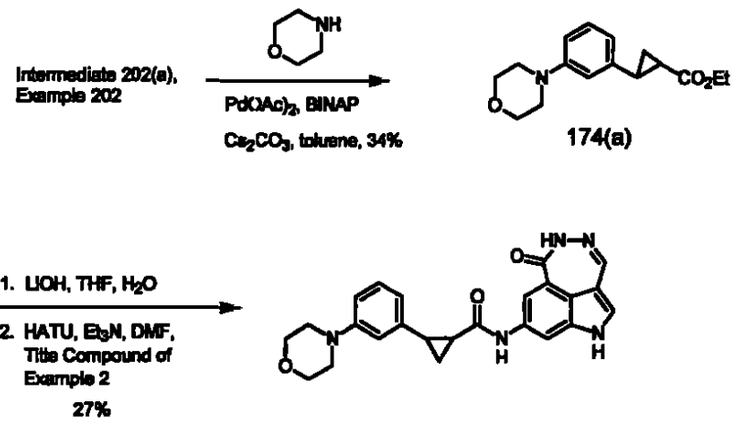
In a manner similar to that described for step 3 of Example **172**, Intermediate 173(a) was treated with 1 M aqueous LiOH to give crude 2-[3-(4-methyl-piperazin-1-yl)-phenyl]-cyclopropanecarboxylic acid. Crude 2-[3-(4-methyl-piperazin-1-yl)-phenyl]-cyclopropanecarboxylic acid was coupled to the title compound of Example **2** (71 mg, 0.3 mmol) also in a manner similar to that described for step 3 of Example **172**. Extractive work-up from ethyl acetate and saturated

aqueous $NaHCO_3$ afforded the crude product, which was purified by silica gel chromatography, eluting with 3% MeOH\CH_2Cl_2, to furnish the title compound (38 mg, 0.086 mmol) in 22% yield.

^1H NMR (d_6-DMSO): δ 11.70 (s, 1H), 10.38 (s, 1H), 10.23 (s, 1H), 8.13 (s, 1H), 7.59 (s, 1H), 7.56 (s, 1H), 7.47 (s, 1H), 7.13 (m, 1H), 6.79-6.74 (m, 2H), 6.58 (m, 1H), 3.22-3.12 (m, 4H), 2.51-2.47 (m, 4H), 2.33 (m, 1H), 2.27 (s, 3H), 2.08 (m, 1H), 1.46 (m, 1H), 1.36 (m, 1H).

LCMS: $(M+H^+)$ 443.2

Example 174: (1,2-*trans*)-2-(3-Morpholin-4-yl-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1. Preparation of 2-[3-Morpholin-4-yl)-phenyl]-cyclopropanecarboxylic acid ethyl ester 174(a)

Preparation of intermediate 174(a) from intermediate 202(a) of Example **202** (239 mg, 0.892 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (50 mg, 0.081 mmol), morpholine (0.12 mL, 1.34 mmol), Cs_2CO_3 (407 mg, 1.25 mmol) and $Pd(OAc)_2$ (12 mg, 0.054 mmol) in toluene (5 mL) was carried analogously to Example **173**. After concentration, the residue was purified by silica gel chromatography, eluting with 1-2 % MeOH/CH_2Cl_2 to afford intermediate 174(a) as a colorless oil (84 mg, 0.31 mmol) in 34% yield:

Step 2. Preparation of Title compound: (1,2-*trans*)-2-(3-Morpholin-4-yl-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

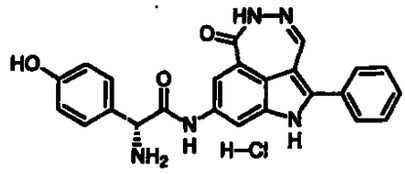
Preparation of the title compound was carried out analogously to step 3 of Example **172** except that Intermediate 174(a) was used instead of Intermediate 172(b). The title compound was obtained in 27% yield.

^1H NMR (d_6-DMSO): δ 10.37 (d, 1H, J = 2.26 Hz), 10.24 (s, 1H), 8.24 (d, 1H, J = 1.88 Hz), 7.58 (d, 1H, J = 1.51 Hz), 7.56 (d, 1H, J = 3.30 Hz), 7.47 (s, 1H), 7.15 (t, J = 8.0 Hz, 1H), 6.79-6.77 (m,

2H), 6.61 (d, 1H, J = 8.0 Hz), 3.74-3.72 (m, 4H), 2.23 (m, 1H), 2.07 (m, 1H), 1.46 (m, 1H), 1.38 (m, 1H).

LCMS: ($M+H^+$) 430.2

Example 175: (2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide hydrochloride

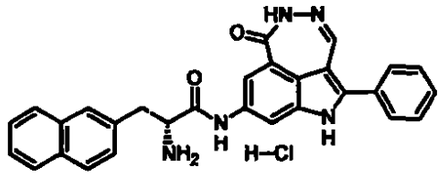


Preparation of example 175 from the title compound of Example **153** (38 mg, 0.072 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included freebasing with triethylamine and subsequent silica gel chromatography eluting with 3:1:1 hexane:ethyl acetate:ethanol. With ice bath cooling, the purified freebase in CH_2Cl_2 (10 mL) was treated with 4M HCl in dioxane (0.1 mL). After removal of the volatile components, the title compound (20 mg, 0.043 mmol) was obtained as an orange/yellow powder in 60% yield.

^{1}H NMR (d_6-DMSO): δ 12.23 (s, 1H), 10.82 (s, 1H), 10.45 (s, 1H), 8.71 (br s, 3H), 8.10 (s, 1H), 7.75-7.65 (m, 3H), 7.63-7.49 (m, 4H), 7.43 (d, 2H, J = 8.47 Hz), 6.86 (d, 2H, J = 8.47 Hz), 5.02 (m, 1H).

LCMS: ($M+H^+$) 426.2.

Example 176: (2*R*)-2-Amino-3-naphthalen-2-yl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride

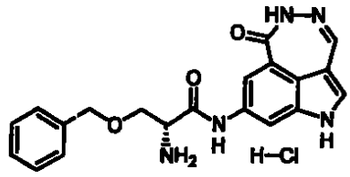


Preparation of example 176 from the title compound of Example **154** (59 mg, 0.103 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner afforded the title compound (52 mg, 0.102 mmol) as an orange/yellow powder in 99% yield.

^{1}H NMR (d_6-DMSO): δ 12.24 (s, 1H), 10.82 (s, 1H), 10.44 (s, 1H), 8.43 (br s, 3H), 8.07 (s, 1H), 7.93-7.81 (m, 5H), 7.71-7.45 (m, 9H), 4.32 (br s, 1H), 3.44 (m, 1H, partially obscured), 3.28 (m, 1H).

LCMS: ($M+H^+$) 474.2, ($M+Na^+$) 496.3.

Example 177: (2*R*)-2-Amino-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-[(phenylmethyl)oxy]propanamide hydrochloride

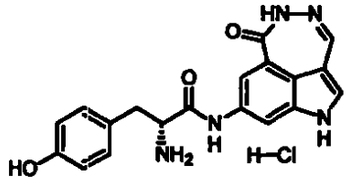


Preparation of example 177 from the title compound of Example **159** (35 mg, 0.072 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner afforded the title compound (30 mg, 0.072 mmol) as an orange/yellow powder in 100% yield.

^{1}H NMR (d_6-DMSO): δ 11.89 (s, 1H), 10.75 (s, 1H), 10.32 (s, 1H), 8.45 (br s, 3H), 8.06 (s, 1H), 7.63 (s, 2H), 7.50 (s, 1H), 7.38-7.26 (m, 5H), 4.59 (dd, 2H, *J* = 12.25, 17.33 Hz), 4.24 (br s, 1H), 3.89 (d, 2H, *J* = 4.15 Hz, partially obscured).

LCMS: (M+H$^+$) 378.2, (M+Na$^+$) 400.1.

Example 178: (2R)-2-Amino-3-(4-hydroxyphenyl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride

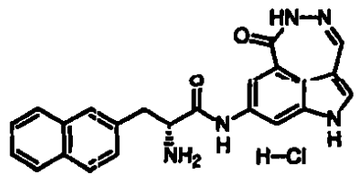


Preparation of example 178 from the title compound of Example **155** (90 mg, 0.194 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner afforded the title compound (56 mg, 0.140 mmol) as an orange/yellow powder in 72% yield.

^{1}H NMR (d_6-DMSO): δ 11.89 (s, 1H), 10.70 (s, 1H), 10.30 (s, 1H), 9.38 (br s, 1H), 8.34 (br s, 3H), 8.03 (s, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 7.49 (s, 1H), 7.08 (d, 2H, *J* = 8.29 Hz), 6.70 (d, 2H, *J* = 8.29 Hz), 4.11 (br s, 1H), 2.93-3.15 (m, 2H).

LCMS:(M+Na$^+$) 386.5, (M-H)$^-$ 362.4.

Example 179: (2R)-2-Amino-3-naphthalen-2-yl-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride

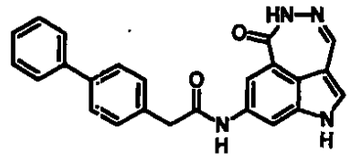


Preparation of example 179 from the title compound of Example **168** (57 mg, 0.115 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner afforded the title compound (48 mg, 0.111 mmol) as an orange/yellow powder in 97% yield.

^{1}H NMR (d_6-DMSO): δ 11.88 (s, 1H), 10.82 (s, 1H), 10.30 (s, 1H), 8.43 (br s, 3H), 8.04 (s, 1H), 7.93-7.78 (m, 4H), 7.64-7.57 (m, 2H), 7.54-7.45 (m, 4H), 4.32 (br s, 1H), 3.22-3.46 (m, 2H, partially obscured).

LCMS: ($M+H^+$) 398.5, ($M+Na^+$) 420.4.

Example 180: 2-(1,1'-Biphenyl-4-yl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide

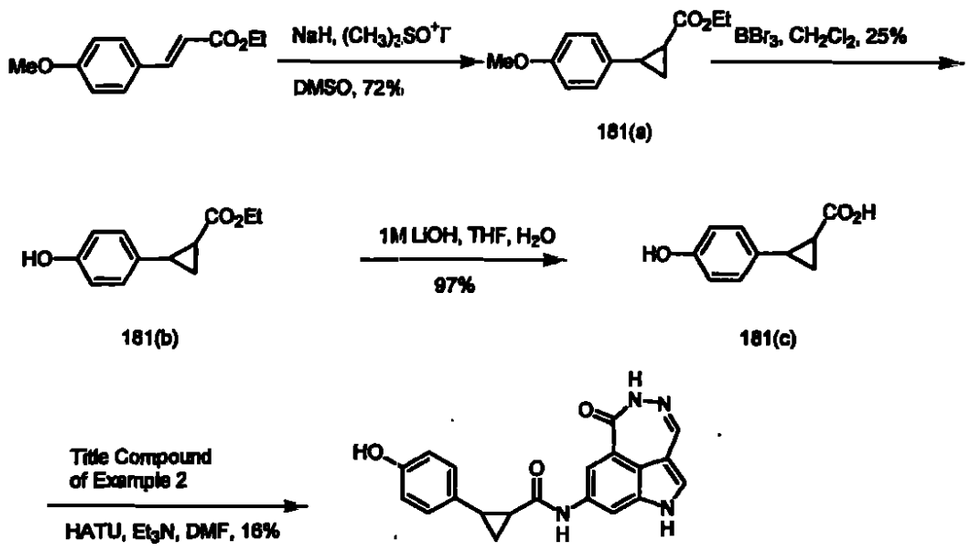


Preparation of example 180 from the title compound of Example **2** (75 mg, 0.38 mmol), 1,1'-biphenyl-4-ylacetic acid (93 mg, 0.44 mmol), triethylamine (0.16 mL, 1.15 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (167 mg, 0.44mmol) in CH_2Cl_2 (1.0 mL) and *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **11**. Silica gel chromatography was performed twice eluting both times with 1:1 hexane:acetone and the purest fractions were combined, evaporated, and the resulting solids triturated with methanol to afford the title compound (5 mg, 0.012mmol) as a yellow powder in 3% yield.

^{1}H NMR (d_6-DMSO): δ 11.74 (s, 1H), 10.35 (s, 1H), 10.25 (s, 1H), 8.14 (s, 1H), 7.69-7.54 (m, 6H), 7.51-7.33 (m, 6H), 3.69 (s, 2H).

LCMS: ($M+H^+$) 395.4, ($M+Na^+$) 417.4.

Example 181: (1*R*,2*R*-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1. Preparation of (1,2-*trans*)-2-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid ethyl ester 181(a)

To a mixture of NaH (200 mg, 5.0 mmol) and trimethylsulfoxonium iodide (1.1 g, 5.0 mmol) was added DMSO (10 mL). After stirring for 30 min, a solution of 3-(4-methoxy-phenyl)-acrylic acid ethyl ester (400mg, 1.92 mmol) in DMSO (5 mL) was added drop-wise. After stirring overnight, the mixture was partitioned between ethyl acetate and water. The aqueous layer was re-extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4 and concentrated. Purification by silica gel chromatography eluting with 10 % ethyl acetate in hexane gave Intermediate 181(a) (318 mg, 1.44 mmol) in 72% yield.

Step 2. Preparation of (1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid ethyl ester 181(b)

To a stirred solution of Intermediate 181(a) (318 mg, 1.45 mmol) in CH_2Cl_2 (8 mL) at –78 °C was added 1M BBr_3 in CH_2Cl_2 (1.7 mL). The resulting mixture was then warmed to 23 °C and stirred for 30 min. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated, and subjected to silica gel chromatography eluting with 15% ethyl acetate in hexane to afford Intermediate 181(b) as a colorless oil (75 mg, 0.364 mmol) in 25% yield.

Step 3. Preparation of (1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid 181(c)

To a stirred solution of Intermediate 181(b) (75mg, 0.36 mmol) in tetrahydrofuran (2.5 mL) was added aqueous 1M LiOH (2.5 mL). The resulting mixture was stirred at 23 °C for 12 hours. The mixture was then acidified with 1M HCl to pH 1 and extracted with ethyl acetate. The organic layer was then washed with brine and concentrated to give Intermediate 181(c) (63 mg, 0.35 mmol) in 97% yield which was carried on without further purification.

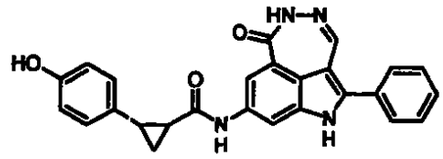
Step 4. Preparation of Title Compound: (1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

Preparation of the title compound from the title compound of Example 2 (66 mg, 0.278 mmol), Intermediate 181(c) (62 mg, 0.348 mmol), triethylamine (0.073 mL, 0.52 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (159 mg, 0.42 mmol) in *N,N*-dimethylformamide (2 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 2% methanol in CH_2Cl_2), also in an analogous manner, afforded the title compound (20 mg, 0.056 mmol) as a yellow powder in 16% yield.

^{1}H NMR (d_6-DMSO): 12.09 (s, 1H), 10.38 (s, 1H), 10.37 (s, 1H), 9.26 (br s, 1H), 8.16 (s, 1H), 7.65-7.67 (m, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 2.33 (m, 1H), 1.98 (m, 1H), 1.43 (m, 1H), 1.24 (m, 1H).

LCMS: ($M+H^+$) 361.3.

Example 182: (1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide

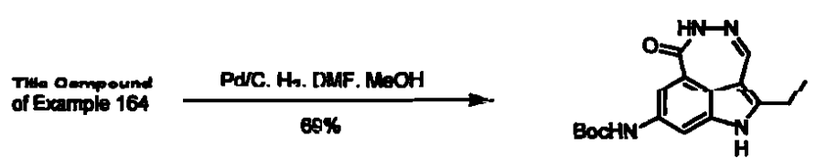


Preparation of example 182 from the title compound of Example 7 (35 mg, 0.127 mmol), Intermediate 181(c) of Example 181 (66 mg, 0.372 mmol), triethylamine (0.062 mL, 0.45 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (156 mg, 0.41 mmol) in *N,N*-dimethylformamide (3 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 2% methanol in CH_2Cl_2), also in an analogous manner, gave the title compound (32 mg, 0.073 mmol) as a yellow powder in 20% yield.

^{1}H NMR (d_4- methanol): 8.04 (s, 1H), 7.44 (s, 1H), 7.35 (s, 1H), 7.34 (s, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 2.31 (m, 1H), 1.87 (m, 1H), 1.43 (m, 1H), 1.24 (m, 1H).

LCMS: ($M+H^+$) 437.4.

Example 183: (2-Ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid *tert*-butyl ester



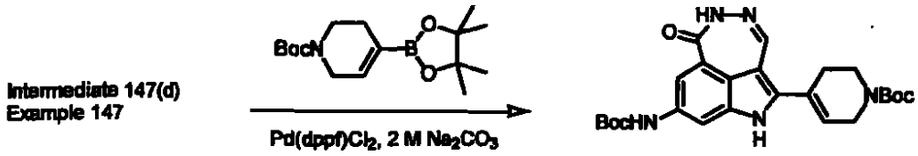
Palladium (10% on activated carbon) (0.23 g, 0.198 mmol) was added to a solution of the title compound of Example 164 (0.65 g, 1.99 mmol) in 1:10 *N,N*-dimethylformamide: methanol (11

mL). The reaction mixture was purged with H_2 and stirred at room temperature under H_2 (1 atm.) for 5 hours. The palladium was filtered and the volatile components were removed *in vacuo*. The resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1.2:1 dichloromethane: ethyl acetate to afford the title compound (0.45 g, 1.37 mmol) as a yellow solid in 69% yield.

^{1}H NMR (d_6-DMSO): δ 11.54 (s, 1H), 10.05 (s, 1H), 9.37 (s, 1H), 7.63 (s, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 2.80 (dd, 2H, *J* = 7.35, 7.54 Hz), 1.48 (s, 9H), 1.23 (t, 3H, *J* = 7.54 Hz).

LCMS: $(M+H^+)$ 329.5, $(M+Na^+)$ 351.5; $(M-H)^-$ 327.4.

Example 184: 4-(8-*tert*-Butoxycarbonylamino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester



Under an argon atmosphere, 2.0 M aqueous Na_2CO_3 (0.66 mL) was added to a mixture of Intermediate 147(d) of Example **147** (100 mg, 0.265 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (122 mg, 0.395 mmol) and [1,1'- bis(diphenylphosphino)ferrocene]dichloropalladium (II) (10.8 mg, 0.013 mmol) in anhydrous *N,N*-dimethylformamide (5 ml). The mixture was heated at 80 °C for 16 hours. The reaction was filtered through a thin pack of diatomaceous earth, and the volatile components were removed *in vacuo*. Silica gel chromatography (eluted with 1:1 ethyl acetate: hexane) afforded the title compound (120 mg, 0.249 mmol) as a yellow powder in 94% yield.

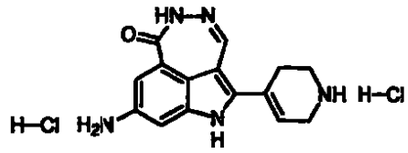
^{1}H NMR (d_6-DMSO): δ 11.62 (s, 1H), 10.22 (s, 1H), 9.46 (s, 1H), 7.69 (s, 1H), 7.65 (d, 1H, *J* = 1.70 Hz), 7.49 (s, 1H), 6.16 (s, 1H), 4.06 (s, 2H), 3.56 (t, 2H, *J* = 5.65, 4.90 Hz), 3.31 (m, 2H, partially obscured), 1.49 (s, 9H), 1.44 (s, 9H).

LCMS: $(M+H^+)$ 482.5, $(M+Na^+)$ 504.5; $(M-H)^-$ 480.5.

HRMS: $(M+H^+)$ calcd for $C_{25}H_{32}N_6O_5$, 482.2403, found 482.2417.

The 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester starting material was prepared according to Eastwood, P.R. (2000) Tetrahedron Letters 41(19):3705-3708 from trifluoromethanesulfonic acid 1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl ester which in turn was prepared according to the procedure outlined by Barrow, J. C. et. al.(2000) J. Med. Chem. 43(14) 2703-2718.

Example 185: 8-Amino-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one



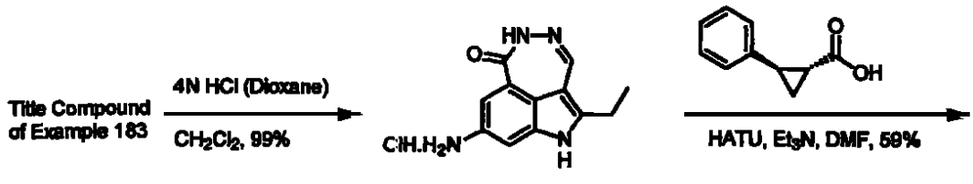
Preparation of example 185 from the title compound of Example **184** (20 mg, 0.042 mmol) and 4.0 M HCl in dioxane (0.1 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (14.7 mg, 0.042 mmol) as a yellow powder in 99% yield.

^{1}H NMR (d_6-DMSO): δ 12.20 (br s, 1H), 10.46 (s, 1H), 9.14 (s, 3H), 7.57 (s, 1H), 7.36 (s, 2H), 6.22 (s, 1H), 3.83 (s, 2H), 3.36 (s, 2H), 2.74 (s, 2H).

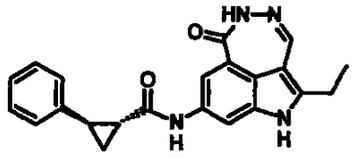
LCMS: $(M+Na^+)$ 304.3; $(M-H)^-$ 280.2.

HRMS: $(M+H^+)$ calcd for $C_{15}H_{16}N_5O$, 282.1355, found 282.1349.

Example 186: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



186(a)



Step 1. Preparation of 8-Amino-2-ethyl-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one (hydrochloric salt) 186(a)

Preparation of intermediate 186(a) from the title compound of Example **183** (120 mg, 0.366 mmol) and 4.0 M HCl in dioxane (0.92 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded Intermediate 186(a) (95.5 mg, 0.366 mmol) as a yellow powder in 99% yield.

LCMS: $(M+H^+)$ 229.1

Step 2. Preparation of Title Compound: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

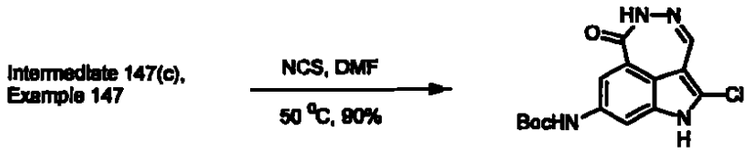
Preparation of the title compound from Intermediate 186(a) (95.5 mg, 0.366 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (65.0 mg, 0.401 mmol), triethylamine (0.510 mL, 3.66 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (210 mg, 0.552 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example 11. The volatile components were removed *in vacuo* and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1.2:1 dichloromethane: ethyl acetate to afford the title compound (80 mg, 0.215 mmol) as a yellow solid in 59% yield.

^{1}H NMR (d_6-DMSO): δ 11.63 (s, 1H), 10.31 (s, 1H), 10.09 (s, 1H), 8.00 (d, 1H, *J* = 1.51 Hz), 7.52 (d, 1H, *J* = 1.51 Hz), 7.45 (s, 1H), 7.34-7.24 (m, 2H), 7.24-7.13 (m, 3H), 2.81 (q, 2H, *J* = 7.54 Hz), 2.41-2.31 (m, 1H), 2.11-2.00 (m, 1H), 1.53-1.43 (m, 1H), 1.40-1.29 (m, 1H), 1.23 (t, 3H, *J* = 7.54 Hz).

LCMS: ($M+H^+$) 373.1.

HRMS: ($M+H^+$) calcd for $C_{22}H_{21}N_4O_2$, 371.1665, found 373.1672.

Example 187: (2-Chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid *tert*-butyl ester

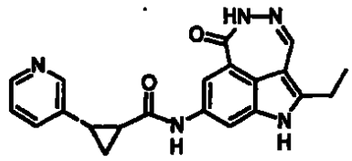


N-Chlorosuccinimide (0.47 g, 3.52 mmol) was added to a solution of Intermediate 147(c) of Example 147 (1.00 g, 3.33 mmol) in anhydrous *N,N*-dimethylformamide (10 ml) and anhydrous chloroform (6.5 mL). The reaction was heated at 50 °C for 3 hours at which point the volatile components were removed *in vacuo*. The resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 23:2:50 dichloromethane: methanol: ethyl acetate to afford the title compound (1 g, 2.99 mmol) as a yellow solid in 90% yield.

^{1}H NMR (d_6-DMSO): δ 12.52 (s, 1H), 10.41 (s, 1H), 9.51 (s, 1H), 7.70 (s, 1H), 7.66 (s, 1H), 7.32 (s, 1H), 1.47 (s, 9H).

LCMS: ($M+H^+$) 335.1, ($M+Na^+$) 357.0; ($M-H^-$) 333.0.

Example 188: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



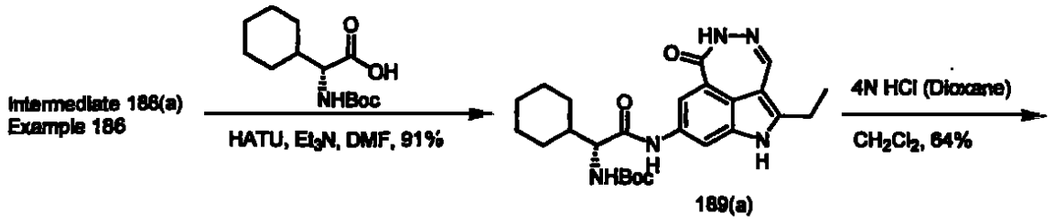
Preparation of example 188 from Intermediate 186(a) of Example 186 (90 mg, 0.341 mmol), crude (1,2-*trans*)-2-pyridin-3-yl-cyclopropanecarboxylic acid (see Example 125 for preparation-estimated purity c.a. 75%) (79.5 mg, c.a. 0.341 mmol), triethylamine (0.237 mL, 1.73 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (194 mg, 0.510 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example 11. The volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 50:3 dichloromethane: methanol to afford the title compound (75 mg, 0.201 mmol) as a yellow solid in 59% yield.

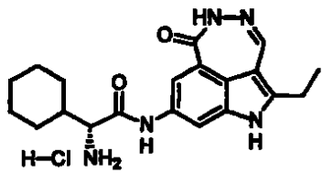
^{1}H NMR (d_6-DMSO): δ 11.65 (s, 1H), 10.36 (s, 1H), 10.11 (s, 1H), 8.51 (d, 1H, J = 1.88 Hz), 8.42 (dd, 1H, J = 1.32, 1.32 Hz), 8.01 (d, 1H, J = 1.70 Hz), 7.57 (dt, 1H, J = 7.91, 1.88 Hz), 7.53 (d, 1H, J = 1.70 Hz), 7.47 (s, 1H), 7.33 (dd, 1H, J = 4.90, 4.71 Hz), 2.82 (q, 2H, J = 7.54 Hz), 2.47-2.38 (m, 1H), 2.17-2.08 (m, 1H), 1.58-1.49 (m, 1H), 1.49-1.39 (m, 1H), 1.24 (t, 3H, J = 7.54 Hz).

LCMS: $(M+H^+)$ 374.2, $(M+Na^+)$ 396.0; $(M-H)^-$ 372.0.

HRMS: $(M+H^+)$ calcd for $C_{21}H_{20}N_5O_2$, 374.1617, found 374.1620.

Example 189: (R)- 2-Amino-2-cyclohexyl-*N*-(2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide (hydrochloride salt)





Step 1. Preparation of (R)-[Cyclohexyl-(2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester 189(a)

Preparation of intermediate 189(a) from Intermediate 186(a) of Example **186** (90 mg, 0.341 mmol), (R)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (88 mg, 0.342 mmol), triethylamine (0.237 mL, 1.73 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (194 mg, 0.510 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example **11**. The volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1.2:1 dichloromethane: ethyl acetate to afford Intermediate 189(a) (146 mg, 0.313 mmol) as a yellow solid in 91% yield.

^{1}H NMR (d_6-DMSO): δ 11.64 (s, 1H), 10.12 (s, 1H), 10.02 (s, 1H), 7.99 (s, 1H), 7.54 (s, 1H), 7.47 (s, 1H), 6.87 (d, 1H, *J* = 7.72 Hz), 3.92 (t, 1H, *J* = 8.48 Hz), 2.82 (q, 2H, *J* = 7.54 Hz), 1.78-1.46 (m, 6H), 1.38 (s, 9H), 1.24 (t, 3H, *J* = 7.54 Hz), 1.19-0.94 (m, 5H).

LCMS: $(M+H^+)$ 468.2, $(M+Na^+)$ 490.2.

Step 2. Preparation of Title Compound: (R)- 2-Amino-2-cyclohexyl-*N*-(2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide (hydrochloric salt)

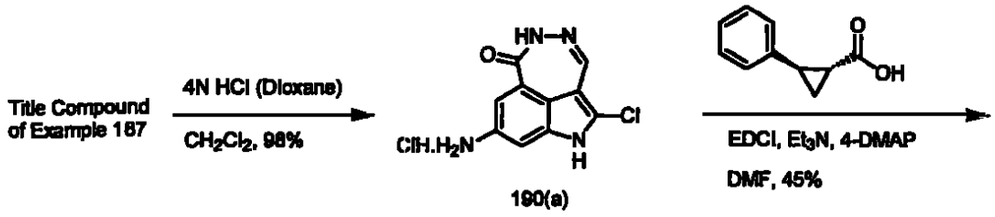
Preparation of the title compound from Intermediate 189(a) (136 mg, 0.291 mmol) and 4.0 M HCl in dioxane (1.5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (75 mg, 0.186 mmol) as a yellow powder in 64% yield.

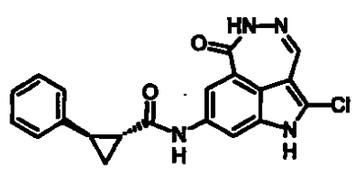
^{1}H NMR (d_6-DMSO): δ 11.81 (s, 1H), 10.66 (s, 1H), 10.19 (s, 1H), 8.42-8.20 (m, 3H), 7.98 (s, 1H), 7.59 (s, 1H), 7.50 (s, 1H), 3.82-3.66 (m, 1H), 2.84 (q, 2H, *J* = 7.54 Hz), 1.94-1.53 (m, 6H), 1.30-0.98 (m, 8H).

LCMS: $(M+H^+)$ 368.1, $(M+Na^+)$ 390.2; $(M-H)^-$ 366.1.

HRMS: $(M+H^+)$ calcd for $C_{20}H_{26}N_5O_2$, 368.2087, found 368.2084.

Example 190: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide





Step 1. Preparation of 8-Amino-2-chloro-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one (hydrochloric salt) 190(a)

Preparation of intermediate 190(a) from the title compound of Example **187** (0.83 g, 2.48 mmol) and 4.0 M HCl in dioxane (6.2 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded Intermediate 190(a) (0.66 g, 2.44 mmol) as a yellow powder in 98% yield.

^{1}H NMR (d_6-DMSO): δ 12.87 (s, 1H), 10.57 (s, 1H), 7.38 (s, 2H), 7.27 (s, 1H).

LCMS: $(M-H)^-$ 233.1.

Step 2. Preparation of Title Compound: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

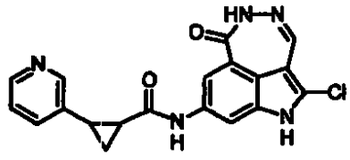
Intermediate 190(a) (120 mg, 0.443 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (86.0 mg, 0.531 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (102 mg, 0.534 mmol), and 4-dimethylaminopyridine (65 mg, 0.533 mmol) were stirred in *N,N*-dimethylformamide (7.0 mL) at room temperature for 16 h at which point the volatile components were removed *in vacuo*. The resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1.2:1 dichloromethane: ethyl acetate to afford the title compound (75 mg, 2.99 mmol) as a yellow solid in 45% yield.

^{1}H NMR (d_6-DMSO): δ 12.65 (s, 1H), 10.46 (s, 2H), 8.09 (s, 1H), 7.63 (s, 1H), 7.36 (s, 1H), 7.34-7.25 (m, 2H), 7.25-7.12 (m, 3H), 2.44-2.30 (m, 1H), 2.13-2.01 (m, 1H), 1.57-1.44 (m, 1H), 1.44-1.31 (m, 1H).

LCMS: $(M-H)^-$ 377.1.

HRMS: $(M+H^+)$ calcd for $C_{20}H_{16}N_4O_2Cl$, 379.0962, found 379.0941.

Example 191: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Preparation of example 191 from Intermediate 190(a) of Example **190** (120 mg, 0.443 mmol), crude 2-pyridin-3-yl-cyclopropanecarboxylic acid (estimated purity c.a. 75%) (124 mg, c.a. 0.532 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (102 mg, 0.534 mmol), and 4-dimethylaminopyridine (65 mg, 0.533 mmol) in *N,N*-dimethylformamide (7.0 mL) was carried out analogously to Example **190**, Step 2. When the reaction was judged complete, the volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with

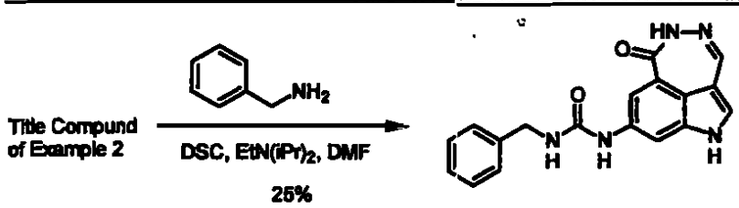
50:3 dichloromethane: methanol to afford the title compound (80 mg, 0.210 mmol) as a yellow solid in 48% yield.

^{1}H NMR (d_6-DMSO): δ 12.65 (s, 1H), 10.48 (s, 1H), 10.46 (s, 1H), 8.51 (s, 1H), 8.42 (d, 1H, *J* = 3.20 Hz), 8.09 (d, 1H, *J* = 1.13 Hz), 7.63 (d, 1H, *J* = 1.32 Hz), 7.57 (d, 1H, *J* = 7.91 Hz), 7.40-7.28 (m, 2H), 2.47-2.37 (m, 1H), 2.19-2.06 (m, 1H), 1.60-1.50 (m, 1H), 1.50-1.40 (m, 1H).

LCMS: $(M+H^+)$ 380.0, $(M+Na^+)$ 402.1; $(M-H)^-$ 378.0.

HRMS: $(M+H^+)$ calcd for $C_{19}H_{16}N_5O_2Cl$, 380.0914, found 380.0922.

Example 192: *N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-*N*'-(phenylmethyl)urea

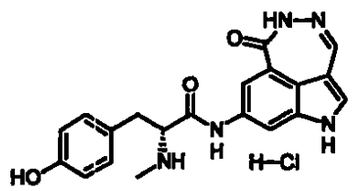


To the title compound of Example 2 (45 mg, 0.19 mmol) and *N,N*'-disuccinimidyl carbonate (49 mg, 0.19 mmol) was added *N,N*-dimethylformamide (0.5mL) and triethylamine (0.084 mL, 0.60 mmol). After 3 to 5 min, benzylamine (0.046 mL, 0.20 mmol) was added, and the reaction was stirred for about an hour. Methylene chloride:methanol (4:1) was added and the resulting solids were removed by trituration. The triturate was loaded onto a silica gel plug and evaporated. The plug was then loaded onto a silica gel column and eluted with hexane:acetone (1:1) and the purest fractions were combined. After solvent removal, the title compound (16 mg, 0.048 mmol) was obtained as brown powder in 25% yield.

^{1}H NMR (d_6-DMSO): δ 11.61 (s, 1H, exchanges), 10.19 (s, 1H, exchanges), 8.75 (s, 1H, exchanges), 7.93 (s, 1H), 7.49 (m, 1H), 7.40-7.30 (m, 7H), 6.55 (m, 1H, exchanges), 4.31 (d, 2H, *J* = 5.84 Hz).

LCMS: $(M+H^+)$ 334.2, $(M+Na^+)$ 356.3

Example 193: (2R)-3-(4-Hydroxyphenyl)-2-(methylamino)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride

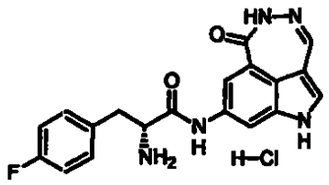


Preparation of example 193 from the title compound of Example 156 (121 mg, 0.25 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example 91. Isolation, also in an analogous manner, afforded the title compound (74 mg, 0.18 mmol) as an orange/yellow powder in 72% yield.

^{1}H NMR (d_6-DMSO): major component/conformer: δ 11.89 (s, 1H, exchanges), 10.73 (s, 1H, exchanges), 10.31 (s, 1H, exchanges), 9.36 (br s, 2H, exchanges), 9.11 (br s, 1H, exchanges), 7.99 (s, 1H), 7.64 (s, 1H), 7.56 (s, 1H), 7.50 (s, 1H), 7.06 (d, 2H, *J* = 8.48 Hz), 6.69 (d, 2H, *J* = 8.48 Hz), 4.11 (m, 1H), 3.18 (m, 1H), 3.08 (m, 1H), 2.55 (s, 3H, partially obscurred).

LCMS: ($M+H^+$) 378.0, ($M+Na^+$) 400.1.

Example 194: (2R)-2-Amino-3-(4-fluorophenyl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride

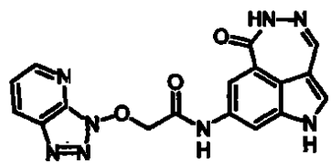


Preparation of example 194 from the title compound of Example **157** (48 mg, 0.10 mmol) and 4M HCl in dioxane (10 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner afforded the title compound (34 mg, 0.08 mmol) as an orange/yellow powder in 80% yield.

^{1}H NMR (d_6-DMSO): δ 11.88 (s, 1H, exchanges), 10.72 (s, 1H, exchanges), 10.32 (s, 1H, exchanges), 8.37 (br s, 4H, exchanges), 8.04 (s, 1H), 7.64 (s, 1H), 7.57 (s, 1H), 7.50 (s, 1H), 7.38-7.29 (m, 2H), 7.22-7.14 (m, 2H), 4.19 (m, 1H), 3.26-3.03 (m, 2H).

LCMS: ($M+H^+$) 366.0, ($M+Na^+$) 388.1.

Example 195: *N*-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)acetamide

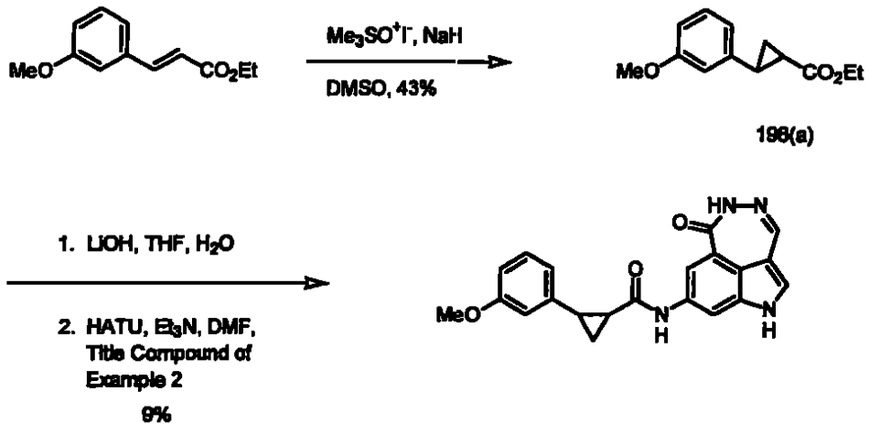


In a manner analogous to that of Example **19**, to a stirred suspension of 8-amino-1,5-dihydro-6*H*-[1,2]diazepino[4,5,6-*cd*] indol-6-one hydrochloride in anhydrous *N,N*-dimethylformamide (9 mL) was added bromoacetic acid (168 mg. 1.2 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (553 mg, 1.4 mmol) and triethylamine. The reaction was stirred at room temperature for 16 hours. The volatile components were evaporated and water was added to the residue. The precipitated orange solids were collected by filtration and washed with water and ethyl acetate. After drying, the title compound (158 mg) was obtained as an orange powder in 35% yield.

^{1}H NMR (DMSO –d_6) d: 5.28 (1H, s), 7.47 (1H, s), 7.58 (3H, m), 8.09 (1H, d, *J* = 1.77 Hz), 8.63 (1H, dd, *J* = 8.59 Hz), 8.83 (1H, dd, *J* = 4.55 Hz), 10.27 (1H, s), 10.52 (1H, s), 11.77 (1H, s).

LCMS: ($M+H^+$) 377.

Example 196: (1,2-*trans*)-2-(3-Methoxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1: Preparation of (1,2-*trans*)-2-(3-Methoxy-phenyl)-cyclopropanecarboxylic acid ethyl ester 196(a)

Preparation of intermediate 196(a) from NaH (1.04 g, 26 mmol) and trimethylsulfoxonium iodide (5.72 g, 26 mmol), 3-(methoxy-phenyl)-acrylic acid ethyl ester (4.12 g, 20 mmol) in DMSO (30 mL) was carried out analogously to step 2 of Example **113** to afford Intermediate 196(a) (1.89 g, 8.6 mmol) in 43% yield.

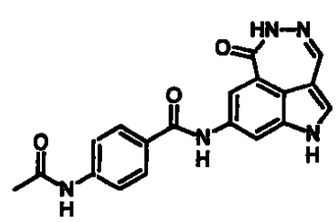
Step 2: Preparation of Title compound: (1,2-*trans*)-2-(3-Methoxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6-]indol-8-yl)-amide

Preparation of the title compound was carried out analogously to step 3 of Example **172** except that Intermediate 196(a) was used instead of Intermediate 172(b). The title compound was obtained in 9% yield.

^{1}H NMR (d_6-DMSO): δ 11.85 (d, 1H, *J* = 2.26 Hz), 10.37 (s, 1H), 10.23 (s, 1H), 8.12 (s, 1H), 7.57 (dd, 1H, *J* = 3.20, 1.51 Hz), 7.46 (s, 2H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.77-6.74 (m, 3H), 3.75 (s, 3H), 2.36 (m, 1H), 2.08 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H).

LCMS: ($M+H^+$) 375.1.

Example 197: 4-Acetylamino-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide



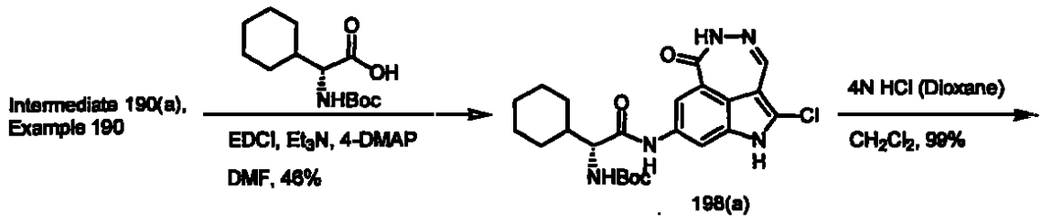
Preparation of example 197 from the title compound of Example **2** (124 mg, 0.525 mmol), 4-acetylamino-benzoic acid (113 mg, 0.631 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (120 mg, 0.628 mmol), and 4-dimethylaminopyridine (77 mg, 0.631 mmol) in *N,N*-dimethylformamide (7.0 mL) was carried out analogously to Example **190**, Step 2. When the reaction was judged complete, the volatile components were evaporated and methanol was added. The mixture was filtered to collect the solids, which were then washed with methanol, dichloromethane and diethyl ether. After drying, the title compound (32 mg, 0.0886 mmol) was obtained as a yellow powder in 17% yield.

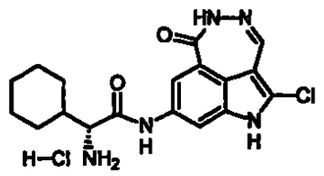
^{1}H NMR (d_6-DMSO): δ 11.79 (d, 1H, *J* = 2.64 Hz), 10.25 (s, 1H), 10.23 (s, 2H), 8.27 (d, 1H, *J* = 1.70 Hz), 7.96 (d, 2H, *J* = 8.67 Hz), 7.85 (d, 1H, *J* = 1.70 Hz), 7.70 (d, 2H, *J* = 8.67 Hz), 7.58 (d, 1H, *J* = 2.64 Hz), 7.48 (s, 1H), 2.09 (s, 3H).

LCMS: $(M-H)^-$ 360.2.

HRMS: $(M+H^+)$ calcd for $C_{19}H_{18}N_5O_3$, 362.1253, found 362.1280.

Example 198: (R)- 2-Amino-*N*-(2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-cyclohexyl-acetamide (hydrochloric salt)





Step 1. Preparation of [(2-Chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-cyclohexyl-methyl]-carbamic acid *tert*-butyl ester 198(a)

Preparation of intermediate 198(a) from Intermediate 190(a) of Example **190** (100 mg, 0.369 mmol), (R)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (114 mg, 0.443 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (85 mg, 0.445 mmol), and 4-dimethylaminopyridine (54 mg, 0.443 mmol) in *N,N*-dimethylformamide (7.0 mL) was carried out analogously to Example **190**, Step 2. When the reaction was judged complete, the volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1.2:1 dichloromethane: ethyl acetate to afford Intermediate 198(a) (80 mg, 0.169 mmol) as a yellow solid in 46% yield.

^{1}H NMR (d_6-DMSO): δ 12.64 (s, 1H), 10.47 (s, 1H), 10.16 (s, 1H), 8.06 (d, 1H, *J* = 1.51 Hz), 7.66 (d, 1H, *J* = 1.51 Hz), 7.36 (s, 1H), 6.91 (d, 1H, *J* = 9.04 Hz), 3.92 (dd, 1H, *J* = 8.29, 7.91 Hz), 1.78-1.46 (m, 6H), 1.38 (s, 9H), 1.21-0.92 (m, 5H).

LCMS: $(M-H)^-$ 472.1.

Step 2. Preparation of Title Compound: (R)- 2-Amino-*N*-(2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-cyclohexyl-acetamide (hydrochloric salt)

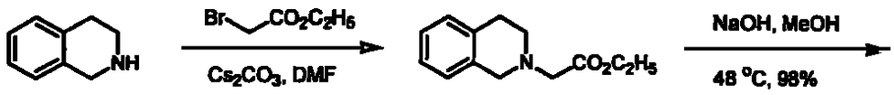
Preparation of the title compound from Intermediate 198(a) (75 mg, 0.159 mmol) and 4.0 M HCl in dioxane (0.8 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (65 mg, 0.159 mmol) as a yellow powder in 99% yield.

^{1}H NMR (d_6-DMSO): δ 12.81 (s, 1H), 10.77 (s, 1H), 10.53 (s, 1H), 8.30 (br s, 3H), 8.03 (d, 1H, *J* = 1.70 Hz), 7.70 (d, 1H, *J* = 1.70 Hz), 7.39 (s, 1H), 3.73 (m, 1H), 1.93-1.55 (m, 6H), 1.27-1.01 (m, 5H).

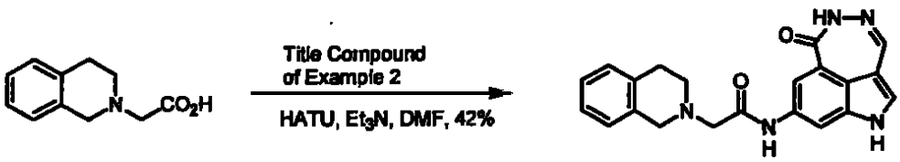
LCMS: $(M+H^+)$ 374.0; $(M-H)^-$ 372.2.

HRMS: $(M+H^+)$ calcd for $C_{18}H_{21}N_5O_2Cl$, 374.1384, found 374.1369.

Example 199: 2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide



199(a)



199(b)

Step 1. Preparation of (3,4-Dihydro-1*H*-isoquinolin-2-yl)-acetic acid ethyl ester 199(a)

To a solution of 1,2,3,4-tetra-hydroisoquinoline (2.664 g, 20 mmol) and ethyl bromoacetate (3.647 g, 22 mmol) in *N,N*-dimethylformamide (23 mL), was added Cs_2CO_3 (7.168 g, 22 mmol) under N_2. The mixture was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure, and the remaining residue was subjected to silica gel chromatography, eluting with ethyl acetate/hexanes (33:66) to afford Intermediate 199(a) (3.39 g, 15.5 mmol) as yellow oil in 77% yield.

^{1}H-NMR ($CDCl_3$): δ 7.13-7.09 (m, 3H), 6.99 (t, 1H), 4.22 (q, 2H), 3.84 (s, 2H), 3.44 (s, 2H), 2.94 (s, 4H), 1.29 (t, 3H).

LCMS: (M+H$^+$) 220.3.

Step 2. Preparation of (3,4-Dihydro-1*H*-isoquinolin-2-yl)-acetic acid 199(b)

To a suspension of Intermediate 199(a) (1.643 g, 7.5 mmol) in methanol (20 mL) was added 2.5 N NaOH (7.8 mL). The reaction solution was heated at 48 °C and stirred overnight. With cooling, the pH was adjusted to 8 by adding 1M HCl. The volatile components were removed under vacuum, and the resulting mixture was suspended in methanol. After filtration to remove the insoluble solids, the filtrate was evaporated to give Intermediate 199(b) (1.4 g, 7.3 mmol) as white foam in 98% yield.

^{1}H-NMR (d_6-DMSO): δ 7.13-7.09 (m, 3H), 7.02 (t, 1H), 3.76 (s, 2H), 3.27 (s, 2H), 2.88-2.82 (m, 4H).

LCMS: (M+H$^+$) 192.2.

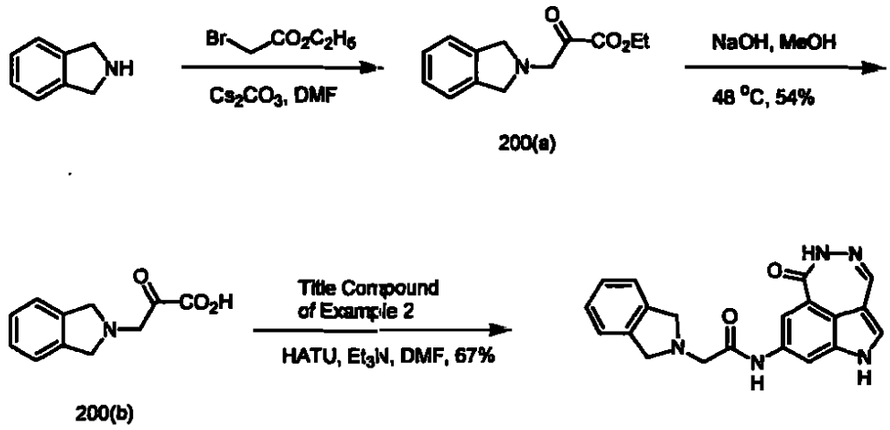
Step 3. Preparation of Title compound: 2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide

Preparation of the title compound from the title compound of Example 2 (185 mg, 0.79 mmol), Intermediate 199(b) (150 mg, 0.79 mmol), triethylamine (0.274 mL, 1.98 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (330 mg, 0.879 mmol) and *N,N*-dimethylformamide (3 mL) was carried out analogously to **11**. Following evaporation of the volatile components, the resulting residue was triturated with a small amount of *N,N*-dimethylformamide and water to give the title compound (123.5 mg, 0.331 mmol) as yellow solid in 42% yield.

^{1}H-NMR (d_6-DMSO): δ 11.73 (s, 1H), 10.22 (s, 1H), 9.97 (s, 1H), 8.13 (s, 1H), 7.62(s, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 7.12-7.04 (m, 4H), 3.72 (s, 2H), 2.88-2.80 (m, 6H).

LCMS: (M+H$^+$) 374.4

Example 200: 2-(1,3-Dihydro-isoindol-2-yl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide



Step 1. Preparation of (1,3-Dihydro-isoindol-2-yl)-acetic acid ethyl ester 200(a)

Into a solution of isoindoline (1.788 g, 15 mmol) and ethyl bromoacetate (2.756 g, 16.5 mmol) in *N,N*-dimethylformamide (20 mL), was added Cs_2CO_3 (5.376 g, 16.5 mmol) under N_2. The mixture was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the resulting mixture was subjected to silica gel chromatography, eluting with 33:66 ethyl acetate:hexane to afford Intermediate 200(a) (1.14 g, 5.56 mmol) as a yellow oil in 37% yield.

^{1}H-NMR ($CDCl_3$): δ 7.20 (s, 4H), 4.22 (q, 6H), 3.66 (s, 2H), 1.29 (t, 3H).

LCMS: ($M+H^+$) 206.3.

Step 2. Preparation of 1,3-Dihydro-isoindol-2-yl)-acetic acid 200(b)

To a suspension of Intermediate 200(a) (1.14 g, 5.56 mmol) in methanol (20 mL) was added 2.5 N NaOH (5.78 mL). The reaction solution was heated at 48 °C and stirred overnight. With cooling, the pH was adjusted to 8 by adding 1M HCl. The volatile components were removed under vacuum and the resulting mixture was suspended in methanol. After filtration to remove the insoluble solids, the filtrate was evaporated to give Intermediate 200(b) (531 mg, 3 mmol) as pale solids in 54% yield.

LCMS: ($M+H^+$) 178.2.

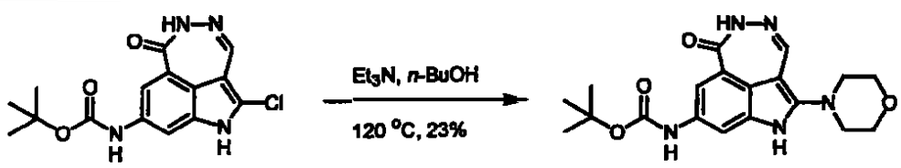
Step 3. Preparation of Title compound: 2-(1,3-Dihydro-isoindol-2-yl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide

Preparation of the title compound from the title compound of Example **2** (118 mg, 0.5 mmol), Intermediate 200(b) (88.5 mg, 0.5 mmol), triethylamine (0.274 mL, 1.98 mmol), O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (209 mg, 0.55 mmol) and *N,N*-dimethylformamide (5 mL) was carried out analogously to Example **11**. Following evaporation of the volatile components, the resulting residue was triturated with a small amount of *N,N*-dimethylformamide and water to give the title compound (121 mg, 0.337 mmol) as a yellow solid in 67% yield.

^{1}H-NMR (d_6-DMSO): δ 11.73 (s, 1H), 10.21 (s, 1H), 10.02 (s, 1H), 8.13 (s, 1H), 7.66(s, 1H), 7.55 (s, 1H), 7.46 (s, 1H), 7.22 (d, 4H), 4.07 (s, 4H), 3.56 (s, 2H).

LCMS: ($M+H^+$) 360.4

Example 201: (2-Morpholin-4-yl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid tert-butyl ester



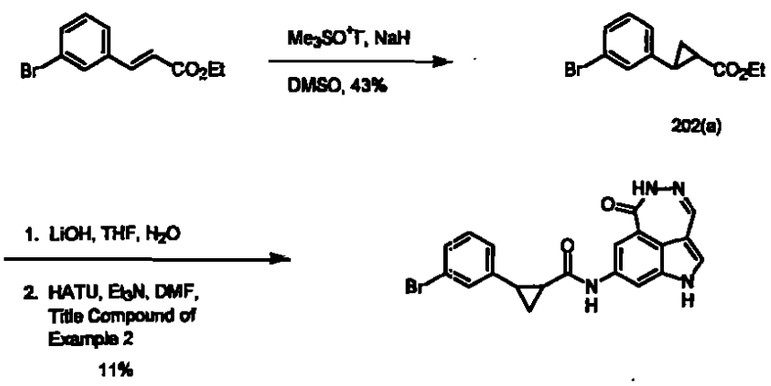
Triethylamine (0.039 mL, 0.28 mmol), the title compound of Example **187** (46 mg, 0.14 mmol), morpholine (96 mg, 1.1 mmol) and n-butanol (5 mL) were stirred in a flask with a condenser at 120 °C overnight. The mixture was allowed to stand at room temperature for two more days. The

volatile components were removed under vacuum and the resulting mixture was subjected to silica gel chromatography, eluting with 95:5 dichloromethane:methanol to afford the title compound (12.5 mg, 0.032 mmol) as a yellow solid in 23% yield.

^{1}H-NMR (d_6-DMSO): δ 9.53 (s, 1H), 8.47 (s, 1H), 7.80 (s, 1H), 7.28 (s, 1H), 6.06 (s, 2H), 3.74 (s, 8H), 1.48 (s, 9H).

LCMS: ($M+H^+$) 386.4.

Example 202: (1,2-*trans*)-2-(3-Bromo-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1. Preparation of (1,2-*trans*)-2-(3-Bromo-phenyl)-cyclopropanecarboxylic acid ethyl ester 202(a)

To a mixture of NaH (186 mg, 4.65 mmol) and trimethylsulfoxonium iodide (1.02 g, 4.65 mmol) was added DMSO (5 mL). After stirring for 30 min, a solution of *trans*-3-(bromo-phenyl)-acrylic acid ethyl ester (933 mg, 3.57 mmol) in DMSO (2 mL) was added drop-wise. After stirring overnight, the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to silica gel chromatography, eluting with 10 % ethyl acetate/hexane, to furnish Intermediate 202(a) as a colorless oil (408 mg, 1.52 mmol) in 43% yield.

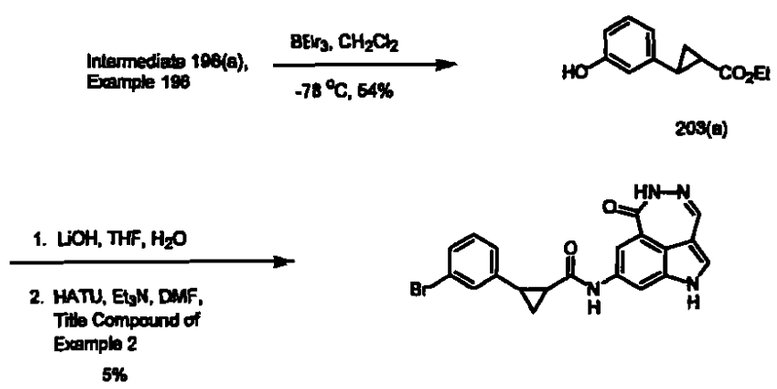
Step 2. Preparation of Title compound: (1,2-*trans*)-2-(3-Bromo-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

To a stirred solution of Intermediate 202(a) (505 mg, 2.25 mmol) in MeOH (10 mL) was added aqueous 10M LiOH (10 mL). The mixture was stirred at 23 °C for 12 hours, acidified with 1 M HCl

to pH 1, and extracted with ethyl acetate. The combined organic layers was then washed with brine and concentrated to give crude (2,3-*trans*)-3-(3'-bromo-phenyl)-cycloprapanecarboxylic acid (632 mg), which was combined with the title compound of Example **2** (111 mg, 0.49 mmol), triethylamine (0.273 mL, 1.96 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (278 mg, 0.73 mmol) in *N,N*-dimethylformamide (4 mL) in a manner analogous to Example **11**. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ follow by silica gel chromatography afforded the title compound (100 mg, 0.24 mmol) as a yellow solid in 11% yield.

^1H NMR (d_6-DMSO): 11.85 (d, 1H, J = 2.26 Hz), 10.50 (s, 1H), 10.35 (s, 1H), 8.23 (s, 1H), 7.69 (s, 1H), 7.67 (d, 1H, J = 4.0 Hz), 7.58 (s, 1H), 7.53-7.51 (m, 2H), 7.40-7.33 (m, 2H), 2.53 (m, 1H), 2.23 (m, 1H), 1.62 (m, 1H), 1.54 (m, 1H).

Example 203: (1,2-*trans*)-2-(3-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1. Preparation of 2-(3-hydroxy-phenyl)-cyclopropanecarboxylic acid ethyl ester 203(a)

To a stirred solution of Intermediate 196(a) of Example **196** (1.56 g, 7.12 mmol) in CH_2Cl_2 at –78 °C was added 1.0M BBr_3 in CH_2Cl_2 (8.56 ml, 8.56 mmol). The mixture was warmed to room temperature and stirred for 1 hour. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ followed by silica gel chromatography afforded Intermediate 203(a) as a pale brown solid (795 mg, 3.86 mmol) in 54% yield.

Step 2. Preparation of Title compound: (1,2-*trans*)-2-(3-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

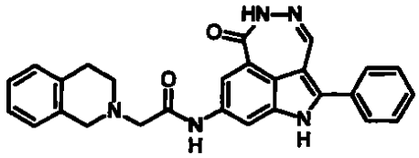
To a solution of Intermediate 203(a) (271 mg, 1.32 mmol) in tetrahydrofuran (2 mL) was added aqueous 1M LiOH (6 mL, 6 mmol). The mixture was stirred overnight. After acidifying to pH 2, the mixture was extracted with ethyl acetate. Concentration of the organic layer gave crude 3-(3-

hydroxy-phenyl)-cycloprapanecarboxylic acid (235 mg), where a portion (155 mg, 0.57 mmol) was combined with the title compound of Example **2** (137 mg, 0.58 mmol), triethylamine (0.24 mL, 1.72 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (331 mg, 0.87 mmol) in *N,N*-dimethylformamide (3 mL) in a manner analogous to Example **11**. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ followed by silica gel chromatography afforded the title compound (10 mg, 0.028 mmol) as a tan solid in 5% yield.

^{1}H NMR (d_6-DMSO): δ 10.35 (s, 1H), 10.27 (s, 1H), 9.35 (s, 1H), 8.12 (s, 1H), 7.67 (dd, 1H, *J* = 3.20, 1.51 Hz), 7.55 (s, 1H), 7.48(s, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.77-6.74 (m, 3H), 2.32 (m, 1H), 2.09 (m, 1H), 1.45 (m, 1H), 1.38 (m, 1H).

LCMS: (M-H$^+$) 359.1

Example 204 2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide

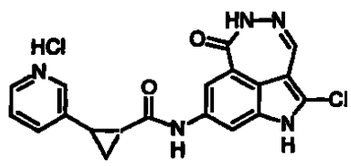


In a manner analogous to that of Example **11**, to a stirred solution of 8-amino-1,5-dihydro-6*H*-[1,2]diazepino[4,5,6-*cd*] indol-6-one in anhydrous *N,N*-dimethylformamide (6 mL) was added 3,4-dihydroisoquinolin-2(1*H*)-ylacetic acid (62 mg, 0.33 mmol) followed by triethylamine (0.14 mL, 0.98 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (372 mg, 0.98 mmol). The reaction was stirred at room temperature for 17 hours. After concentrating, water was added and the precipitated solid was collected by filtration. After preparative HPLC, the title compound (50 mg) was obtained as a yellow powder in 34% yield.

^{1}H NMR (methanol-d_4) d: 3.25 (2H, m), 3.72 (2H, bs), 4.27 (2H, s), 4.58 (2H, s), 7.22 (1H, d, *J* = 7.58 Hz), 7.32 (3H, m), 7.52 (4H, m), 7.63 (3H, m), 8.13 (1H, d, *J* = 1.52 Hz).

LCMS: (M+H$^+$) 450.1.

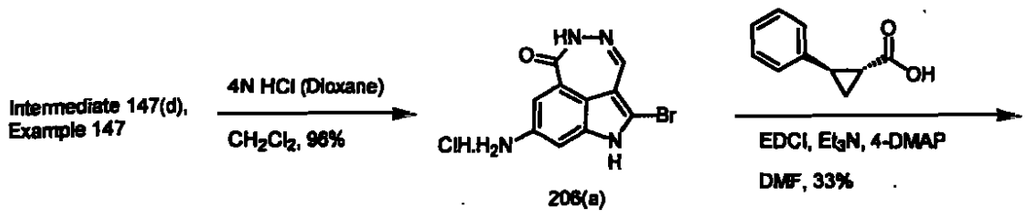
Example 205: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)

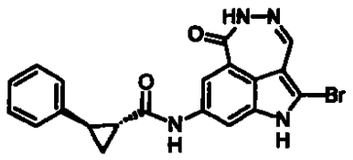


The title compound of Example **191** (20 mg, 0.053 mmol) was converted to an HCl salt in anhydrous CH_2Cl_2 (2mL) with 4.0 M HCl in dioxane (0.026 mL). The mixture was stirred at room temperature for 1 hour. The solid was collected by filtration and washed with CH_2Cl_2 and diethyl ether. After drying, the title compound (20.4 mg, 0.049 mmol) was obtained as a yellow powder in 93% yield.

^{1}H NMR (d_6-DMSO): δ 12.70 (s, 1H), 10.59 (s, 1H), 10.46 (s, 1H), 8.85 (s, 1H), 8.72 (d, 1H, J = 5.84 Hz), 8.25 (d, 1H, J = 8.29 Hz), 8.07 (d, 1H, J = 1.70 Hz), 7.91 (dd, 1H, J = 5.27, 5.27 Hz), 7.63 (d, 1H, J = 1.70 Hz), 7.35 (s, 1H), 2.75-2.59 (m, 1H), 2.33-2.21 (m, 1H), 1.67-1.56 (m, 2H).

Example 206: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-bromo-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide





Step 1. Preparation of 8-Amino-2-bromo-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one (hydrochloric salt) 206(a)

Preparation of intermediate 206(a) from Intermediate 147(d) of Example **147** (2 g, 5.29 mmol) and 4.0 M HCl in dioxane (26.4 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded Intermediate 206(a) (1.59 g, 5.04 mmol) as a yellow powder in 96% yield.

^{1}H NMR (d_6-DMSO): δ 13.13 (s, 1H), 10.67 (s, 1H), 7.52 (s, 1H), 7.51 (s, 1H), 7.35 (s, 1H).

LCMS: $(M+H^+)$ 279.0, 281.1, $(M+Na^+)$ 401.0, 403.0; $(M-H)^-$ 277.0, 279.0.

Step 2. Preparation of Title Compound: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-bromo-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

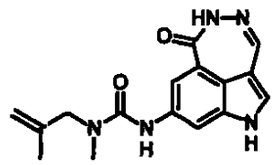
Preparation of the title compound from Intermediate 206(a) (120 mg, 0.380 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (74.0 mg, 0.457 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (88 mg, 0.461 mmol), and 4-dimethylaminopyridine (56 mg, 0.459 mmol) in *N,N*-dimethylformamide (15.0 mL) was carried out analogously to Example **190**, step 2. When the reaction was judged complete, the volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1.2:1 dichloromethane: ethyl acetate to afford the title compound (52.4 mg, 0.124 mmol) as a yellow solid in 33% yield.

^{1}H NMR (d_6-DMSO): δ 12.59 (s, 1H), 10.45 (s, 1H), 10.44 (s, 1H), 8.08 (d, 1H, J = 1.51 Hz), 7.60 (d, 1H, J = 1.70 Hz), 7.33-7.24 (m, 3H), 7.24-7.13 (m, 3H), 2.42-2.32 (m, 1H), 2.11-2.00 (m, 1H), 1.54-1.42 (m, 1H), 1.42-1.30 (m, 1H).

LCMS: $(M+H^+)$ 423.0, 425.0, $(M+Na^+)$ 445.0, 447.0; $(M-H)^-$ 421.0, 423.0.

HRMS: $(M+H^+)$ calcd for $C_{20}H_{16}N_4O_2Br$, 423.0457, found 423.0471.

Example 207: *N*-Methyl-*N*-(2-methylprop-2-enyl)-*N'*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)urea

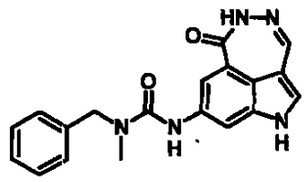


Using a similar route as outlined in Example **192**, the title compound of Example **2** (25 mg, 0.11 mmol) and *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol) were stirred together in *N,N*-dimethylformamide (1 mL) while *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) was added. After stirring three minutes *N*-2-dimethylprop-2-en-1-amine (0.046 mL, 0.21 mmol) was added giving the crude product. Cation-exchange polystyrene scavenging resin (Argonaut Technologies™, MP-TsOH) was added directly to the mixture. After stirring 2 hours the resin was removed by filtration and washed twice with *N,N*-dimethylformamide (1 mL). The combined *N,N*-dimethylformamide solutions were then treated with anion-exchange polystyrene scavenging resin (Argonaut Technologies™, MP-carbonate) and stirred for 2 hours. Again the resin was removed by filtration and washed twice with *N,N*-dimethylformamide (1 mL). The combined *N,N*-dimethylformamide solutions were then reduced under vacuum and subjected to preparative RPHPLC (Peeke Scientific HI-Q, C18 reverse-phase, 5 uM, 100A, 150x20 mm column) eluting with 0.1% acetic acid in CH_3CN and 0.1% acetic acid in H_2O at a flowrate of 20 mL/min using a gradient of 30-70% 0.1% acetic acid in CH_3CN over 30 min. Fractions judged pure were pooled, and the volatile components removed *in vacuo*. After a final trituation with ethyl acetate, the title compound (6 mg, 0.019 mmol) was obtained as brown powder in 18% yield.

^1H NMR ($CDCl_3$/methanol-d_4): δ 7.90 (s, 1H), 7.42 (s, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 4.98 (s, 1H), 4.90 (s, 1H), 3.95 (s, 2H), 3.03 (s, 3H), 1.77 (s, 3H).

LCMS: $(M+H^+)$ 312.2, $(M+Na^+)$ 334.1.

Example 208: *N*-Methyl-*N'*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-*N*-(phenylmethyl)urea



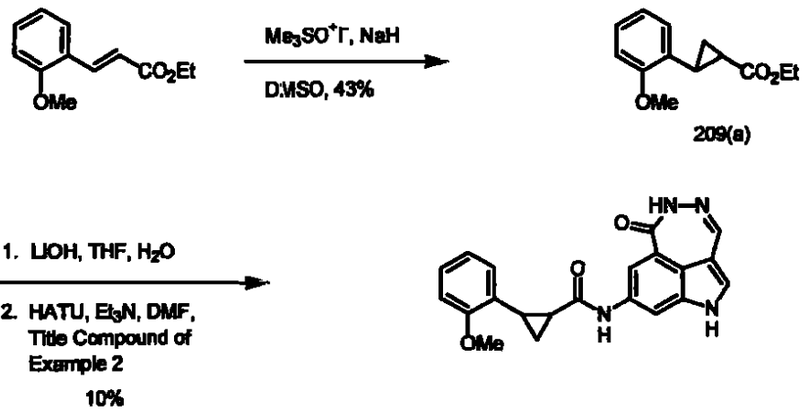
Preparation of example 208 from the title compound of Example **2** (48 mg, 0.20 mmol), *N,N'*-disuccinimidyl carbonate (52 mg, 0.20 mmol), triethylamine (0.084 mL, 0.60 mmol) and *N*-methyl-1-phenylmethanamine (0.052 mL, 0.40 mmol) in *N,N*-dimethylformamide (0.5 mL) was carried out

analogously to Example **192**. Purification, also in an analogous manner, afforded the title compound (8 mg, 0.023 mmol) was obtained as brown powder in 12% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.88 (s, 1H), 7.46-7.23 (m, 8H), 4.64 (s, 2H, obscured), 3.03 (s, 3H).

LCMS: ($M+H^+$) 348.4, ($M+Na^+$) 370.4.

Example 209: (1,2-*trans*)-2-(2'-Methoxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1: Preparation of (1,2-*trans*)-2-(2'-Methoxy-phenyl)-cyclopropanecarboxylic acid ethyl ester 209(a)

Preparation of intermediate 209(a) from NaH (1.04 g, 26 mmol) and trimethylsulfoxonium iodide (5.72 g, 26 mmol), 2-(methoxy-phenyl)-acrylic acid ethyl ester (4.12 g, 20 mmol) in dimethylsulfoxide (30 mL) was carried out analogously to step 2 of Example **113**. Intermediate 209(a) (1.89 g, 8.6 mmol) was obtained in 43% yield.

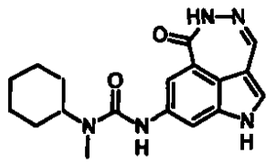
Step 2: Preparation of Title compound: (1,2-*trans*)-2-(2'-Methoxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

Preparation of the title compound was carried out analogously to step 3 of Example **172** except that Intermediate 209(a) was used instead of Intermediate 172(b). The title compound was obtained in 10% yield.

^{1}H NMR (d_6-DMSO): δ 11.74 (d, 1H, J = 2.26 Hz), 10.35 (s, 1H), 10.24 (s, 1H), 8.14 (s, 1H), 7.57 (dd, 1H, J=3.20, 1.51 Hz), 7.46 (s, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.77-6.74 (m, 3H), 3.80 (s, 3H), 2.36 (m, 1H), 2.02 (m, 1H), 1.44 (m, 1H), 1.34 (m, 1H).

LCMS: ($M-H^+$) 373.1.

Example 210: *N*-cyclohexyl-*N*-methyl-*N'*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)urea

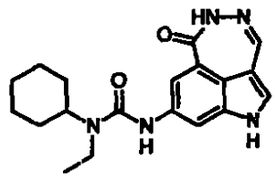


Preparation of example 210 from the title compound of Example **2** (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) and *N*-cyclohexyl-*N*-methylamine (0.028 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (7 mg, 0.021 mmol) as yellow powder in 19% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.90 (s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 7.27 (s, 1H), 4.09 (m, 1H), 2.92 (s, 3H), 1.91-1.80 (m, 2H), 1.79-1.65 (m, 3H), 1.56-1.37 (m, 4H), 1.14 (m, 1H).

LCMS: (M+H$^+$) 340.2, (M+Na$^+$) 362.1.

Example 211: *N*-Cyclohexyl-*N*-ethyl-*N'*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)urea

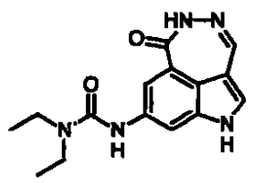


Preparation of example 211 from the title compound of Example **2** (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) and *N*-cyclohexyl-*N*-methylamine (0.032 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (7 mg, 0.020 mmol) as yellow powder in 20% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.94 (s, 1H), 7.40 (s, 1H, obscured), 7.30 (s, 1H, partially obscured), 7.26 (s, 1H), 4.05 (m, 1H, partially obscured), 3.36 (m, 2H, partially obscured), 1.90-1.74 (m, 4H), 1.71 (m, 1H), 1.58-1.33 (m, 4H), 1.26 (t, 3H, *J* = 7.16 Hz), 1.14 (m, 1H).

LCMS: (M+H$^+$) 354.2, (M+Na$^+$) 376.1.

Example 212: *N,N*-Diethyl-*N'*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)urea



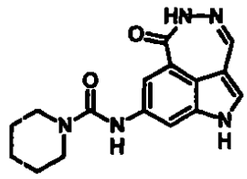
Preparation of example 212 from the title compound of Example **2** (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol)

and *N,N*-diethylamine (0.022 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (5 mg, 0.016 mmol) as yellow powder in 15% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.91 (s, 1H), 7.41 (s, 1H), 7.32 (s, 1H), 7.27 (s, 1H), 3,42 (q, 4H, *J* = 7.16 Hz), 1.24 (t, 6H, *J* = 7.16 Hz).

LCMS: ($M+H^+$) 300.2, ($M+Na^+$) 322.1.

Example 213: *N*-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)piperidine-1-carboxamide

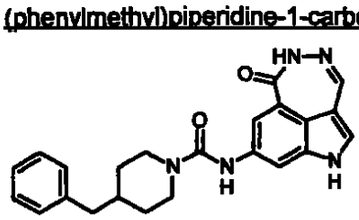


Preparation of example 213 from the title compound of Example **2** (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) and piperidine (0.021 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (7 mg, 0.022 mmol) as yellow powder in 20% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.77 (s, 1H), 7.65 (s, 1H), 7.43 (s, 1H, partially obscured), 7.32 (s, 1H), 3.57-3.47 (m, 4H), 1.76-1.56 (m, 6H).

LCMS: ($M+H^+$) 312.1, ($M+Na^+$) 334.1.

Example 214: *N*-(6-Oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-(phenylmethyl)piperidine-1-carboxamide

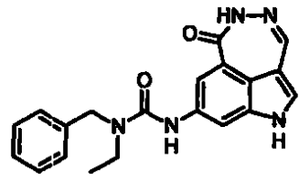


Preparation of example 214 from the title compound of Example **2** (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) and 4-(phenylmethyl)piperidine (0.037 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (7 mg, 0.017 mmol) as yellow powder in 16% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.88 (s, 1H), 7.44-7.39 (m, 2H, partially obscured), 7.34-7.12 (m, 6H), 4.16 (d, 2H, *J* = 13.75 Hz), 2.91-2.78 (m, 2H), 2.62-2.57 (m, 2H), 1.80-1.69 (m, 3H), 1.36-1.14 (m, 2H).

LCMS: ($M+H^+$) 402.2, ($M+Na^+$) 424.1.

Example 215: *N*-Ethyl-*N*'-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-*N*-(phenylmethyl)urea

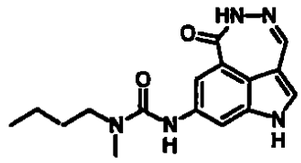


Preparation of example 215 from the title compound of Example 2 (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) and *N*-(phenylmethyl)ethanamine (0.032 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (7 mg, 0.019 mmol) as yellow powder in 18% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.94 (s, 1H), 7.46-7.21 (m, 8H, partially obscured), 4.63 (s, 2H), 3.51-3.34 (m, 2H, partially obscured), 1.28-1.19 (m, 3H).

LCMS: ($M+H^+$) 362.1, ($M+Na^+$) 384.0.

Example 216: *N*-Butyl-*N*-methyl-*N*'-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)urea

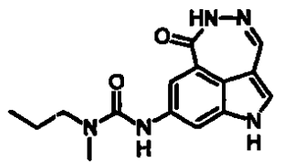


Preparation of example 216 from the title compound of Example 2 (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) and *N*-ethyl-*N*-propylamine (0.025 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (4 mg, 0.013 mmol) as yellow powder in 12% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.92 (s, 1H), 7.41 (s, 1H, partially obscured), 7.29 (s, 1H), 7.26 (s, 1H), 3.04 (s, 3H), 1.66-1.55 (m, 2H), 1.45-1.21 (m, 4H), 0.97 (t, 3H, J = 7.35 Hz).

LCMS: ($M+H^+$) 314.1, ($M+Na^+$) 336.2.

Example 217: *N*-Methyl-*N*'-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-*N*-propylurea



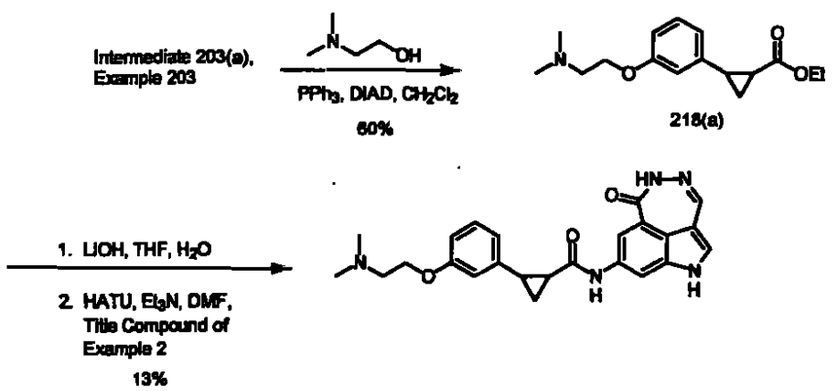
Preparation of example 217 from the title compound of Example 2 (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) and *N*-ethyl-*N*-propylamine (0.022 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was

carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (4 mg, 0.013 mmol) as yellow powder in 12% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 7.87 (s, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 3.05 (s, 3H), 1.72-1.58 (m, 2H), 1.37-1.21 (m, 2H), 0.96 (t, 3H, J = 7.25 Hz)

LCMS: ($M+H^+$) 300.2, ($M+Na^+$) 322.1.

Example 218: (1,2-*trans*)-2-[3-(2-Dimethylamino-ethoxy)-phenyl]-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Step 1. Preparation of (1,2-*trans*)-2-[3-(2-Dimethylamino-ethoxy)-phenyl]-cyclopropanecarboxylic acid 218(a)

To a stirred solution of Intermediate 203(a) of Example **203** (125 mg, 0.607 mmol), 2-dimethylethanol (81 mg, 0.91 mmol) and triphenylphosphine (239 mg, 0.91 mmol) in CH_2Cl_2 was added diisopropyl azodicarboxylate (184 mg, 0.91 mmol). The mixture was stirred at room temperature for 4 hours, concentrated, and subjected to silica el chromatography, eluting with 20-30% ethyl acetate/hexane, to furnish Intermediate 218(a) as a colorless oil (101 mg, 0.36 mmol) in 60% yield.

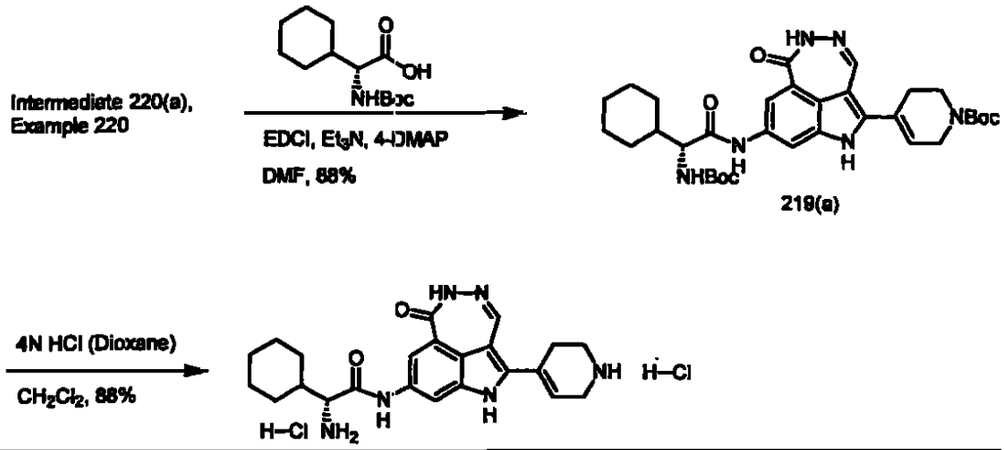
Step 2. Preparation of Title compound: (1,2-*trans*)-2-[3-(2-Dimethylamino-ethoxy)-phenyl]-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

Preparation of the title compound was carried out analogously to step 3 of Example **172** except that Intermediate 218(a) was used instead of Intermediate 172(b). The title compound was obtained in a 13% yield.

^{1}H NMR (d_6-DMSO): δ 11.56 (d, 1H, J = 2.26 Hz), 10.20 (s, 1H), 10.06 (s, 1H), 7.95 (d, 1H, J = 1.88 Hz), 7.38 (dd, 1H, J = 3.20, 1.51 Hz), 7.29 (s, 1H), 7.04 (t, 1H, J =8.0 Hz), 6.62-6.58 (m, 3H), 6.36 (s, 1H), 3.96-3.94 (m, 2H), 3.12-3.10 (m, 2H), 2.29 (m, 1H), 1.91 (m, 1H), 1.31 (m, 1H), 1.20 (m, 1H).

LCMS: $(M+H^+)$ 432.2.

Example 219: (R)- 2-Amino-2-cyclohexyl-*N*-[6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide: dihydrochloride



Step 1. Preparation of (R)- 4-[8-(2-*tert*-Butoxycarbonylamino-2-cyclohexyl-acetylamino)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 219(a)

Preparation of intermediate 219(a) from Intermediate 220(a) of Example **220** (100 mg, 0.262 mmol), (R)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (74.3 mg, 0.289 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (55 mg, 0.288 mmol), and 4-dimethylaminopyridine (35.2 mg, 0.288 mmol) in *N,N*-dimethylformamide (6.0 mL) was carried out analogously to Example **190**, step 2. When the reaction was judged complete, the volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1:1 dichloromethane: ethyl acetate to afford Intermediate 219(a) (143 mg, 0.231 mmol) as a yellow solid in 88% yield.

^{1}H NMR (d_6-DMSO): δ 11.70 (s, 1H), 10.27 (s, 1H), 10.09 (s, 1H), 8.06 (d, 1H, *J* = 1.51 Hz), 7.59 (s, 1H), 7.51 (s, 1H), 6.88 (d, 1H, *J* = 8.10 Hz), 6.17 (s, 1H), 4.06 (br s, 2H), 3.92 (dd, 1H, *J* = 8.48, 7.72 Hz), 3.55 (t, 2H, *J* = 5.65, 5.27 Hz), 3.32 (m, 2H, obscured), 1.76-1.46 (m, 6H), 1.43 (s, 9H), 1.37 (s, 9H), 1.19-0.94 (m, 5H).

LCMS: $(M-H)^-$ 619.2.

Step 2. Preparation of Title Compound: (R)- 2-Amino-2-cyclohexyl-*N*-[6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide; dihydrochloride

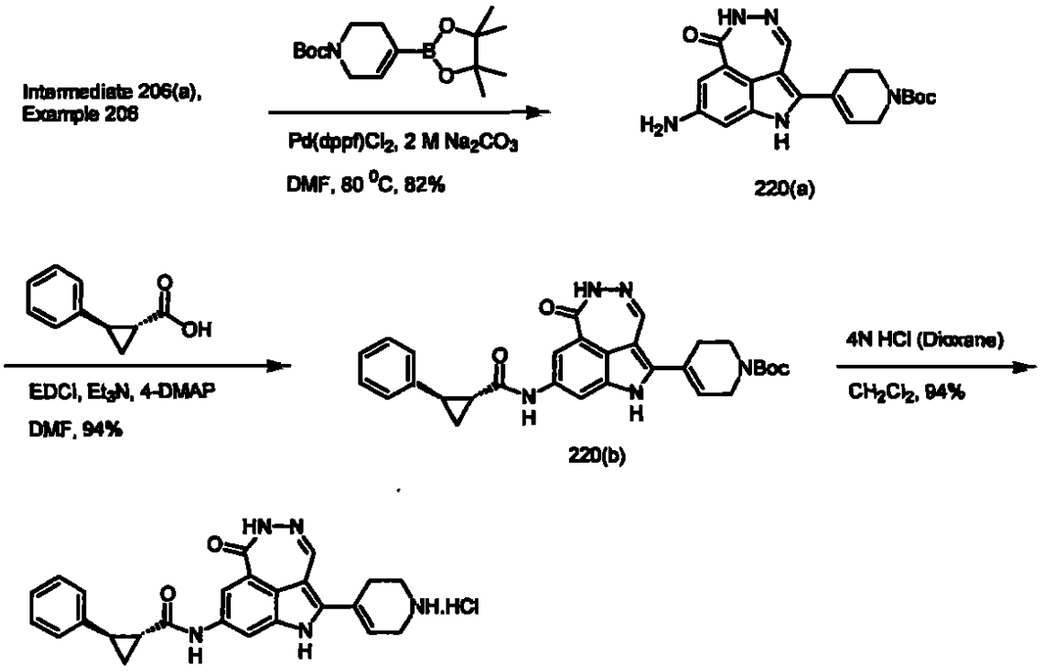
Preparation of the title compound from Intermediate 219(a) (143 mg, 0.231 mmol) and 4.0 M HCl in dioxane (2.3 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (100 mg, 0.203 mmol) as a red powder in 88% yield.

^{1}H NMR (d_6-DMSO): δ 12.18 (s, 1H), 10.87 (s, 1H), 10.39 (s, 1H), 9.32 (br s, 2H), 8.35 (br s, 3H), 8.07 (d, 1H, J = 1.51 Hz), 7.70 (d, 1H, J = 1.51 Hz), 7.55 (d, 1H, J = 1.51 Hz), 6.19 (s, 1H), 3.87-3.74 (m, 3H), 3.41-3.26 (m, 2H), 2.81-2.69 (m, 2H), 1.90-1.55 (m, 6H), 1.28-0.97 (m, 5H).

LCMS: $(M+H^+)$ 421.1, $(M+Na^+)$ 443.1; $(M-H)^-$ 419.1.

HRMS: $(M+H^+)$ calcd for $C_{23}H_{29}N_6O_2$, 421.2352, found 421.2338.

Example 220: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt)



Step 1. Preparation of 4-(8-Amino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 220(a)

In a manner analogous to that of Example **184**, 2.0 M aqueous Na_2CO_3 (0.66 mL) was added to a mixture of Intermediate 206(a) of Example **206** (1 g, 3.17 mmol), 4-(4,4,5,5-tetramethyl-[1,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (1.18 g, 3.82 mmol) and [1,1'- bis(diphenylphosphino)ferrocene]dichloropalladium (II) (0.13 g, 0.159 mmol) in anhydrous *N,N*-dimethylformamide (50 ml), and the reaction was heated at 80 °C for 16 hours.

When the reaction was judged complete, the volatile components were removed *in vacuo*. Ethyl acetate (50 mL), methanol (5 mL) and H_2O (500 mL) were added, and the aqueous layer was extracted with ethyl acetate (3X20 mL). The combined ethyl acetate extracts were washed with H_2O (2X50 mL) and brine (50 mL) and allowed to dry over Na_2SO_4. Following filtration, the volatile components were removed *in vacuo* and CH_2Cl_2 was added to the residue. The resulting solid was collected by filtration and washed with CH_2Cl_2 and diethyl ether to afford Intermediate 220(a) (1 g, 2.62 mmol) as a red solid in 82% yield.

^{1}H NMR (d_6-DMSO): δ 11.15 (s, 1H), 10.04 (s, 1H), 7.42 (s, 1H), 6.92 (d, 1H, *J* = 1.88 Hz), 6.56 (d, 1H, *J* = 1.88 Hz), 6.05 (br s, 1H), 5.17 (s, 2H), 4.03 (s, 2H), 3.53 (t, 2H, *J* = 5.65, 5.27 Hz), 3.36 (m, 2H, partially obscured), 1.42 (s, 9H).

LCMS: $(M+H^+)$ 382.1, $(M+Na^+)$ 404.3; $(M-H)^-$ 380.1.

Step 2. Preparation of (1R,2R)- 4-[6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 220(b)

Preparation of intermediate 220(b) from Intermediate 220(a) (100 mg, 0.262 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (47.0 mg, 0.290 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide, hydrochloride (55 mg, 0.288 mmol), and 4-dimethylaminopyridine (35.2 mg, 0.288 mmol) in *N,N*-dimethylformamide (6.0 mL) was carried out analogously to Example **190**, step 2. When the reaction was judged complete, the volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1:1 dichloromethane: ethyl acetate to afford Intermediate 220(b) (130 mg, 0.248 mmol) as a yellow solid in 94% yield.

^{1}H NMR (d_6-DMSO): δ 11.71 (s, 1H), 10.39 (s, 1H), 10.26 (s, 1H), 8.07 (d, 1H, *J* = 1.70 Hz), 7.57 (d, 1H, *J* = 1.70 Hz), 7.50 (s, 1H), 7.33-7.25 (m, 2H), 7.23-7.15 (m, 3H), 6.16 (s, 1H), 4.08-4.04 (m, 2H), 3.55 (t, 2H, *J* = 5.65, 5.27 Hz), 3.35 (m, 2H, obscured), 2.41-2.33 (m, 1H), 2.11-2.02 (m, 1H), 1.53-1.46 (m, 1H), 1.43 (s, 9H), 1.40-1.30 (m, 1H).

LCMS: $(M-H)^-$ 524.1.

Step 3. Preparation of Title Compound: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt)

Preparation of the title compound from Intermediate 220(b) (130 mg, 0.248 mmol) and 4.0 M HCl in dioxane (1.24 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (107 mg, 0.232 mmol) as a red powder in 94% yield.

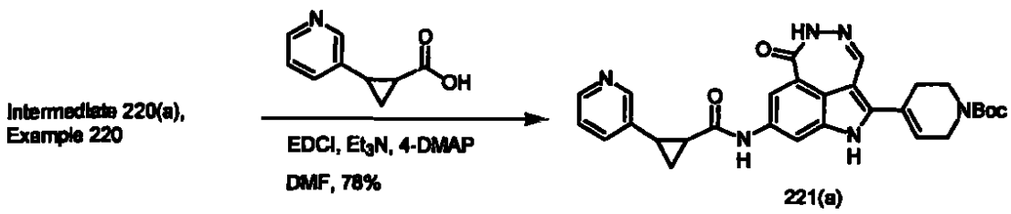
^{1}H NMR (d_6-DMSO): δ 11.97 (s, 1H), 10.47 (s, 1H), 10.33 (s, 1H), 9.31-9.10 (br s, 2H), 8.11 (d, 1H, *J* = 1.70 Hz), 7.61 (d, 2H, *J* = 1.70 Hz), 7.53 (s, 1H), 7.34-7.24 (m, 2H), 7.24-7.12 (m, 3H),

6.17 (s, 1H), 3.87-3.72 (m, 2H), 3.40-3.25 (m, 2H), 2.80-2.66 (m, 2H), 2.42-2.31 (m, 1H), 2.15-2.04 (m, 1H), 1.55-1.42 (m, 1H), 1.42-1.29 (m, 1H).

LCMS: $(M+H^+)$ 426.0, $(M+Na^+)$ 448.1; $(M-H)^-$ 424.1.

HRMS: $(M+H^+)$ calcd for $C_{25}H_{24}N_6O_2$, 426.1930, found 426.1924.

Example 221: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid [6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide: dihydrochloride



Step 1. Preparation of (1,2-*trans*)-4-[6-Oxo-8-[(2-pyridin-3-yl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-cd]indol-2-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 221(a)

Preparation of intermediate 221(a) from Intermediate 220(a) of Example **220** (100 mg, 0.262 mmol), crude 2-pyridin-3-yl-cyclopropanecarboxylic acid (estimated purity c.a. 75%) (67.3 mg, c.a. 0.289 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (55 mg, 0.288 mmol), and 4-dimethylaminopyridine (35.2 mg, 0.288 mmol) in *N,N*-dimethylformamide (10.0 mL) was carried out analogously to Example **190**, step 2. When the reaction was judged complete, the volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 20:1 dichloromethane: methanol to afford Intermediate 221(a) (107.6 mg, 0.204 mmol) as a yellow solid in 78% yield.

^{1}H NMR (d_6-DMSO): δ 11.72 (s, 1H), 10.42 (s, 1H), 10.26 (s, 1H), 8.50 (s, 1H), 8.40 (d, 1H, J = 4.71 Hz), 8.07 (s, 1H), 7.57 (s, 1H), 7.55 (d, 1H, J = 7.91 Hz), 7.50 (s, 1H), 7.32 (dd, 1H, J = 4.71, 3.77 Hz), 6.16 (s, 1H), 4.05 (br s, 2H), 3.55 (t, 2H, J = 4.52, 4.71 Hz), 3.35 (m, 2H, obscured), 2.46-2.37 (m, 1H), 2.16-2.06 (m, 1H), 1.57-1.48 (m, 1H), 1.43 (s, 9H), 1.48-1.38(m, 1H).

LCMS: $(M+H^+)$ 527.2; $(M-H)^-$ 525.0.

Step 2. Preparation of Title Compound: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid [6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide; dihydrochloride

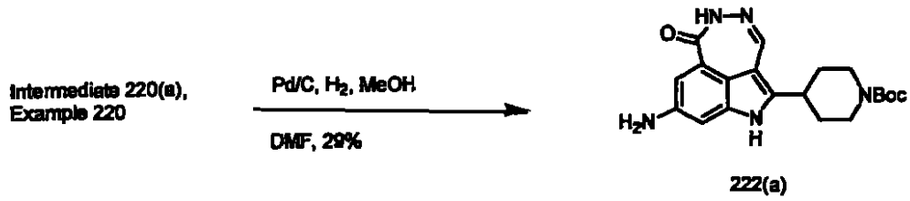
Preparation of the title compound from Intermediate 221(a) (100 mg, 0.190 mmol) and 4.0 M HCl in dioxane (0.95 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (95 mg, 0.190 mmol) as a red powder in 99% yield.

^{1}H NMR (d_6-DMSO): δ 12.05 (s, 1H), 10.66 (s, 1H), 10.34 (s, 1H), 9.29 (br s, 2H), 8.89 (d, 1H, *J* = 1.51 Hz), 8.74 (d, 1H, *J* = 5.27 Hz), 8.32 (d, 1H, *J* = 8.48 Hz), 8.10 (d, 1H, *J* = 1.51 Hz), 7.94 (dd, 1H, *J* = 6.03, 5.65 Hz), 7.65 (d, 1H, *J* = 1.51 Hz), 7.53 (s, 1H), 6.17 (s, 1H), 3.85-3.74 (m, 2H), 3.38-3.25 (m, 2H), 2.80-2.70 (m, 2H), 2.70-2.59 (m, 1H), 2.40-2.29 (m, 1H), 1.69-1.55 (m, 2H).

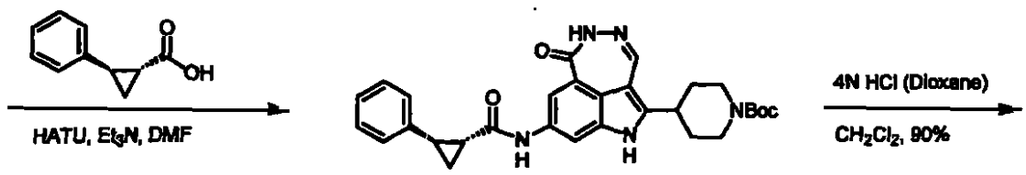
LCMS: $(M+H^+)$ 427.1, $(M+Na^+)$ 449.1; $(M-H)^-$ 425.0.

HRMS: $(M+H^+)$ calcd for $C_{24}H_{23}N_6O_2$, 427.1882, found 427.1895.

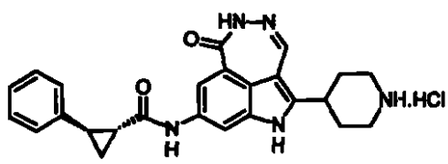
Example 222: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-piperidin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)



222(a)



222(b)



Step 1. Preparation of 4-(8-Amino-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl)-piperidine-1-carboxylic acid *tert*-butyl ester 222(a)

In a manner analogous to that of Example **183**, palladium (10% on activated carbon) (0.186 g) was added to a solution of Intermediate 220(a) of Example **220** (0.61 g, 1.60 mmol) in 9:1 methanol:*N,N*-dimethformamide (50 mL). The reaction mixture was purged with H_2 and stirred at room temperature under H_2 (1 atm.) for 6.5 hours. The mixture was filtered, and the filtrate evaporated. The resulting residue was dissolved in methanol and loaded onto a silica gel plug.

The plug was then loaded onto a silica gel column and eluted with 50:3 dichloromethane:methanol to give Intermediate 222(a) (0.18 g, 0.470 mmol) as a yellow solid in 29% yield.

^{1}H NMR (d_6-DMSO): δ 11.03 (s, 1H), 9.88 (s, 1H), 7.43 (s, 1H), 6.86 (s, 1H), 6.54 (s, 1H), 5.04 (br s, 2H), 4.16-3.99 (m, 3H), 2.95-2.67 (m, 2H), 1.73-1.54 (m, 4H), 1.42 (s, 9H).

LCMS: $(M+H^+)$ 384.1, $(M+Na^+)$ 406.2; $(M-H)^-$ 382.1.

Step 2. Preparation of (1R,2R)- 4-[6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester 222(b)

Preparation of intermediate 222(b) from Intermediate 222(a) (60 mg, 0.157 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (27.9 mg, 0.172 mmol), triethylamine (0.086 mL, 0.617 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (71.5 mg, 0.188 mmol) in *N,N*-dimethylformamide (5.0 mL) was carried out analogously to Example 11. The volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1:1 dichloromethane: ethyl acetate to afford Intermediate 222(b) (104 mg) as a yellow solid contaminated with *N,N*-dimethylformamide which was carried on directly to the next step.

^{1}H NMR (d_6-DMSO): δ 11.57 (s, 1H), 10.32 (s, 1H), 10.12 (s, 1H), 7.98 (s, 1H), 7.55 (d, 1H, J = 1.32 Hz), 7.54 (s, 1H), 7.33-7.25 (m, 2H), 7.22-7.15 (m, 3H), 4.19-4.00 (m, 3H), 2.92-2.77 (m, 2H), 2.41-2.30 (m, 1H), 2.12-2.00 (m, 1H), 1.80-1.56 (m, 4H), 1.53-1.45 (m, 1H), 1.42 (s, 9H), 1.38-1.29 (m, 1H).

LCMS: $(M+H^+)$ 528.2, $(M+Na^+)$ 550.1; $(M-H)^-$ 526.1.

Step 3. Preparation of Title Compound: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-piperidin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt)

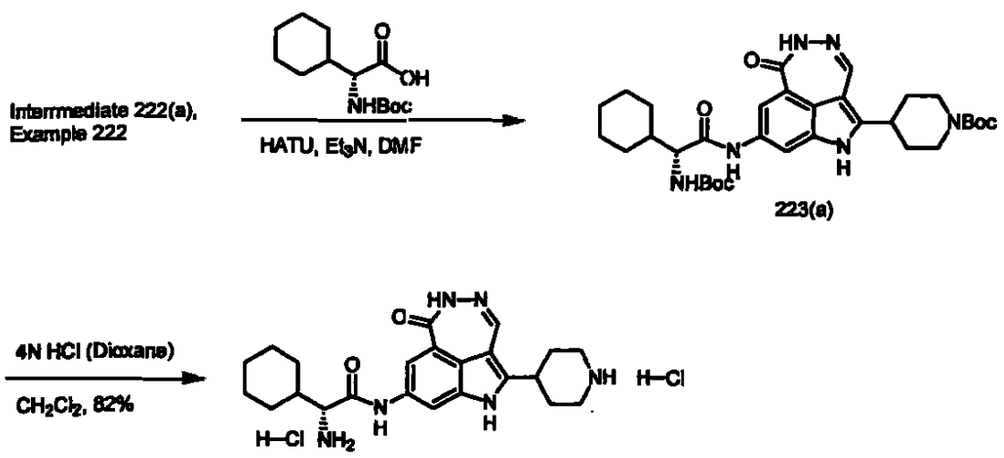
Preparation of the title compound from Intermediate 222(b) (100 mg) and 4.0 M HCl in dioxane (1 mL) was carried out analogously to Example 91. Isolation, also in an analogous manner, afforded the title compound (65.3 mg, 0.141 mmol) as a yellow powder in a combined yield of 90% for steps 2 and 3.

^{1}H NMR (d_6-DMSO): δ 11.82 (s, 1H), 10.41 (s, 1H), 10.18 (s, 1H), 9.16-9.00 (m, 1H), 8.93-8.73 (m, 1H), 8.07 (s, 1H), 7.58 (s, 2H), 7.34-7.23 (m, 2H), 7.23-7.09 (m, 3H), 3.46-3.26 (m, 3H), 3.10-2.90 (m, 2H), 2.41-2.29 (m, 1H), 2.15-2.03 (m, 1H), 2.03-1.85 (m, 4H), 1.53-1.40 (m, 1H), 1.40-1.27 (m, 1H).

LCMS: $(M+H^+)$ 428.1, $(M+Na^+)$ 450.2; $(M-H)^-$ 426.2.

HRMS: $(M+H^+)$ calcd for $C_{25}H_{26}N_6O_2$, 428.2087, found 428.2086.

Example 223: (R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-piperidin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide: dihydrochloride



Step 1. Preparation of (R)- 4-[8-(2-*tert*-Butoxycarbonylamino-2-cyclohexyl-acetylamino)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester 223(a)

Preparation of intermediate 223(a) from Intermediate 222(a) of Example **222** (60 mg, 0.157 mmol), (R)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (44.3 mg, 0.172 mmol), triethylamine (0.086 mL, 0.617 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (71.5 mg, 0.188 mmol) in *N,N*-dimethylformamide (8.0 mL) was carried out analogously to Example **11**. The volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 1:1 dichloromethane: ethyl acetate to afford Intermediate 223(a) (107 mg) as a yellow solid contaminated with *N,N*-dimethylformamide which was carried on directly to the next step.

^{1}H NMR (d_6-DMSO): δ 11.57 (s, 1H), 10.14 (s, 1H), 10.03 (s, 1H), 7.98 (s, 1H), 7.94 (s, 1H), 7.56 (s, 1H), 7.54 (s, 1H), 6.85 (d, 1H, *J* = 8.48 Hz), 4.15-3.99 (m, 2H), 3.99-3.85 (m, 1H), 2.92-2.76 (m, 2H), 1.78-1.45 (m, 10H), 1.42 (s, 9H), 1.37 (s, 9H), 1.22-0.97 (m, 5H).

LCMS: $(M+H^+)$ 623.2, $(M+Na^+)$ 645.2; $(M-H)^-$ 621.2.

Step 2. Preparation of Title Compound: (R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-piperidin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide; dihydrochloride

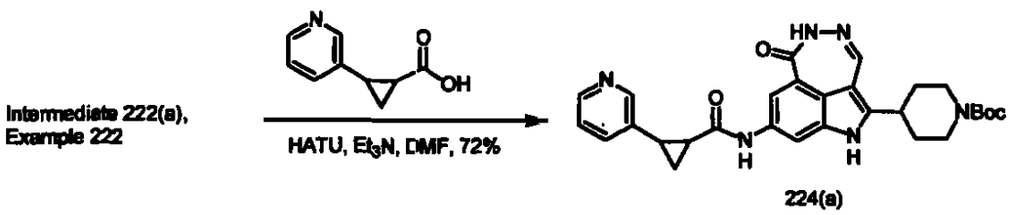
Preparation of the title compound from Intermediate 223(a) (100 mg, 0.161 mmol) and 4.0 M HCl in dioxane (1.6 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (63.2 mg, 0.128 mmol) as a yellow powder in a combined yield of 82% for steps 1 and 2.

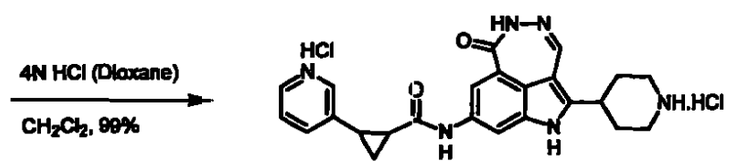
^{1}H NMR (d_6-DMSO): δ 11.98 (s, 1H), 10.82 (s, 1H), 10.24 (s, 1H), 9.21-9.06 (m, 1H), 9.06-8.87 (*m*, 1H), 8.35 (s, 3H), 8.04 (s, 1H), 7.64 (d, 1H, *J* = 1.70 Hz), 7.60(s, 1H), 3.47-3.28 (*m*, 4H), 3.10-3.29 (m, 2H), 2.10-1.86 (m, 4H), 1.86-1.52 (m, 6H), 1.28-0.94 (m, 5H).

LCMS: $(M+H^+)$ 423.2, $(M+Na^+)$ 445.1; $(M-H)^-$ 421.3.

HRMS: $(M+H^+)$ calcd for $C_{23}H_{31}N_6O_2$, 423.2508, found 423.2492.

Example 224: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (6-oxo-2-piperidin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide: dihydrochloride





Step 1. Preparation of 4-{6-Oxo-8-[(1,2-*trans*)-(2-pyridin-3-yl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl}-piperidine-1-carboxylic acid *tert*-butyl ester 224(a)

Preparation of intermediate 224(a) from Intermediate 222(a) of Example **222** (60 mg, 0.157 mmol), (1,2-*trans*)-2-pyridin-3'-yl-cyclopropanecarboxylic acid (40.2 mg, 75%, 0.172 mmol), triethylamine (0.086 mL, 0.617 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (71.5 mg, 0.188 mmol) in *N,N*-dimethylformamide (8.0 mL) was carried out analogously to Example **11**. The volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 25:1 dichloromethane: methanol to afford intermediate 224(a) (59.2 mg, 0.112 mmol) as a yellow solid in 72% yield.

^{1}H NMR (d_6-DMSO): δ 11.59 (s, 1H), 10.39 (s, 1H), 10.14 (s, 1H), 8.65 (d, 1H, *J* = 2.07 Hz), 8.53 (dd, 1H, *J* = 4.99, 1.41 Hz), 7.98 (d, 1H, *J* = 1.70 Hz), 7.84 (d, 1H, *J* = 7.91 Hz), 7.59-7.53 (m, 3H), 4.16-4.02 (m, 3H), 2.95-2.74 (m, 2H), 2.22-2.13 (m, 1H), 1.78-1.45 (m, 7H), 1.42 (s, 9H).

LCMS: $(M+H^+)$ 529.1; $(M-H)^-$ 527.2.

Step 2. Preparation of Title Compound: (1,2-*trans*)-(2-Pyridin-3-yl-cyclopropanecarboxylic acid (6-oxo-2-piperidin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; dihydrochloride

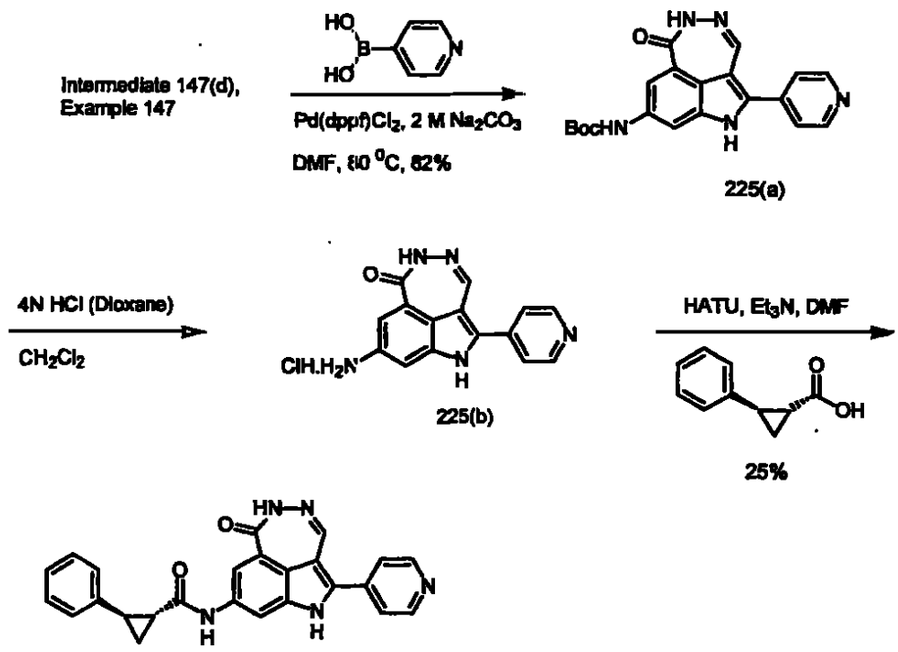
Preparation of the title compound from Intermediate 224(a) (50 mg, 0.095 mmol) and 4.0 M HCl in dioxane (0.5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (47.4 mg, 0.095 mmol) as a yellow powder in 99% yield.

^{1}H NMR (d_6-DMSO): δ 11.87 (s, 1H), 10.59 (s, 1H), 10.20 (s, 1H), 9.18-9.00 (m, 2H), 8.89 (br s, 2H), 8.72 (d, 1H, *J* = 5.09 Hz), 8.33 (d, 1H, *J* = 8.10 Hz), 8.07 (s, 1H), 7.96 (dd, 1H, *J* = 8.10, 7.72 Hz), 7.60 (d, 2H, *J* = 5.09 Hz), 3.47-3.29 (m, 3H), 3.11-2.84 (m, 2H), 2.75-2.61 (m, 1H), 2.40-2.29 (m, 1H), 2.09-1.84 (m, 4H), 1.70-1.54 (m, 2H).

LCMS: $(M+H^+)$ 429.2, $(M+Na^+)$ 451.1; $(M-H)^-$ 427.1.

HRMS: $(M+H^+)$ calcd for $C_{24}H_{25}N_6O_2$, 429.2039, found 429.2021.

Example 225: (1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide



Step 1. Preparation of *tert*-Butyl 6-oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamate 225(a)

A mixture of Intermediate 147(d) of Example **147** (0.50 g, 1.3 mmol), 4-pyridyl boronic acid (0.25 g, 2.0 mmol), [1,1'- bis(diphenylphosphino)ferrocene]dichloropalladium (II) (106 mg, 0.13 mmol) and 3.0 M aqueous sodium carbonate (3.3 ml) in *N,N*-dimethylformamide (20 ml) was stirred at

100 °C for 4 hours. The volatile components were removed *in vacuo* and the residue was subjected to on silica gel chromatography, eluting with CH_2Cl_2:methanol (95:5 increasing to 90:10). Intermediate 225(a) (0.41 g) was obtained in 82% yield.

^{1}H NMR (d_6-DMSO): δ 12.22 (s, 1H), 10.52 (s, 1H), 9.60 (s, 1H), 8.74 (s, 1H), 8.72 (s, 1H), 7.85 (d, 1H, *J* = 1.7 Hz), 7.75 (d, 1H, *J* = 1.7 Hz), 7.60-7.72 (m, 3H), 1.51 (s, 9H).

LCMS (M^++1): 378.1

Step 2. Preparation of 8-Amino-2-pyridin-4-yl-1,6-dihydro-6*H*-[1,2]diazepino[4,5,6-*cd*]indol-6-one hydrochloride 225(b)

To a mixture of Intermediate 225(a) (0.38 g, 1.0 mmol) in CH_2Cl_2 (30 ml), was added 1M HCl in diethyl ether (20 ml). The mixture was then stirred at room temperature for 2 hours. The volatiles were removed *in vacuo* to provide Intermediate 225(b) which was carried on directly to the next step without further purification.

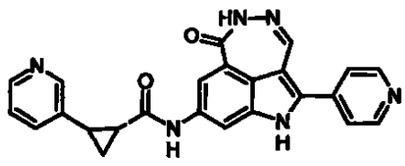
Step 3. Preparation of Title Compound: (1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide

A solution of Intermediate 225(b) (ca. 0.5 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (113 mg, 0.7 mmol), triethylamine (0.4 ml) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.23 g, 0.6 mmol) in 10 ml of *N,N*-dimethylformamide was stirred at room temperature for 3 hours. The mixture was subjected to preparative HPLC to afford the title compound (107 mg, 0.25 mmol) in 25% yield for steps 2 and 3.

^{1}H NMR (d_6-DMSO): δ 12.25 (s, 1H), 10.49 (s, 1H), 10.44 (s, 1H), 8.67 (s, 1H), 8.65 (s, 1H), 8.16 (s, 1H), 7.48-7.91 (m, 4H), 7.20-7.46 (m, 2H), 6.96-7.20 (m, 3H), 2.26-2.40 (m, 1H), 1.94-2.13 (m, 1H) 1.39-1.60 (m, 1H), 1.22-1.39 (m, 1H).

HRMS calculated for $C_{25}H_{19}N_5O_2$ 422.1617 (M+H), found 422.1626.

Example 226: *N*-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-pyridin-3-ylcyclopropanecarboxamide



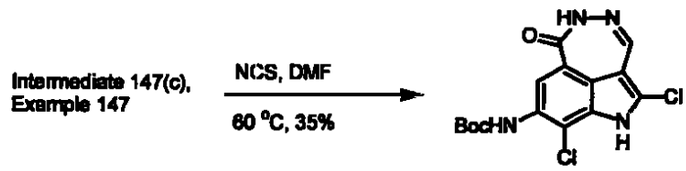
Preparation of example 226 from Intermediate 147(d) of Example **147** (200 mg, 0.529 mmol) was carried out analogously to the preparation of Example **225** in three steps except that (1,2-*trans*)-2-pyridin-3-yl-cyclopropanecarboxylic acid was used instead of (1R,2R)-2-phenyl-

cyclopropanecarboxylic acid in step 3. Isolation, also in an analogous manner, afforded the title compound (54 mg) as a yellow powder in 25% yield overall.

^{1}H NMR (d_6-DMSO): δ 12.26 (s, 1H), 10.49 (s, 1H), 10.47 (s, 1H), 8.67 (s, 1H), 8.65 (s, 1H), 8.46 (s, 1H), 8.30-8.43 (d, 1H, J = 4.7 Hz), 8.16 (s, 1H), 7.57-7.88 (m, 4H), 7.45-7.57 (m, 1H), 7.19-7.41 (m, 1H), 2.32-2.42 (m, 1H), 2.01-2.20 (m, 1H), 1.46-1.65 (m, 1H), 1.32-1.46 (m, 1H).

HRMS calculated for $C_{24}H_{18}N_6O_2$ 423.1569 (M+H), found 423.1598.

Example 227: (2,9-Dichloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid *tert*-butyl ester

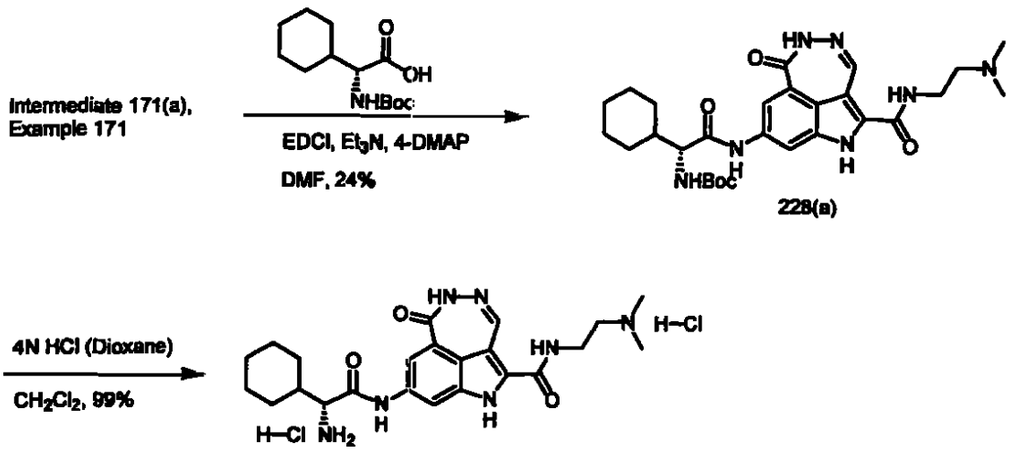


To a solution of Intermediate 147(c) of Example **147** (1.5 g, 5 mmol) in $CHCl_3$ (10 mL) and *N,N*-dimethylformamide (15 mL), was added N-chlorosuccinimide (701 mg, 5.25 mmol). The mixture was heated to 60 °C and stirred for 3 hours. Chloroform, *N,N*-dimethylformamide and water were added. Following extractive work-up with chloroform, the organic layer was dried over Na_2SO_4 and filtered. Evaporation of the volatile components gave a deep brown residue to which methanol was added. Filtration and collection of the solids gave the title compound (648 mg) as deep brown solid whose purity by NMR and HPLC was estimated to be about 70%.

^{1}H-NMR (d_6-DMSO): δ 13.15 (s, 1H), 10.62 (s, 1H), 8.90 (s, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 1.47 (s, 9H).

LCMS: ($M+H^+$) 370.2.

Example 228: (R)- 8-(2-Amino-2-cyclohexyl-acetylamino)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide; dihydrochloride



Step 1. Preparation of (R)-[Cyclohexyl-[2-(2-dimethylamino-ethylcarbamoyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl]-methyl]-carbamic acid *tert*-butyl ester 228(a)

Preparation of intermediate 228(a) from Intermediate 171(a) of Example **171** (200 mg, 0.571 mmol), (R)-tert-butoxycarbonylamino-cyclohexyl-acetic acid (147 mg, 0.571 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (131 mg, 0.686 mmol), and 4-dimethylaminopyridine (84 mg, 0.688 mmol) in *N,N*-dimethylformamide (8.0 mL) was carried out analogously to Example **190**, step 2. When the reaction was judged complete, the volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 40:3:0.3 dichloromethane: methanol: ammonium hydroxide to afford Intermediate 228(a) (77 mg, 0.139 mmol) as a yellow solid in 24% yield.

^{1}H NMR (d_6-DMSO): δ 12.65 (s, 1H), 10.66 (s, 1H), 10.26 (s, 1H), 9.83 (br s, 1H), 8.98 (br s, 1H), 8.16 (s, 2H), 7.76 (s, 1H), 6.93 (d, 1H, *J* = 9.23 Hz), 4.18-4.03 (m, 1H), 4.01-3.85 (m, 1H), 3.71-3.56 (m, 2H), 2.83 (s, 6H), 1.78-1.45 (m, 6H), 1.37 (s, 9H), 1.21-0.93 (m, 5H). LCMS: ($M+H^+$) 554.2, ($M+Na^+$) 576.1; $(M-H)^-$ 552.2.

Step 2. Preparation of Title Compound: (R)- 8-(2-Amino-2-cyclohexyl-acetylamino)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide; dihydrochloride

Preparation of the title compound from Intermediate 228(a) (75 mg, 0.136 mmol) and 4.0 M HCl in dioxane (1.36 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded the title compound (71.3 mg, 0.136 mmol) as a yellow powder in 99% yield.

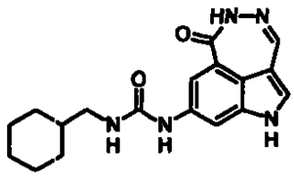
^{1}H NMR (d_6-DMSO): δ 12.95 (s, 1H), 10.98 (s, 1H), 10.70 (s, 1H), 10.08 (br s, 1H), 9.16 (s, 1H), 8.37 (s, 3H), 8.21 (s, 1H), 8.13 (d, 1H, *J* = 1.32 Hz), 7.79 (d, 1H, *J* = 1.51 Hz), 3.85-3.74 (m, 1H),

3.65 (d, 2H, J = 5.84 Hz), 3.30 (d, 2H, J = 6.41 Hz), 2.83 (d, 6H, J = 4.71 Hz), 1.93-1.52 (m, 6H), 1.29-0.97 (m, 5H).

LCMS: $(M+H^+)$ 454.2, $(M+Na^+)$ 476.1; $(M-H)^-$ 452.1.

HRMS: $(M+H^+)$ calcd for $C_{23}H_{32}N_7O_3$, 454.2567, found 454.2574.

Example 229: *N*-(Cyclohexylmethyl)-*N*'-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)urea

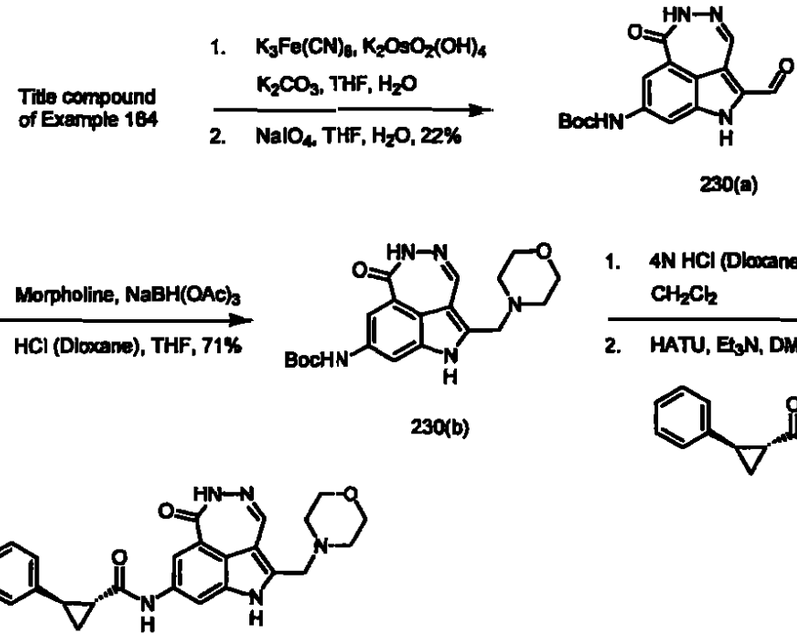


Preparation of example 229 from the title compound of Example **2** (25 mg, 0.11 mmol), *N,N'*-disuccinimidyl carbonate (27 mg, 0.11 mmol), *N,N*-diisopropylethylamine (0.024 mL, 0.21 mmol) and 1-cyclohexylmethanamine (0.028 mL, 0.021 mmol) in *N,N*-dimethylformamide (1.0 mL) was carried out analogously to Example **207**. Purification, also in an analogous manner, afforded the title compound (4 mg, 0.009 mmol) as yellow powder in 8% yield.

^{1}H NMR ($CDCl_3$/methanol-d_4): δ 8.02 (s, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 7.18 (s, 1H), 3.06 (d, 2H, J = 5.84 Hz), 1.82-1.71 (m, 5H), 1.34-1.18 (m, 5H), 0.97 (m, 1H).

LCMS: $(M-H)^-$ 338.1, $(M+Na^+)$ 362.1.

Example 230: (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid (2-morpholin-4-ylmethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide compound with acetic acid



Step 1. Preparation of (2-Formyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid tert-butyl ester 230(a)

To a solution of the title compound of Example **164** (48 mg, 0.146 mmol) in 1:1 tetrahydrofuran:H_2O (4 mL) was added K_2CO_3 (30 mg, 0.219 mmol), $K_2OsO_2(OH)_4$ (7 mg) and $K_3Fe(CN)_6$ (72 mg, 0.219 mmol). The mixture was stirred at room temperature for 2 hours whereupon water and ethyl acetate were added. Following extractive work-up, the organic layer was then dried, filtered, and concentrated. The residue was dissolved in 1:1 tetrahydrofuran:H_2O (2 mL) and sodium periodate (156 mg, 50.73 mmol) was added. The mixture was stirred at room temperature for 30 min whereupon water and ethyl acetate were added. Following extractive work-up, the organic layer was then dried, filtered, and concentrated. Silica gel chromatography of the residue, eluting with 30% ethyl acetate in hexane gave Intermediate 230(a) as a pale yellow solid (11 mg, 0.034 mmol) in 22% yield.

Step 2. Preparation of (2-Morpholin-4-ylmethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid tert-butyl ester 230(b)

To a solution of morpholine (0.32 mL, 3.64 mmol) and powdered 4A molecular sieves (1.0 g) in tetrahydrofuran (5 mL) was added 4M HCl in dioxane (0.91 mL; 3.64 mmol). After 10 min, a solution of Intermediate 230(a) (199 mg, 0.607 mmol) in tetrahydrofuran (2 mL) was added dropwise followed by $NaBH(OAc)_3$ (254 mg, 1.2 mmol). The resulting suspension was stirred at room temperature for 24 hours. The mixture was quenched with saturated aqueous sodium bicarbonate and filtered through diatomaceous earth, which was then washed with ethyl acetate. More ethyl acetate was added to the filtrate, and the aqueous layer was extracted. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to silica gel chromatography eluting with 5 % MeOH/ethyl acetate to give Intermediate 230(b) as a pale yellow powder (173 mg, 0.43 mmol) in 71% yield.

^1H NMR (d_6-DMSO): 11.71 (s, 1H), 10.21 (s, 1H), 7.73 (s, 1H), 7.62 (s, 2H), 3.74 (s, 2H), 3.63-3.61 (m, 4H), 2.43-2.41 (m, 4H), 1.52 (s, 9H).

LCMS: ($M+H^+$) 400.

Step 3. Preparation of Title compound: (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid (2-morpholin-4-ylmethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide compound with acetic acid

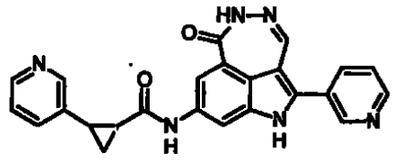
Preparation of the title compound from Intermediate 230(b) (173 mg, 0.433 mmol) in CH_2Cl_2 (2 mL) and 4M HCl in dioxane (2 mL) was carried out analogously to the preparation of Example **91**. After concentration, the residue was dissolved in *N,N*-dimethylformamide (5 mL). (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid (84 mg, 0.52 mmol), triethylamine (0.18 mL, 1.3 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (247 mg, 0.65 mmol) were added. After 12 hours, the mixture was concentrated and subjected to preparative

HPLC in a manner analogous to Example **146**, Step 2. The title compound (59 mg, 0.13 mmol) was obtained as a pale yellow powder in 31% yield.

^{1}H NMR (d_6-DMSO): 11.84 (s, 1H), 10.42 (s, 1H), 10.28 (s, 1H), 8.10 (s, 1H), 7.67 (s, 1H), 7.64 (s, 1H), 7.39-7.24 (m, 5H), 3.78 (s, 2H), 3.68-3.64 (m, 4H), 2.49-2.47 (m, 4H), 2.14 (m, 1H), 1.56 (m, 1H), 1.42 (m, 1H).

LCMS: ($M+H^+$) 444.1

Example 231: *N*-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-pyridin-3-ylcyclopropanecarboxamide

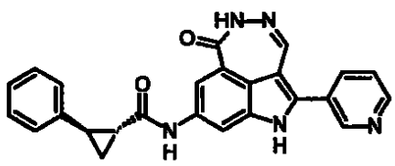


Preparation of example 231 from Intermediate 147(d) of Example **147** was carried out analogously to the preparation of Example **225** in three steps except that 3-pyridyl boronic acid was used instead of 4-pyridyl boronic acid in step 1 and (1,2-*trans*)-2-pyridin-3-yl-cyclopropanecarboxylic acid was used instead of (1R,2R)-2-phenyl-cyclopropanecarboxylic acid in step 3. Isolation, also in an analogous manner, afforded the title compound (69 mg) as a yellow powder in 33% yield overall.

^{1}H NMR (d_6-DMSO): δ 12.19 (s, 1H), 10.30-10.50 (m, 2H), 8.81 (m, 1H), 8.60 (m, 1H), 8.46 (m, 1H), 8.36 (m, 1H), 8.13 (m, 1H), 7.93-8.08 (m, 1H), 7.37-7.69 (m, 4H), 7.27 (m, 1H), 2.40 (m, 1H), 2.08 (m, 1H), 1.28-1.60 (m, 2H).

HRMS calculated for $C_{24}H_{18}N_6O_2$ 423.1569 (M+H), found 423.1590.

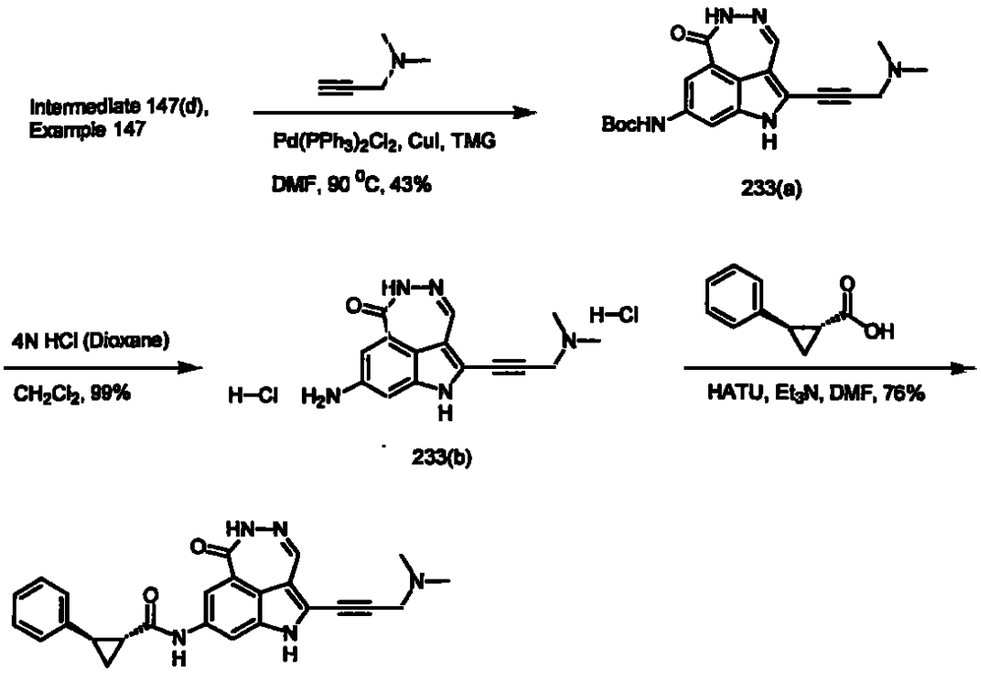
Example 232: (1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide



Preparation of example 232 from Intermediate 147(d) of Example **147** was carried out analogously to the preparation of Example **225** in three steps except that 3-pyridyl boronic acid was used instead of 4-pyridyl boronic acid in step 1. Isolation, also in an analogous manner, afforded the title compound (18 mg) as a yellow powder in 8% yield overall.

^{1}H NMR (d_6-DMSO): δ 12.18 (s, 1H), 10.28-10.54 (m, 2H), 8.81 (m, 1H), 8.60 (m, 1H), 8.13 (m, 1H), 7.95-8.08 (m, 1H), 7.57-7.70 (m, 1H), 7.49-7.57 (m, 1H), 7.38-7.48 (m, 1H), 7.01-7.34 (m, 3H) 4.05 (m, 1H), 2.32 (m, 1H), 2.03 (m, 1H), 1.46 (m, 1H), 1.32 (m, 1H).
HRMS calculated for $C_{25}H_{19}N_5O_2$ 422.1617 (M+H), found 422.1598.

Example 233: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide



Step 1. Preparation of [2-(3-Dimethylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-carbamic acid *tert*-butyl ester 233(a)

Under argon atmosphere, dimethyl-prop-2-ynyl-amine (198 mg, 2.38 mmol), dichlorobis(triphenylphosphine)palladium(II) (27.6 mg, 0.039 mmol), copperI iodide (7.8 mg, 0.041 mmol) and *N,N,N,N*-tetramethylguanidine (912 mg, 7.93 mmol) were added to a solution of Intermediate 147(d) from Example 147 (300 mg, 0.794 mmol) in *N,N*-dimethylformamide (3 mL) and dioxane (12 mL). The reaction was heated at 90 °C for 4 hours at which point the volatile components were removed *in vacuo*. The resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 20:1:0.1 dichloromethane: methanol: ammonium hydroxide to afford Intermediate 233(a) (130 mg, 0.341 mmol) as a yellow solid in 43% yield.

^{1}H NMR (d_6-DMSO): δ 12.09 (s, 1H), 10.45 (s, 1H), 9.54 (s, 1H), 7.71 (s, 1H), 7.65 (d, 1H, J = 1.51 Hz), 7.40 (s, 1H), 3.61 (s, 2H), 2.27 (s, 6H), 1.47 (s, 9H).
LCMS: $(M+H^+)$ 382.1, $(M+Na^+)$ 404.1; $(M-H)^-$ 380.1.

Step 2. Preparation of 8-Amino-2-(3-dimethylamino-prop-1-ynyl)-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one; dihydrochloride 233(b)

Preparation of intermediate 233(b) from Intermediate 233(a) (126 mg, 0.331 mmol) and 4M HCl in dioxane (1.68 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, afforded Intermediate 233(b) (117 mg, 0.331 mmol) as a yellow powder in 99% yield.

^{1}H NMR (d_6-DMSO): δ 12.56 (br s, 1H), 10.68 (s, 1H), 7.58 (s, 1H), 7.36 (s, 1H), 7.24 (s, 1H), 4.46 (s, 2H), 2.88 (s, 6H).

LCMS: $(M+Na^+)$ 304.1; $(M-H)^-$ 280.1.

Step 3. Preparation of Title Compound: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide

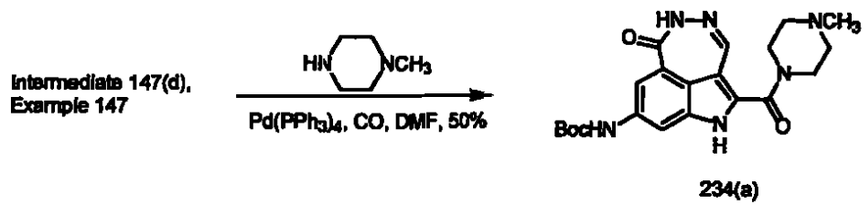
Preparation of the title compound from Intermediate 233(b) (110 mg, 0.312 mmol), (1R,2R)-2-phenyl-cyclopropanecarboxylic acid (55 mg, 0.339 mmol), triethylamine (0.189 mL, 1.36 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (155 mg, 0.408 mmol) in *N,N*-dimethylformamide (10.0 mL) was carried out analogously to Example **11**. The volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 40:3:0.3 dichloromethane: methanol: ammonium hydroxide to afford the title compound (100 mg, 0.235 mmol) as a yellow-brown solid in 76% yield.

^{1}H NMR (d_6-DMSO): δ 12.24 (s, 1H), 10.53 (s, 1H), 10.47 (s, 1H), 8.10 (d, 1H, J = 1.32 Hz), 7.62 (d, 1H, J = 1.51 Hz), 7.45 (s, 1H), 7.33-7.25 (m, 2H), 7.23-7.15 (m, 3H), 3.84 (s, 2H), 2.44 (s, 6H), 2.42-2.32 (m, 1H), 2.12-2.02 (m, 1H), 1.55-1.45 (m, 1H), 1.42-1.32 (m, 1H).

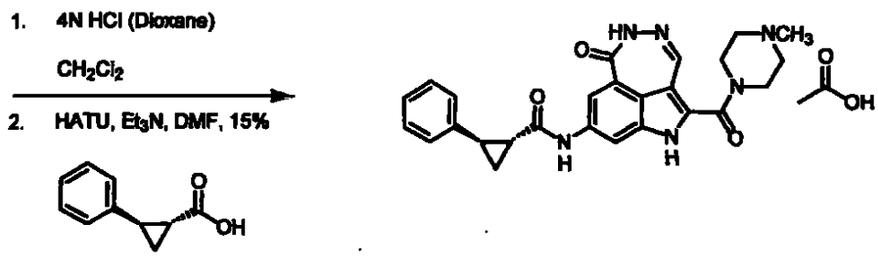
LCMS: $(M+H^+)$ 426.0, $(M+Na^+)$ 448.1; $(M-H)^-$ 424.1.

HRMS: $(M+H^+)$ calcd for $C_{25}H_{24}N_5O_2$, 426.1930, found 426.1911.

Example 234: (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(4-methyl-piperazine-1-carbonyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (acetic acid salt)



234(a)



Step 1. Preparation of [2-(4-Methyl-piperazine-1-carbonyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-carbamic acid tert-butyl ester; compound with acetic acid 234(a)

Preparation of intermediate 234(a) from Intermediate 147(d) of Example **147** (453 mg, 1.2 mmol), *N*-methylpiperazine (0.66 mL, 6 mmol), and tetrakis(triphenylphosphine)palladium(0) (105 mg, 0.09 mmol) in *N,N*-dimethylformamide (7 mL) was carried out analogously to the preparation of Example **161** except that tetrakis(triphenylphosphine)palladium(0) was used as the catalyst instead of bis(diphenylphosphino)ferrocenedichloropalladium (II). After concentration, the residue was subjected to preparative HPLC (Peeke Scientific, HI-Q C18 reverse phase 5u, 100A, 250x21.2 mm column) eluting with CH_3CN and 0.1% acetic acid in water at a flow rate of 20 mL/min using a gradient of 5-95% CH_3CN over 40 min to give Intermediate 234(a) (254 mg, 0.6 mmol) as a pale green powder in 50% yield.

^1H NMR (d_6-DMSO): 12.06 (s, 1H), 10.46 (s, 1H), 9.52 (s, 1H), 7.74 (s, 1H), 7.64 (s, 1H), 7.37 (s, 1H), 3.49-3.48 (m, 4H), 2.29-2.28 (m, 4H), 2.20 (s, 3H), 1.42 (s, 9H).

LCMS: $(M+H^+)$ 426.1

Step 2. Preparation of Title compound: (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(4-methyl-piperazine-1-carbonyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (acetic acid salt)

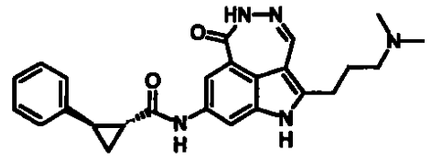
Preparation of the title compound from intermediate 234(a) (445 mg, 1.06 mmol) in CH_2Cl_2 (5 mL) and 4M HCl in dioxane (5 mL) was carried out analogously to Example **91**. After concentration, the residue was dissolved in *N,N*-dimethylformamide (5 mL). (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid (162 mg, 1.0 mmol), triethylamine (0.42 mL, 3 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (456 mg, 1.2 mmol) was

sequentially added. After 12 hours, the mixture was concentrated. The crude product was purified by preparative HPLC in a manner analogous to Example 146, Step 2, to give the title compound as a pale yellow powder (74 mg, 0.16 mmol) in 15% yield.

^{1}H NMR (d_6-DMSO): 12.25 (s, 1H), 10.59(s, 1H), 10.51 (s, 1H), 8.18 (s, 1H), 7.69 (s, 1H), 7.49 (s, 1H), 7.34-7.19 (m, 5H), 3.63 (brs, 4H), 2.56 (s, 3H), 2.40-2.30 (m, 4H), 2.11 (m, 1H), 1.56 (m, 1H), 1.42 (m, 1H).

LCMS: (M+H$^+$) 444.1

Example 235: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-propyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide



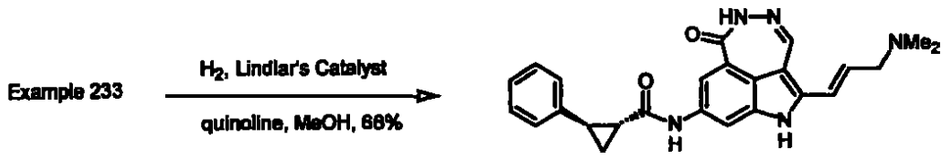
In a manner analogous to that of Example **183**, 10% palladium on activated carbon (20 mg) was added to a solution of the title compound of Example **233** (20 mg, 0.047 mmol) in methanol (3 mL). The reaction mixture was purged with H_2 and stirred at room temperature under H_2 (1 atm.) for 1 hour. The reaction mixture was loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 20:1:0.1 dichloromethane: methanol: ammonium hydroxide to afford the title compound (8 mg, 0.0186 mmol) as a yellow solid in 40% yield.

^{1}H NMR (d_6-DMSO): δ 11.70 (s, 1H), 10.34 (s, 1H), 10.17 (s, 1H), 8.04 (d, 1H, *J* = 1.51 Hz), 7.52 (d, 1H, *J* = 1.51 Hz), 7.48 (s, 1H), 7.33-7.25 (m, 2H), 7.23-7.14 (m, 3H), 2.98-2.81 (m, 4H), 2.66 (br s, 6H), 2.41-2.31 (m, 1H), 2.11-2.02 (m, 1H), 2.01-1.87 (m, 2H), 1.53-1.43 (m, 1H), 1.41-1.31 (m, 1H).

LCMS: (M+H$^+$) 430.1, (M+Na$^+$) 452.1; (M-H)$^-$ 428.1.

HRMS: (M+H$^+$) calcd for $C_{25}H_{28}N_5O_2$, 430.2243, found 430.2240.

Example 236: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-propenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide



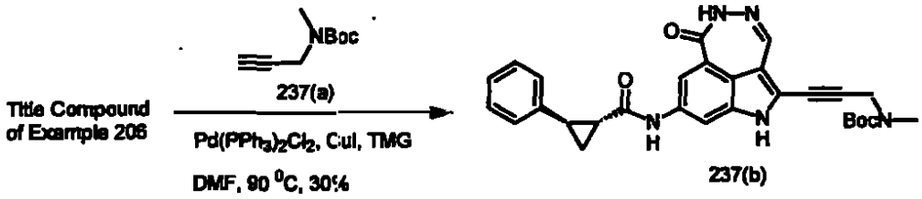
To a mixture of the title compound from Example **233** (45 mg, 0.106 mmol), Lindlar catalyst (45 mg), and quinoline (4.1 mg, 0.032 mmol) was added anhydrous methanol (3 mL). The reaction mixture was purged with H_2 and stirred at room temperature under H_2 (1 atm) for 2.5 hours. The reaction mixture was loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 20:1:0.1 dichloromethane: methanol: ammonium hydroxide to afford the title compound (30 g, 0.070 mmol) as a yellow solid in 66% yield.

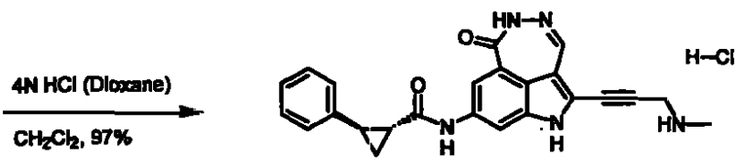
^{1}H NMR (d_6-DMSO): δ 13.07 (s, 1H), 10.41 (s, 1H), 10.32 (s, 1H), 8.11 (d, 1H, *J* = 1.70 Hz), 7.57 (s, 1H), 7.54 (d, 1H, *J* = 1.70 Hz), 7.33-7.25 (m, 2H), 7.23-7.14 (m, 3H), 6.88 (d, 1H, *J* = 12.25 Hz), 5.91 (dt, 1H, *J* = 12.06, 6.22), 3.16 (d, 2H, *J* = 5.65 Hz), 2.42-2.33 (m, 1H), 2.28 (s, 6H), 2.12-2.03 (m, 1H), 1.53-1.44 (m, 1H), 1.41-1.31 (m, 1H).

LCMS: $(M+H^+)$ 428.1, $(M+Na^+)$ 450.0; $(M-H)^-$ 426.0.

HRMS: $(M+H^+)$ calcd for $C_{25}H_{26}N_6O_2$, 428.2087, found 428.2082.

Example 237: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt)





Step 1. Preparation of (1R,2R)-Methyl-(3-[6-oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl}-prop-2-ynyl)-carbamic acid *tert*-butyl ester 237(b)

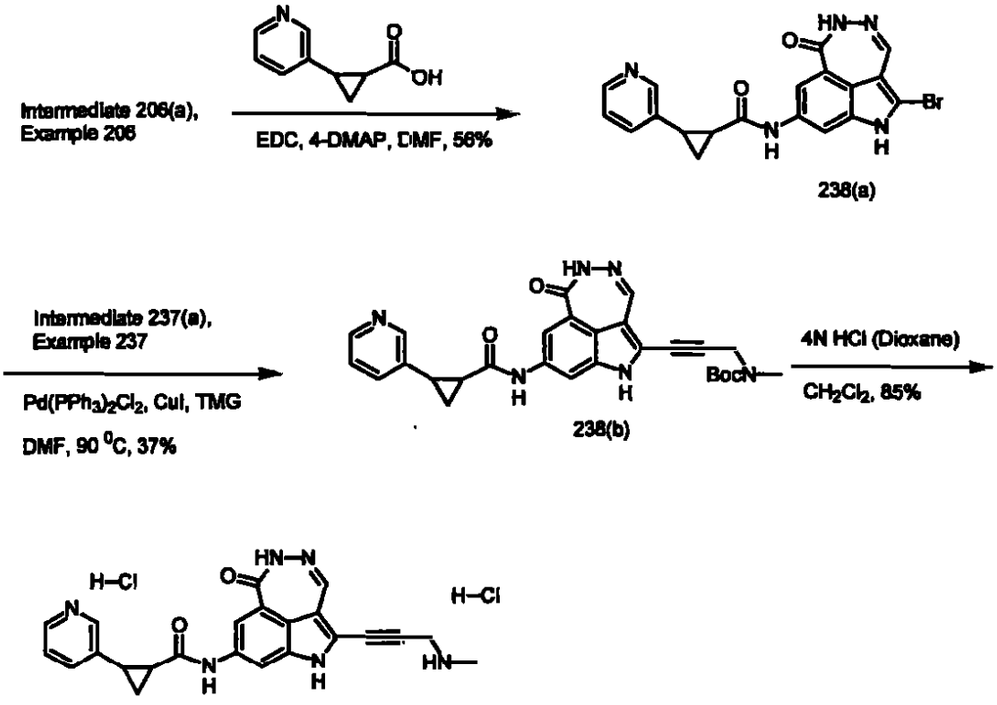
Intermediate 237(a) was prepared by stirring methyl-prop-2-ynyl-amine (0.5 g, 7.23 mmol), di-*tert*-butyl dicarbonate (1.74 g, 7.97 mmol) and 2,6-dimethyl-pyridine (0.088 g, 0.72mmol) in anhydrous acetonitrile (10 mL) at room temperature for 16 hours. The solvent was evaporated and the residue was subjected to silica gel chromatography eluting with ethyl acetate to afford Intermediate 237(a) (1 g, 5.91 mmol) as colorless oil in 82% yield. In a manner analogous to that of Example **233**, Step 1, under an argon atmosphere, intermediate 237(a) (66 mg, 0.39 mmol), dichlorobis(triphenylphosphine)palladium(II) (4.6 mg, 0.0066 mmol), copper iodide (1.2 mg, 0.0063 mmol) and *N,N,N,N*-tetramethylguanidine (150 mg, 1.30 mmol) were added to a solution of the title compound from Example **206** (55 mg, 0.13 mmol) in *N,N*-dimethylformamide (0.5 mL) and dioxane (2 mL). The reaction was heated at 90 °C for 3 hours at which point the volatile components were removed *in vacuo*. The resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 3:2 dichloromethane:ethyl acetate to afford Intermediate 237(b) (20 mg, 0.039 mmol) as a yellow solid in 30% yield.

^{1}H NMR (d_5-DMSO): δ 12.22 (s, 1H), 10.51 (s, 1H), 10.46 (s, 1H), 8.08 (d, 1H, *J* = 1.51 Hz), 7.61 (d, 1H, *J* = 1.70 Hz), 7.41 (s, 1H), 7.33-7.25 (m, 2H), 7.22-7.15 (m, 3H), 4.37 (s, 2H), 2.90 (s, 3H), 2.41-2.33 (m, 1H), 2.11-2.02 (m, 1H), 1.54-1.45 (m, 1H), 1.42 (s, 9H), 1.39-1.32 (m, 1H).
LCMS: $(M-H)^-$ 510.0.

Step 2. Preparation of Title Compound: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt)

Preparation of the title compound from Intermediate 237(b) (20 mg, 0.039 mmol) and 4.0 M HCl in dioxane (0.5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner afforded the title compound (17 mg, 0.038 mmol) as a yellow powder in 97% yield.
^{1}H NMR (d_5-DMSO): δ 12.37 (s, 1H), 10.59 (s, 1H), 10.55 (s, 1H), 9.30 (br s, 2H), 8.14 (s, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 7.36-7.24 (m, 2H), 7.24-7.12 (m, 3H), 4.27 (s, 2H), 2.66 (s, 3H), 2.41-2.29 (m, 1H, partial obscured), 2.17-2.03 (m, 1H), 1.56-1.44 (m, 1H), 1.43-1.31 (m, 1H).
LCMS: $(M-H)^-$ 410.1.
HRMS: $(M+H^+)$ calcd for $C_{24}H_{22}N_5O_2$, 412.1774, found 412.1768.

Example 238: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide: dihydrochloride



Step 1. Preparation of (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (2-bromo-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide 238(a)

Preparation of intermediate 238(a) from Intermediate 206(a) of Example **206** (120 mg, 0.38 mmol), (1,2-*trans*)-2-pyridin-3-yl-cyclopropanecarboxylic acid (106 mg, c.a 0.487 mmol, purity c.a. 75%), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (88 mg, 0.461 mmol), and 4-dimethylaminopyridine (56 mg, 0.459 mmol) in *N,N*-dimethylformamide (15.0 mL) was carried out analogously to the preparation of Example **190**, step 2. When the reaction was judged complete, the volatile components were removed in *vacuo*, the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 50:3 dichloromethane:methanol to afford Intermediate 238(a) (90 mg, 0.212 mmol) as a yellow solid in 56% yield.

^{1}H NMR (d_6-DMSO): δ 12.60 (s, 1H), 10.46 (s, 1H), 10.45 (s, 1H), 8.50 (d, 1H, *J* = 1.88 Hz), 8.40 (dd, 1H, *J* = 4.62, 1.41 Hz), 8.08 (d, 1H, *J* = 1.70 Hz), 7.60 (d, 1H, *J* = 1.51 Hz), 7.56 (dt, 1H, *J* = 7.96, 1.86 Hz), 7.32 (dd, 1H, *J* = 7.91, 4.90 Hz), 7.27 (s, 1H), 2.45-2.37 (m, 1H), 2.16-2.06 (m, 1H), 1.57-1.49 (m, 1H), 1.49-1.40 (m, 1H).

LCMS: $(M-H)^-$ 422.0, 424.0.

Step 2. Preparation of Methyl-(3-(6-oxo-8-[(2-pyridin-3-yl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl)-prop-2-ynyl)-carbamic acid *tert*-butyl ester 238(b)

Under argon in a manner analogous to that of Example **233**, step 1, Intermediate 237(a) of Example 237 (54 mg, 0.32 mmol), dichlorobis(triphenylphosphine)palladium(II) (3.7 mg, 0.0053 mmol), copperI iodide (1.0 mg, 0.0053 mmol) and *N,N,N,N*-tetramethylguanidine (122 mg, 1.06 mmol) were added to a solution of Intermediate 238(a) (45 mg, 0.106 mmol) in *N,N*-dimethylformamide (1 mL) and dioxane (2 mL). The reaction was heated at 90 °C for 2 hours at which point the volatile components were removed *in vacuo*. The resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 20:1:0.1 dichloromethane: methanol: ammonium hydroxide to afford Intermediate 238(b) (20 mg, 0.039 mmol) as a yellow solid in 37% yield.

^{1}H NMR (d_6-DMSO): δ 12.23 (s, 1H), 10.52 (s, 1H), 10.50 (s, 1H), 8.45 (br s, 1H), 8.08 (s, 1H), 7.61 (s, 1H), 7.56 (d, 1H, *J* = 7.91 Hz), 7.41 (s, 1H), 7.35 (br s, 1H), 4.37 (s, 2H), 2.90 (s, 3H), 2.45-2.38 (m, 1H, partial obscured), 2.16-2.07 (m, 1H), 1.59-1.49 (m, 1H), 1.50-1.44 (m, 1H, partial obscured), 1.42 (s, 9H),

LCMS: $(M+H^+)$ 513.2, $(M+Na^+)$ 535.1; $(M-H)^-$ 511.1.

Step 3. Preparation of Title Compound: (1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide; dihydrochloride

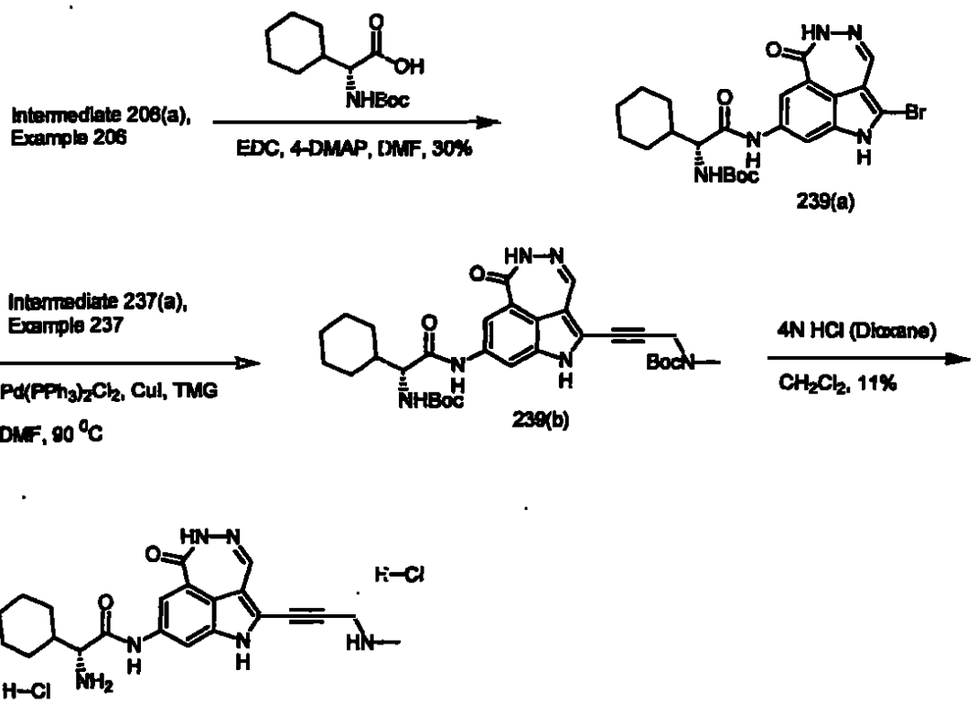
Preparation of the title compound from Intermediate 238(b) (20 mg, 0.039 mmol) and 4M HCl in dioxane (0.5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner afforded the title compound (16 mg, 0.033 mmol) as a dark red solid in 85% yield.

^{1}H NMR (d_6-DMSO): δ 12.46 (s, 1H), 10.77 (s, 1H), 10.59 (s, 1H), 9.46 (br s, 2H), 8.90 (s, 1H), 8.76 (d, 1H, *J* = 3.77 Hz), 8.34 (d, 1H, *J* = 7.35 Hz), 8.11 (s, 1H), 8.03-7.90 (m, 1H), 7.69 (s, 1H), 7.59 (s, 1H), 4.25 (s, 2H), 2.65 (s, 3H), 2.49 (m, 1H, obscured), 2.41-2.29 (m, 1H, partial obscured), 1.73-1.55 (m, 2H).

LCMS: $(M-H)^-$ 411.1.

HRMS: ($M+H^+$) calcd for $C_{23}H_{21}N_6O_2$, 413.1726, found 413.1753.

Example 239: (2R)-2-Amino-2-cyclohexyl-*N*-[2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide; dihydrochloride



Step 1. Preparation of (R)-[(2-Bromo-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ylcarbamoyl)-cyclohexyl-methyl]-carbamic acid *tert*-butyl ester 239(a)

Preparation of intermediate 239(a) from Intermediate 206(a) of Example **206** (120 mg, 0.38 mmol), (R)-*tert*-butoxycarbonylamino-cyclohexyl-acetic acid (120 mg, 0.466 mmol), (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (87 mg, 0.455 mmol), and 4-dimethylaminopyridine (56 mg, 0.459 mmol) in *N,N*-dimethylformamide (7.0 mL) was carried out analogously to the preparation of Example **190**, step 2. When the reaction was judged complete, the volatile components were removed *in vacuo*, and the resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and

eluted with 1.2:1 dichloromethane: ethyl acetate to afford Intermediate 239(a) (60 mg, 0.116 mmol) as a yellow solid in 30% yield.

^{1}H NMR (d_6-DMSO): δ 12.59 (s, 1H), 10.46 (s, 1H), 10.14 (s, 1H), 8.06 (s, 1H), 7.64 (s, 1H), 7.27 (s, 1H), 6.90 (d, 1H, *J* = 8.85 Hz), 3.91 (t, 1H, *J* = 8.29 Hz), 1.76-1.44 (m, 6H), 1.37 (s, 9H), 1.20-0.93 (m, 5H).

LCMS: $(M-H)^-$ 518.0, 516.0.

Step 2. Preparation of (R)-{3-[8-(2-*tert*-Butoxycarbonylamino-2-cyclohexyl-acetylamino)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-prop-2-ynyl}-methyl-carbamic acid *tert*-butyl ester 239(b)

Under an argon atmosphere in a manner analogous to that of Example **233** step 1, Intermediate 237(a) of Example **237** (65 mg, 0.38 mmol), dichlorobis(triphenylphosphine)palladium(II) (4.5 mg, 0.0064 mmol), copperI Iodide (1.2 mg, 0.0063 mmol) and *N,N,N,N*-tetramethylguanidine (146 mg, 1.27 mmol) were added to a solution of Intermediate 239(a) (66 mg, 0.127 mmol) in *N,N*-dimethylformamide (0.5 mL) and dioxane (2 mL). The reaction mixture was heated at 90 °C for 3 hours at which point the volatile components were removed *in vacuo*. The resulting residue was dissolved in methanol and loaded onto a silica gel plug. The plug was then loaded onto a silica gel column and eluted with 4:1 dichloromethane: ethyl acetate to afford Intermediate 239(b) (10 mg) as a yellow solid contaminated with an unknown impurity.

LCMS: $(M+H^+)$ 607.2, $(M+Na^+)$ 629.3; $(M-H)^-$ 605.2.

Step 3. Preparation of Title Compound: (2R)-2-Amino-2-cyclohexyl-*N*-[2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamidede; dihydrochloride

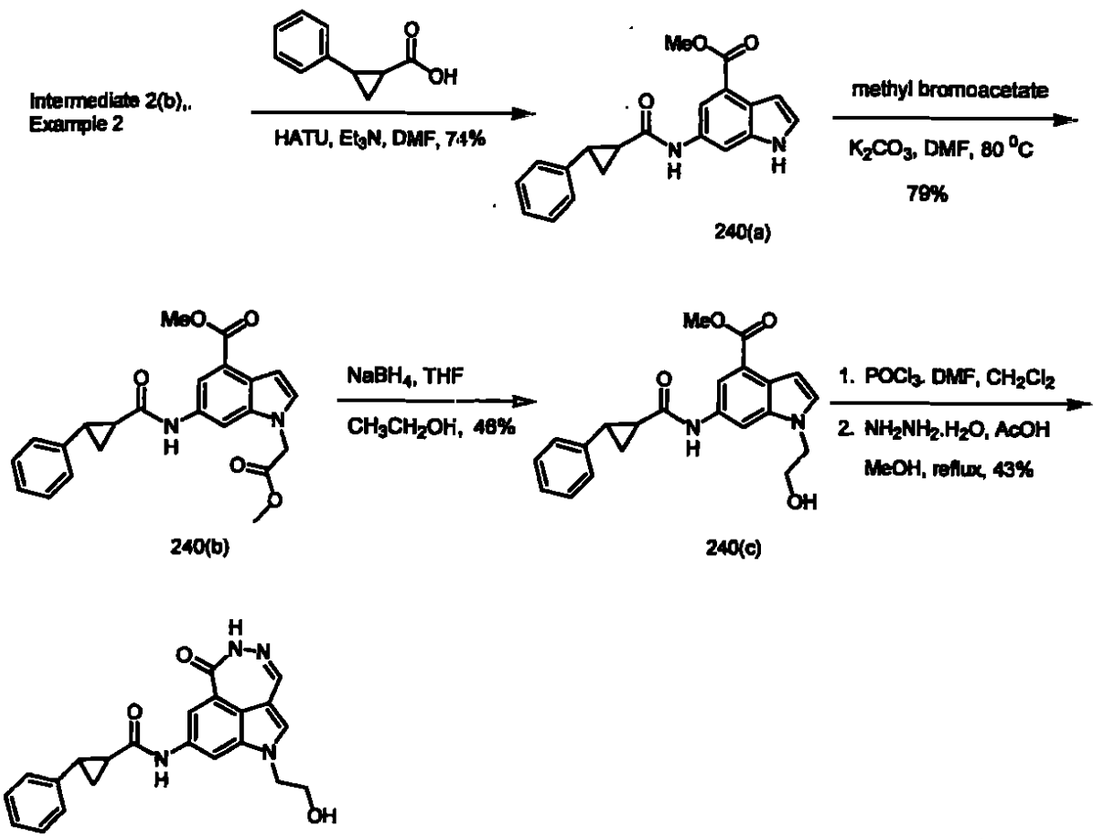
Preparation of the title compound from Intermediate 239(b) (10 mg) and 4 M HCl in dioxane (0.5 mL) was carried out analogously to Example **91**. Isolation, also in an analogous manner, included a further trituration with CH_2Cl_2 which removed the impurity carried along from step 2. The title compound (6 mg, 0.013 mmol) was obtained as a yellow powder in a combined yield of 11% for steps 2 and 3.

^{1}H NMR (d_6-DMSO): δ 12.52 (s, 1H), 10.90 (s, 1H), 10.66 (s, 1H), 9.37 (br s, 2H), 8.33 (br s, 3H), 8.08 (s, 1H), 7.73 (d, 1H, *J* = 0.9 Hz), 7.61 (s, 1H), 4.27 (s, 2H), 3.84-3.74 (m, 1H), 2.67 (s, 3H), 1.90-1.54 (m, 6H), 1.27-0.97 (m, 5H).

LCMS: $(M+Na^+)$ 429.2; $(M-H)^-$ 405.2.

HRMS: $(M+H^+)$ calcd for $C_{22}H_{27}N_6O_2$, 407.2195, found 407.2209.

Example 240: (1*R*,2-*trans*)-*N*-[1-(2-Hydroxyethyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-phenylcyclopropanecarboxamide



Step 1. Preparation of Methyl 6-{[(2-phenylcyclopropyl)carbonyl]amino}-1*H*-indole-4-carboxylate 240(a)

Preparation of intermediate 240(a) from Intermediate 2(b) of Example 2 (2.27 g, 10 mmol), (1,2-*trans*)-2-phenyl-cyclopropanecarboxylic acid (1.79 g, 11 mmol), triethylamine (3.0 g, 30 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (4.18 g, 11 mmol) in *N,N*-dimethylformamide (20 mL) was carried out analogously to Example 11.

Extractive work-up from ethyl acetate, followed by purification on silica gel column eluting with CH_2Cl_2/ ethyl acetate afforded Intermediate 240(a) (2.47 g) in 74% yield.

^1H NMR (d_6-DMSO): δ 11.39 (s, 1H), 10.39 (s, 1H), 8.25 (s, 1H), 7.88 (s, 1H), 7.47 (s, 1H), 7.10-7.40 (m, 5H), 6.86 (s, 1H), 3.89 (s, 3H), 2.33-2.48 (m, 1H), 2.04-2.21, (m, 1H), 1.46-1.63 (m, 1H), 1.29-1.45 (m, 1H).

LCMS (M+H): 335.1.

Step 2. Preparation of Methyl 1-(2-methoxy-2-oxoethyl)-6-{[(2-phenylcyclopropyl)carbonyl]amino}-1*H*-indole-4-carboxylate 240(b)

Intermediate 240(a) (2.40 g, 7.2 mmol), methyl bromoacetate (1.32 g, 8.6 mmol) and K_2CO_3 (2.0 g, 14.4 mmol) were mixed in *N,N*-dimethylformamide (25 mL) and stirred at 80 °C for 3 hours. After filtration the filtrate was evaporated, and the residue was subjected to silica gel chromatography eluting with CH_2Cl_2/ethyl acetate to afford Intermediate 240(b) (2.31 g) in 79 % yield.

^{1}H NMR (d_6-DMSO): δ 10.50 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.48 (m, 1H), 7.10-7.38 (m, 5H), 6.90 (m, 1H), 5.16 (s, 2H), 3.91 (s, 3H), 3.70 (s, 3H), 2.30-2.44 (m, 1H), 2.03-2.21 (m, 1H), 1.44-1.58 (m, 1H), 1.30-1.43 (m, 1H).

LCMS (M+H): 407.1.

Step 3. Preparation of Methyl 1-(2-hydroxyethyl)-6-{[(2-phenylcyclopropyl)carbonyl]amino}-1*H*-indole-4-carboxylate 240(c)

To Intermediate 240(b) (2.0 g, 49 mmol) in 1:1 ethanol:tetrahydrofuran (80 mL) was added $NaBH_4$ (2.0 g, 53 mmol). The mixture was stirred at room temperature overnight. Purification by silica gel chromatography afforded Intermediate 240(c) (0.85 g) in 46% yield.

^{1}H NMR (d_6-DMSO): δ 10.45 (s, 1H), 8.27 (s, 1H), 7.89 (d, 1H, *J* = 1.7 Hz), 7.49 (d, 1H, *J* = 1.5 Hz), 7.15-7.35 (m, 5H), 6.87 (d, 1H, *J* = 3.0 Hz), 4.95 (t, 1H. *J* = 5.2 Hz), 4.20 (t, 2H, *J* = 5.7 Hz), 3.91 (s, 3H), 3.60-3.80 (m, 2H), 2.33-2.46 (m, 1H), 2.05-2.18 (m, 1H), 1.43-1.65 (m, 1H), 1.30-1.43 (m, 1H).

LCMS (M+H): 379.1.

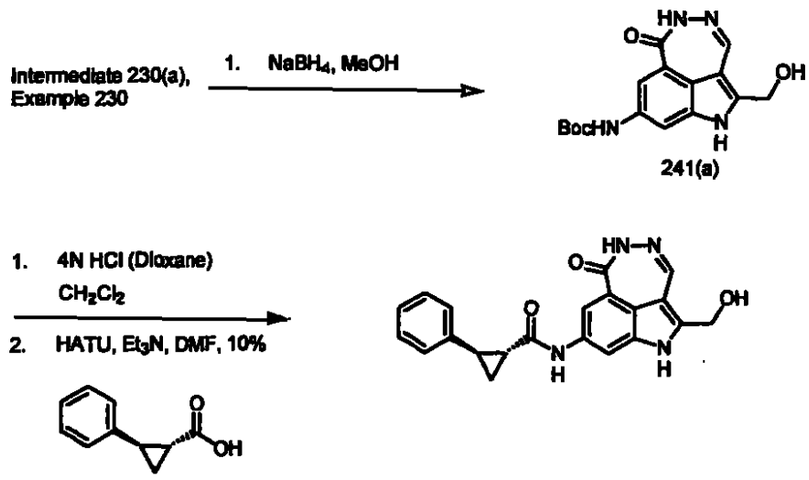
Step 4. Preparation of Title Compound: (1,2-*trans*)-*N*-[1-(2-Hydroxyethyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-phenylcyclopropanecarboxamide

With stirring, Intermediate 240(c) in *N,N*-dimethylformamide (7 ml) was added to a mixture of $POCl_3$ (0.6 ml) and *N,N*-dimethylformamide (5 mL) at 0 °C. After 1 hour, the reaction was quenched with water and extracted with ethyl acetate. The organic phase was dried with Na_2SO_4 and filtered. After evaporation of the volatile components, the residue was mixed with methanol (50 ml) containing hydrazine (1 mL) and refluxed for 5 hours. After the mixture was cooled to ambient temperature, and the resulting yellow precipitate was collected by filtration and washed with methanol to afford the title compound (0.37 g) in 43% yield.

^{1}H NMR (d_6-DMSO): δ 10.41 (s, 1H), 10.25 (s, 1H), 8.12 (d, 1H, *J* = 1.8 Hz), 7.55 (s, 2H), 7.45 (s, 1H), 7.10-7.33 (m, 5H), 4.12 (t, 2H, *J* = 5.1 Hz), 3.67 (t, 2H, *J* = 5.2 Hz), 2.29-2.40 (m, 1H), 1.99-2.10 (m, 1H), 1.41-1.52 (m, 1H), 1.28-1.39 (m, 1H).

HRMS calculated for $C_{22}H_{21}N_5O_3$ 389.1614 (M+H), found 389.1627.

Example 241: (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid (2-hydroxymethyl-6-oxo-5,6-dihydro-1*H*-[1,2-*cd*]diazepino[4,5,6]indol-8-yl)-amide



Step 1. Preparation of (2-Hydroxymethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid tert-butyl ester 241(a)

A solution of intermediate 230(a) of Example **230** (26 mg, 0.079 mmol) in methanol (2 mL) was treated with $NaBH_4$ (6 mg, 0.16 mmol) at 0 °C for 15 min. The solution was quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. After extraction, the organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Silica gel chromatography of the residue (3:1 ethyl acetate:hexane) gave intermediate 241(a) (13 mg) in 50% yield.

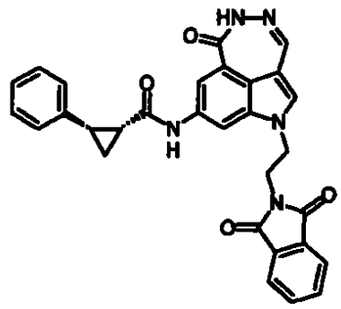
Step 2. Preparation of Title compound: (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid (2-hydroxymethyl-6-oxo-5,6-dihydro-1*H*-[1',2-*cd*]diazepino[4,5,6]indol-8-yl)-amide

To a suspension of Intermediate 241(a) (76 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) was added 4M HCl in dioxane (2 mL, 8 mmol). After stirring at room temperature for 2 hours, the mixture was concentrated and the residue was dissolved in *N,N*-dimethylformamide (2 mL). (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (33.6 mg, 0.21 mmol), triethylamine (0.1 mL, 0.69 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (131 mg, 0.345 mmol) were added. After stirring at room temperature for 2 hours, the mixture was concentrated and the residue was subjected to preparative HPLC in a manner analogous to Example **146**, step 2. The title compound was obtained as a pale yellow powder (9 mg, 0.024 mmol) in 10% yield.

^1H NMR (d_6-DMSO): δ 11.79 (s, 1H), 10.36 (s, 1H), 10.19 (s, 1H), 8.05 (d, 1H, J = 1.88 Hz), 7.57 (s, 1H), 7.56 (s, 1H), 7.32-7.19 (m, 5H), 5.70 (t, 1H, J = 4.0 Hz), 4.70 (d, 2H, J = 5.4 Hz), 2.35 (m, 1H), 2.07 (m, 1H), 1.50 (m, 1H), 1.36 (m, 1H).

LCMS: $(M+H^+)$ 375.2

Example 242: (1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid {1-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl}-amide

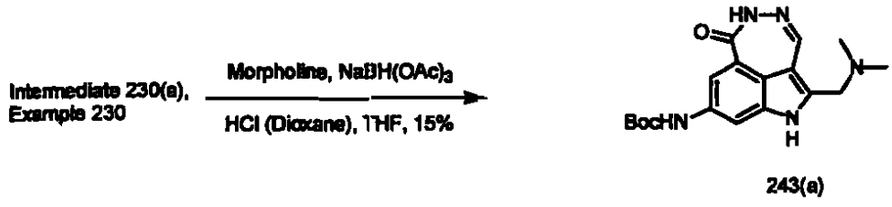


The title compound of Example **100** (130 mg, 0.38 mmol), 2-(2'-bromo-ethyl)-isoindole-1,3-dione (0.48 g, 1.9 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) were stirred in *N,N*-dimethylformamide (6 mL) at 80 °C for 20 hours. After evaporation of the volatile components, the residue was subjected to silica gel chromatography eluting with CH_2Cl_2/MeOH to afford the title compound (130 mg) in 67% yield.

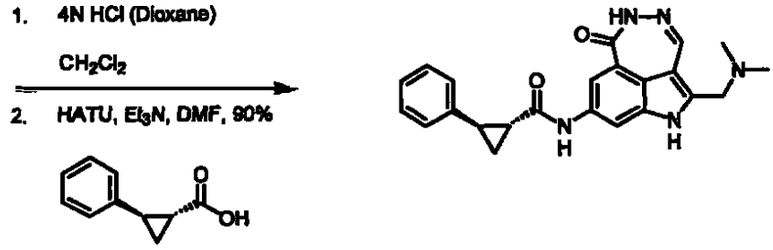
^{1}H NMR (d_6-DMSO): δ 10.33 (s, 1H), 10.31 (s, 1H), 8.07-8.15 (d, 1H, *J* = 1.5 Hz), 7.72-7.85 (m, 4H), 7.58 (s, 1H), 7.46-7.53 (d, 1H, *J* = 1.5 Hz), 7.40 (s, 1H), 7.27-7.37 (m, 2H), 7.12-7.27 (m, 3H), 4.41 (t, 2H, *J* = 4.7 Hz), 3.95 (t, 2H, *J* = 4.9 Hz), 2.31-2.42 (m, 1H), 1.96-2.07 (m, 1H), 1.43-1.55 (m, 1H), 1.30-1.42 (m, 1H).

HRMS calculated for $C_{30}H_{24}N_5O_4$ 518.1828 (M+H), found 518.1852.

Example 243: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-dimethylaminomethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



243(a)



Step 1. Preparation of (2,2-Dimethylaminomethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-carbamic acid tert-butyl ester 243(a)

Preparation of intermediate 243(a) from Intermediate 230(a) of Example **230** (707 mg, 2.16 mmol), 2M dimethylamine in tetrahydrofuran (5.4 mL, 10.8 mmol), 4M HCl in dioxane (10.8 mL; 10.8 mmol) and $NaBH(OAc)_3$ (2.29 g, 10.8 mmol) in tetrahydrofuran (5 mL) with powdered 4A molecular sieves (400 mg) was carried out analogously to Example **230**, step 2. Silica gel chromatography (eluted with 2% methanol in CH_2Cl_2), also in an analogous manner, afforded Intermediate 243(a) a pale yellow powder (112 mg, 0.31 mmol) in 15% yield.

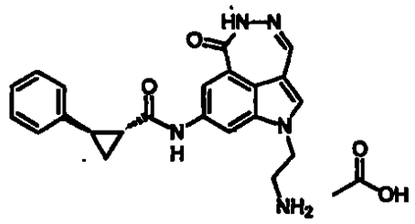
Step 2. Preparation of Title compound: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-dimethylaminomethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

Preparation of the title compound from Intermediate 243(a) (112 mg, 0.31 mmol) was carried out analogously to step 3 of Example **230**. Silica gel chromatography (eluted with 2% methanol in ethylacetate), also in an analogous manner, afforded the title compound (113 mg, 0.28 mmol) as a yellow powder in 90% yield.

^1H NMR (d_6-DMSO): 11.84 (s, 1H), 10.38 (s, 1H), 10.28 (s, 1H), 8.75 (d, J = 4 Hz, 1H), 8.53 (d, J = 4 Hz, 1H), 8.07 (s, 1H), 7.62 (s, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.32-7.18 (m, 3H), 3.31 (s, 2H), 2.49 (s, 6H), 2.33 (m, 4H), 2.09 (m, 1H), 1.50 (m, 1H), 1.36 (m, 1H).

LCMS: $(M-H)^-$ 400.

Example 244: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [1-(2-amino-ethyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide: compound with acetic acid

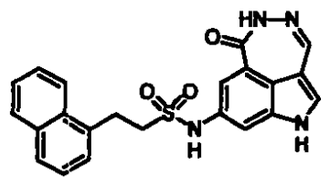


The title compound of Example **242** (92 mg, 0.18 mmol) and hydrazine (0.2 ml) were refluxed together in ethanol (14 mL) 3 hours. After evaporation of the volatile components, the residue was subjected to preparative HPLC which afforded the title compound (71.4 mg) as an acetic acid salt in 89% yield.

^1H NMR (d_6-DMSO): δ 10.44 (s, 1H), 10.27 (s, 1H), 8.15 (s, 1H), 7.58 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.26-7.34 (m, 2H), 7.12-7.23 (m, 3H), 3.99-4.13 (m, 2H), 2.88 (m, 2H), 2.33-2.42 (m, 1H), 2.02-2.12 (m, 1H), 1.43-1.55 (m, 1H), 1.30-1.41 (m, 1H).

HRMS calculated for $C_{22}H_{22}N_5O_2$ 388.1774 (M+H), found 388.1797.

Example 245: 2-Naphthalen-1-yl-ethanesulfonic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide

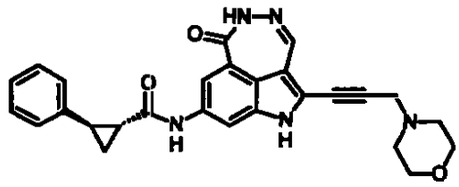


Under nitrogen, the title compound of Example 2 (260 mg, 1.1 mmol), 2-(1-naphthyl)ethanesulphonyl chloride (300 mg, 1.18 mmol), and triethylamine (0.68 mL, 4.89 mmol) were refluxed in tetrahydrofuran (5 mL) for 12 hours. The volatile components were evaporated and silica gel chromatography (eluted with 2% methanol in CH_2Cl_2) of the residue afforded the title compound (61 mg, 0.15 mmol) as a yellow powder in 13% yield.

^{1}H NMR (DMSO): δ 11.58 (s, 1H), 10.13 (s, 1H), 9.85 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 8.0, 4.0 Hz, 1H), 7.43-7.17 (m, 8H), 7.06 (m, 1H), 3.22-3.15 (m, 4H).

LCMS: $(M+H^+)$ 417.0.

Example 246: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-morpholin-4-yl-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide



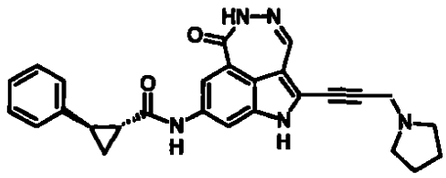
Preparation of example 246 from Intermediate 147(d) of Example 147 (300 mg, 0.794 mmol) was carried out in three steps in a manner similar to that described for the preparation of Example 233 except that 4-prop-2-ynyl-morpholine was used instead of dimethyl-prop-2-ynyl-amine in step 1. 4-Prop-2-ynyl-morpholine was prepared by refluxing 3-bromo-propyne, morpholine and K_2CO_3 in tetrahydrofuran for 1 hour. The title compound (34 mg, 0.073 mmol) was obtained as a yellow powder in 18% overall yield.

^{1}H NMR (d_6-DMSO): δ 12.21 (s, 1H), 10.49 (s, 1H), 10.46 (s, 1H), 8.08 (s, 1H), 7.61 (s, 1H), 7.41 (s, 1H), 7.33-7.24 (m, 2H), 7.23-7.13 (m, 3H), 3.66 (s, 2H), 3.62 (br s, 4H), 2.54 (br s, 4H), 2.42-2.33 (m, 1H), 2.11-2.02 (m, 1H), 1.54-1.44 (m, 1H), 1.42-1.32 (m, 1H).

LCMS: $(M+H^+)$ 468.2, $(M+Na^+)$ 490.1; $(M-H)^-$ 466.1.

HRMS: $(M+H^+)$ calcd for $C_{27}H_{28}N_5O_3$, 468.2036, found 468.2049.

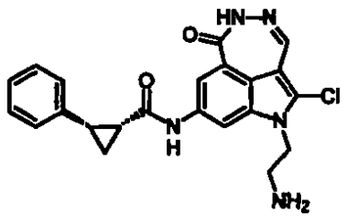
Example 247: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-yl-prop-1-ynyl)-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl]-amide



Preparation of example 247 from Intermediate 147(d) of Example **147** (300 mg, 0.794 mmol) was carried out in three steps in a manner similar to that described for the preparation of Example **233** except that 1-prop-2-ynyl-pyrrolidine was used instead of dimethyl-prop-2-ynyl-amine in step 1. 1-Prop-2-ynyl-pyrrolidine was prepared by stirring 3-bromo-propyne, pyrrolidine and triethylamine at room temperature in tetrahydrofuran for 2 hours. The title compound (80 mg, 0.177 mmol) was obtained as a yellow powder in 36% overall yield.

^{1}H NMR (d_6-DMSO): δ 12.18 (s, 1H), 10.48 (s, 1H), 10.45 (s, 1H), 8.07 (d, 1H, *J* = 1.77 Hz), 7.61 (d, 1H, *J* = 1.52 Hz), 7.39 (s, 1H), 7.32-7.25 (m, 2H), 7.23-7.14 (m, 3H), 3.75 (s, 2H), 2.60 (br s, 4H), 2.41-2.33 (m, 1H), 2.10-2.03 (m, 1H), 1.73 (br s, 4H), 1.52-1.46 (m, 1H), 1.40-1.33 (m, 1H).
LCMS: $(M+H^+)$ 452.1, $(M+Na^+)$ 474.1; $(M-H)^-$ 450.2.
HRMS: $(M+H^+)$ calcd for $C_{27}H_{28}N_5O_2$, 452.2087, found 452.2102.

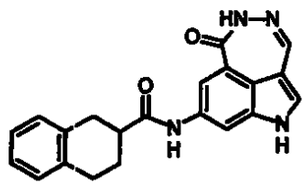
Example 248: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [1-(2-amino-ethyl)-2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl]-amide



Preparation of example 248 was carried out two steps. The first step was carried out in a manner identical to that described for the preparation of Example **242** except that the title compound of Example **190** was used instead of the title compound of Example **100**. This gave the phthaloyl protected intermediate. The second step consisted of phthaloyl deprotection, and the conditions were identical to those described in Example **244**. Purification, analogous to that described for Example **244**, gave the title compound (0.054 g) as a yellow powder in 49% overall yield.

^{1}H NMR (d_6-DMSO): δ 10.56 (s, 1H), 10.53 (s, 1H), 8.22 (s, 1H), 8.00-8.18 (br d, 2H), 7.57 (s, 1H), 7.36 (s, 1H), 7.19-7.29 (m, 2H), 7.05-7.18 (m, 3H), 4.39 (t, 2H, *J* = 6.6 Hz), 3.06 (t, 2H, *J* = 6.5 Hz), 2.28-2.37 (m, 1H), 2.00-2.13(m, 1H), 1.39-1.51 (m, 1H), 1.26-1.38 (m, 1H).
HRMS calculated for $C_{22}H_{22}N_6O_2$ 422.1804 (M+H), found 422.1403.

Example 249: 1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide



Preparation of example 249 from the title compound of Example 2 (freebase) (100 mg, 0.500 mmol), 1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid (100 mg, 0.567 mmol), triethylamine (0.278 mL, 2.00 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (285 mg, 0.750 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with ethyl acetate), also in an analogous manner, afforded the title compound (87 mg, 0.243 mmol) as a yellow powder in 48% yield.

^{1}H NMR (d_6-DMSO): δ 11.73 (d, 1H, *J* = 2.26 Hz), 10.23 (s, 1H), 10.11 (s, 1H), 8.16 (d, 1H, *J* = 1.51 Hz), 7.60 (d, 1H, *J* = 1.70 Hz), 7.55 (d, 1H, *J* = 2.64 Hz), 7.46 (s, 1H), 7.14-7.06 (m, 4H), 2.97-2.88 (m, 2H), 2.86-2.70 (m, 3H), 2.14-2.02 (m, 1H), 1.86-1.68 (m, 1H).

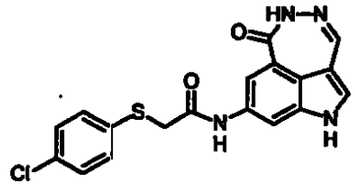
LCMS: $(M+H^+)$ 359.1, $(M+Na^+)$ 381.0; $(M-H)^-$ 357.2.

HRMS: $(M+H^+)$ calcd for $C_{21}H_{19}N_4O_2$, 359.1481, found 359.1484.

Anal. Calcd. for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63.

Found: C, 69.36; H, 5.07; N, 15.21.

Example 250: 2-(4-Chloro-phenylsulfanyl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide



Preparation of example 250 from the title compound of Example 2 (freebase) (100 mg, 0.500 mmol), (4-chloro-phenylsulfanyl)-acetic acid (110 mg, 0.543 mmol), triethylamine (0.278 mL, 2.00 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (285 mg, 0.750 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example 11. When the reaction was judged complete, the *N,N*-dimethylformamide was evaporated and methanol was added. The mixture was filtered to collect the solids, which were then washed with methanol, dichloromethane and diethyl ether. After drying under vacuum, the title compound (115 mg, 0.321 mmol) was obtained as a yellow powder in 72% yield.

^{1}H NMR (d_6-DMSO): δ 11.73 (d, 1H, *J* = 1.70 Hz), 10.35 (s, 1H), 10.26 (s, 1H), 8.06 (d, 1H, *J* = 1.51 Hz), 7.56 (d, 1H, *J* = 2.64 Hz), 7.52 (d, 1H, *J* = 1.51 Hz), 7.48-7.34 (m, 5H), 3.86 (s, 2H).

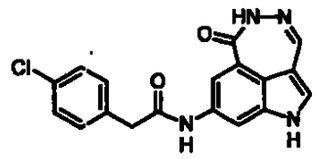
LCMS: $(M-H)^-$ 383.0.

HRMS: $(M+H^+)$ calcd for $C_{18}H_{14}ClN_4O_2S$, 385.0526, found 385.0538.

Anal. Calcd. for $C_{18}H_{13}ClN_4O_2S \cdot 0.25\ CH_2OH$: C, 55.79; H, 3.59; N, 14.26; Cl, 9.02.

Found: C, 55.49; H, 3.65; N, 14.57, Cl, 8.87.

Example 251: 2-(4-Chloro-phenyl)-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide



Preparation of example 251 from the title compound of Example 2 (106 mg, 0.448 mmol), (4-chloro-phenyl)-acetic acid (85.0 mg, 0.498 mmol), triethylamine (0.313 mL, 2.25 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (257 mg, 0.676 mmol) in *N,N*-dimethylformamide (4.0 mL) was carried out analogously to Example 11. Silica gel chromatography (eluted with 1:1 ethyl acetate: hexane), also in an analogous manner, afforded the title compound (130 mg, 0.369 mmol) as a yellow powder in 82% yield.

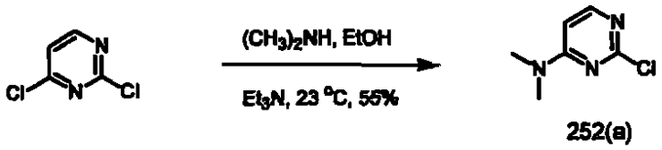
^{1}H NMR (d_6-DMSO): δ 11.73 (d, 1H, J = 1.70 Hz), 10.31 (s, 1H), 10.24 (s, 1H), 8.10 (d, 1H, J = 1.51 Hz), 7.57-7.53 (m, 2H), 7.45 (s, 1H), 7.37 (ddd, 4H, J = 8.67, 8.67, 2.64 Hz), 3.64 (s, 2H).

LCMS: $(M+H^+)$ 353.2; $(M-H)^-$ 351.2.

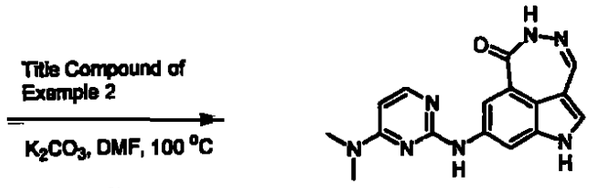
Anal. Calcd. for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88; Cl, 10.05.

Found: C, 62.22; H, 3.88; N, 15.80; Cl, 10.13.

Example 252: 8-(4-Dimethylamino-pyrimidin-2-ylamino)-1,5-dihydro-[1,2]diazepino[4,5,6-*cd*]indol-6-one



252(a)



Step 1. 2-Chloro-4-Dimethylaminopyrimidine 252(a)

To a solution of 2,4-dichloropyridine (2.24 g, 15 mmol) in ethanol (45 mL) was added triethylamine (2.1 mL, 15 mmol) followed by dimethylamine (7.5 mL, 1.0 M in THF). The resulting

mixture was stirred at 23 °C for 2 h. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ afforded the crude product, which was purified by silica gel chromatography, eluting with 30 % ethyl acetate\hexane to furnish Intermediate 252(a) (1.4 g, 8.2 mmol) in 55% yield.

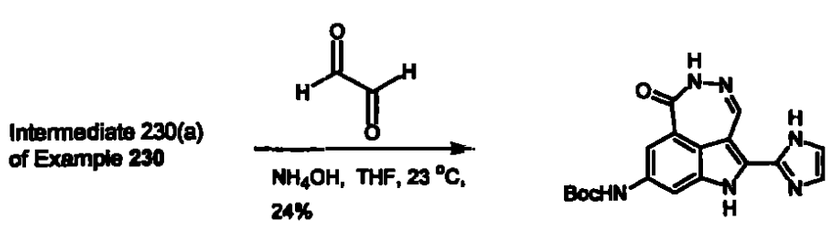
Step 2. Preparation of Title Compound: 8-(4-Dimethylamino-pyrimidin-2-ylamino)-1,5-dihydro-[1,2]diazepino[4,5,6]indol-6-one

A mixture of Intermediate 252(a) (212 mg, 1.35 mmol), the title compound of Example 2 (freebase) (320 mg, 1.6 mmol), K_2CO_3 (560 mg, 4.05 mmol) in *N,N*-dimethylformamide (5 mL) was heated at 100 °C for 4 h. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ afforded the crude product, which was triturated with methanol. The mixture was collected by filtration and washed with methanol to give the title compound as a yellow solid (83 mg, 0.26 mmol) in 19 % yield.

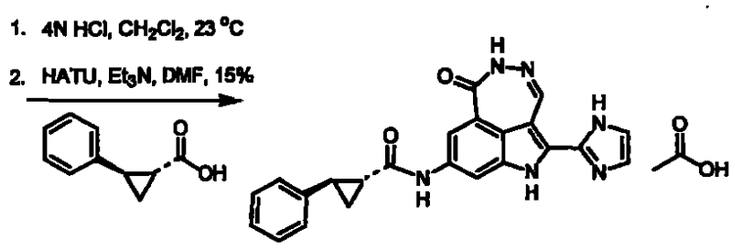
^1H NMR (d_6-DMSO): □ 11.63 (s, 1H), 10.12 (s, 1H), 9.15 (s, 1H), 8.15 (d, 1H, J = 1.8 Hz), 7.94 (d, 1H, J = 6.1 Hz), 7.92 (d, 1H, J = 1.6 Hz), 7.46 (d, 1H, J = 2.5 Hz), 7.43 (s, 1H), 6.11 (d, 1H, J = 6.1 Hz), 3.08 (s, 6H).

LCMS: $(M+H^+)$ 322.3.

Example 253: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(1*H*-imidazol-2-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide



253(a)



Step 1. [2-(1H-Imidazol-2-yl)-6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6-]indol-8-yl]-carbamic acid tert-butyl ester 253(a)

To a solution of Intermediate 230(a) of Example 230 (274 mg , 0.835 mmol) in tetrahydrofuran (5 mL) and ethanol (1 mL) was added 15N ammonium hydroxide (0.5 mL) followed by 40% glycol in

water (0.5 mL). The resulting mixture was stirred at 23 °C overnight. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ afforded the crude product, which was purified by silica gel chromatography, eluting with 50 % ethyl acetate\hexane to furnish the intermediate 253(a) (75 mg, 0.2 mmol) in 24% yield.

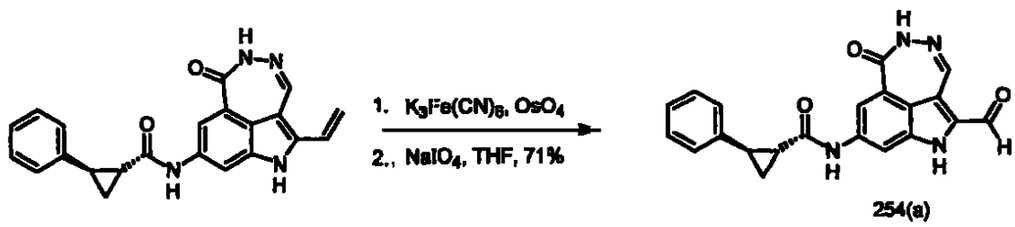
Step 2. Preparation of Title Compound: 2-Phenyl-cyclopropanecarboxylic acid [2-(1H-imidazol-2-yl)-6-oxo-5,6-dihydro-1H-[1,2]diazepino[4,5,6]indol-8-yl]-amide; compound with acetic acid.

Deprotection of Intermediate 253(a) (41 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) using 4M HCl in dioxane (2 mL) was carried out analogously to Example 91 . After concentration, the residue was dissolved in *N,N*-dimethylformamide (5 mL). (1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid (35.6 mg, 0.22 mmol), triethylamine (0.046 mL, 0.33 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (51 mg, 0.13 mmol) were sequentially added. After 12 h, the mixture was concentrated. The crude product was purified by preparative HPLC in a manner analogous to Example **146**, Step 2, to give the title compound as a pale yellow powder (7 mg, 0.017 mmol) in 15% yield.

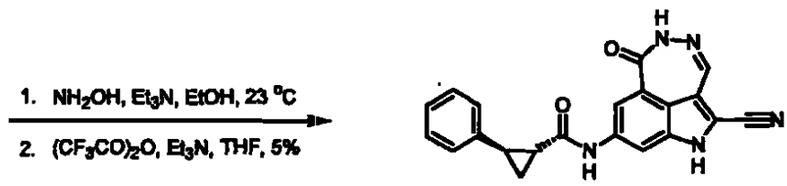
^{1}H NMR (d_6-DMSO): 12.27 (s, 1H), 11.79 (s, 1H), 10.25 (s, 1H), 10.21 (s, 1H), 7.93 (d, 1H, J = 1.7 Hz), 7.90 (s, 1H), 7.45 (d, 1H, J = 1.7 Hz), 7.20 (s, 1H), 7.13-6.99 (m, 5H), 2.19 (m, 1H), 1.89 (m, 1H), 1.31 (m, 1H), 1.18 (m, 1H).

LCMS: ($M+H^+$) 409.

Example 254: (1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-cyano-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide, compound with HOAc salt.



254(a)



Step1: 2-Phenyl-cyclopropanecarboxylic acid (2-formyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide 254(a)

Preparation of starting material, 2-phenyl-cyclopropanecarboxylic acid (6-oxo-2-vinyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide, was carried out by deprotecting the title compound from Example **164** in a manner analogous to Example **91** and then coupling to the amide in a

manner analogous to Example 61. The 2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-vinyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (542 mg, 1.46 mmol) was then treated with $K_3Fe(CN)_6$ (483 mg, 1.46 mmol) and $NaIO_4$ (1.25 g, 5.84 mmol) in tetrahydrofuran (5 mL) and water (2 mL) analogously to Example 230, step 1 . Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ afforded the crude product, which was purified by silica gel chromatography, eluting with 50% ethyl acetate\hexane to furnish intermediate 254(a) (384 mg, 1.17 mmol) in 71% yield.

Step 2. Title compound: 2-Phenyl-cyclopropanecarboxylic acid (2-cyano-6-oxo-5,6-dihydro-1H-[1,2]diazepino[4,5,6]indol-8-yl)-amide, compound with HOAc salt.

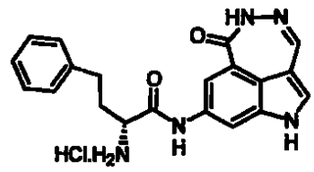
A mixture of Intermediate 254(a) (103 mg, 0.276 mmol), $NH_2OH{\cdot}HCl$ (38 mg, 0.55 mmol) and triethylamine (0.15 mL, 1.1 mmol) in ethanol (2 mL) was stirred at 23 °C for 1 h. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ afforded the crude product, which was dissolved in tetrahydrofuran (2 mL) and triethylamine (0.077 mL, 0.55 mmol). Trifluoroacetic anhydride (0.046 mL, 0.33 mL) was then added dropwise. The resulting mixture was stirred overnight. Extractive work-up from ethyl acetate and saturated aqueous $NaHCO_3$ afforded the crude product, which was purified by preparative HPLC in a manner analogous to Example 146, Step 2, to give title compound (5 mg, 0.014 mmol) in 5% yield.

^1H NMR (d_6-DMSO): 9.05 (s, 1H), 8.74 (s, 1H), 8.09 (s, 1H), 7.58 (s, 1H), 7.47 (s, 1H), 7.24-7.12 (m, 5H), 2.19 (m, 1H), 1.89 (m, 1H), 1.52 (m, 1H), 1.11 (m, 1H).

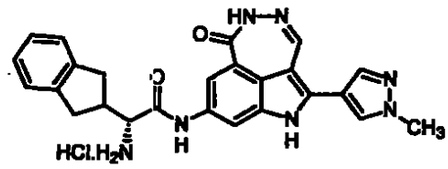
LCMS: ($M+H^+$) 369.1.

Other compounds that were prepared from the appropriate starting materials include the following:

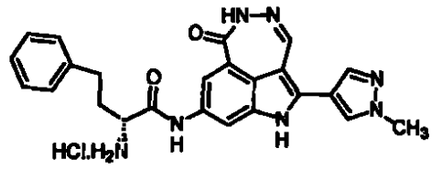
Example 255: (2R-2-Amino-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-phenyl-butyramide (hydrochloric salt):



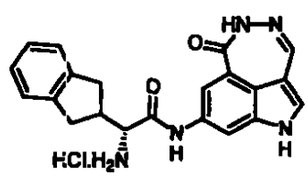
Example 256: (2R)-2-Amino-2-indan-2-yl-*N*-[2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide (hydrochloric salt):



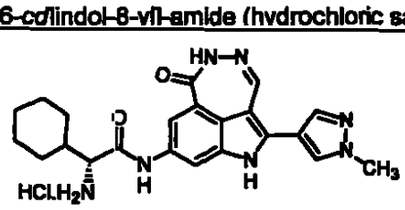
Example 257: (2R)-2-Amino-*N*-[2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-4-phenyl-butyramide(hydrochloric salt):



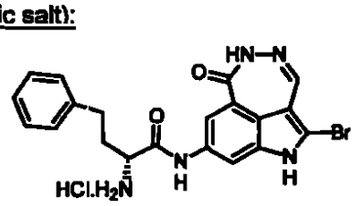
Example 258: (2R)-2-Amino-2-indan-2-yl-*N*-(6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide (hydrochloric salt):



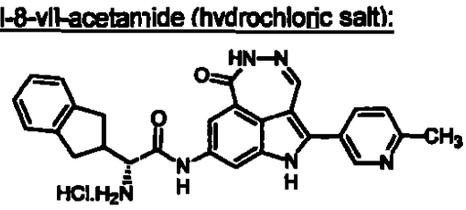
Example 259: (2R)-2-Amino-3-ethyl-heptanoic acid [2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl]-amide (hydrochloric salt):



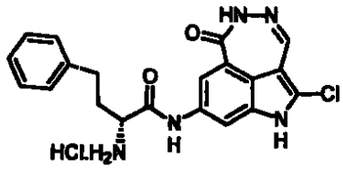
Example 260: (2R)-2-Amino-*N*-(2-bromo-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl)-4-phenyl-butyramide (hydrochloric salt):



Example 261: (2R)-2-Amino-2-indan-2-yl-*N*-[2-(6-methyl-pyridin-3-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl]-acetamide (hydrochloric salt):



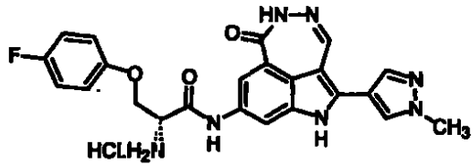
Example 262: (2R)-2-Amino-*N*-(2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-phenyl-butyramide (hydrochloric salt):



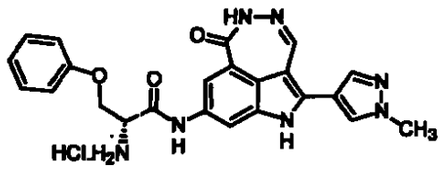
Example 263: (1S,2R)-1-Amino-2-phenyl-cyclopropanecarboxylic acid [2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt):



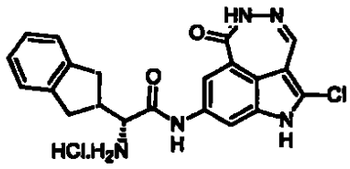
Example 264: (2R)-2-Amino-3-(4-fluoro-phenoxy)-*N*-[2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-propionamide (hydrochloric salt):



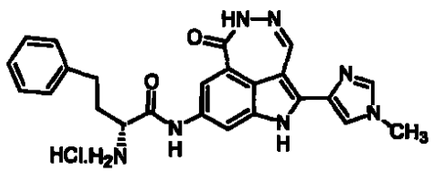
Example 265: (2R)-2-Amino-*N*-[2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-3-phenoxy-propionamide (hydrochloric salt):



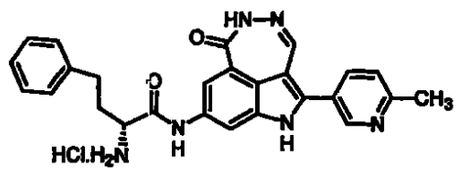
Example 266: (2R)-2-Amino-*N*-(2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-indan-2-yl-acetamide (hydrochloric salt):



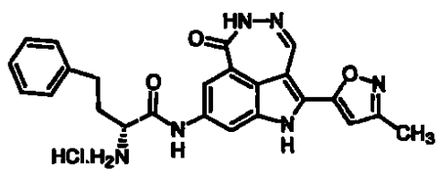
Example 267: (2R)-2-Amino-*N*-[2-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-4-phenyl-butyramide (hydrochloric salt):



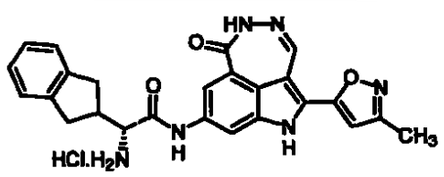
Example 268: (2R)-2-Amino-*N*-[2-(6-methyl-pyridin-3-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-4-phenyl-butyramide (hydrochloric salt):



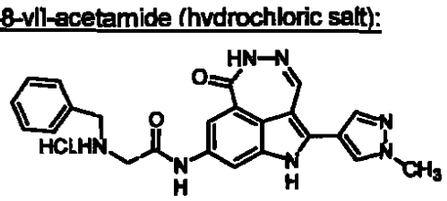
Example 269: (2R)-2-Amino-*N*-[2-(3-methyl-isoxazol-5-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-4-phenyl-butyramide (hydrochloric salt):



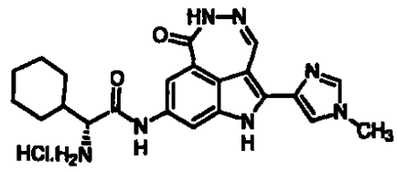
Example 270: (2R)-2-Amino-2-indan-2-yl-*N*-[2-(3-methyl-isoxazol-5-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide (hydrochloric salt):



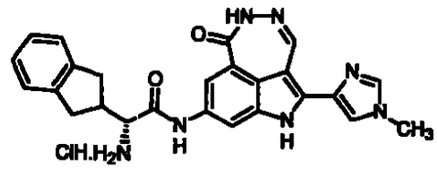
Example 271: 2-Benzylamino-*N*-[2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide (hydrochloric salt):



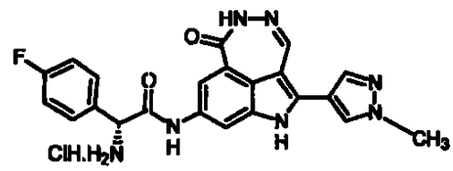
Example 272: (2R)-2-Amino-2-cyclohexyl-*N*-[2-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide (hydrochloric salt):



Example 273: (2R)-2-Amino-2-indan-2-yl-*N*-[2-(1-methyl-1*H*-imidazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl]-acetamide (hydrochloric salt):



Example 274: (2R)-2-Amino-2-(4-fluoro-phenyl)-*N*-[2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4.5.6-*cd*]indol-8-yl]-acetamide (hydrochloric salt):



Example 275: ***In Vitro* Combination Studies**

Cancer cells can be incubated with an antineoplastic agent either alone or in combination with a CHK-1 inhibitor of formula 1. Cell growth data from a combination study (antineoplastic agent together with a fixed concentration of test compound) can be compared to corresponding data obtained from a single agent study (antineoplastic agent without test compound). The concentration of antineoplastic agent causing 50% cell growth inhibition (IC_{50}) can be determined for both single agent treatment and combination treatment. IC_{50} values can be calculated using the linear portion of a semi-log plot of antineoplastic agent concentration versus percent cell growth inhibition. The ratio between the IC_{50} of the antineoplastic agent alone and the IC_{50} of the antineoplastic agent in combination with test compound represents the Potentiation Factor 50 (PF_{50}). The PF_{50} can be used to measure the effectiveness of the combination treatment. Combination treatment with an antineoplastic agent and test compounds of formula I can provide PF_{50} values ranging from 2 to 8 in cancer cells.

Cancer cell viability and proliferation can be evaluated using a tetrazolium salt reduction assay (MTT assay). In viable cells, this colorimetric assay can measure mitochondrial reduction of a tetrazolium component into an insoluble formazan product. Conversely, this assay can be used to determine whether or not mitochondrial function is impaired, for instance, by the metabolic events leading to apoptosis or necrosis. Cancer cell lines can be grown in 96-well plates and can be plated in the appropriate medium at a volume of 100 ul/well. Plates can be incubated for four hours before the addition of test compounds. On the bottom part of the 96 well plate, cells can be treated with increasing concentrations of antineoplastic agent. On the top part of the plate, cells can be treated with increasing concentrations of antineoplastic agent combined with a fixed concentration of test compound. Cells can be incubated at 37^{0}C (5% CO_2) for four to six days (depending on cell type). At the end of the incubation, the tetrazolium component can be added to a final concentration of 0.2 mg/ml, and cells can be incubated for 4 hours at 37^{0}C. After centrifugation of the plates and removal of medium, the absorbance of the formazan (solubilized in dimethylsulfoxide) can be measured at 540nm.

Antineoplastic agents can include cisplatin, hydroxyurea, gemcitibine, carboplatin, 7-ethyl-10-hydroxycamptothecin (SN-38), and cytosine β-D-arabinoside.

Cancer cells can refer to the following:

Cell Line	Cancer Type
CA-46	(human) lymphoma
HT-29	(human) colon
Colo205	(human) colon
MV522	(human) lung
SW620	(human) colon
L1210	(murine) leukemia
PANC-1	(human) pancreas
BXPC-3	(human) pancreas
MCF-7	(human) breast

HCT116	(human) colon
H23	(human) lung

Example 276: *In Vivo* Tumor Models

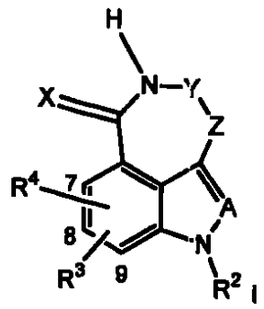
To assess the ability of CHK-1 inhibitors of formula I to augment reduction in tumor volume in combination with gemcitibine in mice, xenograft tumor models using HT-29, MV522 or Colo205 tumor cell lines can be established.

Mice can be randomized (12 mice/group) into treatment groups and used when tumors reach a volume of 150-200 mm^3. Mice can undergo a course of intraperitoneal (i.p) injections consisting of vehicle alone, gemcitibine alone or gemcitibine in combination with the test compound of formula I. Tumor volumes can be measured at times ranging from 2 to 25 days. Control can consist of i.p. injection of vehicle at appropriate intervals. Parallel control can consist of i.p. injection of gemcitibine alone at 15 mg/kg to 240 mg/kg at appropriate intervals. Treatment can consist of i.p. injection of gemcitibine (5 mg/kg to 240 mg/kg) at appropriate intervals in combination with i.p. injection of the test compound of formula I (1 mg/kg to 100 mg/kg) at appropriate intervals. At the end of the study, tumor volume (mm^3) can be measured. An enhancement in the delay of tumor growth can be observed in the mice treated with gemcitibine in combination with the test compound of formula I versus gemcitibine treatment alone.

While the invention has been illustrated by reference to specific and preferred embodiments, those skilled in the art will recognize that variations and modifications may be made through routine experimentation and practice of the invention. Thus, the invention is intended not to be limited by the foregoing description, but to be defined by the appended claims and their equivalents.

We Claim:

1. A compound of the formula:



wherein:

X is =O or =S;

A is $=CR^1-$ or =N-;

The group -Y-Z- has the formula $-O-CH_2-$ or -N=CH-;

R^1 is:

(a) (C_1-C_8)alkyl;

(b) $-C(=O)-R^5$;

(c) $-C(=O)-NR^6R^7$; or

(d) R^{35}, or R^{38}, (C_2-C_8)alkenyl, or (C_2-C_8)alkynyl {wherein each of said (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of F, Cl, OH, $-NH_2$, R^{40}, and R^{42}};

R^2 is

(a) H, OH, or (C_1-C_8)alkyl;

(b) $-C(=O)-R^8$;

(c) $-(C=S)-R^9$ or $-(C=S)-NR^{10}R^{11}$; or

(d) R^{38} or R^{39};

R^3 is

(a) (C_1-C_8)alkyl;

(b) $-C(=O)-R^{12}$;

(c) $-C(=O)-NR^{13}R^{14}$;

(d) $-NR^{15}-C(=O)-R^{16}$;

(e) $-NR^{17}-SO_2R^{18}$;

(f) $-NR^{19}-SO_n-NR^{20}R^{21}$ {wherein n is 1 or 2};

(g) $-NR^{22}-(C=S)-R^{23}$ or $-NR^{22}-(C=S)-NR^{23}R^{24}$;

(h) R^{36}, (C_2-C_8)alkenyl, or (C_2-C_8)alkynyl {wherein each of said R^3 (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected

from the group consisting of -(C=O)-O-(C_1-C_8)alkyl, -O-(C=O)-(C_1-C_8)alkyl, -(C=O)-(C_1-C_8)alkyl, R^{40}, R^{41}, and R^{42}};

(i) R^{37}, $-NH_2$, -NH((C_2-C_8)alkenyl), -NH((C_2-C_8)alkynyl), -N((C_1-C_8)alkyl)((C_2-C_8)alkenyl), or -N((C_1-C_8)alkyl)((C_2-C_8)alkynyl) {wherein each of said R^{26} (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{40}, R^{41}, and R^{42}}; or

(j) R^{38};

R^4 is selected from the group consisting of H, F, Br, Cl, and (C_1-C_8)alkyl;

R^5 is selected from the group consisting of H, (C_1-C_8)alkyl, (C_1-C_8)alkyl-O-, and R^{35};

Each R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_8)alkyl, and R^{38};

R^8 is selected from the group consisting of (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $-NH_2$, R^{36}, and R^{37};

Each of R^9, R^{10} and R^{11} are independently selected from the group consisting of H, (C_1-C_8)alkyl, and R^{38};

R^{12} is selected from the group consisting of H, OH, (C_1-C_8)alkyl, (C_1-C_8)alkyl-O-, and R^{35};

R^{13} is H or (C_1-C_8)alkyl;

R^{14} is selected from the group consisting of H, (C_1-C_8)alkyl, $-CH_2$-(C=O)-O-(C_1-C_8)alkyl, and R^{38};

R^{15} is H or (C_1-C_8)alkyl;

R^{16} is selected from the group consisting of H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $-NH_2$, R^{38}, and R^{37};

wherein each of said R^{15} and R^{16} (C_2-C_8)alkenyl or (C_2-C_8)alkynyl is unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{40}, R^{41}, and R^{42};

R^{17} is selected from the group consisting of H, (C_1-C_8)alkyl, and R^{36};

R^{18} is (C_1-C_8)alkyl or R^{36};

R^{19}, R^{20}, and R^{21} are independently selected from the group consisting of H, (C_1-C_8)alkyl, and R^{36};

R^{22}, R^{23} and R^{24} are independently selected from the group consisting of H, (C_1-C_8)alkyl, and R^{36};

R^{25} is H or (C_1-C_8)alkyl;

R^{26} is selected from the group consisting of -C(=O)-O-$C(CH_3)_3$, (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

or R^{25} and R^{26} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{27} is selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

R^{28} is selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

R^{29} is H or (C_1-C_8)alkyl;

R^{30} is (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl;

or R^{29} and R^{30} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{31} is H or (C_1-C_8)alkyl;

R^{32} is independently selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

or R^{31} and R^{32} may optionally be taken together with the nitrogen to which they are attached to form a 5 to 8-membered heteroaryl or heterocyclyl ring;

R^{33} is (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl;

R^{34} is (C_1-C_8)alkyl, (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl;

Each R^{35} is independently selected from the group consisting of H, F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-NH-C(=O)-O-C(CH_3)_3$, and CF_3;

Each R^{36} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

Each R^{37} is independently selected from the group consisting of:

(c) $-NR^{25}R^{26}$; and

(d) $R^{27}-O-$;

R^{38} is $R^{28}-SO_n-$; wherein n is 0,1, or 2 when $-SO_n-$ is bonded to R^{28} via an R^{28} carbon atom, or wherein n is 1 or 2 when $-SO_n-$ is bonded to R^{28} via an R^{28} ring nitrogen atom;

R^{39} is $R^{29}R^{30}N-SO_n-$; wherein n is 1 or 2;

wherein each of said (C_1-C_8)alkyl, wherever it occurs in any of said R^1(a)-(d), R^2(a)-(d), R^3(a)-(j), R^4, R^{37}, R^{38}, or R^{39}, is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_2-C_8)alkenyl, R^{40}, R^{41}, and R^{42};

wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in said R^{36}, R^{37}, R^{38}, or R^{39}, is independently unsubstituted or substituted with one to four substituents independently selected from R^{40};

R^{40} is selected from the group consisting of (C_1-C_8)alkyl, R^{41}, R^{42}, and R^{43};

Each R^{41} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-NH-C(=O)-O-C(CH_3)_3$, COOH, $-C(=O)(C_1-C_8)$alkyl, $-C(=O)-O-(C_1-C_8)$alkyl, $-NH-SO_2-(C_1-C_8)$alkyl, $-NH-SO_2-(C_6-C_{10})$aryl, and CF_3;

Each R^{42} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

Each R^{43} is independently selected from the group consisting of:

(c) $-NR^{31}R^{32}$;

(d) $R^{33}-O-$; and

(c) $R^{34}-SO_n-$; wherein n is 0,1, or 2 when $-SO_n-$ is bonded to R^{34} via an R^{34} carbon atom, or wherein n is 1 or 2 when $-SO_n-$ is bonded to R^{34} via an R^{34} ring nitrogen atom;

wherein each of said (C_1-C_8)alkyl, wherever it occurs in any of R^{40} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{44} and R^{45};

wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in any of said R^{42} or R^{43}, is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{47} selected from the group consisting of (C_1-C_8)alkyl, R^{44}, and R^{45};

Each R^{44} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-CF_3$, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-(C=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N<[(C_1-C_8)\text{alkyl}]_2$, $-NH-(C=O)-(C_1-C_8)$alkyl, R^{37}, and R^{38};

Each R^{45} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

wherein each of said (C_1-C_8)alkyl wherever it occurs in any of said R^{44} or R^{45} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of R^{46} and R^{47};

wherein each of said (C_3-C_{10})cycloalkyl, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, or (C_1-C_{10})heteroaryl, wherever it occurs in any of said R^{43} or R^{44} is independently unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, R^{46} and R^{47};

Each R^{46} is independently selected from the group consisting of F, Cl, Br, I, CN, OH, NO_2, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-(C=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N<[(C_1-C_8)\text{alkyl}]_2$, $-NH-(C=O)-(C_1-C_8)$alkyl, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-O-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-NH_2$, $-(C=O)-NH(C_1-C_8)$alkyl, $-(C=O)-N>[(C_1-C_8)\text{alkyl}]_2$, $-NH-(C=O)-(C_1-C_8)$alkyl, R^{37}, and R^{38}; and

Each R^{47} is independently selected from the group consisting of (C_3-C_{10})cycloalkyl; (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^3 is $-NR^{15}-C(=O)-R^{16}$; wherein R^{16} is (C_3-C_{10})cycloalkyl unsubstituted or substituted with one or two substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, Cl, CN, OH, NH_2, CF_3, (C_2-C_{10})heterocyclyl, (C_6-C_{10})aryl, and (C_1-C_{10})heteroaryl; wherein said (C_6-C_{10})aryl substituent is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (C_1-C_8)alkyl, F, Cl, Br, CN, OH, and CF_3; and wherein said (C_2-C_{10})heterocyclyl substituent is unsubstituted or substituted with one or two substituents independently selected from the group consisting of (C_1-C_8)alkyl, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-S-(C_1-C_8)$alkyl, F, Br, OH, and CF_3.

3. A compound according to claim 1 wherein R^2 is H or (C_1-C_8)alkyl unsubstituted or substituted with one to four substituents independently selected from the group consisting of OH, $-NH_2$, (C_1-C_8)alkyl-NH-, $[(C_1-C_8)alkyl]_2>N-$, (C_2-C_{10})heterocyclyl, and (C_1-C_{10})heteroaryl.

4. A compound according to claim 1 wherein X is =O.

5. A compound according to claim 1 wherein the group -Y-Z- has the formula -N=CH-.

6. A compound according to claim 1 selected from the group consisting of:

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenyl-acetamide;

2-Cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-phenyl-butyramide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide;

3-Fluoro-2-methyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide;

2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-trifluoromethyl-benzamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-(3-Chlorophenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide;

1-Acetyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)piperidine-4-carboxamide;

3-(2-Methylphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide;

(2S)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-phenyl-butyramide compound with trifluoro-acetic acid;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide trifluoroacetate;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-Ethylsulfanyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-nicotinamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

N-[2-(3-Dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-fluoro-3-trifluoromethyl-benzamide;

6-Oxo-2-phenyl-*N*-(2-phenylcyclopropyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

N-[1-(4-Fluorophenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt);

Acetic acid 3-[6-oxo-8-[((1R, 2R)-2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl]-benzyl ester;

(1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-hydroxymethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide (hydrochloric salt);

N-[1-(4-Hydroxyphenyl)ethyl]-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

2,3-Difluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

N-(4-Fluorobenzyl)-6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-cyclobutylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide(hydrochloric salt);

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-ylmethyl-phenyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide(hydrochloric salt);

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-[6-(trifluoromethyl)pyridin-3-yl]cyclopropanecarboxamide trifluoroacetate;

(2R)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenyl-acetamide (hydrochloric salt);

(2R)-2-Amino-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-phenyl-propionamide(hydrochloric salt);

(3E)-4-Phenyl-but-3-enoic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-Indan-2-yl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

(1,2-*trans*)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt);

(1,2-*trans*)-2-(3-Methoxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-Indan-2-yl-(6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

(2*R*)-2-Hydroxy-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylethanamide;

(1,2-*trans*)-2-Pyridin-2-yl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide acetic acid;

(1,2-*trans*)-2-(1*H*-Imidazol-4-yl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide acetic acid;

(2R)-Piperidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt);

(2S)- 2-Amino-3-cyano-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-propionamide acetic acid;

(2R)-2-amino-3-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide (hydrochloric salt);

(1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester;

(2R)-3-(4-Hydroxyphenyl)-2-(methylamino)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide (hydrochloric salt);

(2R)-2-Amino-3-(4-fluorophenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide (hydrochloric salt);

(1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methylamide;

(1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide;

(1R,2R)- 6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide;

(2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide (hydrochloric salt);

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1,2-*trans*)-2-(3-Bromo-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1,2-*trans*)-2-(3-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid (2-bromo-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt);

(1R,2R)-*N*-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide;

N-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-pyridin-3-ylcyclopropanecarboxamide;

N-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-(1,2-*trans*)-2-pyridin-3-ylcyclopropanecarboxamide;

(1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-propyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)- 2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-propenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (hydrochloric salt);

(1,2-*trans*)-2-Pyridin-3-yl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide (dihydrochloric salt);

(2R)-2-Amino-2-cyclohexyl-*N*-[2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamide (dihydrochloric salt);

(1,2-*trans*)-*N*-[1-(2-Hydroxyethyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-phenylcyclopropanecarboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-dimethylaminomethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [1-(2-amino-ethyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-morpholin-4-yl-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-yl-prop-1-ynyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide; and

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [1-(2-amino-ethyl)-2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(1*H*-imidazol-2-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-cyano-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; and

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(1*H*-imidazol-2-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide; or

a pharmaceutically acceptable salt or solvate thereof.

7. A compound according to claim 1 selected from the group consisting of:

3-Fluoro-2-methyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-benzamide;

2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

Acetic acid 3-(6-oxo-8-[((1R, 2R)-2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-yl)-benzyl ester;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-hydroxymethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-cyclobutylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-ylmethyl-phenyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

2-Indan-2-yl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide;

(1,2-*trans*)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(2*R*)-2-Amino-3-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methyl ester;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid methylamide;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1H-[1,2]diazepino[4,5,6-cd]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1H-[1,2]diazepino[4,5,6-cd]indole-2-carboxylic acid (2-hydroxy-ethyl)-amide;

(2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide;

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)acetamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-4-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide;

(1*R*,2*R*)-*N*-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-dimethylamino-propenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(2R)-2-Amino-2-cyclohexyl-*N*-[2-(3-methylamino-prop-1-ynyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-acetamidede;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-hydroxymethyl-6-oxo-5,6-dihydro-1*H*-[1,2-*cd*]diazepino[4,5,6]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [6-oxo-2-(3-pyrrolidin-1-yl-prop-1-ynyl)-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(1*H*-imidazol-2-yl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-cyano-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; and

(2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide hydrochloride; or

a pharmaceutically acceptable slat or solvate thereof.

8. A compound according to claim 1 selected from the group consisting of:

2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide;

(1R, 2R)-2-Phenyl-cyclopropanecarboxylic acid [2-(3-hydroxymethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide(hydrochloride);

6-Oxo-2-phenyl-*N*-[(1*R*)-1-phenylethyl]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-8-carboxamide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(2*R*)-2-Hydroxy-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylethanamide;

(1,2-*trans*)-2-Pyridin-2-yl-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide.(acetic acid salt);

(1,2-*trans*)-2-(1*H*-Imidazol-4-yl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (acetic acid salt);

(2R)-Piperidine-2-carboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide (hydrochloric salt);

(2*R*)-2-Amino-3-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)propanamide hydrochloride;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide;

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-*N*-(6-Oxo-2-pyridin-3-yl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-phenylcyclopropanecarboxamide; and

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid [1-(2-amino-ethyl)-2-chloro-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-amide; or

a pharmaceutically acceptable salt or solvate thereof.

9. A compound according to claim 1 selected from the group consisting of:

2-Fluoro-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-3-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-2-trifluoromethyl-benzamide;

N-(6-Oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-4-thien-2-ylbutanamide;

N-[2-(3-Dimethylaminomethyl-phenyl)-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl]-2-fluoro-3-trifluoromethyl-benzamide;

(2R)-2-Amino-2-cyclohexyl-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-acetamide(hydrochloride);

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide;

(1R,2R)-6-Oxo-8-[(2-phenyl-cyclopropanecarbonyl)-amino]-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indole-2-carboxylic acid (2-dimethylamino-ethyl)-amide;

(2R)-2-Amino-2-(4-hydroxyphenyl)-*N*-(6-oxo-2-phenyl-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)ethanamide hydrochloride;

(1,2-*trans*)-2-(4-Hydroxy-phenyl)-cyclopropanecarboxylic acid (6-oxo-2-phenyl-5,6-dihydro-1-[1,2]diazepino[4,5,6]indol-8-yl)-amide; and

(1R,2R)-2-Phenyl-cyclopropanecarboxylic acid (2-ethyl-6-oxo-5,6-dihydro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-yl)-amide; or

a pharmaceutically acceptable salt or solvate thereof.

10. A pharmaceutical composition comprising:

(a) an effective amount of a CHK-1-inhibiting agent that is a compound according to claim 1; or a pharmaceutically acceptable salt thereof;

(b) an effective amount of an anti-neoplastic agent or therapeutic radiation; and

(c) a pharmaceutically acceptable carrier for said CHK-1-inhibiting agent.

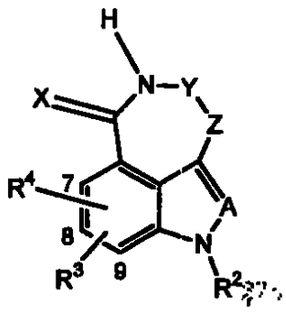
11. A composition containing a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof and an anti-neoplastic agent as a combined preparation for the simultaneous, separate or sequential use in treating a neoplasm.

12. Use of an anti-neoplastic agent or a therapeutic radiation having an anti-neoplastic effect in combination with a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof, for treating a neoplasm in a mammal.

13. Use of a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof, for the treatment of a condition which can be treated by the inhibition of protein kinases in a mammal, including a human.

ABSTRACT OF THE DISCLOSURE

Protein kinase, such as CHK-1, inhibiting tricyclic compounds of the following formula (wherein R^2, R^3 and R^4 are as defined in the specification)



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pharmaceutical compositions containing effective amounts of said compounds or their salts are useful as a single agent or in combination with an anti-neoplastic agent or therapeutic radiation having an anti-neoplastic effect for treating diseases or conditions such as cancers.

COMPUESTOS TRICÍCLICOS INHIBIDORES DE PROTEÍNA QUINASA PARA MEJORAR LA EFICACIA DE AGENTES ANTINEOPLÁSICOS Y TERAPIA DE RADIACIÓN

Campo de la invención

Esta invención se refiere a nuevos compuestos tricíclicos de fórmula I que inhiben proteína quinasas, preferiblemente CHK-1. La invención también se refiere a composiciones farmacéuticas que contienen tales compuestos, y a procedimientos para el tratamiento de una afección que puede tratarse mediante la inhibición de proteína quinasas, preferiblemente CHK-1, en un mamífero administrando cantidades eficaces de tales compuestos junto con un agente anti-neoplásico, una terapia de radiación o en forma de un único agente.

Antecedentes de la invención

Un ciclo celular eucariótico tiene una progresión de fases cuidadosamente regulada: reposo inicial (G_1), síntesis de ADN (S), reposo secundario (G_2) y mitosis (M). G_1, S y G_2 se conocen como interfase. En G_1, la célula, cuyas rutas biosintéticas se ralentizaron durante la mitosis, reanuda la biosíntesis de ARN y proteínas en una alta proporción. La fase S comienza cuando empieza la síntesis de ADN y finaliza cuando se ha reproducido el contenido de ADN de los núcleos. Después, la célula entra en G_2 donde se produce de nuevo la biosíntesis de ARN y proteínas. Después de G_2, la célula entra en la fase M que comienza con la división nuclear y finaliza con la completa división del citoplasma en dos células hijas. Esto marca el comienzo

de la interfase para las nuevas células. Existen células sin dividir en G_0, un momento posterior a la mitosis y anterior a la síntesis del ADN.

Las enzimas de checkpoint (punto de control) tales como la proteína serina/treonina quinasa denominada quinasa 1 de checkpoint (CHK-1 o p56CHK-1), son responsables de mantener el orden y fidelidad de los eventos en el ciclo celular. CHK-1 transduce señales del complejo sensorial de lesión de ADN para inhibir la activación del complejo Cdc2-ciclina B que promueve la entrada mitótica (*Science,* **277,** 1501-1505 (1997); *Science*, 277, 1497-1501 ((1997)). En las células eucariotas, Cdc2 se conoce como Cdk1 (quinasa 1 dependiente de ciclina). CHK-1 regula Cdc25, una fosfatasa de especificidad dual que activa Cdc-2. De esta manera, CHK-1 sirve como enlace directo entre el checkpoint en G_2 y la regulación negativa de Cdc2.

Las células sanas tienen checkpoints tanto en G_1 como en G_2 y sus procedimientos de reparación asociados para asegurar la viabilidad después del tratamiento de la lesión del ADN (quimioterapia y/o radiación). Las células cancerosas, sin embargo, dependen exclusivamente del checkpoint en G_2 y de sus procedimientos de reparación asociados con el fin de seguir siendo viables y de continuar con la replicación. La anulación del checkpoint en G_2 dejará a las células cancerosas sin medio para retardar la evolución en la mitosis después de la lesión del ADN. Se ha demostrado que la inactivación de CHK-1 anula la parada en G_2 inducida por la lesión del ADN infligida por agentes anticancerosos o lesión del ADN endógeno. Además, la inactivación de CHK-1 da como resultado la destrucción de células defectuosas en el Checkpoint con ADN dañado (*Cell,* **91,** 865-867 (1997); *Science,* 277, 1450-1451 (1997); *Nature,* 363, 368-371 (1993); *Mol. Biol. Cell,* **5,** 147-160 (1994)). Por lo tanto,

existe la necesidad de inhibidores de moléculas pequeñas de CHK-1 para anular preferencialmente el checkpoint en G_2 sobre G_1 y para retirar de forma eficaz el único control de checkpoint descubierto en muchos tipos de cánceres. Cuando se administra durante el transcurso de un evento de lesión de ADN, tal como quimioterapia que emplea agentes anti-neoplásicos, terapia de radiación, inmunoterapias y terapias antiangiogénicas, un inhibidor de CHK-1 puede sensibilizar las células cancerosas activando por lo tanto la apoptosis mediada por la lesión. Por lo tanto, existe la necesidad de una terapia de combinación que implique un inhibidor de CHK-1 en el transcurso de un evento de lesión del ADN.

Como las proteínas quinasas son omnipresentes y están interrelacionadas, la modulación selectiva de una sola quinasa, tal como CHK-1 o una familia de quinasas puede no dar lugar a un tratamiento terapéutico eficaz. Existe por tanto la necesidad de inhibidores de molécula pequeña para influenciar una o más proteína quinasas diana cuya inhibición, tomada como un todo, produciría el tratamiento terapéutico deseado. Aunque la selectividad de la quinasa y su relación con la toxicidad generalizada son importantes, la eficacia terapéutica puede depender de la inhibición de más de una proteína quinasa. Las estructuras químicas centrales que pueden unirse adecuadamente para inactuar selectiva y potencialmente con las proteína quinasas diana representan una herramienta valiosa para el descubrimiento de fármacos y para la investigación científica. Por lo tanto existe la necesidad de tal estructura central como inhibidor de una o más proteína quinasas. Ya se administren como un único agente o como co-terapia, los inhibidores de la proteína quinasa, tales como inhibidores de CHK-1, de la presente invención

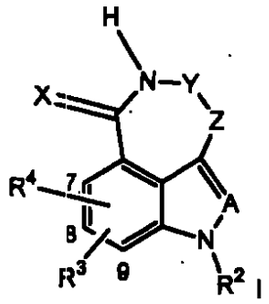
podrían ser beneficiosos en el tratamiento de diversas enfermedades humanas, tales como el cáncer.

Se han propuesto ciertos inhibidores de CHK-1 para la terapia para el cáncer (véase Sanchez, Y. y col., (1997) Science 277: 1497-1501 y Flaggs, G. y col., (1997) Current Biology 7:977-986; Patentes de Estados Unidos Nº 6.413.755, 6.383.744 y 6.211.164; y Publicaciones Internacionales Nº WO 01/16306, WO 01/21771, WO 00/16781 y WO 02/070494).

SUMARIO DE LA INVENCIÓN

Un objeto de la invención es proporcionar compuestos que inhiban la actividad de una o más proteína quinasas, tales como CHK-1.

En un aspecto general, la invención se refiere a compuestos tricíclicos inhibidores de la proteína quinasa, preferiblemente inhibidores de CHK-1, de Fórmula I:



I

en la que:

X es =O o =S;

A es $=CR^1-$ o =N-;

El grupo -Y-Z- tiene la fórmula $-O-CH_2$ o -N=CH-;

R^1 es:

(a) alquilo (C_1-C_8);

(b) $-C(=O)-R^5$;

(c) $-C(=O)-NR^6R^7$; o

(d) R^{35} o R^{36}, alquenilo (C_2-C_8) o alquinilo (C_2-C_8) {donde cada uno de dichos alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por F, Cl, OH, $-NH_2$, R^{40} y R^{42}};

R^2 es

(a) H, OH o alquilo (C_1-C_8);

(b) $-C(=O)-R^8$;

(c) $-(C=S)-R^9$ o $-(C=S)-N\ R^{10}R^{11}$; o

(d) R^{38} o R^{39};

R^3 es

(a) alquilo (C_1-C_8);

(b) $-C(=O)-R^{12}$;

(c) $-C(=O)-NR^{13}R^{14}$;

(d) $-NR^{15}-C(=O)-R^{16}$;

(e) $-NR^{17}-SO_2R^{18}$;

(f) $-NR^{19}-SO_n-NR^{20}R^{21}$ {donde n es 1 ó 2};

(g) $-NR^{22}-(C=S)-R^{23}$ o $-NR^{22}-(C=S)-NR^{23}R^{24}$;

(h) R^{36}, alquenilo (C_2-C_8) o alquinilo (C_2-C_8) {donde cada uno de dichos R^3 alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por -(C=O)-O-alquilo (C_1-C_8), -O-(C=O)-alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), R^{40}, R^{41} y R^{42}};

(i) R^{37}, $-NH_2$, -NH(alquenilo (C_2-C_8)), -NH(alquinilo (C_2-C_8)), -N(alquil (C_1-C_8))(alquenilo (C_2-C_8)) o -N(alquil (C_1-C_8))(alquinilo (C_2-C_8)) {donde cada

uno de dichos R^{26} alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{40}, R^{41} y R^{42}}; o

(j) R^{38};

R^4 se selecciona entre el grupo compuesto por H, F, Br, Cl y alquilo (C_1-C_8);

R^5 se selecciona entre el grupo compuesto por H, alquilo (C_1-C_8), alquil (C_1-C_8)-O- y R^{36};

Cada R^6 y R^7 se selecciona independientemente entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^8 se selecciona entre el grupo compuesto por alquilo (C_1-C_8), alquenilo (C_2-C_8), alquinilo (C_2-C_8), -NH_2, R^{36} y R^{37};

Cada uno de R^9, R^{10} y R^{11} se selecciona independientemente entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^{12} se selecciona entre el grupo compuesto por H, OH, alquilo (C_1-C_8), alquil (C_1-C_8)-O- y R^{36};

R^{13} es H o alquilo (C_1-C_8);

R^{14} se selecciona entre el grupo compuesto por H, alquilo (C_1-C_8), -CH_2-(C=O)-O-alquilo (C_1-C_8) y R^{36};

R^{15} es H o alquilo (C_1-C_8);

R^{16} se selecciona entre el grupo compuesto por H, alquilo (C_1-C_8), alquenilo (C_2-C_8), alquinilo (C_2-C_8), -NH_2, R^{36} y R^{37};

donde cada uno de dichos R^{15} y R^{16}, alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{40}, R^{41} y R^{42};

R^{17} se selecciona entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^{18} es alquilo (C_1-C_8) o R^{36};

R^{19}, R^{20} y R^{21} se seleccionan independientemente entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^{22}, R^{23} y R^{24} se seleccionan independientemente entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^{25} es H o alquilo (C_1-C_8);

R^{26} se selecciona entre el grupo compuesto por -C(=O)-O-C(CH_3)$_3$, alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

o R^{25} y R^{26} pueden tomarse opcionalmente junto con el nitrógeno al que están unidos para formar un anillo heteroarilo o heterociclilo de 5 a 8 miembros;

R^{27} se selecciona entre el grupo compuesto por alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

R^{28} se selecciona entre el grupo compuesto por alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

R^{29} es H o alquilo (C_1-C_8);

R^{30} es alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10});

o R^{29} y R^{30} pueden tomarse opcionalmente junto con el nitrógeno al que están unidos para formar un anillo heteroarilo o heterociclilo de 5 a 8 miembros;

R^{31} es H o alquilo (C_1-C_8);

R^{32} se selecciona independientemente entre el grupo compuesto por alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

o R^{31} y R^{32} pueden tomarse opcionalmente junto con el átomo de nitrógeno al que están unidos para formar un anillo heteroarilo o heterociclilo de 5 a 8 miembros;

R^{33} es alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10});

R^{34} es alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10});

Cada R^{35} se selecciona independientemente entre el grupo compuesto por H, F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-NH-C(=O)-O-C(CH_3)_3$ y CF_3;

Cada R^{36} se selecciona independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

Cada R^{37} se selecciona independientemente entre el grupo compuesto por:

(a) $-NR^{25}R^{26}$; y

(b) R^{27}-O-;

R^{38} es R^{28}-SO_n-; donde n es 0, 1 ó 2 cuando -SO_n- se une a R^{28} mediante un átomo de carbono R^{28} o donde n es 1 ó 2 cuando -SO_n- se une a R^{28} mediante un átomo de nitrógeno del anillo R^{28};

R^{39} es $R^{29}R^{30}N$-SO_n-; donde n es 1 ó 2;

donde cada uno de dichos alquilo (C_1-C_8), cuando aparezca en cualquiera de dichos R^1(a)-(d), R^2(a)-(d), R^3(a)-(j), R^4, R^{37}, R^{38} o R^{39}, está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquenilo (C_2-C_8), R^{40}, R^{41} y R^{42};

donde cada uno de dichos cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10}), cuando aparezca en dichos R^{36}, R^{37}, R^{38} o R^{39}, está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre R^{40};

R^{40} se selecciona entre el grupo compuesto por alquilo (C_1-C_8), R^{41}, R^{42} y R^{43};

Cada R^{41} se selecciona independientemente entre el grupo compuesto por F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, -NH-C(=O)-O-$C(CH_3)_3$, COOH, -C(=O)alquilo (C_1-C_8), -C(=O)-O-alquilo (C_1-C_8), -NH-SO_2-alquilo (C_1-C_8), -NH-SO_2-arilo (C_6-C_{10}) y CF_3;

Cada R^{42} se selecciona independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

Cada R^{43} se selecciona independientemente entre el grupo compuesto por:

(a) $-NR^{31}R^{32}$;

(b) R^{33}-O-; y

(c) R^{34}-SO_n-; donde n es 0,1 ó 2 cuando -SO_n- se une a R^{34} mediante un átomo de carbono R^{34} o donde n es 1 ó 2 cuando -SO_n- se une a R^{34} mediante un átomo de nitrógeno del anillo R^{34};

donde cada uno de dichos alquilo (C_1-C_8), cuando aparezca en cualquiera de R^{40} está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{44} y R^{45};

donde cada uno de dichos cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10}), cuando aparezca en cualquiera de dichos R^{42} o R^{43}, está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{47} seleccionado entre el grupo compuesto por alquilo (C_1-C_8), R^{44} y R^{45};

Cada R^{44} se selecciona independientemente entre el grupo compuesto por F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-CF_3$, $-C(=NH)-NH_2$, -C(=NH)-NH-OH, -C(=NH)-NH-O-alquilo (C_1-C_8), -(C=O)-O-alquilo (C_1-C_8), -O-(C=O)-alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), $-(C=O)-NH_2$, -(C=O)-NH-alquilo (C_1-C_8), -(C=O)-N<[alquilo (C_1-C_8)]$_2$, -NH-(C=O)-alquilo (C_1-C_8), R^{37} y R^{38};

Cada R^{45} se selecciona independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

donde cada uno de dichos alquilo (C_1-C_8) cuando aparezca en cualquiera de dichos R^{44} o R^{45} está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{46} y R^{47};

donde cada uno de dichos cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10}), cuando aparezca en cualquiera de dichos R^{43} o R^{44} está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), R^{46} y R^{47};

Cada R^{46} se selecciona independientemente entre el grupo compuesto por F, Cl, Br, I, CN, OH, NO_2, $-C(=NH)-NH_2$, -C(=NH)-NH-OH, -C(=NH)-NH-O-alquilo (C_1-C_8), -(C=O)-O-alquilo (C_1-C_8), -O-(C=O)-alquilo (C_1-C_8), -(C=O)-

alquilo (C_1-C_8), -(C=O)-NH_2, -(C=O)-NH-alquilo (C_1-C_8), -(C=O)-N<[alquilo (C_1-C_8)]$_2$, -NH-(C=O)-alquilo (C_1-C_8), -C(=NH)-NH_2, -C(=NH)-NH-OH, -C(=NH)-NH-O-alquilo (C_1-C_8), -(C=O)-O-alquilo (C_1-C_8), -O-(C=O)-alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), -(C=O)-NH_2, -(C=O)-NH-alquilo (C_1-C_8), -(C=O)-N>[alquilo (C_1-C_8)]$_2$, -NH-(C=O)-alquilo (C_1-C_8), R^{37} y R^{38}; y

Cada R^{47} se selecciona independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}); heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

o una sal farmacéuticamente aceptable de los mismos.

La invención también se refiere a profármacos farmacéuticamente aceptables, metabolitos farmacéuticamente activos y sales farmacéuticamente aceptables de los compuestos de Fórmula I. También se proporcionan sales farmacéuticamente aceptables de tales metabolitos activos. También se describen procedimientos ventajosos para fabricar los compuestos de Fórmula I.

Los compuestos de esta invención incluyen todos los estereoisómeros (por ejemplo, isómeros *cis* y *trans*) y todos los isómeros ópticos de los compuestos de Fórmula I (por ejemplo, enantiómeros *R* y *S*), así como las mezclas racémicas, diastereoméricas y otras mezclas de tales isómeros.

Los compuestos de la invención también pueden existir en formas diferentes tautoméricas. Esta invención se refiere a todos los tautómeros de Fórmula I.

Los compuestos de esta invención pueden contener dobles enlace de tipo olefina. Cuando tales compuestos están presentes, los compuestos de la

invención existen en forma de las configuraciones *cis* y *trans* y en forma de mezclas de las mismas.

En una realización, la invención se refiere a compuestos de Fórmula I en la que R^3 es alquilo (C_1-C_8) sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por F, OH, $-NH_2$, alquil (C_1-C_8)-NH-, cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_6-C_{10}).

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^3 se selecciona entre el grupo compuesto por alquenilo (C_2-C_8), alquinilo (C_2-C_8), cicloalquilo (C_3-C_6), heterociclilo (C_2-C_{10}), fenilo y heteroarilo (C_1-C_{10}); donde cada uno de dichos alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a tres sustituyentes seleccionados independientemente entre el grupo compuesto por F, OH, $-NH_2$, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}); y donde cada uno de dichos cicloalquilo (C_3-C_6), heterociclilo (C_2-C_{10}), fenilo o heteroarilo (C_1-C_{10}) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, OH, $-NH_2$, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}).

En una realización preferida, la invención se refiere a compuestos de Fórmula I en la que R^3 es $-C(=O)-NR^{13}R^{14}$ {donde R^{13} es H o alquilo (C_1-C_8)}, donde dicho R^{13} alquilo (C_1-C_4) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por F, OH, $-NH_2$, R^{41} y R^{42}; donde cada uno de dichos R^{36} está no sustituido o

sustituido con uno o dos sustituyentes seleccionados independientemente entre el grupo compuesto por arilo (C_6-C_{10}), heteroarilo (C_1-C_{10}), heterociclilo (C_2-C_{10}), alquil (C_1-C_8)-NH- y [alquil (C_1-C_8)]$_2$>N-; y donde cada uno de dichos sustituyente arilo (C_6-C_{10}) está no sustituido o sustituido con uno a tres sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, Cl, -CF_3 y OH.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^{15} es alquilo (C_1-C_8) no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por OH, CN, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, [alquil (C_1-C_8)][cicloalquil (C_3-C_{10})]>N-, cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}); donde dicho sustituyente arilo (C_6-C_{10}) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, Cl, Br, CN, OH y CF_3; y donde dicho sustituyente heterociclilo (C_2-C_{10}) está no sustituido o sustituido con uno o dos sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), -(C=O)-O-alquilo (C_1-C_8), -S-alquilo (C_1-C_8), F, Br, OH y CF_3.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^3 es -NR^{15}-C(=O)-R^{16}; donde R^{16} es alquenilo (C_2-C_8) no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}); donde dicho sustituyente arilo (C_6-C_{10}) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, Cl, Br,

CN, OH y CF_3; y donde dicho sustituyente heterociclilo (C_2-C_{10}) está no sustituido o sustituido con uno o dos sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), -(C=O)-O-alquilo (C_1-C_8), -S-alquilo (C_1-C_8), F, Br, OH y CF_3.

En una realización preferida, la invención se refiere a compuestos de Fórmula I en la que R^3 es -NR^{15}-C(=O)-R^{16}; donde R^{16} es heteroarilo (C_1-C_{10}) no sustituido o sustituido con uno o dos sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), -S-alquilo (C_1-C_8), F, Cl, CN, OH y CF_3. Más preferiblemente el R^{16} heteroarilo (C_1-C_{10}) es piridinilo.

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que R^3 es -NR^{15}-C(=O)-R^{16}; donde R^{16} es cicloalquilo (C_3-C_{10}) no sustituido o sustituido con uno o dos sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, Cl, CN, OH, NH_2, CF_3, heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}); donde dicho sustituyente arilo (C_6-C_{10}) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, Cl, Br, CN, OH y CF_3; y donde dicho sustituyente heterociclilo (C_2-C_{10}) está no sustituido o sustituido con uno o dos sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), -(C=O)-O-alquilo (C_1-C_8), -S-alquilo (C_1-C_8), F, Br, OH y CF_3. Más preferiblemente dicho R^{16} cicloalquilo (C_3-C_{10}) se selecciona entre el grupo compuesto por ciclopropilo y ciclohexilo. Más preferiblemente, dicho sustituyente arilo (C_6-C_{10}) está no sustituido.

En otra realización preferida, la invención se refiere a compuestos de

Fórmula I en la que R^3 es $-NR^{15}-C(=O)-R^{16}$; donde R^{16} es heterociclilo (C_2-C_{10}) no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), -(C=O)-O-alquilo (C_1-C_8), F, Cl, CN, OH y CF_3. Más preferiblemente, dicho R^{16} heterociclilo (C_2-C_{10}) se selecciona entre el grupo compuesto por piperazinilo, piperidinilo, pirrolidinilo, pirrolidinonilo, tiadiazolilo, tetrahidroisoquinolinilo, tetrahidronaftalenilo y indanilo.

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que R^3 es $-NR^{15}-C(=O)-R^{16}$; donde R^{16} es fenilo no sustituido o sustituido con uno a tres sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), alquil (C_1-C_8)-O-, F, Cl, Br, CN, OH y CF_3.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^1 es alquilo (C_1-C_8) sustituido con uno a dos sustituyentes seleccionados independientemente entre el grupo compuesto por F, Cl, -OH, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N- y alquil (C_1-C_8)-O-; donde cada uno de dicho sustituyente alquilo (C_1-C_8), cuando aparezca, está independientemente no sustituido o sustituido con uno a tres sustituyentes seleccionados independientemente entre el grupo compuesto por -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, -O-(C=O)-alquilo (C_1-C_8), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}).

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^1 es alquilo (C_1-C_8) no sustituido; tal como metilo o etilo.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^1 es alquenilo (C_2-C_8) o alquinilo (C_2-C_8); donde cada uno de dichos

alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a dos sustituyentes seleccionados independientemente entre el grupo compuesto por $-NH_2$, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, heterociclilo (C_2-C_{10}) y heteroarilo (C_1-C_{10}); donde cada uno de dicho sustituyente alquilo (C_1-C_8), cuando aparezca, está independientemente no sustituido o sustituido con uno a tres sustituyentes seleccionados independientemente entre el grupo compuesto por $-NH_2$, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, -O-(C=O)-alquilo (C_1-C_8), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}).

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que R^1 es R^{36} seleccionado entre el grupo compuesto por H, Cl y Br.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^1 se selecciona entre el grupo compuesto por cicloalquilo (C_3-C_6), heterociclilo (C_2-C_{10}), fenilo y heteroarilo (C_1-C_{10}); donde cada uno de dichos heterociclilo (C_2-C_{10}), fenilo o heteroarilo (C_1-C_{10}) está no sustituido o sustituido con uno a tres sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, Cl, $-NH_2$, -OH, alquil (C_1-C_8)-NH- y [alquil (C_1-C_8)]$_2$>N-; donde cada uno de dicho sustituyente alquilo (C_1-C_8), cuando aparezca, está no sustituido o sustituido con uno a tres sustituyentes seleccionados entre $-NH_2$, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, -O-(C=O)-alquil (C_1-C_8), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}). Dentro de esta realización, preferiblemente R^1 es fenilo, tetrahidropiridinilo, piperidinilo o piridinilo.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^1 es -C(=O)-R^5 y R^5 es alquil (C_1-C_8)-O- o heterociclilo (C_2-C_{10}), tal

como morfolinilo; donde dicho R^5 heterociclilo (C_2-C_{10}) está no sustituido o sustituido con alquilo (C_1-C_8), tal como metilo o etilo.

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que R^1 es -C(=O)-NR^6R^7; donde cada uno de dichos R^6 y R^7 son independientemente H o alquilo (C_1-C_8); y donde cada uno de dichos R^6 y R^7 alquilo (C_1-C_8) están no sustituidos o sustituidos con uno a tres sustituyentes seleccionados independientemente entre el grupo compuesto por OH, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, heterociclilo (C_2-C_{10}) y heteroarilo (C_1-C_{10}).

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que R^2 es H o alquilo (C_1-C_8) no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por OH, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, heterociclilo (C_2-C_{10}) y heteroarilo (C_1-C_{10}).

En otra realización, la invención se refiere a compuestos de Fórmula I en la que A es =N-.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^2 es -C(=O)-R^8, donde R^8 se selecciona entre el grupo compuesto por alquilo (C_1-C_8), alquenilo (C_2-C_8), alquinilo (C_2-C_8), -NH_2 y R^{37} se selecciona entre el grupo compuesto por alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N- y alquil (C_1-C_8)-O-; donde cada uno de dichos R^8 y R^{37} alquilo (C_1-C_8), cuando aparezca, está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre R^{40} seleccionado entre el grupo compuesto por F, OH, -NH_2, cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}), heteroarilo (C_1-C_{10}); alquil (C_1-C_8)-NH- y [alquil (C_1-C_8)]$_2$>N-;

donde cada uno de dichos R^{40} alquilo (C_1-C_8), cuando aparezca, está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre R^{44} seleccionado independientemente entre el grupo compuesto por OH, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N- y cicloalquil (C_3-C_{10})-NH-;

donde cada uno de dichos R^{40} cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10}), cuando aparezca, está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre R^{47} seleccionado entre el grupo compuesto por alquilo (C_1-C_8), OH, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N- y cicloalquil (C_3-C_{10})-NH-; y

donde cada uno de dicho R^{47} alquilo (C_1-C_8), cuando aparezca, está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por OH, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N- y cicloalquil (C_3-C_{10})-NH.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que R^2 es -C(=O)-R^8, donde R^8 se selecciona entre el grupo compuesto por cicloalquilo (C_3-C_6), heterociclilo (C_2-C_{10}), fenilo o heteroarilo (C_1-C_{10}); donde cada uno de dichos R^8 cicloalquilo (C_3-C_6), heterociclilo (C_2-C_{10}), fenilo o heteroarilo (C_1-C_{10}) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre R^{40} seleccionado entre el grupo compuesto por alquilo (C_1-C_8), F, OH, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10}); donde cada uno de dichos R^{40} alquilo (C_1-C_8), cuando aparezca, está independientemente no sustituido o sustituido con uno a cuatro

sustituyentes seleccionados independientemente entre R^{44} seleccionado independientemente entre el grupo compuesto por OH, $-NH_2$, alquil (C_1-C_8)-NH-, [alquil $(C_1-C_8)]_2$>N- y cicloalquil (C_3-C_{10})-NH-; donde cada uno de dichos R^{40} cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10}) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre R^{47} seleccionado entre el grupo compuesto por alquilo (C_1-C_8), OH, NH_2, alquil (C_1-C_8)-NH-, [alquil $(C_1-C_8)]_2$>N- y cicloalquil (C_3-C_{10})-NH-; donde cada uno de dicho R^{47} alquilo (C_1-C_8), cuando aparezca, está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por OH, $-NH_2$, alquil (C_1-C_8)-NH-, [alquil $(C_1-C_8)]_2$>N- y cicloalquil (C_3-C_{10})-NH.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que dicho R^3 está en una cualquiera de las posiciones 7, 8 ó 9 de dicho compuesto de fórmula I. Preferiblemente, la invención se refiere a compuestos de Fórmula I en la que dicho R^3 está en la posición 8 de dicho compuesto de fórmula I.

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que dicho R^4 está en la posición 7 de dicho compuesto de fórmula I. Más preferiblemente, dicho R^3 está en la posición 8 de dicho compuesto de fórmula I y dicho R^4 está en la posición 7 de dicho compuesto de fórmula I.

En otra realización, la invención se refiere a compuestos de Fórmula I en la que dicho R^4 es Cl o Br en la posición 7 de dicho compuesto de fórmula I.

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que dicho R^4 es H en la posición 7 de dicho compuesto de

fórmula I.

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que X es O.

En otra realización preferida, la invención se refiere a compuestos de Fórmula I en la que el grupo -Y-Z- tiene la fórmula -N=CH-.

Preferiblemente, la invención se refiere a compuestos de Fórmula I seleccionados entre el grupo

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenil-acetamida;

2-Ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida;

3-Fluoro-2-metil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida;

2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-trifluorometil-benzamida;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-Fenil-ciclopropanocarboxílico;

2-(3-Clorofenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida;

1-Acetil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)piperidin-4-carboxamida;

3-(2-Metilfenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida;

(2*S*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida compuesto con ácido trifluoroacético;

Trifluoroacetato de (2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

2-Etilsulfanil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-nicotinamida;

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

N-[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fluoro-3-trifluorometil-benzamida;

6-Oxo-2-fenil-*N*-(2-fenilciclopropil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

N-[1-(4-Fluorofenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

3-{6-Oxo-8-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-bencil éster del ácido acético;

[2-(3-hidroximetil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1R,2R)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (sal clorhidrato);

N-[1-(4-Hidroxifenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

2,3-Difluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida;

(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

N-(4-Fluorobencil)-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

[2-(3-ciclobutilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

[6-oxo-2-(3-pirrolidin-1-ilmetil-fenil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

Trifluoroacetato de *N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,*2-trans*)-2-[6-(trifluorometil)piridin-3-il]ciclopropanocarboxamida;

(2*R*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenil-acetamida (sal clorhidrato);

(2*R*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida (sal clorhidrato);

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (3*E*)-4-fenil-but-3-enoico;

2-Indan-2-il-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-fluoro-fenil)-ciclopropanocarboxílico;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico (sal clorhidrato);

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-metoxi-fenil)-ciclopropanocarboxílico;

2-Indan-2-il-(6-oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

(2*R*)-2-Hidroxi-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-feniletanamida;

Ácido acético de (6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-2-il-ciclopropanocarboxílico;

Ácido acético de (6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(1*H*-imidazol-4-il)-ciclopropanocarboxílico;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*)-piperidin-2-carboxílico (sal clorhidrato);

Ácido acético de (2*S*)-2-amino-3-ciano-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-propionamida;

(2*R*)-2-amino-3-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida (sal clorhidrato);

Éster metílico del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2*R*)-3-(4-Hidroxifenil)-2-(metilamino)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida (sal clorhidrato);

(2*R*)-2-Amino-3-(4-fluorofenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida (sal clorhidrato);

Metilamida del ácido (1R,2R)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2-Hidroxi-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2-Dimetilamino-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2*R*)-2-Amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida (sal clorhidrato);

(6-Oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-bromo-fenil)-ciclopropanocarboxílico;

(6-Oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-hidroxi-fenil)-ciclopropanocarboxílico;

2-(3,4-Dihidroisoquinolin-2(1H)-il)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida;

(2-Bromo-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[6-Oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida;

N-(6-Oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,2-*trans*)-2-piridin-3-ilciclopropanocarboxamida;

N-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,2-*trans*)-2-piridin-3-ilciclopropanocarboxamida;

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida;

[2-(3-dimetilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-dimetilamino-propil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-dimetilamino-propenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico (sal diclorhidrato);

(2*R*)-2-Amino-2-ciclohexil-*N*-[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal diclorhidrato);

(1,2-*trans*)-*N*-[1-(2-Hidroxietil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fenilciclopropanocarboxamida;

(2-dimetilaminometil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[1-(2-amino-etil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-morfolin-4-il-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[6-oxo-2-(3-pirrolidin-1-il-prop-1-inil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; y

[1-(2-amino-etil)-2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(1*H*-imidazol-2-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Ciano-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; y

[2-(1*H*-imidazol-2-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]-indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; o

las sales o solvatos farmacéuticamente aceptables de los mismos.

Otros compuestos preferidos se seleccionan entre el grupo compuesto por:

3-Fluoro-2-metil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida;

2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida;

(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

3-{6-oxo-8-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-bencil éster del ácido acético;

[2-(3-hidroximetil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-ciclobutilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[6-oxo-2-(3-pirrolidin-1-ilmetil-fenil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

2-Indan-2-il-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-fluoro-fenil)-ciclopropanocarboxílico;

(2*R*)-2-Amino-3-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida;

Éster metílico del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

Metilamida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2-Hidroxi-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2-Hidroxi-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2*R*)-2-Amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida;

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido

(1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

2-(3,4-Dihidroisoquinolin-2(1*H*)-il)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida;

2-(3,4-Dihidroisoquinolin-2(1H)-il)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida;

[6-oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida;

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida;

[2-(3-Dimetilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-Dimetilamino-propenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-Metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Amino-2-ciclohexil-*N*-[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida;

(2-Hidroximetil-6-oxo-5,6-dihidro-1*H*-[1,2-*cd*]diazepino[4,5,6]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[6-Oxo-2-(3-pirrolidin-1-il-prop-1-inil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(1*H*-Imidazol-2-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Ciano-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; y

Clorhidrato de (2*R*)-2-amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida; o

las sales o solvatos farmacéuticamente aceptables de los mismos.

Otros compuestos preferidos de fórmula I se seleccionan entre el grupo compuesto por:

2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida;

[2-(3-Hidroximetil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (clorhidrato);

6-Oxo-2-fenil-*N*-[(1*R*)-1-feniletil]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Hidroxi-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-feniletanamida;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-2-il-ciclopropanocarboxílico (sal del ácido acético);

(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(1*H*-Imidazol-4-il)-ciclopropanocarboxílico (sal del ácido acético);

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*)-piperidin-2-carboxílico (sal clorhidrato);

Clorhidrato de (2*R*)-2-amino-3-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida;

(2-Dimetilamino-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

Ejemplo 182: (6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida; y

[1-(2-Amino-etil)-2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; o

las sales o solvatos farmacéuticamente aceptables de los mismos.

En otra realización, la invención también se refiere a compuestos de Fórmula I que son selectivos para CHK-1 sobre CHK-2 con una relación de selectividad entre Aproximadamente 5 veces y aproximadamente 5000 veces; preferiblemente entre aproximadamente 50 veces y aproximadamente 1000 veces; y más preferiblemente entre aproximadamente 70 veces y aproximadamente 830 veces. Dentro de esta realización, los compuestos más preferidos se seleccionan entre el grupo compuesto por:

2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida;

N-[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fluoro-3-trifluorometil-benzamida;

(2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (clorhidrato);

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Dimetilamino-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

Clorhidrato de (2*R*)-2-amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida;

(6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-Hidroxi-fenil)-ciclopropanocarboxílico; y

(2-etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; o

las sales o solvatos farmacéuticamente aceptables de los mismos.

Otro objeto de la invención es proporcionar una composición para el tratamiento de neoplasmas, y para mejorar los efectos antineoplásicos de los agentes anti-neoplásicos y de la radiación terapéutica.

En una realización, la invención se refiere a una composición que contiene un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo y un agente anti-neoplásico en forma de una preparación combinada para el uso simultáneo, separado o secuencial en el tratamiento de un neoplasma.

En otra realización, la invención se refiere a una composición que contiene un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo y un agente anti-neoplásico en forma de una preparación combinada para el uso simultáneo, separado o secuencial en el tratamiento de un neoplasma donde el agente anti-neoplásico se selecciona entre el grupo compuesto por agentes alquilantes, antibióticos y alcaloides de plantas, hormonas y esteroides, agentes sintéticos que tienen actividad anti-neoplásica, antimetabolitos y moléculas biológicas que tienen actividad anti-neoplásica.

En otra realización, la invención se refiere a una composición que contiene un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo y un agente anti-neoplásico en forma

de una preparación combinada para el uso simultáneo, separado o secuencial en el tratamiento de un neoplasma donde el agente anti-neoplásico se selecciona entre el grupo compuesto por Ara-c, VP-16, cis-platina, adriamicina, 2-cloro-2-desoxiadenosina, 9-(3-*D*-arabinosil-2-fluoroadenina, carboplatina, gemcitabina, camptotecina, paclitaxel, BCNU, 5-fluorouracil, irinotecan y doxorubicina.

Otro objeto de la invención es proporcionar un procedimiento para el tratamiento de neoplasmas.

En una realización, la invención se refiere a un procedimiento para tratar un neoplasma que comprende administrar a un mamífero en necesidad del mismo, un agente anti-neoplásico en combinación con un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo.

En otra realización, la invención se refiere a un procedimiento para tratar un neoplasma que comprende administrar a un mamífero en necesidad del mismo, un agente anti-neoplásico en combinanión con un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo, donde el agente anti-neoplásico se selecciona entre el grupo compuesto por Ara-c, VP-16, cis-platina, adriamicina, 2-cloro-2-desoxiadenosina, 9-*p*-*D*-arabinosil-2-fluoroadenina, carboplatina, gemcitabina, camptotecina, paclitaxel, BCNU, 5-fluorouracil, irinotecan y doxorubicina. En otra realización, puede usarse más de un agente anti-neoplásico en combinación con un compuesto de Fórmula I, las sales, solvatos o profármacos farmacéuticamente aceptables del mismo.

Otro objeto de la invención es proporcionar procedimientos para mejorar el efecto anti-neoplásico de la radiación terapéutica.

En una realización, la invención se refiere a un procedimiento para tratar un neoplasma que comprende administrar a un mamífero en necesidad del mismo, radiación terapéutica que tiene un efecto anti-neoplásico en combinación con un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo.

Otro objeto de la invención es proporcionar procedimientos para mejorar el efecto antineoplásico de un agente anti-neoplásico.

En una realización, la invención se refiere a un procedimiento para mejorar el efecto anti-neoplásico de un agente anti-neoplásico en un mamífero que comprende administrar a un mamífero en necesidad del mismo, un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo, en combinación con un agente antineoplásico. Los agentes antineoplásicos incluyen agentes alquilantes, antibióticos y alcaloides de plantas, hormonas y esteroides, agentes sintéticos que tienen actividad anti-neoplásica, antimetabolitos y moléculas biológicas que tienen actividad anti-neoplásica. Los agentes antineoplásicos específicos incluyen Ara-c, VP-16, cis-platina, adriamicina, 2-cloro-2-desoxiadenosina, 9-β-*D*-arabinosil-2-fluoroadenina, carboplatina, gemcitabina, camptotecina, paclitaxel, BCNU, 5-fluorouracil, irinotecan y doxorubicina.

En otra realización, la invención se refiere a un procedimiento para mejorar el efecto antineoplásico de radiación terapéutica en un mamífero que comprende administrar a un mamífero en necesidad del mismo, un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del

mismo, en combinación con radiación terapéutica que tiene un efecto anti-neoplásico.

Otro objeto de la invención es proporcionar un procedimiento para el tratamiento de una afección que puede tratarse mediante la inhibición de proteína quinasas. En una realización de la invención, las proteína quinasas se seleccionan entre el grupo compuesto por *quinasa de checkpoint 1* (CHK-1), *quinasa de checkpoint* 2 (CHK-2), *quinasa 1 dependiente de ciclina* (CDK1), *quinasa regulada por suero y glucocorticoides* (SGK), *proteína quinasa activada por adenosina 5'-monofosfato (AMP)* (AMPK), *tirosina quinasa de células T linfoides* (LCK), *proteína quinasa 2 activada por mitógenos* (MAPK-2), *proteína quinasa 1 activada por mitógenos y estrés* (MSK1), *quinasa Rho* (ROCK-II), *quinasa P70 S6* (p70S6K), *proteína quinasa dependiente de AMPc (adenosina 3',5' cíclica monofosfato)* (PKA), *proteína quinasa activada por mitógenos* (MAPK), *proteína quinasa 1 activada por mitógenos* (MAPK-1), *quinasa 2 relacionada con proteína quinasa C* (PRK2), *quinasa 1 dependiente de 3'-fosfoinositida* (PDK1), *proteína quinasa Fyn* (FYN), *proteína quinasa C* (PKC), *proteína quinasa C Beta* 2 (PKCβII), *proteína quinasa C Gamma* (PKCγ), *receptor del factor de crecimiento vascular endotelial 2* (VEGFR-2), *receptor del factor de crecimiento de fibroblastos* (FGFR), *fosforilasa quinasa* (PHK), *quinasa Wee1* (Wee1) y *proteína quinasa B* (PKB). Preferiblemente, las proteína quinasas se seleccionan entre el grupo compuesto por *quinasa de checkpoint* 1 (CHK-1), *quinasa de checkpoint* 2 (CHK-2), *proteína quinasa activada por mitógenos* (MAPK), *proteína quinasa 1 activada por mitógenos* (MAPK-1), *proteína quinasa 2 activada por mitógenos* (MAPK-2), *receptor del factor de crecimiento vascular endotelial 2* (VEGFR-2), *receptor del factor de*

crecimiento de fibroblastos (FGFR), *fosforilasa quinasa* (PHK), *proteína quinasa B alfa* (PKBα) y *quinasa Wee1* (Wee1).

En una realización, la invención se refiere a un procedimiento para el tratamiento de una afección que puede tratarse mediante la inhibición de proteína quinasas en un mamífero, incluyendo un ser humano, que comprende administrar a un mamífero en necesidad del mismo, un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo.

En otra realización, dicha afección que puede tratarse mediante la inhibición de proteína quinasas se selecciona entre el grupo compuesto por trastornos de tejido conectivo, trastornos de inmunología/alergia, enfermedades infecciosas, enfermedades respiratorias, enfermedades cardiovasculares, enfermedades oculares, enfermedades metabólicas, trastornos del sistema nervioso central (SNC), enfermedades hepáticas/renales, trastornos reproductivos, trastornos gástricos, trastornos de la piel y cánceres.

Otros aspectos, ventajas y características preferidas de la invención serán obvios a partir de la siguiente descripción detallada.

Descripción detallada y realizaciones preferidas de la invención

Para los propósitos de la presente invención, analizados y reivindicados en este documento, se definen los siguientes términos y abreviaturas:

A menos que se indique otra cosa, el término "cuando aparezca" se refiere a cualquier aparición de cualquier grupo funcional (tal como R^1, R^2 o cualquier sustituyente del mismo), incluyendo cualquier aparición de cualquier componente de cualquier grupo funcional indicado en este documento (por ejemplo, el "componente alquilo (C_1-C_8) de alquil (C_1-C_8)-O-).

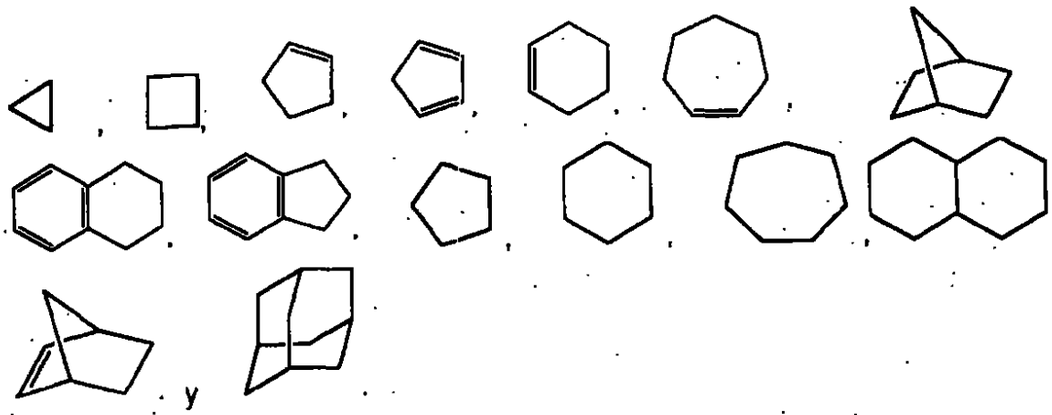
A menos que se indique otra cosa, el término "alquilo (C_1-C_8)" así como el componente alquilo (C_1-C_8) de otros términos indicados en este documento (por ejemplo, el "componente alquilo (C_1-C_8) de alquil (C_1-C_8)-O-), puede ser lineal o ramificado (tal como metilo, etilo, *n*-propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, butilo secundario, butilo terciario).

A menos que se indique otra cosa, el término "alquenilo (C_2-C_8)" significa un radical, sustituyente, resto o sub-resto hidrocarburo lineal o ramificado, que como se indica en este documento tiene de 2 a 8 átomos de carbono que tiene al menos un doble enlace incluyendo, pero sin limitación etenilo, 1-propenilo, 2-propenilo (alilo), *iso*-propenilo, 2-metil-1-propenilo, 1-butenilo, o 2-butenilo.

A menos que se indique otra cosa, el término "alquinilo (C_2-C_8)" se usa en este documento para indicar un radical, sustituyente, resto o sub-resto hidrocarburo lineal o ramificado que como se indica en este documento tiene de 2 a 8 átomos de carbono y que tiene un triple enlace incluyendo, pero sin limitación, etinilo (-C≡C-H), propinilo (-CH_2-C≡C-H o -C≡C-CH_3) o butinilo (-CH_2-CH_2-C≡C-H, o -CH_2-C≡C-CH_3 o -C≡C-CH_2CH_3).

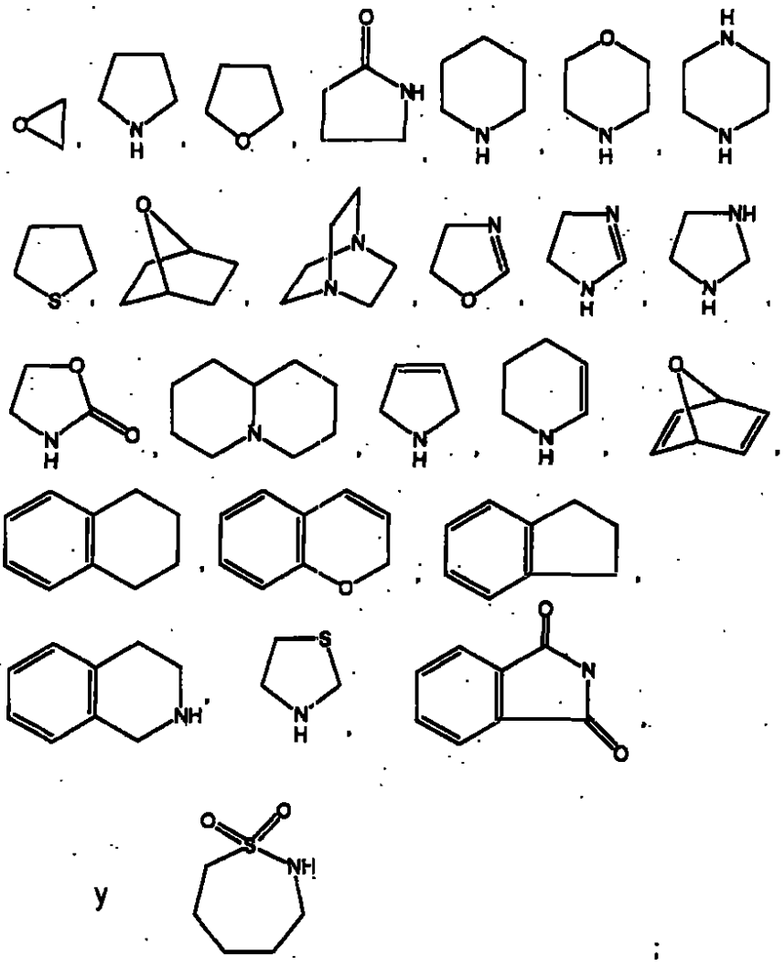
A menos que se indique otra cosa, el término "cicloalquilo (C_3-C_{10})" se refiere a un radical, sustituyente, resto o sub-resto, hidrocarburo, monocíclico o bicíclico o tricíclico condensado, espiro o no condensado, saturado o parcialmente saturado, no aromático que como se indica en este documento tiene un total de 3 a 10 átomos de carbono, preferiblemente 5-8 átomos de carbono en el anillo. Los cicloalquilos (C_3-C_{10}) ilustrativos incluyen anillos monocíclicos de 3-7, preferiblemente 3-6, átomos de carbono, tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Los

ejemplos ilustrativos de cicloalquilo (C_3-C_{10}) se derivan de, pero sin limitación, los siguientes:



y

A menos que se indique otra cosa, el término "heterociclilo (C_2-C_{10})" se refiere a un radical, sustituyente, resto o sub-resto monocíclico o bicíclico o tricíclico condensado, espiro o no condensado, monovalente, saturado o parcialmente saturado, no aromático que como se indica en este documento contiene un total de 2 a 10 átomos de carbono en el anillo y de 1 a 5 heteroátomos en el anillo seleccionados entre nitrógeno, oxígeno y azufre. Los ejemplos ilustrativos de heterociclilo (C_2-C_{10}) incluyen azetidinilo, pirrolidilo, piperidilo, piperazinilo, morfolinilo, cromenilo, tetrahidro-2*H*-1,4-tiazinilo, tetrahidrofurilo, dihidrofurilo, tetrahidropiranilo, dihidropiranilo, 1,3-dioxolanilo, 1,3-dioxanilo, 1,4-dioxanilo, 1,3-oxatiolanilo, 1,3-oxatianilo, 1,3-ditianilo, azabiciclo[3.2.1]octilo, azabiciclo[3.3.1]nonilo, azabiciclo[4.3.0]nonilo, oxabiciclo[2.2.1]heptilo, 1,5,9-triazaciclododecilo y similares. Otros ejemplos ilustrativos se derivan de, pero sin limitación, los siguientes:

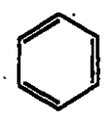
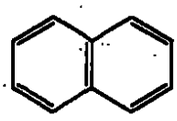


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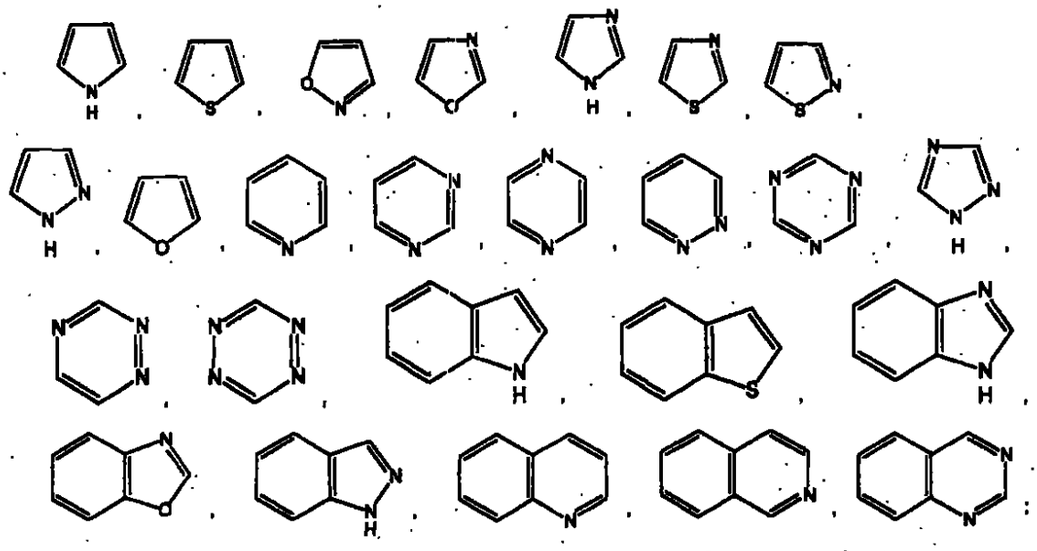
;

a menos que se indique otra cosa, el heterociclilo (C_2-C_{10}) anterior puede estar C-enlazado o N-enlazado donde sea posible. Por ejemplo, piperidilo puede ser piperid-1-ilo (N-enlazado) o piperid-2-ilo (C-enlazado).

A menos que se indique otra cosa, el término "arilo (C_6-C_{10})" se refiere a un radical, sustituyente, resto o sub-resto monocíclico o bicíclico o tricíclico condensado o no condensado, monovalente, aromático que como se indica en este documento contiene un total de 6 a 10 átomos de carbono en el anillo. Los ejemplos ilustrativos se derivan de, pero sin limitación, los siguientes:

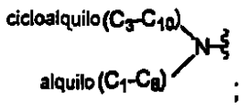
 y 

A menos que se indique otra cosa, el término "heteroarilo (C_1-C_{10})" se refiere a un radical, sustituyente, resto o sub-resto monocíclico, bicíclico o tricíclico condensado o no condensado, monovalente, aromático que como se indica en este documento contiene un total de 1 a 10 átomos de carbono en el anillo y de 1 a 5 heteroátomos en el anillo seleccionados entre nitrógeno, oxígeno y azufre. Los ejemplos ilustrativos de heteroarilo (C_1-C_{10}) incluyen, pero sin limitación, tienilo, pirrolilo, imidazolilo, pirazolilo, furilo, isotiazolilo, furazanilo, isoxazolilo, tiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, benzo[b]tienilo, nafto[2,3-b]tiantrenilo, isobenzofuranilo, cromenilo, xantenilo, fenoxatienilo, indolizinilo, isoindolilo, indolilo, indazolilo, purinilo, isoquinolilo, quinolilo, ftalazinilo, naftiridinilo, quinoxialinilo, quinzolinilo, benzotiazolilo, benzimidazolilo, tetrahidroquinolinilo, cinnolinilo, pteridinilo, carbazolilo, beta-carbolinilo, fenantridinilo, acridinilo, perimidinilo, fenantrolinilo, fenazinilo, isotiazolilo, fenotiazinilo y fenoxazinilo. Otros ejemplos de heteroarilo (C_1-C_{10}) se derivan de, pero sin limitación, los siguientes:



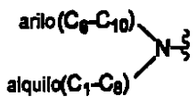
a menos que se indique otra cosa, el heteroarilo (C_1-C_{10}) anterior puede estar C-enlazado o N-enlazado cuando sea posible. Por ejemplo, piridilo puede ser pirid-1-ilo (N-enlazado) o pirid-3-ilo (C-enlazado).

A menos que se indique otra cosa, el término "(cicloalquil (C_3-C_{10}))(alquil (C_1-C_8))>N-" se refiere a un radical, sustituyente, resto o sub-resto que como se indica en este documento tiene la fórmula:



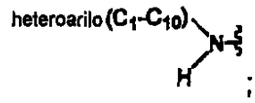
; en la que los términos "cicloalquilo (C_3-C_{10})" y "alquilo (C_1-C_8)" son como se han definido anteriormente.

A menos que se indique otra cosa, el término "(aril (C_6-C_{10}))(alquil (C_1-C_8))>N-" se refiere a un radical, sustituyente, resto o sub-resto que como se indica en este documento tiene la fórmula:



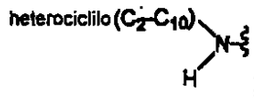
; en la que los términos "arilo (C_6-C_{10})" y "alquilo (C_1-C_8)" son como se han definido anteriormente.

A menos que se indique otra cosa, el término "heteroaril (C_1-C_{10})-NH-" se refiere a un radical, sustituyente, resto o sub-resto que como se indica en este documento tiene la fórmula:



; en la que el término "heteroarilo (C_1-C_{10})" es como se ha definido anteriormente y donde dicho heteroarilo (C_1-C_{10}) se une al -NH- mediante un átomo de carbono del anillo heteroarilo (C_1-C_{10}).

A menos que se indique otra cosa, el término "heterociclil (C_2-C_{10})-NH-" se refiere a un radical, sustituyente, resto o sub-resto que como se indica en este documento tiene la fórmula:



; en la que el término "heterociclilo (C_2-C_{10})" es como se ha definido anteriormente y donde dicho heterociclilo (C_2-C_{10}) se une al -NH- mediante un átomo de carbono del anillo heterociclilo (C_2-C_{10}).

El término "una sal farmacéuticamente aceptable" se refiere a una sal que retiene la eficacia biológica de los ácidos libres y bases del compuesto especificado y que no es biológicamente o de otra forma indeseable. Un compuesto de la invención puede poseer un grupo funcional suficientemente ácido, uno suficientemente básico, o ambos, y por consiguiente puede reaccionar con cualquiera de varias bases inorgánicas u orgánicas y ácidos inorgánicos y orgánicos, para formar una sal farmacéuticamente aceptable. Las sales farmacéuticamente aceptables ilustrativas incluyen las sales preparadas por la reacción de los compuestos de la presente invención con un ácido mineral u orgánico o una base inorgánica, incluyendo tales sales sulfatos, pirosulfatos, bisulfatos, sulfitos, bisulfitos, fosfatos, monohidrogenofosfatos,

dihidrogenofosfatos, metafosfatos, pirofosfatos, cloruros, bromuros, yoduros, acetatos, propionatos, decanoatos, caprilatos, acrilatos, formiatos, isobutiratos, caproatos, heptanoatos, propiolatos, oxalatos, malonatos, succinatos, suberatos, sebacatos, fumaratos, maleatos, butin-1,4-dioatos, hexin-1,6-dioatos, benzoatos, clorobenzoatos, metilbenzoatos, dinitrobenzoatos, hidroxibenzoatos, metoxibenzoatos, ftalatos, sulfonatos, xilenosulfonatos, fenilacetatos, fenilpropionatos, fenilbutiratos, citratos, lactatos, γ-hidroxibutiratos, glicolatos, tartratos, metano-sulfonatos, propanosulfonatos, naftaleno-1-sulfonatos, naftaleno-2-sulfonatos y mandelatos.

El término "profármaco", como se usa en este documento, se refiere a un precursor metabólico de un compuesto de Fórmula I (o una sal del mismo) que es farmacéuticamente aceptable. Un profármaco puede ser inactivo cuando se administra a un sujeto pero se convierte *in vivo* en un compuesto activo de Fórmula I. La expresión "metabolito activo", como se usa en este documento, se refiere a un producto metabólico de un compuesto de Fórmula I que es farmacéuticamente aceptable y eficaz. Los profármacos y metabolitos activos de los compuestos de Fórmula I pueden determinarse usando técnicas conocidas en la técnica. Los profármacos y metabolitos activos de un compuesto pueden identificarse usando técnicas rutinarias conocidas en la técnica. Véase, por ejemplo, Bertolini y col., *J. Med. Chem.*, 40, 2011-2016 (1997); Shan, y col., *J. Pharm. Sci.*, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.*, 34, 220-230 (1995); Bodor, *Advances in Drug Res.*, 13, 224-331 (1984); Bundgaard, Design of Prodrugs (Elsevier Press 1985); y Larsen, Design and Application of Prodrugs. Drug Design and Development (Krogsgaard-Larsen y col., eds., Harwood Academic Publishers, 1991).

El inhibidor de CHK-1 de la presente invención puede administrarse en combinación con otras terapias anti-neoplasma incluyendo agentes anti-neoplásicos y terapia de radiación.

La expresión "en combinación con" significa que el compuesto de Fórmula I puede administrarse justo antes, justo después, simultáneamente o en cualquier combinación de antes, después o simultáneamente, con las otras terapias anti-neoplasma. De esta manera, el compuesto y el agente anti-neoplásico pueden administrarse simultáneamente en forma de una composición unitaria o en forma de dos composiciones separadas o secuencialmente en forma de dos composiciones separadas. Asimismo, el compuesto y la terapia de radiación pueden administrarse simultáneamente, por separado o secuencialmente. El compuesto puede administrarse en combinación con más de una terapia anti-neoplasma. En una realización preferida, el compuesto puede administrarse de 2 semanas a 1 día antes de cualquier quimioterapia, o de 2 semanas a 1 día antes de cualquier terapia de radiación. En otra realización preferida, el inhibidor de CHK-1 puede administrarse durante quimioterapias anti-neoplásicas y terapias de radiación. Si se administra después de tal quimioterapia o terapia de radiación, el inhibidor de CHK-1 puede administrarse en un período de 1 a 14 días después de los tratamientos primarios. El inhibidor de CHK-1 también puede administrarse crónica o semi-crónicamente, durante un período de aproximadamente 2 semanas a aproximadamente 5 años. Un especialista en la técnica reconocerá que la cantidad de inhibidor de CHK-1 administrada de acuerdo con la presente invención en combinación con otros agentes o terapias antineoplásicas es la cantidad suficiente para mejorar los efectos anti-

neoplasma de los agentes neoplásicos o terapias de radiación o la cantidad suficiente para inducir la apoptosis o muerte celular junto con la terapia de radiación o anti-neoplásica y/o para mantener un efecto antiangiogénico. Tal cantidad puede variar, entre otros factores, dependiendo del tamaño y tipo de neoplasia, la concentración del compuesto en la formulación terapéutica, los agentes anti-neoplasma específicos, el tiempo de administración de los inhibidores de CHK-1 en relación con las demás terapias, y la edad, tamaño y afección del paciente.

La expresión "proteína quinasas", como se usa en este documento, se refiere a enzimas que catalizan la fosforilación de grupos hidroxi en los restos tirosina, serina y treonina de las proteínas. Las consecuencias de esta actividad aparentemente simple son asombrosas; crecimiento, diferenciación y proliferación celular, es decir, prácticamente todos los aspectos de la vida celular de un modo u otro dependen de la actividad de la proteína quinasa. Además, la actividad anormal de la proteína quinasa se ha relacionado con un huésped de trastornos, que varía de enfermedades que no amenazan relativamente la vida tales como psoriasis a enfermedades extremadamente virulentas tales como glioblastoma (cáncer cerebral). Las proteína quinasas pueden dividirse convenientemente en dos clases principales, las proteína tirosina quinasas (PTK) y las serina-treonina quinasas (STK). Además, se conoce una tercera clase de quinasas de especificidad dual que pueden fosforilar restos tanto tirosina como serina-treonina. Los ejemplos de proteína quinasas y sus isoformas contempladas en de esta invención incluyen, pero sin limitación, *quinasa de checkpoint* 1 (CHK-1), *quinasa de checkpoint* 2 (CHK-2), *quinasa 1 dependiente de ciclina* (CDK1), *quinasa regulada por suero y*

glucocorticoides (SGK), *proteína quinasa activada por adenosina 5'-monofosfato (AMP)* (AMPK), *tirosina quinasa de células T linfoides* (LCK), *proteína quinasa 2 activada por mitógenos* (MAPK-2), *proteína quinasa 1 activada por mitógenos y estrés* (MSK1), *proteína quinasa B* (PKB), *proteína quinasa B alpha* (PKBa), *quinasa Rho* (ROCK-II), *quinasa P70 S6* (p70S6K), *quinasa dependiente de AMPc (adenosina 3',5 -cíclica monofosfato)* (PKA), *proteína quinasa 1 activada por mitógenos* (MAPK-1), *quinasa 2 relacionada con proteína quinasa C* (PRK2), *quinasa 1 dependiente de 3'-fosfoinosítido* (PDK1), *quinasa Fyn* (FYN), *proteína quinasa C* (PKC), *proteína quinasa C Beta 2* (PKCβII), *proteína quinasa C Gamma* (PKCγ), *receptor del factor de crecimiento endotelial vascular 2* (VEGFR-2), *receptor del factor de crecimiento de fibroblastos* (FGFR), *fosforilasa quinasa* (PHK), *quinasa Wee1* (Wee1) y *proteína quinasa B* (PKB).

La *quinasa de checkpoint* 2 (CHK-2) actúa como un controlador del checkpoint del ciclo celular en respuesta a la lesión del ADN. CHK-2 es un efector corriente debajo de ATM que fosforila la proteína p53 y afecta a la progresión del ciclo celular desde G_1 a la fase S. La activación de CHK-2 también afecta a la progresión de la fase S. Además, junto con CHK-1, CHK2 influye en la transición de G_2/M y juega un papel en la apoptosis de la lesión que no puede repararse. CHK-2 podría jugar un papel en la sensibilización de las células cancerosas a terapias de lesión de ADN. CHK-2 también puede jugar un papel como supresor tumoral. Bartek, J. y col., (2001) *Nature Reviews, Molecular Cell biology* 2: 877-886.

La *quinasa 1 dependiente de ciclina* (CDK1) también se conoce como Cdc2 en las células de levadura. El ciclo celular dirige eventos específicos que

controlan el crecimiento y la proliferación de las células. El complejo ciclina B/Cdk1 promueve la entrada en mitosis. La sobreexpresión de ciclina B1 se ha descubierto en el 90% de los carcinomas colorectales. Como el ciclo celular se desrregula en los cánceres humanos, la modulación de la actividad de CDK es una posible terapia. Se ha demostrado que la olomoucina, un inhibidor de CDK, inhibe la proliferación celular en células cancerosas humanas. En las células de linfoma, la olomoucina detiene el ciclo celular en las fases G_1 y G_2 inhibiendo la ciclina E/CDK2 y ciclina B/CDK1. Buolamwini, J. K. (2000) *Current Pharmaceutical Design* 6: 379-392; Fan, S. y col., (1999) *Chemotherapy* 45: 437-445.

La *quinasa regulada por suero y glucocorticoides* (SGK) se regula rápida y altamente por corticoesteroides en células A6 a los niveles proteicos y de ARNm. SGK también se induce por aldosterona en el riñón de ratas adrenalectomizadas. SGK se activa por la quinasa 1 dependiente de 3'-fosfoinosítido (PDK1). SK puede jugar un papel crítico en células diana de aldosterona y puede ser fisiológicamente importante en la respuesta temprana a la aldosterona. Los antagonistas del receptor de aldosterona han representado recientemente una gran promesa en ensayos clínicos para pacientes con insuficiencia cardíaca. La capacidad para mediar las respuestas fisiológicas a aldosterona puede resultar asimismo beneficiosa. Véase Leslie, N. R. y col., (2001) *Chemical Reviews* 101(8): 2365-2380; Funder, J. W. (1999) *Molecular and Cellular Endocrinology* 151 (1-2): 1-3; Verrey, F. y col., (2000) *Kidney International* 57 (4): 1277-1282.

La isoforma α2 de la *proteína quinasa activada por adenosina 5'-monofosfato (AMP)* (AMPK) (AMPK α2) se presenta en altas concentraciones

en el músculo esquelético, corazón e hígado mientras que la isoforma α1 se distribuye ampliamente. AMPK, probablemente la isoforma α2, fosforila la isoforma acetil-CoA carboxilasa β (ACCβ) y se inactiva en condiciones de estimulación eléctrica o ejercicio. En el músculo esquelético de ratas, malonil-CoA se regula por ACCβis y está implicada en el mecanismo regulador de la ransferencia de ácidos grasos de cadena larga en las mitocondrias donde se oxidan. Por tanto, AMPK podría ligarse a la obesidad y/o resistencia a insulina, y la modulación de AMPK podría ser potencialmente beneficiosa en el tratamiento de estas enfermedades. Los AMPK inhiben enzimas implicadas en la síntesis de glucógeno y colesterol. Es una posible enzima reguladora que en respuesta a la depleción de adenosina 5'-trifosfato (ATP), reduce el consumo adicional de ATP iniciando los ajustes celulares que se dirigen a mantener los niveles de ATP. Además, AMPK se ha relacionado con la transcripción, regulación de creatinina quinasa, apoptosis y transporte de glucosa. Véase Kemp, B. E. y col., (1999) *Trends in Biochemical Sciences* 24 (1): 22-25; Friedman, J. (2002) *Nature* 415 (6869): 268-269; Ruderman, N. B. y col., (1999) *American Journal of Physiology* 276 (1, Pt. 1): E1-E18.

La tirosina quinasa de células T linfoides (LCK) es una tirosina quinasa no receptora citosólica y un miembro T-linfocito de la familia de Src. LCK ha estado implicada en la activación del receptor de células T de fase temprana por antígenos y desempeña un papel importante en las respuestas inmunes mediadas por células T. Después de la activación por autofosforilación, LCK fosforila cadenas ξ del receptor de células T que después pueden reclutar una segunda proteína citosina quinasa citoplásmica ZAP-70 para promover la activación de células T. Los inhibidores pueden usarse para el tratamiento de

artritis reumatiode, enfermedad relacionada con la respuesta inmune y leucemias y linfomas basados en células T. Véase Garcia-Echevarria, C. (2001) Current *Medicinal Chemistry* 8(13):1589-1604; Majolini, M. B. y col. (1999) *Leukemia & Lymphoma* 35(3/4):245-254.

La *proteína quinasa 1 activada por mitógenos y por estrés* (MSK1) en la estimulación de la ruta de la proteína quinasa activada por el mitógeno Ras y también por la ruta de la quinasa de estrés p38. Ambas rutas están implicadas en la tumorigénesis. La estimulación de la ruta de transducción de señales Ras-MAPK mediante factores de crecimiento o ésteres de forbol da lugar a la forsforilación de la histona H3. Se ha demostrado que MSK1 media el factor de crecimiento epidérmico (EGF) o TPA (12-*O*-tetradecanoilforbol-13-acetato, un éster de forbol) inducido por la fosforilación de H3. Hay pruebas de que la activación persistente de la ruta Ras-MAPK y MSK1 resultante en niveles elevados de H3 fosforilado puede contribuir a la expresión aberrante del gen observaba en células transformadas por oncogenes. La inhibición de MSK1 suprimió la inducción de genes c-fos (proto-oncogen) y uPA en células parentales y transformadas por oncogenes. Tanto c-fos como uPA están implicadas en la invasión y metástasis tumoral. Véase Strelkov, I. y col. (2002) *Cancer Research* 62(1):75-78; Zhong, S. y.col (2001) *Jorunal of Biological Chemistry* 276 (35):33213-33219; Nomura, M. y col. (2001) *Journal Biological Chemistry* 276(27); 25558-25567.

La *quinasa Rho* (ROCK-II) también se conoce como ROKa. Inhibiendo ROCK-II, se podría influir bastante en Rho GTPasas que actúan como controles moleculares que regulan muchos procedimientos celulares importantes, incluyendo funcionalidad de actina, progresión del ciclo celular y

adhesión celular. Los efectos biológicos *in vitro* e *in vivo* de Y-27632, un inhibidor específico de ROCK, se han descrito en la bibliografía e incluyen baja presión sanguínea en ratas hipertensivas, inhibición de la formación inducida por ROCK de fibras de estrés y adhesiones focales, e inhibición del crecimiento tumoral. Véase Narumiya, S. y col. (2000) *Methods in Enzymology* 325 (Regulators and Effectors of Small GTPases, Part D): 273-284 (y referencias asociadas indicadas en estos documentos); Bishop, y col. (2000) *Biochem J.* 348: 241-255.

La *quinasa P70 S6* ($p70^{s6k}$) se encuentra como dos isoformas- una un citoplásmica y la otra en el núcleo. Son similares excepto en el extremo N-terminal y ambas se denominan $P70^{s6k}$ o S6K1. También se identificó un segundo homólogo funcional S6K2. $P70^{s6k}$ es una diana corriente abajo de la quinasa lipídica fosfoinosítido 3-OH quinasa (PI(3)K). $P70^{s6k}$ está implicada en el control del ciclo celular y en la diferenciación de células neuronales. $P70^{s6k}$ también puede funcionar en la regulación de la movilidad celular que puede influir en la metástasis tumoral, en la respuesta inmune y en la reparación tisular. Junto con PKB/Akt, $P70^{s6k}$ es un determinante importante en la señalización de la proteína tirosina quinasa oncogénica (PTK). $P70^{s6k}$ puede ser una quinasa mas potente para BAD que para PKB/Akt (véase anteriormente) en respuesta a la estimulación el factor de crecimiento de insulina 1 (IGF-1). Por lo tanto, $P70^{s6k}$ puede desempeñar un papel antipoptótico importante. véase Blume-Jensen, P. y col. (2001) *Nature* 411(6835): 355-365; Accili, D. (2001) *Journal of Clinical Investigation* 108(11): 1575-1576; Hidalgo, M. y col. (2000) *Oncogene* 19(56): 6680-6686; Berven, L. y col. (2000) *Inmunology y Cell Biology* 78(4): 447-451.

Proteína quinasa dependiente de AMPc (adenosina 3',5' cíclica monofosfato) está implicada en una amplia variedad de repuestas fisiológicas que surgen después de la interacción con AMPc. AMPc es un segundo mensajero que regula muchas actividades celulares diferentes tales como transcripción génica, crecimiento y diferenciación celular, conductividad de los canales iónicos, y liberación de neurotransmisores. La interacción de AMPc/PKA actúa como principal mecanismo regulador en los mamíferos, y PKA a demostrado fosforilar una miríada de sustratos fisiológicos. PKA tiene dos isoformas principales - PKAI y PKAII. Los inhibidores de PKAI han demostrado mejorar los efectos cuando se usan en combinación en ciertas terapias citotóxicas para el cáncer. Los oligonucleótidos antisentido que se dirigen a la subunidad Riα de PKAI han demostrado mejorar los efectos antitumorales cuando se combinan con Taxol. El glucagón activa PKA y PKA puede influir en la respuesta a insulina junto con la proteína quinasa dependiente de calmodulina y la proteína quinasa C. PKA está implicada en la regulación de canales de calcio de tipo L cardíacos, y la modulación de las rutas reguladoras implicadas puede ser útil en el tratamiento de enfermedades cardíacas. Además, las células T disfuncionales asiladas de pacientes con VIH se han restaurado mediante la adición de antagonistas de PKAI. Véase Skalhegg, B.S. y col. (2000) *Frontiers in Bioscience* [Publicación Electrónica] 5:D678-D693; *Brandon*, E. P. y col. (1997) *Current Opinion in Neurobiology* 7(3): 397-403; *Nesher, R. y col. (2002) Diabetes 51 (Supl. 1): S68-S73; Shabb, J. B. (2001) Chemical Reviews* 101(8): 2381-2411; Kamp, T.J. y col. (2000) *Circulation Research* 87(12); 1095-1102; Tortora, G. y col. (2002) *Clinical Cancer Research* 8:303-304; Tortora, G. y col. (2000) *Clinical Cancer Research*

6:2506-2512.

La *proteína quinasa activada por mitógenos* (MAPK) también se conoce como ERK. En la tumorigénesis, los oncogenes ras transmiten señales de crecimiento extracelular. La ruta de MPAK es una ruta de señalización importante entre el ras unido a la membrana y el núcleo. Está implicada una cascada de fosforilación que implica tres quinasas clave. Son Raf, MEK (quinasa MAP quinasa) y MAPK/ERK. Las isoformas de raf fosforilan y activan isoformas de MEK1 y MEK2. MEK1 y 2 son quinasas de especificidad dual que a su vez fosforilan y activan las isoformas de MAPK MAPK1/ERK1 y MAPK2/ERK2. Los fibroblastos, tanto MAPK1/ERK1 como MAPK2/REK2 se activan fuertemente mediante factores decrecimiento y mediante ésteres de forbol que estimulan el tumor. MAPK1/ERK1 y MAPK2/REK2 también están implicadas en la regulación de la glucosa, regulación del neurotrasmisor y regulación de secretagogos (en tejidos endocrinos). La ruta de MAPK también está relacionada con la inducción de ARNm D1 ciclina y de esta forma está relacionada con la fase G1 del ciclo celular. Véase Webb, C.P. y col. (2000) *Cancer Research* 60(2), 342-349; Roovers, K. y col. (2000) *BioEssays* 22(9): 818-826; Chen, Z. y col. (2001) *Chemical Reviews* 101(8): 2449-2476; Lee J. y col. (2000) *Immunopharmacology* 47(2-3): 185-201, Sebolt-Leopold J. S. (2000) Oncogene 19: 6594-6599; Cheng, F.U. y col. (2001) *Journal of Biological Chemistry* 276(35): 32552-32558; Cobb, M.H. y col. (2000) Trends in Biochemical Sciences 25(1): 7-9; Cobb, M.H. y col. (1995) *Journal of Biological Chemistry* 270(25): 14843-14846; Deak, M. y col. (1998) *EMBO Journal* 17(15): 4426-4441; Davis, J.D. (1993) *Journal of Biological Chemistry* 268(20): 14553-14556.

cSrc (también conocida como p60 c-src) es la tirosina quinasa no receptora citosólica. c-Src está implicada en la transducción de señales mitogénicas de diversos factores de crecimiento polipeptídico tales como el factor de crecimiento epidérmico (EGF) y el factor de crecimiento derivado de plaquetas (PDGF). c-Src está sobre expresado en cánceres de mama, cánceres pancreáticos, neuroblastomas y otros. Se ha identificado c-Src mutante en el cáncer de colon humano. c-Src fosforila diversas proteínas que están implicadas en la regulación de la interferencia entre la matriz extracelular y el citoesqueleto de actina citoplásmica. La modulación de la actividad de cSrc puede tener consecuencias en enfermedades relacionadas con la proliferación, diferenciación y muerte celular. Véase Bjorge, JD. y col. (2000) *Oncogene* 19(49):5620-5635; Halpern, M. S. y col. (1996) *Proc. Natl. Acad. Sci. U.S.A.* 93(2), 824-7; Belsches, A.P. y col. (1997) *Frontiers in Bioscience* [Publicación Electrónica] 2:D501-D518; Zhan, X y col. (2001) *Chemical Reviews* 101:2477-2496; Haskell, M.D. y col. (2001) *Chemical Reviews* 101:2425-2440.

La *quinasa 2 relacionada con la proteína quinasa C* (PRK2) está regulada por la proteína G Rho. PRK2 se encuentra en regiones de gran renovación de actina. La actividad de la quinasa endógena PRK2 aumenta con la diferenciación de queratinocitos y se asocia con la adhesión célula-célula de queratinocitos y activación de la quinasa Fyn. Véase Gross, C, y col. (2001) *FEBS letters* 496(2,3):101-104; Calautti, E. y col. (2002) *Journal of Cell Biology* 156(1):137-148.

La *quinasa 1 dependiente de 3´-fosfoinositido* (PDK1) fosforila y activa miembros de la familia de la quinasa AGC (quinasa dependiente de AMPc, dependiente de GMPc y proteína quinasa C) que se activan corriente abajo de

la fosfoionosítido 3-quinasa (PI3K). PI3K se vuelve activa mediante la estimulación de insulina. PDK1 activa diversas proteínas quinasas y por lo tanto puede estar relacionada con la regulación de diversos eventos específicos de insulina. La fosforilación de PDK1 y la activación de PKCζ son necesarias para la translocación de GLUT4 dependiente de insulina. La translocación de GLUT4 inducida por insulina está fisiológicamente relacionada con el citoesqueloto basado en actina. Los trastornos en los filamentos de actina están relacionados con la pérdida del efecto de la insulina en el transporte de glucosa y disminuyen la translocación de GLUT4. Véase Wick, K. L. y col. (2001) *Current Drug Targets: Immune, Endocrine and Metabollic Disorders* 1(3):209-221; Peterson, R. T. y col. (1999) *Current Biology* 9(14):R521-R524; Toker, A y col. (2000) *Cell* 103(2):185-188; Leslie, N.R. (2001) *Chem. Rev,* 101:2365-2380.

La *quinasa Fyn* (FYN) es un miembro de la familia Src de tirosina quinasas. Fyn ha estado implicada en el control positivo de la adhesión célula-célula de queratinocitos. La adhesión desempeña una función importante en el establecimiento y cuidado de tejidos organizados. En ratones transgénicos y Knockout para Fyn se estableció que Fyn participa en la señalización del receptor de células T (TCR). La sobreexpresión del transgen de Fyn(T) produce células T que mejoraron la respuesta a la señalización de TCR. Por el contrario, la expresión de una forma de quinasa inactiva es inhibidora. Fyn puede ser una diana apropiada para el tratamiento de enfermedades autoinmunes. Los ratones Fyn -/- son hipersensibles al alcohol lo que sugiere que Fyn puede ser una diana para el tratamiento del alcoholismo. La alteración de los niveles de Fyn también puede ayudar en el tratamiento de trastornos

cutáneos. Fyn ha estado implicada en la regulación de la muerte celular programada, y los ratones Fyn -/- muestran una apoptosis reducida. Véase también PRK2. Véase Calautti, E. y col. (2002) *Jorunal of Cell Biology* 156(1):137-148; Resh, M. D. (1993) *Journal of Biochemistry & Cell Biology* 30(11):1159-1162.

El *receptor del factor de crecimiento endotelial vascular 2* (VEGRF-2) también se conoce como FLK-1 y como KDR (receptor del dominio de inserto de quinasa). Otras tirosina quinasas del receptor de VEGF incluyen VEGFR-1 (Flt-1) y VEGFR-3 (Flt-4). El angiogénesis o el desarrollo de nueva vasculatura es vital para el proceso mediante el cual crecen los tumores sólidos. El grado de vascularización ha estado relacionado con el aumento potencial de la metástasis. VEGFR-2, expresado solo en células endoteliales, une el factor de crecimiento angiogénico fuerte (VEGF) y media la posterior transducción de señales. La inhibición de la actividad de VEGF-R2 ha dado lugar al aumento de la angiogénesis y al crecimiento tumoral en modelos *in vivo* y los inhibidores de VEGFR-1 están actualmente en ensayos clínicos para el tratamiento del cáncer. Véase Strawn y col., (1996) *Cancer Research* 56:3540-3545; Millauer y col., (1996) *Cancer Research* 56:1615-1620; Sakamoto, K. M. (2001) *IDrugs* 4(9):1067; Ellis, L. M y col. (2000) *Oncologist* 5 (Supl. 1):11-15; Mendel, D. B. y col. (2000) *Anti-Cancer Drug Desing* 15:29-41; Kumar, C.C. y col. (2001) *Expert Opin. Emerging Drugs* 6(2):303-315; Vajkoczy, P. y col. (1999) *Neoplasia* 1(1):31-41.

El *receptor del factor de crecimiento de fibroblastos* (FGFR) une los factores de crecimiento angiogénico aFGF y bFGF y media la posterior transducción de señales intracelulares. Los factores de crecimiento tales como

bFGF también desempeñan un papel importante en la inducción de la agiogénesis en tumores sólidos que han alcanzado un cierto tamaño. FGFR se expresa en diversos tipos de células diferentes a lo largo del cuerpo y puede o no desempeñar papeles importantes en los procedimientos fisiológicos normales en seres humanos adultos. Se ha informado de que la administración sistémica de un inhibidor de molécula pequeña de FGFR bloquea la angiogénesis inducida por bFGF en ratones. Véase Yoshiji y col., (1997) *Cancer Research* 57:3924-3928; Mohammad y col., (1998) *EMBO Journal* 17:5996-5904.

La *fosforilasa quinasa* (PHK) activa la glucógeno fosforilasa. La consecuencia principal de esta activación es la liberación de glucosa 1-fosfato del glucógeno. La conversión en glucógeno es el principal medio mediante el cual la glucosa se almacena en mamíferos. Las reservas de glucógeno intracelular se usan para mantener la homeostasis de glucosa en sangre durante el ayuno y son una fuente de energía para la contracción muscular. PHK *in vivo* se fosforila mediante la proteína quinasa dependiente de AMPc (PKA) que aumenta la actividad específica de PHK. Tanto los diabéticos de tipo 1 como de tipo 2 muestran niveles bajos de glucógeno en el hígado y en las células musculares. Los niveles de glucógeno están muy regulados por las hormonas y la señalización metabólica. Los inhibidores de quinasa que pueden aumentar los niveles de glucógeno intracelular pueden ser beneficiosos en el tratamiento de la diabetes. Véase Brushia, R. J. y col. (1999) *Frontiers in Bioscience* [Publicación Electrónica] 4:D618-D641; Newgard, C.B. y col. (2000) *Diabetes* 49:1967-1977; Venien-Bryan, C. y col. (2002) *Structure* 10:30-41; Graves, D. y col. (1999) *Pharmacol. Ther.* 82:(2-3)143-155; Kilimann, M.W.

(1997) Protein Dysfunction and Human Genetic Disease Capítulo 4: 57-75.

Se ha demostrado que la *quinasa Wee1* (Wee1) junto con la quinasa Mik1 fosforila Cdc2. Se ha demostrado que la fosforilación de Cdc2 previene la entrada mitótica. Wee1 puede desempeñar un papel importante en el ciclo de crecimiento normal de células y puede estar implicada en el control de checkpoint del ciclo celular. Rhind, N. y col. (2001) *Molecular and Cellular Biology* 21(5):1499-1508.

La *proteína quinasa B* (PKB) también se conoce como Akt. Hay tres isoformas muy similares conocidas como PKB α, β y γ (o Akt 1, 2 y 3). La irradiación ultravioleta en el intervalo 290-320 nM se ha asociado los con efectos nocivos de la luz del sol. Esta irradiación provoca la activación de PKB/Akt y puede estar implicada en la timorigénesis. Se ha demostrado PKB/Akt sobre expresado en cánceres de ovario, próstata, mama y pancreáticos. PKB/Akt también está implicada en la progresión del ciclo celular. PKB/Akt fomenta la supervivencia celular de diversas formas. Fosforila la proteína proapoptótica, BAD, de forma que es incapaz de unir e inactivar la proteína antiapoptótica Bcl-xl. BKB/Akt también sirve para inhibir la apoptosis inhibiendo la caspasa 9 y el factor de trascripción forkhead y activando la quinasa IKB. Véase Barber, A. J. (2001) *Journal of Biological Chemistry* 276(35):32814-32821; Medema, R.H. y col. (2000) *Nature* 404:278-787 ; Muise-Helmericks, R.C. y col. (1998) *Jorunal of Biological Chemistry* 273(45): 29864-29872; Nomura, M. y col. (2001) *Journal of Biological Chemistry* 276(27): 2558-25567; Nicholson, K. M. y col. (2002) Cellular Signaling 14(5): 381-395; Brazil, D.P. y col. (2001) *Trends in Biochemical Sciences* 26(11): 657-664. Leslie, N.R. (2001) *Chem Rev* 101:2365-2380.

Las isoformas clásicas de la *proteína quinasa C* (PKC) se designan αβ1, β2 y γ y todas son dependientes de Ca^{2+}. Las isoformas de PKC están implicadas en las rutas de transducción de señales relacionadas con diversas respuestas fisiológicas que incluyen el transporte de membrana, diferenciación y proliferación celular, organización de proteínas coitoesqueléticas y la expresión génica. Los ésteres de forbol que fomentan el tumor activan las isoformas clásicas de PKC y los oligonucleótidos antisentido pueden bloquear esta activación. Las isoformas de PKC suelen estar sobre expresadas en diversos cánceres. Se ha demostrado que los inhibidores de PKC invierten la resistencia a multifármacos mediada por *p*-glicoproteína y pueden aumentar las concentraciones intracelulares de otros agentes anticancerosos. En los miocitos, las isoformas de PKC están implicadas en ciertas patologías cardíacas. PKC-γ se expresa a un alto nivel en el cerebro y en la médula espinal y se localiza principalmente en las dendritas y en cuerpos de células neurales. PKC-β2 está implicada en la proliferación celular y la sobreexpresión aumenta la sensibilidad al cáncer. Los inhibidores de PKC-β son una nueva terapia importante para la retinopatia diabética con ensayos clínicos actualmente en desarrollo. Véase Magnelli, L. y col. (1997) Journal of Cancer Research and Clinical *Oncology* 123(7):365-369; Clerk, A. y col. (2001) *Circulation Research* 89(10):847-849; Carter, C. (2000) Current Drug Targets 1(2):163-183; Greenberg, S. y col. (1998) *Alcohol* 16(2);167-175; Rosenzweig, T. y col. (2002) Diabetes 51(6):1921-1930; Deucher, A. y col. (2002) *Journal of Biological Chemistry* 277(19):17031-17040; Frank, R.N. (2002) *American Journal of Ophthalmology* 133(5):693-698; Parekh, D. y col. (2000) *EMBO Journal* 19(4):496-503; Newton, A.C. (2001) *Chem. Rev.*101:2353-2364.

El término "tratar" o "tratado", como se usa en este documento, se refiere a invertir, aliviar, inhibir el progreso de o prevenir el trastorno o afección al que se aplica tal término, o uno o más síntomas de tal término o afección. El término "tratamiento", como se usa en este documento, se refiere al acto de tratar, tal como se acaba de definir "tratar".

"Trastornos del tejido conectivo" como se usa en este documento se refiere a trastornos tales como pérdida degenerativa del cartílago después de una lesión traumática de la articulación, osteoartritis, osteoporosis, enfermedad de Paget, pérdida de implantes artificiales de articulaciones, enfermedad periodontal y gingivitis.

"Destrucción del cartílago articular" como se usa en este documento se refiere a trastornos del tejido conectivo que dan como resultado la destrucción del cartílago articular, preferiblemente lesión articular, artritis reactiva, artritis aguda por pirofosfato (pseudogota), artritis psoriática o artritis reumatoide juvenil, más preferiblemente osteoartritis.

"Trastornos inflamatorios" como se usa en este documento se refiere a trastornos tales como artritis reumatoide, espondilitis anquilosante, artritis psoriática, psoriasis, condrocalcinosis, gota, enfermedad inflamatoria del intestino, colitis ulcerosa, enfermedad de Crohn, fibromialgia y caquexia.

"Trastornos de inmunología/alergia" como se usa en este documento se refiere a trastornos tales como toxicidad por transplante de órganos, reacciones alérgicas, hipersensibilidad alérgica por contacto, trastornos autoinmunes tales como los trastornos asociados con inflamación granulomatosa/remoldeado de tejidos (tal como asma), inmunosupresión y sarcoide.

"Enfermedades infecciosas", incluyendo las mediadas por virus, bacterias, hongos o infección microbacteriana, como se usa en este documento, se refiere a trastornos tales como artritis séptica, SIDA, fiebre; enfermedades priónicas, miastenia grave, Malaria, sépsis, choque hemodinámico y choque séptico.

"Enfermedades respiratorias" como se usa en este documento se refiere a trastornos tales como enfermedad pulmonar obstructiva crónica (incluyendo enfisema), síndrome de insuficiencia respiratoria agudo, asma, lesión alveolar hiperóxica y fibrosis pulmonar idiopática y otras enfermedades pulmonares fibróticas.

"Enfermedades cardiovasculares" como se usa en este documento se refiere a trastornos tales como aterosclerosis incluyendo ruptura de placa aterosclerótica; aneurisma aórtica incluyendo aneurisma aórtica abdominal y aneurisma aórtica cerebral; insuficiencia cardíaca congestiva; infarto de miocardio y cerebral; apoplejía; isquemia cerebral; coagulación y respuesta de fase aguda; dilación del ventrículo izquierdo; lesión por reperfusión post isquémica; angiofibromas; hemangiomas; y reestenosis.

"Enfermedades oculares" como se usa en este documento se refiere a trastornos tales como angiogénesis aberrante, angiogénesis ocular, inflamación ocular, keratoconus, síndrome de Sjogren, miopía, tumores oculares, rechazo del injerto de la cómea, lesión de la cómea, glaucoma neovascular, ulceración de la cómea, cicatrización de la cómea, degeneración macular (incluyendo "Degeneración Macular Relacionada con la Edad (ARMD) incluyendo tanto formas húmedas como secas), vitreoretinopatía proliferativa y retinopatía de premadurez.

"Enfermedades metabólicas" como se usa en este documento se refiere a trastornos tales como diabetes (incluyendo diabetes mellitus no dependiente de insulina, retinopatía diabética, resistencia a la insulina y ulceración diabética).

Trastornos del "sistema nervioso central" (SNC) como se usa en este documento se refiere a trastornos tales como traumatismo craneal, lesión de la médula espinal, enfermedades inflamatorias del sistema nervioso central, trastornos neurodegenerativos (agudos y crónicos), enfermedad de Alzheimer, enfermedades desmielinantes del sistema nervioso, enfermedad de Huntington, enfermedad de Parkinson, neuropatía periférica, dolor, angiopatía amiloide cerebral, aumento nootrópico o de la cognición, esclerosis lateral amiotrófica, esclerosis múltiple, migrañas, depresión y anorexia.

"Enfermedades hepáticas/renales" como se usa en este documento se refiere a trastornos tales como síndromes nefróticos tales como glomerulonefritis y enfermedad glomerular de riñón, proteinuria, cirrosis del hígado y nefritis intersticial.

"Trastornos reproductivos" como se usa en este documento se refiere a trastornos tales como endometriosis, anticoncepción (masculina/femenina), dismenorrea, sangrado uterino disfuncional, ruptura prematura de membranas fetales y aborto.

"Trastornos gástricos" como se usa en este documento se refiere a trastornos tales como anastomosis colónica y úlceras gástricas.

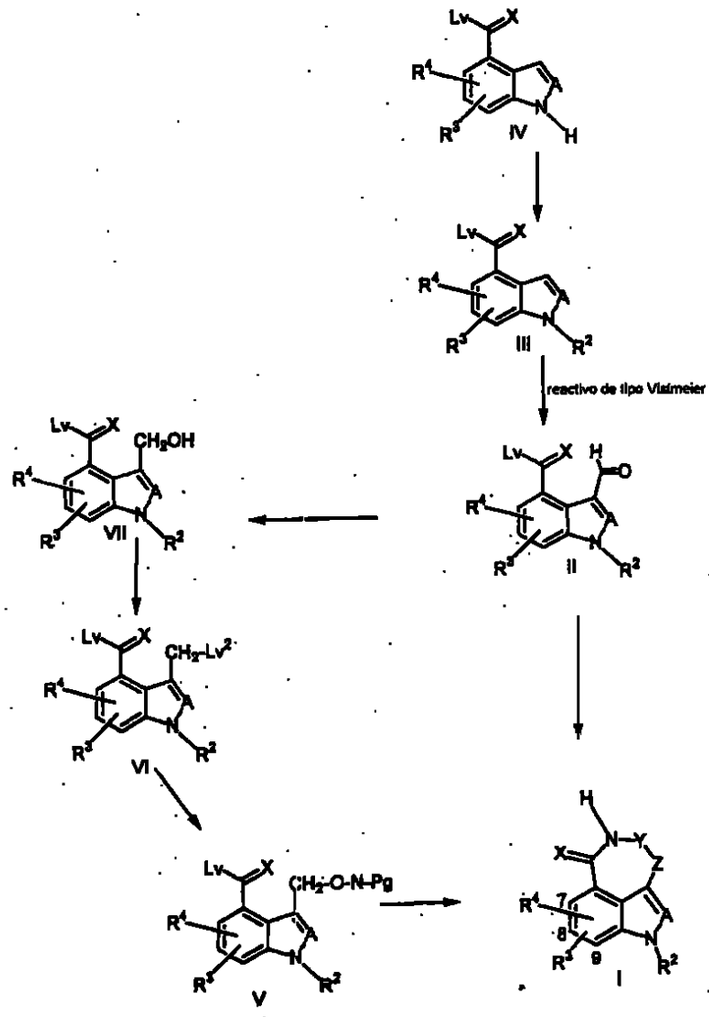
"Trastornos de la piel" como se usa en este documento se refiere a trastornos tales como envejecimiento de la piel, llagas por presión, psoriasis, eccema, dermatitis, lesión por radiación, ulceración de tejidos, úlceras por

decúbito, epidermolisis bulosa, curación anormal de heridas (formulaciones tópicas y orales), quemaduras y escleritis.

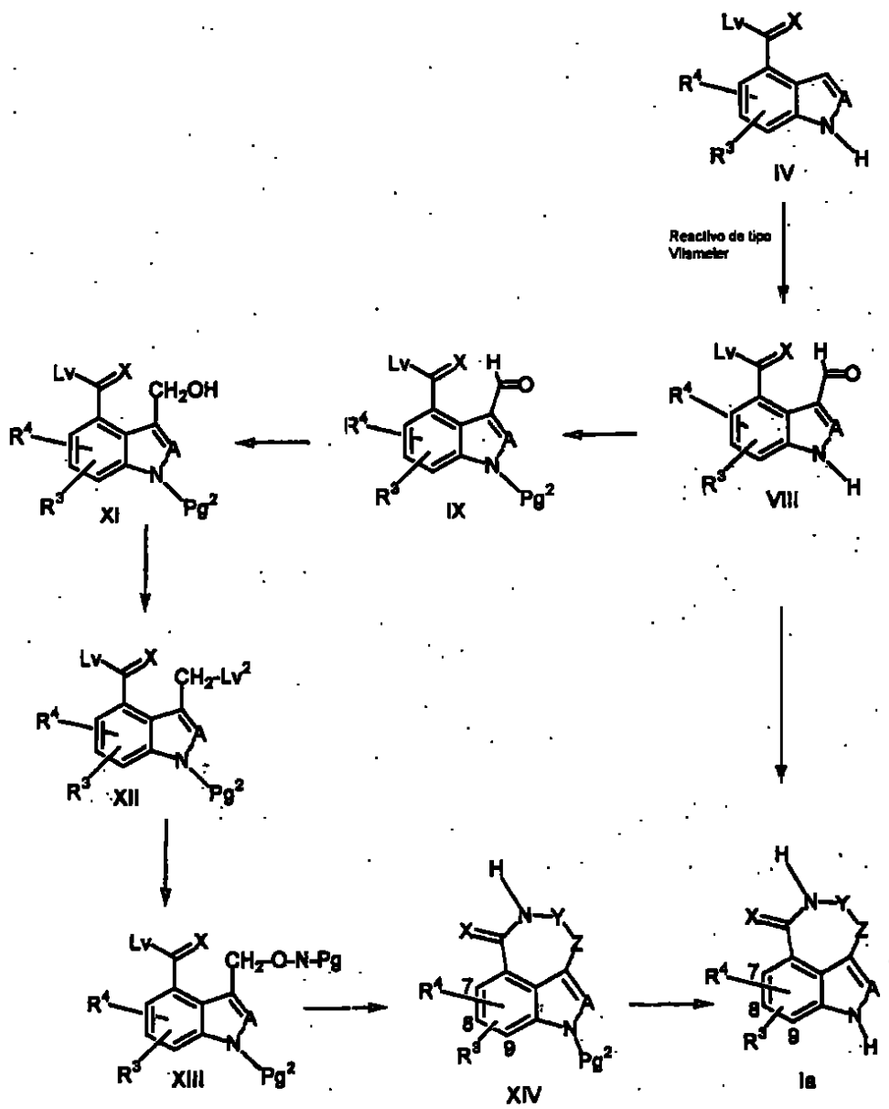
"Cánceres" como se usa en este documento se refiere a trastornos tales como cáncer de tumor sólido incluyendo cáncer de colon, cáncer de mama, cáncer de pulmón y cáncer de próstata, invasión tumoral, metástasis tumoral por crecimiento tumoral, cánceres de la cavidad oral y faringe (labio, lengua, boca, faringe), esófago, estómago, intestino delgado, intestino grueso, recto, conductos hepáticos y biliares, páncreas, laringe, pulmón, hueso, tejido conectivo, piel, cuello del útero, cuerpo uterino, endometrio, ovario, testículos, vejiga, riñón y otros tejidos urinarios, ojo, cerebro y sistema nervioso central, tiroides y otras glándulas endocrinas, enfermedad de Hodgkin, linfomas no Hodgkin, mieloma múltiple y cánceres hematopoyéticos incluyendo leucemias y linfomas incluyendo linfocítico, granulocítico y monocítico.

Los siguientes Esquemas de reacción ilustran la preparación de los compuestos de la presente invención. A menos que se indique otra cosa, cada uno de A, el grupo -Y-Z, X, R^1, R^2, R^3 y R^4 en los Esquemas de reacción y en el análisis que se muestra más adelante se definen como anteriormente.

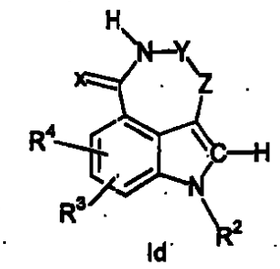
ESQUEMA 1



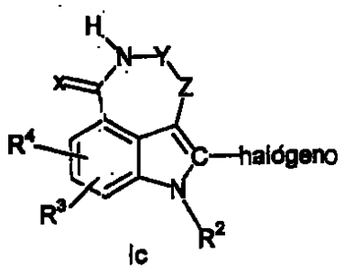
ESQUEMA 2


Lv
X
R4
R3
A
N
H
IV
Reactivo de tipo Vilsmeier
H
O
VIII
IX
CH2OH
XI
CH2-Lv2
XII
CH2-O-N-Pg
XIII
Pg2
XIV
Y
Z
7
8
9
Ia

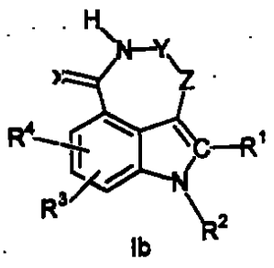
ESQUEMA 3



Id

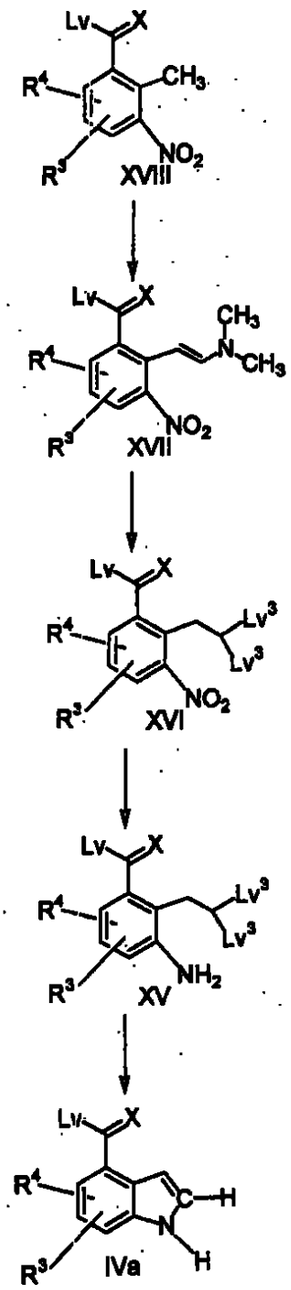


Ic

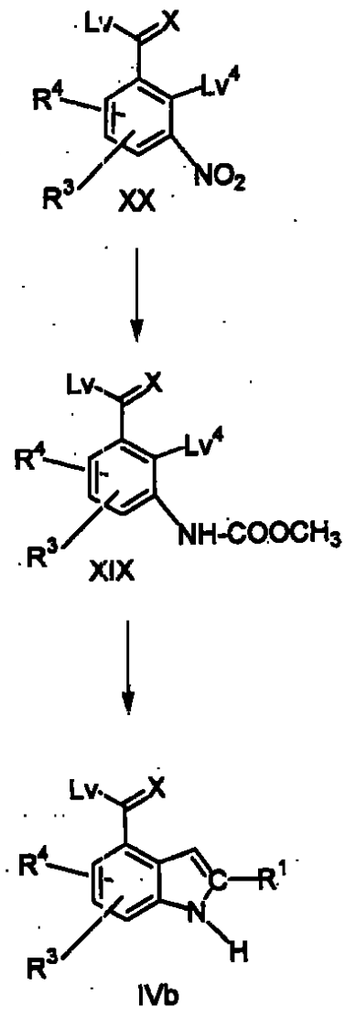


Ib

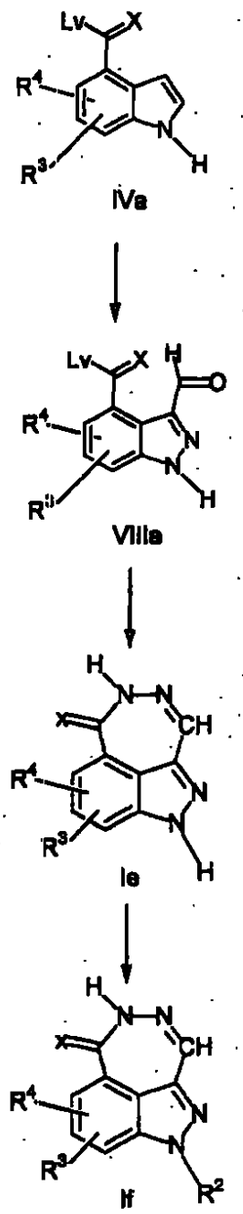
ESQUEMA 4



ESQUEMA 5


Lv
X
R4
Lv4
NO2
R3
XX
Lv
X
R4
Lv4
NH-COOCH3
R3
XIX
Lv
X
R4
C
R1
N
H
R3
IVb

ESQUEMA 6



El Esquema 1 se refiere a la preparación de compuestos de fórmula I. Con respecto al Esquema 1, un compuesto de fórmula I, en la que el grupo -Y-Z- tiene la fórmula -N=CH- y R^2 es diferente de hidrógeno, puede prepararse

haciendo reaccionar un compuesto de fórmula II, en la que R^2 es distinto de hidrógeno y en la que Lv es un grupo saliente, con hidrazina en un disolvente. Los grupos salientes Lv adecuados incluyen metoxi, etoxi o benciloxi, preferiblemente metoxi. Los disolventes adecuados incluyen alcoholes (tales como etanol), preferiblemente metanol. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 25°C a aproximadamente 90°C, preferiblemente a aproximadamente 65°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 0,5 horas.

Los compuestos de fórmula II, en la que R^2 es distinto de hidrógeno y en la que Lv es como se ha descrito anteriormente, pueden prepararse haciendo reaccionar un compuesto de fórmula III, en la que R^2 es distinto de hidrógeno y en la que Lv es como se ha descrito anteriormente, con un reactivo formilante de tipo Vilsmeier en un disolvente. Los reactivos formilantes de tipo Vilsmeier adecuados incluyen $POCl_3$ y DMF o $(CF_3SO_2)_2O$ y DMF; preferiblemente $POCl_3$ y DMF. Los disolventes adecuados incluyen cloroformo, dioxano, tetrahidrofurano, dimetilformamida o cloruro de metileno; preferiblemente cloruro de metileno. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 25°C, preferiblemente a aproximadamente 0°C durante la adición del reactivo dejando después calentar la mezcla de reacción a 23°C durante aproximadamente 0,5 horas. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 0,5 horas.

Los compuestos de fórmula III, en la que R^2 es distinto de hidrógeno y en la que Lv es como se ha descrito anteriormente, pueden prepararse haciendo reaccionar un compuesto de fórmula IV, en la que Lv es como se ha descrito anteriormente, con un compuesto de fórmula:

R^2-Lv^1

en la que Lv^1 es un grupo saliente, tal como halo, preferiblemente bromo o cloro, en presencia de una base adecuada en un disolvente polar. Las bases adecuadas incluyen bases de alcóxido (tales como metóxido sódico, etóxido sódico o *terc*-butóxido potásico); bases de hidruro (tales como hidruro sódico); o bases de carbonato (tales como carbonato potásico o carbonato de cesio); preferiblemente carbonato potásico. Los disolventes polares adecuados incluyen tetrahidrofurano, dimetilformamida, dimetilsulfóxido o alcoholes (tales como etanol), preferiblemente dimetilformamida. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 100°C, preferiblemente a aproximadamente 80°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 0,5 horas a aproximadamente 72 horas, preferiblemente aproximadamente 24 horas.

Un compuesto de fórmula I, en la que el grupo -Y-Z- es -O-CH_2- y en la que R^2 es distinto de hidrógeno, puede prepararse haciendo reaccionar un compuesto de fórmula V, en la que R^2 es distinto de hidrógeno, donde Pg es un grupo protector y Lv es como se ha descrito anteriormente, con un agente de desprotección de Pg. El Pg adecuado incluye ftaloílo, *terc*-butoxicarbonilo, benciloxicarbonilo o etoxicarbonilo; preferiblemente ftaloilo. Los agentes de desprotección de Pg incluyen hidrazina, ácido trifluoroacético, ácido clorhídrico,

cloruro de hidrógeno, bromuro de hidrógeno en ácido acético o gas hidrógeno y catalizador de Pd; preferiblemente hidrazina. Las reacciones ácidas pueden neutralizarse después de la desprotección con una base adecuada incluyendo aminas terciarias (tales como trietilamina o diisopropiletilamina) o bases carbonato (tales como carbonato potásico); preferiblemente trietilamina. Los disolventes adecuados incluyen dimetilformamida, cloruro de metileno, cloroformo o alcohol, (tales como metanol), preferiblemente metanol. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 20°C a aproximadamente 130°C, preferiblemente a aproximadamente 65°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 0,5 horas a aproximadamente 48 horas, preferiblemente durante aproximadamente 2 horas.

Un compuesto de fórmula V, en la que R^2 es distinto de hidrógeno, donde Pg es un grupo protector y Lv es como se ha descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula VI, en la que R^2 es distinto de hidrógeno, Lv^2 es un grupo saliente y Lv es como se ha descrito anteriormente, con un compuesto de fórmula

Pg-N-OH

en presencia de una base en un disolvente. Los grupos salientes Lv^2 adecuados incluyen halo, toluenosulfonilo, metanosulfonilo, trifluorometanosulfonilo o aductos de reacción de tipo Mitsunobu. Los compuestos adecuados de fórmula Pg-N-OH incluyen *N*-hidroxiftalimida, *N*-hidroxilcarbamato de *terc*-butilo, *N*-hidroxiuretano o *N*-hidroxicarbamato de bencilo. Las bases adecuadas incluyen hidruro sódico, 1,8-

diazabiciclo[5.4.0]undec-7-eno, piridina, aminas terciarias (tales como diisopropiletilamina o trietilamina) o bases carbonato (tales como carbonato sódico); preferiblemente carbonato sódico. Los disolventes adecuados incluyen dimetilformamida, dimetilsulfóxido, tetrahidrofurano, cloruro de metileno, cloroformo o alcohol (tales como metanol); preferiblemente dimetilsulfóxido. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente -25°C a aproximadamente 80°C, preferiblemente a aproximadamente 23°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 48 horas, preferiblemente aproximadamente 20 horas.

Un compuesto de fórmula VI, en la que R^2 es distinto de hidrógeno y Lv^2 y Lv son como se han descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula VII, en la que R^2 es distinto de hidrógeno y Lv es como se ha descrito anteriormente, con un agente productor de Lv^2, en un disolvente. Los agentes productores de Lv^2 adecuados incluyen $(C_6H_5)_3P$ y CCl_4; $(C_6H_5)_3P$ y PBr_3; *para*-$CH_3C_6H_4SO_2Cl$; CH_3SO_2Cl; $(CF_3SO_2)_2O$; o reactivos de tipo Mitsunobu (tales como dietilazodicarboxilato y $(C_6H_5)_3P$); preferiblemente $(C_6H_5)_3P$ y CCl_4. Los disolventes adecuados incluyen cloruro de metileno, cloroformo, tetrahidrofurano, tetracloruro de carbono, benceno o tolueno; preferiblemente cloruro de metileno. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente -25°C a aproximadamente 80°C, preferiblemente a aproximadamente 23°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 20 horas.

Un compuesto de fórmula VII, en la que R^2 es distinto de hidrógeno y Lv es como se ha descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula II, en la que R^2 es distinto de hidrógeno y Lv es como se ha descrito anteriormente, con un agente reductor en un disolvente. Los agentes reductores adecuados incluyen borohidruro sódico, borohidruro de litio, borohidruro de cinc, diborano, complejos de borano, triacetoxiborohidruro, cianoborohidruro sódico o cianoborohidruro de litio; preferiblemente borohidruro sódico. Los disolventes adecuados incluyen alcohol (tal como metanol), tetrahidrofurano, una mezcla de metanol y HCl anhidro o una mezcla de metanol y ácido acético; preferiblemente metanol. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 50°C, preferiblemente a aproximadamente 23°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 15 minutos.

El Esquema 2 se refiere a la preparación de compuestos de fórmula Ia, que es un compuesto de fórmula I en la que R^2 es hidrógeno. Con respecto al Esquema 2, un compuesto de fórmula Ia, en la que el grupo -Y-Z- tiene la fórmula -N=CH-, puede prepararse haciendo reaccionar un compuesto de fórmula VIII, en la que Lv es un grupo saliente, como se ha descrito anteriormente, con hidrazina en un disolvente. La condición de reacción es como se ha descrito anteriormente en la descripción del Esquema 1 para la preparación de un compuesto de fórmula I a partir de un compuesto de fórmula II.

Los compuestos de fórmula VIII, en la que Lv es como se ha descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula IV, en la que Lv es como se ha descrito anteriormente, con un reactivo de Vilsmeier en un disolvente. La condición de reacción es como se ha descrito anteriormente en la descripción para el Esquema 1 para la preparación de compuestos de fórmula II a partir de un compuesto de fórmula III.

Un compuesto de fórmula Ia, en la que el grupo -Y-Z- es $-O-CH_2-$, puede prepararse haciendo reaccionar un compuesto de fórmula XIV, en la que Pg^2 es un grupo protector, con un agente de desprotección de Pg^2 en un disolvente. Los grupos protectores de Pg^2 incluyen *terc*-butoxicarbonilo, benciloxicarbonilo o 2-(trimetilsilil)etoximetilo; preferiblemente *terc*-butoxicarbonilo. Los agentes de desprotección de Pg^2 adecuados incluyen ácido trifluoroacético, ácido clorhídrico, cloruro de hidrógeno, bromuro de hidrógeno en ácido acético, gas hidrógeno y catalizador de Pd o fluoruro de tetrabutilamonio; preferiblemente ácido trifluoroacético. Los disolventes adecuados incluyen cloruro de metileno, cloroformo, dioxano, dimetilformamida o alcohol (tal como metanol); preferiblemente cloruro de metileno. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 20°C a aproximadamente 80°C, preferiblemente a aproximadamente 23°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 15 minutos a aproximadamente 48 horas, preferiblemente aproximadamente 2 horas.

Un compuesto de fórmula XIV, en la que Pg^2 es como se ha descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula XIII, en la que Pg es un grupo protector como se ha descrito en el

compuesto de fórmula V del Esquema 1, y Pg^2 y Lv son como se han descrito anteriormente, con un agente de desprotección de Pg. La condición de reacción es como se ha descrito anteriormente en la descripción para el Esquema 1 para la preparación de un compuesto de fórmula I a partir de un compuesto de fórmula V.

Un compuesto de fórmula XIII, en la que Pg^2, Lv y Lv^2 son como se han descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula XII, en la que Pg^2, Lv y Lv^2 son como se han descrito anteriormente, con un compuesto de fórmula

Pg-N-OH

en la que Pg es como se ha descrito anteriormente, en presencia de una base en un disolvente. La condición de reacción es como se ha descrito anteriormente en la descripción para el Esquema 1 para la preparación de un compuesto de fórmula V a partir de un compuesto de fórmula VI.

Un compuesto de fórmula XII, en la que Pg^2, Lv^2 y Lv son como se han descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula XI, en la que Pg^2 y Lv son como se han descrito anteriormente, con un agente productor de Lv^2, en un disolvente. La condición de reacción es como se ha descrito anteriormente en la descripción para el Esquema 1 para la preparación de un compuesto de fórmula VI a partir de un compuesto de fórmula VII.

Un compuesto de fórmula XI, en la que Pg^2 y Lv son como se han descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula IX, en la que Pg^2 y Lv son como se han descrito anteriormente, con un agente reductor en un disolvente. La condición de reacción es como se ha

descrito anteriormente en la descripción para el Esquema 1 para la preparación de un compuesto de fórmula VII a partir de un compuesto de fórmula II.

Un compuesto de fórmula IX, en la que Pg^2 y Lv son como se han descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula VIII, en la que Lv es como se ha descrito anteriormente, con un agente protector de Pg^2 en presencia de una base adecuada en un disolvente. Los agentes protectores de Pg^2 adecuados incluyen dicarbonato de di-*terc*-butilo, cloroformiato de bencilo o cloruro de 2-(trimetilsilil)etoximetilo; preferiblemente dicarbonato de di-*terc*-butilo. Las bases adecuadas incluyen bases hidruro (tales como hidruro sódico, hidruro de litio o hidruro potásico); preferiblemente hidruro sódico. Los disolventes adecuados incluyen tetrahidrofurano o dimetilformamida; preferiblemente tetrahidrofurano. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 60°C, preferiblemente a aproximadamente 23°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 15 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 1 hora.

El Esquema 3 se refiere a la preparación de un compuesto de fórmula Ib, que es un compuesto de fórmula I en la que A es $=CR^1-$. Con respecto al Esquema 3, un compuesto de fórmula Ib, puede prepararse haciendo reaccionar un compuesto de fórmula Ic, donde el halógeno se selecciona entre bromo o yodo, con un agente de acoplamiento de fórmula:

R^1-M

en la que M es un H o metal, en presencia de catalizadores de paladio y cobre en un disolvente. Los metales adecuados incluyen boro y estaño,

preferiblemente boro. Los reactivos de acoplamiento adecuados incluyen reactivo de acoplamiento de Stille (véase Chamoin, S., Houldsworth, S., Snieckus, V. *Tetrahedron Lett.* 1998, *39*, 4175-4178 incorporado en este documento como referencia), reactivo de acoplamiento de Suzuki (véase Littke, A.F., Chaoyang, D., Fu, G. C. *J. Am. Chem. Soc.* 2000, 122, 4020-4028 incorporado en este documento como referencia) o reactivo de acoplamiento de Sonogashira (véase Sonogashira, K., Tohda, Y., Hagihara, N. *Tetrahedron Lett.* 1975, *16*, 44467-4470 incorporado en este documento como referencia); preferiblemente reactivo de acoplamiento de Suzuki o reactivo de acoplamiento de Stille. Los catalizadores de paladio y cobre adecuados incluyen $Pd(C_6H_5)_3P)_4$, $Pd(dba)_2$, $Pd(P(C_6H_5)_3)Cl_2$ y CuI. Los disolventes adecuados incluyen dimetilformamida o tetrahidrofurano; preferiblemente dimetilformamida. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 22°C a aproximadamente 110°C, preferiblemente a aproximadamente 90°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 48 horas, preferiblemente aproximadamente 2 horas.

Algunos compuestos de fórmula Ib, tales como aquellos en los que R^1 es un alquino sustituido (por ejemplo metilaminopropinilo) pueden necesitar etapas adicionales que requieren el uso de un grupo protector (por ejemplo *terc*-butoxicarbonilo). Estos grupos de protección y sus procedimientos de retirada se conocen bien en la técnica y pueden encontrarse en Greene y Wuts, "Protecting Groups in Organic Synthesis," (John Wiley and Sons, 2ª Ed.). Además, los compuestos de fórmula Ib, tales como aquellos en los que R^1, R^2 o R^3 es un alquilo sustituido, alquinilo, aromático o vinilo se someten a más

transformaciones químicas convencionales (por ejemplo hidrogenación catalítica, OsO_4/NMMO/$NaIO_4$, escisión oxidativa, mesilación/desplazamiento, reducciones y aminación reductora). Estos procedimientos también se conocen bien en la técnica y pueden encontrarse en Larock, R.C., "Comprehensive Organic Transformations" (Wiley-VCH, 2ª Ed.).

Un compuesto de fórmula Ib, en la que A es $=CR^1-$ y R^1 es -(C=O)-O-alquilo (C_1-C_6), puede prepararse haciendo reaccionar un compuesto de fórmula Ic, en la que el halógeno se selecciona entre bromo o yodo, con monóxido de carbono en presencia de un catalizador de paladio, una base y un compuesto de fórmula H-O-alquilo (C_1-C_6) (dependiendo de la parte alquilo (C_1-C_6) del R^1 deseado) en un disolvente. Los catalizadores de paladio adecuados incluyen $Pd(dppf)Cl_2$. Las bases adecuadas incluyen bases de amina terciaria tales como trietilamina. Los compuestos adecuados de fórmula H-O-alquilo (C_1-C_6) incluyen metanol, etanol o propanol. Los disolventes adecuados incluyen dimetilformamida o tetrahidrofurano; preferiblemente dimetilformamida. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 22°C a aproximadamente 110°C, preferiblemente a aproximadamente 85°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 30 minutos a aproximadamente 48 horas, preferiblemente aproximadamente 16 horas.

Un compuesto de fórmula Ib, en la que A es $=CR^1-$ y R^1 es -(C=O)-NH-alquilo (C_1-C_6) o (C=O)-NH-alquil (C_1-C_6)-OH o -(C=O)-NH-alquil (C_1-C_6)-$N(CH_3)_2$ o -(C=O)-1-(4-*N*-metilpiperazina) puede prepararse haciendo reaccionar un compuesto de fórmula Ic, en la que el halógeno se selecciona entre bromo o yodo, con monóxido de carbono en presencia de un catalizador

de paladio, una base y un compuesto de fórmula H_2N-alquilo (C_1-C_6) o H_2N-alquil (C_1-C_6)-OH o H_2N-alquil (C_1-C_6)-$N(CH_3)_2$ o *N*-metilpiperazina (dependiendo de la parte alquilo (C_1-C_6) del R^1 deseado) en un disolvente. Los catalizadores de paladio adecuados incluyen $Pd(dppf)Cl_2$. Las bases adecuadas incluyen bases de amina terciaria tales como trietilamina. Los compuestos adecuados de fórmulas H_2N-alquilo (C_1-C_6) o H_2N-alquil (C_1-C_6)-OH o H_2N-alquil (C_1-C_6)-$N(CH_3)_2$ o *N*-metilpiperazina incluyen 2-aminoetanol, *N,N*-dimetiletilendiamina, metilamina *N*-metilpiperazina. Los disolventes adecuados incluyen dimetilformamida o tolueno; preferiblemente dimetilformamida. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 22°C a aproximadamente 110°C, preferiblemente a aproximadamente 85°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 30 minutos a aproximadamente 48 horas, preferiblemente aproximadamente 16 horas.

Un compuesto de fórmula Ic, en la que el halógeno es bromo o yodo, puede prepararse haciendo reaccionar un compuesto de fórmula Id con un agente de halogenación adecuado en un disolvente. Los agentes de halogenación adecuados incluyen *N*-bromosuccinimida o *N*-yodosuccinimida; preferiblemente *N*-bromosuccinimida. Los disolventes adecuados incluyen tetrahidrofurano o dimetilformamida, preferiblemente dimetilformamida. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 75°C, preferiblemente a aproximadamente 22°C. La reacción mencionada anteriormente puede

realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 1 hora.

Un compuesto de fórmula Ic, en la que el halógeno es cloro, puede prepararse haciendo reaccionar un compuesto de fórmula Id con un agente de cloración adecuado en un disolvente. Los agentes de cloración adecuados incluyen *N*-clorosuccinimida. Los disolventes adecuados incluyen tetrahidrofurano o dimetilformamida; preferiblemente dimetilformamida. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 75°C, preferiblemente a aproximadamente 45°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 1 hora.

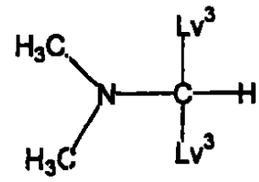
El Esquema 4 se refiere a la preparación de un compuesto de fórmula IVa, que es un compuesto de fórmula IV del Esquema 1, donde A es =CH-. Con respecto al Esquema 4, un compuesto de fórmula IVa, en la que Lv es como se ha descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula XV, en la que Lv es como se ha descrito anteriormente y cada uno de Lv^3 es un grupo saliente, con un ácido adecuado en un disolvente prótico polar (véase Coe, J. W., Vetelino, M.G., Bradlee, M. J. *Tetrahedron Lett.* 1996, *37*, 6045-6047 incorporado en este documento como referencia). Los grupos salientes Lv^3 adecuados incluyen metoxi o etoxi, preferiblemente metoxi. Los ácidos adecuados incluyen HCl, H_2SO_4, ácido *para*-toluenosulfónico, ácido canforsulfónico o ácidos de Lewis; preferiblemente HCl. Los disolventes próticos polares adecuados incluyen alcoholes (tales como metanol o etanol), preferiblemente metanol. La reacción mencionada

anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 100°C, preferiblemente a aproximadamente 65°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 1 hora.

Un compuesto de fórmula XV, en la que Lv y Lv^3 son como se han descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula XVI, en la que Lv y Lv^3 son como se han descrito anteriormente, con un agente reductor en un disolvente polar. Los agentes reductores adecuados incluyen reactivos de transferencia catalítica tales como hidrazina hidrato, formiato amónico, cloruro amónico, ciclohexeno o gas hidrógeno en presencia de catalizadores [tales como Pd sobre carbono (véase Coe, J. W., Vetelino, M. G., Bradlee, M. J. *Tetrahedron Lett.* 1996, *37*, 6045-6047 incorporado en este documento como referencia), Ru, Rh, níquel Raney o Pt]; HCl o ácido acético en presencia de In, Fe, Sn o Zn; $HCl/SnCl_2$; $SnCl_2.2H_2O$; $Bu_3SnH/AIBN$; o $Fe_3(CO)_{12}$; preferiblemente $SnCl_2.2H_2O$ o gas hidrógeno en presencia de Pd sobre carbono o níquel Raney. Los disolventes polares adecuados incluyen alcoholes (tales como metanol o etanol), preferiblemente metanol. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 100°C, preferiblemente a aproximadamente 23°C. Cuando se usa gas hidrógeno, la presión de la reacción puede ser de 1 a 4 atm (de 101,325 kPa a 405,3 kPa), preferiblemente 1 atm (101,325 kPa). La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 2 horas a aproximadamente 48 horas, preferiblemente aproximadamente 24 horas.

Un compuesto de fórmula XVI, en la que Lv y Lv^3 son como se han descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula XVII, en la que Lv es como se ha descrito anteriormente, con un ácido adecuado en un disolvente prótico polar anhidro de fórmula Lv^3-H. Los ácidos adecuados incluyen HCl, H_2SO_4 o ácido *para*-toluenosulfónico, preferiblemente HCl. Como alternativa, puede generarse *in situ* usando un agente generador de HCl tal como TMS-Cl o cloruro de acetilo, preferiblemente TMS-Cl, en un disolvente prótico polar anhidro tal como metanol. Los disolventes próticos polares anhidros adecuados de fórmula Lv^3-H incluyen alcoholes anhidros (tales como metanol o etanol), preferiblemente metanol anhidro. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 23°C a aproximadamente 78°C, preferiblemente a aproximadamente 65°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 30 minutos a aproximadamente 48 horas, preferiblemente aproximadamente 24 horas.

Un compuesto de fórmula XVII, en la que Lv es como se ha descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula XVIII, en la que Lv es como se ha descrito anteriormente, con un compuesto de fórmula



en la que cada uno de Lv^3 es como se ha descrito anteriormente, en un disolvente polar. Los compuestos adecuados de fórmula $(CH_3)_2$-N-CH-$(Lv^3)_2$

incluyen dimetilformamida-dimetilacetal. Los disolventes polares adecuados incluyen dimetilformamida, tolueno o alcohol (tal como etanol), preferiblemente dimetilformamida. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 22°C a aproximadamente 150°C, preferiblemente a aproximadamente 110°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 15 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 6 horas.

Los compuestos de fórmula $(CH_3)_2$-N-CH-$(Lv^3)_2$ están disponibles en el mercado.

Los compuestos de fórmula XVII, en la que Lv es como se ha descrito anteriormente, están disponibles en el mercado o como alternativa pueden fabricarse mediante procedimientos bien conocidos para los especialistas en la técnica.

El Esquema 5 se refiere a la preparación de un compuesto de fórmula IVb, que es un compuesto de fórmula IV del Esquema 1, en la que A es $=CR^1$-. Con respecto al Esquema 5, un compuesto de fórmula IVb puede prepararse haciendo reaccionar un compuesto de fórmula XIX, en la que Lv es como se ha descrito anteriormente y Lv^4 es un grupo saliente, con un alquino sustituido adecuado de fórmula

M^1-C≡C-R^1

en la que M^1 es H o metal (tal como Sn o B), preferiblemente H o Sn, en presencia de un catalizador metálico en un disolvente polar. Los grupos salientes Lv^4 adecuados incluyen halo, preferiblemente bromo o yodo. Los catalizadores metálicos adecuados incluyen catalizadores de paladio o cobre

(véase Fagnola, M. C. y col. *Tetrahedron Lett.* **1997**, 38, 2307-2310 incorporado en este documento como referencia). Los disolventes polares adecuados incluyen dimetilformamida, dioxano, dimetilsulfóxido o mezclas de los mismos, preferiblemente una mezcla de dimetilformamida y dioxano. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 22°C a aproximadamente 120°C, preferiblemente a aproximadamente 90°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 8 horas.

Los compuestos de fórmula M^1-C≡C-R^1 están disponibles en el mercado o pueden fabricarse mediante procedimientos bien conocidos para los especialistas en la técnica.

Un compuesto de fórmula XIX, en la que Lv y Lv^4 son como se han descrito anteriormente, puede prepararse haciendo reaccionar un compuesto de fórmula XX, en la que Lv y Lv^4 son como se han descrito anteriormente, con un agente reductor en presencia de $(CH_3CO)_2O$ en un disolvente polar. Los agentes reductores adecuados incluyen gas hidrógeno en presencia de catalizadores tales como Pd/C (véase Coe, J. W., Vetelino, M. G., Bradlee, M. J. *Tetrahedron Lett.* 1996, *37*, 6045-6047 incorporado en este documento como referencia), Rd, níquel Raney o Pt; ácido acético en presencia de In, Fe o Zn; $SnCl_2$; o $Fe_3(CO)_{12}$; preferiblemente gas hidrógeno en presencia de Pd/C; o ácido acético en presencia de Fe. Los disolventes polares adecuados incluyen dimetilformamida, metanol, etanol o ácido acético; preferiblemente metanol o ácido acético. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 20°C a aproximadamente 100°C,

preferiblemente a aproximadamente 22°C. Cuando se usa gas hidrógeno, la presión de la reacción puede ser de 1 a 4 atm (de 101,325 a 405,3 kPa), preferiblemente 1 atm (101,325 kPa). La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 2 horas a aproximadamente 48 horas, preferiblemente aproximadamente 24 horas.

Los compuestos de fórmula XX están disponibles en el mercado o pueden fabricarse mediante procedimientos bien conocidos para los especialistas en la técnica.

El Esquema 6 se refiere a la preparación de un compuesto de fórmula If, que es un compuesto de fórmula I del Esquema 1, donde el grupo -Y-Z- tiene la fórmula -N=CH-, A es =N- y R^2 es distinto de hidrógeno. Con respecto al Esquema 6, un compuesto de fórmula If puede prepararse haciendo reaccionar un compuesto de fórmula Ie, que es un compuesto de fórmula I del Esquema 1, donde el grupo -Y-Z- tiene la fórmula -N=CH-, A es =N- y R^2 es hidrógeno, con un compuesto de fórmula

R^2-Lv^1

en la que Lv^1 es un grupo saliente, tal como halo, preferiblemente bromo o cloro, en presencia de una base adecuada en un disolvente polar. La condición de reacción es como se ha descrito anteriormente en la descripción para el Esquema 1 para la preparación de compuestos de fórmula III a partir de un compuesto de fórmula IV.

Los compuestos de fórmula Ie pueden prepararse haciendo reaccionar un compuesto de fórmula VIIIa, que es un compuesto de fórmula VIII del Esquema 2, donde A es =N- y Lv es como se ha descrito anteriormente, con hidrazina en un disolvente. La condición de reacción es como se ha descrito

anteriormente en la descripción para el Esquema 1 para la preparación de un compuesto de fórmula I a partir de un compuesto de fórmula II.

Los compuestos de fórmula VIIIa pueden prepararse haciendo reaccionar un compuesto de fórmula IVa, que es un producto del Esquema 4, con un agente productor de ácido nitroso en presencia de un ácido en un disolvente. Los agentes productores de ácido nitroso adecuados incluyen $NaNO_2$, KNO_2, nitrito de isoamilo o nitrito de *terc*-butilo; preferiblemente $NaNO_2$. Los ácidos adecuados incluyen ácido acético o HCl acuoso; preferiblemente ácido acético. Los disolventes adecuados incluyen ácido acético, benceno, dimetilformamida, tolueno o alcoholes (tales como metanol), preferiblemente ácido acético. La reacción mencionada anteriormente puede realizarse a una temperatura de aproximadamente 0°C a aproximadamente 30°C, preferiblemente a aproximadamente 0°C calentando a 23°C. La reacción mencionada anteriormente puede realizarse durante un período de tiempo de aproximadamente 5 minutos a aproximadamente 24 horas, preferiblemente aproximadamente 1 hora.

Dentro de la invención se entiende que un compuesto de Fórmula I puede mostrar el fenómeno de tautomería y que los dibujos de las fórmulas en esta memoria descriptiva sólo representan una de las posibles formas tautoméricas. Se entenderá que la invención abarca cualquier forma tautomérica que module y/o inhiba la actividad de quinasa y no se limitará meramente a una forma cualquiera tautomérica utilizada en los dibujos de las fórmulas.

Algunos de los compuestos de la invención pueden existir en forma de estereoisómeros unitarios (es decir, esencialmente libres de otros

estereosiómeros), racematos y/o mezclas de enantiómeros y/o diastereómeros. Todos estos estereoisómeros unitarios, racematos y mezclas de los mismos pretenden incluirse dentro del alcance de la presente invención. Preferiblemente, los compuestos de la invención que son ópticamente activos se usan en forma ópticamente pura.

Como se entiende generalmente por parte de los especialistas en la técnica, un compuesto ópticamente puro que tiene un centro quiral (es decir, un átomo de carbono asimétrico) es aquel que consta esencialmente de uno de los dos posibles enantiómeros (es decir, es enantioméricamente puro), y un compuesto ópticamente puro que tiene más de un centro quiral es aquel que es tanto diastereoméricamente puro como enantioméricamente puro. Preferiblemente, los compuestos de la presente invención se usan en una forma que es al menos ópticamente pura al 90%, es decir, una forma que contiene al menos un 90% de un único isómero (exceso enantiomérico del 80% ("e. e.")) o exceso diastereomérico ("d. e.")), más preferiblemente al menos el 95% (e.e. o d.e. del 90%), aún más preferiblemente al menos el 97,5% (e.e. o d.e. del 95%) y aún más preferiblemente al menos el 99% (e.e. o d.e. del 98%).

Además, la Fórmula I pretende cubrir las formas solvatadas así como las no solvatadas de las estructuras identificadas. Por ejemplo, la Fórmula I incluye compuestos de la estructura indicada en formas tanto hidratadas como no hidratadas. Otros ejemplos de solvatos incluyen las estructuras en combinación con isopropanol, etanol, metanol, DMSO, acetato de etilo, ácido acético o etanolamina.

Si el compuesto de la invención es una base, la sal farmacéuticamente aceptable deseada puede prepararse mediante cualquier procedimiento

adecuado disponible en la técnica, por ejemplo, tratamiento de la base libre con un ácido inorgánico, tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares, o con un ácido orgánico, tal como ácido acético, ácido maleico, ácido succínico, ácido mandélico, ácido fumárico, ácido malónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, un ácido de piranosidilo, tal como ácido glucurónico o ácido galacturónico, un ácido alfa-hidroxi, tal como ácido cítrico o ácido tartárico, un aminoácido, tal como ácido aspártico o ácido glutámico, un ácido aromático, tal como ácido benzoico o ácido cinnámico, un ácido sulfónico, tal como ácido *p*-toluenosulfónico o ácido etanosulfónico, y similares.

Si el compuesto de la invención es un ácido, la sal farmacéuticamente aceptable deseada puede prepararse mediante cualquier procedimiento adecuado, por ejemplo, tratamiento del ácido libre con una base inorgánica u orgánica, tal como una amina (primaria, secundaria o terciaria), un hidróxido de metal alcalino o hidróxido de metal alcalinotérreo, o similares. Los ejemplos ilustrativos de sales adecuadas incluyen sales orgánicas derivadas de aminoácidos, tales como glicina y arginina, amoniaco, aminas primarias, secundarias y terciarias y aminas cíclicas, tales como piperidina, morfolina y piperazina, y sales inorgánicas derivadas de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, cinc, aluminio y litio.

En el caso de agentes que son sólidos, se entiende por parte de los especialistas en la técnica que los compuestos y sales de la invención pueden existir en diferentes formas cristalinas o polimórficas, todas las cuales se pretende que estén dentro del alcance de la presente invención y de las fórmulas específicas.

Las sales farmacéuticamente aceptables del compuesto de Fórmula I también pueden existir en diversos solvatos, tales como con agua, metanol, etanol, dimetilformamida, acetato de etilo y similares. También pueden prepararse mezclas de tales solvatos. La fuente de tal solvato puede ser del disolvente de cristalización, inherente en el disolvente de preparación o cristalización o adventicio a tal disolvente.

El compuesto de Fórmula I puede usarse en combinación con terapias antineoplasma convencionales para tratar mamíferos, especialmente seres humanos, con neoplasia. Los procedimientos para terapias anti-neoplasma convencionales, incluyendo quimioterapias que usan agentes anti-neoplásicos y radiación terapéutica, están fácilmente disponibles, y se practican normalmente en la técnica, por ejemplo, véase Harrison's PRINCIPLES OF INTERNAL MEDICINE 11ª edición, McGraw-Hill Book Company.

La neoplasia se caracteriza por un crecimiento anormal de las células que normalmente da como resultado la invasión de tejidos normales, por ejemplo, tumores primarios o la propagación a órganos distantes, por ejemplo, metástasis. El tratamiento de cualquier neoplasia mediante terapias convencionales anti-neoplasma no quirúrgicas puede mejorarse mediante la presente invención. Tal crecimiento neoplásico incluye pero sin limitación tumores primarios, tumores primarios que se retiran de manera incompleta mediante técnicas quirúrgicas, tumores primarios que se han tratado adecuadamente pero que tienen un alto riesgo de desarrollar posteriormente una enfermedad metastásica, y una enfermedad metastásica establecida.

Específicamente, el inhibidor de CHK-1 de Fórmula I anterior puede mejorar los efectos anti-neoplasma de una gente anti-neoplásico. Para la

terapia de combinación de acuerdo con al presente invención se contempla la gran variedad de agentes anti-neoplásicos disponibles. En una realización preferida, los agentes anti-neoplásicos que imponen sus efectos citotóxicos activando la muerte celular programada o la apoptosis pueden usarse en combinación con el inhibidor de CHK-1 descrito. Los agentes anti-neoplásicos contemplados de acuerdo con la presente invención incluyen, pero sin limitación, agentes alquilantes, incluyendo bisulfano, clorambucil, ciclofosfamida, ifosfamida, melfalan, mostaza de nitrógeno, estreptozocina, tiotepa, mostaza nitrogenada de uracilo, trietilenomelamina, temozolomida y SARCnu; antibióticos y alcaloides de plantas incluyendo actinomicina-D, bleomicina, criptoficinas, daunorubicina, doxorubicina, idarubicina, irinotecan, *L*-asparaginasa, mitomicina-C, mitramicina, navelbina, paclitaxel, docetaxel, topotecán, vinblastina, vincristina, VM-26 y VP-16-213; hormonas y esteroides incluyendo inhibidor de 5α-reductasa, aminoglutetimida, anastrozol, bicalutamida, clorotrianiseno, DES, dromostanolona, estramustina, etinil estradiol, flutamida, fluoximesterona, goserelina, hidroxiprogesterona, letrozol, leuprolida, acetato de medroxiprogesterona, acetato de megestrol, metilprednisolona, metiltestosterona, mitotano, nilutamida, prednisolona, SERM3, tamoxifeno, testolactona, testosterona, triamicnolona y zoladex; compuestos sintéticos incluyendo todos los ácidos *trans*-retinoicos, BCNU (carmustina), CBDCA carboplatina (paraplatina), CCNU (lomustina), *cis*-diamindicloroplatino (cisplatina), dacarbazina, gliadel, hexametilmelamina, hidroxiurea, levamisol, mitoxantrona, o, p'-DDD (lisodren, mitotano), oxaliplatina, porfímero sódico, procarbazina, GleeVec; antimetabolitos incluyendo clorodesoxiadenosina, citosina arabinósida, 2'-desoxicoformicina,

fosfato de fludarabina, 5-fluorouracil, 5-FUDR, gemcitabina, camptotecina, 6-mercaptopurina, metotrexato, MTA y tioguanina; y compuestos biológicos incluyendo alfa-interferón, BCG, G-CSF, GM-CSF, interleuquina-2, herceptina; y similares.

En una realización preferida de la invención, el agente anti-neoplásico se selecciona entre el grupo compuesto por agentes alquilantes, antibióticos y alcaloides de plantas, hormonas y esteroides, agentes sintéticos que tienen actividad anti-neoplásica, antimetabolitos y moléculas biológicas que tienen actividad anti-neoplásica.

En una realización preferida de la invención, el agente antineoplásico se selecciona entre el grupo compuesto por Ara-c, VP-16, *cis*-platina, adriamicina, 2-cloro-2-desoxiadenosina, 9-β-D-arabinosil-2-fluoroadenina, carboplatina, gemcitabina, camptotecina, paclitaxel, BCNU, 5-fluorouracil, irinotecan y doxorubicina; más preferiblemente gemcitabina.

Todas las afecciones neoplásicas que pueden tratarse con tales agentes anti-neoplásicos pueden tratarse de acuerdo con la presente invención usando una combinación del compuesto de Fórmula I con uno o más agentes anti-neoplásicos. Los agentes anti-neoplásicos ejercen su citotoxicidad o efectos anti-neoplasma en diversas afecciones neoplásicas específicas. Por ejemplo, Ara-c se usa normalmente para el tratamiento de leucemia linfoide aguda en adultos (LLA), LLA tímica, LLA de células B, leucemia mieloide aguda, leucemia granulocítica aguda y sus variantes, linfoma no Hodgkins, leucemia mielomonocitoide, leucemia megacariocitoide aguda y linfoma de Burkitt, LLA B en adultos, leucemia mieloide aguda, leucemia linfoide crónica, leucemia mieloide crónica y leucemia de células T. VP-16 se usa normalmente para el

tratamiento de carcinoma testicular, carcinoma pulmonar macrocítico pequeño y grande, linfoma de Hodgkin, linfoma no Hodgkin, coricocarcinoma, sarcoma de Ewing y leucemia granulocítica aguda. La *cis*-plantina puede emplearse para el tratamiento de carcinoma testicular, tumores celulares germinales, carcinomas de ovario, cáncer de próstata, cáncer de pulmón, sarcomas, cáncer cervical, cáncer del endometrio, cáncer gástrico, cáncer de mama y cáncer de la cabeza y el cuello. Pueden usarse 2-cloro-2-desoxiadenosina y 9-β-*D*-arabinosil-2-fluoroadenina para tratar leucemia linfoide crónica, linfomas y leucemia de células capilares. Puede usarse doxorubicina para tratar leucemia granulocítica aguda y sus variantes, LLA, cáncer de mama, cáncer de vejiga, cáncer de ovario, cáncer de tiroides, cáncer de pulmón, linfoma de Hodgkin, linfoma no Hodgkin, sarcomas, carcinoma gástrico, cáncer de próstata, cáncer del endometrio, tumor de Wilm y neuroblastoma.

Los efectos clínicos de los agentes anti-neoplásicos en todas las afecciones neoplásicas tratables con agentes anti-neoplásicos incluyendo los analizados anteriormente pueden potenciarse mediante el uso de una terapia de combinación con el inhibidor de CHK-1 identificado de acuerdo con la presente invención.

El inhibidor de CHK-1 identificado en la presente invención también puede mejorar los efectos contra los neoplasmas de la terapia de radiación. Normalmente, puede usarse radiación para tratar directamente el sitio de un tumor sólido o puede administrarse mediante implantes de braquiterapia. Los diversos tipos de radiación terapéutica que se contemplan para la terapia de combinación de acuerdo con la presente invención pueden ser los usados en el tratamiento del cáncer que incluyen, pero sin limitación, rayos X, radiación

gamma, electrones de alta energía y radiación de alta LET (Transferencia de Energía Lineal) tal como protones, neutrones y partículas alfa. La radiación ionizante puede emplearse mediante técnicas bien conocidas por los especialistas en la técnica. Por ejemplo, se aplican rayos X y rayos gamma por medios externo y/o intersticial desde aceleradores lineales o fuentes radiactivas. Los electrones de alta energía pueden producirse mediante aceleradores lineales. La radiación de alta LET se aplica también a partir de fuentes radiactivas implantadas intersticialmente.

La cantidad de dosificación específica de un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo que se administra para obtener efectos terapéuticos o inhibidores puede determinarse de manera conocida en la técnica de acuerdo con las circunstancias particulares que rodean al caso, incluyendo, por ejemplo, el agente específico a administrar, la vía de administración, la afección a tratar y el sujeto u hospedador a tratar. Una dosis diaria total ilustrativa de un compuesto de Fórmula I, que puede administrarse en dosis unitarias o múltiples, contiene un nivel de dosificación de aproximadamente 0,01 mg/kg de peso corporal a aproximadamente 50 mg/kg de peso corporal.

Los compuestos de Fórmula I de la invención pueden administrarse mediante diversas de vías adecuadas, tales como por vía oral, rectal, transdérmica, subcutánea, intravenosa, intramuscular o intranasal. Los compuestos de Fórmula I se formulan preferiblemente en composiciones adecuadas para las vías deseadas antes de la administración.

Una composición o preparación farmacéutica de acuerdo con la invención comprende una cantidad eficaz de un compuesto de Fórmula I,

opcionalmente uno o más agentes activos y un vehículo farmacéuticamente aceptable, tal como un diluyente o excipiente para el agente; cuando el vehículo sirve como diluyente, éste puede ser un material sólido, semi-sólido o líquido que actúa como vehículo, excipiente o medio para el/los ingrediente(s) activo(s). Las composiciones de acuerdo con la invención pueden fabricarse mezclando el/los ingrediente(s) activo(s) con un vehículo, o diluyéndolo con un vehículo, o encerrándolo o encapsulándolo dentro de un vehículo, que puede estar en forma de una cápsula, sello, recipiente de papel o similar. Los ingredientes ilustrativos, además de uno o más compuestos de Fórmula I y cualquier otro ingrediente activo, incluyen Avicel (celulosa microcristalina), almidón, lactosa, sulfato de calcio dihidrato, alabastro, sacarosa, talco, gelatina, agar, pectina, goma arábiga, estearato de magnesio, ácido esteárico, aceite de cacahuete, aceite de oliva, monoestearato de glicerilo, Tween 80 (polisorbato 80), 1,3-butanodiol, manteca de cacao, cera de abejas, polietilenglicol, propilenglicol, monoestearato de sorbitán, polisorbato 60, 2-octildodecanol, alcohol bencílico, glicina, ácido sórbico, sorbato potásico, fosfato ácido disódico, cloruro sódico y agua.

Las composiciones pueden prepararse en cualquiera diversidad de formas adecuadas para el modo de administración deseado. Por ejemplo, las composiciones farmacéuticas pueden prepararse en forma de comprimidos, píldoras, polvos, grageas, sellos, obleas, elixires, suspensiones, emulsiones, soluciones, jarabes, aerosoles (en forma de sólidos o en medios líquidos), pomadas (por ejemplo, conteniendo hasta un 10% en peso de un compuesto de Fórmula I), cápsulas de gel blandas y duras, supositorios, soluciones inyectables estériles, polvos envasados estériles y similares.

Igualmente, el vehículo o diluyente puede incluir material de liberación o retardo en el tiempo conocido en la técnica, tal como monoestearato de glicerilo o diestearato de glicerilo solo o con una cera, etilcelulosa, hidroxipropilmetilcelulosa, metilmetacrilato y similares.

Pueden emplearse diversas formas farmacéuticas. De esta manera, si se usa un vehículo sólido, la preparación puede comprimirse, puede ponerse en una cápsula de gelatina dura en forma de polvo o sedimento o en forma de un trocisco o gragea. La cantidad de vehículo sólido puede variar, pero generalmente será de aproximadamente 25 mg a aproximadamente 1 g. Si se usa un vehículo líquido, la preparación puede estar en forma de jarabe, emulsión, cápsula de gelatina blanda, solución o suspensión inyectable estéril en una ampolla o vial o suspensión líquida no acuosa.

Para obtener una forma de dosis soluble en agua estable, una sal farmacéuticamente aceptable de un agente de la invención se disuelve en una solución acuosa de un ácido orgánico o inorgánico, tal como solución 0,3 M de ácido succínico o ácido cítrico. Si no está disponible una forma de sal soluble, el agente puede disolverse en un co-disolvente adecuado o en combinaciones de co-disolventes. Los ejemplos de co-disolventes adecuados incluyen, pero sin limitación, alcohol, propilenglicol, polietilenglicol 300, polisorbato 80, glicerina y similares en concentraciones que varían del 0-60% del volumen total. Un compuesto de Fórmula I puede disolverse en DMSO y diluirse con agua. La composición también puede estar en forma de una solución de una forma de sal del ingrediente activo en un vehículo acuoso apropiado tal como agua o solución salina isotónica o solución de dextrosa.

Las composiciones de la invención pueden fabricarse de maneras generalmente conocidas para preparar composiciones farmacéuticas, por ejemplo, usando técnicas convencionales tales como mezclado, disolución, granulación, fabricación de grageas, levigación, emulsión, encapsulación, atrapamiento o liofilización. Las composiciones farmacéuticas pueden formularse de manera convencional usando uno o más vehículos fisiológicamente aceptables, que pueden seleccionarse entre excipientes y auxiliares que facilitan el procesamiento de los compuestos activos en preparaciones que pueden usarse farmacéuticamente.

La formulación adecuada depende de la vía de administración seleccionada. Para inyección, los agentes de la invención pueden formularse en soluciones acuosas, preferiblemente en tampones fisiológicamente compatibles tales como solución de Hanks, solución de Ringer o tampón de solución salina fisiológico. Para la administración transmucosal, en la formulación se usan penetrantes apropiados para que la barrera sea atrevesada. Tales penetrantes se conocen generalmente en la técnica.

Para la administración oral, los compuestos pueden formularse fácilmente combinando los compuestos activos con vehículos farmacéuticamente aceptables conocidos en la técnica. Tales vehículos permiten que los compuestos de la invención se formulen como comprimidos, píldoras, grageas, cápsulas, líquidos, geles, jarabes, suspensiones y similares, para ingestión oral por un paciente a tratar. Las preparaciones farmacéuticas para uso oral pueden obtenerse usando un excipiente sólido mezclado con el ingrediente activo (agente), opcionalmente triturando la mezcla resultante, y procesando la mezcla de gránulos después de añadir auxiliares adecuados, si

se desea, para obtener comprimidos o núcleos de grageas. Los excipientes adecuados incluyen: cargas tales como azúcares, incluyendo lactosa, sacarosa, manitol o sorbitol; y preparaciones en celulosa, por ejemplo, almidón de maíz, almidón de trigo, almidón de arroz, almidón de patata, gelatina, goma, hidroxipropilmetil-celulosa, carboximetilcelulosa sódica, metilcelulosa o polivinilpirrolidona (PVP). Si se desea, pueden añadirse agentes disgregantes, tales como polivinilpirrolidona reticulada, agar o ácido algínico o una sal del mismo tal como alginato sódico.

Los núcleos de gragea se proporcionan con recubrimientos adecuados. Para este propósito, pueden usarse soluciones de azúcar concentradas, que pueden contener además goma arábiga, polivinilpirrolidona, gel de Carbopol, polietilenglicol y/o dióxido de titanio, soluciones de laca y disolventes orgánicos adecuados o mezclas de disolventes. Pueden añadirse tintes o pigmentos a los comprimidos o recubrimientos de gragea para la identificación o para caracterizar diferentes combinaciones de agentes activos.

Las preparaciones farmacéuticas que pueden usarse por vía oral incluyen cápsulas de ajuste por presión hechas de gelatina, así como cápsulas blandas cerradas herméticamente hechas de gelatina y un plastificante, tal como glicerol o sorbitol. Las cápsulas de ajuste por presión pueden contener los ingredientes activos mezclados con cargas tales como lactosa, aglutinantes tales como almidones y/o lubricantes tales como talco o estearato de magnesio, y, opcionalmente, estabilizantes. En las cápsulas blandas, los agentes activos pueden disolverse o suspenderse en líquidos adecuados, tales como aceites grasos, parafina líquida o polietilenglicoles líquidos. Además, pueden añadirse estabilizantes. Todas las formulaciones para administración

oral deben estar en dosis adecuadas para tal administración. Para la administración bucal, las composiciones pueden tomar la forma de comprimidos o grageas formuladas de manera convencional.

Para la administración intranasal o por inhalación, los compuestos para uso de acuerdo con la presente invención se liberan convenientemente en forma de una presentación en pulverización por aerosol desde envases presurizados o un nebulizador, con el uso de un propulsor adecuado, por ejemplo, diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas adecuado. En el caso de un aerosol presurizado, la unidad de dosificación puede determinarse proporcionando una válvula para liberar una cantidad medida. Las cápsulas y cartuchos de gelatina para uso en un inhalador o insuflador y similares pueden formularse conteniendo una mezcla en polvo del compuesto y una base en polvo adecuada tal como lactosa o almidón.

Los compuestos pueden formularse para administración parenteral por inyección, por ejemplo, por inyección en embolada o infusión continua. Las formulaciones para inyección pueden presentarse en una forma de dosificación unitaria, por ejemplo, en ampollas o recipientes multi-dosis, con un conservante añadido. Las composiciones pueden tomar formas tales como suspensiones, soluciones o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilización y/o dispersión.

Las formulaciones farmacéuticas para administración parenteral incluyen soluciones acuosas de los compuestos activos en forma soluble en agua. Además, las suspensiones de los agentes activos pueden prepararse como

suspensiones oleosas para inyección. Los disolventes o vehículos lipofílicos adecuados incluyen aceites grasos tales como aceite de sésamo o ésteres sintéticos de ácidos grasos, tales como oleato de etilo o triglicéridos, o liposomas. Las suspensiones acuosas para inyección pueden contener sustancias que aumentan la viscosidad de la suspensión, tales como carboximetilcelulosa sódica, sorbitol o dextrano. Opcionalmente, la suspensión también puede contener estabilizantes o agentes adecuados que aumenten la solubilidad de los compuestos permitiendo la preparación de soluciones altamente concentradas.

Para la administración en el ojo, el agente activo se libera en un vehículo oftálmico farmacéuticamente aceptable de forma que el compuesto se mantiene en contacto con la superficie ocular durante un período de tiempo suficiente para permitir que el compuesto penetre en la córnea y en las regiones internas del ojo, incluyendo, por ejemplo, la cámara anterior, cámara posterior, cuerpo vítreo, humor acuoso, humor vítreo, córnea, iris/ciliar, lentes, coroides/retina y esclerótica. El vehículo oftálmico farmacéuticamente aceptable puede ser una pomada, aceite vegetal o material de encapsulación. Un compuesto de la invención también puede inyectarse directamente en el humor vítreo y acuoso.

Como alternativa, el ingrediente activo puede estar en forma de polvo para constitución con un vehículo adecuado, por ejemplo, agua estéril sin pirógenos, antes del uso. Los compuestos también pueden formularse en composiciones rectales tales como supositorios o enemas de retención, por ejemplo, conteniendo bases para supositorio convencionales tales como manteca de cacao u otros glicéridos.

Los compuestos también pueden formularse en forma de una preparación de liberación prolongada. Tales formulaciones de larga actuación pueden administrarse por implantación (por ejemplo, por vía subcutánea o intramuscular) o por inyección intramuscular. De esta manera, por ejemplo, los compuestos pueden formularse con materiales poliméricos o hidrófobos adecuados (por ejemplo, en forma de una emulsión en un aceite aceptable) o resinas de intercambio iónico, o en forma de derivados poco solubles, por ejemplo, en forma de una sal poco soluble.

Un vehículo farmacéutico para compuestos hidrófobos es un sistema co-disolvente que comprende alcohol bencílico, un tensioactivo no polar, un polímero orgánico miscible en agua y una fase acuosa. El sistema co-disolvente puede ser un sistema co-disolvente VPD. VPD es una solución de alcohol bencílico al 3% p/v, 8% p/v del tensioactivo no polar polisorbato 80, y polietilenglicol 300 al 65% p/v, fabricada en volumen en etanol absoluto. El sistema co-disolvente VPD (VPD:5W) contiene VPD diluido 1:1 con dextrosa al 5% en solución de agua. Este sistema co-disolvente disuelve bien compuestos hidrófobos, y produce por sí mismo una baja toxicidad después de la administración sistémica. Naturalmente, las proporciones de un sistema co-disolvente puede variar considerablemente sin destruir sus características de solubilidad y toxicidad. Además, la identidad de los componentes co-disolventes puede variar; por ejemplo, pueden usarse otros tensioactivos no polares de baja toxicidad en lugar de polisorbato 80; el tamaño de la fracción del polietilenglicol puede variar; otros polímeros biocompatibles pueden reemplazar al polietilenglicol, por ejemplo, polivinilpirrolidona; y otros azúcares o la dextrosa puede sustituirse por polisacáridos.

Como alternativa, pueden emplearse otros sistemas de liberación para compuestos farmacéuticos hidrófobos. Los liposomas y emulsiones son ejemplos conocidos de vehículos o excipientes de liberación para fármacos hidrófobos. También pueden emplearse ciertos disolventes orgánicos tales como dimetilsulfóxido, aunque normalmente a costa de una mayor toxicidad. Además, los compuestos pueden liberarse usando un sistema de liberación sostenida, tal como matrices semipermeables de polímeros hidrófobos sólidos que contienen el agente terapéutico. Se han establecido diversos materiales de liberación sostenida y se conocen por parte de los especialistas en la técnica. Las cápsulas de liberación sostenida pueden, dependiendo de su naturaleza química, liberar los compuestos durante unas semanas hasta más de 100 días. Dependiendo de la naturaleza química y de la estabilidad biológica del reactivo terapéutico, pueden emplearse otras estrategias para la estabilización de proteínas.

Las composiciones farmacéuticas también pueden comprender vehículos o excipientes de fase sólida o gel adecuados. Los ejemplos de tales vehículos o excipientes incluyen carbonato cálcico, fosfato cálcico, azúcares, almidones, derivados de celulosa, gelatina y polímeros tales como polietilenglicoles.

Algunos de los compuestos de la invención pueden proporcionarse en forma de sales con contraiones farmacéuticamente compatibles. Las sales farmacéuticamente compatibles pueden formularse con muchos ácidos, incluyendo clorhídrico, sulfúrico, acético, láctico, tartárico, málico, succínico, etc. Las sales tienden a ser más solubles en disolventes acuosos u otros protónicos que en las formas de base libre correspondientes.

Los compuestos de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable de los mismos son útiles como agentes anti-angiogénesis y como agentes para modular y/o inhibir la actividad de proteína quinasas, proporcionando de esta manera tratamientos para el cáncer u otras enfermedades asociadas con la proliferación celular mediada por proteína quinasas.

Pueden usarse cantidades terapéuticamente eficaces de los agentes de la invención para tratar enfermedades mediadas por la modulación o regulación de proteína quinasas. Una "cantidad eficaz" pretende significar la cantidad de un agente que, cuando se administra a un mamífero en necesidad de tal tratamiento, es suficiente para efectuar el tratamiento para una enfermedad mediada por la actividad de una o más quinasas. De esta manera, por ejemplo, una cantidad terapéuticamente eficaz de un compuesto de Fórmula I, una sal, solvato o profármaco farmacéuticamente aceptable del mismo es una cantidad suficiente para modular, regular o inhibir la actividad de una o más quinasas de forma que un estado de enfermedad que está mediado por esa actividad se reduzca o alivie.

EVALUACIÓN BIOQUÍMICA Y BIOLÓGICA

Ensayos enzimáticos

Construcción de CHK-1 para ensayos

Como se ha detallado previamente en la Solicitud de Patente Europea Nº 1 096 014 A2 (presentada el 31 de octubre de 2000) el dominio que quinasa con señal de His C-terminal de CHK-1 humana (KH289), restos aminoacídicos 1-289, pueden expresarse usando el sistema celular de baculovirus/insecto. Se ha demostrado que esta construcción posee actividad catalítica

aproximadamente 10 veces más que CHK-1 de longitud completa. El sistema Bac to Bac (Life Technologies) puede usarse para generar baculovirus recombinante para la expresión de KH289 según las instrucciones. Los virus recombinantes pueden confirmarse mediante PCR con respecto a la presencia de la inserción de ADNc de CHK-1. La expresión proteica puede confirmarse por SDS-PAGE o transferencia de Western con anticuerpos policlonales de CHK-1. Las células de insecto Sf9 (Invitrogen, Carlsbad, CA, Estados Unidos) pueden usarse para la ampliación inicial de la solución madre del virus recombinante. Las soluciones madre de alta titulación de virus recombinantes pueden generarse mediante de 2 a 3 series de amplificación usando células de insecto Sf21. Las células de insecto Hi-S (Invitrogen, Carlsbad, CA, Estados Unidos) pueden usarse para la producción proteica. Tanto las líneas celulares Sf9 como Hi-S pueden adaptarse al crecimiento en medio de insecto que contiene suero bovino fetal al 1% (Life Technologies, Grand Island, NY, Estados Unidos). La solución madre viral se almacenó a 10°C y se usó para la producción proteica a gran escala en un período de 2 meses para evitar la inestabilidad viral. Para la producción proteica, las células Hi-S infectadas pueden recogerse por centrifugación y almacenarse a -80°C. A partir de estas células, KH289 con señal de 6X-His (identificada por SDS-PAGE) puede obtenerse después de la purificación y puede congelarse de forma rápida en N_2 líquido y almacenarse a -80°C. Se descubrió que mantener la concentración salina a NaCl de aproximadamente 500 mM incluyendo glicerol al 5% era crucial para evitar la agregación de proteínas de CHK-1 durante la purificación y el almacenamiento.

Ensayo de CHK-1

Como se ha detallado previamente en la Solicitud de Patente Europa Nº 1 096 014 A2 (presentada el 31 de octubre de 2000), la actividad enzimática de una quinasa puede medirse mediante su capacidad para catalizar la transferencia de un resto fosfato de un trifosfato nucleósido a una cadena lateral aminoacídica en una diana proteica seleccionada. La conversión de ATP en ADP generalmente acompaña a la reacción catalítica. Por lo tanto, puede utilizarse una péptido sustrato sintético, Syntide-2, que tiene la secuencia aminoacídica PLARTLSVAGLPGKK. La producción de ADP a partir de ATP que acompaña a la transferencia de fosforilo en el sustrato puede acoplarse a la oxidación de NADH usando fosfoenolpiruvato (PEP) mediante las acciones de la piruvato quinasa (PK) y la deshidrogenasa láctica (LDH). La oxidación de NADH puede controlarse siguiendo la disminución de la absorbancia a 340 nm (e340 = 6,22 cm-1 mM-1) usando un espectrofotómetro HP8452. Las soluciones de reacción típicas contenían: PEP 4 mM, NADH 0,15 mM, 28 unidades de LDH/ml, 16 unidades de PK/ml, DTT 3 mM, Syntide-2 0,125 mM, ATP 0,15 mM y MgCl2 25 mM en TRIS 50 mM pH 7,5; NaCl 400 mM. Los ensayos pueden iniciarse con 10 mM del dominio de quinasa de CHK-1, KH289. Los valores de Ki pueden determinarse midiendo la actividad enzimática inicial en presencia de diversas concentraciones de inhibidores. Los datos pueden analizarse usando la cinética enzimática y el software Kaleidagraph.

Construcción de VEGF-R2 para el ensayo

Esta construcción determina la capacidad de un compuesto de ensayo para inhibir la actividad de tirosina quinasa. Una construcción (VERF-R2Δ50) del dominio citosólico del receptor del factor de crecimiento endotelial vascular

2 (humano) (VEGF-R2) que carece de 50 restos centrales de los 68 restos del dominio de inserción de quinasa puede expresarse en un sistema celular de baculovirus/insecto. De los 1356 restos de VEGF-R2 de longitud completa, VEGF-R2Δ50 contiene los restos 806-939 y 990-1171, y también un punto de mutación (E990V) en el dominio de inserción de quinasa con relación a VEGF-R2 de tipo silvestre. La autofosforilación de la construcción purificada puede realizarse mediante la incubación de la enzima a una concentración de 4 μM en presencia de ATP 3 mM y $MgCl_2$ 40 mM en HEPES 100 mM, pH 7,5 que contiene glicerol al 5% y DTT 5 mM, a 4°C durante 2 horas. Después de la autofosforilación, se ha demostrado que esta construcción posee actividad catalítica esencialmente equivalente a la de la construcción del dominio de quinasa autofosforilada de tipo silvestre. Véase Parast y col. (1998) Biochemistry 37:16788-16801.

Ensayo de VEGF-R2

Ensayo Espectrofotométrico Acoplado (FLVK-P)

La producción de ADP a partir de ATP que acompaña la trasferencia de fosforilo puede acoplarse a la oxidación de NADH usando fosfoenolpiruvato (PEP) y un sistema que tiene la piruvato quinasa (PK) y la deshidrogenada láctica (LDH). La oxidación de NADH puede controlarse siguiendo la disminución e la absorbancia a 340 mM (e_{340} = 6,22 cm^{-1} mM^{-1}) usando un espectrofotómetro Beckman DU 650. Las condiciones de ensayo para VEGF-R2Δ50 fosforilado pueden ser las siguientes: PEP 1 mM; NADH 250 μM; 50 unidades de LDH/ml; 20 unidades de PK/ml; DTT 5 mM; poli(E_4Y_1) 5,1 mM; ATP 1 mM; y $MgCl_2$ 25 mM en HEPES 200 mM, pH 7,5. Las condiciones de ensayo para VEGF-R2Δ50 no fosforilado son las siguientes: PEP 1 mM; NADH

250 μM; 50 unidades de LDH/ml; 20 unidades de PK/ml; DTT 5 mM; poli(E_4Y_1) 20 mM; ATP 3 mM; y $MgCl_2$ 60 mM y $MnCl_2$ 2 mM en HEPES 200 mM, pH 7,5. Los ensayos pueden iniciarse con 5 a 40 mM de enzima. Los valores del porcentaje de inhibición enzimática pueden determinarse midiendo la actividad enzimática en presencia del compuesto de ensayo 0,05 μM. Los datos pueden analizarse usando cinética enzimática y el software Kaleidagraph.

FGFR

Construcción de FGF-R1 para el ensayo

El dominio de quinasa intracelular de FGF-R1 (humano) puede expresarse usando el sistema de expresión del vector de baculovirus comenzando por el resto de metionina endógena 456 a glutamato 766, de acuerdo con el sistema de numeración de restos de Mohammadi y col. (1996) Mol. Cell. Biol. 16:977-989. Además, la construcción también tiene las siguientes 3 sustituciones aminoacídicas: L457V, C488A, y C584S.

Ensayo de FGF-R

El ensayo espectrofotométrico puede realizarse como se ha descrito anteriormente para VEGF-R2 excepto para los siguientes cambios en la concentración: FGF-R = 50 nM, ATP = 2 mM, y poli(E4Y1) = 15 mM. Los valores de K_i pueden determinarse midiendo la actividad enzimática en presencia de diversas concentraciones de compuestos de ensayo.

PHK

Construcción de la fosforilasa quinasa para el ensayo

La subunidad catalítica truncada (unidad gamma) de la fosforilasa quinasa (aminoácidos 1-298) puede expresarse en E. coli y asilarse a partir de cuerpos de inclusión. Después, la fosforilasa quinasa puede replegarse y

almacenarse en glicerol a -20°C.

Ensayo de la fosforilasa quinasa

En este ensayo, la subunidad catalítica purificada puede usarse para fosforilar la fosforilasa b usando ATP radiomarcado. En resumen, pueden incubarse 1,5 mg/ml de fosforilasa b con fosforilasa quinasa 10 nM en $MgCl_2$ 10 mM, Hepes 50 mM pH 7,4, a 37°C. La reacción puede empezarse con la adicción de ATP a 100 μM y puede incubarse durante 15 minutos a 25°C o a 37°C. La reacción puede terminarse y las proteínas pueden precipitarse mediante la adición de TCA a la concentración final al 10%. Las proteínas precipitadas pueden asilarse en una placa de filtro Millipore MADP NOB de 96 pocillos. La placa de filtro puede lavarse abundantemente con TCA al 20% y puede secarse. Después, el fluido de escintilación puede añadirse a la paca y el radiomarcaje incorporado puede contabilizarse en un contador microbeta Wallac. Después, puede medirse el % de inhibición del fosforilo transferido de ATP a la fosforilasa b en presencia de 10 μM del compuesto.

Ensayo de CHK-2

La enzima CHK-2 puede obtenerse de Upstate Group, Inc. y es una proteína de fusión de señal de His C-terminal y de señal de GST N-terminal que corresponde a los aminoácidos 5-543 de la CHK-2 humana que se confirma mediante identificación genética tríptica de masas, expresado en E. coli; Mr~87 kDa. La condición del ensayo para CHK-2 puede ser como se ha descrito anteriormente para CHK-1, excepto por el hecho de que la enzima CHK-2 (0,059 μM) puede utilizarse en lugar de KH289. Además, no puede añadirse NaCl.

Ensayo de CDK-1

El complejo activo de CDK-1/ciclina B puede obtenerse de Upstate Group, Inc. y es una CDK-1 de señal de His C-terminal y una ciclina B de señal de GST N-terminal mediante identificación genética tríptica de masas y la secuenciación proteica, producida individualmente en células Sf21 y después complejada *in vitro*. La condición del ensayo para CDK-1 puede ser como se ha descrito anteriormente para CHK-1 excepto por el hecho de que el complejo enzimático CDK-1/ciclina 20 (0,2 µM) puede utilizarse en lugar de KH289, y la histona-H1 (Upstate Estados Unidos, Inc) (0,59µM) puede utilizarse como sustrato en lugar de Syntide-2. Además no puede añadirse NaCl.

Ensayo de WEE-1

Protocolo de ensayo Delfia(R) para WEE-1

La enzima WEE-1 puede obtenerse de Upstate Group, Inc. y es una proteína de fusión de señal de GST N-terminal para WEE-1 de longitud completa de rata, expresada en E. coli; Mr~100 kDa. Este ensayo de quinasa puede realizarse en placas de filtro de 96 pocillos recubiertas con poli (Glu-Tyr) 4:1 (copolímero aleatorio) (NoAb Diagnostics). El volumen de ensayo puede ser de 100 µl por pocillo más 2 µl de DMSO (control) o 2 µl de compuesto en DMSO. El tampón A puede ser glicerol al 10%, TRIS 20 mM (pH 7,5), $MgCl_2$ 10 mM, NaCl 50 mM y DTT 5 mM. Las placas pueden preparase por automatización.

A un pocillo apropiado se le pueden añadir 2 µl de DMSO (control) o 2 µl de compuesto en DMSO. A los pocillos de control positivo se les pueden añadir 30 µl de EDTA 0,5 M. A cada pocillo se le pueden añadir 50 µl de ATP en tampón A de forma que la concentración del ensayo de ATP pueda ser de 33 µM. Para empezar la reacción, se pueden añadir a cada reacción 50 µl de

Wee1 en tampón A de forma que la concentración del ensayo de Wee1 pueda ser de 0,1 ng/µl. La placa puede mezclarse mediante agitación y después se la deja permanecer a temperatura ambiente durante 30 minutos. Para interrumpir la reacción, la placa puede lavarse una vez con lavado Delfia en una lavadora de placas EL 405. A cada pocillo se le pueden añadir 100 µl de EuPY en tampón de ensayo Delfia(R) de forma que la concentración del ensayo de EuPY pueda ser de 0,0149 ng/µl. La placa se puede dejar reposar durante 1 hora o durante toda la noche. La placa puede lavarse de nuevo una vez con lavado Delfia(R) (lavadora de placas EL405), y se deja secar. A cada pocillo se le pueden añadir 100 µl de solución de potenciación Delfia(R) y la placa se deja reposar durante 10 minutos. La placa puede leerse en un lector de fluorescencia Wallac's Victor (Protocolo Europium). Los valores de K_i pueden determinarse midiendo la actividad enzimática en presencia de diversas concentraciones de compuestos de ensayo.

Ensayo de SGK

SGK (humana) (Upstate Group, Inc., KINASEPROFILER™ (5-10 mU) puede incubarse con MOPS 8 mM pH 7,0, EDTA 0,2 mM, Crosstide 30 µM, acetato de Mg 10 mM y [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentraciones según se requiera) para formar un volumen de reacción final de 25 µl. Los compuestos pueden ensayarse a 1 µM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 µM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 µl de una solución de ácido fosfórico al 3%. Después puede aplicarse de forma puntual en una rejilla de filtro P30 y puede lavarse 3 veces durante 5

minutos en ácido fosfórico 50 mM y una vez en metanol antes de secarse y de realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como porcentaje de lo obtenido en las incubaciones de control sin los compuestos de ensayo.

Ensayo de AMPK

AMPK (rata) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Hepes 50 mM pH 7,4, DTT 1 mM, Brij35 al 0,02%, AMP 200 μM, AMARAASAAALARRR 200 μM, acetato de Mg 10 mM [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adicción de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después pueden aplicarse de forma puntual 10 μl de reacción en una rejilla de filtro P30 y puede lavarse 3 veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y de establecer el recuento por escintilación. Los resultados representan una media de 2 experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin el compuesto de ensayo.

Ensayo de LCK

LCK (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Tris 50 mM pH 7,5, EGTA 0,1 mM, NaVanadato, 0,1 mM, KVEKIGEGTYGVVYK (péptido CDC2) 250 μM, acetato de Mg 10 mM [γ-^{33}P-

ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 µl. Los compuestos pueden ensayarse a 1 µM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 µM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 µl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 µl de la reacción en una rejilla de filtro P30 y puede lavarse 3 veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y de establecer el recuento por escintilación. Los resultados representan una media de 2 experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de MAPK2

MAPK2 (ratón) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Tris 25 mM pH 7,5, EGTA 0,02 mM, 0,33 mg/ml de proteína básica de mielina, acetato de Mg 10 mM [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 µl. Los compuestos pueden ensayarse a 1 µM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 µM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 µl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 µl de la reacción en una rejilla de filtro P30 y puede lavarse 3 veces durante 5 minutos en ácido fosfórico 75

mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de 2 experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de MSK1

MSK1 (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con MOPS 8 mM pH 7,0, EGTA 0,2 mM, Crosstide 30 pM, acetato de Mg 10 mM [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 µl. Los compuestos pueden ensayarse a 1 µM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 µM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 µl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 µl de la reacción en una rejilla de filtro P30 y puede lavarse 3 veces durante 5 minutos en ácido fosfórico 50 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de 2 experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de PKBα

PKBα (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con MOPS 8 mM pH 7, EDTA, Crosstide 30 µM, acetato de Mg 10 mM [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de

reacción final de 25 µl. Los compuestos pueden ensayarse a 1 µM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 µM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 µl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 µl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 50 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de ROCKII

ROCKII (rata) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Tris 50 mM pH 7,5, EDTA 0,1 mM, KEAKEKRQEQIAKRRRLSSLRASTSKSGGSQK 30 µM, acetato de Mg 10 mM [ψ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 µl. Los compuestos pueden ensayarse a 1 µM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 µM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 µl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 µl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de

dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de p70 S6K

p70S6K (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con MOPS 8 mM pH 7,0, EDTA 2 mM, KKRNRTLTV 100 μM, acetato de Mg 10 mM y [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de PKA

PKA (bovina) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con MOPS 8 mM pH 7,0, EDTA 0,2 mM, LRRASLG 30 μM (Kemptide), acetato de Mg 10 mM [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1

μM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 50 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de MAPK1

MAPK1 (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Tris 25 mM pH 7,5, EGTA 0,02 mM, péptido sintético, acetato de Mg 10 mM [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las

incubaciones de control sin compuesto de ensayo.

Ensayo de cSRC

cSRC (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con MOPS 8 mM pH 7,0, EDTA 0,2 mM, KVEKIGEGTYGVVYK 250 μM (péptido CDC2), acetato de Mg 10 mM [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de PRK2

PRK2 (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Tris 50 mM pH 7,5, EGTA 0,1 mM, β-mercaptoetanol 0,1%, AKRRRLSSLRA 30 μM, acetato de Mg 10 mM y [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adición de

Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de PDK1

PDK1 (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Tris 50 mM pH 7,5, KTFCGTPEYLAPEVRREPRILSEEEQEMFRDFDYIADWC 100 μM (PDKtido), β-mercaptoetanol 0,1%, acetato de Mg 10 mM y [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en

las incubaciones de control sin compuesto de ensayo.

Ensayo de FYN.

FYN (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Tris 50 mM pH 7,5, EGTA 0,1 mM, NaVadate 0,1 mM, KVEKIOEGTYGVVYK 250 μM (péptido.CDC2), acetato de Mg 10 mM y [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

PKCβII (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Hepes 20 mM, pH 7,4, Triton X-100 al 0,03%, $CaCl_2$ 0,1 mM, 0,1 mg/ml de fosfatidilserina, 10 μg/ml de diacilglicerol, 0,1 mg/ml de histona H1, acetato de Mg 10 mM y [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La

concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las incubaciones de control sin compuesto de ensayo.

Ensayo de PKCγ

PKCγ (humana) (Upstate Group, Inc., KINASEPROFILER™) (5-10 mU) puede incubarse con Hepes 20 mM, pH 7,4, Triton X-100 al 0,03%, $CaCl_2$ 0,1 mM, 0,1 mg/ml de fosfatidilserina, 10 μg/ml de diacilglicerol, 0,1 mg/ml de histona H1, acetato de Mg 10 mM y [γ-^{33}P-ATP] (actividad específica de aproximadamente 500 cpm/pmol, concentración según se requiera) para formar un volumen de reacción final de 25 μl. Los compuestos pueden ensayarse a 1 μM. La reacción puede iniciarse mediante la adición de Mg^{2+} [γ-^{33}P-ATP]. La concentración de ATP puede ser de 10 μM. Después de la incubación durante 40 minutos a temperatura ambiente, la reacción puede interrumpirse mediante la adición de 5 μl de una solución de ácido fosfórico al 3%. Después, pueden aplicarse puntualmente 10 μl de reacción en una rejilla de filtro P30 y puede lavarse tres veces durante 5 minutos en ácido fosfórico 75 mM y una vez en metanol antes de secarse y realizar el recuento por escintilación. Los resultados representan una media de dos experimentos y la actividad enzimática puede expresarse como el porcentaje de lo obtenido en las

incubaciones de control sin compuesto de ensayo.

Ensayo de anulación de Chekpoint de Célula Entera

Ensayo ELISA de índice mitótico de Chk1

Para examinar los efectos in vitro de los compuestos inhibidores de ChK1, puede diseñarse un ensayo ELISA para controlar la anulación del control de checkpoint inducido por la lesión de ADN. El ensayo puede basarse en atrapar y detener células mitóticas después de la parada inducida por la lesión de ADN. Se ha demostrado que las fosforilación de la histona H3 en la serina 10 está relacionada con la mitosis y por lo tanto puede requerirse para la condensación de cromosomas; por consiguiente puede usarse un fosfo-epítopo específico de mitosis en la Histona 3 como señal para la anulación del chekpoint.

Las células CA-46 (linfoma) pueden tratarse con un agente de lesión de ADN, tal como camptotecina (Sigma), a 50 nM durante 8 horas para inducir la lesión de ADN. Después, puede añadirse el compuesto de control o inhibidor de Chk1 para aumentar las concentraciones con Nocodazol (Sigma) a 0,1 µg/ml y las placas pueden incubarse durante 16 horas. Las células de control, cuando sólo pueden añadirse inhibidores de Ckk1, pueden preparase también para asegurarse de que los inhibidores solos no tienen efecto en el ciclo celular. Después, las células pueden recogerse, lavarse con PBS y puede realizarse la extracción con ácido bruto. Los sedimentos pueden resuspenderse en 80 µl de tampón de extracción con ácido (Hepes 10 mM pH 7,9, $MgCl_2$ 1,5 mM, KCl 10 mM, DTT 0,5 mM, PMSF 1,5 mM, ácido sulfúrico 0,4 N), pueden agitarse vorticialmente brevemente, e incubarse durante 30 minutos en hielo. Después, las muestras pueden centrifugarse y pueden transferirse 75 µl del

sobrenadante a una placa de fondo liso de 96 pocillos (VWR 3596). Después, pueden añadirse 15 µl de cóctel neutralizante (Nº de muestras x (10 µl de NaOH 10 N + 5 µl de Tris Base 1 M)) a cada pocillo, y después de mezclarse, pueden transferirse 5 µl de esto a otra placa de 96 pocillos con 100 µl de base Tris 50 mM (pH 9,6) en cada pocillo. Las muestras pueden secarse durante toda la noche. Después, los pocillos pueden lavarse con 200 µl de tampón de lavado ELISA (PBS con Tris 20 mM pH 7,5, Tween 20 al 0,05%) 5 veces y bloquearse con 200 µl de tampón de bloqueo (PBS con Tris 20 mM pH 7,5, Tween 20 al 0,05%, leche deshidratada al 3,5%, BSA al 1,05%, pH a 7,5 después de la preparación) durante 1 hora a temperatura ambiente. Después de lavar y bloquear, los anticuerpos antifosfohistona H3 (Upstate Estados Unidos, Inc., policlonal de conejo) pueden añadirse a 0,5 µg/ml en bloque (100 µl por pocillo) y pueden incubarse durante 2 horas a temperatura ambiente. Los pocillos pueden lavarse de nuevo para retirar el anticuerpo primario no unido y pueden añadirse durante 1 hora temperatura ambiente 100 µl de anticuerpos secundarios conjugados con fosfatasa alcalina a 0,3 mg/ml (Pierce, IgG de cabra anti conejo (HORAS+L)) en bloque. Los pocillos pueden lavarse 5 veces para retirar el anticuerpo secundario no unido, y pueden lavarse de nuevo 3 veces con PBS solo para retirar los detergentes. Después, pueden añadirse a los pocillos 100 µl de sustrato de fosfatasa alcalina (Pierce etapa 1 de pNPP). Las placas pueden protegerse de la luz e incubarse a temperatura ambiente durante 1 hora. La DO puede leerse en un lector de micro placas Vmaz Kinetic de Molecular Devices a 405 nM. La relación de la DO (densidad óptica) entre una muestra tratada con compuesto y una muestra tratada sólo con Nocodazol (aproximadamente mitótica o anulada al 100%) puede expresarse en un

porcentaje, y cuantifica el porcentaje de anulación del chekpoint. La concentración a la que un compuesto provoca la anulación del 50% del chekpoint puede denominarse la CE_{50}. Los valores de DO brutos pueden representarse gráficamente en Excel y el valor de CE_{50} puede generarse un software Kaleidograph. La señal fuerte resulta de las células tratadas sólo con Nocodazole, y es igual a la mitosis del 100% en este ensayo. Las muestras de control tratadas con Camptotetina + Nocodazol tienen una señal baja, lo que significa que no hay mitosis y que por lo tanto no hay anulación del chekpoint. Cuando los inhibidores de CHK1 potentes se añaden a las células tratadas con Cantotecina y Nococadazol, puede generarse una señal alta (generalmente de una forma dependiente de la dosis), debido a la actividad de la anulación del chekpoint causada por el tratamiento de combinación.

Los ejemplos anteriores ilustran compuestos de acuerdo con la fórmula I y ensayos que pueden realizarse fácilmente para determinar sus niveles de actividad contra los complejos de diversas quinasas. Será evidente que tales ensayos u otros ensayos adecuados conocidos en la técnica puedan usarse para seleccionar un inhibidor que tenga un nivel deseado de actividad contra una diana seleccionada.

Los compuestos ilustrativos descritos anteriormente pueden formularse en composiciones farmacéuticas de acuerdo con los siguientes ejemplos generales.

Composición parenteral

Para preparar una composición farmacéutica parenteral adecuada para la administración por inyección, pueden disolverse 100 mg de una sal soluble en agua de un compuesto de Fórmula I o II en DMSO y después mezclarse con

10 ml de solución salina estéril al 0,9%. La mezcla puede incorporarse en una forma de unidad de dosificación para la administración por inyección.

Composición oral

Para preparar una composición farmacéutica para liberación oral, pueden mezclarse 100 mg de un compuesto de Fórmula I o II con 750 mg de lactosa. La mezcla puede incorporarse en una unidad de dosificación unitaria oral, tal como una cápsula de gelatina dura, que puede ser adecuada para administración oral.

Los materiales de partida usados en los ejemplos están disponibles en el mercado y/o pueden prepararse por técnicas conocidas en la técnica. Se usaron indistintamente bases libres y sales de materiales de partida e intermedios y se indicaron. Las bases libres se prepararon mediante la adición de una base terciaria a la sal seguido de la cromatografía sobre gel de sílice de la base libre resultante si fuese necesario. Las sales se prepararon añadiendo una cantidad equivalente del ácido apropiado a la base libre en una suspensión o solución.

La preparación de compuestos preferidos específicos de la invención se describe con detalle en los ejemplos mostrados más adelante. El especialista reconocerá que las reacciones químicas descritas pueden adaptarse fácilmente para preparar otros inhibidores de quinasa de la invención. Por ejemplo, la síntesis de los compuestos no ilustrativos de acuerdo con la invención puede realizarse satisfactoriamente mediante modificaciones obvias para los especialistas en la técnica, por ejemplo, mediante grupos interferentes protectores apropiados, cambiando los demás reactivos adecuados conocidos en la técnica, o realizando modificaciones convencionales de las condiciones

de reacción. Como alternativa, se reconocerá que otras reacciones descritas en este documento o conocidas en la técnica tienen aplicabilidad para preparar otros compuestos de la invención.

En los ejemplos descritos más adelante, a menos que se indique otra cosa, todas las temperaturas se indican en grados Celsius y todas las partes y porcentajes están en peso. Los reactivos se adquirieron de proveedores comerciales tales como Aldrich Chemical Company o Lancaster Synthesis Ltd. y se usaron sin purificación adicional a menos que se indique otra cosa. Se adquirieron tetrahidrofurano (THF) destilado a partir de hidruro de calcio y *N,N*-dimetilformamida (DMF) de Aldrich en botellas Sure cerradas herméticamente y se usaron cuando se recibieron. Todos los disolventes se purificaron usando procedimientos convencionales conocidos fácilmente para los especialistas en la técnica, a menos que se indique otra cosa.

Las reacciones indicadas a continuación se realizaron generalmente a presión positiva de argón o con un tubo de secado, a temperatura ambiente (a menos que se indique otra cosa), en disolventes anhidros, y los matraces de reacción se ajustaron con tabiques de goma para la introducción de sustratos y reactivos mediante una jeringa. Los objetos de cristal se secaron en la estufa y/o se secaron con calor. Se realizó cromatografía analítica de capa fina (CCF) sobre placas Analtech de gel de sílice 60 F254 con soporte de vidrio (0,25 mm), se eluyó con las relaciones apropiadas de disolvente (v/v) y se indicó cuando fue apropiado. Las reacciones se ensayaron por CCF y finalizaron en función del consumo del material de partida.

La visualización de las placas de CCF se realizó con una cámara de yodo, UV, reactivo de pulverización de *p*-anisaldehído o reactivo de ácido

fosfomolíbdico (Aldrich Chemical al 20% en etanol), reactivo de ninhidrina y se activó con calor. Los tratamientos se realizaron típicamente doblando el volumen de la reacción con el disolvente de reacción o disolvente de extracción y después lavándolo con las soluciones acuosas indicadas usando un 25% en volumen del volumen de extracción a menos que se indique otra cosa. Las soluciones del producto se secaron sobre Na_2SO_4 o $MgSO_4$ anhidro antes de la filtración y la evaporación de los disolventes a presión reducida sobre un rotavapor y se observaron como disolventes retirados al vacío. La cromatografía en columna ultrarrápida (Still y col., *J. Org. Chem.*, 43, 2923 (1978)) se realizó usando gel de sílice ultrarrápido de calidad Baker (47-69 μm) y una relación de gel de sílice:material bruto de aproximadamente 20:1 a 50:1 a menos que se indique otra cosa. La hidrogenación se realizó a la presión indicada en los ejemplos o a presión atmosférica.

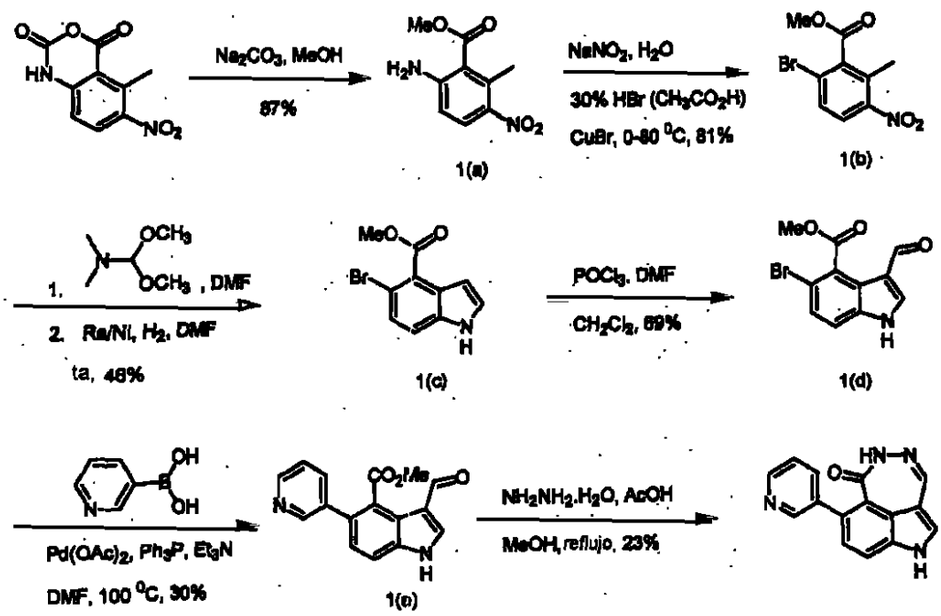
Los espectros de ^1H RMN se registraron en un instrumento Bruker que funciona a 300 MHz, 400 MHz o 500 MHz y los espectros de ^{13}C RMN se registraron funcionando a 75 MHz. Los espectros de RMN se obtuvo como soluciones de $CDCl_3$ (presentado en ppm), usando cloroformo como patrón de referencia (7,25 ppm y 77,00 pprn) o DMSO-D_6 (2,50 ppm y 39,51 ppm) o CD_3OD (3,4 ppm y 4,8 ppm y 49,3 ppm) o tetrametilsilano interno (0,00 ppm) cuando fue apropiado. Se usaron otros disolventes de RMN según fue necesario. Cuando se presentan las multiplicidades de pico, se usan las siguientes abreviaturas: s (singlete), d (doblete), t (triplete), m (multiplete), a (ancho), dd (doblete de dobletes), dt (doblete de tripletes). Las constantes de acoplamiento, cuando se dan, se presentan en Hercios (Hz).

Los materiales de partida usados en los ejemplos están disponibles en el mercado y/o pueden prepararse por técnicas conocidas en la técnica. Las bases libres y sales de materiales de partida e intermedios preparados se usaron indistintamente y se indican. Las bases libres se prepararon mediante la adición de una base terciaria a la sal seguido de la cromatografía sobre gel de sílice de la base libre resultante, si fuese necesario. Las sales se prepararon añadiendo una cantidad equivalente del ácido apropiado a la base libre en una suspensión o solución.

En este documento pueden usarse las siguientes abreviaturas: Et_2O (éter dietílico); DMF (*N,N*-dimetilformamida); DMSO (dimetilsulfóxido); MeOH (metanol); EtOH (etanol); EtOAc (acetato de etilo); THF (tetrahidrofurano); Ac (acetilo); Me (metilo); Et (etilo); y Ph (fenilo).

EJEMPLOS:

Ejemplo 1: 7-Piridin-3-il-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona



Etapa 1. Preparación de éster metílico del ácido 6-amino-2-metil-3-nitro-benzoico 1(a)

5-metil-6-nitro-1*H*-benzo[*d*][1,3]oxazin-2,4-diona (8 g, 36,0 mmol) preparada a partir del ácido 2-amino-6-metil-benzoico (Aldrich) como se describe por Abood, N. A., y col. (1997) Bioorganic & Med. Chem. Lett. 7: 2105-2108 y carbonato sódico (3,82, 36,0 mmol) se agitaron en metanol (180 ml, 0,1 M) a 0°C durante 0,5 horas y después a temperatura ambiente durante 3 horas. Se añadió resina de intercambio iónico fuertemente ácida (Dowex® 50 WX4-200) hasta pH neutro y la solución se filtró. El disolvente se retiró a presión reducida y la cromatografía sobre gel de sílice (60:40 de hexano/acetato de etilo) proporcionó el Intermedio 1(a) (6,59 g) con un rendimiento del 87%.

^{1}H RMN (d_6-DMSO): δ 7,88 (d, 1H, *J* = 9,1 Hz), 6,65 (d, 1H, J = 9,2 Hz), 6,55 (s, 2H), 3,86 (s, 3H), 2,38 (s, 3H). EMCL: ($M-H^+$) 209,1

Etapa 2. Preparación de éster metílico del ácido 6-bromo-2-metil-3-nitro-benzoico 1(b)

El Intermedio 1(a) (0,29 g, 1,38 mmol) se añadió a una solución enfriada con hielo de HBr (al 30% en ácido acético, 1,6 ml) y agua (3,0 ml). Se añadió gota a gota nitrito sódico (0,103 g, 1,5 mmol) en agua (2,0 ml) y la mezcla se agitó a 0°C durante 0,5 horas. El exceso de ácido nítrico se destruyó mediante la adición de urea. Se añadió la solución de sal de diazonio a una mezcla de CuBr (0,6 g, 4,18 mmol), HBr (al 30% en ácido acético, 3,5 ml) y agua (5,0 ml) a 35°C y la mezcla de reacción se calentó a 80°C durante 1,5 horas. El precipitado resultante se filtró y se lavó con agua, proporcionando el Intermedio 1(b) (0,307 g) con un rendimiento del 81%. ^{1}H RMN (d_6-DMSO): δ 7,99 (d, 1H, *J* = 8,8 Hz), 7,85 (d, 1H, *J* = 8,8 Hz), 3,94 (s, 3H), 2,39 (s, 3H).

Etapa 3. Preparación de éster metílico del ácido 5-bromo-1*H*-indol-4-carboxílico 1(c)

El Intermedio 1(b) (2,6 g, 9,5 mmol) se disolvió en *N,N*-dimetilformamida anhidra (0,5 M, 20 ml). Se añadió *N,N*-dimetilformamida dimetil acetal (3,0 equiv., 3,8 ml, 28,5 mmol) en una atmósfera de argón a temperatura ambiente con agitación. La mezcla se calentó a 130°C durante 5 horas y se enfrió a temperatura ambiente. La *N,N*-dimetilformamida y la *N,N*-dimetilformamida dimetil acetal sin reaccionar se retiraron a presión reducida (35°C, aprox. 5 mm de Hg). Se añadió tolueno (~50 ml) y los volátiles se retiraron al vacío. La enamina bruta se disolvió en *N,N*-dimetilformamida (0,2 M, 50 ml) seguido de la adición de Ra/Ni (~300 mg). La mezcla de reacción se agitó en atmósfera de hidrógeno durante 7 horas, se filtró sobre celite y se concentró. La cromatografía sobre gel de sílice (80:20 de hexano/acetato de etilo) proporcionó el Intermedio 1(c) (1,1 g) con un rendimiento del 46%.

^{1}H RMN (d_6-DMSO): δ 11,54 (s, 1H), 7,51 (d, 1H, J = 1,8 Hz), 7,49 (dd, 1H, J = 8,5, 0,8 Hz), 7,33 (dd, 1H, J = 8,7 Hz), 6,50-6,47 (m, 1H), 3,92 (s, 3H).

EMCL: ($M+H^+$) 252,1

Etapa 4. Preparación de éster metílico del ácido 5-bromo-3-formil-1*H*-indol-4-carboxílico 1(d)

Un reactivo de Vilsmeier premezclado compuesto por $POCl_3$ (0,53 ml, 5,7 mmol) en *N,N*-dimetilformamida (1,2 ml, 15,6 mmol) se añadió gota a gota a 0°C al Intermedio 1(c) (0,66 g, 2,6 mmol) en CH_2Cl_2 anhidro (13 ml, 0,2 M) con agitación vigorosa. La mezcla se agitó durante 0,5 horas a temperatura ambiente, se inactivó con acetato sódico acuoso (2,0 M, 10 ml) y se neutralizó con Na_2CO_3 sólido. La mezcla se repartió entre acetato de etilo (50 ml) y H_2O

(10 ml). Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (1 x 20 ml). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron, dando el Intermedio 1(d) (0,51 g) con un rendimiento del 69%.

^{1}H RMN (d_6-DMSO): δ 12,54 (s, 1H), 9,80 (s, 1H), 8,43 (s, 1H), 7,59-7,48 (m, 2H), 3,91 (s, 3H).

EMCL: ($M+H^+$) 306,0

Etapa 5. Preparación de éster metílico del ácido 3-formil-5-piridin-3-il-1*H*-indol-4-carboxílico 1(e)

Una solución del Intermedio 1(d) (0,05 g, 0,18 mmol), piridina del ácido 3-bórico (0,034 g, 0,27 mmol), acetato de paladio (II) (0,004 g, 0,0018 mmol), trifenilfosfina (0,009 g, 0,035 mmol) y trietilamina (0,08 ml, 0,55 mmol) en *N,N*-dimetilformamida (0,7 ml, 0,25 M) se calentó a 100°C durante 96 horas. La mezcla de reacción se enfrió y se filtró a través de celite, proporcionando después de la cromatografía en columna el Intermedio 1(e) (0,015 g) con un rendimiento del 30%.

EMCL: ($M+H^+$) 281,1

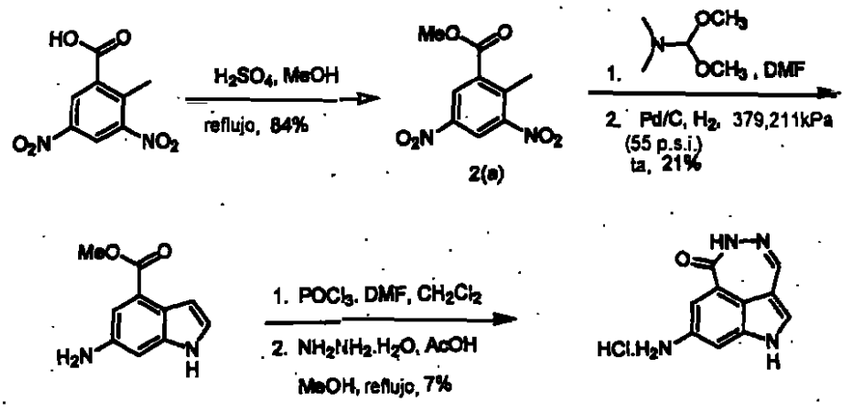
Etapa 6. Preparación del compuesto del título: 7-piridin-3-il-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona

Una solución del Intermedio 1(e) (0,015 g, 0,054 mmol), hidrazina (0,008 ml, 0,135 mmol) y ácido acético (0,020 ml, 2%) en metanol anhidro (1,0 ml, 0,05 M) se calentó a 80°C durante 24 horas. La mezcla de reacción se enfrió a temperatura ambiente y el compuesto del título (0,0035 g) se obtuvo después de una purificación por HPLC preparativa con un rendimiento del 23%.

^{1}H RMN (d_6-DMSO): δ 12,03 (s, 1H), 9,97 (s, 1H), 8,69 (s, 1H), 8,65 (d, 1H, *J* = 4,6 Hz), 8,09 (d, 1H, *J* = 8,3 Hz), 7,77 (d, 1H, *J* = 2,7 Hz), 7,76-7,68 (m, 1H), 7,61 (d, 1H, *J* = 8,4 Hz), 7,54 (s, 1H), 7,01 (d, 1H, J = 8,4 Hz).

EMCL: ($M+H^+$) 263,1

Ejemplo 2: 8-Amino-1,5-dihidro-[2,1]diazepino[4,5,6-*cd*]indol-6-ona (sal clorhidrato)



Etapa 1. Preparación de éster metílico del ácido 2-metil-3,5-dinitro-benzoico 2(a)

Se añadió lentamente ácido sulfúrico concentrado (0,5 ml) a temperatura ambiente con agitación a ácido 2-metil-3,5-dinitro-benzoico (5,22 g, 23,06 mmol) en metanol anhidro (200 ml). Después de calentar a reflujo durante una noche en una atmósfera de argón, se determinó que la reacción estaba aproximadamente al 50% completa. Se usó tolueno (100 ml) para formar un azeótropo con el H_2O generado a partir de la reacción y se añadieron metanol anhidro preparado reciente (300 ml) y H_2SO_4 (0,5 ml) y la mezcla se calentó de nuevo a reflujo durante una noche en una atmósfera de argón, momento en el que los componentes volátiles se redujeron al vacío. Se añadieron acetato de etilo y NaOH acuoso al 5% con agitación, y el producto se extrajo en el acetato

de etilo. Después, el acetato de etilo se lavó dos veces cada una con NaOH acuoso al 5% y $NaHCO_3$ saturado acuoso, una vez con salmuera y se secó con Na_2SO_4, dando el Intermedio 2(a) (4,65 g, 19,37 mmol) en forma de un sólido blanco con un rendimiento del 84%.

Etapa 2. Preparación de éster metílico del ácido 6-amino-1*H*-indol-4-carboxílico 2(b)

Usando una modificación del procedimiento descrito por Coe, J.W., y col., (1996) Tetrahedron Letters 37 (34): 6045-6048, el Intermedio 2(a) (268 mg, 1,12 mmol) se disolvió en *N,N*-dimetilformamida anhidra (0,56 ml) y se le añadió *N,N*-dimetilformamida dimetil acetal (0,445 ml, 3,35 mmol) en una atmósfera de Ar con agitación. La mezcla se calentó a 120°C durante una noche, momento en el que la *N,N*-dimetilformamida dimetil acetal sin reaccionar se retiró al vacío (35-40°C, aprox. 5 mm de Hg). A la enamina roja resultante se le añadieron *N,N*-dimetilformamida anhidra (aprox. 10 ml) y paladio al 10% sobre carbono (230 mg) y la mezcla se hidrogenó a 379,211 kPa (55 psi) durante 5 horas. El catalizador de Pd se filtró a través de tierra diatomácea y al filtrado se le añadió H_2O. Después, el componente acuoso se extrajo múltiples veces con acetato de etilo y los extractos combinados se secaron con Na_2SO_4, se filtraron y los componentes volátiles se retiraron al vacío, dando el Intermedio 2 bruto (90 mg) en forma de un vidrio pardo. La purificación se realizó eluyendo a través de un lecho corto de sílice con acetato de etilo al 20% y etanol al 20% en hexano, dando el Intermedio 2(b) (45 mg, 0,24 mmol) en forma de un sólido pardo con un rendimiento del 21%.

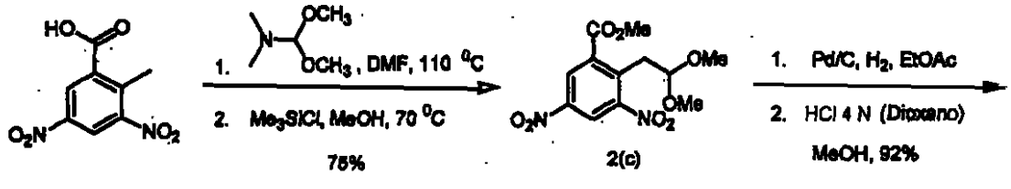
Etapa 3. Preparación del compuesto del título: 8-Amino-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona (sal clorhidrato)

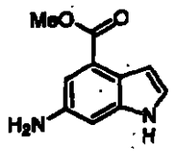
Con refrigeración con un baño de hielo en atmósfera de argón, al Intermedio 2(b) (45 mg, 0,24 mmol) en CH_2Cl_2 anhidro (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se le añadió gota a gota un reactivo de Vilsmeier premezclado (0,1 ml) compuesto por $POCl_3$ (0,47 ml) en *N,N*-dimetilformamida (0,77 ml). Después de retirar el baño de hielo, la mezcla se agitó durante 0,5 horas, momento en el que la reacción se enfrió de nuevo en un baño de hielo y se le añadió más reactivo de Vilsmeier (0,1 ml). Después de la retirada del baño de hielo, la reacción se agitó 0,5 horas y después se vertió en hielo. Se añadió acetato de etilo seguido de $NaHCO_3$ saturado acuoso. Después, el producto se extrajo en acetato de etilo, se lavó con salmuera, se secó con Na_2SO_4 y se filtró, dando (por EMCL) éster metílico del ácido 3-formil-1*H*-indol-4-carboxílico di-*N*-formilado (37 mg, 0,13 mmol) en forma de un vidrio pardo que después se disolvió en metanol anhidro (2,2 ml). Se añadieron ácido acético (0,022, 0,384 mmol) y $H_2NNH_2.H_2O$ (0,038 ml, 0,78 mmol) y la mezcla se calentó a reflujo durante 2 horas. Después de retirar los componentes volátiles al vacío, el producto bruto se disolvió en H_2O y se filtró, el agua se liofilizó y el vidrio amarillo resultante (36 mg) se cromatografió sobre gel de sílice eluyendo con metanol al 10% en CH_2Cl_2. Las fracciones consideradas puras se reunieron y el producto en metanol se acidificó con HCl 1 M. Los componentes volátiles se retiraron al vacío usando acetonitrilo para formar un azeótropo con el agua restante, proporcionando el compuesto del título (4 mg, 0,016 mmol) en forma de un sólido pardo con un rendimiento del 7%.

^{1}H RMN (d_6-DMSO): δ 11,99 (s, 1H), 10,40 (s, 1H), 7,70 (s, 1H), 7,55 (s, 1H), 7,52-7,41 (*m*, 2H).

EMAR (MALDI M+H$^+$) Calc. para $C_{10}H_8N_4O$: 201,0771, Encontrado: 201,0776.

Procedimiento alternativo para la preparación del clorhidrato del Intermedio 2(b):





2(b) clorhidrato

Etapa 4. Preparación de éster metílico del ácido 2-(2,2-dimetoxi-etil)-3,5-dinitro-benzoico 2(c)

[Atención: ¡el éster metílico del ácido 2-(2-dimetilamino-vinil)-3,5-dinitro-benzoico generado durante (primera etapa de la Etapa 4) la formación de la enamina podría conducir a una descomposición explosiva!]

Se disolvió ácido 2-metil-3,5-dinitro-benzoico (100 g, 0,442 mol) en *N,N*-dimetilformamida anhidra (1 M, 400 ml). Se añadió *N,N*-dimetilformamida dimetil acetal (188 ml, 1,33 mol) en una atmósfera de argón durante 10 min a temperatura ambiente con agitación. La mezcla se calentó a 110°C durante 5 horas detrás de un protector, y se enfrió a temperatura ambiente. La *N,N*-dimetilformamida y la *N,N*-dimetilformamida dimetil acetal sin reaccionar se retiraron a presión reducida (35°C, aprox. 5 mm de Hg). Se añadió tolueno (~50

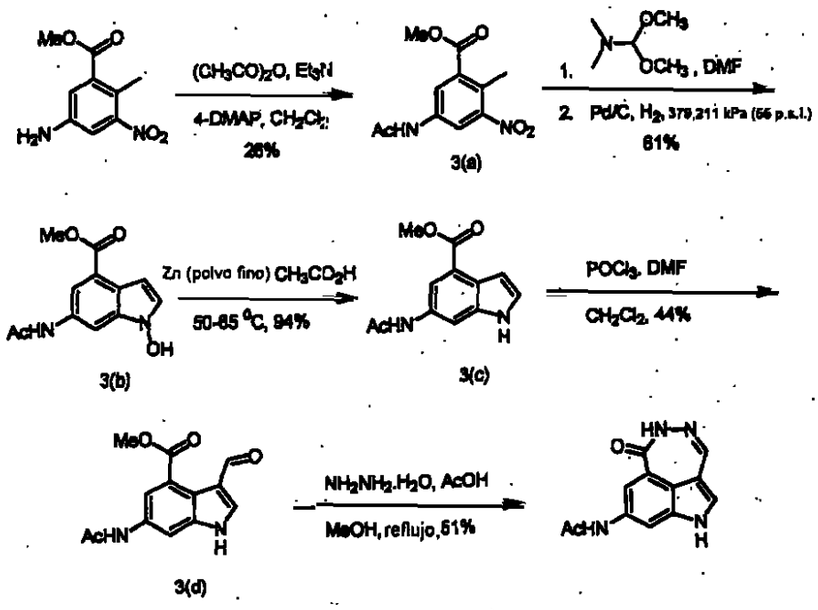
ml) y los volátiles se retiraron al vacío. Se mezcló éster metílico del ácido 2-(2-dimetilamino-vinil)-3,5-dinitro-benzoico, aislado en forma de un sólido rojo oscuro, con metanol anhidro (880 ml) y se añadió clorotrimetilsilano (140 ml, 1,10 mol) durante 10 min. La solución se calentó a reflujo (baño de aceite a 67-70°C) en atmósfera de argón durante 20 horas, se enfrió a temperatura ambiente y el volumen de la mezcla se redujo al vacío a aproximadamente 100 ml. El sólido precipitado se recogió por filtración y se lavó con metanol frío (100 ml). El sólido pardo oscuro se secó al vacío, se trituró con acetona (100 ml), se recogió de nuevo por filtración y se lavó con éter dietílico (150 ml), proporcionando el Intermedio 2(c) (79 g). Las aguas madre de la primera precipitación y las diversas trituraciones se combinaron y se concentraron. Después, se añadió recristalizó más Intermedio 2(c) (21 g) en ciclohexano/acetato de etilo (9:1) proporcionando un segundo lote. De nuevo, las aguas madre resultantes se redujeron al vacío y se recristalizó un tercer lote del Intermedio 2(c) (4 g) en acetona/H_2O (6:4). El rendimiento combinado para los tres lotes del Intermedio 2(c) (104 g) fue del 75%.

Etapa 5. Preparación de clorhidrato del éster metílico del ácido 6-amino-1*H*-indol-4-carboxílico 2(b)

El Intermedio 2(c) (20 g, 63,6 mmol) se disolvió en acetato de etilo anhidro (350 ml) y se añadió paladio al 10% sobre carbono (7,4 g, 6,36 mmol) en atmósfera de argón. La mezcla se hidrogenó a 1 atm (101,325 kPa) hasta que la reacción se consideró completa por EMCL. El catalizador de Pd se retiró por filtración a través de tierra diatomácea y el filtrado se redujo al vacío. El éster metílico del ácido 3,5-diamino-2-(2,2-dimetoxi-etil)-benzoico bruto se disolvió en metanol anhidro (40 ml) y se añadió HCl 4,0 M en dioxano (160 ml).

La mezcla se agitó a temperatura ambiente durante una hora. El sólido precipitado se recogió por filtración y se lavó con CH_2Cl_2 y éter dietílico y se secó al vacío, proporcionando el Intermedio 2(b) (clorhidrato) (11,85 g) en forma de un sólido gris. El filtrado se concentró y se precipitó más clorhidrato del Intermedio 2(b) (1,48 g). El rendimiento combinado para ambos lotes del Intermedio 2(b) (13,33 g) fue del 92%

Ejemplo 3: *N*-(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



Etapa 1. Preparación de éster metílico del ácido 5-acetilamino-2-metil-3-nitro-benzoico 3(a)

A éster metílico del ácido 5-amino-2-metil-3-nitro-benzoico (428 mg, 2,04 mmol), preparado como se describe por Cannon y col., (1984) J. Med. Chem. 27: 386-389, en CH_2Cl_2 (4 ml) se le añadieron trietilamina (1,71 ml, 12,2 mmol), anhídrido acético (0,77 ml, 8,14 mmol) y 4-(dimetilamino)piridina (30 mg, 0,25 mmol) con agitación a temperatura ambiente. Después de agitar durante una

noche, la EMCL indicó una mezcla de productos mono y diacetilados. Se añadió $NaHCO_3$ saturado acuoso y la mezcla se dejó de nuevo agitar durante una noche. Se añadió más CH_2Cl_2 y las fases se separaron. La fase orgánica se redujo y se añadió acetato de etilo. La fase orgánica se lavó con $NaHCO_3$ saturado acuoso, con H_2O, con $KHSO_4$ saturado acuoso y con salmuera, se secó (Na_2SO_4), se filtró y se evaporó hasta un aceite que después se re-disolvió en una cantidad mínima de acetato de etilo. Se añadió hexano y el precipitado resultante se aisló en forma de sólidos castaños (469 mg) que después se purificaron sobre gel de sílice, eluyendo con 1:2 de acetato de etilo:hexano seguido de 1:1 de acetato de etilo:hexano, proporcionando el Intermedio 3(a) (133 mg, 0,53 mmol) en forma de un sólido crema con un rendimiento del 26%. (También se aisló éster metílico del ácido 5-diacetilamino-2-metil-3-nitro-benzoico (248 mg, 0,84 mmol)).

^{1}H RMN (d_6-DMSO): δ 10,46 (s a, 1H, intercambios), 8,34 (s, 1H), 8,14 (s, 1H), 3,89 (s, 3H), 2,43 (s, 3H), 2,08 (s, 3H).

EMCL: $(M-H)^-$ 251,3.

Etapa 2. Preparación de éster metílico del ácido 6-acetilamino-1-hidroxi-1*H*-indol-4-carboxílico 3(b)

Al Intermedio 3(a) (117 mg, 0,46 mmol) en *N,N*-dimetilformamida anhidra (0,5 ml) se le añadió, en una atmósfera de Ar con agitación, *N,N*-dimetilformamida dimetil acetal (0,185 ml, 1,39 mmol). La mezcla se calentó a 120°C durante 5-6 horas, momento en el que la *N,N*-dimetilformamida dimetil acetal sin reaccionar se retiró al vacío (35-40°C, aprox. 5 mm de Hg). A la enamina roja resultante se le añadieron *N,N*-dimetilformamida anhidra (aprox. 20 ml), acetato de etilo (10 ml) y paladio al 10% sobre carbono (150 mg). La

mezcla se hidrogenó a 379,211 kPa (55 psi) durante 4 horas, momento en el que la *N,N*-dimetilformamida se retiró al vacío, se añadió metanol y el catalizador de Pd se retiró por filtración. De nuevo, los componentes volátiles se retiraron al vacío. Después de la trituración con éter dietílico, el triturado se evaporó, proporcionando el Intermedio 3(b) bruto (70 mg, 0,28 mmol) en forma de sólidos castaños con un rendimiento del 61% que se utilizaron sin purificación adicional.

EMCL: $(M-H)^-$ 247,3.

Etapa 3. Preparación de éster metílico del ácido 6-acetilamino-1*H*-indol-4-carboxílico 3(c)

Al Intermedio 3(b) (39 mg, 0,16 mmol) en ácido acético (1 ml) se le añadió polvo de cinc (206 mg, 3,15 mmol) con agitación. La mezcla se calentó a 50°C durante 0,5 horas y después a 65°C durante 0,5 horas tiempo durante el cual la mezcla se volvió verde. Después de enfriar a temperatura ambiente, se añade metanol y la mezcla se filtra a través de tierra diatomácea aclarando varias veces con metanol. Después de la evaporación, los sólidos castaños resultantes se trituran con metanol y los componentes volátiles del triturado se retiran al vacío, proporcionando el Intermedio 3(c) bruto (35 mg, 0,15 mmol) en forma de sólidos castaños con un rendimiento bruto del 94% que después se utilizaron sin purificación adicional.

EMCL: $(M-H)^-$ 231,2.

Etapa 4. Preparación de éster metílico del ácido 6-acetilamino-3-formil-1*H*-indol-4-carboxílico 3(d)

Con refrigeración en un baño de hielo en atmósfera de argón, se añadieron 0,2 ml de un reactivo de Vilsmeier premezclado compuesto por

$POCl_3$ (0,47 ml) en *N,N*-dimetilformamida (0,77 ml) en dos porciones iguales al Intermedio 3(c) (35 mg, 0,15 mmol) en 1:1 de CH_2Cl_2: *N,N*-dimetilformamida (1 ml). Después de 0,5 horas, la reacción se interrumpió con agua y se extrajo con acetato de etilo. Después, la fase acuosa se basificó a aproximadamente pH 8 con NaOH acuoso al 5% y se extrajo de nuevo con acetato de etilo. Los extractos de acetato de etilo combinados se secaron con Na_2SO_4, se filtraron y se evaporaron, dando el Intermedio 3(d) (19 mg, 0,07 mmol) en forma de sólidos amarillos con un rendimiento bruto del 44% que después se utilizaron sin purificación adicional. EMCL: $(M-H)^-$ 259,3.

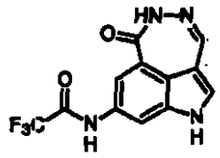
Etapa 5. Preparación del compuesto del título: *N*-(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida

Al Intermedio 3(d) (19 mg, 0,07 mmol) en metanol anhidro (2,0 ml) se le añadieron ácido acético (0,006 ml, 0,1 mmol) y $H_2NNH_2 \cdot H_2O$ (11 mg, 0,22 mmol) y la mezcla se calentó a reflujo durante aproximadamente 1 hora, después de lo cual los componentes volátiles se retiraron al vacío y el vidrio amarillo resultante se disolvió de nuevo en metanol. Después de la recristalización en metanol/éter dietílico, se obtuvo el compuesto del título (9 mg, 0,04 mmol) en forma de un polvo amarillo con un rendimiento del 51%.

^1H RMN (d_6-DMSO): δ 11,60 (s a, 1H, intercambios), 10,10 (s, 1H, intercambios), 9,90 (s, 1H, intercambios), 8,00 (s, 1H), 7,45 (s a, 2H), 7,30 (s, 1H), 1,90 (s, 3H).

EMCL: $(M+H^+)$ 243,1, $(M+Na^+)$ 265,1.

Ejemplo 4: 2,2,2-Trifluoro-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida

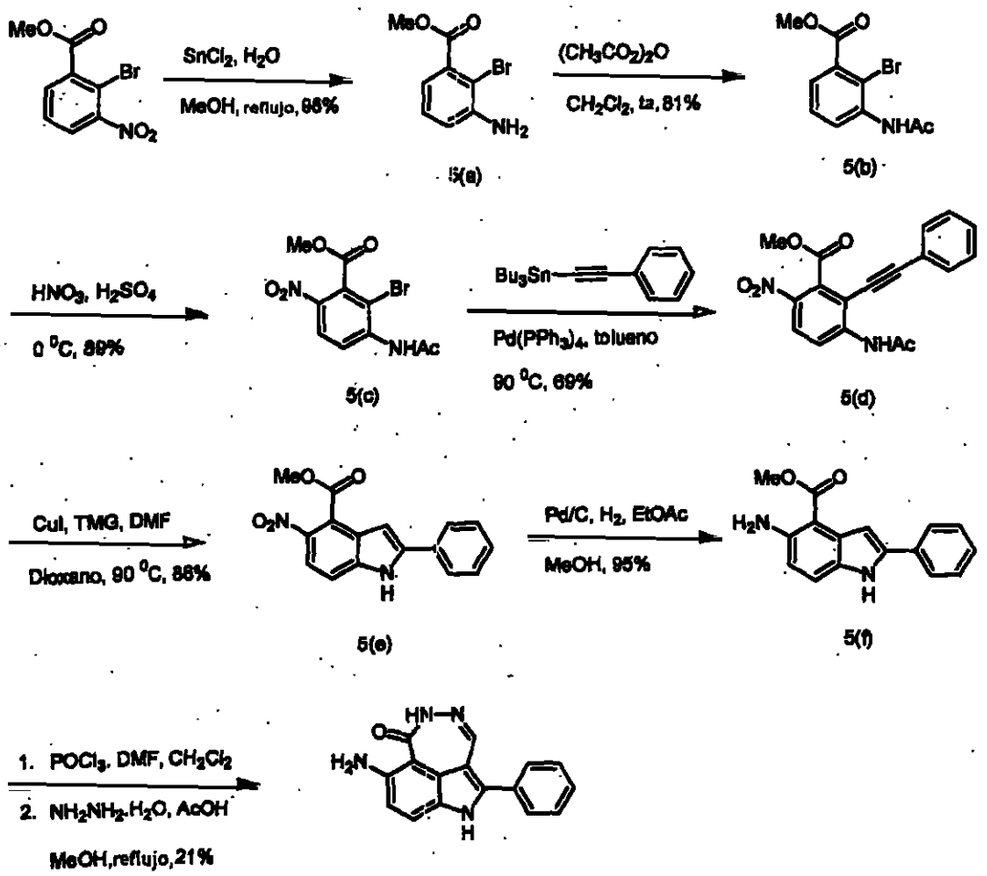


Con agitación, se añadió gota a gota anhídrido trifluoroacético (0,032 ml, 0,23 mmol) a trietilamina (0,088 ml, 0,63 mmol) y el compuesto del título del Ejemplo 2 (base libre) (43 mg, 0,21 mmol) en *N,N*-dimetilformamida (2 ml). Después de 2,5 horas, se añadió más anhídrido trifluoroacético (0,032 ml, 0,23 mmol) para completar la reacción, momento en el que se añadió éter dietílico para precipitar sólidos pardos (25 mg), que se desecharon. El triturado se redujo en volumen y se sometió a HPLC preparativa (MetaChem Metasil AQ C18 de fase inversa 10 µm, 120A, columna de 250 x 21,2 mm eluyendo con CH_3CN/TFA al 0,1% en H_2O a un caudal de 20 ml/min usando un gradiente de CH_3CN al 5-95% durante 20 min) proporcionando, después del aislamiento, el compuesto del título (3,7 mg, 0,01 mmol) en forma de un sólido pardo con un rendimiento del 6%.

^{1}H RMN (d_6-DMSO): δ 12,01 (s, 1H), 11,41 (s, 1H), 10,40 (s, 1H), 8,15 (s, 1H), 7,91 (s, 1H), 7,78 (s, 1H), 7,61 (s, 1H).

EMCL: $(M-H)^-$ 295,2.

Ejemplo 5: 7-Amino-2-fenil-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona



Etapa 1. Preparación de éster metílico del ácido 3-amino-2-bromo-benzoico 5(a)

Se calentaron a reflujo éster metílico del ácido 2-bromo-3-nitro-benzoico (12,9 g, 49,5 mmol) (preparado a partir de ácido 2-amino-3-nitro-benzoico como se describe por Webber E. S. y col., véase la solicitud de patente número **WO 01/16136 A2**) y $SnCl_2$ (42 g, 223 mmol) en metanol (225 ml, 0,2 M) y H_2O (5,3 g, 243 mmol) durante 2 horas. Después de enfriar a temperatura ambiente, se añadieron tierra diatomácea (20 g) y diclorometano (1 l) seguido de hidróxido

sódico acuoso 3 N (150 ml) con agitación vigorosa. La mezcla se filtró y la fase orgánica se lavó con cloruro sódico saturado acuoso. La solución orgánica se secó sobre sulfato sódico, se filtró y todos los volátiles se retiraron a presión reducida, proporcionando el Intermedio 5(a) (11,4 g) con un rendimiento del 98%. ^{1}H RMN (d_6-DMSO): δ 7,12 (dd, 1H, J = 8,1, 7,5 Hz), 6,93 (dd, 1H, *J* = 8,1, 1,6 Hz), 6,80 (dd, 1H, *J* = 7,4, 1,6 Hz), 5,57 (s, 2H), 3,81 (s, 3H).

Etapa 2. Preparación de éster metílico del ácido 3-acetilamino-2-bromo-benzoico 5(b)

El Intermedio 5(a) (2,21 g, 9,6 mmol) y anhídrido acético (1,82 ml, 19,2 mmol) se agitaron en CH_2Cl_2 (100 ml, 0,1 M) a 22°C durante 24 horas. Los volátiles se retiraron al vacío y la cromatografía sobre gel de sílice proporcionó el Intermedio 5(b) (2,08 g) con un rendimiento del 79%.

^{1}H RMN (d_6-DMSO): δ 9,58 (s, 1H), 7,70 (dd, 1H, J = 6,9, 2,7 Hz), 7,50-7,41 (m, 2H), 3,86 (s, 3H), 2,09 (s, 3H).

EMCL: ($M+H^+$) 272,0, 274,0

Etapa 3. Preparación de éster metílico del ácido 3-acetilamino-2-bromo-6-nitro-benzoico 5(c)

El Intermedio 5(b) (1,0 g, 3,7 mmol) se nitró de manera análoga a la etapa 1 del Ejemplo **2**. El Intermedio 5(c) (1,0 g, 89%) se obtuvo después de la cromatografía sobre gel de sílice.

^{1}H RMN (d_6-DMSO): δ 9,83 (s, 1H), 8,3 (d, 1H, J = 9,0 Hz), 8,15 (d, 1H, *J* = 9,0 Hz), 3,93 (s, 3H), 2,20 (s, 3H).

EMCL: ($M+H^+$) 315,0, 317,0

Etapa 4. Preparación de éster metílico del ácido 3-acetilamino-6-nitro-2-feniletinil-benzoico 5(d)

El Intermedio 5(c) (0,85 g, 2,7 mmol) se acetiló de manera análoga a la etapa 3 del Ejemplo **6**, proporcionando el Intermedio 5(d) (0,4 g, 44%) después de la cromatografía sobre gel de sílice.

^{1}H RMN (d_6-DMSO): δ 9,93 (s, 1H), 8,32-8,25 (m, 2H), 7,65-7,59 (m, 2H), 7,53-7,47 (m, 3H), 3,97 (s, 3H), 2,25 (s, 3H).

EMCL: ($M-H^+$) 337,1

Etapa 5. Preparación de éster metílico del ácido 5-nitro-2-fenil-1*H*-indol-4-carboxílico 5(e)

El Intermedio 5(d) (0,096 g, 0,28 mmol), yoduro de cobre (0,076 g, 0,4 mmol) y *N,N,N,N*-tetrametilguanidina (0,36 ml, 2,8 mmol) se agitaron en una mezcla de dimetilformamida/dioxano (1:4, 2 ml, 0,15 M) a 90°C durante 2 horas. La mezcla de reacción se enfrió a temperatura ambiente y se vertió en acetato de etilo (30 ml). La fase orgánica se lavó posteriormente con una solución saturada de cloruro amónico (3 x 5 ml), H_2O (2 x 5 ml) y una solución saturada acuosa de cloruro sódico (2 x 5 ml), se secó sobre sulfato sódico, se filtró y los volátiles se retiraron al vacío. La cromatografía sobre gel de sílice proporcionó el Intermedio 5(e) (0,073 g) con un rendimiento del 86%.

^{1}H RMN (d_6-DMSO): δ 12,50 (s, 1H), 7,98-7,88 (m, 3H), 7,69-7,40 (m, 4H), 7,13 (s ancho, 1H), 3,97 (s, 3H).

EMCL: ($M-H^+$) 295,1

Etapa 6. Preparación de éster metílico del ácido 5-amino-2-fenil-1*H*-indol-4-carboxílico 5(f)

De manera análoga a la preparación del Ejemplo **2** (etapa 5), el Intermedio 5(e) (0,072 g, 0,24 mmol) se hidrogenó, proporcionando el Intermedio 5(f) (0,06 g, 95%).

^{1}H RMN (d_6-DMSO): δ 11,68 (s, 1H), 7,86 (d, 2H, J = 7,4 Hz), 7,52-7,43 (m, 3H), 7,31 (dd, 1H, J = 7,4, 7,2 Hz), 7,20 (s, 1H), 6,83 (d, 1H, J = 8,5 Hz), 3,94 (s, 3H).

EMCL: ($M+H^+$) 235,1

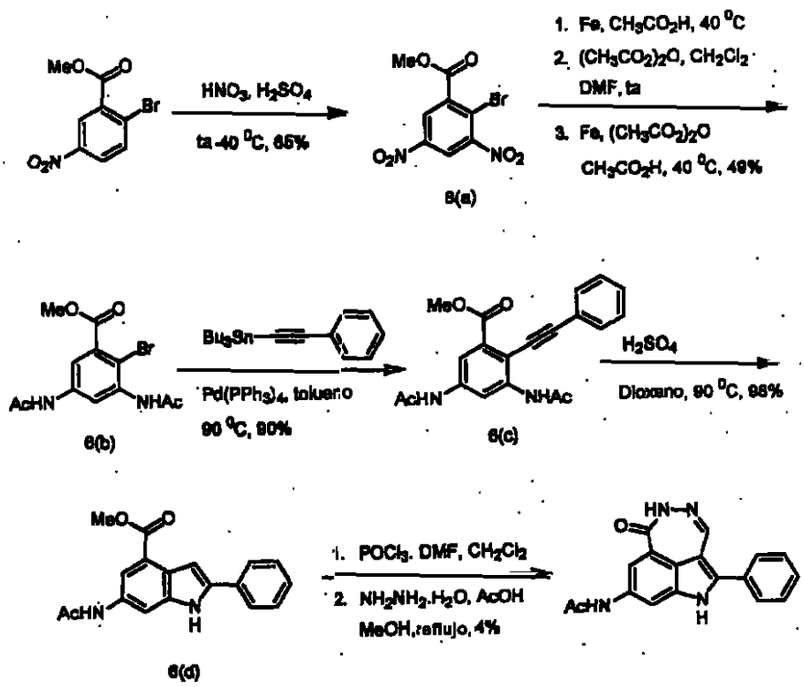
Etapa 7. Preparación del compuesto del título: 7-Amino-2-fenil-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona

Realizado análogamente a las etapas 4 y 5 del Ejemplo **3**, el Intermedio 5(f) (0,055 g, 0,21 mmol) se formiló y se cicló, proporcionando el compuesto del título (0,012 g, 21%).

^{1}H RMN (d_6-DMSO): δ 12,17 (s, 1H), 8,32 (s, 1H), 7,95-7,84 (m, 3H), 7,74 (d, 1H, J = 1,8 Hz), 7,55-7,47 (m, 2H), 7,42 (d, 1H, *J* = 8,6 Hz), 7,37 (dd, 1H, *J* = 7,4, 7,3 Hz), 5,91 (s, 2H).

EMCL: ($M+H^+$) 277,1

Ejemplo 6: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il-acetamida



Etapa 1. Preparación de éster metílico del ácido 2-bromo-3,5-dinitro-benzoico 6(a)

Se añadió lentamente ácido sulfúrico concentrado (20 ml) a éster metílico del ácido 2-bromo-5-nitro-benzoico (20,52 g, 78,91 mmol) con agitación. Después de unos minutos, se añadió ácido nítrico fumante (20 ml) y la mezcla se tapó y se calentó a 40°C durante aproximadamente 60 horas, momento en el que el matraz se enfrió a temperatura ambiente, se abrió cuidadosamente y la reacción se vertió sobre agua con hielo y acetato de etilo. El producto se extrajo en acetato de etilo y se lavó dos veces con H_2O, dos veces con $NaHCO_3$ saturado acuoso y salmuera, se secó (Na_2SO_4) y se filtró,

proporcionando el Intermedio 6(a) (15,64 g, 51,26 mmol) en forma de un sólido crema con un rendimiento del 65%.

^{1}H RMN (d_6-DMSO): δ 9,07 (s, 1H), 8,73 (s, 1H), 3,98 (s, 3H).

EMCL: (M-CO_2CH_3)$^-$ 245,1, 247,1.

Etapa 2. Preparación de éster metílico del ácido 3,5-*bis*-acetilamino-2-bromo-benzoico 6(b)

A ácido acético (250 ml) a temperatura ambiente se le añadió el Intermedio 6(a) (15,49 g, 50,79 mmol). La mezcla se puso en un baño de aceite a 40°C durante aprox. 10 min y se agitó vigorosamente en una atmósfera de Ar hasta que la solución se hizo transparente. Se añadió polvo de hierro (25,34 g, 453,72 mmol) y la mezcla se calentó a 40°C durante aprox. 6 horas. La mezcla se filtró a través de tierra diatomácea, aclarando con metanol. El filtrado combinado y los aclarados se evaporaron, dando sólidos naranjas, que se determinó que eran una mezcla de productos (13,2 g) resultantes de la incompleta reducción de los grupos nitro. Después, esta mezcla (13,1 g) en CH_2Cl_2 (48 ml) y *N,N*-dimetilformamida (5 ml) se trató con anhídrido acético (36 ml, 382 mmol) y se agitó durante una noche en una atmósfera de Ar. El CH_2Cl_2 se evaporó y la mezcla se repartió entre acetato de etilo y $NaHCO_3$ saturado acuoso. La fase acuosa se extrajo dos veces con acetato de etilo y los extractos combinados se lavaron sucesivamente con 1:1 de H_2O:$NaHCO_3$ saturado acuoso (múltiples lavados), HCl 0,5 M acuoso (x 2), $NaHCO_3$ saturado acuoso (x 2) y salmuera. Después, la solución de acetato de etilo se secó (Na_2SO_4), se filtró y se evaporó, dando sólidos amarillos, que después se trituraron con éter dietílico (aprox. 75 ml), dando una mezcla de productos acetilados (11,4 g) en forma de sólidos amarillos. Después, una porción de esta

mezcla de productos acetilados (5,5 g) en ácido acético (17,4 ml) se trató con anhídrido acético (16,5 ml, 174 mmol) y polvo de hierro (9,74 g, 174 mmol) y se calentó a 40°C en una atmósfera de Ar durante una noche. Después, se añadió metanol y la reacción se agitó a temperatura ambiente durante aprox. 1,5 horas. Después, se añadió 9:1 de CH_2Cl_2:metanol y la mezcla se filtró a través de tierra diatomácea, aclarando con 9:1 de CH_2Cl_2:metanol. El filtrado combinado y los aclarados se evaporaron y se añadió de nuevo metanol y la mezcla se agitó durante aprox. 0,5 horas, después de lo cual el metanol se evaporó. Se añadió acetato de etilo seguido de hexano, precipitando sólidos naranjas (6,9 g) que se recogieron. La cromatografía sobre gel de sílice eluyendo con 1:1 de acetona:hexano proporcionó, después del aislamiento, el Intermedio 6(b) (4,1 g, 12,46 mmol) en forma de un sólido crema con un rendimiento del 49%.

Etapa 3. Preparación de éster metílico del ácido 3,5-*bis*-acetilamino-2-feniletinil-benzoico 6(c)

Con agitación, se burbujeó argón en tolueno anhidro (18 ml) que contenía el Intermedio 6(b) (1,08 g, 3,29 mmol). Se añadieron secuencialmente tributil-feniletinil-estannano (1,73 ml, 4,94 mmol) y *tetraquis*(trifenilfosfina)paladio (0) (310 mg, 0,28 mmol) y se burbujeó más Ar en la reacción. Después de tapar fuertemente, la mezcla se calentó a 90°C durante una noche en una atmósfera de argón. Después de enfriar a temperatura ambiente, se añadieron H_2O y $KHSO_4$ saturado acuoso y el producto se extrajo en acetato de etilo y se aisló. Después de la cromatografía sobre gel de sílice eluyendo con 2:3 de acetona:hexano, las fracciones que se consideraron puras se reunieron. Se aisló el Intermedio 6(c) (1,14 g, 3,25

mmol) y se descubrió que estaba contaminado por óxido de trifenilfosfina aproximadamente al 5-10% y se utilizó en la siguiente etapa sin purificación adicional.

^{1}H RMN (d_6-DMSO): δ 10,30 (s, 1H), 9,50 (s, 1H), 8,23 (s, 1H), 8,08 s, 1H), 7,63-7,51 (*m*, 2H, *contaminado con* Ph_3PO), 7,50-7,38 (*m*, 3H, contaminado con Ph_3PO), 3,90 (s, 3H), 2,17 (s, 3H), 2,05 (s, 3H).

EMCL: ($M+H^+$) 351,1, ($M+Na^+$) 373,1, ($M-H^-$) 349,1.

Etapa 4. Preparación de éster metílico del ácido 6-acetilamino-2-fenil-1*H*-indol-4-carboxílico

Al Intermedio 6(c) impuro (853 mg, 2,4 mmol) se le añade ácido sulfúrico concentrado (15 ml). Después de agitar durante 0,5 horas, la mezcla se vierte cuidadosamente en metanol (30 ml) con agitación vigorosa. Se añaden acetato de etilo (aprox. 300 ml) y H_2O (aprox. 100 ml). La fase acuosa se extrae tres veces con acetato de etilo y los extractos combinados se lavan con $NaHCO_3$ saturado acuoso hasta que cesa el desprendimiento de CO_2. Después, el producto en acetato de etilo se lava con salmuera, se seca (Na_2SO_4), se filtra y los componentes volátiles se evaporan, proporcionando el Intermedio 6(d) bruto (790 mg, aprox. 2,4 mmol) en forma de un polvo amarillo que se utilizó sin purificación adicional.

^{1}H RMN (d_6-DMSO): δ 11,75 (s, 1H, intercambios), 10,07 (s, 1H, intercambios), 8,33 (s, 1H), 7,90-7,80 (m, 3H), 7,66-7,23 (m, 4H, parcialmente oscurecido), 3,93 (s, 3H), 2,07 (s, 3H).

EMCL: ($M+H^+$) 309,1, ($M+Na^+$) 331,1, ($M-H^-$) 307,1.

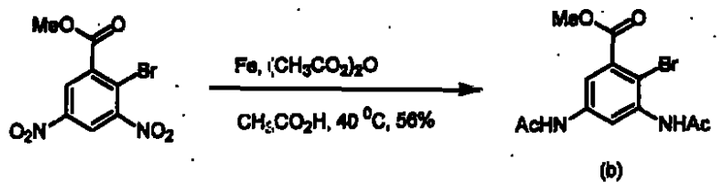
Etapa 5. Preparación del compuesto del título: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il-acetamida

El Intermedio 6(d) bruto (312 mg, aprox. 1 mmol) en *N,N*-dimetilformamida (2 ml) y CH_2Cl_2 (5 ml) se trató con reactivo de Vilsmeier (0,9 ml) de manera similar a la descrita para el Ejemplo **3**, etapa 4. Después de retirar el CH_2Cl_2, de ajustar el pH a aprox. 8 con NaOH 1 N y de retirar los componentes volátiles al vacío, los sólidos amarillos se trituraron con acetato de etilo y metanol. El triturado se evaporó, proporcionando el éster metílico del ácido 6-acetilamino-3-formil-2-fenil-1*H*-indol-4-carboxílico bruto (405 mg) en forma de un sólido amarillo contaminado con sales de la inactivación acuosa. Después, en un procedimiento similar al descrito para el Ejemplo **3**, etapa 5, se añadieron metanol anhidro (15 ml), ácido acético (0,084 ml, 1,47 mmol) y $H_2NNH_2 \cdot H_2O$ (0,147 ml, 3,03 mmol) y la mezcla se calentó a reflujo durante 2 horas. Los componentes volátiles se evaporaron y los sólidos resultantes se trituraron con metanol para disolver el producto mientras se dejaban atrás la mayor parte de los sólidos insolubles. El triturado se evaporó y este procedimiento se repitió. El segundo triturado se evaporó, dando sólidos amarillos (70 mg) enriquecidos en producto que después se sometieron a cromatografía sobre gel de sílice eluyendo con hexano:acetato de etilo:etanol (4:1:1), dando el compuesto del título (12 mg, 0,04 mmol) después del aislamiento en forma de un polvo amarillo con un rendimiento total de aproximadamente el 4%.

^{1}H RMN (d_6-DMSO): δ 12,10 (s, 1H, intercambios), 10,33 (s, 1H, intercambios), 10,06 (s, 1H, intercambios), 8,17 (s, 1H), 7,70-7,43 (m, 7H), 2,05 (s, 3H).

EMCL: $(M+H^+)$ 319,1, $(M+Na^+)$ 341,1, $(M-H)^-$ 317.

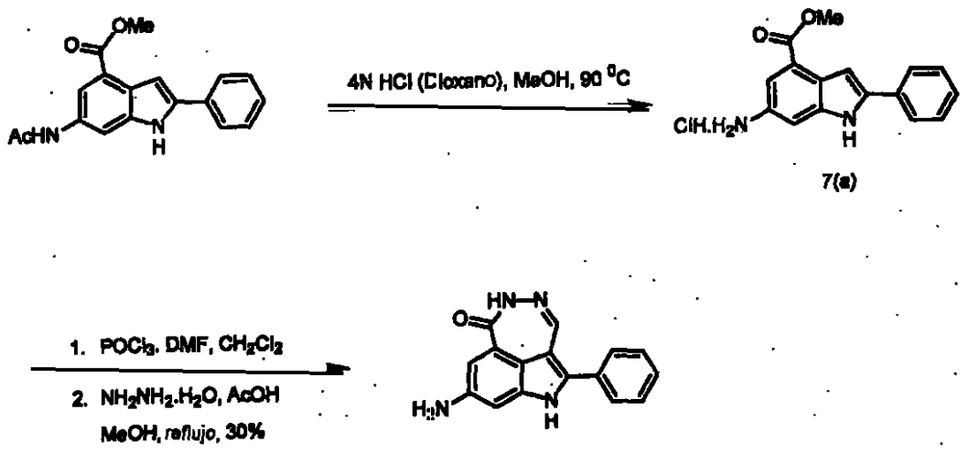
Procedimiento Alternativo para la Preparación del Intermedio 6(b).



(b)

Al ácido acético (10 ml) a temperatura ambiente se le añadieron anhídrido acético (10,0 ml, 106 mmol), polvo de hierro (5,5 g, 98 mmol) y el Intermedio 6(a) (3,0 g, 9,8 mmol). La mezcla se colocó en un baño de aceite a 43°C y se agitó vigorosamente en una atmósfera de argón durante 48 horas. La suspensión densa fue de color naranja a castaño. Se añadieron más ácido acético (2 ml), anhídrido acético (2 ml, 21,2 mmol) y polvo de hierro (1,0 g, 17,9 mmol) y la mezcla se agitó a 43°C durante 24 horas más tras lo cual la mezcla se vertió en metanol al 10% en CH_2Cl_2 (300 ml) y se filtró a través de tierra diatomácea. El filtrado se concentró y se añadieron acetato de etilo (300 ml) y H_2O (300 ml). El producto se extrajo en acetato de etilo y se lavó dos veces con H_2O y dos veces con salmuera, se secó ($MgSO_4$) y se filtró. Después de la recristalización en acetato de etilo caliente (10 ml), de la recogida por filtración y el posterior lavado de los sólidos con CH_2Cl_2 (5 ml) y éter dietílico (30 ml), se obtuvo el Intermedio 6(b) (1,8 g, 5,47 mmol) en forma de un sólido blanco con un rendimiento del 56%.

Ejemplo 7: 8-Amino-2-fenil-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona



Etapa 1. Preparación de sal 7(a) del éster metílico del ácido 6-amino-2-fenil-1*H*-indol-4-carboxílico (sal clorhidrato)

El Intermedio 6(d) del Ejemplo 6 (9,3 g, 30,2 mmol) y HCl anhidro 4 M en dioxano (160 ml, 604 mmol) se calentaron en metanol anhidro (160 ml) a reflujo durante 3 horas, se enfriaron a temperatura ambiente y los volátiles se retiraron al vacío. El sólido resultante se trituró con acetato de etilo/CH_2Cl_2 (1:1, 50 ml) y se secó, proporcionando el Intermedio 7(a) (8,7 g) con un rendimiento del 95%.

^{1}H RMN (d_6-DMSO): δ 12,26 (s, 1H), 10,10 (ancho, 1H), 7,93 (d, 2H, J = 7,7 Hz), 7,71 (d, 2H, J = 12,2 Hz), 7,52 (dd, 2H, J = 7,7, 7,6 Hz), 7,43-7,36 (m, 2H), 3,96 (s, 3H).

EMCL: ($M+H^+$) 267,2.

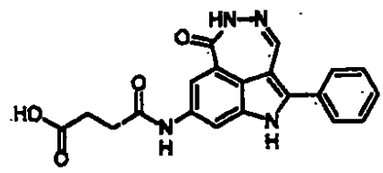
Etapa 2. Preparación del compuesto del título: 8-Amino-2-fenil-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona

En dos etapas, de forma análoga a las etapas 4 y 5 del Ejemplo **3**, el Intermedio 7(a) (8,7 g, 28,7 mmol) se cicló, proporcionando el compuesto del título (5,47 g, 69%).

^{1}H RMN (d_6-DMSO): δ 11,53 (s, 1H), 10,15 (s, 1H), 7,62-7,40 (m, 6H), 6,98 (d, 1H, J = 1,8 Hz), 6,65 (d, 1H, J = 1,8 Hz), 5,21 (s, 2H).

EMCL: ($M+H^+$) 277,2.

Ejemplo 8: Ácido *N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-succinámico

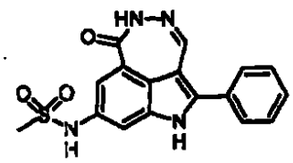


Se añadió anhídrido succínico (3 equiv., 0,022 g) a una solución del compuesto del título del Ejemplo 7 (0,02 g, 0,072 mmol) en *N,N*-dimetilformamida (0,7 M, 1 ml) y metanol (2,5 M, 0,3 ml). La mezcla de reacción se agitó a 22°C durante 24 horas y se concentró a presión reducida. El sólido amarillo se trituró con metanol (1,0 ml) y se recogió por filtración. Después de los lavados con metanol (4 ml) y éter dietílico (5,0 ml), se obtuvo el compuesto del título (21 mg) con un rendimiento del 77%.

^{1}H RMN (d_6-DMSO): δ 12,03 (s, 1H), 10,31 (s, 1H), 10,09 (s, 1H), 8,12 (s, 1H), 7,68-7,45 (m, 7H), 2,60-2,53 (m, 4H).

EMCL: ($M+H^+$) 377,1.

Ejemplo 9: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-metanosulfonamida



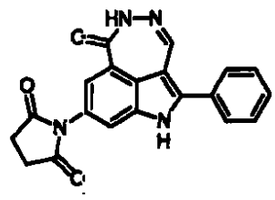
Se añadió cloruro de metanosulfonilo (1,5 equiv., 0,003 g) a una solución del compuesto del título del Ejemplo 7 (0,005 g, 0,018 mmol) en CH_2Cl_2 (0,045

M, 0,4 ml) y piridina (0,045 M, 0,4 ml). La mezcla se agitó a 22°C durante 24 horas y se concentró a presión reducida. La cromatografía sobre gel de sílice (trietilamina/metanol/CH_2Cl_2; 1:5:94) proporcionó el compuesto del título (1,7 mg) con un rendimiento del 30%.

^{1}H RMN (d_6-DMSO): δ 12,15 (s, 1H), 10,40 (s, 1H), 9,71 (s, 1H), 7,70-7,43 (m, 8H), 2,30 (m, 3H).

EMCL: (M+H*) 355,1.

Ejemplo 10: 1-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-pirrolidin-2,5-diona

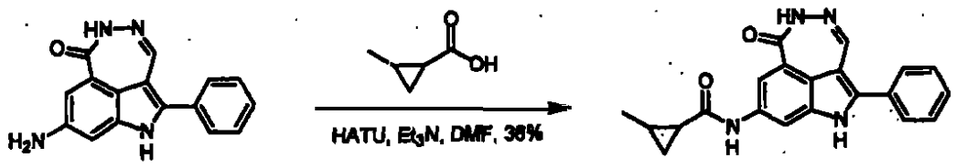


Se añadieron trietilamina (0,18 mmol, 0,025 ml) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,04 mmol, 0,013 g) a una solución del compuesto del título del Ejemplo **8** (0,013 g, 0,036 mmol) en *N,N*-dimetilformamida (0,05 M, 0,75 ml). La mezcla de reacción se agitó a 22°C durante 12 horas y se concentró a presión reducida. El sólido amarillo se trituró con metanol (3,0 ml), se recogió por filtración, se lavó con metanol (4,0 ml) y éter dietílico (5,0 ml), proporcionando el compuesto del título (5,8 mg) con un rendimiento del 47%.

^{1}H RMN (d_6-DMSO): δ 12,38 (s, 1H), 10,44 (s, 1H), 9,71 (s, 1H), 7,74-7,42 (m, 8H), 2,79 (m, 3H).

EMCL: (M+H$^+$) 359,1.

Ejemplo 11: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 2-metil-ciclopropanocarboxílico

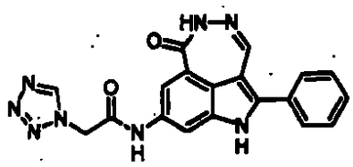


Se agitaron trietilamina (0,030 ml, 0,22 mmol), el compuesto del título del Ejemplo **7** (15 mg, 0,054 mmol) y ácido 2-metil-ciclopropanocarboxílico (6 mg, 0,062 mmol) en *N,N*-dimetilformamida (1,0 ml). Se añadió hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol) y la reacción se agitó durante una noche, momento en el que los componentes volátiles se retiraron al vacío. La mezcla resultante se purificó sobre gel de sílice, eluyendo con 3:2 de hexano:acetato de etilo. Las fracciones más puras se combinaron y después de la retirada del disolvente, los sólidos resultantes se trituraron con éter dietílico, dando el compuesto del título (7 mg, 0,020 mmol) en forma de un polvo amarillo con un rendimiento del 36%.

^{1}H RMN (d_6-DMSO): δ 12,03 (s, 1H), 10,32 (s, 1H), 10,27 (s, 1H), 8,13 (s, 1H), 7,67-7,48 (m, 7H), 1,54 (m, 1H), 1,11(s, 1H), 1,09 (d, 3H), 1,07 (m, 1H), 1,03 (m, 1H).

EMCL: ($M+H^+$) 359,1, ($M+Na^+$) 381,1.

Ejemplo 12: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-tetrazol-1-il-acetamida



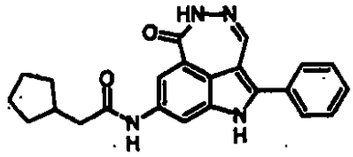
La preparación del ejemplo 12 a partir del compuesto del título del Ejemplo **7** (15 mg, 0,054 mmol), ácido tetrazol-1-il-acético (8 mg, 0,062 mmol), trietilamina (0,030 ml, 0,22 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-

1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. Se añadieron más ácido tetrazol-1-il-acético (1,0 mg, 0,008 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (3,0 mg, 0,008 mmol) después de aprox. 18 horas, completando la reacción. La filtración, la concentración y la recristalización proporcionaron el compuesto del título (12 mg, 0,031 mmol) en forma de un polvo amarillo con un rendimiento del 58%.

^{1}H RMN (d_6-DMSO): δ 12,13 (s, 1H), 10,71 (s, 1H), 10,39 (s, 1H), 9,44 (s, 1H), 8,07 (m, 1H), 7,68-7,47 (m, 7H), 5,05 (s, 2H).

EMCL: ($M+H^+$) 387,2, ($M+Na^+$) 409,1.

Ejemplo 13: 2-Ciclopentil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida

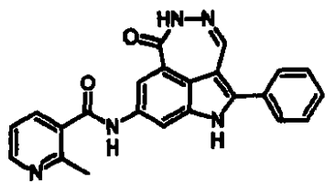


La preparación del ejemplo 13 a partir del compuesto del título del Ejemplo **7** (15 mg, 0,054 mmol), ácido ciclopentil-acético (8 mg, 0,062 mmol), trietilamina (0,030 ml, 0,22 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol) en dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (1:1 de acetato de etilo:hexano), también de manera análoga, seguido de trituración en éter dietílico proporcionó el compuesto del título (3 mg, 0,008 mmol) en forma de un polvo amarillo con un rendimiento del 14%.

^{1}H RMN (d_6-DMSO): δ 12,03 (s, 1H), 10,32 (s, 1H), 9,99 (s, 1H), 8,17 (s, 1H), 7,67-7,49 (m, 7H), 2,33-2,26 (m, 3H), 1,78 (m, 2H), 1,65-1,53 (m, 4H), 1,22 (m, 2H).

EMCL: ($M+H^+$) 387,2, ($M+Na^+$) 409,2.

Ejemplo 14: 2-Metil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-nicotinamida

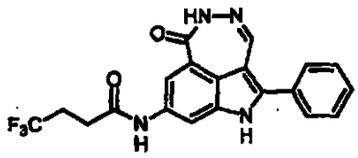


La preparación del ejemplo 14 a partir del compuesto del título del Ejemplo **7** (15 mg, 0,054 mmol), ácido 2-metil-nicotínico (9 mg, 0,062 mmol), trietilamina (0,030 ml, 0,22 mmol) y hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (acetato de etilo), también de manera análoga, seguido de trituración con éter dietílico proporcionó el compuesto del título (7 mg, 0,018 mmol) en forma de un polvo amarillo con un rendimiento del 33%.

^{1}H RMN (d_6-DMSO): δ 12,13 (s, 1H), 10,57 (s, 1H), 10,36 (s, 1H), 8,57 (m, 1H), 8,25 (s, 1H), 7,90 (m, 1H), 7,84 (m, 1H), 7,68 (m, 2H), 7,61-7,50 (m, 4H), 7,34 (m, 1H), 2,60 (s, 3H).

EMCL: ($M+H^+$) 396,2, ($M+Na^+$) 418,1.

Ejemplo 15: 4,4,4-Trifluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-butiramida

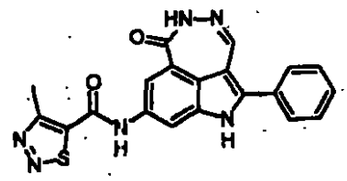


La preparación del ejemplo 15 a partir del compuesto del título del Ejemplo **7** (15 mg, 0,054 mmol), ácido 4,4,4-trifluorobutírico (9 mg, 0,062 mmol), trietilamina (0,030 ml, 0,22 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (1:1 de acetato de etilo:hexano), también de manera análoga, seguido de trituración en éter dietílico proporcionó el compuesto del título (7 mg, 0,017 mmol) en forma de un polvo amarillo con un rendimiento del 32%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,34 (s, 1H), 10,22 (s, 1H), 8,14 (s, 1H), 7,68-7,50 (m, 7H), 2,62 (m, 4H).

EMCL: ($M+H^+$) 401,1, ($M+Na^+$) 423,0.

Ejemplo 16: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 4-metil-[1,2,3]tiadiazol-5-carboxílico



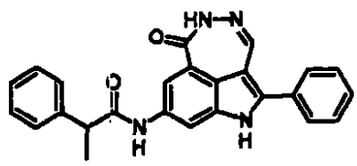
La preparación del ejemplo 16 a partir del compuesto del título del Ejemplo **7** (15 mg, 0,054 mmol), ácido 4-metil-[1,2,3]tiadiazol-5-carboxílico (8 mg, 0,062 mmol), trietilamina (0,030 ml, 0,22 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol) en *N,N*-

dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. Se añadieron más ácido 4-metil-[1,2,3]tiadiazol-5-carboxílico (1,0 mg, 0,006 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (2,0 mg, 0,006 mmol) después de aprox. 18 horas para completar la reacción. La cromatografía sobre gel de sílice, también de manera análoga, seguido de trituración en éter dietílico proporción el compuesto del título (7 mg, 0,017 mmol) en forma de un polvo amarillo con un rendimiento del 32%.

^{1}H RMN (d_6-DMSO): δ 12,21 (s, 1H), 10,85 (s, 1H), 10,41 (s, 1H), 8,18 (s, 1H), 7,81 (m, 1H), 7,69 (m, 2H), 7,61-7,51 (m, 4H), 2,85 (s, 3H).

EMCL: ($M+H^+$) 403,1, ($M+Na^+$) 425,0.

Ejemplo 17: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenil-propionamida

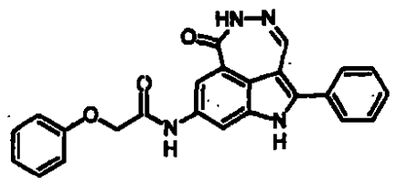


La preparación del ejemplo 17 a partir del compuesto del título del Ejemplo **7** (15 mg, 0,054 mmol), ácido 2-fenil-propiónico (9 mg, 0,062 mmol), trietilamina (0,030 ml, 0,22 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (1:1 de acetato de etilo:hexano), también de manera análoga, seguido de trituración en éter dietílico proporcionó el compuesto del título (7 mg, 0,017 mmol) en forma de un polvo amarillo con un rendimiento del 32%.

^{1}H RMN (d_6-DMSO): δ 12,08 (s, 1H), 10,33 (s, 1H), 10,21 (s, 1H), 8,16 (s, 1H), 7,64 (m, 3H), 7,59 (m, 2H), 7,55 (m, 2H), 7,43 (m, 2H), 7,37 (m, 2H), 7,32 (m, 1H), 3,31 (cuart., 1H), 1,45 (d, 3H).

EMCL: ($M+H^+$) 409,1, ($M+Na^+$) 431,1.

Ejemplo 18: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenoxi-acetamida

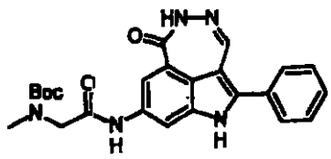


La preparación del ejemplo 18 a partir del compuesto del título del Ejemplo **7** (15 mg, 0,054 mmol), ácido fenoxi-acético (9 mg, 0,062 mmol), trietilamina (0,030 ml, 0,22 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (1:1 de acetato de etilo:hexano aumentando a acetato de etilo al 100%), también de manera análoga, seguido de trituración en éter dietílico proporcionó el compuesto del título (4,5 mg, 0,011 mmol) en forma de un polvo amarillo con un rendimiento del 20%.

^{1}H RMN (d_6-DMSO): δ 12,13 (s, 1H), 10,36 (s, 1H), 10,26 (s, 1H), 8,16 (s, 1H), 7,73 (m, 1H), 7,66 (m, 2H), 7,57 (m, 2H), 7,51 (m, 2H), 7,31 (m, 2H), 7,03 (m, 3H), 4,71 (s, 2H).

EMCL: ($M+H^+$) 411,0, ($M+Na^+$) 433,1.

Ejemplo 19: Éster *terc*-butílico del ácido metil-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-metil]-carbámico

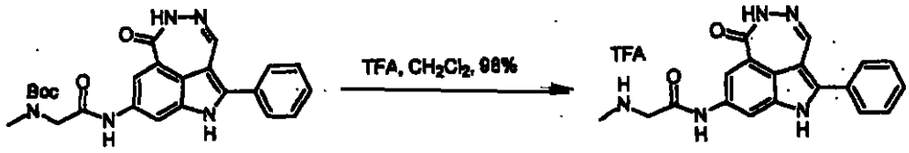


La preparación del ejemplo 19 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (18 mg, 0,065 mmol), ácido (*terc*-butoxicarbonil-metil-amino)-acético (12 mg, 0,065 mmol), trietilamina (0,012 ml, 0,085 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (27 mg, 0,072 mmol) en CH_2Cl_2 (0,5 ml) y *N,N*-dimetilformamida (0,5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (10:9:1 de hexano:CH_2Cl_2:metanol), también de manera análoga, seguido de trituración en éter dietílico proporcionó el compuesto del título (28 mg, 0,063 mmol) en forma de un polvo amarillo con un rendimiento del 96%.

^{1}H RMN ($CDCl_3$): δ 9,11 (s a, 1H), 8,38 (s a, 2H), 7,62-7,46 (m, 7 H), 7,43 (s, 1H), 4,02 (s, 2H), 3,03 (s, 3H), 1,50 (s, 9H).

EMCL: ($M+H^+$) 448,1, ($M+Na^+$) 470, ($M-H^-$) 446,1.

Ejemplo 20: 2-Metilamino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-metil]-acetamida; compuesto con ácido trifluoroacético



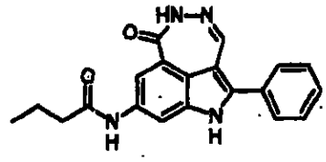
El compuesto de título del Ejemplo **19** (19 mg, 0,042 mmol) en CH_2Cl_2 (0,65 ml) se trató con ácido trifluoroacético (0,45 ml) y se dejó en agitación durante 0,5 horas. Los componentes volátiles se retiraron al vacío y se añadió éter dietílico y se evaporó tres veces, dando el compuesto del título (19 mg,

0,041 mmol) en forma de un polvo amarillo naranja con un rendimiento del 98%.

^{1}H RMN (d_4-metanol): δ 8,15 (s, intercambiado parcialmente), 7,68-7,52 (m, 8H), 4,00 (s, 2H), 2,80 (s, 3H).

EMCL: ($M+H^+$) 348,2.

Ejemplo 21: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-butiramida

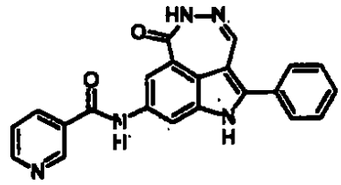


La preparación del ejemplo 21 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (22 mg, 0,080 mmol), ácido *n*-butírico (0,007 ml, 0,080 mmol), trietilamina (0,014 ml, 0,10 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (32 mg, 0,084 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (10:9:1 de hexano:CH_2Cl_2:metanol seguido de 9:5:1 de CH_2Cl_2:hexano:metanol), también de manera análoga, proporcionó el compuesto del título (14 mg, 0,04 mmol) en forma de un polvo amarillo con un rendimiento del 50%.

^{1}H RMN (d_6-DMSO): δ 12,05 (s, 1H, intercambios), 10,22 (s, 1H, intercambios), 10,00 (s, 1H, intercambios), 8,15 (s, 1H), 7,39-7,71 (m, 7H), 2,30 (m, 2H), 1,67 (m, 2H)[2], 0,95 (m, 3H)[1, 1] Se convierte en triplete después de la adición de DCl. [2] Se convierte en cuadruplete después de la adición de DCl.

EMCL: ($M+H^+$) 347,1, ($M+Na^+$) 369,1.

Ejemplo 22: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-nicotinamida



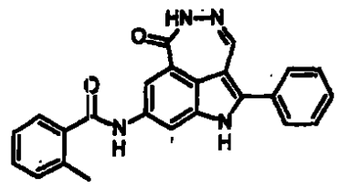
La preparación del ejemplo 22 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (21 mg, 0,076 mmol), ácido nicotínico (7 mg, 0,076 mmol), trietilamina (0,014 ml, 0,10 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (32 mg, 0,084 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (9:1 de CH_2Cl_2:metanol), también de manera análoga, proporcionó el compuesto del título (20 mg, 0,052 mmol) en forma de un polvo amarillo con un rendimiento del 69%.

^{1}H RMN (d_6-DMSO): δ 12,18 (s, 1H, intercambios), 10,59 (s, 1H, intercambios), 10,38 (s, 1H, intercambios), 9,17(s, 1H), 8,80 (s, 1H, parcialmente oscurecido, con suave división), 8,40-8,26 (m, 2H), 7,91 (s, 1H), 7,73-7,65 (m, 2H), 7,62-7,47 (m, 5H).

^{1}H RMN (d_6-DMSO/DCl): δ 9,44 (s, 1H), 9,10 (d, 1H, *J* = 5,0 Hz), 9,00 (d, 1H, *J* = 9,5), 8,32 (s, 1H), 8,15 (dd, 1H, *J* = 7,0, 7,5 Hz), 7,92 (s, 1H), 7,73 (s, 1H, solapamiento), 7,68 (s, 1H, solapamiento), 7,64-7,50 (m, 4H).

EMCL: ($M+H^+$) 382,1, ($M+Na^+$) 404,1.

Ejemplo 23: 2-Metil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida

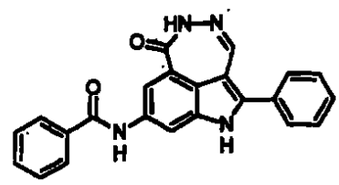


La preparación del ejemplo 23 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (22 mg, 0,08 mmol), ácido 2-metil-benzoico (11 mg, 0,08 mmol), trietilamina (0,014 ml, 0,10 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (33 mg, 0,088 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de manera análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (8:5:2 de CH_2Cl_2:hexano:metanol), también de manera análoga, proporcionó el compuesto del título (23 mg, 0,058 mmol) en forma de un polvo amarillo con un rendimiento del 73%.

^{1}H RMN (d_6-DMSO): δ 12,11 (s, 1H, intercambios), 10,42 (s, 1H, intercambios), 10,34 (s, 1H, intercambios), 8,24 (s, 1H), 7,88 (s, 1H), 7,71-7,65 (m, 2H), 7,63-7,45 (m, 3H), 7,43-7,35 (m, 2H), 7,34-7,25 (m, 3H), 2,4 (s, 3H).

EMCL: ($M+H^+$) 395,1, ($M+Na^+$) 417,0.

Ejemplo 24: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida



La preparación del ejemplo 24 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (23 mg, 0,082 mmol), ácido benzoico (11 mg, 0,09 mmol), trietilamina (0,016 ml, 0,115 mmol) y hexafluorofosfato de *O*-(7-

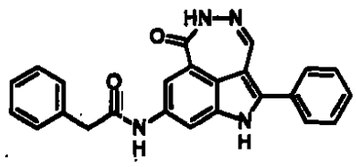
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azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (34 mg, 0,090 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (10:9:1 de hexano:CH_2Cl_2:metanol seguido de 8:5:2 de CH_2Cl_2:hexano:metanol), también de manera análoga, proporcionó el compuesto del título (20 mg, 0,053 mmol) en forma de un polvo amarillo con un rendimiento del 64%.

^{1}H RMN (d_6-DMSO): δ 12,13 (s, 1H), 10,41 (s, 1H), 10,35 (s, 1H), 8,32 (s, 1H), 8,03 (d, 2H, J = 8 Hz), 7,94 (s, 1H), 7,70 (s, 1H, solapamiento), 7,67 (s, 1H, solapamiento), 7,63-7,48 (m, 7H).

EMCL: ($M+H^+$) 381,1, ($M+Na^+$) 403,1.

Ejemplo 25: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenil-acetamida

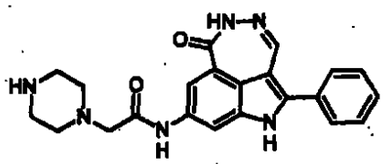


La preparación del ejemplo 25 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (20 mg, 0,072 mmol), ácido fenil-acético (11 mg, 0,08 mmol), trietilamina (0,014 ml, 0,10 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (30 mg, 0,080 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (8:5:2 de CH_2Cl_2:hexano:metanol), también de manera análoga, proporcionó el compuesto del título (27 mg, 0,068 mmol) en forma de un polvo amarillo con un rendimiento del 95%.

^{1}H RMN (d_6-DMSO): δ 12,08 (s, 1H, intercambios), 10,31 (s, 2H, intercambios), 8,18 (s, 1H), 7,72-7,62 (m, 3H), 7,60-7,45 (m, 4H), 7,41-7,21 (m, 5H), 3,68 (s, 2H).

EMCL: ($M+H^+$) 395,1, ($M+Na^+$) 417,1.

Ejemplo 26: Sal del ácido *di*-trifluoroacético de *N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-piperazin-1-il-acetamida



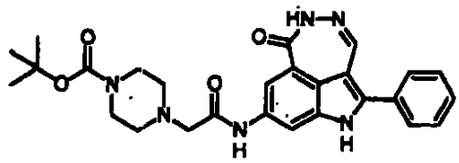
2X TFA

A una suspensión del compuesto del título del Ejemplo **27** en diclorometano (0,3 M, 0,6 ml) se le añadió ácido trifluoroacético (0,3 M, 0,6 ml). La mezcla de reacción se agitó a 22°C durante 0,5 horas y se concentró a presión reducida. El sólido se trituró con diclorometano (3,0 ml), se recogió por filtración y se lavó con éter dietílico (5,0 ml), proporcionando el compuesto del título (9,8 mg) con un rendimiento del 95%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,36 (s, 1H), 9,98 (s, 1H), 8,53 (s a, 2H), 8,16 (d, 1H, *J* = 1,6 Hz), 7,66 (m, 2H), 7,69-7,48 (m, 7H), 3,32 (s, 2H), 3,20 (m, 4H), 2,82 (m, 4H).

EMAR: ($M+H^+$) calculado para $C_{22}H_{23}N_6O_2$, 403,1882, encontrado 403,1902.

Ejemplo 27: Éster *terc*-butílico del ácido 4-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-metil]-piperazin-1-carboxílico

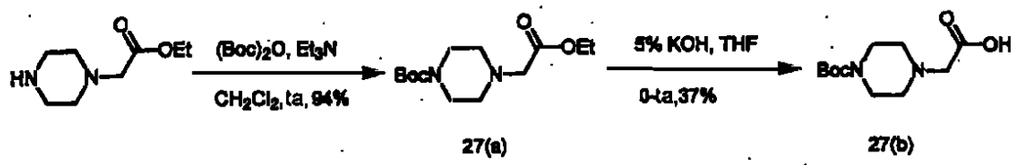


La preparación del ejemplo 27 a partir del compuesto del título del Ejemplo **7** (0,025 g, 0,09 mmol), éster *terc*-butílico del ácido 4-carboximetil-piperazina-1-carboxílico (0,044 g, 0,18 mmol), trietilamina (0,05 ml, 0,4 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (38 mg, 0,1 mmol) y *N,N*-dimetilformamida (0,05 M, 1,8 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol), también de manera análoga, proporcionó el compuesto del título (15 mg) en forma de un polvo amarillo con un rendimiento del 33%.

^{1}H RMN (d_6-DMSO): δ 12,07 (s, 1H), 10,34 (s, 1H), 9,92 (s, 1H), 8,17 (s, 1H), 7,69-7,64 (m, 3H), 7,61-7,54 (m, 2H), 7,52-7,47 (m, 2H), 3,40 (m, 4H), 3,29 (m enterrado, 4H), 3,18 (s, 2H).

EMAR: ($M+H^+$) calculado para $C_{29}H_{31}N_6O_4$, 503,2407, encontrado 503,2407.

El material de partida éster *terc*-butílico del ácido 4-carboximetil-piperazin-1-carboxílico se preparó como se indica a continuación:



Etapa 1. Preparación de éster *terc*-butílico del ácido 4-metoxicarbonilmetil-piperazin-1-carboxílico 27(a)

Se agitaron éster etílico del ácido piperazin-1-il-acético (2,84 g, 15,7 mmol), trietilamina (7,6 ml, 55,0 mmol) y dicarbonato de di-*terc*-butilo (4,45 g,

20,4 mmol) en CH_2Cl_2 (0,3 M, 55 ml) a 22°C durante 24 horas. Los volátiles se retiraron al vacío y la cromatografía sobre gel de sílice (60:40 acetato de etilo/hexanos) proporcionó el Intermedio 27(a) (4,01 g) con un rendimiento del 94%.

^{1}H RMN (d_6-DMSO): δ 4,08 (c, 2H, *J* = 7,1 Hz), 3,35-3,21 (m, 6H), 2,52-2,41 (m, 4H), 1,39 (s, 9H), 1,18 (t, 7,1 Hz).

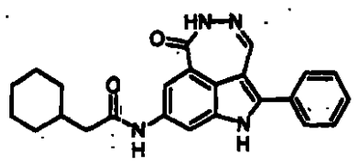
^{13}C-RMN (d_6-DMSO): δ 170,2, 154,2, 79,1, 60,2, 58,6, 52,0, 28,4, 14,5.

Etapa 2. Preparación de éster *terc*-butílico del ácido 4-carboximetil-piperazin-1-carboxílico 27(b)

El Intermedio 27(a) (3,6 g, 13,2 mmol) y una solución acuosa al 5% de KOH (90 ml, 80,0 mmol) se agitaron en tetrahidrofurano (30 ml, 0,44 M) a 22°C durante 2 horas. Los volátiles se retiraron al vacío y el tratamiento con Dowex-50™ fuertemente ácido (WX8-200), la elución con hidróxido amónico (1,0 N) y el tratamiento con Amberlite™ CG-50 proporcionaron el intermedio 27(b) (1,2 g) con un rendimiento del 37%.

^{1}H RMN (d_6-DMSO): δ 3,35-3,31 (m, 4H), 3,21 (s, 2H), 2,52-2,41 (m, 4H), 1,39 (s, 9H).

Ejemplo 28: 2-Ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



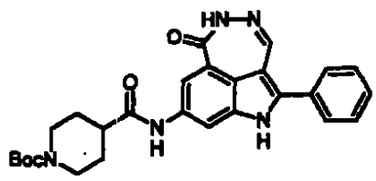
La preparación del ejemplo 28 a partir del compuesto del título del Ejemplo 7 (0,025 g, 0,09 mmol), ácido ciclohexil-acético (0,015 g, 0,11 mmol), trietilamina (0,05 ml, 0,4 mmol), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-

N,N,N',N'-tetrametiluronio (38 mg, 0,1 mmol) y *N,N*-dimetilformamida (0,05 M, 1,8 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol) también de manera análoga seguido de trituración en éter dietílico proporcionó el compuesto del título (13 mg) en forma de un polvo amarillo con un rendimiento del 36%.

^{1}H RMN (d_6-DMSO): δ 12,03 (s, 1H), 10,32 (s, 1H), 9,99 (s, 1H), 8,17 (s, 1H), 7,68-7,45 (m, 7H), 2,20 (d, 2H, J = 7,0 Hz), 1,86-1,58 (m, 6H), 1,31-1,10 (m, 3H), 1,10-0,91 (m, 2H).

EMAR: ($M+H^+$) calculado para $C_{24}H_{25}N_4O_2$, 401,1978, encontrado 401,1987.

Ejemplo 29: Éster *terc*-butílico del ácido 4-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-piperidin-1-carboxílico

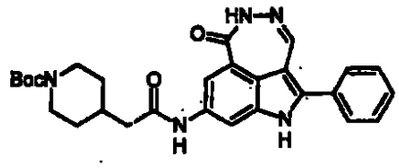


La preparación del ejemplo 29 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (22 mg, 0,07 mmol), mono-*terc*-butil éster del ácido piperidin-1,4-dicarboxílico (19 mg, 0,084 mmol), trietilamina (0,015 ml, 0,105 mmol) y hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (32 mg, 0,084 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (8:5:2 de CH_2Cl_2:hexano:metanol), también de manera análoga, proporcionó el compuesto del título (24 mg, 0,049 mmol) en forma de un polvo amarillo con un rendimiento del 70%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,38 (s, 1H), 10,12 (s, 1H), 8,17 (s, 1H), 7,70-7,64 (m, 3H), 7,62-7,54 (m, 2H), 7,53-7,49 (m, 2H), 4,01 (d a, 2H, *J* = 12,06 Hz), 2,86-2,72 (m, 2H), 1,81 (d a, 2H, *J* = 13,00 Hz), 1,58-1,44 (m, 2H), 1,42 (s, 9H), 1,40 (m, 1H, parcialmente oscurecido).

EMCL: $(M-H)^-$ 486,2.

Ejemplo 30: Éster *terc*-butílico del ácido 4-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-metil]-piperidin-1-carboxílico

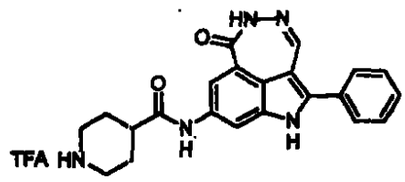


La preparación del ejemplo 30 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (22 mg, 0,07 mmol), éster *terc*-butílico del ácido 4-carboximetil-piperidin-1-carboxílico (20 mg, 0,084 mmol), trietilamina (0,015 ml, 0,105 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (32 mg, 0,084 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (8:5:2 de CH_2Cl_2:hexano:metanol), también de manera análoga, proporcionó el compuesto del título (35 mg, 0,070 mmol) en forma de un polvo amarillo con un rendimiento del 100%.

^{1}H RMN (d_6-DMSO): 12,08 (s, 1H), 10,38 (s, 1H), 10,09 (s, 1H), 8,19 (s, 1H), 7,70-7,46 (m, 7H), 3,93 (d a, 2H, *J* = 12,24 Hz), 2,81-2,66 (m, 2H), 2,27 (d, 2H, *J* = 7,16 Hz), 1,96 (s a, 1H), 1,67 (d a, 2H, J = 13,94 Hz), 1,40 (s, 9H), 1,17-1,01 (m, 2H).

EMCL: $(M+Na^+)$ 524,2, $(M-H)^-$ 500,1.

Ejemplo 31: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido piperidin-4-carboxílico; compuesto con ácido trifluoroacético

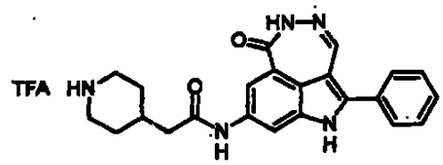


La preparación del ejemplo 31 a partir del compuesto del título del Ejemplo **29** (20 mg, 0,041 mmol) y TFA al 45% en CH_2Cl_2 (1 ml) se realizó de forma análoga al Ejemplo **20**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (20 mg, 0,040 mmol) en forma de un polvo amarillo con un rendimiento del 97%.

^{1}H RMN (d_4-metanol): 8,03 (s, 1H), 7,56-7,31 (m, 7H), 3,43-3,32 (m, 2H), 3,01-2,90 (m, 2H), 2,61 (m, 1H), 2,04-1,78 (m, 4H).

EMCL: ($M+H^+$) 388,1

Ejemplo 32: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-piperidin-4-il-acetamida; compuesto con ácido trifluoroacético



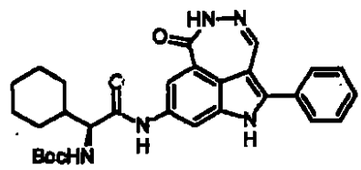
La preparación del ejemplo 32 a partir del compuesto del título del Ejemplo **30** (31 mg, 0,062 mmol) y TFA al 45% en CH_2Cl_2 (1 ml) se realizó de forma análoga al Ejemplo **20**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (29 mg, 0,056 mmol) en forma de un polvo amarillo con un rendimiento del 91%.

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^{1}H RMN (d_4-metanol): δ 8,20 (s, 1H), 7,70-7,50 (m, 7H), 3,50-3,40 (m, 2H, parcialmente oscurecido), 3,10 (dd, 2H, *J* = 9,0, 9,2 Hz), 2,45 (d, 2H, *J* = 7,2 Hz), 2,25 (m a, 1H), 2,0-2,11 (m, 2H), 1,68-1,45 (m, 2H).

EMCL: ($M+H^+$) 402,2

Ejemplo 33: (1*S*)-1-ciclohexil-2-oxo-2-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de *terc*-butilo

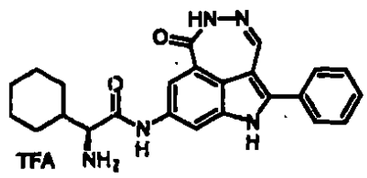


La preparación del ejemplo 33 a partir del compuesto del título del Ejemplo **7** (35 mg, 0,13 mmol), ácido (2*S*)-[(*terc*-butoxicarbonil)amino](ciclohexil)etanoico (39 mg, 0,15 mmol), trietilamina (0,073 ml, 0,52 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (58 mg, 0,15 mmol) en *N,N*-dimetilformamida (2,0 ml) se realizó de forma análoga al Ejemplo **11** con la excepción de que después de 24 horas se añadieron más ácido (2*S*)-[(*terc*-butoxicarbonil)amino](ciclohexil)etanoico (17 mg, 0,065 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (25 mg, 0,065 mmol), para completar la reacción. La cromatografía sobre gel de sílice (1:1 de acetato de etilo:hexano), también de manera análoga, seguido de trituración en éter dietílico proporcionó el compuesto del título (45 mg, 0,087 mmol) en forma de un polvo amarillo con un rendimiento del 67%.

^{1}H RMN (d_6-DMSO): δ 12,08 (s, 1H), 10,38 (s, 1H), 10,13 (s, 1H), 8,14 (s, 1H), 7,71-7,44 (m, 6H), 6,90 (m, 1H), 3,95 (m, 1H), 1,78-1,44 (m, 5H), 1,43-1,24 (m, 10H, contiene un singlete en 1,39), 1,23-1,02 (m, 5H).

EMCL: $(M+H)^+$ 514,1.

Ejemplo 34: Trifluoroacetato de (2*S*)-2-amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida

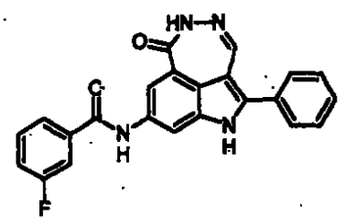


La preparación del ejemplo 34 a partir del compuesto del título del Ejemplo **33** (40 mg, 0,078 mmol) y 1:1 de TFA/CH_2Cl_2 (5 ml) se realizó de forma análoga al Ejemplo **20**. El aislamiento, también de manera análoga, incluyó otra trituración con metanol/éter dietílico y proporcionó el compuesto del título (10 mg, 0,019 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 24%.

^{1}H RMN (d_6-DMSO): δ 12,19 (s, 1H), 10,60 (s, 1H), 10,44 (s, 1H), 8,25 (s a, 3H), 8,11 (s, 1H), 7,71-7,46 (*m*, 7H), 3,69 (*m*, 1H), 1,93-1,52 (*m*, 6H), 1,29 - 0,97 (m, 5H).

EMCL: $(M+H^+)$ 415,1.

Ejemplo 35: 3-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida



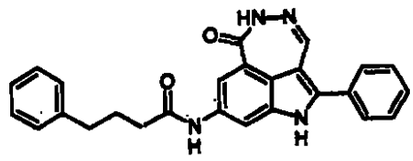
La preparación del ejemplo 35 a partir del compuesto del título del Ejemplo **7** (0,025 g, 0,09 mmol), ácido 3-fluoro-benzoico (0,015 g, 0,11 mmol),

trietilamina (0,05 ml, 0,4 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (38 mg, 0,1 mmol) y *N,N*-dimetilformamida (0,05 M, 1,8 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2:metanol), también de manera análoga, proporcionó el compuesto del título (15 mg) en forma de un polvo amarillo con un rendimiento del 42%.

^{1}H-RMN (d_6-DMSO): δ 12,18 (s, 1H), 10,47 (s, 1H), 10,40 (s, 1H), 8,31 (d, 1H, *J* = 1,3 Hz), 7,92 (d, 1H, J = 1,5 Hz), 7,90-7,81 (m, 2H), 7,72-7,41 (m, 8H).

EMAR: ($M+H^+$) calculado para $C_{23}H_{16}N_4O_2F$, 399,1257, encontrado 399,1257.

Ejemplo 36: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida



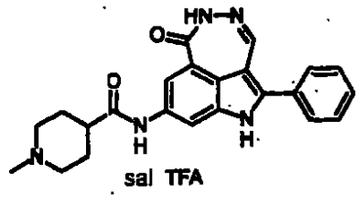
La preparación del ejemplo 36 a partir del compuesto del título del Ejemplo **7** (0,030 g, 0,11 mmol), ácido 4-fenil-butírico (0,027 g, 0,16 mmol), trietilamina (0,077 ml, 0,44 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (63 mg, 0,16 mmol) y *N,N*-dimetilformamida (0,05 M, 2,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol) proporcionó el compuesto del título (15 mg) en forma de un polvo amarillo con un rendimiento del 33%.

^{1}H-RMN (d_6-DMSO): δ 12,06 (s, 1H), 10,35 (s, 1H), 10,06 (s, 1H), 8,18 (d, 1H, J = 1,5 Hz), 7,69-7,46 (m, 7H), 7,33-7,16 (m, 5H), 2,64 (dd, 2H, J = 7,4, 7,0 Hz), 2,35 (m, 5H), 1,97-1,86 (m, 2H).

EMAR: ($M+H^+$) calculado para $C_{26}H_{22}N_4O_2$, 423,1821, encontrado 423,1826.

Análisis calculado para $C_{26}H_{22}N_4O_2 \cdot 0{,}2\ H_2O$: C, 73,29; H, 5,30; N, 13,15, Encontrado: C, 73,33; H, 5,28; N, 13,23.

Ejemplo 37: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 1-metil-piperidin-4-carboxílico: sal del ácido 2,2,2-trifluoro-acético

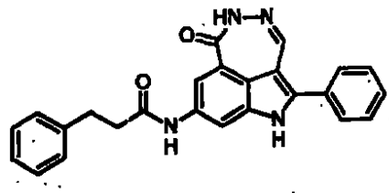


La preparación del ejemplo 37 a partir del compuesto del título del Ejemplo **7** (0,030 g, 0,11 mmol), ácido 1-metil-piperidin-4-carboxílico (0,023 g, 0,16 mmol), trietilamina (0,077 ml, 0,44 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (63 mg, 0,16 mmol) y *N,N*-dimetilformamida (0,05 M, 2,0 ml) se realizó de forma análoga al Ejemplo **11**. La purificación por HPLC proporcionó el compuesto del título (23 mg) en forma de un polvo amarillo con un rendimiento del 41%.

^{1}H RMN (d_6-DMSO): δ 12,10 (s, 1H), 10,39 (s, 1H), 10,23 (s, 1H), 9,17 (s a, 1H), 8,12 (d, 1H, *J* = 1,5 Hz), 7,69-7,47 (m, 7H), 3,05-2,93 (m, 2H), 2,80 (d, 3H), 2,65-2,48 (m oculto, 1H), 2,10-2,01 (m, 2H), 1,92-1,80 (m, 2H).

EMAR: ($M+H^+$) calculado para $C_{23}H_{24}N_5O_2$, 402,1930, encontrado 402,1937.

Ejemplo 38: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida

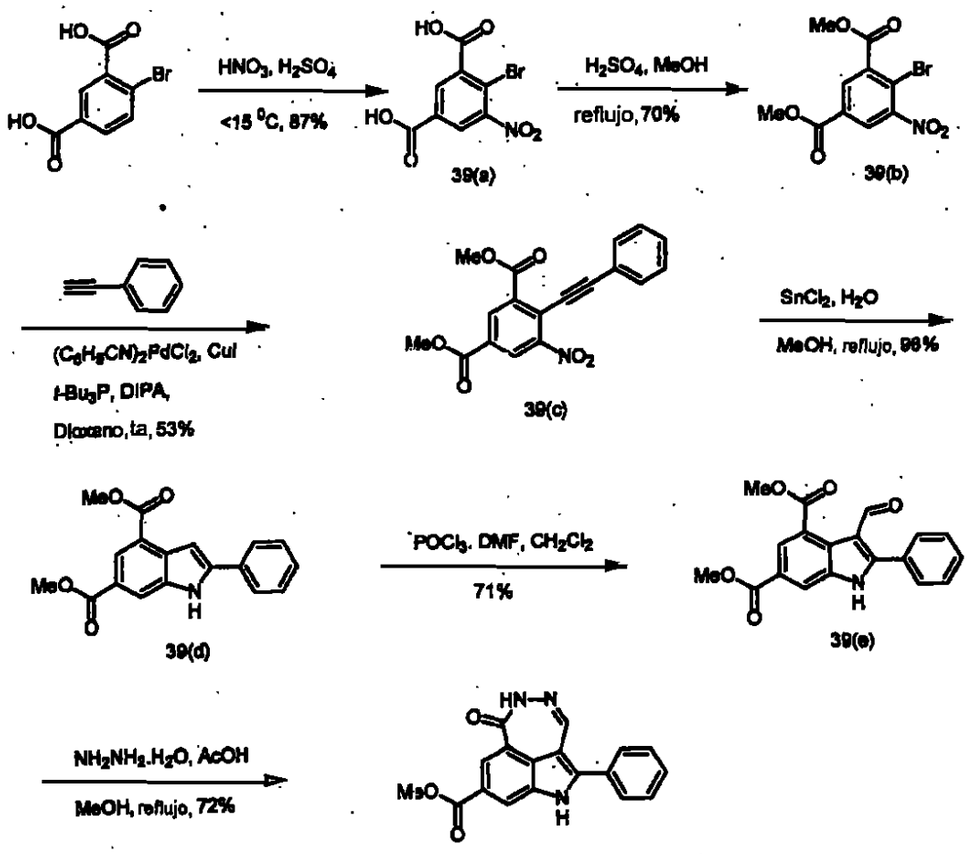


La preparación del ejemplo 38 a partir del compuesto del título del Ejemplo **7** (0,030 g, 0,11 mmol), ácido 3-fenil-propiónico (0,025 g, 0,16 mmol), trietilamina (0,077 ml, 0,44 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (63 mg, 0,16 mmol) y *N,N*-dimetilformamida (0,05 M, 2,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol) proporcionó el compuesto del título (15 mg) en forma de un polvo amarillo con un rendimiento del 34%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,38 (s, 1H), 10,36 (s, 1H), 10,13 (s, 1H), 8,15 (d, 1H, *J* = 1,5 Hz), 7,68-7,46 (m, 11H), 7,31 (d, 2H, *J* = 8,4 Hz), 7,24 (d, 1H, *J* = 8,2 Hz), 3,65 (s, 2H), 3,45 (s, 2H).

EMAR: ($M+H^+$) calculado para $C_{25}H_{21}N_4O_2$, 409,1665, encontrado 409,1683.

Ejemplo 39: Éster metílico del ácido 6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxílico



Etapa 1. Preparación del ácido 4-bromo-5-nitroisoftálico 39(a)

A un matraz de fondo redondo de 4 bocas y 3 l equipado con un agitador mecánico, termómetro, embudo de adición de 250 ml y cargado con H_2SO_4 concentrado (577 ml), se le añadió ácido 4-bromoisoftálico (75,0 g, 306 mmol). La suspensión blanca se enfrió a temperatura del baño de hielo y se añadió lentamente un reactivo de nitración (preparado previamente mediante la adición cuidadosa de H_2SO_4 (169 ml) a HNO_3 (107 ml)) mientras se mantenía una temperatura interna de la reacción de menos de 15°C. Cuando se completó la adición, el baño de hielo se retiró y la suspensión se agitó durante una noche a

temperatura ambiente. Después de aproximadamente 14 horas, el matraz se puso en un baño de hielo y se añadió hielo picado para inactivar el exceso de reactivo de nitración mientras se mantenía una temperatura interna de menos de 40°C. La suspensión de color crema se filtró, y los sólidos se recogieron por filtración y se lavaron con un pequeño volumen de agua enfriada con hielo. Los sólidos se disolvieron en metanol y los componentes volátiles se evaporaron. Los sólidos resultantes se secaron a 60°C en una estufa de vacío durante una noche, proporcionando el Intermedio 39(a) (79,6 g) con un rendimiento del 87%.

^{1}H RMN (d_4-metanol): δ 8,47 (d, 1H, J = 1,8 Hz), 8,39 (d, 1H, J = 1,8 Hz). EMCL: (M-H) 289.

Etapa 2. Preparación de 4-bromo-5-nitroisoftalato de dimetilo 39(b)

A una solución del Intermedio 39(a) (77,6 g, 267 mmol) en metanol (500 ml) se le añadió H_2SO_4 concentrado (10 ml). El matraz de reacción se calentó en un baño de aceite a temperatura de reflujo con agitación durante aproximadamente 8 horas, momento en el que el análisis por CL/EM indicó el consumo del material de partida. La mezcla se dejó enfriar a temperatura ambiente y los sólidos blancos comenzaron a cristalizar en el matraz. Después de agitar durante una noche, los cristales se recogieron por filtración y se lavaron con agua hasta que el pH de filtrado fue neutro. Los cristales (51,9 g) se secaron en un aparato de secado Abderhalden sobre acetona a reflujo. Las aguas madre se concentraron, proporcionando un segundo cultivo (7,58 g) que se combinó con el primero, proporcionando el Intermedio 39(b) (59,4 g) con un rendimiento del 70%.

^{1}H RMN (d_6-DMSO): δ 8,62 (s, 1H), 8,45 (s, 1H), 3,95 (s, 3H), 3,93 (s, 3H).

Etapa 3. Preparación de 5-nitro-4-(feniletinil)isoftalato de dimetilo 39(c)

Un matraz que contenía 1,4-dioxano (16 ml) se purgó con nitrógeno. Se añadieron en porciones CuI (0,12 g, 0,628 mmol) y *bis*(benzonitrilo)dicloropaladio (II) (0,361 g, 0,942 mmol). Se añadió tri-*terc*-butilfosfina (7,83 ml, 1,88 mmol) en forma de una solución 0,24 M en 1,4-dioxano mediante una jeringa. La solución se dejó en agitación durante aproximadamente 5 min, momento en el que se añadió diisopropilamina (2,65 ml, 18,9 mmol) mediante una jeringa. Se añadió en una porción sólida el Intermedio 39(b) (5,00 g, 15,7 mmol) seguido de fenilacetileno (2,08 ml, 18,9 mmol). Se formó inmediatamente un precipitado. La reacción se tapó y se agitó a temperatura ambiente durante una noche. La mezcla se filtró a través de tierra diatomácea que después se lavó con acetato de etilo, recuperando cualquier producto atrapado. El filtrado combinado y los lavados se concentraron y se disolvieron en una cantidad mínima de acetato de etilo caliente. Se añadió hexano para cristalizar las agujas pardas que se recogieron por filtración y se lavaron de nuevo con hexano. Las aguas (4,5 g) se secaron en una estufa de vacío a 60°C durante una noche. Las aguas madre se concentraron y se sometieron a cromatografía sobre gel de sílice (acetato de etilo al 10-30%/hexanos), produciendo 1,2 g más de un sólido pardo oscuro que se combinó con el primer lote, proporcionando el Intermedio 39(c) (5,7 g) con un rendimiento del 53%.

^{1}H RMN ($CDCl_3$): δ 8,73 (d, 1H, J = 1,5 Hz), 8,65 (d, 1H, J = 1,8 Hz), 7,61-7,64 (m, 2H), 7,37-7,46 (m, 3H), 4,03 (s, 3H), 4,00 (s, 3H).

EMCL: (M+H) 340.

Etapa 4. Preparación de 2-fenil-1*H*-indol-4,6-dicarboxilato de dimetilo 39(d)

Al Intermedio 39(c) (6,37 g, 18,8 mmol) se le añadió metanol anhidro (120 ml). A la suspensión resultante se le añadió cloruro de estaño (II) (35,6 g, 188 mmol) y el matraz de reacción se calentó a reflujo durante 55 horas. El metanol se retiró a presión reducida y el residuo resultante se suspendió en un volumen pequeño de acetato de etilo. Después, se añadió diclorometano de tal forma que la concentración resultante fue de aproximadamente diclorometano al 95%:acetato de etilo al 5%. Después, esta suspensión se filtró a través de un lecho corto de gel de sílice. El filtrado se concentró y se purificó dos veces por cromatografía ultrarrápida sobre gel de sílice (acetato de etilo al 5-40%/diclorometano), obteniendo 3,1 g del Intermedio 39(d) con un rendimiento del 53%.

^{1}H RMN (d_6-DMSO): δ 12,35 (s, 1H), 8,37 (s, 1H), 8,28 (s, 1H), 7,98-8,00 (m, 2H), 7,47-7,60 (m, 4H), 3,99 (s, 3H), 3,93 (s, 3H).

EMCL: (M+H) 310.

Etapa 5. Preparación de 3-formil-2-fenil-1*H*-indol-4,6-dicarboxilato de dimetilo 39(e)

A una solución del Intermedio 39(d) (0,052 g, 0,17 mmol) en *N,N*-dimetilformamida anhidra (2 ml) a temperatura ambiente se le añadió $POCl_3$ (0,2 ml, 2,1 mmol). La solución violeta resultante se agitó durante 1 hora a temperatura ambiente. La mezcla se vertió en carbonato sódico saturado acuoso (15 ml) y se extrajo con acetato de etilo. La fase orgánica se secó sobre sulfato sódico, se concentró y se purificó por cromatografía sobre gel de sílice

(acetato de etilo al 33%/hexanos), dando el Intermedio 39(e) (0,0404 g) con un rendimiento del 71%.

^{1}H RMN (d_6-DMSO): δ 13,00 (s, 1H), 9,95 (s, 1H), 8,21 (s, 1H), 7,94 (s, 1H), 7,85-7,75 (m, 2H), 7,70-7,55 (m, 3H), 3,90 (s, 3H), 3,86 (s, 3H).

EMCL: (M+H) 338, (M-H) 336.

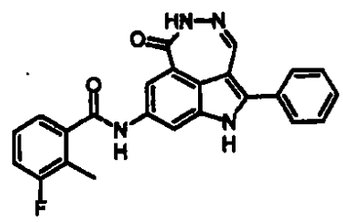
Etapa 6. Preparación del compuesto del título: éster metílico del ácido 6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxílico

A una solución del Intermedio 39(e) (1,39 g, 4,12 mmol) en metanol anhidro (70 ml) se le añadió hidrazina anhidra (0,19 ml, 6,18 mmol). La mezcla se calentó a reflujo durante una noche. Después de enfriar, el precipitado amarillo se recogió por filtración y se lavó con metanol enfriado con hielo. Después de secar al vacío a 60°C durante una noche, se obtuvo el compuesto del título (1,06 g) en forma de un sólido amarillo brillante con un rendimiento del 72%.

^{1}H-RMN (d_6-DMSO): δ 12,58 (s, 1H), 10,54 (s, 1H), 8,13 (d, 1H, J = 1,3 Hz), 8,07 (d, 1H, *J* = 1,3 Hz), 7,77-7,67(m, 2H), 7,65-7,54 (m, 3H), 7,52 (s, 1H), 3,88 (s, 3H).

EMCL: (M+H$^+$) 320,3

Ejemplo 40: 3-Fluoro-2-metil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida

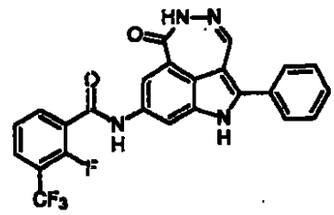


La preparación del ejemplo 40 a partir del compuesto del título del Ejemplo **7** (0,030 g, 0,11 mmol), ácido 3-fluoro-2-metil-benzoico (0,025 g, 0,16 mmol), trietilamina (0,077 ml, 0,44 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (63 mg, 0,16 mmol) y *N,N*-dimetilformamida (0,05 M, 2,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol) proporcionó el compuesto del título (14 mg) en forma de un polvo amarillo con un rendimiento del 33%.

^{1}H-RMN (d_6-DMSO): 6 12,15 (s, 1H), 10,55 (s, 1H), 10,39 (s, 1H), 8,23 (d, 1H, *J* = 1,5 Hz), 7,84 (d, 1H, *J* = 1,4 Hz), 7,72-7,48 (m, 6H), 7,39-7,27 (m, 3H), 2,31 (s, 3H).

EMCL: ($M-H^+$) 411,0.

Ejemplo 41: 2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida



La preparación del ejemplo 41 a partir del compuesto del título del Ejemplo **7** (0,1 g, 0,36 mmol), ácido 2-fluoro-3-trifluorometil-benzoico (0,113 g, 0,54 mmol), trietilamina (0,2 ml, 1,45 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,207 g, 0,54 mmol) y *N,N*-dimetilformamida (0,1 M, 3,6 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol) proporcionó el

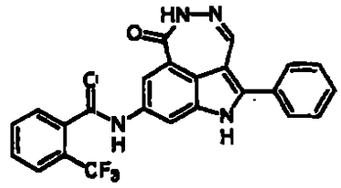
compuesto del título (0,147 g) en forma de un polvo amarillo con un rendimiento del 87%.

^{1}H-RMN (d_6-DMSO): δ 12,20 (s, 1H), 10,81 (s, 1H), 10,43 (s, 1H), 8,24 (d, 1H, J = 1,5 Hz), 8,05-7,93 (m, 2H), 7,79 (d, 1H, J = 1,4 Hz), 7,72-7,67 (m, 2H), 7,62-7,49 (m, 5H).

EMAR: ($M+H^+$) calculado para $C_{24}H_{15}N_4O_2F_4$, 467,1131, encontrado 467,1119.

Análisis calculado para $C_{24}H_{14}N_4O_2F_4 \cdot 0,2\ H_2O$: C, 61,33; H, 3,09; N, 11,92; F, 16,17, Encontrado: C, 61,17; H, 3,09; N, 11,93; F, 16,65.

Ejemplo 42: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-trifluorometil-benzamida

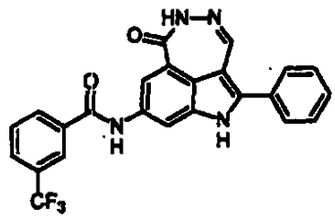


La preparación del ejemplo 42 a partir del compuesto del título del Ejemplo **7** (0,1 g, 0,36 mmol), ácido 2-trifluorometil-benzoico (0,103 g, 0,54 mmol), trietilamina (0,2 ml, 1,45 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,207 g, 0,54 mmol) y *N,N*-dimetilformamida (0,1 M, 3,6 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol) proporcionó el compuesto del título (0,075 g) en forma de un polvo amarillo con un rendimiento del 46%.

^{1}H-RMN (d_6-DMSO): δ 12,14 (s, 1H), 10,71 (s, 1H), 10,40 (s, 1H), 8,17 (d, 1H, J = 1,4 Hz), 7,89-7,66 (m, 7H), 7,62-7,49 (m, 4H).

EMAR: (M+H$^+$) calculado para $C_{24}H_{16}N_4O_2F_3$, 449,1225, encontrado 449,1223.

Ejemplo 43: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida

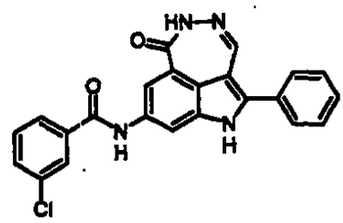


La preparación del ejemplo 43 a partir del compuesto del título del Ejemplo **7** (0,03 g, 0,11 mmol), ácido 3-trifluorometil-benzoico (0,031 g, 0,16 mmol), trietilamina (0,078 ml, 0,43 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,062 g, 0,11 mmol) y *N,N*-dimetilformamida (0,05 M, 2,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol) proporcionó el compuesto del título (0,030 g) en forma de un polvo amarillo con un rendimiento del 61%.

^{1}H-RMN (d_6-DMSO): δ 12,20 (s, 1H), 10,62 (s, 1H), 10,42 (s, 1H), 8,39-8-30 (m, 3H), 7,98 (d, 1H, *J* = 7,4 Hz), 7,91 (d, 1H, J = 1,6 Hz), 7,80 (dd, *J* = 7,7, 7,5 Hz),7,69 (d, 2H, *J* = 7,2 Hz), 7,62-7,48 (m, 4H).

EMAR: (M+H$^+$) calculado para $C_{24}H_{16}N_4O_2F_3$, 449,1225, encontrado 449,1229.

Ejemplo 44: 3-Cloro-*N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida



La preparación del ejemplo 44 a partir del compuesto del título del Ejemplo **7** (0,03 g, 0,11 mmol), ácido 3-clorometil-benzoico (0,025 g, 0,16 mmol), trietilamina (0,078 ml, 0,43 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,062 g, 0,11 mmol) y *N,N*-dimetilformamida (0,05 M, 2,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (95:5 de CH_2Cl_2/metanol) proporcionó el compuesto del título (0,015 g) en forma de un polvo amarillo con un rendimiento del 33%.

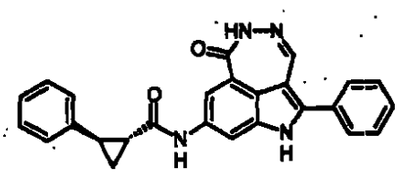
^{1}H RMN (d_6-DMSO): δ 12,18 (s, 1H), 10,50 (s, 1H), 10,41 (s, 1H), 8,32 (d, 1H, J = 1,5 Hz), 8,09 (s, 1H), 7,98 (d, 1H, *J* = 7,8 Hz), 7,91 (d, 1H, J = 1,6 Hz), 7,72-7,65 (m, 3H), 7,62-7,47 (m, 5H).

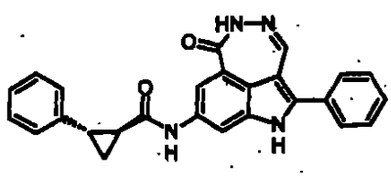
EMAR: ($M+H^+$) calculado para $C_{23}H_{16}N_4O_2Cl$, 415,0962, encontrado 415,0981,

Ejemplo 45:

(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; y

(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*S*,2*S*)-2-fenil-ciclopropanocarboxílico



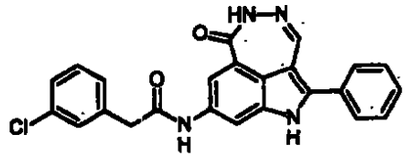


La preparación del ejemplo 45 a partir del compuesto del título del Ejemplo **7** (30 mg, 0,11 mmol), ± ácido *trans*-2-fenil-1-ciclopropanocarboxílico (26 mg, 0,16 mmol), trietilamina (0,076 ml, 0,55 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (62 mg, 0,16 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (1:1 de acetato de etilo:hexano), también de manera análoga, seguido de trituración con acetato de etilo/éter dietílico proporcionó el compuesto del título (6,5 mg, 0,015 mmol) (mezcla de diastereómeros *trans*) en forma de un polvo amarillo con un rendimiento del 14%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,44 (s, 1H), 10,37 (s, 1H), 8,17 (s, 1H), 7,71-7,44 (m, 7H), 7,35-7,25 (m, 2H), 7,24-7,10 (m, 3H), 2,39 (m, 1H), 2,10 (m, 1H), 1,52 (m, 1H), 1,38 (m, 1H).

EMCL: $(M+H)^+$ 419,1.

Ejemplo 46: 2-(3-Clorofenil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



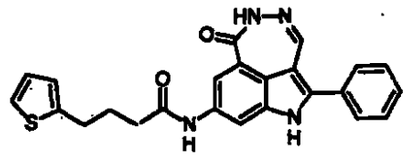
La preparación del ejemplo 46 a partir del compuesto del título del Ejemplo **7** (30 mg, 0,11 mmol), ácido (3-clorofenil)acético (28 mg, 0,16 mmol), trietilamina (0,076 ml, 0,55 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (62 mg, 0,16 mmol) en *N,N*-dimetilformamida (1,5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (1:1 de acetato de etilo:hexano), también de manera análoga, seguido

de trituración en metanol proporcionó el compuesto del título (6,5 mg, 0,015 mmol) en forma de un polvo amarillo con un rendimiento del 14%.

^{1}H-RMN (d_6-DMSO): δ 12,10 (s, 1H), 10,39 (s, 1H), 10,17 (s, 1H), 8,16 (s, 1H), 7,70 -7,18 (m, 11H), 3,69 (s, 1H), 3,50 (8,1 H).

EMCL: $(M+H)^+$ 427,1.

Ejemplo 47: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida

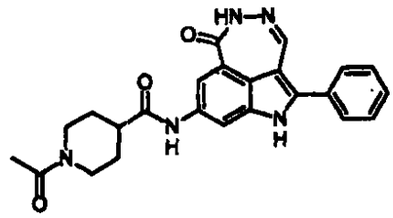


La preparación del ejemplo 47 a partir del compuesto del título del Ejemplo **7** (30 mg, 0,11 mmol), ácido 4-tien-2-ilbutanoico (24 mg, 0,16 mmol), trietilamina (0,076 ml, 0,55 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluronio (62 mg, 0,16 mmol) en *N,N*-dimetilformamida (1,5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (metanol al 3% en CH_2Cl_2 aumentando a metanol al 6% en CH_2Cl_2), también de manera análoga, seguido de trituración en metanol proporcionó el compuesto del título (6,5 mg, 0,015 mmol) en forma de un polvo amarillo con un rendimiento del 14%.

^{1}H-RMN (d_6-DMSO): δ 12,07 (s, 1H), 10,38 (s, 1H), 10,09 (s, 1H), 8,18 (s, 1H), 7,69-7,61 (m, 3H), 7,60-7,53 (m, 2H), 7,52-7,45 (m, 2H), 7,33 (m, 1H), 6,96 (m, 1H), 6,89 (m, 1H), 2,86 (t, 2H, J = 7,53 Hz), 2,40 (t, 2H, *J* = 7,35 Hz), 2,02 -1,89 (m, 2H).

EMCL: $(M+H)^+$ 427,1.

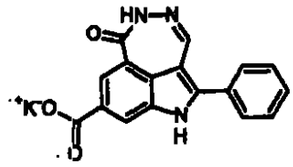
Ejemplo 48: 1-Acetil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)piperidin-4-carboxamida



La preparación del ejemplo 48 a partir del compuesto del título del Ejemplo **7** (30 mg, 0,11 mmol), ácido 1-acetilpiperidin-4-carboxílico (28 mg, 0,16 mmol), trietilamina (0,076 ml, 0,55 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (62 mg, 0,16 mmol) en *N,N*-dimetilformamida (1,5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (aumentando el metanol al 3% en CH_2Cl_2 a metanol al 6% en CH_2Cl_2), también de manera análoga, seguido de trituración en metanol proporcionó el compuesto del título (12 mg, 0,028 mmol) en forma de un polvo amarillo con un rendimiento del 25%.

^{1}H-RMN (d_6-DMSO): δ 12,07 (s, 1H), 10,37 (s, 1H), 10,10, s, 1H), 8,17 (s, 1H), 7,72-7,43 (m, 7H), 4,41 (d, 1H, J = 15,07 Hz), 3,87 (d, 1H, J = 14,13 Hz), 3,07 (t, 1H, *J* = 12,81 Hz), 2,65-2,53 (m, 2H, parcialmente oscurecido), 2,02 (s, 3H), 1,76-1,90 (m, 2H), 1,70-1,37 (m, 2H). EMCL: ($M+H^+$) 430,1, ($M+Na^+$) 452,1.

Ejemplo 49: Ácido 6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxílico, sal potásica

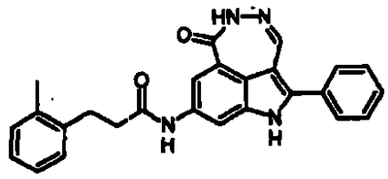


Al compuesto del título del Ejemplo **39** (3,0 g, 9,39 mmol) se le añadió DMSO (20 ml). A esta semi-suspensión se le añadió KOH 2 N (19 ml, 37,8 mmol). La solución se volvió de color rojo oscuro y se agitó durante aproximadamente 1,5 horas a temperatura ambiente. La reacción se purificó por HPLC preparativa (CH_3CN al 5-60%/H_2O) durante 60 minutos. Las fracciones que contenían el producto se liofilizaron, proporcionando el compuesto del título (0,8 g) en forma de un sólido naranja con un rendimiento del 25%.

^{1}H-RMN (d_6-DMSO): δ 12,21 (s, 1H), 10,12 (s, 1H), 8,16 (d, 1H, *J* = 1,0 Hz), 8,01 (d, 1H, *J* = 1,0 Hz), 7,73-7,65 (m, 2H), 7,62-7,46 (m, 3H), 7,44 (s, 1H).

EMCL: ($M+H^+$) 306,1

Ejemplo 50: 3-(2-Metilfenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida



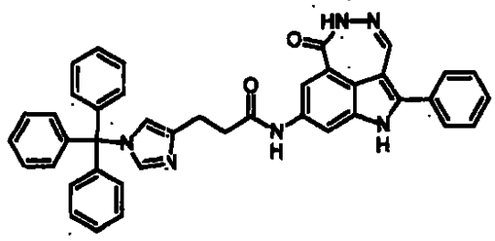
La preparación del ejemplo 50 a partir del compuesto del título del Ejemplo **7** (30 mg, 0,11 mmol), ácido 3-(2-metilfenil)propanoico (27 mg, 0,16 mmol), trietilamina (0,076 ml, 0,55 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluronio (62 mg, 0,16 mmol) en *N,N*-

dimetilformamida (1,5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (aumentado el metanol al 3% en CH_2Cl_2 a metanol al 5% en CH_2Cl_2), también de manera análoga, seguido de trituración en metanol proporcionó el compuesto del título (6 mg, 0,014 mmol) en forma de un polvo amarillo con un rendimiento del 13%.

^{1}H-RMN (d_6-DMSO): δ 12,08 (s, 1H), 10,37 (s, 1H), 10,10 (s, 1H), 8,20 (s, 1H), 7,72-7,42 (m, 7H), 7,26-7,05 (m, 4H), 2,96-2,87 (m, 2H), 2,64-2,55 (m, 2H, parcialmente oscurecido), 2,32 (s, 3H).

EMCL: $(M+H)^+$ 421,1.

Ejemplo 51: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-(1-tritil-1*H*-imidazol-4-il)-propionamida

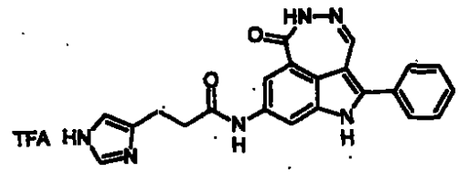


La preparación del ejemplo 51 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (31 mg, 0,10 mmol), ácido 3-(1-tritil-1*H*-imidazol-4-il)-propiónico (46 mg, 0,12 mmol), trietilamina (0,021 ml, 0,15 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (46 mg, 0,12 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (trietilamina al 3% en 5:4:1 de hexano:CH_2Cl_2:metanol), también de manera análoga, proporcionó el compuesto del título (40 mg, 0,062 mmol) en forma de un polvo amarillo con un rendimiento del 62%.

^{1}H RMN ($CDCl_3$/d_4-metanol): δ 8,21 (s, 1H), 7,65-7,25 (m, 15H, parcialmente oscurecido), 7,10-7,02 (m, 8H), 6,65 (s, 1H), 2,99-2,89 (m, 2H), 2,71-2,62 (m, 2H).

EMCL: ($M+H^+$) 641,2.

Ejemplo 52: 3-(1*H*-Imidazol-4-il)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-propionamida; compuesta con ácido trifluoroacético

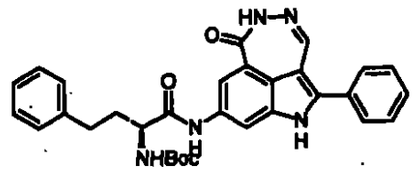


La preparación del ejemplo 52 a partir del compuesto del título del Ejemplo **51** (32 mg, 0,050 mmol) y TFA al 45% en CH_2Cl_2 (1 ml) se realizó de forma análoga al Ejemplo **20**. (La desprotección del grupo tritilo se realizó usando las mismas condiciones que para la desprotección de *terc*-butoxicarbonilo). El aislamiento, también de manera análoga, incluyó además la recristalización en metanol/acetato de etilo y éter dietílico, proporcionando el compuesto del título (16 mg, 0,031 mmol) en forma de un polvo amarillo con un rendimiento del 62%.

^{1}H RMN (d_6-DMSO): 13,95 (s a, 1H), 12,10 (s, 1H), 10,40 (s, 1H), 10,20 (s, 1H), 8,83 (s, 1H), 8,13 (s, 1H), 7,70-7,63 (m, 3H), 7,62-7,47 (m, 5H), 7,38 (s, 1H), 3,02 -2,93 (m, 2H), 2,78-2,70 (m, 2H).

EMCL: ($M+H^+$) 399,2.

Ejemplo 53: Éster *terc*-butílico del ácido [(*S*)-1-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-3-fenil-propil]-carbámico

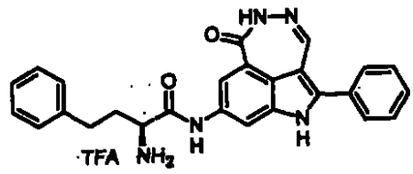


La preparación del ejemplo 53 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (31 mg, 0,10 mmol), ácido (S)-2-*terc*-butoxicarbonilamino-4-fenil-butírico (34 mg, 0,12 mmol), trietilamina (0,021 ml, 0,15 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (46 mg, 0,12 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice, (5:4:1 de hexano:CH_2Cl_2:metanol), también de manera análoga, proporcionó el compuesto del título (40 mg, 0,074 mmol) en forma de un polvo amarillo con un rendimiento del 74%.

^{1}H RMN (d_6-DMSO): 12,11 (s, 1H), 10,40 (s, 1H), 10,17 (s, 1H), 8,40 (s a, 1H), 8,16 (s, 1H), 7,71-7,45 (m, 6H), 7,35-7,15 (m, 6H), 4,06 (m, 1H), 2,77-2,53 (m, 2H, parcialmente oscurecido), 1,92 (m, 2H), 1,42 (s, 9H).

EMCL: $(M+H^+)$ 538,1, $(M+Na^+)$ 560,2, $(M-H)^-$ 536,0.

Ejemplo 54: (2*S*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida; compuesto con ácido trifluoroacético



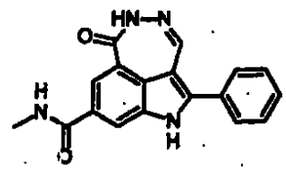
La preparación del ejemplo 54 a partir del compuesto del título del Ejemplo **53** (30 mg, 0,056 mmol) y TFA al 45% en CH_2Cl_2 (1 ml) se realizó de forma análoga al Ejemplo **20**. El aislamiento, también de manera análoga,

proporcionó el compuesto del título (26 mg, 0,047 mmol) en forma de un polvo amarillo con un rendimiento del 84%.

^{1}H RMN (d_6-DMSO): δ 12,22 (s, 1H), 10,71 (s, 1H), 10,47 (s, 1H), 8,38 (s a, 3H), 8,13 (s, 1H), 7,72-7,66 (m, 2H), 7,64-7,49 (m, 4H), 7,36-7,28 (m, 2H), 7,27-7,19 (m, 4H), 4,05 (s a, 1H), 2,77-2,65 (m, 2H), 2,21-2,09 (m, 2H).

EMCL: $(M+H^+)$ 438,2, $(M+Na^+)$ 460,1, $(M-H)^-$ 436,1.

Ejemplo 55: *N*-Metil-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

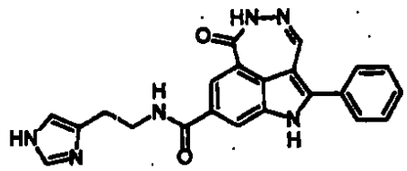


A una solución del compuesto del título del Ejemplo **49** (0,058 g, 0,17 mmol) en DMSO (4 ml) se le añadieron trietilamina (0,069 ml, 0,5 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,084 g, 0,22 mmol). Después de aproximadamente 5 min, se añadió metilamina 2,0 M en tetrahidrofurano (0,5 ml, 0,25 mmol) y la solución se agitó durante 2 horas. La mezcla se purificó usando HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía HOAc al 0,1%). Las fracciones puras se combinaron y se liofilizaron, proporcionando el compuesto del título (0,0036 g) con un rendimiento del 6,7%.

^{1}H-RMN (d_6-DMSO): δ 12,46 (s, 1H), 10,45 (s, 1H), 8,58 (s, 1H), 8,20-7,90 (m, 2H), 7,85-7,35 (m, 6H), 2,79 (s, 3H).

EMCL: $(M+H^+)$ 319,1.

Ejemplo 56: *N*-[2-(1*H*-Imidazol-4-il)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



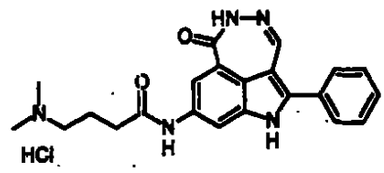
La preparación del ejemplo 56 a partir del compuesto del título del Ejemplo **49** (0,0956 g, 0,28 mmol), diclorhidrato de 2-(1*H*-imidazol-4-il)etilamina (0,0618 g, 0,34 mmol), trietilamina (0,2 ml, 1,4 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,129 g, 0,34 mmol) en DMSO (6 ml) se realizó de forma análoga al Ejemplo **58**. La HPLC preparativa (CH_3CN al 10-80%/H_2O), también de manera análoga, proporcionó el compuesto del título (0,0021 g) con un rendimiento del 18%.

^{1}H-RMN (d_6-DMSO): δ 12,48 (s, 1H), 10,49 (s, 1H), 8,77 (t, 1H, *J* = 5,7 Hz), 8,08 (s, 1H), 8,01 (s, 1H), 7,75-7,66 (m, 2H), 7,64-7,54 (m, 5H), 7,51 (s, 1H), 6,85 (s, 1H), 3,55-3,45 (m, 2H), 2,84-2,73 (t, 2H, *J* = 7,2 Hz).

EMCL: ($M+H^+$) 399,1

Análisis calculado para $C_{22}H_{18}N_6O_2 \cdot 0{,}60$ HCl $\cdot$ 0,75 H_2O: C, 60,91; H, 4,67; N, 19,37, Encontrado: C, 60,74; H, 4,74; N, 19,48.

Ejemplo 57: 4-Dimetilamino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-butiramida (sal clorhidrato)



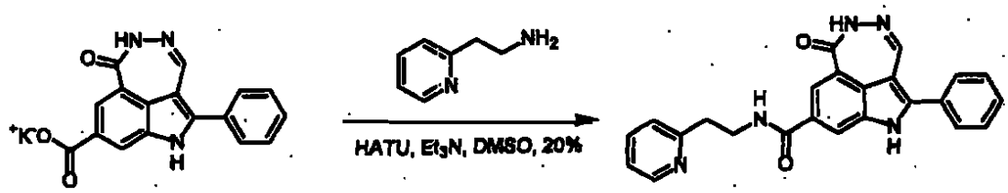
La preparación del ejemplo 57 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (27 mg, 0,086 mmol), ácido 4-dimetilamino-butírico (clorhidrato) (17 mg, 0,104 mmol), trietilamina (0,036 ml, 0,258 mmol) y

hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (40 mg, 0,104 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (trietilamina al 2% en 9:1 de CH_2Cl_2:metanol) de la base libre proporcionó, después de la acidificación con HCl, el compuesto del título (18 mg, 0,042 mmol) en forma de un polvo amarillo con un rendimiento del 49%.

^{1}H RMN (d_6-DMSO): δ 12,10 (s, 1H), 10,39 (s, 1H), 10,21 (s, 1H), 9,60 (s a, 1H, HCl), 8,13 (s, 1H), 7,69-7,46 (m, 7H), 3,15-3,04 (m, 2H), 2,80 (s, 6H, con suave división), 2,45 (t, 2H, parcialmente oscurecido), 2,02-1,90 (m, 2H).

EMCL: ($M+H^+$) 390,2.

Ejemplo 58: 6-Oxo-2-fenil-*N*-(2-piridin-2-iletil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

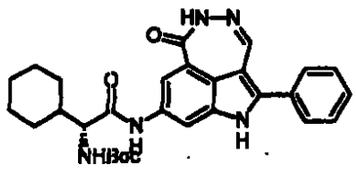


A una solución del compuesto del título del Ejemplo **49** (0,0548 g, 0,16 mmol) en DMSO (1,8 ml) se le añadieron trietilamina (0,0268 ml, 0,192 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,0669 g, 0,176 mmol). Después de aproximadamente 5 min, se añadió 2-piridin-2-iletilamina (0,0215 g, 0,176 mmol) y la solución se dejó en agitación durante una noche. El producto se purificó usando HPLC preparativa (CH_3CN al 5-35%/H_2O). Las fracciones puras se combinaron y se liofilizaron, proporcionando el compuesto del título (0,013 g) en forma de un polvo amarillo con un rendimiento del 20%.

^{1}H RMN (d_6-DMSO): δ 10,37 (s, 1H), 8,74 (s, 1H), 8,51 (d, 1H, *J* = 3,0 Hz), 8,01 (d, 2H, *J* = 11 Hz), 7,49-7,71 (m, 7H), 7,20-7,29 (m, 2H), 3,62 (d, 1H, *J* = 4,9 Hz), 3,02 (t, 1H, *J* = 6,4 Hz).

EMCL: (M+H) 410.

Ejemplo 59: (1*R*)-1-Ciclohexil-2-oxo-2-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de *terc*-butilo



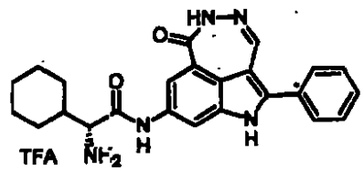
La preparación del ejemplo 59 a partir del compuesto del título del Ejemplo **7** (70 mg, 0,25 mmol), ácido (2*R*)-[(*terc*-butoxicarbonil)amino](ciclohexil)etanoico (98 mg, 0,38 mmol), trietilamina (0,139 ml, 1,0 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (144 mg, 0,38 mmol) en *N,N*-dimetilformamida (2,0 ml) se realizó de forma análoga al Ejemplo **11** con la excepción de que después de 24 horas se añadieron más ácido (2*R*)-[(*terc*-butoxicarbonil)amino](ciclohexil)etanoico (32 mg, 0,13 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (48 mg, 0,13 mmol) para completar la reacción. La cromatografía sobre gel de sílice (1:1 de acetato de etilo:hexano), también de manera análoga, seguido de trituración en éter dietílico proporcionó el compuesto del título (90 mg, 0,17 mmol) en forma de un polvo amarillo con un rendimiento del 70%.

^{1}H-RMN (d_6-DMSO): δ 12,09 (s, 1H), 11,43 (s, 1H), 10,39 (s, 1H), 10,14 (s, 1H), 8,16 (s, 1H), 7,70-7,64 (m, 3H), 7,61-7,54 (m, 2H), 7,53-7,46 (m, 2H),

3,96 (m, 1H), 1,79-1,49 (m, 6H), 1,41-1,29 (m, 14H, contiene un singlete en 1,38).

EMCL: $(M+H)^+$ 514,2.

Ejemplo 60: Trifluoroacetato de (2*R*)-2-amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida

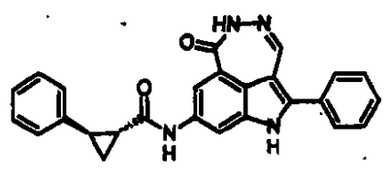


La preparación del ejemplo 60 a partir del compuesto del título del Ejemplo **59** (90 mg, 0,17 mmol) y 1:1 de TFA/CH_2Cl_2 (5 ml) se realizó de forma análoga al Ejemplo **20**. El aislamiento, también de manera análoga, incluyó otra trituración con metanol/éter dietílico y proporcionó el compuesto del título (70 mg, 0,013 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 78%.

^{1}H-RMN (d_6-DMSO): δ 12,22 (s, 1H), 10,63 (s, 1H), 10,47 (s, 1H), 8,22 (s a, 2H), 8,14 (s, 1H), 7,72-7,66 (m, 3H), 7,64-7,49 (m, 4H), 3,72 (m, 1H), 1,91-1,59 (m, 6H), 1,29-1,14 (m, 5H, parcialmente oscurecido con éter dietílico).

EMCL: $(M+H^+)$ 416,2, $(M+Na^+)$ 438,2.

Ejemplo 61: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

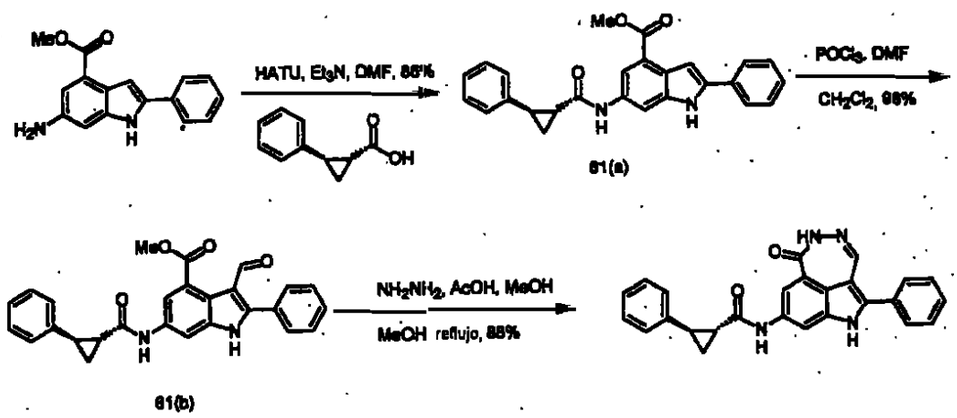


La preparación del ejemplo 61 a partir del compuesto del título del Ejemplo **7** (198 mg, 0,72 mmol), ácido (1*R*,2*R*)-2-fenilciclopropanocarboxílico (175 mg, 1,08 mmol; como se describe por A. Thurkauf, y col., *J. Med. Chem.* *43*, 3923-3932, (2000)), trietilamina (0,401 ml, 2,88 mmol) y hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (411 mg, 1,08 mmol) en *N,N'*-dimetilformamida (10,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (metanol al 3% en CH_2Cl_2), también de manera análoga, seguido de la recogida en una frita y el posterior lavado con éter dietílico proporcionó el compuesto del título (86 mg, 0,20 mmol) en forma de un polvo amarillo con un rendimiento del 28%.

^{1}H-RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,44 (s, 1H), 10,37 (s, 1H), 8,16 (d, 1H, *J* = 1,6 Hz), 7,69-7,63 (m, 3H), 7,60-7,46 (m, 4H), 7,34-7,17 (m, 5H), 2,44-2,35 (m, 1H), 2,13-2,05 (m, 1H), 1,55-1,46 (m, 1H), 1,42-1,34 (m, 1H).

EMCL: ($M+H^+$) 421,1.

Procedimiento alternativo para la preparación del Ejemplo 61



Etapa 1. Preparación de éster metílico del ácido 2-fenil-6-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-1*H*-indol-4-carboxílico 61 (a)

La preparación a partir del Intermedio 7(a) (3,83 g, 12,64 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (2,27 mg, 13,97 mmol), trietilamina (3,52 ml, 25,28 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (5,31 g, 13,97 mmol) en CH_2Cl_2 (6,5 ml) y *N,N*-dimetilformamida (6,5 ml) se realizó de manera análoga al Ejemplo **11**. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso proporcionó el producto bruto en forma de un aceite en *N,N*-dimetilformamida. Se añadieron éter dietílico (aprox. 500 ml) y CH_2Cl_2 (80 ml) y la mezcla se tapó y se agitó vigorosamente durante una noche, tras lo cual el aceite se convirtió en sólidos castaños verdosos que se recogieron por filtración y se lavaron con éter dietílico, metanol y agua. El filtrado se evaporó hasta un aceite y se añadió agua para precipitar un segundo lote de sólidos que también se recogieron por filtración y también se lavaron con metanol y agua. Ambos lotes de sólidos precipitados y lavados se combinaron, dando 4,18 g del producto deseado. Además, el filtrado final se evaporó y se sometió a cromatografía sobre gel de sílice eluyendo con 1:1 de hexano:acetona, dando una pequeña cantidad de producto adicional (0,275 mg). Los lotes combinados proporcionaron el Intermedio 61 (a) (4,46 g, 10,86 mmol) en forma de un sólido castaño con un rendimiento del 86%.

Etapa 2. Preparación de éster metílico del ácido 3-formil-2-fenil-6-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-1*H*-indol-4-carboxílico 61 (b)

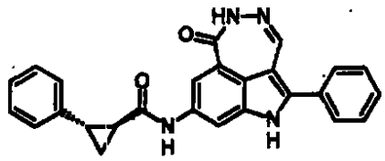
El Intermedio 61 (a) (4,02 g, 9,79 mmol) se disolvió en CH_2Cl_2 (80 ml) y se trató con reactivo de Vilsmeier (2,94 ml) de manera similar a lo descrito en la etapa 4 del Ejemplo **3**. Después de aprox. 10 min de agitación a temperatura

del baño de hielo seguido de 10 min a temperatura ambiente, el volumen de CH_2Cl_2 se redujo al vacío. Con refrigeración en un baño de hielo y agitación, a la reacción se le añadió en forma de una pasta Na_2CO_3 (aprox. 1,2 g) en H_2O (10 ml). Después, a la reacción aún fría se le añadió más H_2O (20 ml). Se añadió metanol (aprox. 100 ml) y la reacción se dejó calentar a temperatura ambiente, mientras se agitaba, tras lo cual se observó un lento desprendimiento de gas. Después de 4 horas, el volumen de la mezcla se redujo al vacío y se añadió CH_2Cl_2 para ajustar la composición del disolvente a aproximadamente 4:1 de CH_2Cl_2:metanol. Después, el Na_2CO_3 precipitado se retiró por filtración y el volumen del filtrado se redujo al vacío, dejando metanol en su mayor parte en forma del disolvente. Se añadió acetato de etilo y después la mezcla se secó (Na_2SO_4), se filtró y se evaporó, dando sólidos amarillos. La cromatografía sobre gel de sílice (eluyendo con 4:1 de hexano:acetona aumentando a 1:1 de hexano:acetona) proporcionó el Intermedio 61 (b) (4,2 g, 9,64 mmol) en forma de un polvo amarillo con un rendimiento de aprox. el 98%.

Etapa 3. Preparación del compuesto del título: (6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

El Intermedio 61(b) (4,1 g, 9,41 mmol) ácido acético (0,78 ml, 13,63 mmol) y $H_2NNH_2 \cdot H_2O$ (1,37 ml, 28,23 mmol) en metanol anhidro (100 ml) se calentaron a reflujo de manera similar a la descrita para el Ejemplo **3**, etapa 5. El precipitado resultante se recogió por filtración y se lavó con una cantidad mínima de metanol, proporcionando el compuesto del título (3,5 g, 8,28 mmol) en forma de un polvo amarillo con un rendimiento del 88%.

Ejemplo 62: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*S*,2*S*)-2-fenil-ciclopropanocarboxílico

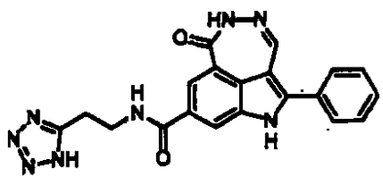


La preparación del ejemplo 62 a partir del compuesto del título del Ejemplo 7 (79 mg, 0,28 mmol), ácido (1*S*,2*S*)-2-fenilciclopropanocarboxílico (60 mg, 0,37 mmol; como se describe por A. Thurkauf, y col., *J. Med. Chem. 43*, 3923-3932, (2000)), trietilamina (0,160 ml, 1,14 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (141 mg, 0,37 mmol) en *N,N*-dimetilformamida (10,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (metanol al 5% en CH_2Cl_2), también de manera análoga, seguido de trituración con metanol proporcionó el compuesto del título (26 mg, 0,06 mmol) en forma de un polvo amarillo con un rendimiento del 22%.

^{1}H RMN (d_6-DMSO): δ 12,10 (s, 1H), 10,44 (s, 1H), 10,37 (s, 1H), 8,17 (s, 1H), 7,72-7,43 (m, 7H), 7,35-7,26 (m, 2H), 7,24-7,17 (m, 3H), 2,40 (m, 1H), 2,10 (m, 1H), 1,52 (m, 1H), 1,38 (m, 1H).

EMCL: ($M+H^+$) 421,3, ($M+Na^+$) 423,2.

Ejemplo 63: 6-Oxo-2-fenil-*N*-[2-(1*H*-tetrazol-5-il)etil]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

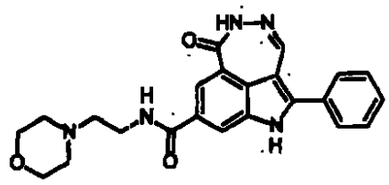


La preparación del ejemplo 63 a partir del compuesto del título del Ejemplo **49** (0,0989 g, 0,288 mmol), 2-(1*H*-tetrazol-5-il)etilamina (0,072 g, 0,317 mmol), trietilamina (0,0883 ml, 0,634 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,121 g, 0,317 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **58**. La HPLC preparativa (CH_3CN al 25-80%/H_2O), también de manera análoga, proporcionó el compuesto del título (0,002 g) con un rendimiento del 1,7%.

^1H RMN (d_6-DMSO): δ 12,50 (s, 1H), 10,49 (s, 1H), 8,83 (t, 1H, *J* = 4,9 Hz), 8,05 (s, 1H), 7,98 (s, 1H), 7,70 (d, 2H, *J* = 7,6 Hz), 7,51-7,62 (m, 4H), 3,64 (c, 2H, *J* = 6,1 Hz), 3,14 (t, 2H, J = 6,8 Hz).

EMAR calculado para $C_{20}H_{17}N_8O_2$ 401,1474 (M+H), encontrado 401,1476.

Ejemplo 64: *N*-[2-(4-Morfolinil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

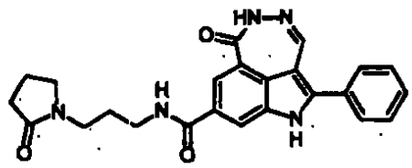


La preparación del ejemplo 64 a partir del compuesto del título del Ejemplo **49** (0,0991 g, 0,289 mmol), 2-morfolin-4-iletilamina (0,041 g, 0,317 mmol), trietilamina (0,0483 ml, 0,347 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,121 g, 0,317 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **58**. La HPLC preparativa (CH_3CN al 10-80%/H_2O), también de manera análoga, proporcionó el compuesto del título (0,018 g) con un rendimiento del 15%.

^{1}H RMN (d_6-DMSO): δ 12,48 (s, 1H), 10,49 (s, 1H), 8,62 (t, 1H, J = 5,3 Hz), 8,07 (s, 1H), 8,00 (s, 1H), 7,70 (d, 2H, *J* = 6,8 Hz), 7,51-7,62 (m, 4H), 3,57 (t, 4H, J = 4,3 Hz), 3,37-3,43 (m, 2H), 2,41 (s a, 6H).

EMAR calculado para $C_{23}H_{24}N_5O_3$ 418,1879 (M+H), encontrado 418,1858.

Ejemplo 65: 6-Oxo-*N*-[3-(2-oxo-1-pirrolidinil)propil]-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

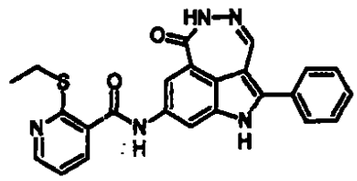


La preparación del ejemplo 65 a partir del compuesto del título del Ejemplo **49** (0,109 g, 0,319 mmol), 1-(3-aminopropil)pirrolidin-2-ona (0,05 g, 0,351 mmol), trietilamina (0,0534 ml, 0,383 mmol) y hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,133 g, 0,351 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **58**. La HPLC preparativa (CH_3CN al 10-80%/H_2O), también de manera análoga, proporcionó el compuesto del título (0,035 g) con un rendimiento del 26%.

^{1}H RMN (d_6-DMSO): δ 12,54 (s, 1H), 10,51 (s, 1H), 8,66 (s, 1H), 8,08 (s, 1H), 8,01 (s, 1H), 7,70 (d, 2H, J = 7,2 Hz), 7,53-7,62 (m, 4H), 3,23-3,37 (m, 6H), 2,21 (t, 2H, *J* = 7,9 Hz), 1,89-1,96 (m, 2H), 1,72(t, 2H,J = 6,8 Hz).

EMAR calculado para $C_{24}H_{24}N_5O_3$ 430,1879 (M+H), encontrado 430,1899.

Ejemplo 66: 2-Etilsulfanil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-nicotinamida



La preparación del ejemplo 66 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (30 mg, 0,096 mmol), ácido 2-etilsulfanil-nicotínico (22 mg, 0,12 mmol), trietilamina (0,020 ml, 0,14 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (46 mg, 0,12 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (sílice aclarada previamente con trietilamina al 3% en acetato de etilo, eluida con trietilamina al 3% en 19:6:1 de acetato de etilo:hexano:metanol), también de manera análoga, proporcionó el compuesto del título (7 mg, 0,016 mmol) en forma de un polvo amarillo con un rendimiento del 17%.

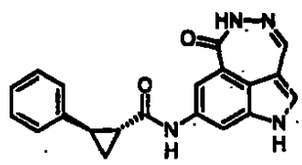
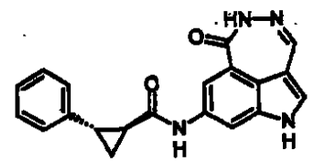
^{1}H RMN (d_6-DMSO): δ 12,15 (s, 1H), 10,60 (s, 1H), 10,39 (s, 1H), 8,59 (s, 1H, con suave división), 8,22 (s, 1H), 7,95 (m, 1H), 7,82 (s, 1H), 7,72-7,48 (m, 6H), 7,25 (m, 1H), 3,21-3,10 (m, 2H, parcialmente oscurecido), 1,35-1,23 (m, 3H).

EMCL: ($M+H^+$) 442,3, ($M+Na^+$) 464,1.

Ejemplo 67:

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; y

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*S*,2*S*)-2-fenil-ciclopropanocarboxílico

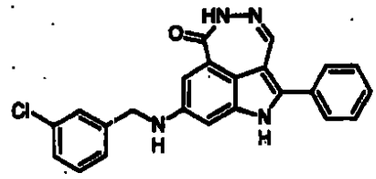



La preparación del ejemplo 67 a partir del compuesto del título del Ejemplo **2** (base libre) (21 mg, 0,105 mmol), ácido ± *trans*-2-fenil-i-ciclopropanocarboxílico (20 mg, 0,126 mmol), trietilamina (0,044 ml, 0,315 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (48 mg, 0,126 mmol) en CH_2Cl_2 (0,3 ml) y *N,N*-dimetilformamida (0,3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (5:4:1 de hexano:CH_2Cl_2:metanol seguido de 9:1 de CH_2Cl_2:metanol), también de manera análoga, proporcionó el compuesto del título (20 mg, 0,053 mmol) (mezcla de diastereómeros *trans*) en forma de un polvo amarillo con un rendimiento del 55%.

^{1}H RMN (d_6-DMSO): δ 11,72 (s, 1H), 10,38 (s, 1H), 10,25 (s, 1H), 8,13 (s, 1H), 7,56 (s, 1H, solapamiento), 7,55 (s, 1H, solapamiento), 7,46 (s, 1H), 7,37-7,13 (m, 5H), 2,39 (m, 1H), 2,10 (m, 1H), 1,51 (m, 1H), 1,39 (m, 1H).

EMCL: ($M+H^+$) 345,4, ($M+Na^+$) 367,3.

Ejemplo 68: 8-(3-Cloro-bencilamino)-2-fenil-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona



Al compuesto del título del Ejemplo 7 (clorhidrato) (40 mg, 0,13 mmol) y trietilamina (0,053 ml, 0,38 mmol) en *N,N*-dimetilformamida (0,9 ml) se les

486
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añadió gota a gota 1-bromometil-3-cloro-benceno (0,17 ml, 0,13 mmol) con agitación. Después de agitar durante una noche, la mezcla se cromatografió sobre sílice eluyendo con 2:1 de hexano:acetato de etilo, proporcionando, después del aislamiento, el compuesto del título (36 mg, 0,090 mmol) en forma de un polvo amarillo con un rendimiento del 71%.

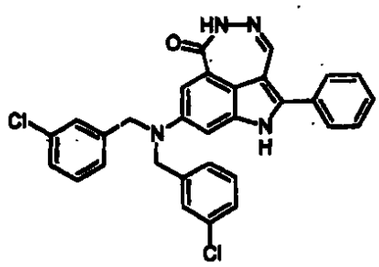
^{1}H RMN (d_6-DMSO): δ 11,59 (s, 1H, intercambios), 10,22 (s, 1H, intercambios), 7,60-7,27 (m, 10H), 7,08 (s, 1H), 6,60 (t, 1H, *J* = 4,9 Hz, intercambios), 6,45 (s, 1H), 4,36 (m, 2H).

EMCL: $(M+H^+)$ 401,3, 403,3.

Análisis calculado para $C_{23}H_{17}N_4OCl \cdot 0,3\ H_2O$: C, 67,99; H, 4,37; N, 13,79.

Encontrado: C, 67,98; H, 4,35; N, 13,58.

Ejemplo 69: 8-[*bis*-(3-cloro-bencil)-amino]-2-fenil-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona

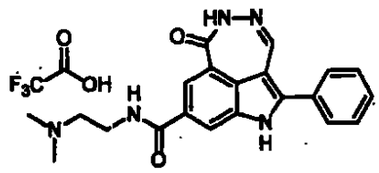


El compuesto del título (7 mg, 0,013 mmol) se aisló en forma de un polvo amarillo con un rendimiento del 10% en forma de un subproducto a partir de la síntesis indicada en el Ejemplo **68**.

^{1}H RMN (d_4-metanol): δ 7,51-7,31 (m, 6H), 7,25-7,10 (m, 9H), 6,64 (s, 1H), 4,64 (s, 4H).

EMCL: $(M+H)^+$ 525,3.

Ejemplo 70: Trifluoroacetato de *N*-[2-(dimetilamino)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



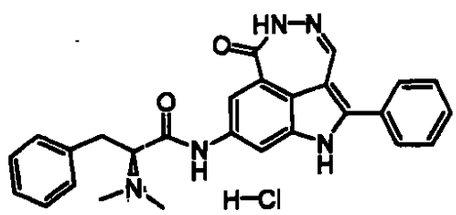
La preparación del ejemplo 70 a partir del compuesto del título del Ejemplo **49** (0,08 g, 0,23 mmol), *N,N*-dimetiletano-1,2-diamina (0,0247 g, 0,28 mmol), trietilamina (0,17 ml, 1,2 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,106 g, 0,28 mmol) en DMSO (6 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%) también de manera análoga proporcionó el compuesto del título (0,0076 g) con un rendimiento del 6,8%.

^1H RMN (d_6-DMSO): δ 12,53 (s, 1H), 10,54 (s, 1H), 9,30 (s, 1H), 8,84 (t, 1H, J = 5,5 Hz), 8,12 (s, 1H), 8,04 (s, 1H), 7,75-7,67(m, 2H), 7,66-7,53 (m, 3H), 7,52 (s, 1H), 3,62 (m, 2H), 3,39 (m, 2H), 2,86 (s, 6H).

EMCL: ($M+H^+$) 376,1

EMAR: $C_{21}H_{21}N_5O_2 \cdot H$: 376,1774, Encontrado: 376,1785.

Ejemplo 71a: (*S*)-2-Dimetilamino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida (sal clorhidrato)

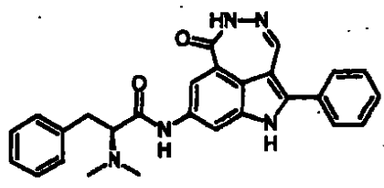


La preparación a partir del compuesto del título del Ejemplo **7** (clorhidrato) (40 mg, 0,128 mmol), ácido (*S*)-2-dimetilamino-3-fenil-propiónico (30 mg, 0,154 mmol), trietilamina (0,071 ml, 0,512 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (59 mg, 0,154 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con trietilamina al 1,5% en CH_2Cl_2 seguido de trietilamina al 1,5% en 9:1 de CH_2Cl_2:metanol), también de manera análoga, proporcionó la base libre del compuesto del título (46 mg, 0,10 mmol) en tres lotes separados para un rendimiento combinado del 80%. Dos de los lotes se utilizaron en los Ejemplos 71b y 71c respectivamente. Al tercer lote (8 mg, 0,018 mmol) se le añadieron tetrahidrofurano y 1,2 equivalentes de HCl en dioxano (de una solución madre 4 M). Después de la evaporación, la trituración con éter dietílico y 1:1 de CH_2Cl_2:hexano dio el compuesto del título (6 mg, 0,012 mmol) en forma de un polvo amarillo con un rendimiento del 67% para la formación de la sal.

^{1}H RMN (d_6-DMSO): δ 12,25 (s, 1H, intercambios), 10,76 (s a, 2H, intercambios), 10,42 (s, 1H, intercambios), 7,95 (s, 1H), 7,72-7,45 (m, 7H), 7,35-7,16 (m, 5H), 4,28 (m, 1H), 3,05 -2,90 (m, 6H).

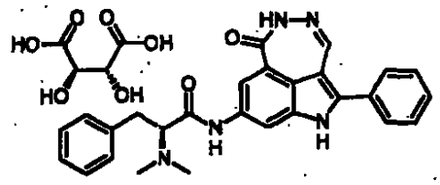
EMCL (base libre): ($M+H^+$) 452,3, ($M+Na^+$) 474,3.

Ejemplo 71b: (*S*)-2-Dimetilamino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida



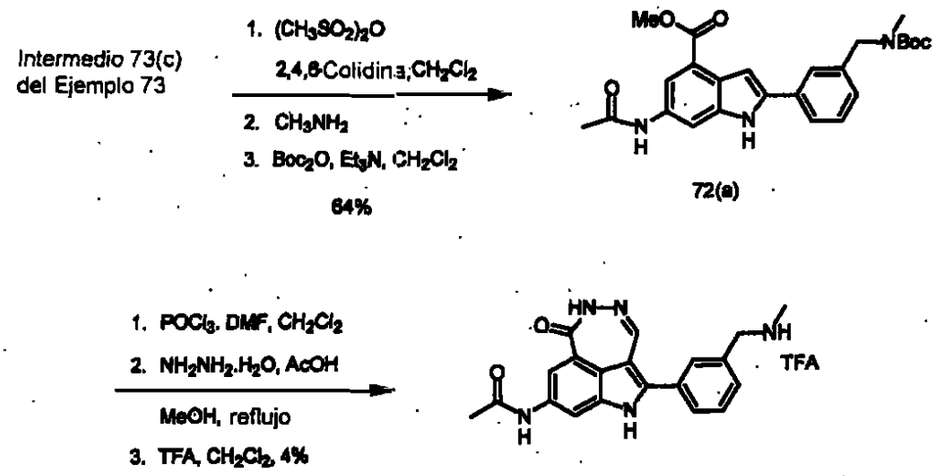
Un lote de la base libre (*S*)-2-dimetilamino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida (13 mg, 0,029 mmol) del Ejemplo 71a se trituró con 1:1 de éter dietílico:hexano, dando el compuesto del título purificado (12 mg, 0,027 mmol) en forma de un polvo amarillo con un rendimiento del 93% para la trituración.

Ejemplo 71c: (*S*)-2-Dimetilamino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-cd]indol-8-il)-3-fenil-propionamida; compuesta con ácido (2*R*,3*R*)-2,3-dihidroxi-succínico



Un lote de la base libre (*S*)-2-dimetilamino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida (22 mg, 0,049 mmol) del Ejemplo 71a se trituró con 1:1 de éter dietílico:hexano, dando el material purificado (20 mg, 0,044 mmol). Después, se disolvió una porción (10 mg, 0,022 mmol) en una pequeña cantidad de aprox. 1:1 de tetrahidrofurano:metanol y se trató con ácido *L*-tartárico (3,3 mg, 0,022 mmol). Los componentes volátiles de la solución transparente resultante se retiraron en una atmósfera de argón. Al aceite amarillo resultante se le añadió éter dietílico más una gota de metanol, dando un precipitado amarillo fino que se aisló decantando la mayor parte del líquido, y la posterior eliminación a alto vacío de los componentes volátiles, proporcionando el compuesto del título en forma de una sal tartrato (13 mg, 0,022 mmol) con rendimiento cuantitativo.

Ejemplo 72: Trifluoroacetato de *N*-(2-{4-[(metilamino)metil]fenil}-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida



Etapa 1. Preparación de 6-(acetilamino)-2-(3-{[{[(1,1-dimetiletil)oxi]carbonil}(metil)amino]metil}fenil)-1*H*-indol-4-carboxilato de metilo 72(a)

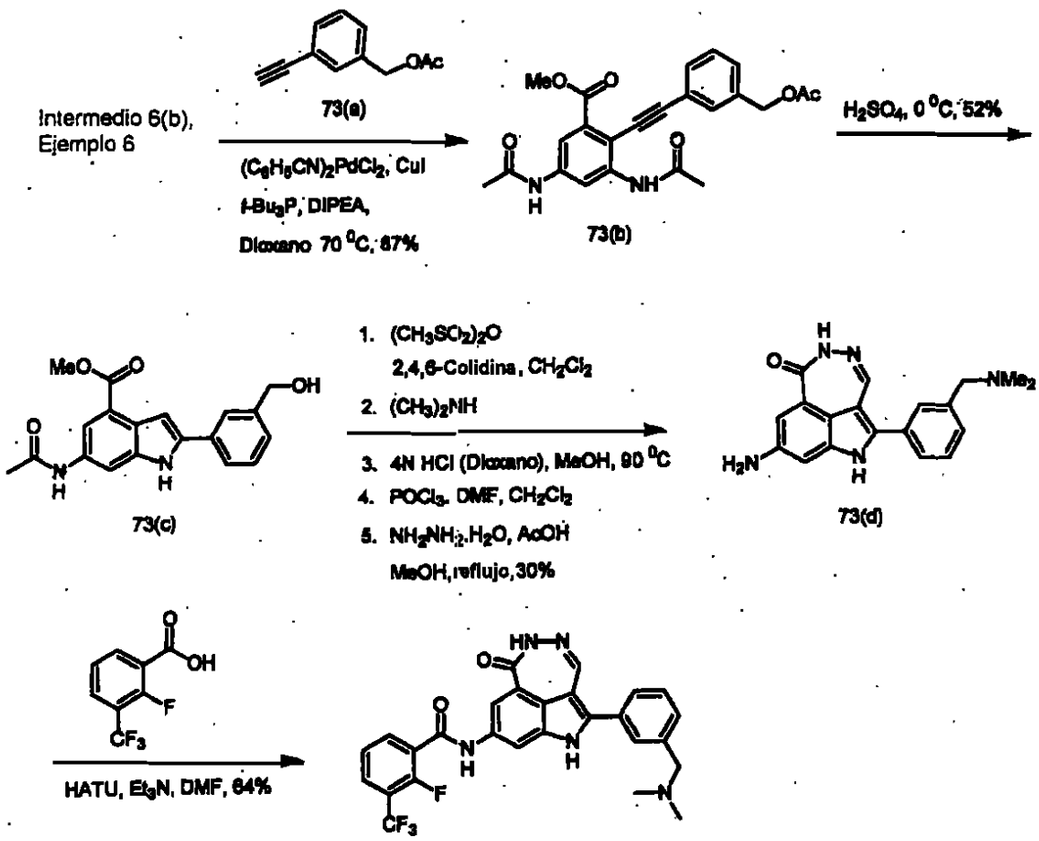
Con agitación, al Intermedio 73(c) del Ejemplo **73** (54 mg, 0,16 mmol) en CH_2Cl_2 (2,5 ml) se le añade 2,4,6-trimetilpiridina (0,11 ml, 0,80 mmol) seguido de anhídrido metanosulfónico (42 mg, 0,23 mmol). Después de 3,5 horas, se añade más anhídrido metanosulfónico (7 mg, 0,04 mmol) y la mezcla se agita durante 1 hora más, tras lo cual se añade metilamina en tetrahidrofurano (2,0 ml, 2,0 M) y la reacción se agita durante una noche a temperatura ambiente. Después de la evaporación de los componentes volátiles, se añaden CH_2Cl_2 (2,0 ml), trietilamina (0,064 ml, 0,46 mmol) y dicarbonato de di-*terc*-butilo (50 mg, 0,23 mmol) y la reacción se agita durante 2,5 horas, tras lo cual, después de la retirada de los componentes volátiles, el producto bruto se purificó por cromatografía sobre gel de sílice eluyendo con 1:1 de acetato de etilo:hexano, proporcionando el Intermedio 72(a) (46 mg, 0,10 mmol) con un rendimiento del 64%.

Etapa 2. Preparación del compuesto del título: trifluoroacetato de *N*-(2-{4-[(metilamino)metil]fenil}-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida

De manera similar a la descrita para el Ejemplo **3**, etapa 4, el Intermedio 72(a) (45 mg, 0,10 mmol), en CH_2Cl_2 (1,5 ml) se trató con un reactivo de Vilsmeier premezclado compuesto por $POCl_3$ (0,021 ml, 0,23 mmol) y *N,N*-dimetilformamida (0,05 ml, 0,65 mmol). Después de 2 h, se añadió acetato sódico 2 N en agua y el producto 3-formilado bruto se aisló por tratamiento de extracción usando acetato de etilo. Después de la evaporación de los componentes volátiles, se añadieron metanol (1,5 ml), $H_2NNH_2 \cdot H_2O$ (0,015 ml, 0,31 mmol) y ácido acético (0,010 ml, 0,17 mmol) y la mezcla se calentó en un baño de aceite a 70°C durante 45 min. La purificación se realizó usando cromatografía sobre gel de sílice eluyendo con 3:2 de acetato de etilo:hexano. El intermedio protegido, {4-[8-(acetilamino)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il]fenil}metil(metil)carbamato de 1,1-dimetiletilo, se trató con 1:1 de TFA/CH_2Cl_2 (5 ml) de forma análoga al Ejemplo **20**. El aislamiento proporcionó el compuesto del título (2 mg, 0,004 mmol) con un rendimiento del 4%.

EMCL: $(M+H^+)$ 362,3.

Ejemplo 73: *N*-[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fluoro-3-trifluorometil-benzamida



Etapa 1. Preparación de éster metílico del ácido 2-(3-acetoximetil-feniletinil)-3,5-*bis*-acetilamino-benzoico 73(b)

Una mezcla de $(C_6H_5CN)_2PdCl_2$ (0,8 g, 2 mmol), CuI (0,267 g, 1,4 mmol) y tri-*terc*-butil-fosfano (1,05 ml, 4 mmol) en dioxano (35 ml, 2,0 M) se agitó a 22°C durante 0,25 horas. Se añadieron secuencialmente diisopropilamina (17,1 ml, 122 mmol), el Intermedio 6(b) del Ejemplo **6** (23 g, 69,9 mmol), 3-etinil-bencil éster del ácido acético (17 g, 98,0 mmol) (véase más adelante para la preparación) y *N,N*-dimetilformamida (35 ml, 2,0 M). La mezcla de reacción se

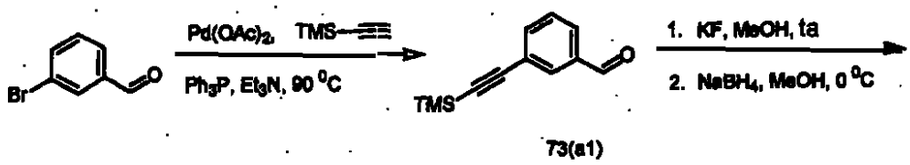
agitó a 70°C durante 16 horas. Se añadió acetato de etilo (300 ml) y las sales se filtraron a través de tierra diatomácea. El disolvente se retiró a presión reducida y el sólido resultante se trituró con acetato de etilo (25 ml), diclorometano (50 ml) y éter dietílico (25 ml). El precipitado se recogió por filtración y se lavó con diclorometano al 5% en éter dietílico (100 ml), proporcionando, después del secado, el Intermedio 73(b) (25,7 g) con un rendimiento del 87% en forma de un polvo blanco.

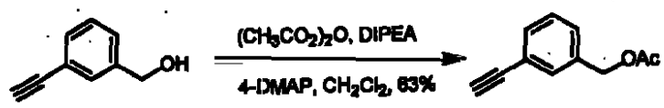
^{1}H-RMN (d_6-DMSO): δ 10,35 (s, 1H), 9,54 (s, 1H), 8,21 (d, 1H, J = 2,1 Hz), 8,08 (d, 1H, J = 2,1 Hz), 7,58-7,38 (m, 4H), 5,12 (s, 2H), 3,90 (s, 3H), 2,17 (s, 3H), 2,09 (s, 3H), 2,07 (s, 3H).

EMCL: (M-H$^+$) 421,3

Para la etapa 1, el compuesto 73(a) (3-etinil-bencil éster del ácido acético) se preparó como se indica a continuación:

Etapa 1a-1c.





Etapa 1a: Preparación de 3-trimetilsilaniletinil-benzaldehído bruto 73(a1)

Se calentaron 3-bromobenzaldehído (30 g, 162 mmol), etinil-trimetil-silano (30 ml, 211 mmol), trifenilfosfina (2,13 g, 8 mmol), acetato de paladio (II) (0,91 g, 4 mmol) y trietilamina (540 ml, 0,3 M) a 90°C durante 5 horas y

después de enfriar a temperatura ambiente, la mezcla se filtró. El filtrado se evaporó y el residuo se sometió a cromatografía sobre gel de sílice (de hexano a 4:96 de éter dietílico/hexano), proporcionado 3-trimetilsilaniletinil-benzaldehído 73(a1).

Etapa 1b: Preparación de (3-etinil-fenil)-metanol bruto 73(a2)

A 3-trimetilsilaniletinil-benzaldehído 73(a1) de la etapa 1a en metanol (540 ml, 0,3 M) se le añadió KF (18,8 g, 324 mmol) y la mezcla resultante se agitó a 22°C durante 6 horas. Después de enfriar a 0°C, se añadió cuidadosamente $NaBH_4$ (6,13 g, 162 mmol) durante 0,5 horas. Se añadió cuidadosamente NH_4Cl saturado acuoso y los volátiles se retiraron al vacío. Se añadió acetato de etilo (200 ml) y la fase orgánica se lavó con agua y una solución saturada acuosa de NaCl, se secó sobre $MgSO_4$ y se filtró. Los volátiles se retiraron al vacío, proporcionando (3-etinil-fenil)-metanol bruto 73(a2).

Etapa 1c: Preparación de 3-etinil-bencil éster del ácido acético 73(a)

Se agitaron (3-etinil-fenil)-metanol bruto 73(a2) de la etapa 1b, anhídrido acético (20 ml, 21 mmol), diisopropiletilamina (85 ml, 486 mmol) y 4-dimetilamino-piridina (0,3963,2 mmol) en CH_2Cl_2 (540 ml, 0,3 M) durante 0,5 horas. Se añadió cuidadosamente NH_4Cl saturado acuoso (100 ml) y la fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se filtró. Los volátiles se retiraron al vacío, proporcionando, después de la cromatografía sobre gel de sílice (de hexanos a 12:88 de éter dietílico/hexanos), 3-etinil-bencil éster del ácido acético (a) (17,83 g) con un rendimiento del 63%.

^{1}H-RMN (d_6-DMSO): δ 7,32-7,01 (m, 4H), 4,85 (s, 2H), 4,01 (s, 1H), 1,89 (s, 3H).

Etapa 2. Preparación de éster metílico del ácido 6-acetilamino-2-(3-hidroximetil-fenil)-1*H*-indol-4-carboxílico 73(c)

De manera análoga a la Etapa 4 del Ejemplo **6**, el Intermedio 73(b) (24 g, 56,8 mmol) se cicló para dar el Intermedio 73(c) (10,1 g) con un rendimiento del 52%.

^{1}H-RMN (d_6-DMSO): δ 11,89 (s, 1H), 10,16 (s, 1H), 8,35 (s, 1H), 7,89 (s a, 2H), 7,51 (d, 1H, *J* = 7,9 Hz), 7,49 (dd, 1H, *J* = 7,7, 7,5 Hz), 7,33 (s a, 2H), 5,37 (dd, 1H, *J* = 5,8, 5,7 Hz), 4,64 (d, 2H, *J* = 5,65 Hz), 3,99 (s, 3H), 2,13 (s, 3H).

EMCL: ($M+H^+$) 339,0

Etapa 3. Preparación de 8-amino-2-(3-dimetilaminometil-fenil)-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona 73(d)

A una solución del Intermedio 73(c) (1 g, 3 mmol) en diclorometano (0,1 M, 30 ml) se le añadió 2,4,6-colidina (1,56 ml, 12 mmol) seguido de $(CH_3SO_2)_2O$ (0,62 g, 3,6 mmol). Después de agitar durante 2 horas, se añadió dimetilamina (solución 5,6 M en etanol, 2,6 ml, 15 mmol) y la mezcla de reacción se agitó durante 24 horas a 22°C. Los volátiles se retiraron al vacío y la mezcla bruta se disolvió en metanol (15 ml). Se añadió cuidadosamente HCl anhidro 4 M en dioxano (15 ml, 60 mmol) y la solución se calentó a 90°C durante 2,5 horas. Después de enfriar a 22°C, los volátiles se retiraron al vacío y el éster metílico del ácido 6-amino-2-(3-dimetilaminometil-fenil)-1*H*-indol-4-carboxílico bruto se formiló y se cicló de manera análoga a las etapas 4 y 5 del Ejemplo **3**. La cromatografía sobre gel de sílice (de 90:10 a 75:25 CH_2Cl_2/amoniaco 2 M en isopropilalcohol) proporcionó el Intermedio 73(d) (0,3 g, 0,9 mmol) con un rendimiento del 30%.

^{1}H RMN (d_6-DMSO): δ 11,54 (s, 1H), 10,15 (s, 1H), 7,55-7,32 (m, 5H), 6,98 (d, 1H, *J* = 1,3 Hz), 6,65 (d, 1H, J = 1,4 Hz), 5,2 (s a, 2H), 3,49 (a, 2H), 2,20 (s a, 6H).

EMCL: ($M+H^+$) 334,2

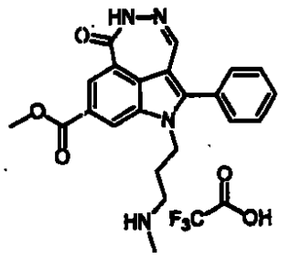
Etapa 4. Preparación del compuesto del título: *N*-[2-(3-dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fluoro-3-trifluorometil-benzamida

La preparación a partir del Intermedio 73(d) (0,11 g, 0,4 mmol), ácido 2-fluoro-3-trifluorometil-benzoico (0,103 g, 0,6 mmol), trietilamina (0,183 ml, 1,6 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,188 g, 0,6 mmol) y *N,N*-dimetilformamida (0,2 M, 1,7 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (de 90:10 a 80:20 de CH_2Cl_2/amoniaco 2 M en isopropilalcohol) proporcionó el compuesto del título (0,11 g) en forma de un polvo amarillo con un rendimiento del 64%.

^{1}H-RMN (d_6-DMSO): δ 12,26 (s, 1H), 10,84 (s, 1H), 10,51 (s, 1H), 9,62 (a, 1H), 8,29 (d, 1H, J = 1,4 Hz), 8,08-7,94 (m, 2H), 7,85-7,53 (m, 7H), 4,39 (s, 2H), 2,73 (s, 6H).

EMCL: ($M+H^+$) 524,2.

Ejemplo 74: Trifluoroacetato de 1-[3-(metilamino)propil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-6-carboxilato de metilo

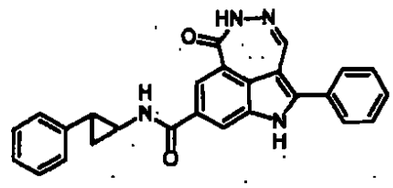


A una solución del compuesto del título del Ejemplo **39** (0,32 g, 1 mmol) en DMSO anhidro (10 ml) se le añadió NaH (suspensión al 60% en aceite mineral) (0,088 g, 2,2 mmol). La mezcla se dejó en agitación durante 5 min, tras lo cual se añadió 1,2-dibromopropano (0,24 g, 1,2 mmol). La mezcla se dejó en agitación durante una noche a temperatura ambiente, momento en el que se añadió una solución 2 M de metilamina en metanol (4 ml, 8 mmol). La mezcla se sometió a HPLC preparativa (CH_3CN al 20-50%/H_2O que contenía ácido trifluoroacético al 0,1%). Las fracciones más puras se combinaron y se liofilizaron, proporcionando el compuesto del título (0,0209 g) con un rendimiento del 4,1%.

^{1}H RMN (d_6-DMSO): δ 10,61 (s, 1H), 8,39 (d, 1H, *J* = 1,0 Hz), 8,22 (d, 1H, *J* = 1,0 Hz), 7,70-7,55 (m, 5H), 7,07 (s, 1H), 4,41 (t, 2H, *J* = 7,2 Hz), 3,92 (s, 3H), 2,80-2,60 (ancho, 2H), 2,43 (s, 3H), 1,95-1,75 (m, 2H).

EMCL: ($M+H^+$) 391,2 EMAR: $C_{22}H_{22}N_4O_3$ · H: 391,1770, Encontrado: 391,1768.

Ejemplo 75: 6-Oxo-2-fenil-*N*-((1,2-*trans*)-2-fenilciclopropil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

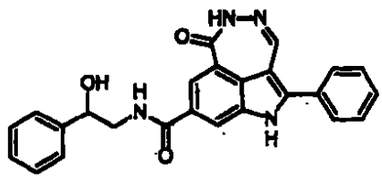


La preparación del ejemplo 75 a partir del compuesto del título del Ejemplo **49** (0,34 g, 1 mmol), clorhidrato de ±(1,2-*trans*)-fenilciclopropilamina (0,2 g, 1,2 mmol), trietilamina (0,28 ml, 2 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,46 g, 1,2 mmol) en DMSO (10 ml) se realizó de forma análoga al Ejemplo 76. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0145 g) con un rendimiento del 3,5%.

^1H RMN (d_6-DMSO): δ 12,46 (s, 1H), 10,47 (s, 1H), 8,88 (d, 1H, *J* = 4,4 Hz), 8,10 (d, 1H, J = 1,4 Hz), 8,02 (d, 1H, *J* = 1,4 Hz), 7,75-7,66 (m, 2H), 7,64-7,53 (m, 3H), 7,51 (s, 1H), 7,32-7,25 (m, 2H), 7,23-7,10 (m, 3H), 3,08 (m, 1H), 2,11 (m, 1H), 1,41 (m, 1H), 1,23 (m, 1H).

EMCL: ($M+H^+$) 421,1.

Ejemplo 76: *N*-(2-Hidroxi-2-feniletil)-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



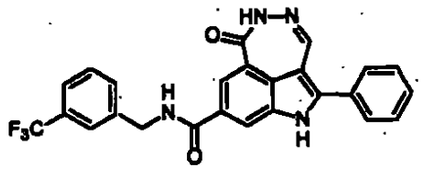
A una solución del compuesto del título del Ejemplo **49** (0,105 g, 0,306 mmol) en DMSO (2 ml) se le añadieron trietilamina (0,085 ml, 0,612 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio

(0,232 g, 0,612 mmol). Después de aproximadamente 5 min, se añadió 2-amino-1-feniletanol (0,084 g, 0 612 mmol) y la mezcla se agitó durante una noche. La mezcla se sometió a HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%) y las fracciones más puras se combinaron y se liofilizaron, proporcionando el compuesto del título (0,018 g) en forma de un polvo amarillo con un rendimiento del 14%.

^1H RMN (d_6-DMSO): δ 12,47 (s, 1H), 10,45 (s, 1H), 8,68 (t, 1H, J = 4,5 Hz), 8,09 (s, 1H), 8,01 (s, 1H), 7,71 (d, 2H, *J* = 6,8 Hz), 7,51-7,62 (m, 4H), 7,24-7,41 (m, 5H), 4,80-4,84 (m, 1H), 3,46-3,54 (m, 2H).

EMAR calculado para $C_{25}H_{21}N_4O_3$ 425,1614 (M+H), encontrado 425,1633.

Ejemplo 77: 6-Oxo-2-fenil-*N*-[3-(trifluorometil)bencil]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

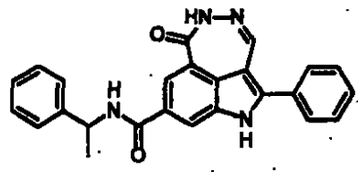


La preparación del ejemplo 77 a partir del compuesto del título del Ejemplo **49** (0,1 g, 0,291 mmol), 3-(trifluorometil)bencilamina (0,102 g, 0,582 mmol), trietilamina (0,081 ml, 0,582 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,221 g, 0,582 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,024 g) en forma de un polvo amarillo con un rendimiento del 18%.

^{1}H RMN (d_6-DMSO): δ 12,49 (s, 1H), 10,48 (s, 1H), 9,33 (t, 1H, *J* = 6,0 Hz), 8,14 (s, 1H), 8,06 (s, 1H), 7,52-7,72 (m, 10H), 4,58 (d, 3H, *J* = 5,7 Hz).

EMAR calculado para $C_{25}H_{18}N_4O_2F_3$ 463,1382 (M+H), encontrado 463,1391.

Ejemplo 78: 6-Oxo-2-fenil-*N*-(1-feniletil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

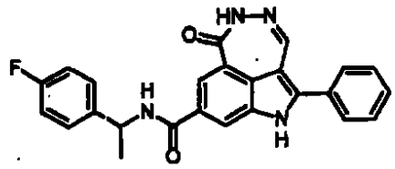


La preparación del ejemplo 78 a partir del compuesto del título del Ejemplo **49** (0,103 g, 0,3 mmol), 1-feniletilamina (0,0727 g, 0,6 mmol), trietilamina (0,084 ml, 0,6 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,228 g, 0,6 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0081 g) en forma de un polvo amarillo con un rendimiento del 6,6%.

^{1}H RMN (d_6-DMSO): δ 12,44 (s, 1H), 10,46 (s, 1H), 9,03 (d, 1H, J = 7,9 Hz), 8,14 (s, 1H), 8,03 (s, 1H), 7,71 (d, 2H, *J* = 7,2 Hz), 7,51-7,62 (m, 4H), 7,41 (d, 2H, *J* = 7,6 Hz), 7,32 (t, 2H, *J* = 7,6 Hz), 7,22 (t, 1H, J = 7,2 Hz), 5,16-5,25 (m, 1H), 1,51 (d, 3H, *J* = 6,8 Hz).

EMAR calculado para $C_{25}H_{21}N_4O_2$ 409,1665 (M+H), encontrado 409,1679.

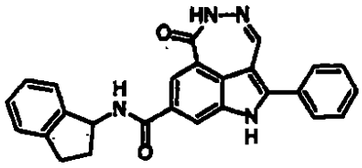
Ejemplo 79: *N*-[1-(4-Fluorofenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



La preparación del ejemplo 79 a partir del compuesto del título del Ejemplo **49** (0,0979 g, 0,285 mmol), 1-(4-*fluorofenil*)*etilamina* (0,0793 g, 0,57 mmol), trietilamina (0,079 ml, 0,57 mmol) y *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,217 g, 0,57 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0043 g) en forma de un polvo amarillo con un rendimiento del 3,5%.

^1H RMN (d_6-DMSO): δ 12,44 (s, 1H), 10,47 (s, 1H), 9,03 (d, 1H, *J* = 7,9 Hz), 8,13 (s, 1H), 8,02 (s, 1H), 7,71 (d, 2H, *J* = 6,8 Hz), 7,51-7,62 (m, 4H), 7,42-7,47 (m, 2H), 7,12-7,18 (m, 2H), 5,15-5,24 (m, 1H), 1,50 (d, 3H, *J* = 7,2 Hz). EMAR calculado para $C_{25}H_{20}N_4O_2F$ 427,1570 (M+H), encontrado 427,1584.

Ejemplo 80: *N*-(2,3-Dihidro-1*H*-inden-1-il)-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



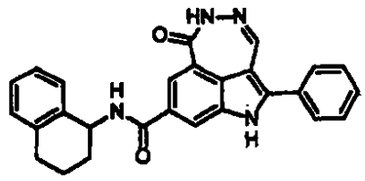
La preparación del ejemplo 80 a partir del compuesto del título del Ejemplo **49** (0,1 g, 0,291 mmol), 2,3-dihidro-1*H*-inden-1-ilamina (0,0775 g, 0,582 mmol), trietilamina (0,081 ml, 0,582 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,221 g, 0,582 mmol) en

DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0045 g) en forma de un polvo amarillo con un rendimiento del 3,7%.

^1H RMN (d_6-DMSO): δ 12,45 (s, 1H), 10,45 (s, 1H), 9,01 (d, 1H, *J* = 8,3 Hz), 8,15 (s, 1H), 8,09 (s, 1H), 7,71 (d, 2H, J = 6,8 Hz), 7,51-7,62 (m, 4H), 7,18-7,28 (m, 4H), 5,56-5,64 (m, 1H), 2,79-3,06 (m, 2H), 1,98-2,46 (m, 2H).

EMAR calculado para $C_{25}H_{20}N_4O_2F$ 427,1570 (M+H), encontrado 427,1584.

Ejemplo 81: 6-Oxo-2-fenil-*N*-(1,2,3,4-tetrahidronaftalen-1-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



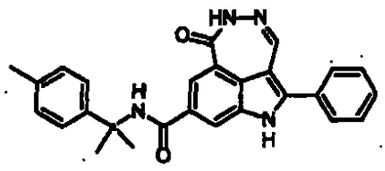
La preparación del ejemplo 81 a partir del compuesto del título del Ejemplo **49** (0,103 g, 0,3 mmol), 1,2,3,4-tetrahidronaftalen-1-ilamina (0,0883 g, 0,6 mmol), trietilamina (0,084 ml, 0,6 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,228 g, 0,6 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0136 g) en forma de un polvo amarillo con un rendimiento del 10%.

^1H RMN (d_6-DMSO): δ 12,44 (s, 1H), 10,44 (s, 1H), 9,01 (d, 1H, J = 8,7 Hz), 8,15 (s, 1H), 8,09 (s, 1H), 7,71 (d, 2H, *J* = 6,8 Hz), 7,51-7,62 (m, 4H), 7,10-

7,23 (m, 4H), 5,23-5,30 (m, 1H), 2,75-2,81 (m, 2H), 1,96-2,01 (m, 2H), 1,74-1,90 (m, 2H).

EMAR calculado para $C_{27}H_{23}N_4O_2$ 435,1821 (M+H), encontrado 435,1810.

Ejemplo 82: *N*-[1-Metil-1-(4-metilfenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

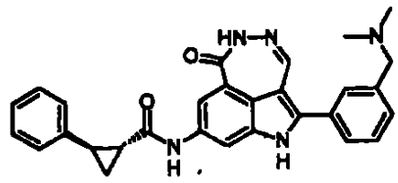


La preparación del ejemplo 82 a partir del compuesto del título del Ejemplo **49** (0,103 g, 0,3 mmol), 1-metil-1-(4-metilfenil)etilamina (0,0895 g, 0,6 mmol), trietilamina (0,084 ml, 0,6 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,228 g, 0,6 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0304 g) en forma de un polvo amarillo con un rendimiento del 23%.

^{1}H RMN (d_6-DMSO): δ 12,41 (s, 1H), 10,45 (s, 1H), 8,60 (s, 1H), 8,05 (s, 1H), 7,94 (s, 1H), 7,70 (d, 2H, *J* = 6,80 Hz), 7,51-7,62 (m, 4H), 7,26 (d, 2H, *J* = 8,3 Hz), 7,08 (d, 2H, *J* = 7,9 Hz), 2,25 (s, 3H), 1,67 (s, 6H).

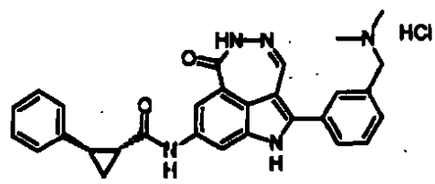
EMAR calculado para $C_{27}H_{25}N_4O_2$ 437,1978 (M+H), encontrado 437,1987.

Ejemplo 83a: [2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



La preparación del ejemplo 83a a partir del Intermedio 73(d) del Ejemplo **73** (0,11 g, 0,33 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (0,08 g, 0,5 mmol), trietilamina (0,183 ml, 1,32 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,188 g, 0,5 mmol) y *N,N*-dimetilformamida (0,2 M, 1,7 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (de 90:10 a 80:20 de CH_2Cl_2/amoniaco 2 M en isopropilalcohol) proporcionó el compuesto del título (0,12 g) en forma de un polvo amarillo con un rendimiento del 76%.

Ejemplo 83b: sal HCl de [2-(3-dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



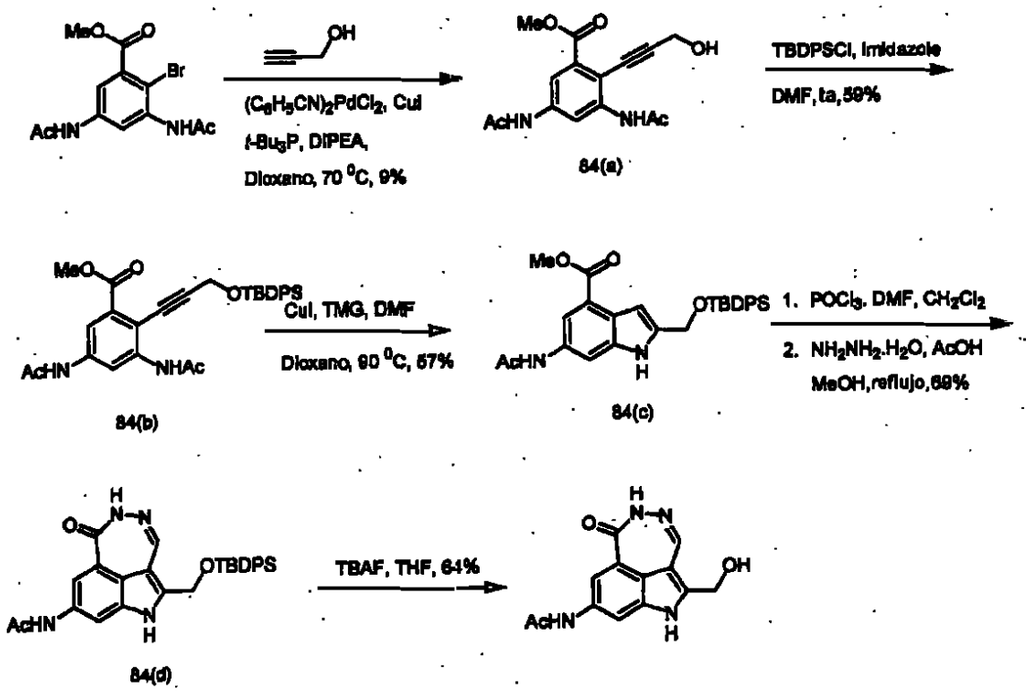
El compuesto de título del Ejemplo **83a** (0,075 g, 0,16 mmol) en diclorometano (1,0 ml) se trató con HCl 4 M en dioxano (0,043 ml, 0,17 mmol). Después de concentrar a sequedad, el compuesto del título (0,08 g) se obtuvo con rendimiento cuantitativo.

^{1}H RMN (d_6-DMSO): δ 12,19 (s, 1H), 10,48 (s, 1H), 10,44 (s, 1H), 10,02 (a, 1H), 8,20 (d, 1H, *J* = 1,5 Hz), 7,84 (s, 1H), 7,76 (d, 1H, J = 7,4 Hz), 7,71-

7,59 (m, 4H), 7,34-7,17 (m, 5H), 4,38 (d, 1H, J = 5,0 Hz), 2,78 (d, 6H, J = 4,6 Hz), 2,45-2,37 (m, 1H), 2,14-2,07 (m, 1H), 1,56-1,47 (m, 1H), 1,42-1,35 (m, 1H).

EMAR: ($M+H^+$) calculado para $C_{29}H_{28}N_5O_2$, 478,2243, encontrado 478,2261.

Ejemplo 84: *N*-(2-Hidroximetil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



Etapa 1. Preparación de éster metílico del ácido 3,5-*bis*-acetilamino-2-(3-hidroxi-prop-1-inil)-benzoico 84(a)

Se hicieron reaccionar el Intermedio 6(b) (10 g, 30,4 mmol) del Ejemplo **6** y alcohol de propargilo de manera análoga a la etapa 1 del Ejemplo **73**. Se obtuvo el Intermedio 84(a) (0,85 g) con un rendimiento del 9%.

^{1}H RMN (d_6-DMSO): δ 10,29 (s, 1H), 9,11 (s, 1H), 8,30 (s, 1H), 8,00 (s, 1H), 5,34 (t, 1H, J = 5,84 Hz), 4,38 (d, 2H, *J* = 5,84 Hz), 3,83 (s, 3H), 2,13 (s, 3H), 2,05 (s, 3H).

Etapa 2. Preparación de éster metílico del ácido 3,5-*bis*-acetilamino-2-[3-(*terc*-butil-difenil-silaniloxi)-prop-1-inil]-benzoico 84(b)

Se agitaron cloro-*terc*-butil-difenil-silano (1,3 g, 2 mmol), imidazol (0,54 g, 7,9 mmol) y el Intermedio 84(a) (0,48 g, 1,6 mmol) en *N,N*-dimetilformamida (0,2 M, 15 ml) durante 0,5 horas a 22°C. Se añadió metanol, los volátiles se retiraron al vacío y se añadió acetato de etilo (50 ml). La fase orgánica se lavó con HCl acuoso 1 N y salmuera, se secó sobre $MgSO_4$, se filtró y los volátiles se retiraron al vacío. La cromatografía sobre gel de sílice (80:20 de acetato de etilo/hexanos) proporcionó el Intermedio 84(b) (0,5 g) con un rendimiento del 59%.

^{1}H RMN (d_6-DMSO): δ 10,31 (s, 1H), 9,18 (s, 1H), 8,25 (d, 1H, *J* = 1,8 Hz), 8,00 (d, 1H, J = 1,8 Hz), 7,74-7,68 (*m*, 4H), 7,50-7,41 (*m*, 6H), 4,67 (s, 2H), 3,81 (s, 3H), 2,05 (s, 6H), 1,01 (s, 9H).

EMCL: ($M\text{-}H^+$) 541,1

Etapa 3. Preparación de éster metílico del ácido 6-acetilamino-2-(*terc*-butil-difenil-silaniloximetil)-1*H*-indol-4-carboxílico 84(c)

De manera análoga a la etapa 5 del Ejemplo **5**, se hizo reaccionar el Intermedio 84(b) (0,46 g, 0,84 mmol), proporcionando el Intermedio 84(c) (0,24 g) con un rendimiento del 57%.

^{1}H RMN (d_6-DMSO): δ 11,36 (s, 1H), 10,04 (s, 1H), 8,25 (s, 1H), 7,78 (d, 1H, J = 1,5 Hz), 7,74-7,66 (m, 4H), 7,50-7,41 (m, 6H), 6,72 (s, 1H), 4,85 (s, 2H), 3,87 (s, 3H), 2,06 (s, 3H), 1,03 (s, 9H).

EMCL: (M-H$^+$) 499,1

Etapa 4. Preparación de N-[2-(*terc*-butil-difenil-silaniloximetil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida 84(d)

De manera análoga a las etapas 4 y 5 del Ejemplo **3**, el Intermedio 84(c) (0,2 g, 0,4 mmol) se formiló y se cicló, proporcionando Intermedio 84(d) (0,14 g) con un rendimiento del 69%.

EMCL: (M-H$^+$) 509,1.

Etapa 5. Preparación del compuesto del título: *N*-(2-Hidroximetil-6-xo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida

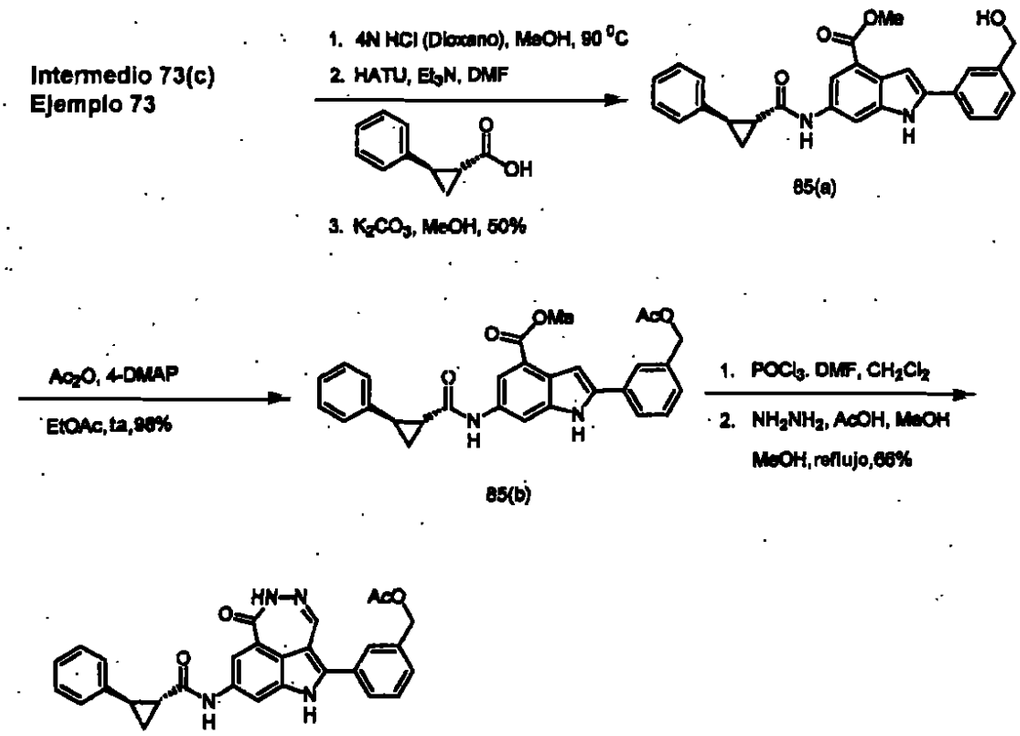
A una solución del Intermedio 84(d) (0,085 g, 0,17 mmol) en tetrahidrofurano (0,1 M, 1,6 ml) se le añadió una solución 1 M de fluoruro de *terc*-butilamonio en tetrahidrofurano (0,184 ml, 0,18 mmol). La mezcla se agitó a 22°C durante 2 horas y el sólido amarillo se recogió por filtración y se lavó con metanol (5,0 ml) y éter dietílico (5,0 ml), proporcionando el compuesto del título (0,029 g) con un rendimiento del 64%.

^{1}H RMN (d$_6$-DMSO): δ 11,74 (s, 1H), 10,17 (s, 1H), 10,02 (s, 1H), 8,04 (d, 1H, *J* = 1,3 Hz), 7,54 (s, 1H), 7,53 (s, 1H), 5,47 (dd, 1H, *J* = 5,5, 5,5 Hz), 4,68 (d, 2H, *J* = 5,4 Hz).

EMCL: (M+H$^+$) 273,1.

EMAR: (M+H$^+$) calculado para $C_{13}H_{13}N_4O_3$, 273,1001, encontrado 273,0988.

Ejemplo 85: 3-{6-Oxo-8-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-bencil-éster del ácido acético



Etapa 1. Preparación de éster metílico del ácido 2-(3-hidroximetil-fenil)-6-[(1*R*,2*R*)-(2-fenil-ciclopropanocarbonil)-amino]-1*H*-indol-4-carboxílico 85(a)

El Intermedio 73(c) del Ejemplo **73** (1,8 g, 5 mmol) se disolvió en metanol (22 ml). Se añadió cuidadosamente HCl 4 M en dioxano (22 ml, 75 mmol) y la solución se calentó a 90°C durante 1 hora. Después de enfriar a 22°C, los volátiles se retiraron al vacío, dando éster metílico del ácido 6-amino-2-(3-hidroximetil-fenil)-1*H*-indol-4-carboxílico que después se combinó con ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (2 g, 12,5 mmol), trietilamina (3,5 ml, 25 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (4,7 g, 12,5 mmol) en *N,N*-dimetilformamida (0,2 M, 25 ml) y se agitó a 22°C durante 12 horas. Los volátiles se retiraron al vacío y la mezcla

bruta se disolvió en metanol (25 ml, 0,2 M) y se trató con K_2CO_3 (1,38 g, 10 mmol) durante 1 hora a 22°C. El exceso de K_2CO_3 se retiró por filtración y al filtrado se le añadió ácido acético (2 gotas). Después de la evaporación del filtrado, el residuo se sometió a cromatografía sobre gel de sílice (de 90:10 a 100:0 de acetato de etilo/hexano), lo que proporcionó el Intermedio 85(a) (1,1 g, 2,5 mmol) con un rendimiento del 50%.

^{1}H RMN (d_6-DMSO): δ 11,83 (s, 1H), 10,41 (s, 1H), 8,25 (s, 1H), 7,90 (s, 1H), 7,84 (s, 1H), 7,75 (d, 1H, *J* = 7,9 Hz), 7,43 (dd, 1H, *J* = 7,7, 7,5 Hz), 7,35-7,17 (m, 7H), 5,30 (dd, 1H, *J* = 5,8, 5,6 Hz), 4,59 (d, 2H, *J* = 5,4 Hz), 2,45-2,36 (m, 1H), 2,14-2,07 (m, 1H), 1,58-1,47 (m, 1H), 1,42-1,34 (m, 1H).

EMAR: (M+H*) calculado para $C_{27}H_{25}N_2O_4$, 441,1828, encontrado 441,1814.

Etapa 2. Preparación de éster metílico del ácido 2-(3-acetoximetil-fenil)-6-[(1*R*,2*R*)-(2-fenil-ciclopropanocarbonil)-amino]-1*H*-indol-4-carboxílico 85(b)

A una suspensión del Intermedio 85(a) (1,1 g, 2,3 mmol) en acetato de etilo (22 ml, 0,1 M) se le añadieron 4-(dimetilamino)-piridina (0,28 g, 2,3 mmol) y anhídrido acético (0,47 g, 4,6 mmol). La mezcla se agitó a 22°C durante 1 h y los volátiles se retiraron al vacío. La cromatografía sobre gel de sílice (de 70:30 a 100:0 de acetato de etilo/Hexanos) proporcionó el Intermedio 85(b) (1,1 g, 2,3 mmol) con rendimiento cuantitativo.

^{1}H RMN (d_6-DMSO): δ 11,85 (s, 1H), 10,43 (s, 1H), 8,26 (s, 1H), 7,92-7,81 (m, 3H), 7,49 (dd, 1H, *J* = 7,7, 7,6 Hz), 7,37-7,13 (m, 7H), 5,15 (s, 2H), 3,92 (s, 3H), 2,45-2,36 (m, 1H), 2,14-2,07 (m, 1H), 1,58-1,47 (m, 1H), 1,42-1,34

(m, 1H). EMAR: ($M+H^+$) calculado para $C_{29}H_{27}N_2O_5$, 483,1920, encontrado 483,1945.

Etapa 3. Preparación del compuesto del título: 3-{6-oxo-8-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-bencil-éster del ácido acético

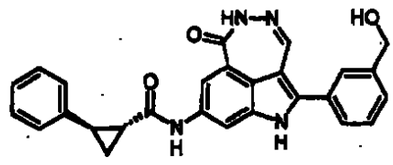
De manera análoga a las etapas 4 y 5 del Ejemplo **3**, el Intermedio 85(b) (0,75 g, 1,56 mmol) se formiló y se cicló. La purificación por cromatografía sobre gel de sílice (de 40:60 a 100:0 de acetato de etilo/Hexanos) proporcionó el compuesto del título (0,505 g, 1,03 mmol) en forma de un polvo amarillo con un rendimiento del 66%.

^{1}H RMN (d_6-DMSO): δ 12,13 (s, 1H), 10,44 (s, 1H), 10,39 (s, 1H), 8,16 (d, 1H, *J* = 1,5 Hz), 7,68-7,45 (m, 6H), 7,34-7,17 (m, 5H), 5,18 (s, 2H), 2,50-2,34 (m, 1H), 2,14-2,07 (m, 4H), 1,58-1,47 (m, 1H), 1,43-1,35 (m, 1H).

EMAR: ($M+H^+$) calculado para $C_{29}H_{25}N_4O_4$, 493,1876, encontrado 493,1882.

Análisis calculado para $C_{29}H_{25}N_4O_4 \cdot 0,4\ H_2O$: C, 69,70; H, 5,00; N, 11,21, Encontrado: C, 69,71; H, 5,03; N, 11,33.

Ejemplo 86: [2-(3-Hidroximetil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



El compuesto de título del Ejemplo **85** (0,288 g, 0,58 mmol) y K_2CO_3 (0,161 g, 1,17 mmol) se agitaron en metanol (0,2 M, 1,7 ml) y tetrahidrofurano (0,2 M, 1,7 ml) durante 1,5 horas a 22°C. Después de filtrar y acidificar la

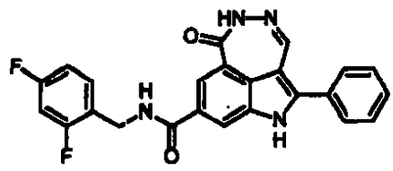
solución con dos gotas de ácido acético glacial, los volátiles se retiraron al vacío. La cromatografía sobre gel de sílice (de 40:60 a 0:100 de hexano/acetato de etilo) proporcionó el compuesto del título (0,26 g) en forma de un polvo amarillo con un rendimiento del 95%.

^{1}H RMN (d_6-DMSO): δ 12,11 (s, 1H), 10,43 (s, 1H), 10,36 (s, 1H), 8,15 (d, 1H, *J* = 1,0 Hz), 7,64 (d, 1H, J = 1,0 Hz), 7,61 (s, 1H), 7,55-7,17 (m, 9H), 5,35 (dd, 1H, *J* = 5,8, 5,6 Hz), 4,60 (d, 2H, *J* = 5,6 Hz), 2,45-2,36 (m, 1H), 2,14-2,07 (m, 1H), 1,58-1,47 (m, 1H), 1,42-1,34 (m, 1H).

EMCL: ($M-H^+$) 449,1.

Análisis calculado para $C_{27}H_{22}N_4O_3 \bullet 0,1\ CH_2Cl_2 \bullet 0,1\ C_2H_5O_2CCH_3$: C, 70,61; H, 4,96; N, 11,98, Encontrado: C, 70,01; H, 4,95; N, 11,95.

Ejemplo 87: *N*-(2,4-Difluorobencil)-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

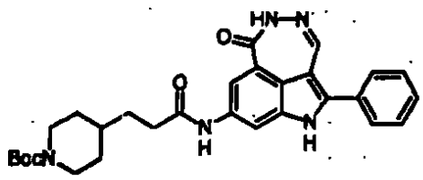


La preparación del ejemplo 87 a partir del compuesto del título del Ejemplo **49** (0,102 g, 0,297 mmol), 2,4-difluorobencilamina (0,085 g, 0,594 mmol), trietilamina (0,083 ml, 0,594 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,226 g, 0,594 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0044 g) en forma de un polvo amarillo con un rendimiento del 3,4%.

^{1}H RMN (d_6-DMSO): δ 12,48 (s, 1H), 10,48 (s, 1H), 9,20 (t, 1H, *J* = 5,5 Hz), 8,13 (s, 1H), 8,05 (s, 1H), 7,71 (d, 2H, *J* = 7,2 Hz), 7,52-7,62 (m, 4H), 7,40-7,47 (m, 1H), 7,16-7,25 (m, 1H), 7,03-7,10 (m, 1H),4,49(d, 2H, J = 5,3 Hz).

EMAR calculado para $C_{24}H_{17}N_4O_2F_2$ 431,1320 (M+H), encontrado 431,1324.

Ejemplo 88: Éster *terc*-butílico del ácido 4-[2-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-etil]-piperidin-1-carboxílico

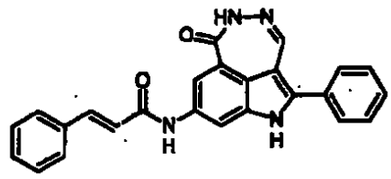


La preparación del ejemplo 88 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (44 mg, 0,141 mmol), éster *terc*-butílico del ácido 4-(2-carboxi-etil)-piperidin-1-carboxílico (43 mg, 0,169 mmol), trietilamina (0,059 ml, 0,423 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (64 mg, 0,169 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 8:5:2 de CH_2Cl_2:hexano:metanol), también de manera análoga, proporcionó el compuesto del título (62 mg, 0,120 mmol) en forma de un polvo amarillo con un rendimiento del 85%.

^{1}H RMN (d_6-DMSO): δ 12,15 (s, 1H), 10,37 (s, 1H), 10,06 (s, 1H), 8,20 (s, 1H), 7,70-7,46 (m, 7H), 3,96-3,87 (m, 2H), 2,75-2,63 (m, 2H), 2,42-2,34 (m, 2H), 1,72-1,55 (m, 5H), 1,40 (s, 9H), 1,06-0,98 (m, 2H).

EMCL: ($M+H^+$) 416,3, ($M+Na^+$) 538,3.

Ejemplo 89: (*E*)-*N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-acrilamida



La preparación del ejemplo 89 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (40 mg, 0,128 mmol), ácido (*E*)-3-fenil-acrílico (23 mg, 0,154 mmol), trietilamina (0,054 ml, 0,384 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (59 mg, 0,154 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de manera análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 2:1 de hexano:acetona), también de manera análoga, después de una trituración final con metanol, proporcionó el compuesto del título (47 mg, 0,116 mmol) en forma de un polvo amarillo con un rendimiento del 90%.

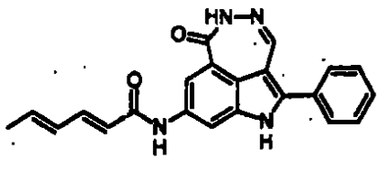
^{1}H RMN (d_6-DMSO): δ 12,14 (s, 1H), 10,43 (s, 1H), 10,40 (s, 1H), 8,38 (s, 1H), 7,71-7,40 (m, 13H), 6,87 (d, 1H, J =16,2 Hz).

EMCL: ($M+H^+$) 407,1, ($M+Na^+$) 429,0, (M-H) 405,2.

Análisis calculado para $C_{25}H_{18}N_4O_2 \cdot 2,7\ H_2O$: C, 65,98; H, 5,18; N, 12,31.

Encontrado: C, 65,62; H, 4,63; N, 12,10.

Ejemplo 90: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*E*,4*E*)-hexa-2,4-dienoico



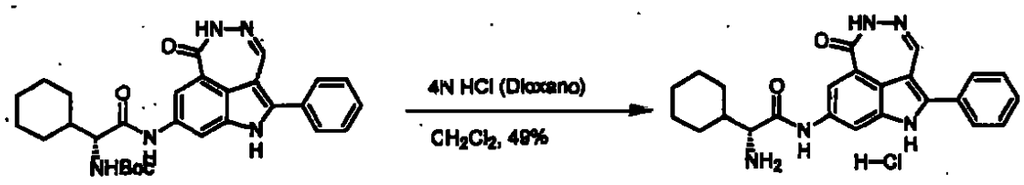
La preparación del ejemplo 90 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (41 mg, 0,131 mmol), ácido (2*E*,4*E*)-hexa-2,4-dienoico

(18 mg, 0,157 mmol), trietilamina (0,055 ml, 0,393 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (60 mg, 0,157 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de manera análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 2:1 de hexano:acetona), también de manera análoga, después de una trituración final con metanol proporcionó el compuesto del título (8 mg, 0,022 mmol) en forma de un polvo amarillo con un rendimiento del 16%.

^{1}H RMN (d_6-DMSO): δ 12,13 (s, 1H), 10,38 (s, 1H), 10,21 (s, 1H), 8,30 (s, 1H), 7,71-7,48 (m, 7H), 7,15 (m, 1H), 6,38-6,07 (m, 3H), 1,84 (d, 3H, *J* = 5,8 Hz).

EMCL: ($M+H^+$) 371,1, ($M+Na^+$) 393,0.

Ejemplo 91: (2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (clorhidrato)



El compuesto de título del Ejemplo **59** (210 mg, 0,41 mmol) se trató con HCl 4 M en dioxano y se dejó en agitación tapado fuertemente en forma de una suspensión durante aproximadamente 4 horas después de lo cual los componentes volátiles se evaporaron y se añadió éter dietílico y se evaporó varias veces. Los sólidos resultantes se disolvieron en metanol, se precipitaron con éter dietílico y se recogieron, proporcionando el compuesto del título (161 mg, 0,36 mmol) en forma de un polvo amarillo con un rendimiento del 87%.

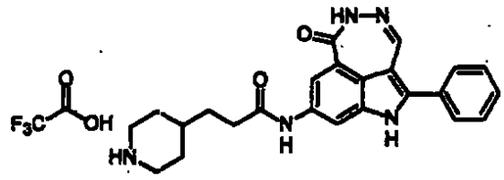
^{1}H RMN (d_6-DMSO): δ 12,27 (s, 1H), 10,83 (s, 1H), 10,44 (s, 1H), 8,36 (s a, 2H), 8,13 (s, 1H), 7,78-7,64 (m, 3H), 7,63-7,48 (m, 4H), 3,81 (s a, 1H), 1,91-1,58 (m, 6H), 1,31-1,00 (m, 5H).

EMCL: ($M+H^+$) 416,1 ,($M+Na^+$) 438,2.

Análisis calculado para $C_{24}H_{25}N_5O_2 \cdot 1,5\ HCl \cdot 2,0\ H_2O$: C, 56,94; H, 6,07; N, 13,84.

Encontrado: C, 57,20; H, 6,01; N, 13,57.

Ejemplo 92: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-piperidin-4-il-propionamida; compuesta con ácido trifluoroacético



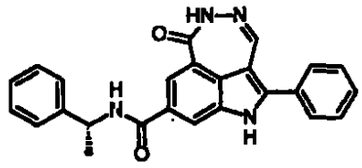
La preparación del ejemplo 92 a partir del compuesto del título del Ejemplo **88** (52 mg, 0,101 mmol) y TFA al 45% en CH_2Cl_2 (1 ml) se realizó de forma análoga al Ejemplo **20**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (50 mg, 0,084 mmol) en forma de un polvo amarillo con un rendimiento del 82%.

^{1}H RMN (d_6-DMSO): δ 12,07 (s, 1H), 10,38 (s, 1H), 10,09 (s, 1H), 8,45 (s a, 1H), 8,17 (s, 1H), 7,70-7,44 (m, 7H), 3,31-3,20 (m, 2H, parcialmente oscurecido), 2,93-2,76 (m, 2H), 2,41-2,31 (m, 2H), 1,91-1,76 (m, 2H), 1,64-1,49 (m, 3H), 1,38-1,19 (m, 2H).

Análisis calculado para $C_{24}H_{25}N_5O_2 \cdot 1,5\ TFA \cdot 0,8\ H_2O$: C, 53,64; H, 4,75; N, 11,58.

Encontrado: C, 53,59; H, 4,74; N, 11,55.

Ejemplo 93: 6-Oxo-2-fenil-*N*-[(1R)-1-feniletil]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

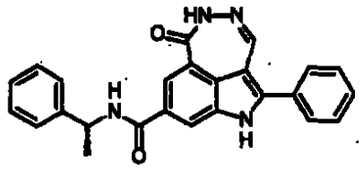


La preparación del ejemplo 93 a partir del compuesto del título del Ejemplo **49** (0,105 g,. 0,306 mmol), (1*R*)-1-feniletilamina (0,0742 g, 0,612 mmol), trietilamina (0,085 ml, 0,612 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,233 g, 0,612 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0235 g) en forma de un polvo amarillo con un rendimiento del 19%.

^1H RMN (d_6-DMSO): δ 12,44 (s, 1H), 10,46 (s, 1H), 9,03 (d, 1H, J = 7,9 Hz), 8,14 (s, 1H), 8,04 (s, 1H), 7,70 (d, 2H, J = 6,8 Hz), 7,51 -7,62 (m, 4H), 7,42 (d, 2H, J = 7,2 Hz), 7,30-7,36 (m, 2H), 7,20-7,24 (m, 1H), 5,16-5,25 (m, 1H), 1,50 (d, 3H, J = 7,2 Hz).

EMAR calculado para $C_{25}H_{21}N_4O_2$ 409,1665 (M+H), encontrado 409,1666.

Ejemplo 94: 6-Oxo-2-fenil-*N*-[(1*S*)-1-feniletil]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

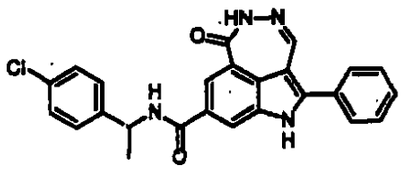


La preparación del ejemplo 94 a partir del compuesto del título del Ejemplo **49** (0,0976 g, 0,284 mmol), (1*S*)-1-feniletilamina (0,0688 g, 0,568 mmol), trietilamina (0,079 ml, 0,568 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,216 g, 0,568 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0197 g) en forma de un polvo amarillo con un rendimiento del 17%.

^{1}H RMN (d_6-DMSO): δ 12,44 (s, 1H), 10,46 (s, 1H), 9,04 (d, 1H, J = 7,9 Hz), 8,14 (s, 1H), 8,03 (s, 1H), 7,70 (d, 2H, J = 8,3 Hz), 7,51 -7,62 (m, 4H), 7,42 (d, 2H, J = 7,2 Hz), 7,30-7,36 (m, 2H), 7,20-7,24 (m, 1H), 5,16-5,25 (m, 1H), 1,50 (d, 3H, J = 7,2 Hz).

EMAR calculado para $C_{25}H_{21}N_4O_2$ 409,1665 (M+H), encontrado 409,1666.

Ejemplo 95: *N*-[1-(4-Clorofenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



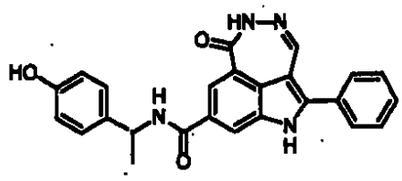
La preparación del ejemplo 95 a partir del compuesto del título del Ejemplo **49** (0,104 g, 0,303 mmol), 1-(4-clorofenil)etilamina (0,0943 g, 0,606

mmol), trietilamina (0,084 ml, 0,606 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,606 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0025 g) en forma de un polvo amarillo con un rendimiento del 1,9%.

^1H RMN (d_6-DMSO): δ 12,45 (s, 1H), 10,47 (s, 1H), 9,06 (d, 1H, J = 7,9 Hz), 8,14 (s, 1H), 8,03 (s, 1H), 7,70 (d, 2H, J = 7,9 Hz), 7,51 -7,62 (m, 4H), 7,38-7,44 (m, 4H), 5,13-5,22 (m, 1H), 1,49 (d, 3H, J = 7,2 Hz).

EMAR calculado para $C_{25}H_{20}N_4O_2Cl$ 443,1275 (M+H), encontrado 443,1265.

Ejemplo 96: *N*-[1-(4-Hidroxifenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

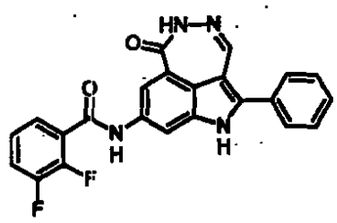


La preparación del ejemplo 96 a partir del compuesto del título del Ejemplo **49** (0,104 g, 0,303 mmol), 1-(4-hidroxifenil)etilamina (0,0831 g, 0,606 mmol), trietilamina (0,084 ml, 0,606 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,606 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0205 g) en forma de un polvo amarillo con un rendimiento del 16%.

^{1}H RMN (d_6-DMSO): δ 12,42 (s, 1H), 10,45 (s, 1H), 9,21 (s a, 1H), 8,91 (d, 1H, *J* = 8,3 Hz), 8,11 (s, 1H), 8,02 (s, 1H), 7,70 (d, 2H, *J* = 6,8 Hz), 7,51-7,61 (m, 4H), 7,21 (d, 2H, J = 8,3 Hz), 6,71 (d, 2H, *J* = 8,3 Hz), 5,08-5,16 (m, 1H), 1,46 (d, 3H, *J* = 7,2 Hz).

EMAR calculado para $C_{25}H_{21}N_4O_3$ 425,1614 (M+H), encontrado 425,1626.

Ejemplo 97: 2,3-Difluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida

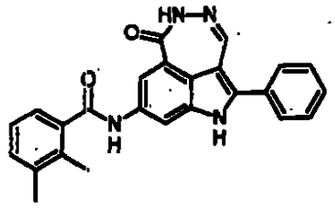


La preparación del ejemplo 97 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (40 mg, 0,128 mmol), ácido 2,3-difluoro-benzoico (24 mg, 0,154 mmol), trietilamina (0,054 ml, 0,384 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluronio (59 mg, 0,154 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de manera análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 2:1 de hexano.acetona aumentando a 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (24 mg, 0,058 mmol) en forma de un polvo amarillo con un rendimiento del 45%.

^{1}H RMN (d_6-DMSO): δ 12,20 (s, 1H), 10,72 (s, 1H), 10,42 (s, 1H), 8,24 (s, 1H), 7,81 (s, 1H), 7,72-7,45 (m, 8H), 7,37 (m, 1H).

EMCL: ($M+H^+$) 417,0, ($M+Na^+$) 439,1.

Ejemplo 98: 2,3-Dimetil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida

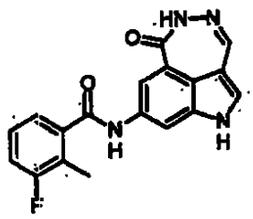


La preparación del ejemplo 98 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (42 mg, 0,134 mmol), ácido 2,3-dimetil-benzoico (24 mg, 0,161 mmol), trietilamina (0,056 ml, 0,402 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (61 mg, 0,161 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La mezcla se agitó en forma de una suspensión densa y se añadieron más ácido 2,3-dimetil-benzoico (12 mg, 0,08 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-N,*N,N,N*-tetrametiluronio (30 mg, 0,08 mmol) después de 48 horas para completar la reacción. La mezcla se filtró para recoger los sólidos que después se lavaron con metanol. Después de secar los sólidos a alto vacío, se obtuvo el compuesto del título (32 mg, 0,078 mmol) en forma de un polvo amarillo con un rendimiento del 58%.

^{1}H RMN (d_6-DMSO): δ 12,14 (s, 1H), 10,47 (s, 1H), 10,39 (s, 1H), 8,25 (s, 1H), 7,86 (m, 1H), 7,72-7,66 (m, 2H), 7,63-7,49 (m, 4H), 7,33-7,25 (m, 2H), 7,21 (m, 1H), 2,31 (s, 3H), 2,29 (s, 3H).

EMCL: ($M+H^+$) 409,1, ($M+Na^+$) 431,1.

Ejemplo 99: 3-Fluoro-2-metil-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida

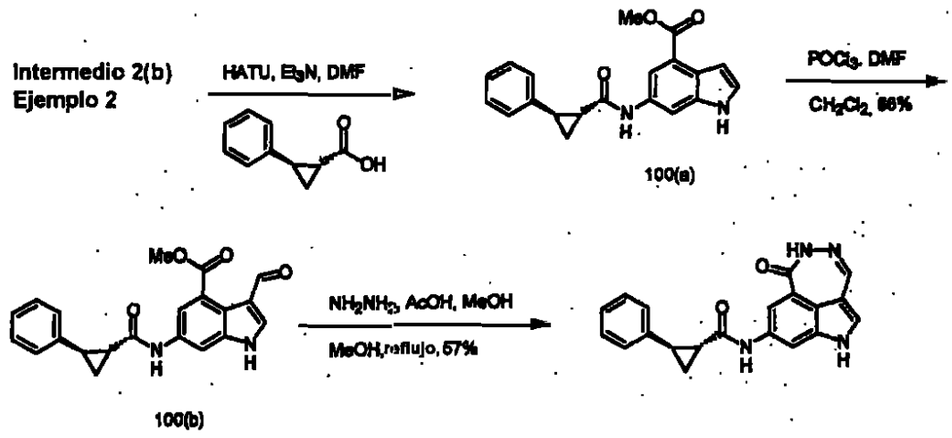


La preparación del ejemplo 99 a partir del compuesto del título del Ejemplo **2** (21 mg, 0,105 mmol), ácido 3-fluoro-2-metil-benzoico (19 mg, 0,126 mmol), trietilamina (0,044 ml, 0,315 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (48 mg, 0,126 mmol) en CH_2Cl_2 (0,2 ml) y *N,N*-dimetilformamida (0,2 ml) se realizó de forma análoga al Ejemplo **11**. La mezcla se agitó en forma de una suspensión densa y se añadieron más ácido 3-fluoro-2-metil-benzoico (11 mg, 0,07 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluronio (27 mg, 0,07 mmol) después de 24 horas para completar la reacción. La purificación, también de manera análoga, con la excepción de que requirió dos cromatografías sucesivas sobre gel de sílice (ambas eluidas con 2:1 de hexano:acetona aumentando a 1:1 de hexano:acetona) proporcionó el compuesto del título (14 mg, 0,042 mmol) en forma de un polvo amarillo con un rendimiento del 40%.

^{1}H RMN (d_6-DMSO): δ 11,79 (s, 1H), 10,50 (s, 1H), 10,25 (s, 1H), 8,20 (s, 1H), 7,78 (s, 1H), 7,60 (s, 1H), 7,49 (s, 1H), 7,46-7,17 (m, 3H), 2,30 (s, 3H).

EMCL: $(M+H^+)$ 337,1, $(M+Na^+)$ 359,1.

Ejemplo 100: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



Etapa 1. Preparación de éster metílico del ácido 6-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-1*H*-indol-4-carboxílico 100(a)

La preparación del intermedio 100(a) a partir del Intermedio 2(b) del Ejemplo **2** (111 mg, 0,49 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (119 mg, 0,73 mmol), trietilamina (0,273 ml, 1,96 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (278 mg, 0,73 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso proporcionó el Intermedio 100(a) bruto (222 mg) en forma de un sólido castaño que se utilizó sin purificación.

Etapa 2. Preparación de éster metílico del ácido 3-formil-6-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-1*H*-indol-4-carboxílico 100(b)

El Intermedio 100(a) (214 mg) se disolvió en CH_2Cl_2 (3 ml) y *N,N*-dimetilformamida (0,2 ml) y se trató con reactivo de Vilsmeier (0,147 ml) de manera similar a la descrita para el Ejemplo 3, Etapa 4. Después de la adición, se formó un precipitado inmediato provocando una suspensión densa. Se añadieron más CH_2Cl_2 (5,0 ml) y *N,N*-dimetilformamida (0,2 ml) para facilitar la

agitación. También se añadió más reactivo de Vilsmeier (0,147 ml). Después de aprox. 10 min, se añadió hexano y los sólidos se dejaron reposar. Después de decantar el sobrenadante, se añadió más hexano y la trituración se repitió desechando ambos triturados. A los sólidos restantes se les añadió metanol (8 ml) junto con K_2CO_3 (750 mg, 5,43 mmol) y H_2O (4 ml) y la mezcla se dejó en agitación. Después de aprox. 30 min, se añadió acetato de etilo y los agregados de K_2CO_3/H_2O se retiraron decantando el producto de la solución. Después, los disolventes se redujeron en volumen, se añadió más acetato de etilo y el producto se sometió a tratamiento de extracción, proporcionando el Intermedio 100(b) (117 mg, 0,32 mmol) en forma de un polvo parduzco con un rendimiento bruto combinado de aproximadamente el 66% en las etapas 1 y 2.

Etapa 3. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

El Intermedio 100(b) (105 mg), ácido acético (0,048 ml, 0,84 mmol) y $H_2NNH_2 \cdot H_2O$ (0,084 ml, 1,74 mmol) en metanol anhidro (4,4 ml) se calentaron a reflujo de manera similar a la descrita para el Ejemplo **3**, Etapa 5. El producto bruto se purificó sobre gel de sílice eluyendo con 2:1 y después 1:1 de hexano:acetona, proporcionando el compuesto del título (61 mg, 0,17 mmol) con un rendimiento de aproximadamente el 57% para la última etapa.

^{1}H RMN (d_6-DMSO): δ 11,74 (s, 1H), 10,38 (s, 1H), 10,23 (s, 1H), 8,13 (s, 1H), 7,60-7,53 (m, 2H), 7,46 (s, 1H), 7,35-7,26 (m, 2H), 7,24-7,15 (m, 3H), 2,38 (m, 1H), 2,08 (m, 1H), 1,50 (m, 1H), 1,36 (m, 1H).

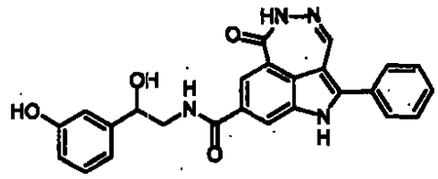
EMCL: ($M+H^+$) 345,2, ($M+Na^+$) 367,1.

Análisis calculado para $C_{20}H_{16}N_4O_2 \cdot H_2O \cdot 0{,}1$ metanol $\cdot 0{,}1\ CH_2Cl_2$: C, 66,13; H, 4,89; N, 15,27, Encontrado: C, 66,19; H, 5,03; N, 15,07.

Procedimiento alternativo para la preparación del Ejemplo 100.

La preparación del ejemplo 100 a partir del compuesto del título del Ejemplo **2** (3,0 g, 12,7 mmol), ácido (1*R*,2*R*)-2-fenilciclopropanocarboxílico (2,36 g, 14,6 mmol) (preparado como se describe por A. Thurkauf, y col. (2000) J. Med. Chem. 43: 3923-3932), trietilamina (8,8 ml, 63,4 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (5,3 g, 14,5 mmol) en *N,N*-dimetilformamida (30,0 ml, 0,4 M) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (5:50:45 de metanol/acetato de etilo/CH_2Cl_2), también de manera análoga, proporcionó el compuesto del título (3,67 g, 10,7 mmol) en forma de un polvo amarillo con un rendimiento del 84%.

Ejemplo 101: *N*-[2-Hidroxi-2-(3-hidroxifenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



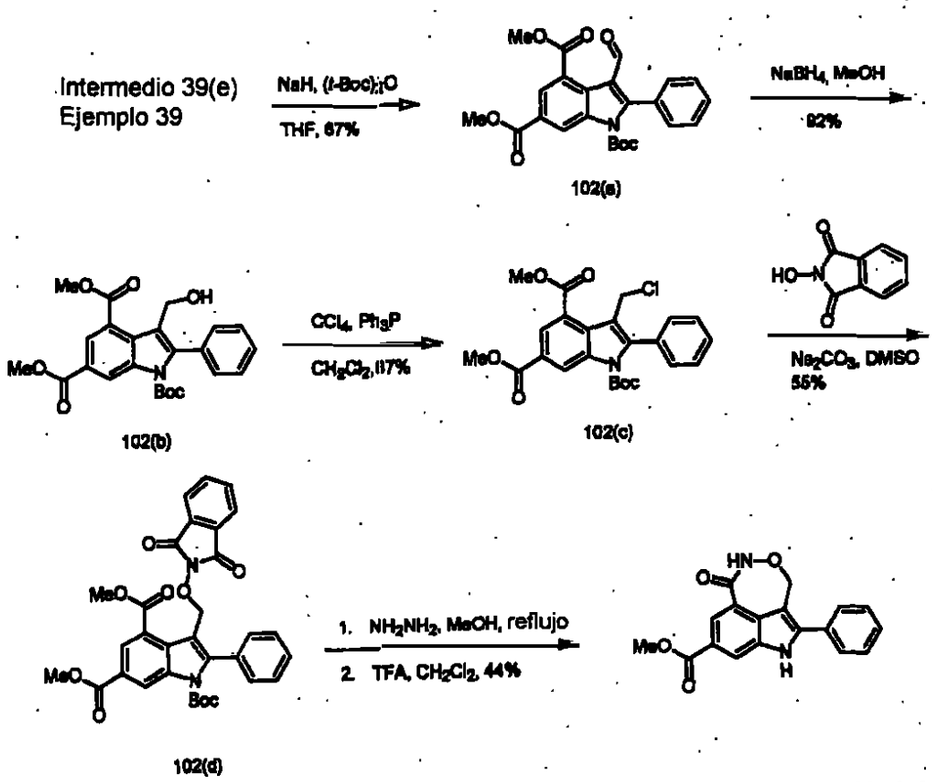
La preparación del ejemplo 101 a partir del compuesto del título del Ejemplo **49** (0,238 g, 0,693 mmol), clorhidrato de 2-hidroxi-2-(3-hidroxifenil)etilamina (0,264 g, 1,39 mmol), trietilamina (0,29 ml, 2,08 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,528 g, 1,39 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido

trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0414 g) en forma de un polvo amarillo con un rendimiento del 14%.

^{1}H RMN (d_6-DMSO): δ 12,47 (s, 1H), 10,45 (s, 1H), 9,27 (s a, 1H), 8,68 (t, 1H, *J* = 5,7 Hz), 8,10 (s, 1H), 8,02 (s, 1H), 7,71 (d, 2H, *J* = 7,2 Hz), 7,51-7,62 (m, 4H), 7,08-7,13 (m, 1H), 6,76-6,81 (m, 2H), 6,61-6,64 (m, 1H), 4,70-4,74 (m, 1H).

EMAR calculado para $C_{25}H_{21}N_4O_4$ 441,1563 (M+H), encontrado 441,1543.

Ejemplo 102:6-Oxo-2-fenil-1,3,5,6-tetrahidro[1,2]oxazepino[6,5,4-*cd*]indol-8-carboxilato de metilo



Etapa 1. Preparación de 4,6-dimetil-3-formil-2-fenil-1*H*-indol-1,4,6-tricarboxilato de 1-*terc*-butilo 102(a)

A una solución del Intermedio 39(e) del Ejemplo 39 (2,25 g, 6,7 mmol) y dicarbonato de di-*terc*-butilo (11,68 g, 54 mmol) en 150 ml de tetrahidrofurano se le añadió una suspensión al 60% de NaH en aceite mineral (1,60 g, 40 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso seguido de cromatografía sobre gel de sílice proporcionó el Intermedio 102(a) (1,97 g), con un rendimiento del 67%.

^{1}H RMN (d_6-DMSO): δ 9,56 (s, 1H), 8,96 (s, 1H), 8,08 (s, 1H), 7,70-7,50 (m, 5H), 3,93 (s, 3H), 3,83 (s, 3H), 1,20 (s, 9H).

Etapa 2. Preparación de ácido 1-(*terc*-butoxicarbonil)-3-(hidroximetil)-6-(metoxicarbonil)-2-fenil-1*H*-indol-4-carboxílico 102(b)

El Intermedio 102(a) (1,95 g) se disolvió en metanol (200 ml), se le añadió $NaBH_4$ (1,70 g) y se agitó durante 15 min. Después de retirar el disolvente, la cromatografía sobre gel de sílice proporcionó el Intermedio 102(b)(1,81 g) con un rendimiento del 92%.

^{1}H RMN (d_6-DMSO): δ 8,97 (d, 1H, J = 1,5 Hz), 8,10 (d, 1H, J = 1,5 Hz), 7,35-7,55 (m, 5H), 4,61 (t, 1H, *J* = 5,1 Hz), 4,41 (d, 2H, J = 5,0 Hz), 3,92 (s, 3H), 3,87 (s, 3H), 1,16 (s, 9H).

Etapa 3. Preparación de 4,6-dimetil-3-(clorometil)-2-fenil-1*H*-indol-1,4,6-tricarboxilato de 1-*terc*-butilo 102(c)

A una solución del Intermedio 102(b) (1,68 g, 3,8 mmol) y CCl_4 (3,50 g, 23 mmol) en 20 ml de diclorometano se le añadió Ph_3P (2,42 g, 9,2 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 24 horas. La

mezcla de reacción se concentró y el residuo se purificó usando cromatografía sobre gel de sílice, proporcionando el Intermedio 102(c) (1,53 g) con un rendimiento del 87%.

^{1}H RMN (d_6-DMSO): δ 8,97 (d, 1H, J = 1,5 Hz), 8,10 (d, 1H, *J* = 1,5 Hz), 7,35-7,55 (m, 5H), 4,61 (t, 1H, *J* = 5,1 Hz), 4,41 (d, 2H, J = 5,0 Hz), 3,92 (s, 3H), 3,87 (s, 3H), 1,16 (s, 9H).

Etapa 4. Preparación de 4,6-dimetil-3-{[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)oxi]metil}-2-fenil-1*H*-indol-1,4,6-tricarboxilato de 1-*terc*-Butilo 102(d)

Una mezcla del Intermedio 102(c) (0,23 g, 0,5 mmol), *N*-hidroxiftalimida (0,24 g, 1,5 mmol) y $Na2CO_3$ (0,32 g, 3 mmol) se agitó en DMSO anhidro (10 ml) a temperatura ambiente durante una noche. El tratamiento de extracción en acetato de etilo, seguido de cromatografía sobre gel de sílice proporcionó el Intermedio 102(d) (0,16 g) con un rendimiento del 55%.

^{1}H RMN (d_6-DMSO): δ 9,02 (d, 1H, J = 1,1 Hz), 8,31 (d, 1H, J = 1,1 Hz), 7,75-7,82 (m, 2H), 7,64-7,71(m, 2H), 7,39 (t, 1H, *J* = 7,6 Hz), 7,26 (t, 2H, J = 7,6), 7,18 (d, 2H, *J* = 7,8 Hz), 5,32 (s, 2H), 3,94 (s, 3H), 3,92 (s, 3H), 1,11 (s. 9H).

Etapa 5. Preparación del compuesto del título: 6-oxo-2-fenil-1,3,5,6-tetrahidro[1,2]oxazepino[6,5,4-*cd*]indol-8-carboxilato de metilo

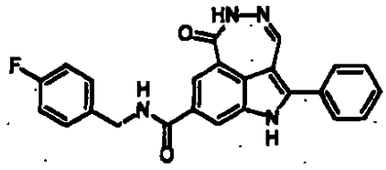
Una mezcla del Intermedio 102(d) (0,15 g, 0,26 mmol) e hidrazina (0,20 g, 6,3 mmol) en metanol (15 ml) se calentó a reflujo durante 2 horas. Después de la evaporación del disolvente, el residuo se mezcló con CH_2Cl_2 (15 ml) y ácido trifluoroacético (7,5 ml) y se agitó durante 2 horas. Después de la retirada

del disolvente, el residuo se sometió a HPLC preparativa de fase inversa proporcionando el compuesto del título (34,8 mg) con un rendimiento del 42%.

^{1}H RMN (d_6-DMSO): δ 12,20 (s, 1H), 11,23 (s, 1H), 8,30 (d, 1H, *J* = 1,2 Hz), 8,21 (d, 1H, J = 1,2 Hz), 7,40-7,75 (m, 5H), 5,44 (d, 1H, J = 14,7 Hz), 5,22 (d, 1H, J = 14,7 Hz), 3,92 (s, 3H).

EMCL(M^++1): 323,0

Ejemplo 103: *N*-(4-Fluorobencil)-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

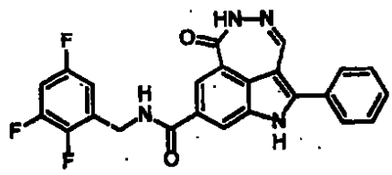


La preparación del ejemplo 103 a partir del compuesto del título del Ejemplo **49** (0,108 g, 0,314 mmol), 4- fluorobencilamina (0,079 g, 0,628 mmol), trietilamina (0,088 ml, 0,628 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,239 g, 0,628 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0121 g) en forma de un polvo amarillo con un rendimiento del 9,3%.

^{1}H RMN (d_6-DMSO): δ 12,47 (s, 1H), 10,47 (s, 1H), 9,23 (t, 1H, *J* = 5,9 Hz), 8,13 (s, 1H), 8,05 (s, 1H), 7,71 (d, 2H, *J* = 6,8 Hz), 7,51-7,63 (m, 4H), 7,35-7,40 (m, 2H), 7,12-7,18 (m, 2H), 4,46 (d, 2H, *J* = 5,7 Hz).

EMAR calculado para $C_{24}H_{18}N_4O_2F$ 413,1414 (M+H), encontrado 413,1394.

Ejemplo 104: 6-Oxo-2-fenil-*N*-(2,3,5-trifluorobencil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

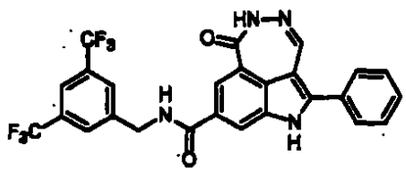


La preparación del ejemplo 104 a partir del compuesto del título del Ejemplo **49** (0,101 g, 0,294 mmol), 2,3,5-trifluorobencilamina (0,0947 g, 0,588 mmol), trietilamina (0,082 ml, 0,588 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,224 g, 0,588 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,006 g) en forma de un polvo amarillo con un rendimiento del 4,5%.

^{1}H RMN (d_6-DMSO): δ 12,50 (s, 1H), 10,49 (s, 1H), 9,27 (t, 1H, J = 5,9 Hz), 8,13 (s, 1H), 8,05 (s, 1H), 7,71 (d, 2H, *J* = 6,8 Hz), 7,52-7,62 (m, 4H), 7,40-7,48 (m, 1H), 7,05-7,08 (m, 1H), 4,56 (d, 2H, *J* = 4,9 Hz).

EMAR calculado para $C_{24}H_{16}N_4O_2F_3$ 449,1225 (M+H), encontrado 449,1209.

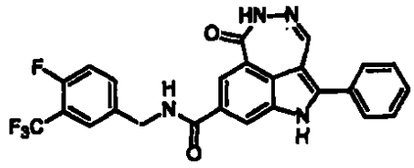
Ejemplo 105: *N*-[3,5-*bis*(Trifluorometil)bencil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



La preparación del ejemplo 105 a partir del compuesto del título del Ejemplo **49** (0,101 g, 0,294 mmol), 3,5-*bis*(trifluorometil)bencilamina (0,143 g, 0,588 mmol), trietilamina (0,082 ml, 0,588 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,224 g, 0,588 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,004 g) en forma de un polvo amarillo con un rendimiento del 2,6%.

^1H RMN (d_6-DMSO): δ 12,50 (s, 1H), 10,50 (s, 1H), 9,37 (t, 1H, *J* = 5,9 Hz), 8,14 (s, 1H), 8,05 (m, 3H), 8,00 (s, 1H), 7,71 (d, 2H, *J* = 8,3 Hz), 7,52-7,62 (m, 4H), 4,67 (d, 2H, *J* = 5,7 Hz). EMAR calculado para $C_{26}H_{17}N_4O_2F_6$ 531,1256 (M+H), encontrado 531,1272.

Ejemplo 106: *N*-[4-Fluoro-3-(trifluorometil)bencil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

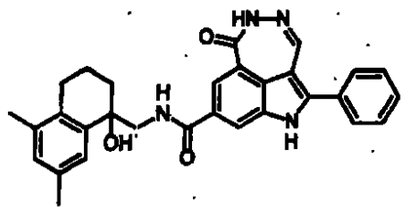


La preparación del ejemplo 106 a partir del compuesto del título del Ejemplo **49** (0,105 g, 0,306 mmol), 4-fluoro-3-(trifluorometil)bencilamina (0,118 g, 0,612 mmol), trietilamina (0,085 ml, 0,612 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,233 g, 0,612 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0205 g) en forma de un polvo amarillo con un rendimiento del 14%.

^{1}H RMN (d_6-DMSO): δ 12,49 (s, 1H), 10,48 (s, 1H), 9,30 (t, 1H, *J* = 5,9 Hz), 8,13 (s, 1H), 8,05 (m, 3H), 7,69-7,75 (m, 4H), 7,45-7,63 (m, 5H), 4,53 (d, 2H, *J* = 5,7 Hz).

EMAR calculado para $C_{25}H_{17}N_4O_2F_4$ 481,1287 (M+H), encontrado 481,1291.

Ejemplo 107: *N*-[(1-Hidroxi-5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-il)metil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

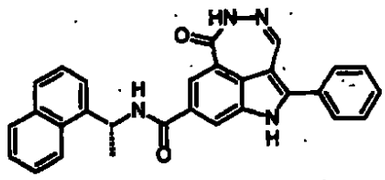


La preparación del ejemplo 107 a partir del compuesto del título del Ejemplo **49** (0,104 g, 0,303 mmol), 1-(aminometil)-5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-ol (0,124 g, 0,606 mmol), trietilamina (0,084 ml, 0,606 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluronio (0,23 g, 0,606 mmol) en DMSO (2 ml) se realizó de manera análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%) también de manera análoga proporcionó el compuesto del título (0,0145 g) en forma de un polvo amarillo con un rendimiento del 9,7%.

^{1}H RMN (d_6-DMSO): δ 12,47 (s, 1H), 10,48 (s, 1H), 8,48-8,52 (m, 1H), 8,10 (s, 1H), 8,03 (s, 1H), 7,70-7,73 (m, 2H), 7,52-7,62 (m, 4H), 7,25 (s, 1H), 6,86 (s, 1H), 3,66-3,73 (m, 2H), 2,55-2,63 (m, 2H), 2,22 (s, 3H), 2,14 (s, 3H), 1,81-1,98 (m, 4H).

EMAR calculado para $C_{30}H_{29}N_4O_3$ 493,2240 (M+H), encontrado 493,2252.

Ejemplo 108: *N*-[(1*R*)-1-(1-Naftil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida

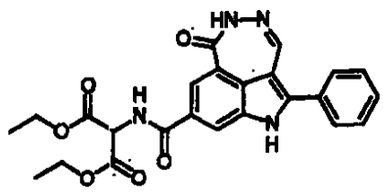


La preparación del ejemplo 108 a partir del compuesto del título del Ejemplo **49** (0,105 g, 0,306 mmol), 1-(1-naftil)etilamina (0,105 g, 0,612 mmol), trietilamina (0,085 ml, 0,612 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,233 g, 0,612 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0161 g) en forma de un polvo amarillo con un rendimiento del 12%.

^{1}H RMN (d_6-DMSO): δ 12,44 (s, 1H), 10,46 (s, 1H), 9,14 (d, 1H, J = 7,9 Hz), 8,17 (s, 1H), 8,05 (s, 1H), 7,87-7,90 (m, 4H), 7,69-7,72 (m, 2H), 7,46-7,63 (m, 7H), 5,34-5,140 (m, 1H), 1,61 (d, 3H, J = 6,8 Hz).

EMAR calculado para $C_{29}H_{23}N_4O_2$ 459,1821 (M+H), encontrado 459,1795.

Ejemplo 109: 2-{[(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)carbonil]amino}malonato de dietilo

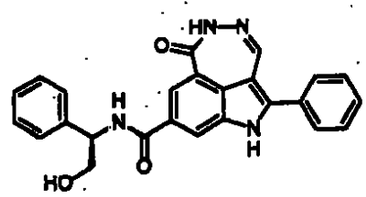


La preparación del ejemplo 109 a partir del compuesto del título del Ejemplo **49** (0,106 g, 0,309 mmol), clorhidrato de 2-aminomalonato de dietilo (0,131 g, 0,618 mmol), trietilamina (0,129 ml, 0,926 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,235 g, 0,618 mmol) en DMSO (2 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0064 g) en forma de un polvo amarillo con un rendimiento del 4,5%.

^1H RMN (d_6-DMSO): δ 12,53 (s, 1H), 10,50 (s, 1H), 9,55 (t, 1H, *J* = 7,6 Hz), 8,14 (s, 1H), 8,07 (s, 1H), 7,71-7,73 (m, 2H), 7,52-7,62 (m, 4H), 5,29-5,32 (m, 2H), 4,15-4,25 (m, 4H), 1,23 (t, 6H, *J* = 7,2 Hz).

EMAR calculado para $C_{24}H_{23}N_4O_6$ 463,1618 (M+H), encontrado 463,1606.

Ejemplo 110: *N*-[(1*R*)-2-Hidroxi-1-feniletil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida



La preparación del ejemplo 110 a partir del compuesto del título del Ejemplo **49** (0,17 g, 0,5 mmol), (2*R*)-2-amino-2-feniletanol (0,0822 g, 0,6 mmol),

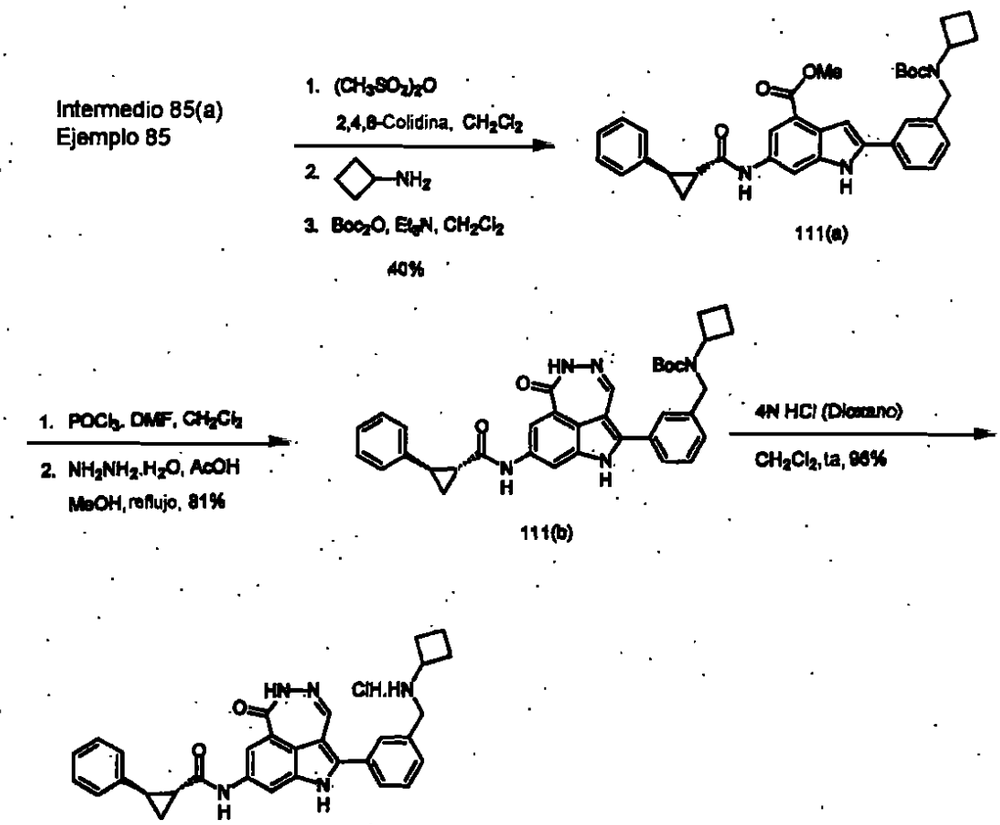
trietilamina (0,14 ml, 1 mmol) y hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluronio (0,23 g, 0,6 mmol) en DMSO (8 ml) se realizó de forma análoga al Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,0351 g) con un rendimiento del 17%.

^1H RMN (d_6-DMSO): δ 12,45 (s, 1H), 10,47 (s, 1H), 8,92 (d, 1H, J = 7,9 Hz), 8,17 (s, 1H), 8,04 (s, 1H), 7,75-7,65 (m, 2H), 7,65-7,50 (m, 4H), 7,45-7,37 (m, 2H), 7,37-7,27 (m, 2H), 7,27-7,15 (m, 1H), 5,18-5,01 (m, 1H), 3,83-3,60 (m, 2H).

EMCL: ($M+H^+$) 425,1

Análisis calculado para $C_{25}H_{20}N_4O_3$ · 0,2 ácido trifluoroacético · 1,68 H_2O: C, 63,88; H, 4,97; N, 11,73, Encontrado: C, 63,86; H, 4,97; N, 11,66.

Ejemplo 111: [2-(3-Ciclobutilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)



Etapa 1. Preparación de éster metílico del ácido (1*R*,2*R*)-2-{3-[(*terc*-butoxicarbonil-ciclobutil-amino)-metil]-fenil}-6-[(2-fenil-ciclopropanocarbonil)-amino]-1*H*-indol-4-carboxílico 111(a)

A una suspensión del Intermedio 85(a) del Ejemplo **85** (0,260 g, 0,6 mmol) en diclorometano (6,0 ml, 0,1 M) se le añadió 2,4,6-Colidina (0,312 ml, 2,4 mmol) seguido de $(CH_3SO_2)_2O$ (0,123 g, 0,7 mmol). Después de agitar durante 1 hora, se añadió ciclobutilamina (0,252 ml, 3,0 mmol) y la mezcla de reacción se agitó durante 24 horas a 22°C. Los volátiles se retiraron al vacío y

se añadieron diclorometano (6,0 ml), trietilamina (3 mmol) y dicarbonato de di-*terc*-butilo (1,2 mmol). La mezcla se agitó a 22°C durante 12 horas y los volátiles se retiraron al vacío. La cromatografía sobre gel de sílice proporcionó el Intermedio 111 (a) (0,14 g, 0,24 mmol) con un rendimiento del 40%.

^{1}H RMN (d_6-DMSO): δ 11,82 (s, 1H), 10,42 (s, 1H), 8,27 (s, 1H), 7,89 (d, 1H, J = 1,6 Hz), 7,72 (d, 1H, J = 8,1 Hz), 7,67 (s, 1H), 7,44 (dd, 1H, J = 7,7, 7,6 Hz), 7,36-7,08 (m, 7H), 4,51 (s, 2H), 3,91 (s, 3H), 2,45-2,37 (m, 1H), 2,14-1,95 (m, 5H), 1,62-1,22 (m, 14H).

Etapa 2. Preparación de éster *terc*-butílico del ácido (1*R*,2*R*)-ciclobutil-(3-{6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-bencil)-carbámico 111(b)

De manera análoga a las etapas 4 y 5 del Ejemplo **3**, el Intermedio 111 (a) (0,13 g, 0,22 mmol) se formiló y se cicló. Después de la cromatografía sobre gel de sílice, se obtuvo el Intermedio 111(b) (0,107 g, 0,18 mmol) en forma de un polvo amarillo con un rendimiento del 81%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,43 (s, 1H), 10,37 (s, 1H), 8,16 (d, 1H, *J* = 1,2 Hz), 7,63 (d, 1H, *J* = 1,4 Hz), 7,55-7,42 (m, 4H), 7,35-7,16 (m, 6H), 4,53 (s, 2H), 2,45-2,37 (m, 1H), 2,14-1,95 (m, 5H), 1,60-1,23 (m, 14H).

EMCL: ($M-H^+$) 602,2.

Etapa 3. Preparación del compuesto del título: [2-(3-ciclobutilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)

La preparación a partir del Intermedio 111(b) (0,105 g, 0,17 mmol) y HCl 4 M en dioxano (1,7 ml) se realizó de forma análoga al Ejemplo **91**. El

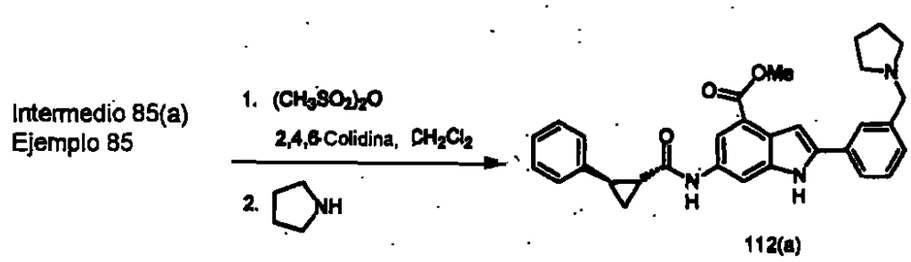
aislamiento, también de manera análoga, incluyó una trituración más con CH_2Cl_2/éter dietílico y produjo el compuesto del título (0,09 g, 0,17 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 96%.

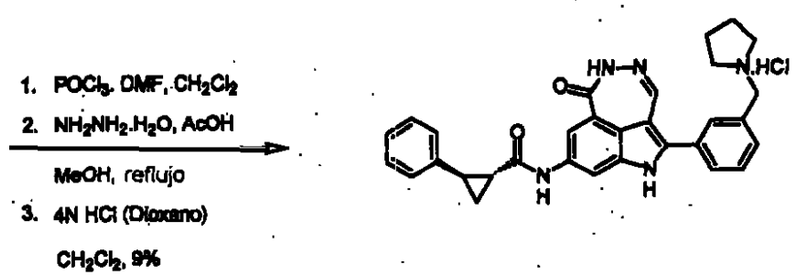
^{1}H RMN (d_6-DMSO): δ 12,20 (s, 1H), 10,49 (s, 1H), 10,43 (s, 1H), 9,32 (a, 1H), 8,18 (d, 1H, J = 1,4 Hz), 7,83 (s, 1H), 7,75-7,58 (m, 5H), 7,35-7,15 (m, 5H), 4,13 (s, 2H), 3,80-3,50 (m enterrado, 1H), 2,45-2,35 (m, 1H), 2,28-2,08 (m, 5H), 188-1,75 (m, 2H), 1,55-1,47 (m, 1H), 1,42-1,34 (m, 1H).

EMCL: ($M+H^+$) 504,2.

EMAR: ($M+H^+$) calculado para $C_{31}H_{30}N_5O_2$, 504,2400, encontrado 504,2378.

Ejemplo 112: [6-Oxo-2-(3-pirrolidin-1-ilmetil-fenil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)





Etapa 1. Preparación de (1*R*,2*R*) éster metílico del ácido 6-[(2-fenil-ciclopropanocarbonil)-amino]-2-(3-pirrolidin-1-ilmetil-fenil)-1*H*-indol-4-carboxílico 112(a)

A una suspensión del Intermedio 85(a) del Ejemplo **85** (0,260 g, 0,6 mmol) en diclorometano (6,0 ml, 0,1 M) se le añadió 2,4,6-Colidina (0,312 ml, 2,4 mmol) seguido de $(CH_3SO_2)_2O$ (0,123 g, 0,7 mmol). Después de agitar durante 1 hora, se añadió pirrolidina (0,252 ml, 3,0 mmol) y la mezcla de reacción se agitó durante 24 horas a 22°C. Los volátiles se retiraron al vacío y el Intermedio 112(a) bruto se llevó directamente a la siguiente etapa.

Etapa 2. Preparación del compuesto del título: [6-oxo-2-(3-pirrolidin-1-ilmetil-fenil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)

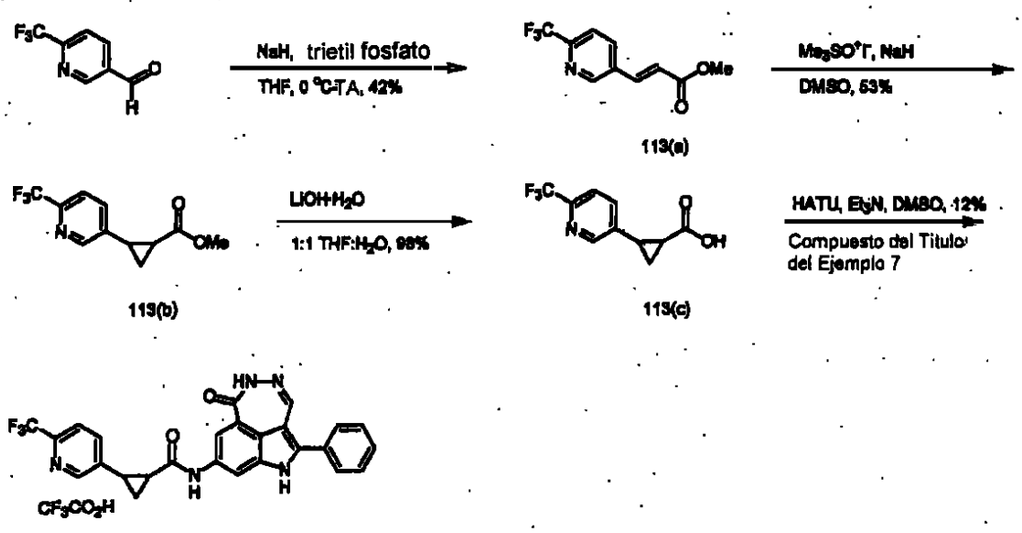
De manera análoga a las etapas 4 y 5 del Ejemplo 3, el Intermedio 112(a) (0,42 g, 0,85 mmol) se formiló y se cicló. La cromatografía sobre gel de sílice (de 90:10:0 a 70:20:10 de CH_2Cl_2/amoniaco 2,0 M en isopropilalcohol/alcohol metílico) y la conversión en la sal HCl (HCl 4 M en dioxano) proporcionaron el compuesto del título (0,04 g, 0,18 mmol) en forma de un polvo amarillo-naranja con un rendimiento del 9%.

^{1}H RMN (d_6-DMSO): δ 12,20 (s, 1H), 10,55 (s, 1H), 10,49 (s, 1H), 10,43 (a, 1H), 8,19 (d, 1H, *J* = 1,3 Hz), 8,13 (s, 1H), 7,76-7,62 (m, 5H), 7,34-7,16 (m, 5H), 4,45 (d, 2H, *J* = 5,5 Hz), 3,45-3,35 (m, 2H), 3,19-3,07 (m, 2H), 2,45-2,35 (m, 1H), 2,14-1,85 (m, 5H), 1,55-1,47 (m, 1H), 1,42-1,34 (m, 1H).

EMCL: $(M+H^+)$ 504,2.

EMAR: $(M+H^+)$ calculado para $C_{31}H_{30}N_5O_2$, 504,2400, encontrado 504,2404.

Ejemplo 113: Trifluoroacetato de *N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,2-*trans*)-2-[6-trifluorometil)piridin-3-il]ciclopropanocarboxamida



Etapa 1. Preparación de éster metílico del ácido 3-(6-trifluorometil-piridin-3-il)-acrílico 113(a)

A una solución de trietilfosfito en tetrahidrofurano anhidro (25 ml) enfriada a 0°C se le añadió en pequeñas porciones una suspensión al 60% de hidruro sódico en aceite mineral (472 mg, 19,7 mmol). Esta mezcla se dejó en agitación durante 30 min a la misma baja temperatura, momento en el que el baño de refrigeración se retiró y la mezcla se dejó calentar a temperatura ambiente durante 60 min. La mezcla se enfrió de nuevo a 0°C y se le añadió gota a gota una solución de 6-trifluorometil-3-piridinacarboxaldehído en tetrahidrofurano anhidro (20 ml). La mezcla de reacción se dejó calentar lentamente a temperatura ambiente durante una noche. Después de 19 horas, la mezcla de reacción se inactivó con agua (100 ml) y se extrajo con acetato de etilo (3 x 50 ml). Las fracciones orgánicas combinadas se secaron sobre sulfato

de magnesio anhidro y se concentraron hasta un aceite verde pálido. La purificación se realizó usando cromatografía ultrarrápida sobre gel de sílice eluyendo con 5:95 y después 1:9 de acetato de etilo:hexano. Las fracciones puras se combinaron y se concentraron, proporcionando el Intermedio 113(a) (1,68 g, 6,85 mmol) en forma de un sólido blanco con un rendimiento del 42%.

Etapa 2. Preparación de ácido (1,2-*trans*)-2-(6-trifluorometil-piridin-3-il)-ciclopropanocarboxílico 113(b)

Se añadió yoduro de trimetilsulfoxonio (574 mg, 2,61 mmol) a NaH al 60% en aceite mineral (63 mg, 2,61 mmol) y el matraz se purgó con nitrógeno. Se añadió lentamente metilsulfóxido (10 ml) durante 20 minutos hasta que cesó el desprendimiento de gas. A esta solución lechosa se le añadió gota a gota el Intermedio 113(a) (493 mg, 2,01 mmol) en metilsulfóxido (15 ml). La solución se dejó en agitación a temperatura ambiente durante una noche. Después de 26 horas, el exceso de NaH se inactivó cuidadosamente con agua (100 ml). Se añadió éter etílico (100 ml) y las fases se separaron. La fase acuosa se extrajo con éter etílico preparado recientemente (3 x 50 ml). Las fases etéreas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio anhidro y se concentraron al vacío. La cromatografía ultrarrápida sobre gel de sílice del residuo bruto eluyendo con 1:9 y después 1:4 de acetato de etilo:hexano dio dos fracciones puras que después de combinarse y concentrarse a presión reducida produjeron el Intermedio 113(b) (275 mg, 1,06 mmol) en forma de plumas blancas con un rendimiento del 53%.

Etapa 3. Preparación de ácido (1,2-*trans*)-2-[6-(trifluorometil)piridin-3-il]ciclopropanocarboxílico 113(c)

A una solución del Intermedio 113(b) (275 mg, 1,06 mmol) en una mezcla 1:1 de tetrahidrofurano:agua (4 ml) se le añadió hidróxido de litio monohidrato (133 mg, 3,18 mmol). La semi-suspensión se dejó en agitación a temperatura ambiente durante 2 días. La mezcla de reacción se acidificó con ácido clorhídrico acuoso 2 M (aprox. 2 ml). Después, la mezcla de reacción se concentró y se liofilizó, obteniendo el Intermedio 113(c) en forma de un polvo blanco que contenía cloruro de litio y que se lleva a continuación directamente sin purificación adicional.

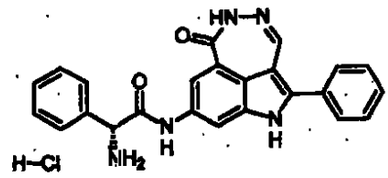
Etapa 4. Preparación del compuesto del título: trifluoroacetato de *N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-[6-(trifluorometil)piridin-3-il]ciclopropanocarboxamida

A una solución del Intermedio 113(c) (85 mg, 0,368 mmol) en metilsulfóxido (2 ml) se le añadieron trietilamina (0,056 ml, 0,405 mmol) y hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (154 mg, 0,405 mmol). Después de aprox. 10 min, se añadió el compuesto del título del Ejemplo 7 (0,102 g, 0,368 mmol). La reacción se tapó y se agitó durante una noche a temperatura ambiente. La mezcla se sometió a HPLC preparativa (acetonitrilo al 20-100%/agua que contenía ácido trifluoroacético al 0,1%). Las fracciones puras se combinaron y se liofilizaron, proporcionando el compuesto del título (27 mg, 0,045 mmol) en forma de un polvo naranja con un rendimiento del 12%.

^{1}H RMN (d_6-DMSO): δ 12,11 (a, 1H), 10,50 (a, 1H), 10,39 (a, 1H), 8,71 (a, 1H), 8,15 (a, 2H), 7,90-7,80 (m, 2H), 7,70-7,45 (m, 6H), 2,65-2,55 (m, 1H), 2,27-2,18 (m, 1H), 1,67-1,51 (m, 2H).

EMCL: ($M+H^+$) 490,1.

Ejemplo 114:(2*R*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenil-acetamida (sal clorhidrato)



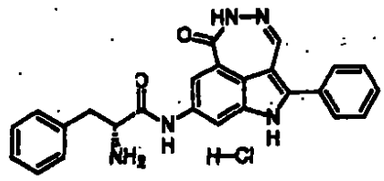
La preparación del ejemplo 114 a partir del compuesto del título impuro del Ejemplo **117** (90 mg, 0,18 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (65 mg, 0,10 mmol) en forma de un polvo amarillo con un rendimiento del 71% en dos etapas (incluyendo el Ejemplo 117).

^{1}H RMN (d_6-DMSO): δ 12,26 (s, 1H, intercambios), 11,08 (s, 1H, intercambios), 10,42 (s, 1H, intercambios), 8,86 (s a, 3H, intercambios), 8,07 (s, 1H), 7,72-7,63 (m, 5H), 7,62-7,41 (m, 7H), 5,22 (m, 1H).

EMCL: ($M+H^+$) 410,1; (M+Na+) 432,0.

Análisis calculado para $C_{24}H_{19}N_5O_2 \cdot 5{,}6\ HCl \cdot 0{,}2$ éter dietílico: C, 47,40; H, 4,27; N, 11,14, Encontrado: C, 47,64; H, 4,21; N, 10,91.

Ejemplo 115:(2*R*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida (sal clorhidrato)



La preparación del ejemplo 115 a partir del compuesto del título del Ejemplo **118** (71 mg, 0,136 mmol) y HCl 4 M en dioxano (20 ml) se realizó de

forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (66 mg, 0,12 mmol) en forma de un polvo amarillo con un rendimiento del 87% en dos etapas (a partir del Ejemplo 118).

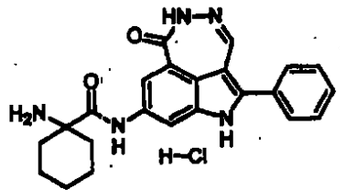
^{1}H RMN (d_6-DMSO): δ 12,20 (s, 1H, intercambios), 10,66 (s, 1H, intercambios), 10,44 (s, 1H, intercambios), 8,39 (s a, 3H, intercambios), 8,05 (s, 1H), 7,73-7,46 (m, 7H), 7,39-7,22 (m, 5H), 4,19 (m, 1H), 3,21-3,06 (m, 2H, parcialmente oscurecido).

EMCL: ($M+H^+$) 424,1.

Análisis calculado para $C_{25}H_{21}N_5O_2 \cdot 2{,}8\ HCl \cdot 0{,}1$ éter dietílico $\cdot$ 0,2 dioxano: C, 57,15; H, 4,83; N, 12,72.

Encontrado: C, 57,33; H, 5,01; N, 12,56.

Ejemplo 116: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 1-amino-ciclohexanocarboxílico (sal clorhidrato)



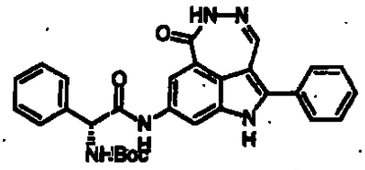
La preparación del ejemplo 116 a partir del compuesto del título del Ejemplo **119** (311 mg, 0,062 mmol) y HCl 4 M en dioxano (5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó otra trituración con CH_2Cl_2/hexano y proporcionó el compuesto del título (29 mg, 0,053 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 85%.

^{1}H RMN (d_6-DMSO): δ 12,29 (s, 1H, intercambios), 10,44 (s, 1H, intercambios), 10,28 (s, 1H, intercambios), 8,36 (s a, 3H, intercambios), 8,11 (s, 1H), 7,81 (s, 1H), 7,74-7,46 (m, 6H), 2,37-2,14 (m, 2H), 1,96-1,35 (m, 8H).

EMCL: ($M+H^+$) 402,2, ($M+Na^+$) 424,1.

Análisis calculado para $C_{23}H_{23}N_5O_2 \cdot 3{,}1$ HCl · 0,1 éter dietílico · 0,3 dioxano: C, 53,88; H, 5,42; N, 12,77, Encontrado: C, 53,86; H, 5,60; N, 12,70.

Ejemplo 117:Éster *terc*-butílico del ácido [(*R*)-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-fenil-metil]-carbámico

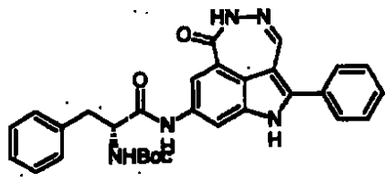


La preparación del ejemplo 117 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (44 mg, 0,141 mmol), ácido (*R*)-*terc*-butoxicarbonilamino-fenil-acético (42 mg, 0,169 mmol), trietilamina (0,059 ml, 0,423 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (64 mg, 0,169 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (102 mg) en forma de un polvo amarillo contaminado con una impureza desconocida. El compuesto fue un intermedio y se llevó sin purificación adicional al Ejemplo **91**.

^{1}H RMN (d_6-DMSO): δ 12,12 (s, 1H), 10,41 (s, 2H), 8,12 (s, 1H), 7,69-7,48 (m, 10H), 7,42-7,27 (m, 3H), 5,36 (d, 1H, J = 8,67 Hz), 1,41 (s, 9H).

EMCL: ($M-H^-$) 508,1, ($M+H^+$) 510,2, ($M+Na^+$) 532,2.

Ejemplo 118:Éster *terc*-butílico del ácido [(*R*)-1-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-2-fenil-etil]-carbámico

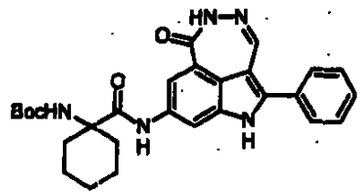


La preparación del ejemplo 118 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (43 mg, 0,138 mmol), ácido (*R*)-*terc*-butoxicarbonilamino-3-fenil-propiónico (44 mg, 0,166 mmol), trietilamina (0,058 ml, 0,414 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (63 mg, 0,166 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (80 mg) en forma de un polvo amarillo contaminado con una impureza desconocida. El compuesto se llevó sin purificación adicional al Ejemplo **115**.

^{1}H RMN (d_6-DMSO): δ 12,12 (1H), 10,41 (s, 1H), 10,25 (s, 1H), 8,18 (s, 1H), 7,71-7,48 (m, 7H), 7,38-7,11 (m, 6H), 4,34 (s a, 1H), 3,02 (m, 1H), 2,87 (m, 1H, parcialmente oscurecido por singlete de *N,N*-dimetilformamida), 1,34 (s, 9H).

EMCL: ($M+H^+$) 524,2, ($M+Na^+$) 546,2.

Ejemplo 119:Éster *terc*-butílico del ácido [1-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-ciclohexil]-carbámico

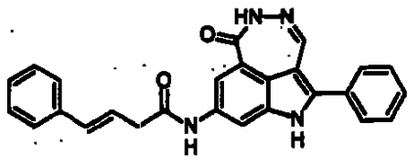


La preparación del ejemplo 119 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (45 mg, 0,142 mmol), ácido 1-*terc*-butoxicarbonilamino-ciclohexanocarboxílico (42 mg, 0,171 mmol), trietilamina (0,059 ml, 0,426 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (65 mg, 0,171 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (38 mg, 0,076 mmol) en forma de un polvo amarillo con un rendimiento del 53%.

^{1}H RMN (d_6-DMSO): δ 12,08 (s, 1H), 10,37 (s, 1H), 9,59 (s, 1H), 8,14 (s, 1H), 7,70-7,48 (m, 8H), 2,03-1,92 (m, 2H), 1,81-1,71 (m, 2H), 1,47 (m, 5H), 1,40-1,31 (m, 10H).

EMCL: ($M+H^+$) 502,1, ($M+Na^+$) 524,1.

Ejemplo 120: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (3*E*)-4-fenil-but-3-enoico



La preparación del ejemplo 120 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (44 mg, 0,141 mmol), ácido (*E*)-4-fenil-but-3-enoico (27 mg, 0,169 mmol), trietilamina (0,059 ml, 0,423 mmol) y hexafluorofosfato de *O*-

(7-azabenzotriazol-1-il)-*N,N,N',*W-tetrametiluronio (64 mg, 0,169 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. Cuando se juzgó que la reacción se había completado, la mezcla se filtró para recoger los sólidos que después se lavaron con metanol. Después de secar al vacío, se obtuvo el compuesto del título (41 mg, 0,0,095 mmol) en forma de un polvo amarillo con un rendimiento del 68%.

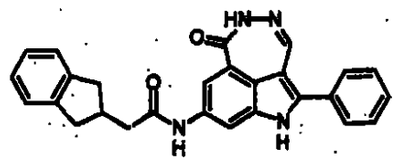
^{1}H RMN (d_6-DMSO): δ 12,10, (s, 1H, intercambios), 10,38 (s, 1H, intercambios), 10,22 (s, 1H, intercambios), 8,21 (s, 1H), 7,77-7,63 (m, 3H), 7,60-7,53 (m, 2H), 7,53-7,42 (m, 4H), 7,38-7,30 (m, 2H), 7,24 (m, 1H), 6,57 (d, 1H, J = 16,01 Hz), 6,45 (m, 1H).

^{1}H RMN (d_6-DMSO/DCl): δ 8,20 (s, 1H), 7,75 (s, 1H), 7,71-7,65 (m, 2H), 7,60-7,47 (m, 4H), 7,43-7,37 (m, 2H), 7,38-7,29 (m, 2H), 7,22 (m, 1H), 6,55 (d, 1H, *J* = 16,23 Hz), 6,44 (m, 1H), 3,33 (d, 2H, *J* = 9,09 Hz).

EMCL: ($M+H^+$) 421,1, ($M+Na^+$) 443,1.

Análisis calculado para $C_{28}H_{20}N_4O_2 \cdot 0,1\ H_2O \cdot 0,1$ *N,N*-dimetilformamida: C, 73,53; H, 4,90; N, 13,37, Encontrado: C, 73,26; H, 4,50; N, 13,61.

Ejemplo 121: 2-Indan-2-il-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



La preparación del ejemplo 121 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (41 mg, 0,131 mmol), ácido indan-2-il-acético (28 mg, 0,157 mmol), trietilamina (0,055 ml, 0,393 mmol) y hexafluorofosfato de *O*-(7-

azabenzotriazol-1-il)-N,*N*,N',W-tetrametiluronio (60 mg, 0,157 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de manera análoga al Ejemplo **11**. Cuando se juzgó que la reacción se había completado, la mezcla se filtró para recoger los sólidos, que después se lavaron con metanol. Después de secar al vacío, se obtuvo el compuesto del título (45 mg, 0,101 mmol) en forma de un polvo amarillo con un rendimiento del 77%.

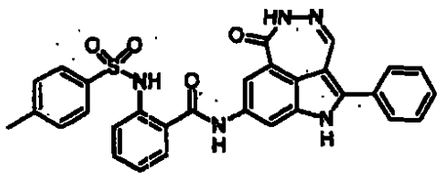
^{1}H RMN (d_6-DMSO): δ 12,08, (s, 1H, intercambios), 10,37 (s, 1H, intercambios), 10,11 (s, 1H, intercambios), 8,20 (s, 1H), 7,70,-7,45 (m, 7H), 7,26-7,18 (m, 2H), 7,16-7,08 (m, 2H), 3,07 (dd, 2H, *J* = 7,72, 15,83 Hz), 2,87 (m, 1H), 2,65 (dd, 2H, *J* = 6,59, 15,26 Hz).

EMCL: ($M+H^+$) 435,2, ($M+Na^+$) 457,1.

Análisis calculado para $C_{27}H_{22}N_4O_2 \cdot 0{,}5\ H_2O$: C, 73,12; H, 5,23; N, 12,63.

Encontrado: C, 72,84; H, 4,99; N, 12,99.

Ejemplo 122: *N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-(tolueno-4-sulfonilamino)-benzamida



La preparación del ejemplo 122 a partir del compuesto del título del Ejemplo **7** (100 mg, 0,362 mmol), ácido 2-(tolueno-4-sulfonilamino)-benzoico (158 mg, 0,542 mmol), trietilamina (0,201 ml, 1,446 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (206 mg, 0,542 mmol) en *N,N*-dimetilformamida (4,0 ml) se realizó de forma análoga al Ejemplo **11**. Cuando se juzgó que la reacción se había completado, la *N,N*-dimetilformamida

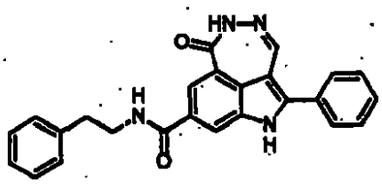
se evaporó y se añadió metanol. La mezcla se filtró y los sólidos se recogieron y se lavaron con metanol, diclorometano y éter dietílico. Después de secar al vacío, se obtuvo el compuesto del título (121 mg, 0,220 mmol) en forma de un polvo amarillo con un rendimiento del 61%.

^{1}H RMN (d_6-DMSO): δ 12,19 (s, 1H), 10,63 (s, 1H), 10,45 (s, 1H), 10,42 (s, 1H), 8,12 (s, 1H), 7,85-7,78 (m, 2H), 7,74-7,67 (m, 2H), 7,64-7,56 (m, 4H), 7,56-7,42 (m, 4H), 7,29-7,20 (m, 3H), 2,27 (s, 3H).

EMCL: ($M+H^+$) 550,1; ($M-H)^-$ 548,2.

EMAR: ($M+H^+$) calculado para $C_{30}H_{24}N_5O_4S$, 550,1549, encontrado 550,1551, Análisis calculado para $C_{30}H_{23}N_5O_4S \cdot 0,5\ H_2O$: C, 64,50; H, 4,33; N, 12,54, Encontrado: C, 64,51; H, 4,20; N, 12,71.

Ejemplo 123:Fenetil-amida del ácido 6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxílico

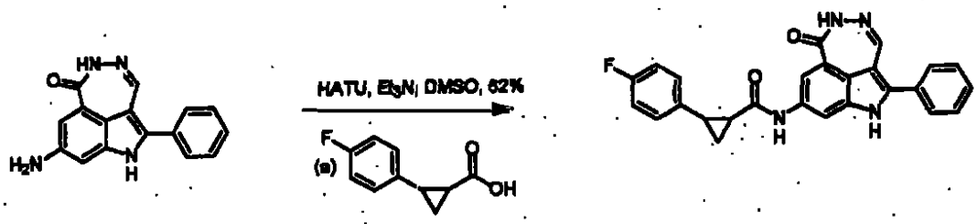


La preparación del ejemplo 123 a partir del compuesto del título del Ejemplo **49** (0,17 g, 0,5 mmol), fenetilamina (73 mg, 0,6 mmol), trietilamina (100 mg, 1,0 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,6 mmol) en DMSO (8 ml) se realizó de forma análoga a la preparación del Ejemplo **76**. La HPLC preparativa (CH_3CN al 20-100%/H_2O que contenía ácido trifluoroacético al 0,1%), también de manera análoga, proporcionó el compuesto del título (0,021 g) en forma de un polvo amarillo con un rendimiento del 9%.

^{1}H RMN (d_6-DMSO): δ 12,49 (s, 1H), 10,49 (s, 1H), 8,77 (t, 1H, J = 5,5 Hz), 8,07 (s, 1H), 8,00 (s, 1H), 7,10-7,80 (m, 11H), 3,48 (m, 2H), 2,86 (t, 2H, *J* = 7,5 Hz).

EMCL (M^++1): 409,1

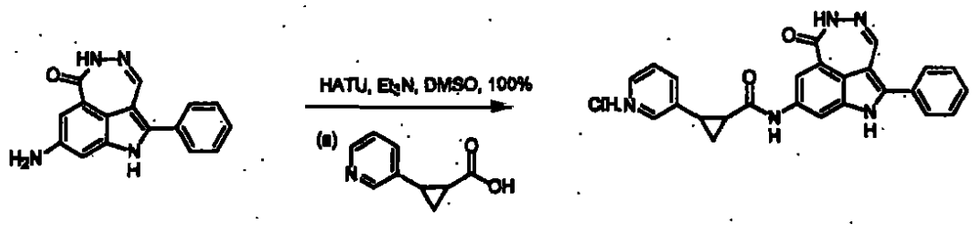
Ejemplo 124: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-Fluoro-fenil)-ciclopropanocarboxílico



La preparación del ejemplo 124 se realizó de manera análoga a la preparación del Ejemplo **113** con al excepción de que se usó ácido (1,2-*trans*)-2-(4'-fluorofenil)-ciclopropanocarboxílico en lugar de ácido (1,2-*trans*)-2-(6-trifluorometil-piridin-3-il)-ciclopropanocarboxílico en la etapa 4, se preparó ácido (1,2-*trans*)-2-(4'-Fluorofenil)-ciclopropanocarboxílico usando procedimientos similares a los descritos en las etapas 1-3 del Ejemplo **113** con la excepción de que se usó 4-fluoro-benzaldehído en lugar de 6-trifluorometil-3-piridinacarboxaldehído. La purificación final por HPLC, también de forma análoga al Ejemplo **113**, proporcionó el compuesto del título (100 mg, 0,228 mmol) en forma de un polvo amarillo con un rendimiento del 62%.

^{1}H RMN (d_6-DMSO): δ 12,12 (a, 1H), 10,46 (a, 1H), 10,41 (a, 1H), 8,18 (a, 1H), 7,70-7,45 (m, 7H), 7,30-7,10 (m, 4H), 2,65-2,55 (m, 1H), 2,27-2,18 (m, 1H), 1,67-1,51 (m, 2H). EMAR: $C_{21}H_{21}N_5O2$ · H: 439,1570, Encontrado: 439,1584.

Ejemplo 125:(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico (sal clorhidrato)

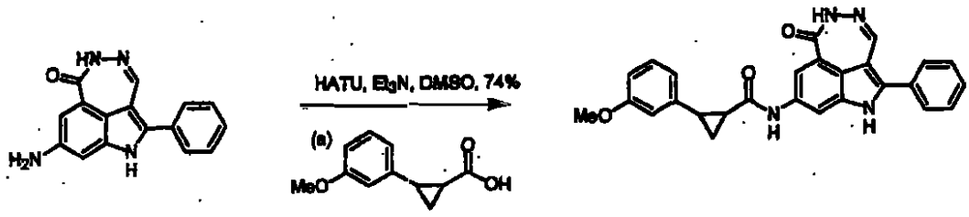


La preparación del ejemplo 125 se realizó de manera análoga a la preparación del Ejemplo **113** con la excepción de que se usó ácido (1,2-*trans*)-2-piridin-3'-il-ciclopropanocarboxílico en lugar de ácido (1,2-*trans*)-2-(6-trifluorometil-piridin-3-il)-ciclopropanocarboxílico en la etapa 4, se preparó ácido (1,2-*trans*)-2-piridin-3'-il-ciclopropanocarboxílico usando procedimientos similares a los descritos en las etapas 1-3 del Ejemplo **113** con la excepción de que se usó piridina-3-carbaldehído en lugar de 6-trifluorometil-3-piridinacarboxaldehído. La purificación final por HPLC, también de forma análoga al Ejemplo **113**, proporcionó el compuesto del título (230 mg, 0,381 mmol) en forma de un sólido mullido naranja con rendimiento cuantitativo.

^{1}H RMN (d_6-DMSO): δ 12,15 (s, 1H), 10,58 (s, 1H), 10,38 (s, 1H), 8,81 (s, 1H), 8,15 (a, 2H), 7,82-7,45 (m, 9H), 2,35-2,25 (m, 1H), 1,70-1,51 (m, 1H), 1,35-1,10 (m, 1H), 0,90-0,65 (m, 1H).

EMCL: ($M+H^+$) 422,1.

Ejemplo 126:(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-metoxi-fenil)-ciclopropanocarboxílico

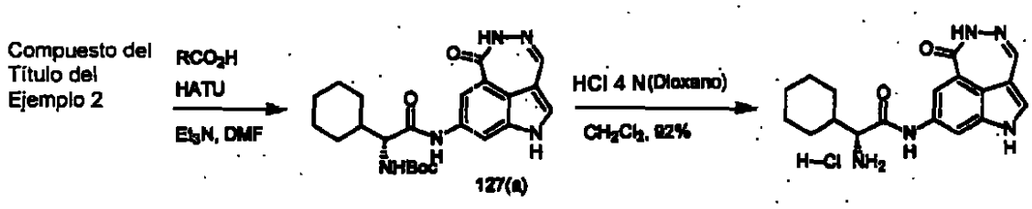


La preparación del ejemplo 126 se realizó de manera análoga a la preparación del Ejemplo **113** con la excepción de que se usó ácido (1,2-*trans*)-2-(3'-metoxifenil)-ciclopropanocarboxílico en lugar de ácido (1,2-*trans*)-2-(6-trifluorometil-piridin-3-il)-ciclopropanocarboxílico en la etapa 4, se preparó ácido (1,2-*trans)*-2-(3'-Metoxifenil)-ciclopropanocarboxílico usando procedimientos similares a los descritos en las etapas 1-3 del Ejemplo **113** con la excepción de que se usó 3-metoxi-benzaldehído en lugar de 6-trifluorometil-3-piridinacarboxaldehído. La purificación final por HPLC, también de forma análoga al Ejemplo **113**, proporcionó el compuesto del título (132 mg, 0,293 mmol) en forma de un sólido naranja pálido con un rendimiento del 74%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,43 (s, 1H), 10,38 (s, 1H), 8,15 (s, 1H), 7,70-7,40 (m, 7H), 7,25-7,15 (m, 1H), 6,77 (a, 3H), 3,74 (s, 3H), 2,40-2,30 (m, 1H), 2,12-2,05 (m, 1H), 1,55-1,47 (m, 1H), 1,42-1,33 (m, 1H).

EMCL: ($M+H^+$) 451,1.

Ejemplo 127: (*R*)-2-Amino-2-ciclohexil-(6-oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (sal clorhidrato)



Etapa 1. Preparación de éster *terc*-butílico del ácido [(*R*)-ciclohexil-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-metil]-carbámico 127(a)

La preparación de Intermedio 127(a) a partir del compuesto del título del Ejemplo **2** (105 mg, 0,445 mmol), ácido (*R*)-*terc*-butoxicarbonilamino-ciclohexil-acético (172 mg, 0,668 mmol), trietilamina (0,248 ml, 1,782 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (254 mg, 0,668 mmol) en *N,N*-dimetilformamida (4,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetato de etilo), también de manera análoga, proporcionó el Intermedio 127(a) (110 mg, 0,250 mmol) en forma de un polvo amarillo con un rendimiento del 56%.

^{1}H RMN (d_6-DMSO): δ 11,71 (d, 1H, *J* = 2,26 Hz), 10,23 (s, 1H), 10,07 (s, 1H), 8,10 (s, 1H), 7,59 (s, 1H), 7,55 (d, 1H, J = 2,45 Hz), 7,46 (s, 1H), 6,86 (d, 1H, *J* = 8,85 Hz), 3,92 (dd, 1H, J = 8,10, 7,91 Hz), 1,77-1,46 (m, 6H), 1,37 (s, 9H), 1,24-0,93 (m, 5H).

EMCL: $(M+H^+)$ 440,1, $(M+Na^+)$ 462,2; $(M-H)^-$ 438,2.

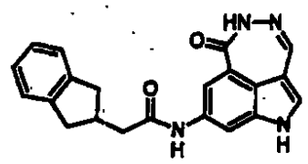
Etapa 2. Preparación del compuesto del título: (*R*)-2-Amino-2-ciclohexil-(6-oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (sal clorhidrato)

La preparación del compuesto del título a partir del Intermedio 127(a) (66,1 mg, 0,150 mmol) y HCl 4,0 M en dioxano (1,5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (52,0 mg, 0,138 mmol) en forma de un polvo amarillo con un rendimiento del 92%.

^{1}H RMN (d_6-DMSO): δ 11,86 (s, 1H), 10,69 (s, 1H), 10,31 (s, 1H), 8,29 (s a, 3H), 8,08 (s, 1H), 7,63 (s, 1H), 7,49 (s, 1H), 3,80-3,69 (m, 1H), 1,93-1,55 (m, 6H), 1,29-0,98 (m, 5H).

EMCL: ($M+H^+$) 340,3, ($M+Na^+$) 362,3.

Ejemplo 128: 2-Indan-2-il-(6-oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida

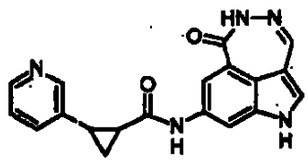


La preparación del ejemplo 128 a partir del compuesto del título del Ejemplo **2** (base libre) (88,7 mg, 0,443 mmol), ácido indan-2-il-acético (117 mg, 0,665 mmol), trietilamina (0,247 ml, 1,774 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (253 mg, 0,665 mmol) en *N,N*-dimetilformamida (4,0 ml) se realizó de forma análoga al Ejemplo **11**. Cuando se juzgó que la reacción se había completado, la *N,N*-dimetilformamida se evaporó y se añadió metanol. La mezcla se filtró para recoger los sólidos, que después se lavaron con metanol, diclorometano y éter dietílico. Después de secar al vacío, se obtuvo el compuesto del título (115 mg, 0,321 mmol) en forma de un polvo amarillo con un rendimiento del 72%.

^{1}H RMN (d_6-DMSO): δ 11,71 (s, 1H), 10,23 (s, 1H), 10,05 (s, 1H), 8,15 (s, 1H), 7,58(s, 1H), 7,55 (d, 1H, J = 2,26 Hz), 7,46 (s, 1H), 7,26-7,16 (m, 2H), 7,16-7,06 (m, 2H), 3,06 (dd, 2H, J = 7,54, 5,54 Hz), 2,92-2,79 (m, 1H), 2,65 (dd, 2H, J = 6,59, 6,78 Hz), 2,47 (d, 2H, J = 9,80 Hz).

EMCL: ($M+H^+$) 359,1, ($M+Na^+$) 381,0; $(M-H)^-$ 357,2.

Ejemplo 129: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico



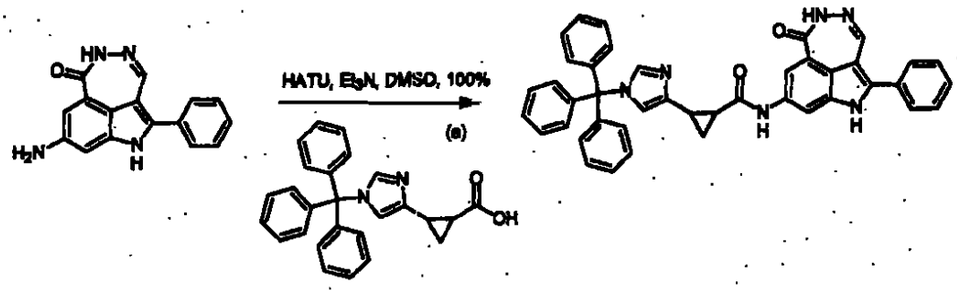
La preparación del ejemplo 129 a partir del compuesto del título del Ejemplo **2** (base libre) (200 mg, 1,00 mmol), ácido (1,2-*trans*)-2-piridin-3'-il-ciclopropanocarboxílico (véase Ejemplo 125 para una pureza estimada de la preparación de aprox. el 75%) (240 mg, aprox. 1,10 mmol), trietilamina (0,550 ml, 3,96 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (570 mg, 1,50 mmol) en *N,N*-dimetilformamida (8,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 100:10:1 de acetato de etilo:metanol:hidróxido amónico), también de manera análoga, proporcionó el compuesto del título (38 mg, 0,110 mmol) en forma de un polvo amarillo con un rendimiento del 11%.

^{1}H RMN (d_6-DMSO): δ 11,73 (d, 1H, *J* = 2,26 Hz), 10,41 (s, 1H), 10,23 (s, 1H), 8,50 (d, 1H, *J* = 1,88 Hz), 8,41 (dd, 1H, *J* = 3,20, 1,51 Hz), 8,11 (d, 1H, *J* = 1,51 Hz), 7,61-7,48 (m, 3H), 7,45 (s, 1H), 7,32 (dd, 1H, J = 5,09, 3,20 Hz), 2,45-2,36 (m, 1H), 2,18-2,05 (m, 1H), 1,58-1,49 (m, 1H), 1,49-1,36 (m, 1H).

EMCL: ($M+H^+$) 346,1; ($M-H^-$) 344,1.

EMAR: ($M+H^+$) calculado para $C_{19}H_{16}N_5O_2$, 346,1304, encontrado 346,1316.

Ejemplo 130:(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(1'-tritil-1*H*-imidazol-4'-il)-ciclopropanocarboxílico

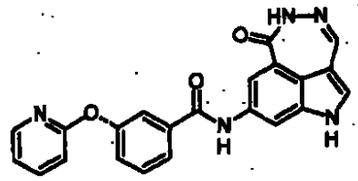


La preparación del ejemplo 130 se realizó de manera análoga a la preparación del Ejemplo **113** con la excepción de que se usó ácido (1,2-*trans*)-2-(1'-tritil-1*H*-imidazol-4'-il)-ciclopropanocarboxílico en lugar de ácido (1,2-*trans*)-2-(6-trifluorometil-piridin-3-il)-ciclopropanocarboxílico en la etapa 4, se preparó (1,2-*trans*)-2-(1'-tritil-1*H*-imidazol-4'-il)-ciclopropanocarboxílico usando procedimientos similares a los descritos en las etapas 1-3 del Ejemplo **113** con la excepción de que se usó 1-tritil-1*H*-imidazol-4-carbaldehído en lugar de 6-trifluorometil-3-piridinacarboxaldehído. La purificación final consistió en trituración con metanol. Los sólidos resultantes se aislaron por filtración, se lavaron con metanol frío y se secaron durante una noche al vacío a temperatura ambiente, proporcionando el compuesto del título (263 mg, 0,366 mmol) en forma de un polvo amarillo con rendimiento cuantitativo.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,43 (s, 1H), 10,38 (s, 1H), 8,13 (s, 1H), 7,70-7,30 (m, 18H), 7,25 (s, 1H), 7,15-7,05 (m, 6H), 6,87 (s, 1H), 2,35-2,24 (m, 1H), 2,20-2,13 (m, 1H), 1,38-1,23 (m, 2H).

EMCL: ($M+H^+$) 653,3

Ejemplo 131: (6-Oxo-5,6-dihidro-1[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-(piridin-2-iloxi)-benzamida

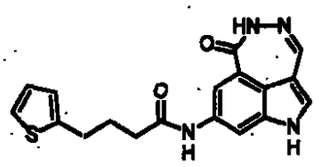


La preparación del ejemplo 131 a partir del compuesto del título del Ejemplo **2** (25 mg, 0,125 mmol), ácido 3-(piridin-2-iloxi)-benzoico (88 mg, 0,348 mmol), *N,N*-diisopropiletilamina (0,19 ml, 1,04 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (159 mg, 0,42 mmol) en *N,N*-dimetilformamida (3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con metanol al 2% en CH_2Cl_2), también de manera análoga, proporcionó el compuesto del título (20 mg, 0,05 mmol) en forma de un polvo amarillo con un rendimiento del 40%.

^{1}H RMN (d_6-Acetona): δ 7,92 (s, 1H), 7,89 (s, 1H), 7,55-7,52 (m, 4H), 7,39 (s, 1H), 7,37 (s, 1H), 7,34 (m, 1H), 7,32-7,24 (m, 2H), 7,15 (m, 1H), 6,95 (m, 1H), 6,93 (m, 1H), 6,77-6,73 (m, 5H), 6,88 (m, 1H).

EMCL: ($M+H^+$) 398,1.

Ejemplo 132: *N*-(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tiofen-2-il-butiramida



La preparación del ejemplo 132 a partir del compuesto del título del Ejemplo **2** (base libre) (200 mg, 1,00 mmol), ácido 4-tiofen-2-il-butírico (187 mg, 1,10 mmol), trietilamina (0,550 ml, 3,96 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (570 mg, 1,50 mmol) en *N,N*-

dimetilformamida (8,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con acetato de etilo), también de manera análoga, proporcionó el compuesto del título (72 mg, 0,204 mmol) en forma de un polvo amarillo con un rendimiento del 20%.

^{1}H RMN (d_6-DMSO): δ 11,70 (d, 1H, J = 2,07 Hz), 10,22 (s, 1H), 10,03 (s, 1H), 8,13 (d, 1H, J = 1,51 Hz), 7,55 (d, 1H, J = 1,51 Hz), 7,53 (d, 1H, J = 2,45 Hz), 7,45 (s, 1H), 7,31 (dd, 1H, J = 4,33, 0,94 Hz), 6,94 (dd, 1H, J = 3,39, 1,70 Hz), 6,86 (d, 1H, J = 2,83 Hz), 3,84 (t, 2H, J = 7,54 Hz), 2,37 (t, 2H, J = 7,35 Hz), 1,93 (tt, 2H, J = 7,54, 7,35 Hz).

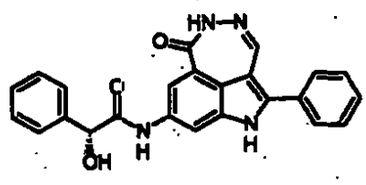
EMCL: ($M+H^+$) 353,2, (M+Na+) 375,2; $(M-H)^-$ 351,2.

EMAR: ($M+H^+$) calculado para $C_{18}H_{17}N_4O_2S$, 353,1072, encontrado 353,1056.

Análisis calculado para $C_{18}H_{16}N_4O_2S$: C, 61,35; H, 4,58; N, 15,90.

Encontrado: C, 61,06; H, 4,52; N, 15,71.

Ejemplo 133: (2*R*)-2-Hidroxi-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-feniletanamida



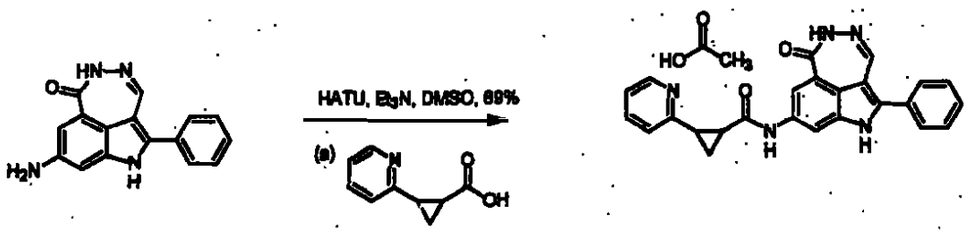
La preparación del ejemplo 133 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (46 mg, 0,147 mmol), ácido (2*R*)-hidroxi(fenil)etanoico (27 mg, 0,177 mmol), trietilamina (0,061 ml, 0,44 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (67 mg, 0,177 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 3:1:1 de

hexano:acetato de etilo:etanol), también de manera análoga, seguido de dos trituraciones sucesivas (acetato de etilo/éter dietílico y después metanol/éter dietílico) proporcionó el compuesto del título (34 mg, 0,082 mmol) en forma de un polvo amarillo con un rendimiento del 56%.

^{1}H RMN (d_6-DMSO): δ 12,12, (s, 1H), 10,38 (s, 1H), 10,16 (s, 1H), 8,14 (s, 1H), 7,81 (s, 1H), 7,70-7,64 (m, 2H), 7,61-7,45 (m, 6H), 7,42-7,26 (m, 3H), 6,35 (s a, 1H, intercambiado parcialmente), 5,13 (s, 1H).

EMCL: $(M-H)^-$ 409,2.

Ejemplo 134:(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-2-il-ciclopropanocarboxílico (sal del ácido acético)



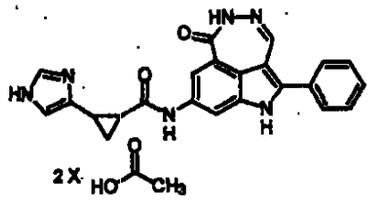
La preparación del ejemplo 134 se realizó de manera análoga a la preparación del Ejemplo **113** con la excepción de que se usó ácido (1,2-*trans*)-2-piridin-2'-il-ciclopropanocarboxílico en lugar de ácido (1,2-*trans*)-2-(6-trifluorometil-piridin-3-il)-ciclopropanocarboxílico en la etapa 4. Se preparó ácido (1,2-*trans*)-2-piridin-2'-il-ciclopropanocarboxílico usando procedimientos similares a los descritos en las etapas 1-3 del Ejemplo **113** con la excepción de que se usó piridina-2-carbaldehído en lugar de 6-trifluorometil-3-piridina carbaldehído. La purificación final por HPLC, también de manera análoga pero usando ácido acético al 0,1% en lugar de TFA al 0,1%, proporcionó el

compuesto del título (107 mg, 0,254 mmol) en forma de un sólido verdoso-amarillo con un rendimiento del 69%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,43 (s, 1H), 10,38 (s, 1H), 8,15 (s, 1H), 7,70-7,40 (m, 7H), 7,25-7,15 (m, 1H), 6,77 (a, 3H), 3,74 (s, 3H), 2,40-2,30 (m, 1H), 2,12-2,05 (m, 1H), 1,55-1,47 (m, 1H), 1,42-1,33 (m, 1H).

EMCL: ($M+H^+$) 422,1.

Ejemplo 135: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amida del ácido (1,2-*trans*)-2-(1*H*-imidazol-4-il)-ciclopropanocarboxílico (sal del ácido acético)

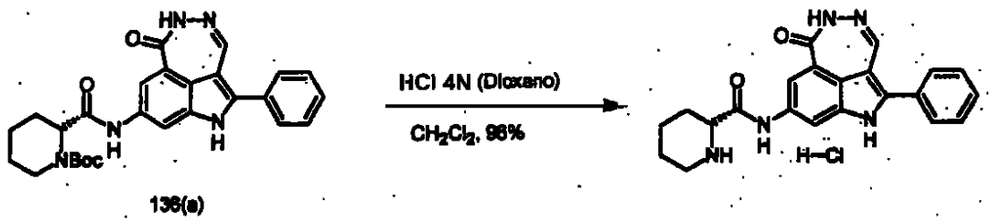


La preparación del ejemplo 135 se realizó suspendiendo el compuesto del título del Ejemplo **130** (260 mg, 0,398 mmol) en diclorometano anhidro (5 ml) y añadiendo ácido trifluoroacético anhidro (5 ml) a temperatura ambiente. Después de 30 minutos, la mezcla se concentró y se sometió a HPLC preparativa, de manera análoga al Ejemplo **134**, proporcionando el compuesto del título (72 mg, 0,175 mmol) en forma de un sólido mullido amarillo con un rendimiento del 44%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,43 (s, 1H), 10,37 (s, 1H), 8,15 (s, 1H), 7,97 (a, 1H), 7,70-7,45 (m, 7H), 7,13 (a, 1H), 2,40-2,30 (m, 1H), 2,12-2,04 (m, 1H), 1,45-1,33 (m, 2H).

EMCL: ($M+H^+$) 422,1.

Ejemplo 136:(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*)-piperidin-2-carboxílico (sal clorhidrato)



136(a)

Etapa 1. Preparación de éster *terc*-butílico del ácido (2*R*)-2-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-cd]indol-8-ilcarbamoil)-piperidin-1-carboxílico 136(a)

La preparación del Intermedio 136(a) a partir del compuesto del título del Ejemplo **7** (0,11 g, 0,4 mmol), 1-*terc*-butil-éster del ácido (2*R*)-piperidin-1,2-dicarboxílico (0,143 g, 0,6 mmol), trietilamina (0,3 ml, 2 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,63 mmol) y *N,N*-dimetilformamida (0,1 M, 5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice proporcionó el Intermedio 136(a) (0,21 g) en forma de un polvo amarillo con un rendimiento del 88%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,40 (s, 1H), 10,11 (s, 1H), 8,10 (s, 1H), 7,74-7,44 (m, 7H), 4,64-4,55 (m, 1H), 3,83 (d, 1H, *J* = 12,25 Hz), 3,35-3,20 (*m* enterrado, 1H), 2,20-2,05 (*m*, 1H), 1,80-1,50 (*m*, 3H), 1,45-1,25 (s a, 11H).

EMCL: ($M+H^+$) 488,2.

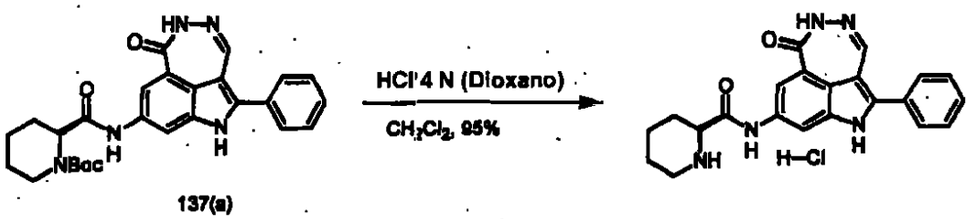
Etapa 2. Preparación del compuesto del título: (6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*)-piperidin-2-carboxílico (sal clorhidrato)

La preparación del compuesto del título a partir del Intermedio 136(a) (0,16 g, 0,33 mmol) y HCl 4 M en dioxano (1,6 ml, 6,6 mmol) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó otra trituración con CH_2Cl_2/éter dietílico y proporcionó el compuesto del título (0,137 g) en forma de un polvo naranja/amarillo con un rendimiento del 96%.

^{1}H RMN (d_6-DMSO): δ 12,31 (s, 1H), 10,90 (s, 1H), 10,45 (s, 1H), 9,26 (a, 1H), 8,80-8,75 (m, 1H), 8,11 (s, 1H), 7,76-7,46 (m, 7H), 3,95-3,81 (m, 1H), 3,35-3,25 (m, 1H), 3,10-2,92 (m, 1H), 2,36-2,26 (m, 1H), 1,76-1,51 (m, 5H).

EMCL: ($M+H^+$) 388,1.

Ejemplo 137: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*S*)-piperidin-2-carboxílico (sal clorhidrato)



137(a)

Etapa 1. Preparación de éster *terc*-butílico del ácido (2*S*)-2-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-piperidin-1-carboxílico 137(a)

La preparación del Intermedio 137(a) a partir del compuesto del título del Ejemplo **7** (0,138 g, 0,5 mmol), 1-*terc*-butil-éster del ácido (2*S*)-piperidin-1,2-dicarboxílico (0,143 g, 0,6 mmol), trietilamina (0,3 ml, 2 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,63 mmol) y *N,N*-dimetilformamida (0,1 M, 5 ml) se realizó de manera análoga al Ejemplo **11**. La cromatografía sobre gel de sílice proporcionó el

Intermedio 137(a) (0,20 g) en forma de un polvo amarillo con un rendimiento del 84%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,40 (s, 1H), 10,11 (s, 1H), 8,10 (s, 1H), 7,74-7,44 (m, 7H), 4,64-4,55 (m, 1H), 3,83 (d, 1H, *J* = 12,25 Hz), 3,35-3,20 (m enterrado, 1H), 2,20-2,05 (m, 1H), 1,80-1,50 (m, 3H), 1,45-1,25 (s a, 11H).

EMCL: ($M+H^+$) 488,1.

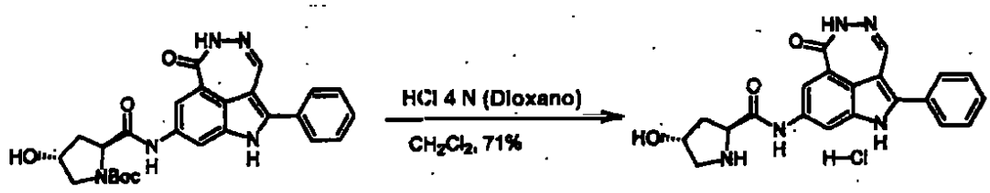
Etapa 2. Preparación del compuesto del título: (6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*S*)-piperidin-2-carboxílico (sal clorhidrato)

La preparación del compuesto del título a partir del Intermedio 137(a) (0,16 g, 0,33 mmol) y HCl 4 M en dioxano (1,6 ml, 6,6 mmol) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó otra trituración con CH_2Cl_2/éter dietílico y proporcionó el compuesto del título (0,132 g) en forma de un polvo naranja/amarillo con un rendimiento del 95%.

^{1}H RMN (d_6-DMSO): δ 12,31 (s, 1H), 10,90 (s, 1H), 10,45 (s, 1H), 9,26 (a, 1H), 8,80-8,75 (m, 1H), 8,11 (s, 1H), 7,76-7,46 (m, 7H), 3,95-3,81 (m, 1H), 3,35-3,25 (m, 1H), 3,10-2,92 (m, 1H), 2,36-2,26 (m, 1H), 1,76-1,51 (m, 5H).

EMCL: ($M+H^+$) 388,2.

Ejemplo 138: (6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*S*,4*R*)-4-hidroxi-pirrolidin-2-carboxílico (sal clorhidrato)



138(a)

Etapa 1. Preparación de éster *terc*-butílico del ácido (2*S*,4*R*)-4-hidroxi-2-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-pirrolidin-1-carboxílico 138(a)

La preparación del Intermedio 138(a) a partir del compuesto del título del Ejemplo **7** (0,138 g, 0,5 mmol), 1-*terc*-butil-éster del ácido (2*S*,4*R*)-4-hidroxi-pirrolidin-1,2-dicarboxílico (0,144 g, 0,6 mmol), trietilamina (0,3 ml, 2 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,63 mmol) y *N,N*-dimetilformamida (0,1 M, 5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice proporcionó el Intermedio 138(a) (0,127 g) en forma de un polvo amarillo con un rendimiento del 52%.

^{1}H RMN (d_6-DMSO): δ 12,19 (s, 1H), 10,46 (s, 1H), 10,28 (s, 1H), 8,29 (s, 0,8H, rotámero mayoritario), 8,29 (s, 0,2H, rotámero minoritario), 7,75-7,51 (m, 7H), 4,50-4,35 (m, 2H), 3,60-3,30 (m, 3H), 2,30-2,17 (m, 1H), 2,10-1,90 (m, 1H), 1,48 (s, 2H, rotámero minoritario), 1,34 (s, 2H, rotámero mayoritario).

EMCL: ($M+H^+$) 490,1.

Etapa 2. Compuesto del título: (6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*S*,4*R*)-4-hidroxi-pirrolidin-2-carboxílico (sal clorhidrato)

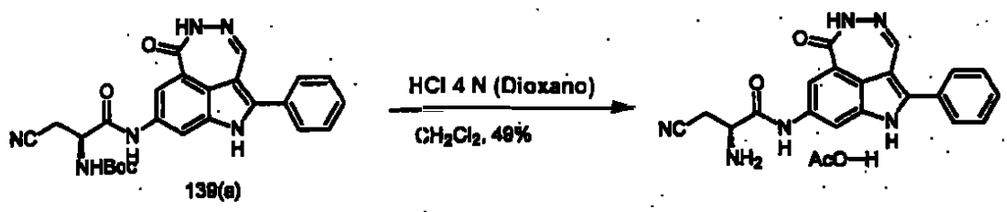
La preparación del compuesto del título a partir del Intermedio 138(a) (0,105 g, 0,21 mmol) y HCl 4 M en dioxano (1 ml, 4,2 mmol) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó otra

trituración con CH_2Cl_2/éter dietílico y proporcionó el compuesto del título (0,065 g) en forma de un polvo naranja/amarillo con un rendimiento del 71%.

^{1}H RMN (d_6-DMSO): δ 12,33 (s, 1H), 10,93 (s, 1H), 10,44 (s, 1H), 10,10-9,95 (m, 1H), 8,90-8,45 (m, 1H), 8,08 (s, 1H), 7,75-7,45 (m, 7H), 4,75-4,35 (m a, 3H), 3,45-3,30 (m, 1H), 3,20-3,10 (m, 1H), 2,50-2,35 (m, 1H), 2,10-1,95 (m, 1H).

EMCL: ($M+H^+$) 390,1.

Ejemplo 139: Sal del ácido acético de (2*S*)-2-amino-3-ciano-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-propanamida



Etapa 1. Preparación de éster *terc*-butílico del ácido (1*S*)-[2-ciano-1-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-etil]-carbámico 139(a)

La preparación del Intermedio 139(a) a partir del compuesto del título del Ejemplo **7** (0,138 g, 0,5 mmol), ácido (2S)-2-*terc*-butoxicarbonilamino-3-ciano-propiónico (0,134 g, 0,6 mmol), trietilamina (0,3 ml, 2 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,63 mmol) y *N,N*-dimetilformamida (0,1 M, 5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice proporcionó el Intermedio 139(a) (0,094 g) en forma de un polvo amarillo con un rendimiento del 40%.

^{1}H RMN (d_6-DMSO): δ 12,15 (s, 1H), 10,42 (s, 1H), 10,37 (s, 1H), 8,11 (s, 1H), 7,75-7,48 (m, 8H), 4,55-4,40 (m, 1H), 3,02 (dd, 1H, *J* = 17,1, 4,9 Hz), 2,85 (dd, 1H, *J* = 17,0, 9,0 Hz), 1,43 (s, 9H).

EMCL: ($M+H^+$) 473,2.

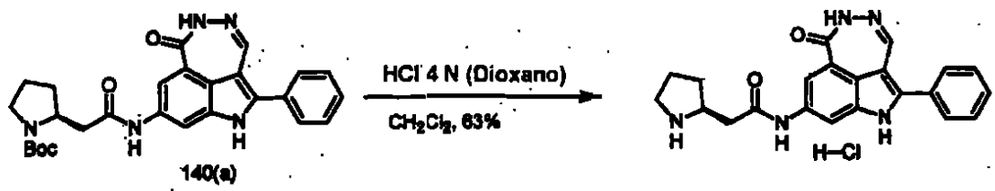
Etapa 2. Preparación del compuesto del título: sal del ácido acético de (2*S*)-2-amino-3-ciano-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-propionamida

La preparación del compuesto del título a partir del Intermedio 139(a) (0,084 g, 0,18 mmol) y HCl 4 M en dioxano (0,9 ml, 3,6 mmol) se realizó de forma análoga al Ejemplo **91**. Una HPLC preparativa proporcionó el compuesto del título (0,038 g) en forma de un polvo naranja/amarillo con un rendimiento del 49%.

^{1}H RMN (d_6-DMSO): δ 12,31 (s, 1H), 10,50 (s, 1H), 10,35 (s a, 1H), 8,24 (s, 1H), 7,80-7,55 (m, 7H), 3,84 (dd, 1H, *J* = 7,0, 6,9 Hz), 2,99 (dd, 1H, J = 16,8, 5,7 Hz), 2,85 (dd, 1H, J = 16,6, 7,2 Hz), 2,73 (s, 6H).

EMCL: ($M+H^+$) 373,1.

Ejemplo 140: (2*S*)-*N*-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-pirrolidin-2-il-acetamida (sal clorhidrato)



Etapa 1. Preparación de éster *terc*-butílico del ácido (2*S*)-2-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-metil]-pirrolidin-1-carboxílico 140(a)

La preparación del Intermedio 140(a) a partir del compuesto del título del Ejemplo 7 (0,138 g, 0,5 mmol), éster *terc*-butílico del ácido (2*S*)-2-carboximetil-pirrolidin-1-carboxílico (0,143 g, 0,6 mmol), trietilamina (0,3 ml, 2 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,63 mmol) y *N,N*-dimetilformamida (0,1 M, 5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice proporcionó el Intermedio 140(a) (0,155 g) en forma de un polvo amarillo con un rendimiento del 64%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,39 (s, 1H), 10,17 y 10,10 (2s, 1H, rotámero minoritario y mayor), 8,20 (s, 1H), 7,75-7,45 (m, 7H), 4,10 (s, 1H), 4,20-4,05 (m, 1H), 3,50-3,25 (m, 2H), 2,10-1,75 (m, 4H), 1,40 y 1,29 (2s, 9H, rotámero minoritario y mayor).

EMCL: (M-Boc+H$^+$) 388,2.

Etapa 2. Preparación del compuesto del título: (2*S*)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-pirrolidin-2-il-acetamida (sal clorhidrato)

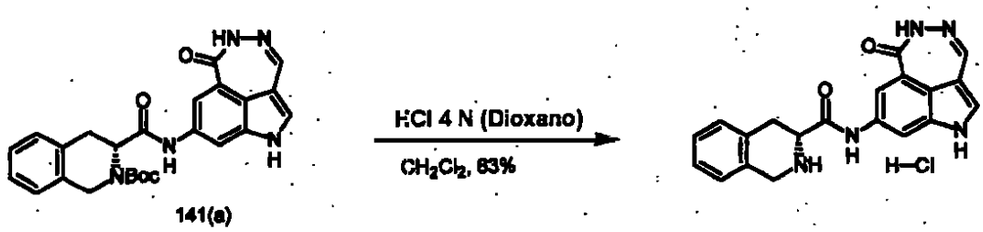
La preparación del compuesto del título a partir del Intermedio 140(a) (0,1 g, 0,20 mmol) y HCl 4 M en dioxano (1 ml, 4,2 mmol) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó otra trituración con CH_2Cl_2/éter dietílico y proporcionó el compuesto del título (0,055 g) en forma de un polvo naranja/amarillo con un rendimiento del 63%.

rotámero mayoritario; ^{1}H RMN (d_6-DMSO): δ 12,23 (s, 1H), 10,48 (s, 1H), 10,41 (s, 1H), 9,25-9,10 (m, 1H), 8,95-8,80 (m, 1H), 8,11 (s, 1H), 7,75-7,45 (m, 7H), 4,10 (m enterrado, 1H), 3,90-3,75 (m, 1H), 3,25-3,15 (m, 2H), 2,95-2,85 (m, 2H), 2,25-1,55 (m, 5H).

rotámero minoritario; ^{1}H RMN (d_6-DMSO): δ 12,31 (s, 1H), 10,92 (s, 1H), 10,45 (s, 1H), 9,85-9,75 (*m*, 1H), 8,75-8,60 (*m*, 1H), 3,35-3,25 (*m*, 2H).

EMCL: ($M+H^+$) 388,2.

Ejemplo 141: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]*indol*-8-il)-amida del ácido (3*R*)-1,2,3,4-tetrahidro-isoquinolina-3-carboxílico (sal clorhidrato)



141(a)

Etapa 1. Preparación de éster *terc*-butílico del ácido (3*R*)-3-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-3,4-dihidro-1*H*-isoquinolina-2-carboxílico 141 (a)

La preparación del intermedio 141 (a) a partir del compuesto del título del Ejemplo **2** (0,1 g, 0,5 mmol), 2-*terc*-butil-éster del ácido (3*R*)-3,4-dihidro-1*H*-isoquinolina-2,3-dicarboxílico (0,103 g, 0,6 mmol), trietilamina (0,3 ml, 2 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,63 mmol) y *N,N*-dimetilformamida (0,1 M, 5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice proporcionó el Intermedio 141(a) (0,094 g) en forma de un polvo amarillo con un rendimiento del 41%.

^{1}H RMN (d_6-DMSO): δ 11,72 (s a, 1H), 10,25 (s, 1H), 10,14 (s a, 1H), 8,09 y 7,96 (2s, 1H, rotámero mayoritario y minoritario), 7,57 (s, 2H), 7,47 (s, 1H), 7,30-7,10 (m, 4H), 4,75-4,60 (m, 1H), 4,48-4,34 (m, 1H), 3,40-3,00 (m, 3H), 1,47 (s, 3H), 1,31(s, 6H).

EMCL: ($M-H^+$) 458,3.

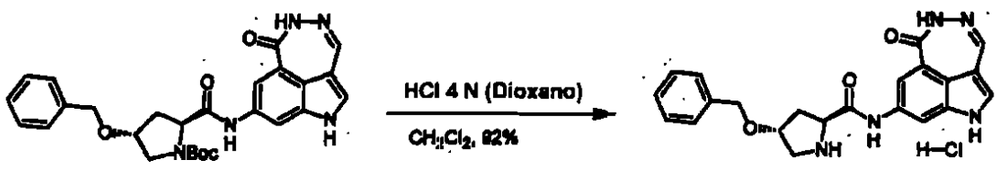
Etapa 2. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (3*R*)-1,2,3,4-tetrahidro-isoquinolina-3-carboxílico (sal clorhidrato)

La preparación del compuesto del título a partir del Intermedio 141 (a) (0,094 g, 0,20 mmol) y HCl 4 M en dioxano (1 ml, 4,2 mmol) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó otra trituración con CH_2Cl_2/éter dietílico y proporcionó el compuesto del título (0,051 g) en forma de un polvo naranja/amarillo con un rendimiento del 63%.

^{1}H RMN (d_6-DMSO): δ 11,98 (s, 1H), 11,08 (s, 1H), 10,32 (s, 1H), 9,93 (a, 1H), 9,64 (a, 1H), 8,09 (s, 1H), 7,74 (s, 1H), 7,64 (s, 1H), 7,51 (s, 1H), 7,29 (s, 5H), 4,50-4,10 (m enterrado, 3H), 3,53 (dd, 1H, J = 16,4, 4,0 Hz), 3,14 (dd, 1H, *J* = 16,8,12,06 Hz).

EMCL: ($M+H^+$) 360,1.

Ejemplo 142:(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*S*,4*R*)-4-benciloxi-pirrolidin-2-carboxílico (sal clorhidrato)



142(a)

Etapa 1. Preparación de éster *terc*-butílico del ácido (2*S*,4*R*)-4-benciloxi-2-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-pirrolidin-1-carboxílico 142(a)

La preparación del intermedio 142(a) a partir del compuesto del título del Ejemplo **2** (0,1 g, 0,5 mmol), 1-*terc*-butil-éster del ácido (2*S*,4*R*)-4-benciloxi-pirrolidin-1,2-dicarboxílico (0,103 g, 0,6 mmol), trietilamina (0,3 ml, 2 mmol),

hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,63 mmol) y *N,N*-dimetilformamida (0,1 M, 5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice proporcionó el Intermedio 142(a) (0,126 g) en forma de un polvo amarillo con un rendimiento del 50%.

^{1}H RMN (d_6-DMSO): δ 11,76 (s, 1H), 10,26 (s, 1H), 10,18 (s, 1H), 8,18 y 8,10 (s, 1H, rotámeros), 7,60 (s, 1H), 7,58 (s, 1H), 7,48 (s, 1H), 7,42-7,26 (m, 5H), 4,53 (s, 2H), 4,39-4,26 (m, 1H), 4,22 (s a, 1H), 3,54 (s a, 2H), 3,32 (s, 2H), 1,27 (s, 6H).

EMCL: ($M-H^+$) 502,2.

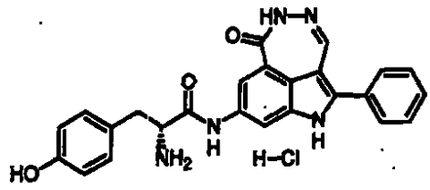
Etapa 2. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*S*,4*R*)-4-benciloxi-pirrolidin-2-carboxílico (sal clorhidrato)

La preparación del compuesto del título a partir del Intermedio 142(a) (0,106 g, 0,21 mmol) y HCl 4 M en dioxano (1 ml, 4,2 mmol) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó otra trituración con CH_2Cl_2/éter dietílico y proporcionó el compuesto del título (0,085 g) en forma de un polvo naranja/amarillo con un rendimiento del 92%.

^{1}H RMN (d_6-DMSO): δ 11,96 (s, 1H), 10,94 (s, 1H), 10,33 (s, 1H), 10,12 (a, 1H), 8,89 (a, 1H), 8,06 (s, 1H), 7,70 (s, 1H), 7,64 (s, 1H), 7,51 (s, 1H), 7,45-7,28 (m, 7H), 4,40 (a, 2H), 3,47 (a, 2H), 2,80-2,65 (m, 1H), 2,15-2,01 (m, 1H).

EMCL: ($M+H^+$) 404,2.

Ejemplo 143:Clorhidrato de (2*R*)-2-amino-3-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida

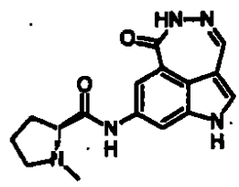


La preparación del ejemplo 143 a partir del compuesto del título del Ejemplo **150** (64 mg, 0,119 mmol) y HCl 4 M en dioxano (5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó la basificación libre con trietilamina y la posterior cromatografía sobre gel de sílice eluyendo con 3:1:1 de hexano:acetato de etilo:etanol. Con refrigeración con un baño de hielo, la base libre purificada en CH_2Cl_2 (5 ml) se trató con HCl 4 M en dioxano (0,1 ml). Después de la retirada de los componentes volátiles, se obtuvo el compuesto del título (32 mg, 0,067 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 57%.

^{1}H RMN (d_6-DMSO): δ 12,25 (s, 1H, intercambios), 10,71 (s, 1H, intercambios), 10,45 (s, 1H, intercambios), 9,44 (s a, 1H, intercambios), 8,45-8,31 (m a, 2H, intercambios), 8,08 (s, 1H), 7,76-7,45 (m, 7H), 7,09 (d, 2H, J = 8 Hz), 6,72 (d, 2H, J = 8 Hz), 4,13 (m, 1H), 3,19-2,97 (m, 2H).

EMCL: ($M+H^+$) 440,0, (M-H)'438,2.

Ejemplo 144: (6-Oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (*S*)-1-metil-pirrolidin-2-carboxílico



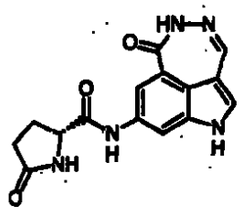
La preparación del ejemplo 144 a partir del compuesto del título del Ejemplo **2** (190 mg, 0,95 mmol), *N*-metilprolina (129 mg, 1,47 mmol),

trietilamina (0,19 ml, 1,43 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (470 mg, 1,3 mmol) en *N,N*-dimetilformamida (5 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con metanol al 10% en CH_2Cl_2), también de manera análoga, proporcionó el compuesto del título (100 mg, 0,32 mmol) en forma de un polvo amarillo con un rendimiento del 34%.

^{1}H RMN (d_6-DMSO): 11,83 (s, 1H), 10,33 (s, 1H), 9,96 (s, 1H), 8,24 (s, 1H), 7,73 (s, 1H), 7,65 (s, 1H), 7,55 (s, 1H), 3,20 (m, 1H), 3,03 (m, 1H), 2,63 (m, 1H), 2,23 (m, 1H), 1,91-1,88 (m, 3H). Anál. calc. para $C_{16}H_{17}N_5O_2 \cdot 0,2\ H_2O$: C, 61,02; H, 5,57; N, 22,24, Encontrado: C, 60,83; H, 5,29; N, 22,23.

EMCL: ($M+H^+$) 312,1.

Ejemplo 145:(6-Oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*)-5-oxo-pirrolidin-2-carboxílico



La preparación del ejemplo 145 a partir del compuesto del título del Ejemplo **2** (base libre) (190 mg, 0,95 mmol), ácido (*R*)-(+)-pirrolidoncarboxílico (167 mg, 1,29 mmol), trietilamina (0,25 ml, 1,77 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (538 mg, 1,42 mmol) en *N,N*-dimetilformamida (5 ml) se realizó de forma análoga al Ejemplo **11.** La mezcla se concentró y el residuo se trituró con metanol. Después, los sólidos resultantes se recogieron por filtración y se lavaron con metanol, dando el

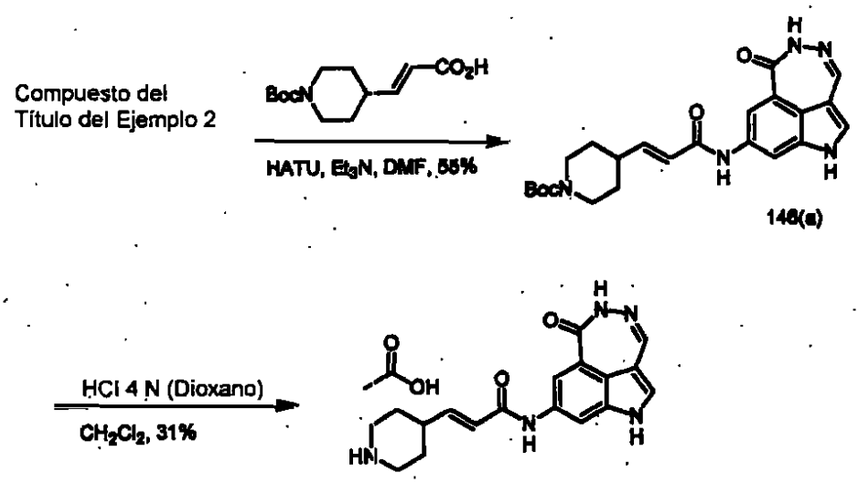
compuesto del título (220 mg, 0,57 mmol) en forma de un polvo amarillo con un rendimiento del 60%.

^{1}H RMN (d_6-DMSO): 11,79 (s, 1H), 10,27 (s, 1H), 10,20 (s, 1H), 8,11 (s, 1H), 7,91 (s, 1H), 7,62 (s, 1H), 7,59 (s, 1H), 7,49 (s, 1H), 4,21 (m, 1H), 2,36 (m, 1H), 2,24-2,16 (m, 2H), 2,03 (m, 1H).

Anál. calc. para $C_{15}H_{13}N_5O_3 \cdot 1\ H_2O$: C, 54,71; H, 4,59; N, 21,27, Encontrado: C, 54,51; H, 4,68; N, 21,05.

EMCL: ($M+H^+$) 312,2.

Ejemplo 146:sal del ácido acético de *N*-(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-piperidin-4-il-acrilamida



Etapa 1. Preparación de éster *terc*-butílico del ácido 4-[2-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-vinil]-piperidin-1-carboxílico 146(a)

La preparación del intermedio 146(a) a partir del compuesto del título del Ejemplo **2** (base libre) (49 mg, 0,245 mmol), éster *terc*-butílico del ácido 4-(2-carboxi-vinil)-piperidin-1-carboxílico (99 mg, 0,39 mmol), trietilamina (0,069 ml,

0,49 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (148 mg, 0,39 mmol) en *N,N*-dimetilformamida (3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con metanol al 10% en CH_2Cl_2), también de manera análoga, proporcionó el Intermedio 146(a) (58 mg, 0,13 mmol) en forma de un polvo amarillo con un rendimiento del 55%.

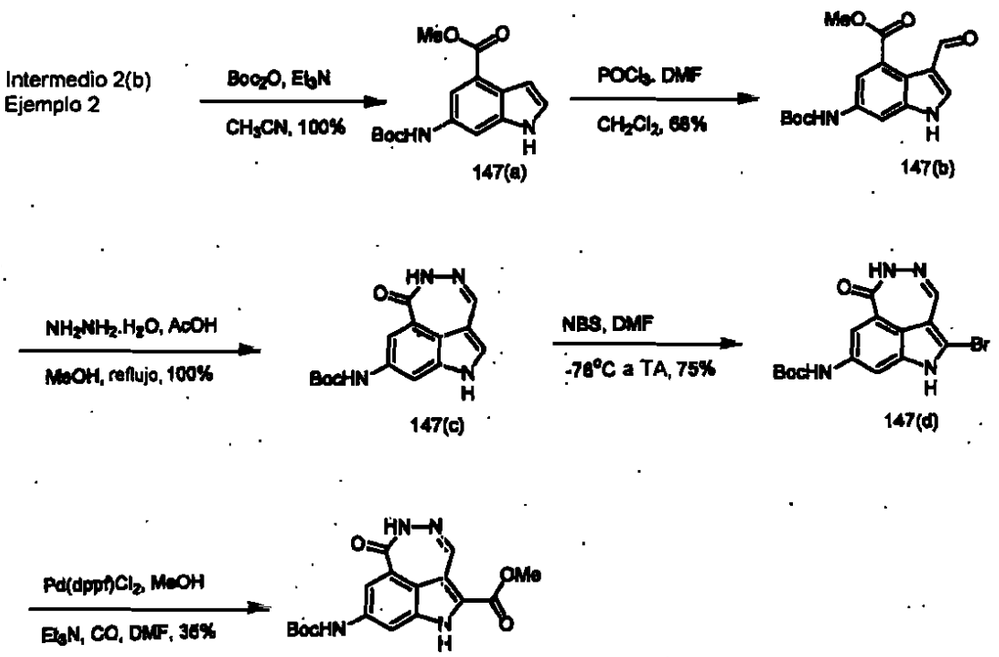
Etapa 2. Preparación del compuesto del título: sal del ácido acético de *N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-piperidin-4-il-acrilamida

La preparación del compuesto del título a partir del Intermedio 146(a) (58 mg, 0,13 mmol) en CH_2Cl_2 (2 ml) y HCl 4 M en dioxano (2 ml) se realizó de forma análoga al Ejemplo **91**. Después de la concentración, el residuo se purificó por HPLC preparativa (Peeke Scientific, fase inversa Hi-Q C18 5 µ, 100A, columna de 250 x 21,2 mm) eluyendo con CH_3CN y ácido acético al 0,1% en agua a un caudal de 20 ml/min usando un gradiente de CH_3CN al 5-95% durante 40 min, dando el compuesto del título (16 mg, 0,04 mmol) en forma de un polvo amarillo pálido con un rendimiento del 31%.

^{1}H RMN (d_6-DMSO): 11,55 (s, 1H), 10,00 (s, 1H), 9,91 (s, 1H), 8,00 (s, 1H), 7,32 (d, J = 8 Hz, 2H), 7,22 (s, 1H), 6,50 (m, 1H), 5,82 (m, 1H), 2,77-2,77 (m, 2H), 2,03 (m, 1H), 1,65-1,53 (m, 2H), 1,29-1,28 (m, 2H), 1,10-1,02 (m, 2H).

EMCL: ($M+H^+$) 337.

Ejemplo 147: Éster metílico del ácido 8-*terc*-butoxicarbonilamino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico



Etapa 1. Preparación de éster metílico del ácido 6-*terc*-butoxicarbonilamino-1*H*-indol-4-carboxílico 147(a)

Se añadió lentamente trietilamina (17,1 ml, 123 mmol) al Intermedio 2(b) del Ejemplo **2** (clorhidrato) (27,5 g, 121 mmol) enfriado a 0°C en 400 ml de CH_3CN anhidro. Después de 0,5 horas, se añadió dicarbonato de di-*terc*-butilo (26,76 g, 123 mmol) en CH_3CN anhidro (50 ml) y la mezcla se dejó en agitación a temperatura ambiente durante 24 h, momento en el que los componentes volátiles se retiraron al vacío. Se añadieron acetato de etilo (500 ml) y H_2O (500 ml) y la fase acuosa se extrajo con acetato de etilo (4 x 120 ml). Los extractos de acetato de etilo combinados se lavaron con H_2O (2 x 70 ml) y salmuera (100 ml) y se dejaron secar sobre Na_2SO_4. Después de la filtración, los componentes volátiles se retiraron al vacío, proporcionando el Intermedio 147(a) (35,1 g, 121 mmol) en forma de un sólido pardo con rendimiento cuantitativo.

^{1}H RMN (d_6-DMSO): δ 12,28 (s, 1H), 9,43 (s, 1H), 7,91 (s a, 1H), 7,89 (s, 1H), 7,42 (t, 1H, *J* = 2,73 Hz), 6,83 (t, 1H, J = 2,17 Hz), 3,89 (s, 3H), 1,50 (s, 9H).

EMCL: ($M+Na^+$) 313,1; $(M-H)^-$ 289,2, Análisis calculado para $C_{15}H_{18}N_2O_4$: C, 62,06; H, 6,25; N, 9,65, Encontrado: C, 62,08; H, 6,30; N, 9,59.

Etapa 2. Preparación de éster metílico del ácido 6-*terc*-butoxicarbonilamino-3-formil-1*H*-indol-4-carboxílico 147(b)

Un reactivo de Vilsmeier premezclado compuesto por oxicloruro de fósforo (33,67 ml, 3624 mmol) en *N,N*-dimetilformamida (81,40 ml) se añadió gota a gota a 0°C al Intermedio 147(a) (33,87 g, 116 mmol) agitando en CH_2Cl_2 anhidro (584 ml). La mezcla se agitó durante 1 hora a temperatura ambiente, se inactivó con acetato sódico acuoso 2,0 M (700 ml) a 0°C y se neutralizó con Na_2CO_3 sólido. Se formó un sólido y la mezcla se repartió entre acetato de etilo (4000 ml) y H_2O (2000 ml). Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (4 x 500 ml). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. Al residuo se le añadió metanol (3500 ml) seguido de K_2CO_3 (70 g). La mezcla se agitó a temperatura ambiente durante 16 horas, momento en el que los componentes volátiles se retiraron al vacío. Se añadieron acetato de etilo (500 ml) y H_2O (500 ml). Después, toda la mezcla se filtró y los sólidos insolubles se recogieron y se secaron al vacío, proporcionando el Intermedio 147(b) (14,35 g, 45,1 mmol) en forma de un sólido blanco. La fase acuosa se extrajo de nuevo con acetato de etilo (4 x 120 ml) y los extractos de acetato de etilo se combinaron, se lavaron con H_2O (2 x 170 ml) y salmuera y se dejaron secar sobre Na_2SO_4. Después de la filtración, los componentes volátiles se retiraron

al vacío, proporcionando más Intermedio 147(b) (10,74 g, 33,8 mmol) en forma de un sólido blanco. El rendimiento combinado para los dos lotes fue del 68%.

^{1}H RMN (d_6-DMSO): δ 12,28 (s, 1H), 10,09 (s, 1H), 9,60 (s, 1H), 8,23 (d, 1H, *J* = 3,01 Hz), 7,96 (d, 1H, *J* = 1,32 Hz), 7,65 (d, 1H, J = 1,88 Hz), 3,84 (s, 3H), 1,50 (s, 9H).

EMCL: $(M+H^+)$ 319, $(M+Na^+)$ 341,1; $(M-H)^-$ 317,1

Etapa 3. Preparación de éster *terc*-butílico del ácido (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico 147(c)

Se añadió ácido acético (7,89 ml) al Intermedio 147(b) (25,1 g, 78,9 mmol) en metanol anhidro (789 ml). La suspensión se agitó a temperatura ambiente durante 10 minutos y se le añadió $H_2NNH_2H_2O$ (21,43 ml, 395 mmol). La mezcla se agitó a temperatura ambiente durante 10 minutos más, se calentó a 70°C durante 0,5 horas y se enfrió a temperatura ambiente. Los componentes volátiles se retiraron al vacío y el aceite residual se trituró con metanol y tolueno, proporcionando el Intermedio 147(c) (23,6 g, 78,9 mmol) en forma de un polvo amarillo con rendimiento cuantitativo.

^{1}H RMN (d_6-DMSO): δ 11,63 (s, 1H), 10,19 (s, 1H), 9,45 (s, 1H), 7,76 (s, 1H), 7,62 (s, 1H), 7,51 (d, 1H, *J* = 2,07 Hz), 7,44 (s, 1H), 1,49 (s, 9H).

EMCL: $(M+H^+)$ 301,1, $(M+Na^+)$ 323,1; $(M-H)^-$ 299,1, Análisis calculado para $C_{15}H_{16}N_4O_3 \cdot 0{,}5\ H_2O$: C, 59,10; H, 5,46; N, 18,38, Encontrado: C, 59,49; H, 5,43; N, 17,97.

Etapa 4. Preparación de éster *terc*-butílico del ácido (2-bromo-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico 147(d)

El Intermedio 147(c) (1,00 g, 3,33 mmol) se disolvió en *N,N*-dimetilformamida anhidra (15 ml) y se enfrió a -78°C. Se añadió gota a gota *N*-

bromosuccinimida (0,564 g, 3,17 mmol) en *N,N*-dimetilformamida anhidra (3,5 ml) durante 2 min. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. Después, se añadió en porciones más *N*-bromosuccinimida (0,337 g, 2,00 mmol) en *N,N*-dimetilformamida (aprox. 1,5 ml) durante un periodo de 0,5 horas, completando la reacción. La mezcla de reacción se vertió en H_2O (70 ml) y precipitó un sólido oscuro. El sólido se recogió por filtración y se secó al vacío, dando el Intermedio 147(d) (0,95 g, 2,51 mmol) en forma de un sólido oscuro con un rendimiento del 75%.

^{1}H RMN (d_6-DMSO): δ 12,54 (s, 1H), 10,47 (s, 1H), 9,57 (s, 1H), 7,77 (s, 1H), 7,71 (d, 1H; *J* = 1,70 Hz), 7,31 (s, 1H), 1,53 (s, 9H).

EMCL: ($M+H^+$) 379,0, 381,0, ($M+Na^+$) 401,0, 403,0; $(M-H)^-$ 377,1, 379,1, Análisis calculado para $C_{15}H_{15}BrN_4O_3$: C, 47,51; H, 3,99; N, 14,77, Encontrado: C, 47,42; H, 3,99; N, 14,51.

Etapa 5. Preparación del compuesto del título: éster metílico del ácido 8-*terc*-butoxicarbonilamino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico

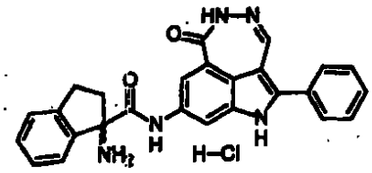
El Intermedio 147(d) (0,200 g, 0,529 mmol), trietilamina (0,147 ml, 1,06 mmol) y metanol anhidro (2 ml) en *N,N*-dimetilformamida anhidra (2 ml) se purgaron con Ar. Se añadió [1,1'-*bis*(difenilfosfino)ferroceno]dicloropaladio (II) (86,4 mg, 0,106 mmol) y se burbujeó CO en la mezcla de reacción durante 5 minutos. Después, la reacción se cerró herméticamente y se calentó a 85°C durante 16 horas. La mezcla se filtró a través de un lote fijo de tierra diatomácea y el filtrado se redujo al vacío. La cromatografía sobre gel de sílice (eluida con 1:1 de acetato de etilo:hexano) proporcionó el compuesto del título

(66 mg, 0,184 mmol) en forma de un polvo amarillo con un rendimiento del 35%.

^{1}H RMN (d_6-DMSO): δ 12,42 (s, 1H), 10,80 (s, 1H), 9,69 (s, 1H), 8,14 (s, 1H) 7,91 (s, 1H), 7,76 (s, 1H), 3,92 (s, 3H), 1,49 (s, 9H).

EMCL: ($M+H^+$) 359,1, ($M+Na^+$) 381,2; $(M-H)^-$ 357,0.

Ejemplo 148:Clorhidrato de 1-amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2,3-dihidro-1*H*-inden-1-carboxamida

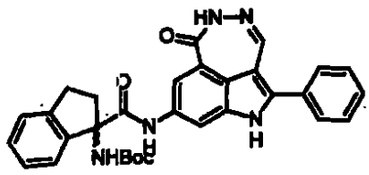


La preparación del ejemplo 148 a partir del compuesto del título del Ejemplo **149** (52 mg, 0,097 mmol) y HCl 4 M en dioxano (5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (46 mg, 0,097 mmol) en forma de un polvo amarillo con rendimiento cuantitativo.

^{1}H RMN (d_6-DMSO): δ 12,42 (s, 1H), 10,60 (s, 1H), 10,20 (s, 1H), 9,05-8,86 (m, 3H), 8,23 (s, 1H), 7,90-7,73 (m, 3H), 7,72-7,57 (m, 6H), 7,55-7,41 (m 2H), 3,42 (m, 1H), 3,31 (m, 1H), 3,08 (m, 1H), 2,55 (m, 1H, parcialmente oscurecido).

EMCL: ($M+H^+$) 436,2, 419,2.

Ejemplo 149:1-{[(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]carbonil}-2,3-dihidro-1*H*-inden-1-ilcarbamato de 1,1-dimetiletilo

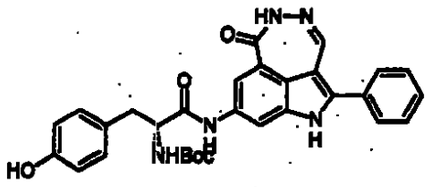


La preparación del ejemplo 149 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (52 mg, 0,17 mmol), ácido 1-({[(1,1-dimetiletil)oxi]carbonil}amino)-2,3-dihidro-1*H*-inden-1-carboxílico (72 mg, 0,26 mmol), trietilamina (0,071 ml, 0,51 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (99 mg, 0,26 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (63 mg, 0,12 mmol) en forma de un polvo amarillo con un rendimiento del 69%.

^{1}H RMN (d_6-DMSO): δ 12,05 (s, 1H), 10,36 (s, 1H), 10,01 (m, 1H), 8,09 (m, 1H), 7,87-7,74 (m, 2H), 7,70-7,52 (m, 2H), 7,63-7,53 (m, 2H), 7,52-7,47 (m, 2H), 7,31-7,22 (m, 3H), 3,08-2,95 (m, 3H), 2,09 (m, 1H), 1,40 (m, 9H).

EMCL: $(M-H)^-$ 534,0.

Ejemplo 150: (1*R*)-1-[(4-Hidroxifenil)metil]-2-oxo-2-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de 1,1-dimetiletilo



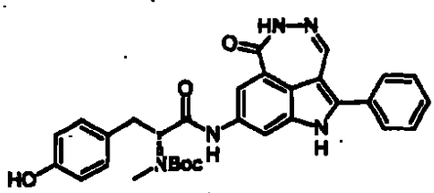
La preparación del ejemplo 150 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (44 mg, 0,144 mmol), ácido (2*R*)-2-({[(1,1-dimetiletil)oxi]carbonil}amino)-3-(4-hidroxifenil)propanoico (46 mg, 0,173 mmol),

trietilamina (0,060 ml, 0,43 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (66 mg, 0,173 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (74 mg, 0,137 mmol) en forma de un polvo amarillo con un rendimiento del 95%.

^{1}H RMN (d_6-DMSO): δ 12,11 (s, 1H), 10,41 (s, 1H), 10,20 (s, 1H), 9,20 (s, 1H), 8,17 (s, 1H), 7,71-7,45 (m, 7H), 7,14 (d, 2H, *J* = 8,50 Hz), 6,68 (d, 2H, J = 8,40 Hz), 4,24 (m, 1H), 2,94 (m, 1H), 2,72 (m, 1H), 1,35 (s, 9H).

EMCL: $(M-H)^-$ 538,1.

Ejemplo 151: [1*R*)-1-[(4-Hidroxifenil)metil]-2-oxo-2-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etil(metil)carbamato de 1,1-dimetiletilo



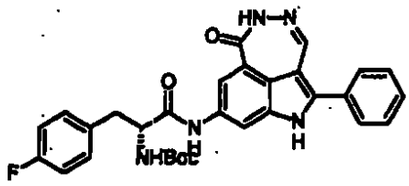
La preparación del ejemplo 151 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (40 mg, 0,128 mmol), ácido (2*R*)-2-[{[(1,1-dimetiletil)oxi]carbonil}(metil)amino]-3-(4-hidroxifenil)propanoico (57 mg, 0,192 mmol), trietilamina (0,054 ml, 0,384 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (73 mg, 0,192 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. Se añadieron más ácido (2*R*)-2-[{[(1,1-dimetiletil)oxi]carbonil}(metil)amino]-3-(4-hidroxifenil)propanoico (14 mg, 0,047 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (18 mg, 0,047 mmol) después

de 24 horas, completando la reacción. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (55 mg, 0,099 mmol) en forma de un polvo amarillo con un rendimiento del 78%.

^{1}H RMN (d_6-DMSO) múltiple: δ 12,10 (s a, 1H), 10,38 (s a, 1H), 9,20 (m, 1H), 8,13 (m, 1H), 7,72-7,63 (m, 3H), 7,61-7,43 (m, 4H), 7,09-7,00 (m, 2H), 6,72-6,62 (m, 2H), 4,82-4,60 (m, 1H), 3,19-3,08 (m, 1H), 2,93-2,85 (m, 1H), 2,80-2,62 (m, 3H), 1,37-1,21 (m, 9H).

EMCL: $(M+H^+)$ 554,2, $(M+Na^+)$ 576,2 $(M-H)^-$ 552,0.

Ejemplo 152: (1*R*)-1-[(4-Fluorofenil)metil]-2-oxo-2-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de 1,1-dimetiletilo

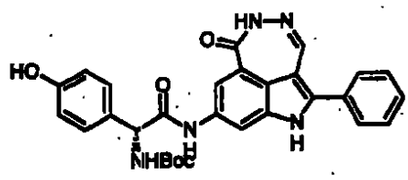


La preparación del ejemplo 152 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (40 mg, 0,128 mmol), ácido (2*R*)-2-({[(1,1-dimetiletil)oxi]carbonil}amino)-3-(4-fluorofenil)propanoico (54 mg, 0,192 mmol), trietilamina (0,054 ml, 0,384 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (73 mg, 0,192 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (61 mg, 0,113 mmol) en forma de un polvo amarillo con un rendimiento del 88%.

^{1}H RMN (d_6-DMSO): δ 12,12 (s, 1H), 10,42 (s, 1H), 10,25 (s, 1H), 8,18 (s, 1H), 7,71-7,46 (m, 7H), 7,42-7,34 (m, 2H), 7,21-7,09 (m, 3H), 4,41 (m, 1H), 3,03 (m, 1H), 2,85 (m 1H), 1,34 (s, 9H).

EMCL: $(M-H)^-$ 540,2.

Ejemplo 153: (1*R*)-1-(4-Hidroxifenil)-2-oxo-2-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de 1,1-dimetiletilo

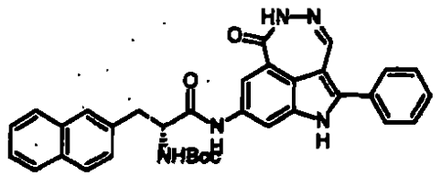


La preparación del ejemplo 153 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (42 mg, 0,134 mmol), ácido (2*R*)-({[(1,1-dimetiletil)oxi]carbonil}amino)(4-hidroxifenil)etanoico (54 mg, 0,202 mmol), trietilamina (0,056 ml, 0,402 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (77 mg, 0,202 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*-dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. Se añadieron más ácido (2*R*)-({[(1,1-dimetiletil)oxi]carbonil}amino)(4-hidroxifenil)etanoico (27 mg, 0,10 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (39 mg, 0,10 mmol) después de 24 horas, completando la reacción. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (48 mg, 0,091 mmol) en forma de un polvo amarillo con un rendimiento del 68%.

^{1}H RMN (d_6-DMSO): δ 12,11 (s, 1H), 10,40 (s, 1H), 10,30 (s, 1H), 9,46 (s, 1H), 8,12 (s, 1H), 7,71-7,48 (m, 7H), 7,33-7,27 (m, 2H), 6,80-6,69 (m, 2H), 5,22 (m, 1H), 1,41 (s, 1H).

EMCL: $(M+H^+)$ 526,2.

Ejemplo 154: (1*R*)-1-(Naftalen-2-ilmetil)-2-oxo-2-[(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de 1,1-dimetiletilo

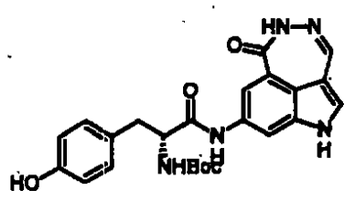


La preparación del ejemplo 154 a partir del compuesto del título del Ejemplo **7** (clorhidrato) (40 mg, 0,128 mmol), ácido (2*R*)-2-({[(1,1-dimetiletil)oxi]carbonil}amino)-3-naftalen-2-ilpropanoico (58 mg, 0,192 mmol), trietilamina (0,054 ml, 0,384 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (73 mg, 0,192 mmol) en CH_2Cl_2 (0,4 ml) y *N,N*- dimetilformamida (0,4 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de hexano:acetona), también de manera análoga, proporcionó el compuesto del título (69 mg, 0,120 mmol) en forma de un polvo amarillo con un rendimiento del 94%.

^{1}H RMN (d_6-DMSO): δ 12,12 (s, 1H), 10,41 (s, 1H), 10,31 (s, 1H), 8,18 (s, 1H), 7,90-7,81 (m, 4H), 7,71-7,66 (m, 3H), 7,62-7,56 (m, 3H), 7,54-7,46 (m, 4H), 7,23 (d, 1H, *J* = 8,1 Hz), 4,46 (m, 1H), 3,23 (m, 1H), 3,02 (m, 1H), 1,30 (s, 9H).

EMCL: $(M-H)^-$ 572,2.

Ejemplo 155: (1*R*)-1-[(4-Hidroxifenil)metil]-2-oxo-2-[(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de 1,1-dimetiletilo

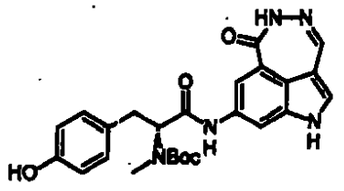


La preparación del ejemplo 155 a partir del compuesto del título del Ejemplo **2** (71 mg, 0,30 mmol), ácido (2*R*)-2-({[(1,1-dimetiletil)oxi]carbonil}amino)-3-(4-hidroxifenil)propanoico (121 mg, 0,45 mmol), trietilamina (0,125 ml, 0,9 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (171 mg, 0,45 mmol) en CH_2Cl_2 (0,5 ml) y *N,N*-dimetilformamida (0,5 ml) se realizó de forma análoga al Ejemplo **11**. La purificación, también de manera análoga (eluida con 1:1 de hexano:acetona) produjo el compuesto del título (100 mg, 0,22 mmol) en forma de un polvo amarillo con un rendimiento del 72%.

^{1}H RMN (d_6-DMSO): δ 11,75 (s, 1H), 10,26 (s, 1H), 10,13 (s, 1H),9,19 (s, 1H), 8,16 (s, 1H), 7,61-7,56 (m, 2H), 7,14 (d, 2H, *J* = 8,10 Hz), 7,04 (d, 1H, J = 8,48 Hz), 6,66 (d, 2H, *J* = 8,10 Hz), 4,22 (m, 1H), 3,08 (m, 1H), 2,87 (m, 1H), 1,34 (s, 9H).

EMCL: ($M+H^+$) 464,2, ($M+Na^+$) 486,2.

Ejemplo 156:(1*R*)-1-[4-Hidroxifenil)metil]-2-oxo-2-[(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etil(metil)carbamato de 1,1-dimetiletilo

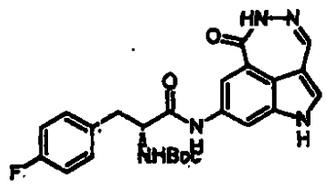


La preparación del ejemplo 156 a partir del compuesto del título del Ejemplo **2** (74 mg, 0,31 mmol), ácido (2*R*)-2-[{[(1,1-dimetiletil)oxi]carbonil}(metil)amino]-3-(4-hidroxifenil)propanoico (138 mg, 0,47 mmol), trietilamina (0,130 ml, 0,93 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (179 mg, 0,47 mmol) en CH_2Cl_2 (0,5 ml) y *N,N*-dimetilformamida (0,5 ml) se realizó de forma análoga al Ejemplo **11**. La purificación, también de manera análoga (eluida con 1:1 de hexano:acetona) proporcionó el compuesto del título (131 mg, 0,27 mmol) en forma de un polvo amarillo con un rendimiento del 88%.

^{1}H RMN (d_6-DMSO): δ 11,77 (s, 1H), 10,26 (s, 1H), 9,21 (s, 1H), 8,12 (m, 1H), 7,65 (d, 1H, *J* = 1,32 Hz), 7,58 (d, 1H), J = 2,26 Hz), 7,48 (s, 1H), 7,07 (d, 2H, *J* = 8,29 Hz), 6,73-6,64 (m, 2H), 4,75 (m, 1H), 3,12 (m, 1H), 2,86-2,65 (m, 4H, parcialmente oscurecido por *N,N*-dimetilformamida), 1,35-1,25 (m, 9H).

EMCL: ($M+H^+$) 478,3, ($M+Na^+$) 500,3.

Ejemplo 157: (1*R*)-1-[(4-fluorofenil)metil]-2-oxo-2-[(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de 1,1-dimetiletilo



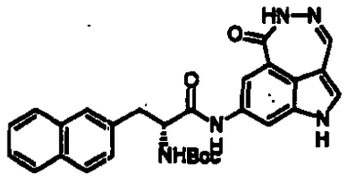
La preparación del ejemplo 157 a partir del compuesto del título del Ejemplo **2** (80 mg, 0,34 mmol), ácido (2*R*)-2-({[(1,1-dimetiletil)oxi]carbonil}amino)-3-(4-fluorofenil)-propanoico (145 mg, 0,51 mmol), trietilamina (0,142 ml, 1,02 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (193 mg, 0,51 mmol) en CH_2Cl_2 (0,5 ml) y *N,N*-dimetilformamida (0,5 ml) se realizó de forma análoga al Ejemplo **11**. La

purificación, también de manera análoga (eluida con 1:1 de hexano:acetona) proporcionó el compuesto del título (56 mg, 0,12 mmol) en forma de un polvo amarillo con un rendimiento del 35%.

^{1}H RMN (d_6-DMSO): δ 11,73 (s, 1H), 10,24 (s, 1H), 10,16 (s, 1H), 8,10 (s, 1H), 7,55 (s, 1H con suave división), 7,45 (s, 1H), (7,38-7,29 (m, 2H), 7,16-7,04 (m, 3H), 4,25 (m, 1H), 2,97 (m, 1H), 2,79 (m, 1H), 1,30 (s, 9H).

EMCL: ($M+H^+$) 466,2, ($M+Na^+$) 488,3.

Ejemplo 158: (1*R*)-1-(naftalen-2-ilmetil)-2-oxo-2-[(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]etilcarbamato de 1,1-dimetiletilo

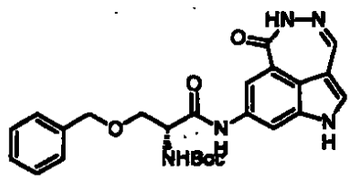


La preparación del ejemplo 158 a partir del compuesto del título del Ejemplo **2** (76 mg, 0,32 mmol), ácido (2*R*)-2-({[(1,1-dimetiletil)oxi]carbonil}amino)-3-naftalen-2-ilpropanoico (145 mg, 0,48 mmol), trietilamina (0,134 ml, 0,96 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluronio (182 mg, 0,48 mmol) en CH_2Cl_2 (0,5 ml) y *N,N*-dimetilformamida (0,5 ml) se realizó de forma análoga al Ejemplo **11**. La purificación, también de manera análoga (eluida con 1:1 de hexano:acetona) proporcionó el compuesto del título (67 mg, 0,13 mmol) en forma de un polvo amarillo con un rendimiento del 42%.

^{1}H RMN (d_6-DMSO): δ 11,73 (s a, 1H), 10,27 (s,1H), 10,27 (s a, 1H), 8,15 (s, 1H), 7,90-7,79 (m, 4H), 7,62-7,42 (m, 5H), 7,21 (d, 1H, *J* = 7,73 Hz), 4,43 (m, 1H), 3,18 (m, 1H), 3,02 (m, 1H), 1,29 (s, 9H).

EMCL: ($M+H^+$) 498,2, ($M+Na^+$) 520,2.

Ejemplo 159: (1*R*)-2-oxo-2-[(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)amino]-1-{[(fenilmetil)oxi]metil}etilcarbamato de 1,1-dimetiletilo

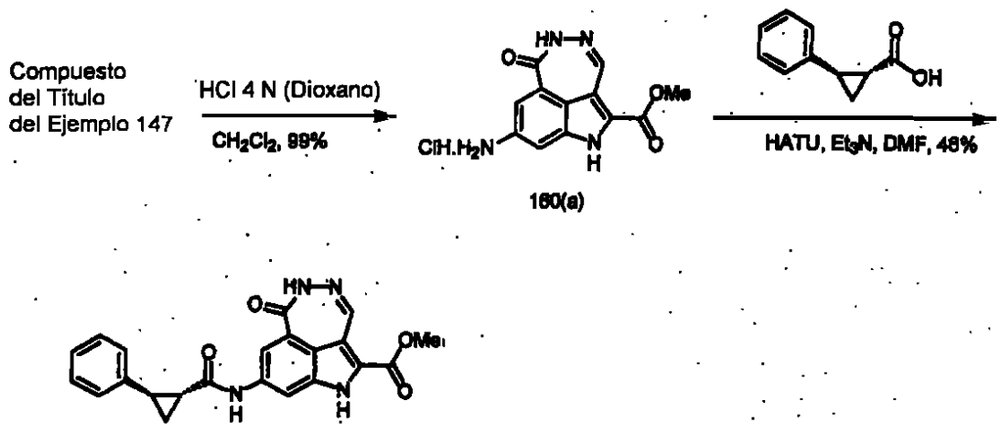


La preparación del ejemplo 159 a partir del compuesto del título del Ejemplo **2** (97 mg, 0,41 mmol), ácido (2*R*)-2-({[(1,1-dimetiletil)oxi]carbonil}amino)-3-[(fenilmetil)oxi]propanoico (182 mg, 0,62 mmol), trietilamina (0,171 ml, 1,23 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (236 mg, 0,62 mmol) en CH_2Cl_2 (0,5 ml) y *N,N*-dimetilformamida (0,5 ml) se realizó de forma análoga al Ejemplo **11**. La purificación, también de manera análoga (eluida con 1:1 de hexano:acetona) proporcionó el compuesto del título (40 mg, 0,083 mmol) en forma de un polvo amarillo con un rendimiento del 20%.

^{1}H RMN (d_6-DMSO): δ 11,78 (s a, 1H), 10,29 (s, 1H), 10,22 (s, 1H), 8,14 (s, 1H), 7,65 (s, 1H), 7,61 (s, 1H, con suave división), 7,75 (s, 1H), 7,38-7,26 (m, 4H), 7,08 (d, 1H, *J* = 6,02 Hz), 4,54 (s, 2H), 4,42 (m, 1H), 3,74-3,63 (m, 2H), 1,42 (s, 9H).

EMCL: ($M+H^+$) 478,3, ($M+Na^+$) 500,2.

Ejemplo 160: Éster metílico del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico



Etapa 1. Preparación de éster metílico del ácido 8-amino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico (sal clorhidrato) 160(a)

La preparación del intermedio 160(a) a partir del compuesto del título del Ejemplo **147** (45,0 mg, 0,125 mmol) y HCl 4,0 M en dioxano (0,32 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, proporcionó el Intermedio 160(a) (36,9 mg, 0,125 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

Etapa 2. Preparación del compuesto del título: éster metílico del ácido (1*R*,2*R*)-6-Oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico

La preparación del compuesto del título a partir del Intermedio 160(a) (36,9 mg, 0,125 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (22,0 mg, 0,136 mmol), trietilamina (0,175 ml, 1,26 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio (72,0 mg, 0,189 mmol) en *N*,*N*-dimetilformamida (2,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de acetato de etilo:hexano),

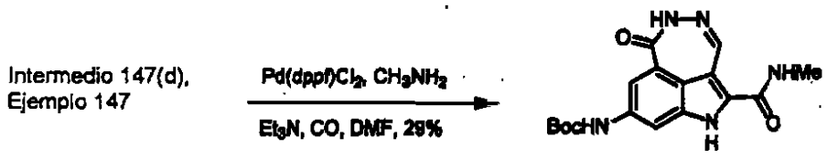
también de manera análoga, incluyó otra trituración con metanol y éter y proporcionó el compuesto del título (23 mg, 0,0572 mmol) en forma de un polvo amarillo con un rendimiento del 46%.

^{1}H RMN (d_6-DMSO): δ 12,53 (s, 1H), 10,83 (s, 1H), 10,58 (s, 1H), 8,23 (d, 1H, *J* = 1,51 Hz), 8,15 (s, 1H), 7,76 (d, 1H, *J* = 1,51 Hz), 7,37-7,25 (m, 2H), 7,25-7,14 (m, 3H), 3,93 (s, 3H), 2,45-2,35 (m, 1H), 2,15-2,05 (m, 1H), 1,58-1,47 (m, 1H), 1,45-1,33 (m, 1H).

EMCL: $(M+H^+)$ 403,3, $(M+Na^+)$ 425,1; $(M-H)^-$ 401,0.

EMAR: $(M+H^+)$ calculado para $C_{22}H_{19}N_4O_4$, 403,1406, encontrado 403,1413.

Ejemplo 161: Éster *terc*-butílico del ácido (2-metilcarbamoil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico

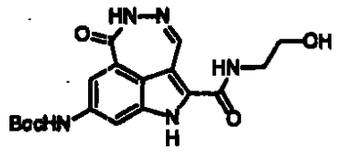


La preparación del ejemplo 161 se realizó de manera análoga a la etapa 5 del Ejemplo **147**, con la excepción de que se sustituyó por clorhidrato de metilamina el metanol. De esta manera, se burbujeó CO a través de una mezcla del Intermedio 147(d) del Ejemplo 147 (200 mg, 0,529 mmol), trietilamina (0,29 ml, 2,11 mmol), metilamina clorhidrato (71 mg, 1,06 mmol) y 1,1'-*bis*(difenilfosfino)ferrocenodicloropaladio (II) (86 mg, 0,106 mmol). Las condiciones de reacción, el tratamiento y la cromatografía sobre gel de sílice (eluida con 46:4:25 de diclorometano:metanol:acetato de etilo) también se realizaron de manera análoga y proporcionaron el compuesto del título (55 mg, 0,154 mmol) con un rendimiento del 29%.

^{1}H RMN (d_6-DMSO): δ 12,01 (s, 1H), 10,55 (s, 1H), 9,58 (s, 1H), 8,33-8,25 (m, 1H) 7,98 (s, 1H), 7,80 (s, 1H), 7,71 (d, 1H, *J* = 1,51 Hz), 2,81 (d, 3H, *J* = 4,52 Hz), 1,48 (s, 9H).

EMCL: ($M+H^+$) 358,3, ($M+Na^+$) 380,1; ($M-H^-$) 356,1.

Ejemplo 162: Éster *terc*-butílico del ácido [2-(2-hidroxi-etilcarbamoil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-carbámico

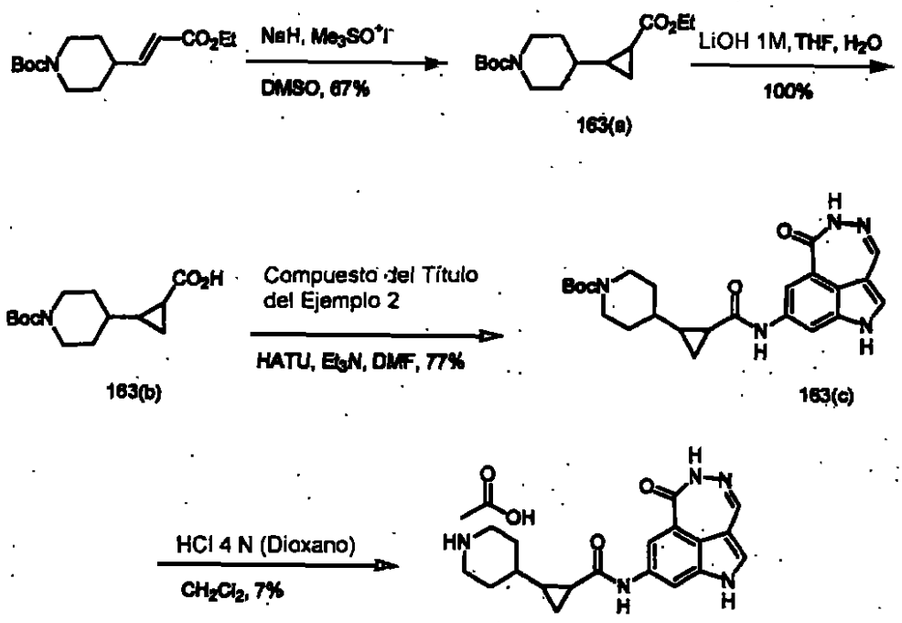


La preparación del ejemplo 162 se realizó de manera análoga a la etapa 5 del Ejemplo **147**, con la excepción de que se sustituyó por 2-aminoetanol el metanol y no se requirió cromatografía. De esta manera, se burbujeó CO a través de una mezcla del Intermedio 147(d) del Ejemplo 147 (60 mg, 0,16 mmol), trietilamina (0,044 ml, 0,32 mmol), 2-aminoetanol (19 mg, 0,32 mmol) y 1,1'-*bis*(difenilfosfino)ferrocenodicloropaladio (II) (26 mg, 0,032 mmol) en *N*,*N*-dimetilformamida (3,0 ml). Después de que se completara la reacción, la mezcla se filtró a través de tierra diatomácea. El filtrado se concentró y se añadió metanol. Los sólidos resultantes se recogieron por filtración y se lavaron con metanol, diclorometano y éter dietílico. Después de secar al vacío, se obtuvo el compuesto del título (24 mg, 0,062 mmol) en forma de un polvo amarillo con un rendimiento del 39%.

^{1}H RMN (d_6-DMSO): 8 12,08 (s, 1H), 10,56 (s, 1H), 9,58 (s, 1H), 8,30 (t, 1H, *J* = 5,84 Hz) 8,06 (s, 1H), 7,79 (s, 1H), 7,74 (s, 1H), 4,80 (s a, 1H), 3,60-3,48 (m, 2H), 3,38 (m, 2H, parcialmente oscurecido), 1,48 (s, 9H).

EMCL: ($M+H^+$) 388,1, ($M+Na^+$) 410,1.

Ejemplo 163: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piperidin-4-il-ciclopropanocarboxílico (sal del ácido acético)



Etapa 1. Preparación de éster *terc*-butílico del ácido 4-((1,2-*trans*)-2-etoxicarbonil-ciclopropil)-piperidin-1-carboxílico 163(a)

A una mezcla de NaH (303 mg, 7,57 mmol) y yoduro de trimetilsulfoxonio (1,67 g, 7,57 mmol) se le añadió dimetilsulfóxido (10 ml). Después de agitar durante 30 min, se añadió gota a gota una solución de éster *terc*-butílico del ácido 4-(2-etoxicarbonil-vinil)-piperidin-1-carboxílico en dimetilsulfóxido (5 ml). Después de agitar durante una noche, a la mezcla se le añadieron acetato de etilo y agua. La fase acuosa se extrajo varias veces con acetato de etilo. Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con acetato de etilo al 10%/hexano, dando el Intermedio 163(a) (1,16 g, 67%).

Etapa 2. Preparación de éster *terc*-butílico del ácido 4-((1,2-*trans*)-2-carboxi-ciclopropil)-piperidin-1-carboxílico 163(b)

A una mezcla del Intermedio 163(a) (555 mg, 1,87 mmol) en 3:1 de tetrahidrofurano-H_2O (12 ml) se le añadió LiOH acuoso 1 M (5,61 ml). La mezcla resultante se agitó durante una noche. Después, la mezcla se acidificó con HCl 1 M a pH 1 y se extrajo con varias veces con acetato de etilo. Después, las fases orgánicas combinadas se lavaron con salmuera y se concentraron, dando el Intermedio 163(b) (515 mg, 1,87 mmol) con rendimiento cuantitativo que se lleva a continuación sin purificación adicional.

Etapa 3. Preparación de éster *terc*-butílico del ácido 4-[(1,2-*trans*)-2-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-ciclopropil]-piperidin-1-carboxílico 163(c)

La preparación del Intermedio 163(c) a partir del compuesto del título del Ejemplo 2 (base libre) (374 mg, 1,87 mmol), el Intermedio 163(b) (500 mg, 1,87 mmol), trietilamina (0,31 ml, 2,24 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (782 mg, 2,06 mmol) en *N,N*-dimetilformamida (10 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con acetona al 40% en hexano), también de manera análoga, proporcionó el Intermedio 163(c) en forma de un polvo amarillo (649 mg, 1,44 mmol) con un rendimiento del 77%.

Etapa 4. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-piperidin-4-il-ciclopropanocarboxílico (sal del ácido acético)

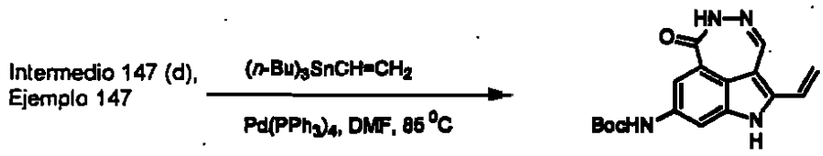
La preparación del compuesto del título a partir del Intermedio 163(c) (603 mg, 1,34 mmol) en CH_2Cl_2 (10 ml) y HCl 4 M en dioxano (10 ml) se realizó

de forma análoga al Ejemplo 91. Después de la concentración, el producto bruto se purificó por HPLC preparativa de manera análoga al Ejemplo **146**, Etapa 2, dando el compuesto del titulo en forma de un polvo amarillo pálido (37 mg, 0,09 mmol) con un rendimiento del 7%.

^{1}H RMN (d_6-DMSO): 11,71 (s, 1H), 10,26 (s, 1H), 10,23 (s, 1H), 8,11 (s, 1H), 7,55 (d, J = 8 Hz, 2H), 7,46 (s, 1H), 3,05-3,03 (m, 2H), 2,51 (m, 1H), 1,65-1,53 (m, 3H), 1,29-1,28 (m, 2H), 1,10 (m, 1H), 0,99 (m, 1H), 0,96 (m, 1H), 0,73 (m, 1H).

EMCL: $(M+H^+)$ 352.

Ejemplo 164:Éster *terc*-butílico del ácido (6-oxo-2-vinil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico

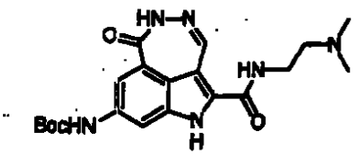


En una atmósfera de argón, el Intermedio 147(d) del Ejemplo **147** (0,250 g, 0,661 mmol), tributil-vinil-estaño (0,420 g, 1,32 mmol) y *tetraquis*(trifenilfosfina)paladio (0) (38 mg, 0,033 mmol) en *N,N*-dimetilformamida anhidra (5 ml) se calentaron a 85°C durante 16 horas. La reacción se filtró a través de un lote fino de tierra diatomácea y el filtrado se concentró al vacío. La cromatografía sobre gel de sílice (eluida con 1:4 de acetato de etilo:diclorometano) proporcionó el compuesto del título (0,18 g, 0,552 mmol) en forma de un polvo amarillo con un rendimiento del 84%.

^{1}H RMN (d_6-DMSO): δ 11,80 (s, 1H), 10,32 (s, 1H), 9,51 (s, 1H), 7,72-7,62 (m, 3H), 7,05 (dd, 1H, J = 11,37, 6,59 Hz), 5,89 (d, 1H, *J* = 17,33 Hz), 5,43 (d, 1H, *J* = 11,11 Hz), 1,49 (s, 9H).

EMCL: ($M+H^+$) 327,2, ($M+Na^+$) 349,1.

Ejemplo 165: Éster *terc*-butílico del ácido [2-(2-dimetilamino-etilcarbamoil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-carbámico

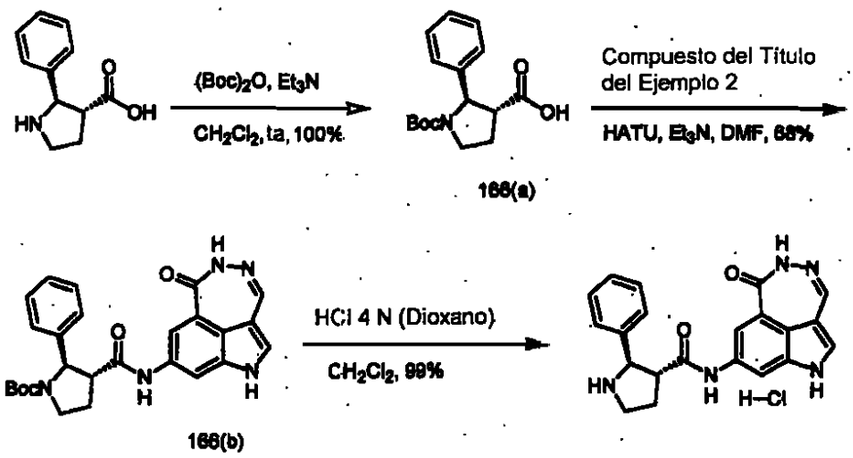


La preparación del ejemplo 165 se realizó de manera análoga a la etapa 5 del Ejemplo **147**, con la excepción de que se sustituyó por *N,N*-dimetiletilenodiamina el metanol. De esta manera, se burbujeó CO a través de una mezcla del Intermedio 147(d) del Ejemplo 147 (1,5 g, 3,97 mmol), trietilamina (1,1 ml, 7,92 mmol), *N,N*-dimetiletilenodiamina (0,7 g, 7,94 mmol) y 1,1'-*bis*(difenilfosfino)ferrocenodicloropaladio (II) (0,65 g, 0,796 mmol) en *N,N*-dimetilformamida (30,0 ml). Las condiciones de reacción, el tratamiento y la cromatografía sobre gel de sílice (eluida con 46:4:25 de diclorometano:metanol:acetato de etilo) también se realizaron de manera análoga y proporcionaron el compuesto del título (1,25 g, 3,02 mmol) con un rendimiento del 76%.

^{1}H RMN (d_6-DMSO): δ 10,55 (s, 1H), 9,59 (s, 1H), 8,25 (t, 1H, *J* = 5,65, 4,71 Hz) 8,06 (s, 1H), 7,80 (s; 1H), 7,74 (s, 1H), 3,45-3,37 (m, 2H, parcialmente oscurecido), 2,42 (t, 2H, *J* = 6,59, 6,41 Hz), 2,20 (s, 6H), 1,49 (s, 9H).

EMCL: ($M+H^+$) 415,3, ($M+Na^+$) 437,1; $(M-H)^-$ 413,1.

Ejemplo 166:(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*,3*R*)-2-fenil-pirrolidin-3-carboxílico (sal clorhidrato)



Etapa 1. Preparación de 1-*terc*-butil-éster del ácido 2-fenil-pirrolidin-1,3-dicarboxílico 166(a)

A una suspensión de ácido (2*R*,3*R*)-3-fenilpirrolidin-2-carboxílico (100 mg, 0,556 mmol) en dioxano (2 ml) y H_2O (2 ml) se le añadió trietilamina seguido de dicarbonato de di-*terc*-butilo (127 mg, 0,583 mmol). La mezcla resultante se agitó durante una noche. Después, la mezcla se repartió entre acetato de etilo y HCl 0,1 M. Las fases orgánicas combinadas se secaron sobre Na_2SO_4 anhidro, se filtraron y se concentraron, dando el Intermedio 166(a) (162 mg, 0,56 mmol) con un rendimiento del 100% que se lleva a continuación sin purificación.

Etapa 2. Preparación de éster *terc*-butílico del ácido 3-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-2-fenil-pirrolidin-1-carboxílico 166(b)

La preparación del intermedio 166(b) a partir del compuesto del título del Ejemplo 2 (300 mg, 1,0 mmol), el Intermedio 166(a) (162 mg, 0,56 mmol),

trietilamina (0,15 ml, 1,1 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (254 mg, 0,667 mmol) en *N,N*-dimetilformamida (10 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con acetona al 40% en hexano), también de manera análoga, proporcionó el Intermedio 166(b) en forma de un polvo amarillo (180 mg, 0,38 mmol) con un rendimiento del 68%.

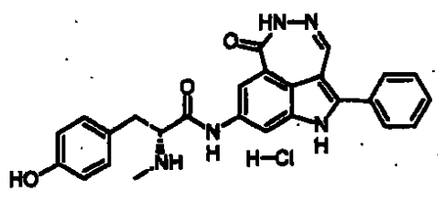
Etapa 3. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*,3*R*)-2-fenil-pirrolidin-3-carboxílico (sal clorhidrato)

La preparación del compuesto del título a partir del Intermedio 166(b) (180 mg, 0,38 mmol) en CH_2Cl_2 (5 ml) y HCl 4 M en dioxano (5 ml) se realizó de forma análoga al Ejemplo **91**. Los sólidos se recogieron por filtración y se lavaron con éter dietílico, dando el compuesto del título en forma de un polvo amarillo pálido (154 mg, 0,37 mmol) con un rendimiento del 99%.

^{1}H RMN (d_6-DMSO): 12,03 (s, 1H), 10,72 (s, 1H), 10,46 (s, 1H), 10,20 (s a, 1H), 9,24 (s a, 1H), 8,17 (s, 1H), 7,79 (d, *J* = 4,0 Hz, 1H), 7,69 (d, J = 4,0 Hz, 1H), 7,58-7,52 (m, 5H), 7,48 (m, 1H), 4,43 (m, 1H), 3,77 (c, J = 8,0 Hz, 1H), 3,75 (m, 1H), 3,59 (m, 1H), 2,66 (m, 1H), 2,62 (m, 1H).

EMCL: ($M+H^+$) 374,2.

Ejemplo 167: Clorhidrato de (2*R*)-3-(4-hidroxifenil)-2-(metilamino)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida

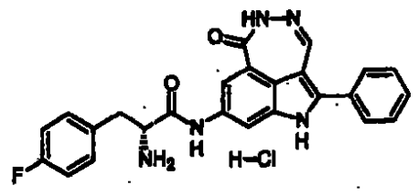


La preparación del ejemplo 167 a partir del compuesto del título del Ejemplo **151** (47 mg, 0,085 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, incluyó la basificación libre con trietilamina y la posterior cromatografía sobre gel de sílice eluyendo con 3:1:1 de hexano:acetato de etilo:etanol. Con refrigeración con un baño de hielo, la base libre purificada en CH_2Cl_2 (10 ml) se trató con HCl 4 M en dioxano (0,1 ml). Después de la retirada de los componentes volátiles, se obtuvo el compuesto del título (20 mg, 0,041 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 48%.

^{1}H RMN (d_6-DMSO): δ 12,21 (s, 1H), 10,70 (s, 1H), 10,43 (s, 1H), 9,44-9,06 (m, 1H), 8,02 (s, 1H), 7,72-7,64 (m, 2H), 7,61-7,54 (m, 3H), 7,53-7,47 (m, 2H) 7,05 (d, 2H, J = 8,0 Hz), 6,65 (d, 2H, *J* = 8,0 Hz), 4,09 (m, 1H), 3,40-3,31 (m, 2H), 3,16 (dd, 1H, *J* = 6,07, 13,90 Hz), 3,07 (dd, 1H, *J* = 7,58, 13,89 Hz), 2,55 (s,3H).

EMCL: ($M+H^+$) 454,1, ($M+Na^+$) 476,1.

Ejemplo 168:Clorhidrato de (2*R*)-2-amino-3-(4-fluorofenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida



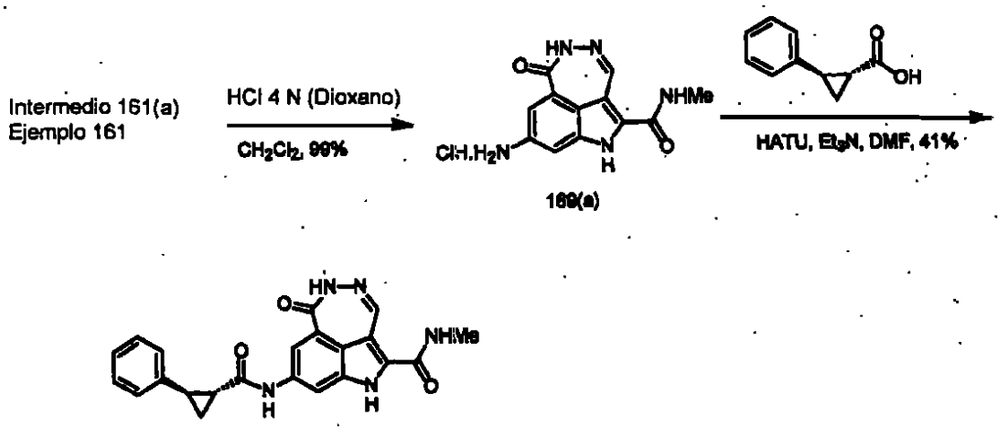
La preparación del ejemplo 168 a partir del compuesto del título del Ejemplo 152 (49 mg, 0,091 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó la basificación libre con trietilamina y la posterior cromatografía sobre gel de sílice eluyendo con 3:1:1 de hexano:acetato de etilo:etanol. Con

refrigeración con un baño de hielo, la base libre purificada en CH_2Cl_2 (10 ml) se trató con HCl 4 M en dioxano (0,1 ml). Después de la retirada de los componentes volátiles, se obtuvo el compuesto del título (21 mg, 0,044 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 49%.

^{1}H RMN (d_6-DMSO): δ 12,26 (s, 1H), 10,83 (s, 1H), 10,46 (s, 1H), 8,48 (s a, 3H), 8,08 (s, 1H), 7,73-7,48 (m, 7H), 7,40-7,30 (m, 2H), 7,24-7,13 (m, 2H), 4,22 (m, 1H), 3,24 (m, 1H), 3,13 (m, 1H).

EMCL: ($M+H^+$) 442,1, ($M+Na^+$) 464,1.

Ejemplo 169: Metilamida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico



Etapa 1. Preparación de metilamida del ácido 8-amino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico (sal clorhidrato) 169(a)

La preparación del intermedio 169(a) a partir de 161(a) del Ejemplo **161** (55,0 mg, 0,154 mmol) y HCl 4,0 M en dioxano (0,77 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga,

proporcionó el Intermedio 169(a) (45,0 mg, 0,154 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

^{1}H RMN (d_6-DMSO): δ 12,46 (s, 1H), 10,71 (s, 1H), 8,54 (m, 1H), 8,05 (s, 1H), 7,43 (s, 1H), 7,34 (s, 1H), 2,81 (s, 3H).

EMCL: ($M+H^+$) 258,1; ($M-H^-$) 256,1.

Etapa 2. Preparación del compuesto del título: metilamida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico

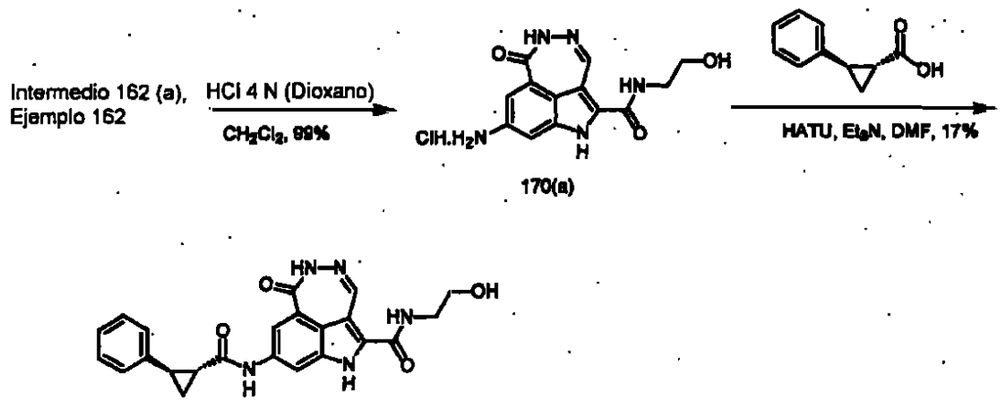
La preparación del compuesto del título a partir del Intermedio 169(a) (45,0 mg, 0,154 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (59,4 mg, 0,231 mmol), trietilamina (0,086 ml, 0,616 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (87,8 mg, 0,231 mmol) en *N,N*-dimetilformamida (2,0 ml) se realizó de forma análoga al Ejemplo **11**. Cuando se juzgó que la reacción se había completado, la *N,N*-dimetilformamida se evaporó y se añadió metanol. La mezcla se filtró para recoger los sólidos, que se lavaron con metanol y éter dietílico. Después de secar al vacío, se obtuvo el compuesto del título (25,0 mg, 0,0623 mmol) en forma de un polvo amarillo con un rendimiento del 41%.

^{1}H RMN (d_6-DMSO): δ 12,13 (s, 1H), 10,60 (s, 1H), 10,51 (s, 1H), 8,36 (d, 1H, J = 4,52 Hz), 8,17 (s, 1H), 8,01 (s, 1H), 7,70 (s, 1H), 7,37-7,25 (m, 2H), 7,25-7,14 (m, 3H), 2,83 (d, 3H, J = 4,52 Hz), 2,45-2,35 (m, 1H), 2,14-2,04 (m, 1H), 1,57-1,47 (m, 1H), 1,45-1,33 (m, 1H).

EMCL: ($M+H^+$) 402,1, ($M+Na^+$) 424,1.

EMAR: ($M+H^+$) calculado para $C_{22}H_{20}N_5O_3$, 402,1566, encontrado 402,1551.

Ejemplo 170: (2-Hidroxi-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico



Etapa 1. Preparación de (2-hidroxi-etil)-amida del ácido 8-amino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico (sal clorhidrato) 170(a)

La preparación del intermedio 170(a) a partir del intermedio 162(a) del Ejemplo **162** (80,0 mg, 0,206 mmol) y HCl 4,0 M en dioxano (1,10 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, proporcionó el Intermedio 170(a) (66,7 mg, 0,206 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

EMCL: ($M+H^+$) 288,2.

Etapa 2. Preparación del compuesto del título: (2-hidroxi-etil)-amida del ácido (1*R*,2*R*)-6-Oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico

La preparación del compuesto del título a partir del Intermedio 170(a) (66,7 mg, 0,206 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (46,0 mg, 0,284 mmol), trietilamina (0,143 ml, 1,03 mmol) y hexafluorofosfato de *O*-(7-

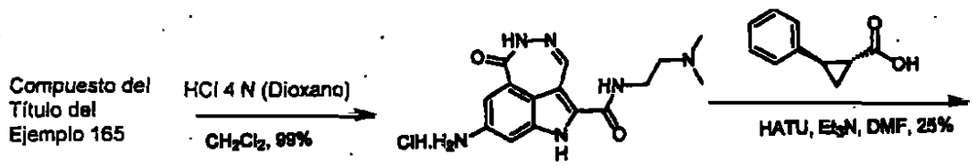
azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (147 mg, 0,387 mmol) en *N,N*-dimetilformamida (2,0 ml) se realizó de forma análoga al Ejemplo **11.** La mezcla de reacción se redujo en volumen y se sometió a HPLC preparativa (H1-Q C18 de fase inversa 5 μM, 100A, columna de 150 x 20 eluyendo con CH_3CN/ácido acético al 0,1% en H_2O a un caudal de 20 ml/min usando un gradiente de CH_3CN al 20-60% durante 30 min), proporcionando el compuesto del título (15 mg, 0,0348 mmol) en forma de un polvo amarillo con un rendimiento del 17%.

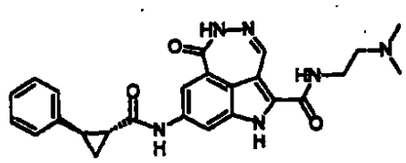
^{1}H RMN (d_6-DMSO): δ 12,19 (s, 1H), 10,61 (s, 1H), 10,52 (s, 1H), 8,36 (t, 1H, *J* = 5,65 Hz), 8,18 (d, 1H, J = 1,70 Hz), 8,09 (s, 1H), 7,70 (d, 1H, J = 1,70 Hz), 7,35-7,26 (m, 2H), 7,25-7,16 (m, 3H), 4,82 (t, 1H, *J* = 5,46 Hz), 3,54 (dd, 2H, *J* = 5,84, 5,65 Hz), 3,43-3,32 (m, 2H), 2,45-2,35 (m, 1H), 2,14-2,04 (m, 1H), 1,57-1,47 (m, 1H), 1,44-1,33 (m, 1H).

EMCL: ($M+H^+$) 432,0, ($M+Na^+$) 454,0.

EMAR: ($M+H^+$) calculado para $C_{23}H_{22}N_5O_4$, 432,1672, encontrado 432,1648.

Ejemplo 171: (2-dimetilamino-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico





Etapa 1. Preparación de (2-dimetilamino-etil)-amida del ácido 8-amino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico; diclorhidrato 171 (a)

La preparación del intermedio 171(a) a partir del compuesto del título del Ejemplo **165** (55,0 mg, 0,133 mmol) y HCl 4,0 M en dioxano (0,66 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, proporcionó el Intermedio 171 (a) (51,3 mg, 0,132 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

EMCL: $(M+H^+)$ 315,2.

Etapa 2. Preparación del compuesto del título: (2-dimetilamino-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-cd]indol-2-carboxílico

La preparación del compuesto del título a partir del Intermedio 171(a) (51,3 mg, 0,132 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (24,0 mg, 0,148 mmol), trietilamina (0,074 ml, 0,535 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (76,0 mg, 0,200 mmol) en *N,N*-dimetilformamida (2,0 ml) se realizó de forma análoga al Ejemplo **11**. La mezcla de reacción se redujo en volumen y se sometió a HPLC preparativa (H1-Q C18 de fase inversa 5 µM, 100A, columna de 150 x 20 eluyendo con CH_3CN/ácido acético al 0,1% en H_2O a un caudal de 20 ml/min usando un gradiente de CH_3CN al 20-60% durante 30 min), proporcionando el compuesto del título (15 mg, 0,0328 mmol) en forma de un polvo amarillo-verde con un rendimiento del 25%.

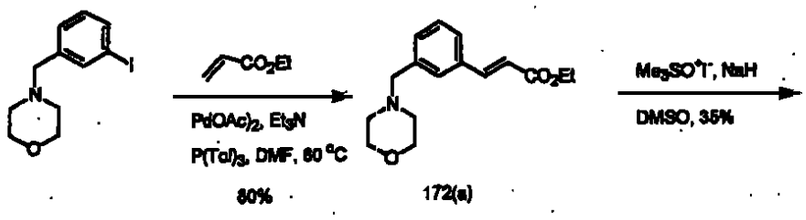
^{1}H RMN (d_6-DMSO): δ 10,63 (s, 1H), 10,53 (s, 1H), 8,71 (s a, 1H), 8,20 (d, 1H, *J* = 1,13 Hz), 8,06 (s, 1H), 7,70 (d, 1H, *J* = 0,94 Hz), 7,37-7,26 (m, 2H),

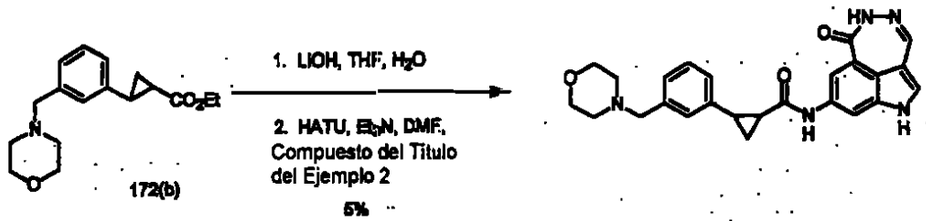
7,26-7,15 (m, 3H), 3,70-3,60 (m, 2H), 3,22-3,11 (m, 2H), 2,76 (s, 6H), 2,42-2,32 (m, 1H), 2,16-2,04 (m, 1H), 1,58-1,46 (m, 1H), 1,46-1,33 (m, 1H).

EMCL: $(M+H^+)$ 459,1, $(M+Na^+)$ 481,1.

EMAR: $(M+H^+)$ calculado para $C_{25}H_{27}N_6O_3$, 459,2145, encontrado 459,2151.

Ejemplo 172: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-morfolin-4-ilmetil-fenil)-ciclopropanocarboxílico





Etapa 1. Preparación de éster etílico del ácido 3-(3-morfolin-4-ilmetil-fenil)-acrílico 172(a)

A una solución de 4-(3-yodo-bencil)-morfolina (3,44 g, 11,4 mmol) en *N,N*-dimetilformamida (20 ml) se le añadieron trietilamina (1,7 ml, 12,5 mmol), acrilato de etilo (4,1 ml, 45,4 mmol), tri-*o*-tolilfosfina (346 mg, 1,14 mmol) y acetato de paladio (II) (127 mg, 0,57 mmol). La mezcla se calentó a 80°C durante una noche. Después de la concentración, la mezcla se cromatografió

sobre gel de sílice, proporcionando el Intermedio 172(a) en forma de un aceite incoloro (2,37 g, 9,1 mmol) con un rendimiento del 80%.

Etapa 2. Preparación de éster etílico del ácido (1,2-*trans*)-2-(3-morfolin-4-ilmetil-fenil)-ciclopropanocarboxílico 172(b)

La preparación del intermedio 172(b) a partir del Intermedio 172(a) (472 mg, 1,81 mmol), NaH (94 mg, 2,35 mmol) y yoduro de trimetilsulfoxonio (517 mg, 2,35 mmol) se realizó de manera análoga a la etapa 1 del Ejemplo **181**. Después del tratamiento, el residuo se purificó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo al 40%/hexano, dando el Intermedio 172(b) en forma de un aceite incoloro (175 mg, 0,64 mmol) con un rendimiento del 35%.

Etapa 3. Preparación del compuesto del título (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-morfolin-4-ilmetil-fenil)-ciclopropanocarboxílico

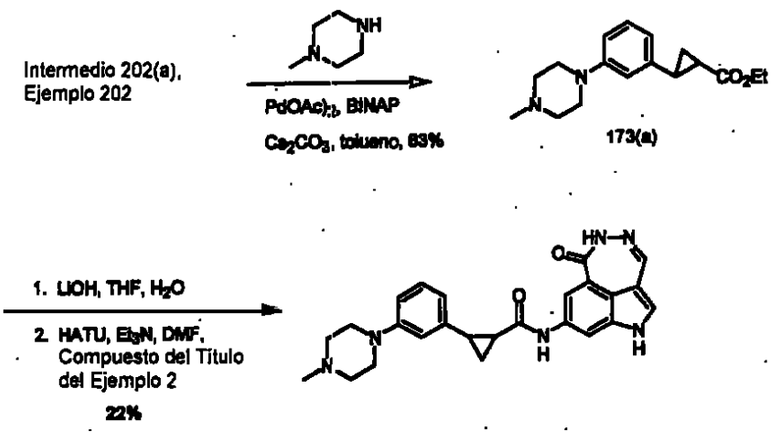
A una solución del Intermedio 172(b) (175 mg, 0,64 mmol) en tetrahidrofurano (2 ml) se le añadió LiOH acuoso 1 M (3,8 ml, 3,8 mmol). La mezcla resultante se agitó durante una noche, tras lo cual la mezcla se acidificó a pH 2 y se extrajo con acetato de etilo. La concentración de la fase orgánica dio ácido 2-(3-morfolin-4-ilmetil-fenil)-ciclopropanocarboxílico bruto que se combinó con el compuesto del título del Ejemplo 2 (227 mg, 0,756 mmol), trietilamina (0,32 ml, 2,27 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (345 mg, 0,907 mmol) en *N,N*-dimetilformamida (5 ml). Después de agitar durante una noche, los componentes volátiles se retiraron al vacío y el residuo se purificó por cromatografía sobre gel de sílice,

dando el compuesto del título en forma de un sólido amarillo (15 mg, 0,03 mmol) con un rendimiento del 5%.

^{1}H RMN (CD_3OD): δ 8,30 (s, 1H), 7,69 (s, 1H), 7,61 (s, 2H), 7,51-7,28 (m, 4H), 3,84 (s, 4H), 3,66 (s, 2H), 2,61 (s, 4H), 2,45 (m, 1H), 2,21 (m, 1H), 1,76 (m, 1H), 1,53 (m, 1H).

EMCL: ($M+H^+$) 444,2

Ejemplo 173: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-[3-(4-metil-piperazin-1-il)-fenil]-ciclopropanocarboxílico



Etapa 1. Preparación de éster etílico del ácido 2-[3-(4-metil-piperazin-1-il)-fenil]-ciclopropanocarboxílico 173(a)

A una solución del Intermedio 202(a) del Ejemplo **202** (165 mg, 0,616 mmol) en tolueno (4 ml) se le añadieron 2,2'-*bis*(difenilfosfino)-1,1'-binaftilo (34,5 mg, 0,055 mmol), 4-metilpiperazina (0,082 ml, 0,74 mmol), Cs_2CO_3 (281 mg, 0,862 mmol) y $Pd(OAc)_2$ (8,3 mg, 0,037 mmol). La mezcla se calentó a reflujo durante una noche. Después, la mezcla parda se filtró y la torta de filtro se lavó con acetato de etilo. Después de concentrar el filtrado, el residuo se purificó por cromatografía sobre gel de sílice, eluyendo con MeOH al 2-

5%/CH_2Cl_2, proporcionando el Intermedio 173(a) en forma de un aceite incoloro (111 mg, 0,39 mmol) con un rendimiento del 63%.

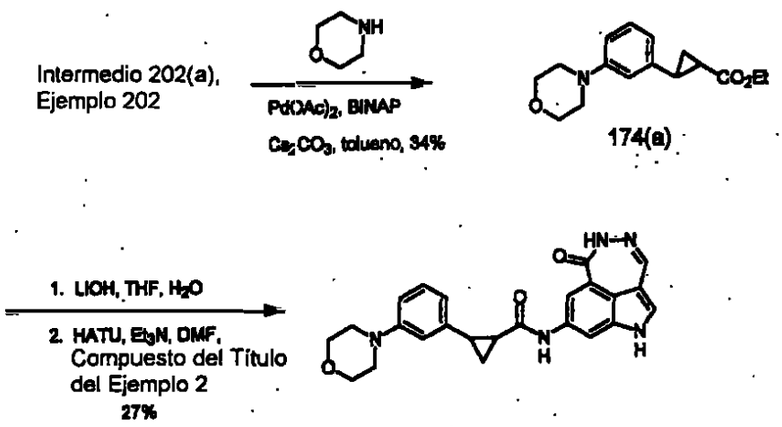
Etapa 2: Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-[3-(4-metil-piperazin-1-il)-fenil]-ciclopropanocarboxílico

De manera similar a la descrita para la etapa 3 del Ejemplo **172**, el Intermedio 173(a) se trató con LiOH acuoso 1 M, dando ácido 2-[3-(4-metil-piperazin-1-il)-fenil]-ciclopropanocarboxílico bruto. El ácido 2-[3-(4-metil-piperazin-1-il)-fenil]-ciclopropanocarboxílico bruto se acopló al compuesto del título del Ejemplo 2 (71 mg, 0,3 mmol) también de manera similar a la descrita para la etapa 3 del Ejemplo **172**. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso produjo el producto bruto, que se purificó por cromatografía sobre gel de sílice, eluyendo con MeOH al 3%/CH_2Cl_2, formando el compuesto del título (38 mg, 0,086 mmol) con un rendimiento del 22%.

^{1}H RMN (d_6-DMSO): δ 11,70 (s, 1H), 10,38 (s, 1H), 10,23 (s, 1H), 8,13 (s, 1H), 7,59 (s, 1H), 7,56 (s, 1H), 7,47 (s, 1H), 7,13 (m, 1H), 6,79-6,74 (m, 2H), 6,58 (m, 1H), 3,22-3,12 (m, 4H), 2,51-2,47 (m, 4H), 2,33 (m, 1H), 2,27 (s, 3H), 2,08 (m, 1H), 1,46 (m, 1H), 1,36 (m, 1H).

EMCL: ($M+H^+$) 443,2

Ejemplo 174: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-morfolin-4-il-fenil)-ciclopropanocarboxílico



Etapa 1. Preparación de éster etílico del ácido 2-[3-morfolin-4-il)-fenil]-ciclopropanocarboxílico 174(a)

La preparación del intermedio 174(a) a partir del Intermedio 202(a) del Ejemplo **202** (239 mg, 0,892 mmol), 2,2'-*bis*(difenilfosfino)-1,1'-binaftilo (50 mg, 0,081 mmol), morfolina (0,12 ml, 1,34 mmol), Cs_2CO_3 (407 mg, 1,25 mmol) y $Pd(OAc)_2$ (12 mg, 0,054 mmol) en tolueno (5 ml) se realizó de forma análoga al Ejemplo **173**. Después de la concentración, el residuo se purificó por cromatografía sobre gel de sílice, eluyendo con MeOH al 1-2%/CH_2Cl_2, proporcionando el Intermedio 174(a) en forma de un aceite incoloro (84 mg, 0,31 mmol) con un rendimiento del 34%.

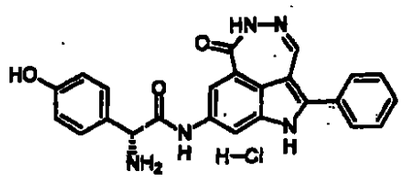
Etapa 2. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-morfolin-4-il-fenil)-ciclopropanocarboxílico

La preparación del compuesto del título se realizó de manera análoga a la etapa 3 del Ejemplo **172** con la excepción de que se usó Intermedio 174(a) en lugar de Intermedio 172(b). Se obtuvo el compuesto del título con un rendimiento del 27%.

^{1}H RMN (d_6-DMSO): δ 10,37 (d, 1H, J = 2,26 Hz), 10,24 (s, 1H), 8,24 (d, 1H, *J* = 1,88 Hz), 7,58 (d, 1H, *J* = 1,51 Hz), 7,56 (d, 1H, J = 3,30 Hz), 7,47 (s, 1H), 7,15 (t, *J* = 8,0 Hz, 1H), 6,79-6,77 (m, 2H), 6,61 (d, 1H, *J* = 8,0 Hz), 3,74-3,72 (m, 4H), 2,23 (m, 1H), 2,07 (m, 1H), 1,46 (m, 1H), 1,38 (m, 1H).

EMCL: ($M+H^+$) 430,2

Ejemplo 175: Clorhidrato de (2*R*)-2-amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida

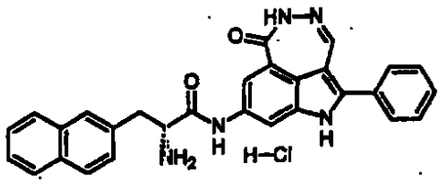


La preparación del ejemplo 175 a partir del compuesto del título del Ejemplo **153** (38 mg, 0,072 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, incluyó la basificación libre con trietilamina y la posterior cromatografía sobre gel de sílice eluyendo con 3:1:1 de hexano:acetato de etilo:etanol. Con refrigeración con un baño de hielo, la base libre purificada en CH_2Cl_2 (10 ml) se trató con HCl 4 M en dioxano (0,1 ml.). Después de la retirada de los componentes volátiles, se obtuvo el compuesto del título (20 mg, 0,043 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 60%.

^{1}H RMN (d_6-DMSO): δ 12,23 (s, 1H), 10,82 (s, 1H), 10,45 (s, 1H), 8,71 (s a, 3H), 8,10 (s, 1H), 7,75-7,65 (m, 3H), 7,63-7,49 (m, 4H), 7,43 (d, 2H, *J* = 8,47 Hz), 6,86 (d, 2H, *J* = 8,47 Hz), 5,02 (m, 1H).

EMCL: ($M+H^+$) 426,2.

Ejemplo 176: Clorhidrato de (2*R*)-2-amino-3-naftalen-2-il-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida

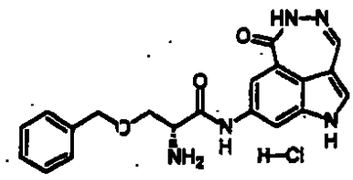


La preparación del ejemplo 176 a partir del compuesto del título del Ejemplo **154** (59 mg, 0,103 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga proporcionó el compuesto del título (52 mg, 0,102 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 99%.

^{1}H RMN (d_6-DMSO): δ 12,24 (s, 1H), 10,82 (s, 1H), 10,44 (s, 1H), 8,43 (s a, 3H), 8,07 (s, 1H), 7,93-7,81 (m, 5H), 7,71-7,45 (m, 9H), 4,32 (s a, 1H), 3,44 (m, 1H, parcialmente oscurecido), 3,28 (m, 1H).

EMCL: ($M+H^+$) 474,2, ($M+Na^+$) 496,3.

Ejemplo 177: Clorhidrato de (2*R*)-2-amino-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-[(fenilmetil)oxi]propanamida



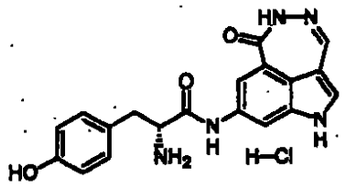
La preparación del ejemplo 177 a partir del compuesto del título del Ejemplo **159** (35 mg, 0,072 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga proporcionó el compuesto del título (30 mg, 0,072 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 100%.

^{1}H RMN (d_6-DMSO): δ 11,89 (s, 1H), 10,75 (s, 1H), 10,32 (s, 1H), 8,45 (s a, 3H), 8,06 (s, 1H), 7,63 (s, 2H), 7,50 (s, 1H), 7,38-7,26 (m, 5H), 4,59 (dd, 2H,

J = 12,25, 17,33 Hz), 4,24 (s a, 1H), 3,89 (d, 2H, J = 4,15 Hz, parcialmente oscurecido).

EMCL: (M+H$^+$) 378,2, (M+Na$^+$) 400,1.

Ejemplo 178: Clorhidrato de (2*R*)-2-amino-3-(4-hidroxifenil)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida

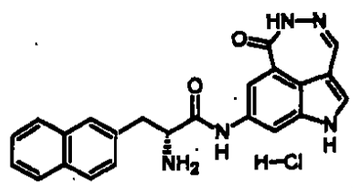


La preparación del ejemplo 178 a partir del compuesto del título del Ejemplo **155** (90 mg, 0,194 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga proporcionó el compuesto del título (56 mg, 0,140 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 72%.

^{1}H RMN (d$_6$-DMSO): δ 11,89 (s, 1H), 10,70 (s, 1H), 10,30 (s, 1H), 9,38 (s a, 1H), 8,34 (s a, 3H), 8,03 (s, 1H), 7,62 (s, 1H), 7,58 (s, 1H), 7,49 (s, 1H), 7,08 (d, 2H, J = 8,29 Hz), 6,70 (d, 2H, J = 8,29 Hz), 4,11 (s a, 1H), 2,93-3,15 (m, 2H).

EMCL: (M+Na$^+$) 386,5, (M-H$^-$) 362,4.

Ejemplo 179: Clorhidrato de (2*R*)-2-amino-3-naftalen-2-il-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida

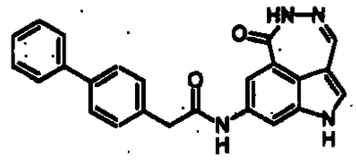


La preparación del ejemplo 179 a partir del compuesto del título del Ejemplo **158** (57 mg, 0,115 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga proporcionó el compuesto del título (48 mg, 0,111 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 97%.

^{1}H RMN (d_6-DMSO): δ 11,88 (s, 1H), 10,82 (s, 1H), 10,30 (s, 1H), 8,43 (s a, 3H), 8,04 (s, 1H), 7,93-7,78 (m, 4H), 7,64-7,57 (m, 2H), 7,54-7,45 (m, 4H), 4,32 (s a, 1H), 3,22-3,46 (m, 2H, parcialmente oscurecido).

EMCL: ($M+H^+$) 398,5, ($M+Na^+$) 420,4.

Ejemplo 180: 2-(1,1'-Bifenil-4-il)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida

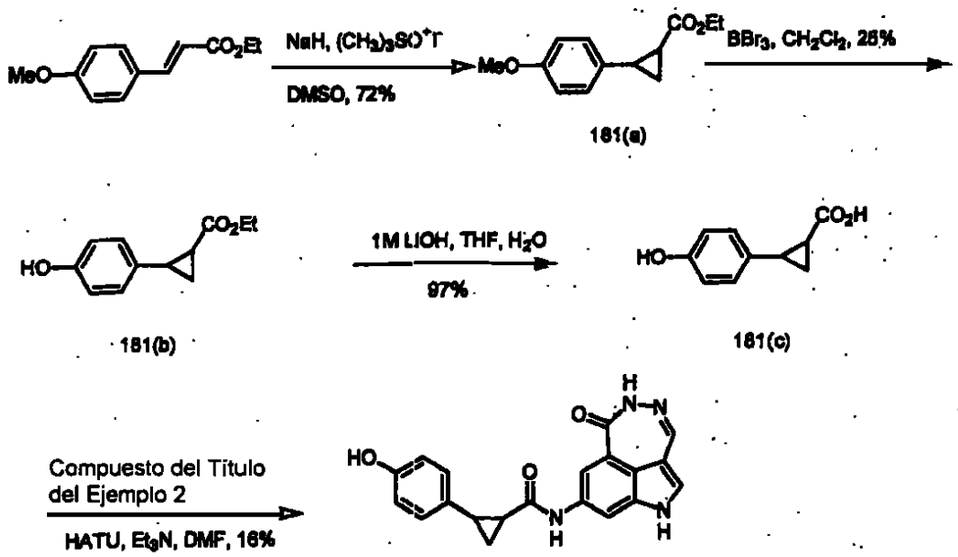


La preparación del ejemplo 180 a partir del compuesto del título del Ejemplo 2 (75 mg, 0,38 mmol), ácido 1,1'-bifenil-4-ilacético (93 mg, 0,44 mmol), trietilamina (0,16 ml, 1,15 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (167 mg, 0,44 mmol) en CH_2Cl_2 (1,0 ml) y *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice se realizó dos veces eluyendo ambas veces con 1:1 de hexano:acetona y las fracciones más puras se combinaron, se evaporaron y los sólidos resultantes se trituraron con metanol, proporcionando el compuesto del título (5 mg, 0,012 mmol) en forma de un polvo amarillo con un rendimiento del 3%.

^{1}H RMN (d_6-DMSO): δ 11,74 (s, 1H), 10,35 (s, 1H), 10,25 (s, 1H), 8,14 (s, 1H), 7,69-7,54 (m, 6H), 7,51-7,33 (m, 6H), 3,69 (s, 2H).

EMCL: ($M+H^+$) 395,4, ($M+Na^+$) 417,4.

Ejemplo 181: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico



Etapa 1. Preparación de éster etílico del ácido (1,2-*trans*)-2-(4-metoxi-fenil)-ciclopropanocarboxílico 181 (a)

A una mezcla de NaH (200 mg, 5,0 mmol) y yoduro de trimetilsulfoxonio (1,1 g, 5,0 mmol) se le añadió DMSO (10 ml). Después de agitar durante 30 min, se añadió gota a gota una solución de éster etílico del ácido 3-(4-metoxi-fenil)-acrílico (400 mg, 1,92 mmol) en DMSO (5 ml). Después de agitar durante una noche, la mezcla se repartió entre acetato de etilo y agua. La fase acuosa se extrajo de nuevo con acetato de etilo y las fases orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron. La purificación por cromatografía

sobre gel de sílice eluyendo con acetato de etilo al 10% en hexano dio el Intermedio 181 (a) (318 mg, 1,44 mmol) con un rendimiento del 72%.

Etapa 2. Preparación de éster etílico del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico 181 (b)

A una solución agitada del Intermedio 181(a) (318 mg, 1,45 mmol) en CH_2Cl_2 (8 ml) a -78°C se le añadió BBr_3 1 M en CH_2Cl_2 (1,7 ml). Después, la mezcla resultante se calentó a 23°C y se agitó durante 30 min. La mezcla se inactivó con $NaHCO_3$ saturado acuoso y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre Na_2SO_4 anhidro, se filtró, se concentró y se sometió a cromatografía sobre gel de sílice eluyendo con acetato de etilo al 15% en hexano, proporcionando el Intermedio 181(b) en forma de un aceite incoloro (75 mg, 0,364 mmol) con un rendimiento del 25%.

Etapa 3. Preparación de ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico 181(c)

A una solución agitada del Intermedio 181(b) (75 mg, 0,36 mmol) en tetrahidrofurano (2,5 ml) se le añadió LiOH acuoso 1 M (2,5 ml). La mezcla resultante se agitó a 23°C durante 12 horas. Después, la mezcla se acidificó con HCl 1 M a pH 1 y se extrajo con acetato de etilo. Después, la fase orgánica se lavó con salmuera y se concentró, dando el Intermedio 181(c) (63 mg, 0,35 mmol) con un rendimiento del 97% que se lleva a continuación sin purificación adicional.

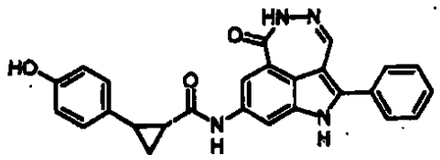
Etapa 4. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico

La preparación del compuesto del título a partir del compuesto del título del Ejemplo 2 (66 mg, 0,278 mmol), el Intermedio 181(c) (62 mg, 0,348 mmol), trietilamina (0,073 ml, 0,52 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (159 mg, 0,42 mmol) en *N,N*-dimetilformamida (2 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con metanol al 2% en CH_2Cl_2), también de manera análoga, proporcionó el compuesto del título (20 mg, 0,056 mmol) en forma de un polvo amarillo con un rendimiento del 16%.

^{1}H RMN (d_6-DMSO): 12,09 (s, 1H), 10,38 (s, 1H), 10,37 (s, 1H), 9,26 (s a, 1H), 8,16 (s, 1H), 7,65-7,67 (m, 2H), 7,58 (t, *J* = 8,0 Hz, 1H), 7,50 (s, 1H), 7,00 (d, J = 8,0 Hz, 2H), 6,70 (d, *J* = 8,0 Hz, 2H), 2,33 (m, 1H), 1,98 (m, 1H), 1,43 (m, 1H), 1,24 (m, 1H).

EMCL: ($M+H^+$) 361,3.

Ejemplo 182: (6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico



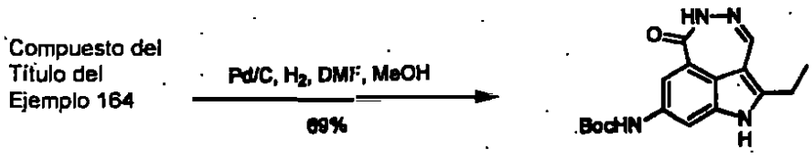
La preparación del ejemplo 182 a partir del compuesto del título del Ejemplo 7 (35 mg, 0,127 mmol), el Intermedio 181(c) del Ejemplo 181 (66 mg, 0,372 mmol), trietilamina (0,062 ml, 0,45 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (156 mg, 0,41 mmol) en *N,N*-dimetilformamida (3 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con metanol al 2% en CH_2Cl_2),

también de manera análoga, dio el compuesto del título (32 mg, 0,073 mmol) en forma de un polvo amarillo con un rendimiento del 20%.

^{1}H RMN (d_4-metanol): 8,04 (s, 1H), 7,44 (s, 1H), 7,35 (s, 1H), 7,34 (s, 1H), 6,91 (d, *J* = 9,0 Hz, 2H), 6,62 (d, J = 9,0 Hz, 2H), 2,31 (m, 1H), 1,87 (m, 1H), 1,43 (m, 1H), 1,24 (m, 1H).

EMCL: ($M+H^+$) 437,4.

Ejemplo 183: Éster *terc*-butílico del ácido (2-etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico

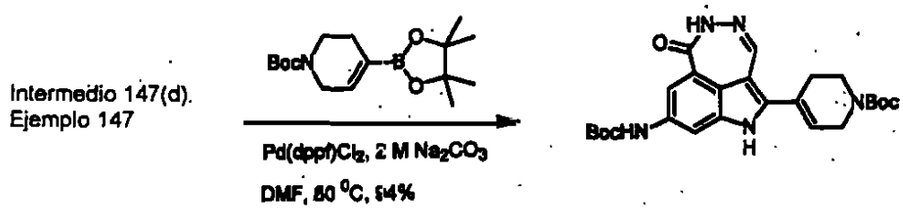


Se añadió paladio (al 10% sobre carbono activado) (0,23 g, 0,198 mmol) a una solución del compuesto del título del Ejemplo **164** (0,65 g, 1,99 mmol) en 1:10 de *N,N*-dimetilformamida:metanol (11 ml). La mezcla de reacción se purgó con H_2 y se agitó a temperatura ambiente en una atmósfera de H_2 (1 atm) durante 5 horas. El paladio se filtró y los componentes volátiles se retiraron al vacío. El residuo resultante se disolvió en metanol y se cagó en un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1,2:1 de diclorometano:acetato de etilo, proporcionando el compuesto del título (0,45 g, 1,37 mmol) en forma de un sólido amarillo con un rendimiento del 69%.

^{1}H RMN (d_6-DMSO): δ 11,54 (s, 1H), 10,05 (s, 1H), 9,37 (s, 1H), 7,63 (s, 1H), 7,58 (s, 1H), 7,44 (s, 1H), 2,80 (dd, 2H, *J* = 7,35, 7,54 Hz), 1,48 (s, 9H), 1,23 (t, 3H, *J* = 7,54 Hz).

EMCL: ($M+H^+$) 329,5, ($M+Na^+$) 351,5; $(M-H)^-$ 327,4.

Ejemplo 184: Éster *terc*-butílico del ácido 4-(8-*terc*-butoxicarbonilamino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il)-3,6-dihidro-2H-piridina-1-carboxílico



En una atmósfera de argón, se añadió Na_2CO_3 acuoso 2,0 M (0,66 ml) a una mezcla del Intermedio 147(d) del Ejemplo **147** (100 mg, 0,265 mmol), éster *terc*-butílico del ácido 4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-3,6-dihidro-2*H*-piridina-1-carboxílico (122 mg, 0,395 mmol) y [1,1'-*bis*(difenilfosfino)ferroceno]dicloropaladio (II) (10,8 mg, 0,013 mmol) en *N,N*-dimetilformamida anhidra (5 ml). La mezcla se calentó a 80°C durante 16 horas. La reacción se filtró a través de un lote fino de tierra diatomácea y los componentes volátiles se retiraron al vacío. La cromatografía sobre gel de sílice (eluida con 1:1 de acetato de etilo:hexano) produjo el compuesto del título (120 mg, 0,249 mmol) en forma de un polvo amarillo con un rendimiento del 94%.

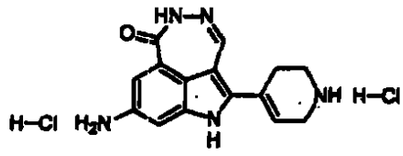
^{1}H RMN (d_6-DMSO): δ 11,62 (s, 1H), 10,22 (s, 1H), 9,46 (s, 1H), 7,69 (s, 1H), 7,65 (d, 1H, J = 1,70 Hz), 7,49 (s, 1H), 6,16 (s, 1H), 4,06 (s, 2H), 3,56 (t, 2H, *J* = 5,65, 4,90 Hz), 3,31 (m, 2H, parcialmente oscurecido), 1,49 (s, 9H), 1,44 (s, 9H).

EMCL: $(M+H^+)$ 482,5, $(M+Na^+)$ 504,5; $(M-H)^-$ 480,5.

EMAR: $(M+H^+)$ calculado para $C_{25}H_{32}N_5O_5$, 482,2403, encontrado 482,2417.

El material de partida éster *terc*-butílico del ácido 4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-3,6-dihidro-2H-piridina-1-carboxílico se preparó de acuerdo con Eastwood, P.R. (2000) Tetrahedron Letters 41 (19): 3705-3708 a partir de 1-*terc*-butoxicarbonil-1,2,3,6-tetrahidropiridin-4-il-éster del ácido trifluorometanosulfónico que a su vez se preparó de acuerdo con el procedimiento indicado por Barrow, J. C. y col., (2000) J. Med. Chem. 43 (14) 2703-2718.

Ejemplo 185: 8-Amino-2-(1,2,3,6-tetrahidro-piridin-4-il)-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona



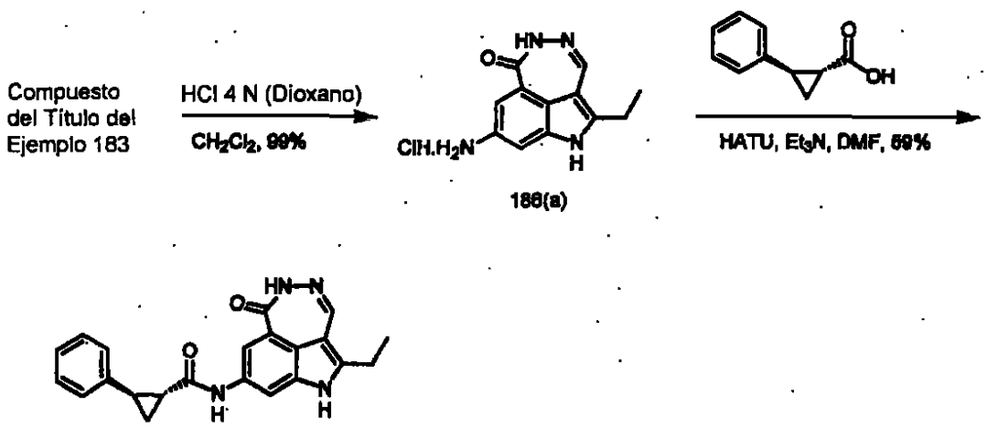
La preparación del ejemplo 185 a partir del compuesto del título del Ejemplo **184** (20 mg, 0,042 mmol) y HCl 4,0 M en dioxano (0,1 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, proporcionó el compuesto del título (14,7 mg, 0,042 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

^{1}H RMN (d_6-DMSO): δ 12,20 (s a, 1H), 10,46 (s, 1H), 9,14 (s, 3H), 7,57 (s, 1H), 7,36 (s, 2H), 6,22 (s, 1H), 3,83 (s, 2H), 3,36 (s, 2H), 2,74 (s, 2H).

EMCL: ($M+Na^+$) 304,3; $(M-H)^-$ 280,2.

EMAR: ($M+H^+$) calculado para $C_{15}H_{16}N_5O$, 282,1355, encontrado 282,1349.

Ejemplo 186: (2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



Etapa 1. Preparación de 8-amino-2-etil-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona (sal clorhidrato) 186(a)

La preparación del intermedio 186(a) a partir del compuesto del título del Ejemplo **183** (120 mg, 0,366 mmol) y HCl 4,0 M en dioxano (0,92 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, proporcionó el Intermedio 186(a) (95,5 mg, 0,366 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

EMCL: $(M+H^+)$ 229,1.

Etapa 2. Preparación del compuesto del título: (2-etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

La preparación del compuesto del título a partir del Intermedio 186(a) (95,5 mg, 0,366 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (65,0 mg, 0,401 mmol), trietilamina (0,510 ml, 3,66 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio (210 mg, 0,552 mmol) en *N*,*N*-dimetilformamida (4,0 ml) se realizó de forma análoga al Ejemplo **11**. Los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó

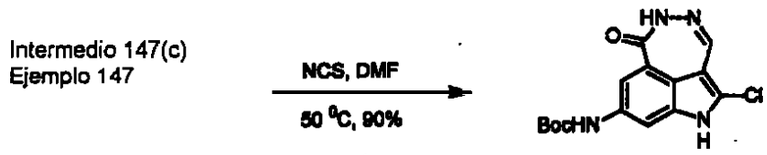
sobre una columna de gel de sílice y se eluyó con 1,2:1 de diclorometano:acetato de etilo, proporcionando el compuesto del título (80 mg, 0,215 mmol) en forma de un sólido amarillo con un rendimiento del 59%.

^{1}H RMN (d_6-DMSO): δ 11,63 (s, 1H), 10,31 (s, 1H), 10,09 (s, 1H), 8,00 (d, 1H, J = 1,51 Hz), 7,52 (d, 1H, J = 1,51 Hz), 7,45 (s, 1H), 7,34-7,24 (m, 2H), 7,24-7,13 (m, 3H), 2,81 (c, 2H, J = 7,54 Hz), 2,41-2,31 (m, 1H), 2,11-2,00 (m, 1H), 1,53-1,43 (m, 1H), 1,40-1,29 (m, 1H), 1,23 (t, 3H, J = 7,54 Hz).

EMCL: ($M+H^+$) 373,1.

EMAR: ($M+H^+$) calculado para $C_{22}H_{21}N_4O_2$, 371,1665, encontrado 373,1672.

Ejemplo 187: Éster *terc*-butílico del ácido (2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico

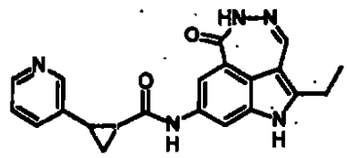


Se añadió *N*-clorosuccinimida (0,47 g, 3,52 mmol) a una solución del Intermedio 147(c) del Ejemplo **147** (1,00 g, 3,33 mmol) en *N,N*-dimetilformamida anhidra (10 ml) y cloroformo anhidro (6,5 ml). La reacción se calentó a 50°C durante 3 horas, momento en el que los componentes volátiles se retiraron al vacío. El residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 23:2:50 de diclorometano:metanol:acetato de etilo, proporcionando el compuesto del título (1 g, 2,99 mmol) en forma de un sólido amarillo con un rendimiento del 90%.

^{1}H RMN (d_6-DMSO): δ 12,52 (s, 1H), 10,41 (s, 1H), 9,51 (s, 1H), 7,70 (s, 1H), 7,66 (s, 1H), 7,32 (s,1H),1,47(s, 9H).

EMCL: $(M+H^+)$ 335,1, $(M+Na^+)$ 357,0; $(M-H)^-$ 333,0.

Ejemplo 188: (2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico



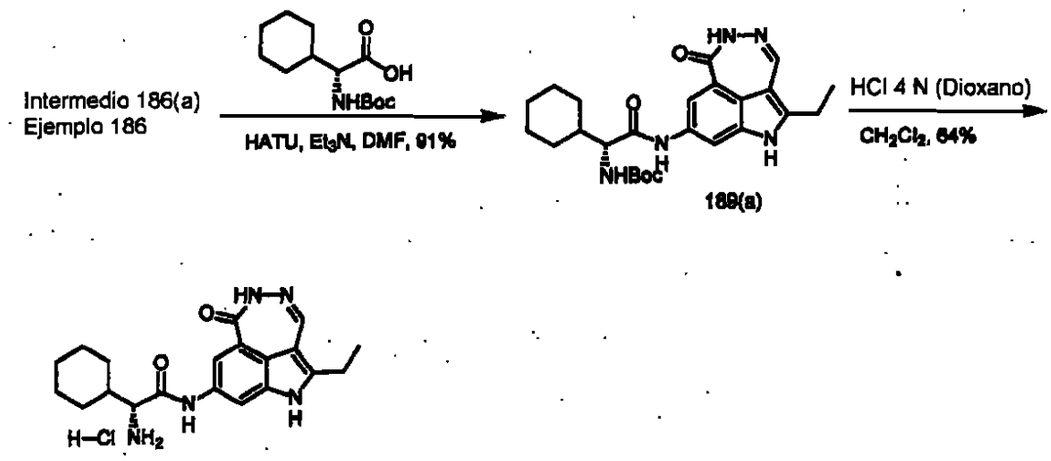
La preparación del ejemplo 188 a partir del Intermedio 186(a) del Ejemplo **186** (90 mg, 0,341 mmol), ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico bruto (véase el Ejemplo 125 para la pureza estimada de la preparación aprox. 75%) (79,5 mg, aprox. 0,341 mmol), trietilamina (0,237 ml, 1,73 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (194 mg, 0,510 mmol) en *N,N*-dimetilformamida (4,0 ml) se realizó de forma análoga al Ejemplo **11**. Los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 50:3 de diclorometano:metanol, proporcionando el compuesto del título (75 mg, 0,201 mmol) en forma de un sólido amarillo con un rendimiento del 59%.

^{1}H RMN (d_6-DMSO): δ 11,65 (s, 1H), 10,36 (s, 1H), 10,11 (s, 1H), 8,51 (d, 1H, J = 1,88 Hz), 8,42 (dd, 1H, *J* = 1,32, 1,32 Hz), 8,01 (d, 1H, J = 1,70 Hz), 7,57 (dt, 1H, J = 7,91, 1,88 Hz), 7,53 (d, 1H, J = 1,70 Hz), 7,47 (s, 1H), 7,33 (dd, 1H, J = 4,90, 4,71 Hz), 2,82 (c, 2H, *J* = 7,54 Hz), 2,47-2,38 (m, 1H), 2,17-2,08 (m, 1H), 1,58-1,49 (m, 1H), 1,49-1,39 (m, 1H), 1,24 (t, 3H, *J* = 7,54 Hz).

EMCL: $(M+H^+)$ 374,2, $(M+Na^+)$ 396,0; $(M-H)^-$ 372,0.

EMAR: $(M+H^+)$ calculado para $C_{21}H_{20}N_5O_2$, 374,1617, encontrado 374,1620.

Ejemplo 189:(*R*)-2-Amino-2-ciclohexil-*N*-(2-etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (sal clorhidrato)



Etapa 1. Preparación de éster *terc*-butílico del ácido (*R*)-[ciclohexil-(2-etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-metil]-carbámico 189(a)

La preparación del intermedio 189(a) a partir del Intermedio 186(a) del Ejemplo **186** (90 mg, 0,341 mmol), ácido (*R*)-*terc*-butoxicarbonilamino-ciclohexil-acético (88 mg, 0,342 mmol), trietilamina (0,237 ml, 1,73 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (194 mg, 0,510 mmol) en *N,N*-dimetilformamida (4,0 ml) se realizó de forma análoga al Ejemplo **11.** Los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1,2:1 de diclorometano:acetato de etilo, proporcionando el Intermedio 189(a)

(146 mg, 0,313 mmol) en forma de un sólido amarillo con un rendimiento del 91%.

^{1}H RMN (d_6-DMSO): δ 11,64 (s, 1H), 10,12 (s, 1H), 10,02 (s, 1H), 7,99 (s, 1H), 7,54 (s, 1H), 7,47 (s, 1H), 6,87 (d, 1H, *J* = 7,72 Hz), 3,92 (t, 1H, *J* = 8,48 Hz), 2,82 (c, 2H, *J* = 7,54 Hz), 1,73-1,46 (m, 6H), 1,38 (s, 9H), 1,24 (t, 3H, *J* = 7,54 Hz), 1,19-0,94 (m, 5H)..

EMCL: ($M+H^+$) 468,2, ($M+Na^+$) 490,2.

Etapa 2. Preparación del compuesto del título: (*R*)-2-Amino-2-ciclohexil-*N*-(2-etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (sal clorhidrato)

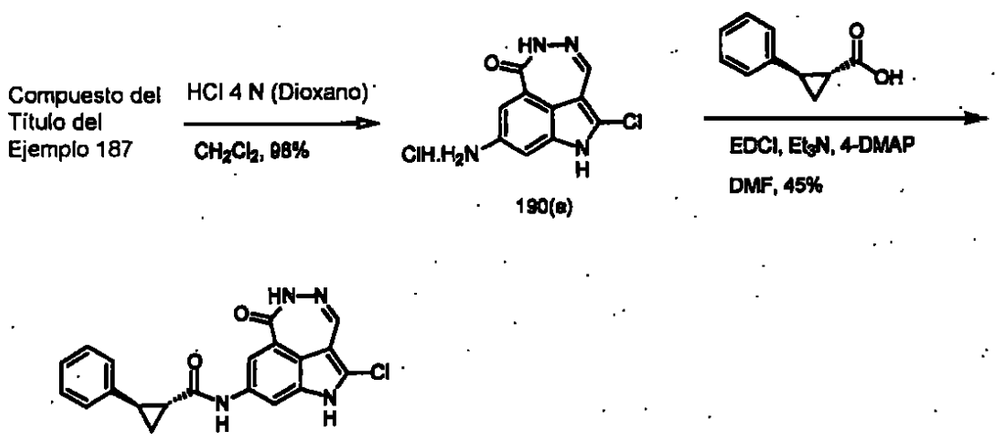
La preparación del compuesto del título a partir del Intermedio 189(a) (136 mg, 0,291 mmol) y HCl 4,0 M en dioxano (1,5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (75 mg, 0,186 mmol) en forma de un polvo amarillo con un rendimiento del 64%.

^{1}H RMN (d_6-DMSO): δ 11,81 (s, 1H), 10,66 (s, 1H), 10,19 (s, 1H), 8,42-8,20 (m, 3H), 7,98 (s, 1H), 7,59 (s, 1H), 7,50 (s, 1H), 3,82-3,66 (m, 1H), 2,84 (c, 2H, *J* = 7,54 Hz), 1,94-1,53 (m, 6H), 1,30-0,98 (m, 8H).

EMCL: ($M+H^+$) 368,1, ($M+Na^+$) 390,2; $(M-H)^-$ 366,1.

EMAR: ($M+H^+$) calculado para $C_{20}H_{26}N_5O_2$, 368,2087, encontrado 368,2084.

Ejemplo 190: (2-Cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



Etapa 1. Preparación de 8-Amino-2-cloro-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona (sal clorhidrato) 190(a)

La preparación del intermedio 190(a) a partir del compuesto del título del Ejemplo **187** (0,83 g, 2,48 mmol) y HCl 4,0 M en dioxano (6,2 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el Intermedio 190(a) (0,66 g, 2,44 mmol) en forma de un polvo amarillo con un rendimiento del 98%.

^{1}H RMN (d_6-DMSO): δ 12,87 (s, 1H), 10,57 (s, 1H), 7,38 (s, 2H), 7,27 (s, 1H).

EMCL: $(M-H)^-$ 233,1.

Etapa 2. Preparación del compuesto del título: (2-Cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

El Intermedio 190(a) (120 mg, 0,443 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (86,0 mg, 0,531 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (102 mg, 0,534 mmol) y 4-dimetilaminopiridina (65 mg, 0,533 mmol) se agitaron en *N,N*-dimetilformamida (7,0 ml) a temperatura

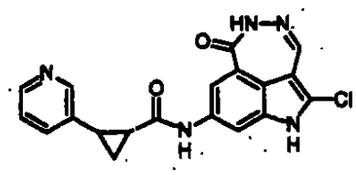
ambiente durante 16 h, momento en el que los componentes volátiles se retiraron al vacío. El residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1,2:1 de diclorometano:acetato de etilo, proporcionando el compuesto del título (75 mg, 2,99 mmol) en forma de un sólido amarillo con un rendimiento del 45%.

^{1}H RMN (d_6-DMSO): δ 12,65 (s, 1H), 10,46 (s, 2H), 8,09 (s, 1H), 7,63 (s, 1H), 7,36 (s, 1H), 7,34-7,25 (m, 2H), 7,25-7,12 (m, 3H), 2,44-2,30 (m, 1H), 2,13-2,01 (m, 1H), 1,57-1,44 (m, 1H), 1,44-1,31 (m, 1H).

EMCL: $(M-H)^-$ 377,1.

EMAR: $(M+H^+)$ calculado para $C_{20}H_{16}N_4O_2Cl$, 379,0962, encontrado 379,0941.

Ejemplo 191: (2-Cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico



La preparación del ejemplo 191 a partir del Intermedio 190(a) del Ejemplo **190** (120 mg, 0,443 mmol), ácido 2-piridin-3-il-ciclopropanocarboxílico bruto (pureza aproximada aprox. 75%) (124 mg, aprox. 0,532 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (102 mg, 0,534 mmol) y 4-dimetilaminopiridina (65 mg, 0,533 mmol) en *N,N*-dimetilformamida (7,0 ml) se realizó de forma análoga al Ejemplo **190,** Etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de

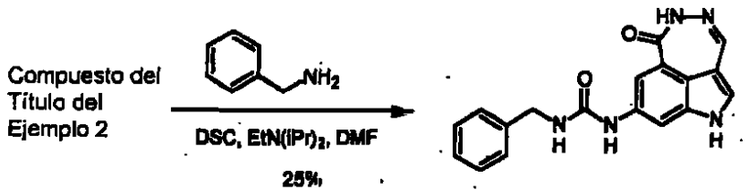
sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 50:3 de diclorometano:metanol, proporcionando el compuesto del título (80 mg, 0,210 mmol) en forma de un sólido amarillo con un rendimiento del 48%.

^{1}H RMN (d_6-DMSO): δ 12,65 (s, 1H), 10,48 (s, 1H), 10,46 (s, 1H), 8,51 (s, 1H), 8,42 (d, 1H, *J* = 3,20 Hz), 8,09 (d, 1H, *J* = 1,13 Hz), 7,63 (d, 1H, *J* = 1,32 Hz), 7,57 (d, 1H, J = **7,91** Hz), 7,40-7,28 (m, 2H), 2,47-2,37 (m, 1H), 2,19-2,06 (m, 1H), 1,60-1,50 (m, 1H), 1,50-1,40 (m, 1H).

EMCL: ($M+H^+$) 380,0, ($M+Na^+$) 402,1; $(M-H)^-$ 378,0.

EMAR: ($M+H^+$) calculado para $C_{19}H_{15}N_5O_2Cl$, 380,0914, encontrado 380,0922.

Ejemplo 192: *N*-(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-*N'*-(fenilmetil)urea



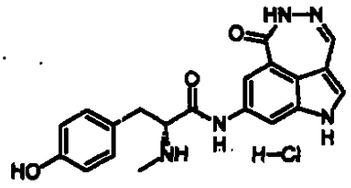
Al compuesto del título del Ejemplo **2** (45 mg, 0,19 mmol) y carbonato de *N,N'*-disuccinimidilo (49 mg, 0,19 mmol) se le añadieron *N,N*-dimetilformamida (0,5 ml) y trietilamina (0,084 ml, 0,60 mmol). Después de 3 a 5 min, se añadió bencilamina (0,046 ml, 0,20 mmol) y la reacción se agitó durante aproximadamente una hora. Se añadió cloruro de metileno:metanol (4:1) y los sólidos resultantes se retiraron por filtración. El triturado se cargó sobre un lecho de gel de sílice y se evaporó. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con hexano:acetona (1:1) y las fracciones más puras se combinaron. Después de la retirada del disolvente, se obtuvo el

compuesto del título (16 mg, 0,048 mmol) en forma de un polvo pardo con un rendimiento del 25%.

^{1}H RMN (d_6-DMSO): δ 11,61 (s, 1H, intercambios), 10,19 (s, 1H, intercambios), 8,75 (s, 1H, intercambios), 7,93 (s, 1H), 7,49 (m, 1H), 7,40-7,30 (m, 7H), 6,55 (m, 1H, intercambios), 4,31 (d, 2H, J = 5,84 Hz).

EMCL: ($M+H^+$) 334,2, ($M+Na^+$) 356,3

Ejemplo 193: Clorhidrato de (2*R*)-3-(4-hidroxifenil)-2-(metilamino)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida

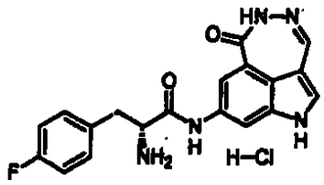


La preparación del ejemplo 193 a partir del compuesto del título del Ejemplo **156** (121 mg, 0,25 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, proporcionó el compuesto del título (74 mg, 0,18 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 72%.

^{1}H RMN (d_6-DMSO): componente/confórmero mayoritario: δ 11,89 (s, 1H, intercambios), 10,73 (s, 1H, intercambios), 10,31 (s, 1H, intercambios), 9,36 (s a, 2H, intercambios), 9,11 (s a, 1H, intercambios), 7,99 (s, 1H), 7,64 (s, 1H), 7,56 (s, 1H), 7,50 (s, 1H), 7,06 (d, 2H, J = 8,48 Hz), 6,69 (d, 2H, *J* = 8,48 Hz), 4,11 (m, 1H), 3,18 (m, 1H), 3,08 (m, 1H), 2,55 (s, 3H, parcialmente oscurecido).

EMCL: ($M+H^+$) 378,0, ($M+Na^+$) 400,1.

Ejemplo 194: Clorhidrato de (2*R*)-2-amino-3-(4-fluorofenil)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida

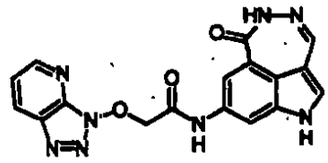


La preparación del ejemplo 194 a partir del compuesto del título del Ejemplo **157** (48 mg, 0,10 mmol) y HCl 4 M en dioxano (10 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga proporcionó el compuesto del título (34 mg, 0,08 mmol) en forma de un polvo naranja/amarillo con un rendimiento del 80%.

^{1}H RMN (d_6-DMSO): δ 11,88 (s, 1H, intercambios), 10,72 (s, 1H, intercambios), 10,32 (s, 1H, intercambios), 8,37 (s a, 4H, intercambios); 8,04 (s, 1H), 7,64 (s, 1H), 7,57 (s, 1H), 7,50 (s, 1H), 7,38-7,29 (m, 2H), 7,22-7,14 (m, 2H), 4,19 (m, 1H), 3,26-3,03 (m, 2H).

EMCL: ($M+H^+$) 366,0, ($M+Na^+$) 388,1.

Ejemplo 195: *N*-(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-(3*H*-[1,2,3]triazolo[4,5-*b*]piridin-3-iloxi)acetamida



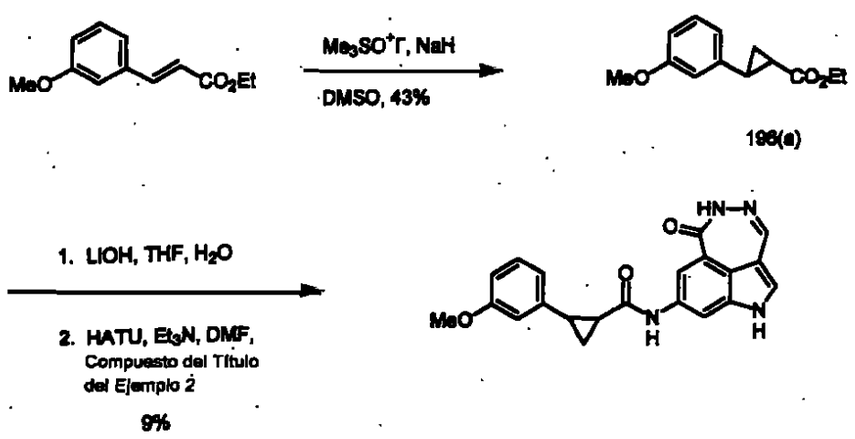
De manera análoga a la del Ejemplo **19**, a una suspensión agitada de clorhidrato de 8-amino-1,5-dihidro-6*H*-[1,2]diazepino[4,5,6-*cd*]indol-6-ona en *N,N*-dimetilformamida anhidra (9 ml) se le añadieron ácido bromoacético (168 mg. 1,2 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-

tetrametiluronio (553 mg, 1,4 mmol) y trietilamina. La reacción se agitó a temperatura ambiente durante 16 horas. Los componentes volátiles se evaporaron y al residuo se le añadió agua. Los sólidos naranjas precipitados se recogieron por filtración y se lavaron con agua y acetato de etilo. Después de secar, se obtuvo el compuesto del título (158 mg) en forma de un polvo naranja con un rendimiento del 35%.

^{1}H RMN (DMSO-d_6) δ: 5,28 (1H, s), 7,47 (1H, s), 7,58 (3H, m), 8,09 (1H, d, J = 1,77 Hz), 8,63 (1H, dd, J = 8,59 Hz), 8,83 (1H, dd, J = 4,55 Hz), 10,27 (1H, s), 10,52 (1H, s), 11,77 (1H, s).

EMCL: ($M+H^+$) 377.

Ejemplo 196: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-metoxi-fenil)-ciclopropanocarboxílico



Etapa 1: Preparación de éster etílico del ácido (1,2-*trans*)-2-(3-metoxi-fenil)-ciclopropanocarboxílico 196(a)

La preparación del intermedio 196(a) a partir de NaH (1,04 g, 26 mmol) y yoduro de trimetilsulfoxonio (5,72 g, 26 mmol) y éster etílico del ácido 3-(metoxi-fenil)-acrílico (4,12 g, 20 mmol) en DMSO (30 ml) se realizó de manera

análoga al etapa 2 del Ejemplo **113**, proporcionando el Intermedio 196(a) (1,89 g, 8,6 mmol) con un rendimiento del 43%.

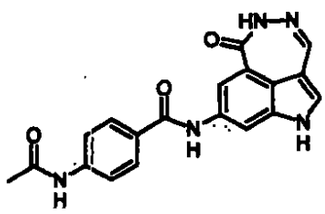
Etapa 2: Preparación del compuesto del título: (6-oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-metoxi-fenil)-ciclopropanocarboxílico

La preparación del compuesto del título se realizó de manera análoga al etapa 3 del Ejemplo **172** con la excepción de que se usó el Intermedio 196(a) en lugar del Intermedio 172(b). Se obtuvo el compuesto del título con un rendimiento del 9%.

^{1}H RMN (d_6-DMSO): δ 11,85 (d, 1H, *J* = 2,26 Hz), 10,37 (s, 1H), 10,23 (s, 1H),8,12(s, 1H), 7,57 (dd, 1H, *J* = 3,20, 1,51 Hz), 7,46 (s, 2H), 7,20 (t, J = 8,0 Hz, 1H), 6,77-6,74 (m, 3H), 3,75 (s, 3H), 2,36 (m, 1H), 2,08 (m, 1H), 1,48 (m, 1H), 1,38 (m, 1H).

EMCL: ($M+H^+$) 375,1.

Ejemplo 197: 4-Acetilamino-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida



La preparación del ejemplo 197 a partir del compuesto del título del Ejemplo 2 (124 mg, 0,525 mmol), ácido 4-acetilamino-benzoico (113 mg, 0,631 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (120 mg, 0,628 mmol) y 4-dimetilaminopiridina (77 mg, 0,631 mmol) en *N,N*-dimetilformamida (7,0 ml) se realizó de forma análoga al Ejemplo **190**, Etapa 2. Cuando se juzgó

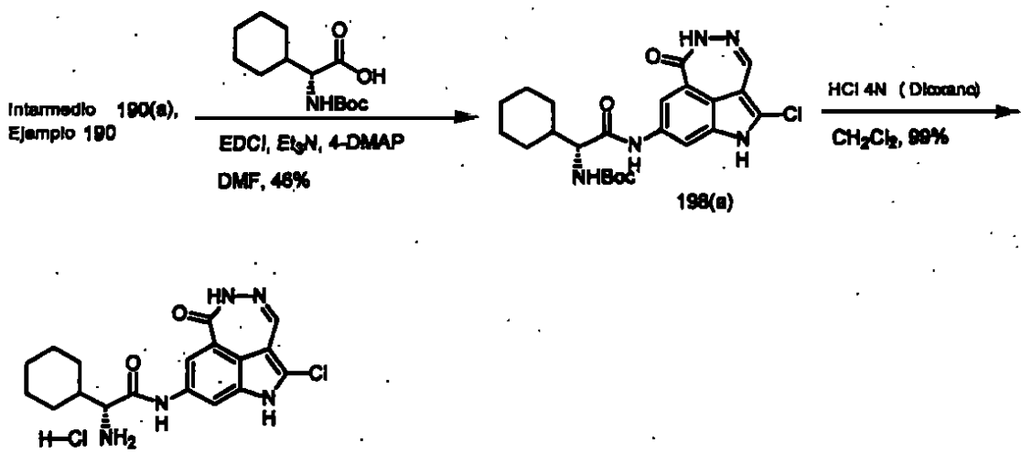
que la reacción se había completado, los componentes volátiles se evaporaron y se añadió metanol. La mezcla se filtró para recoger los sólidos, que después se lavaron con metanol, diclorometano y éter dietílico. Después de secar, se obtuvo el compuesto del título (32 mg, 0,0886 mmol) en forma de un polvo amarillo con un rendimiento del 17%.

^{1}H RMN (d_6-DMSO): δ 11,79 (d, 1H, *J* = 2,64 Hz), 10,25 (s, 1H), 10,23 (s, 2H), 8,27 (d, 1H, *J* = 1,70 Hz), 7,96 (d, 2H, *J* = 8,67 Hz), 7,85 (d, 1H, *J* = 1,70 Hz), 7,70 (d, 2H, *J* = 8,67 Hz), 7,58 (d, 1H, J = 2,64 Hz), 7,48 (s, 1H), 2,09 (s, 3H).

EMCL: $(M-H)^-$ 360,2.

EMAR: $(M+H^+)$ calculado para $C_{19}H_{16}N_5O_3$, 362,1253, encontrado 362,1280.

Ejemplo 198: (*R*)-2-Amino-*N*-(2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-ciclohexil-acetamida (sal clorhidrato)



Etapa 1. Preparación de éster *terc*-butílico del ácido [(2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-ciclohexil-metil]-carbámico 198(a)

La preparación del intermedio 198(a) a partir del Intermedio 190(a) del Ejemplo **190** (100 mg, 0,369 mmol), ácido (*R*)-*terc*-butoxicarbonilamino-ciclohexil-acético (114 mg, 0,443 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (85 mg, 0,445 mmol) y 4-dimetilaminopiridina (54 mg, 0,443 mmol) en *N,N*-dimetilformamida (7,0 ml) se realizó de forma análoga al Ejemplo **190,** Etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1,2:1 de diclorometano:acetato de etilo, proporcionando el Intermedio 198(a) (80 mg, 0,169 mmol) en forma de un sólido amarillo con un rendimiento del 46%.

^{1}H RMN (d_6-DMSO): δ 12,64 (s, 1H), 10,47 (s, 1H), 10,16 (s, 1H), 8,06 (d, 1H, J = 1,51 Hz), 7,66 (d, 1H, *J* = 1,51 Hz), 7,36 (s, 1H), 6,91 (d, 1H, *J* = 9,04 Hz), 3,92 (dd, 1H, *J* = 8,29, 7,91 Hz), 1,78-1,46 (m, 6H), 1,38 (s, 9H), 1,21-0,92 (m, 5H).

EMCL: $(M-H)^-$ 472,1.

Etapa 2. Preparación del compuesto del título: (*R*)-2-amino-*N*-(2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-ciclohexil-acetamida (sal clorhidrato)

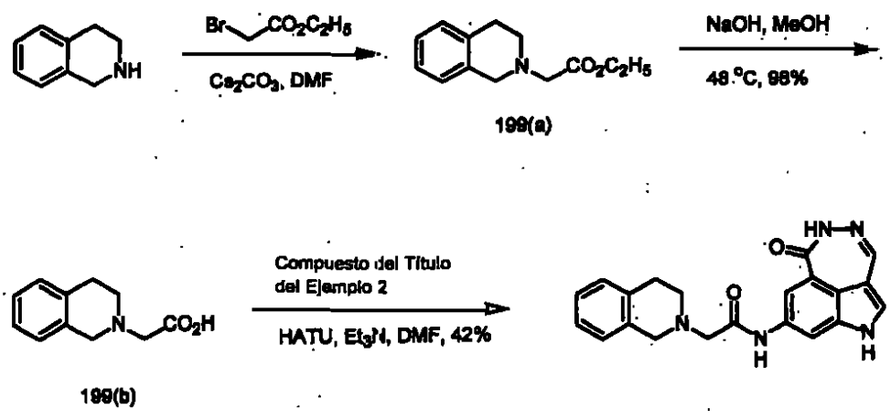
La preparación del compuesto del título a partir del Intermedio 198(a) (75 mg, 0,159 mmol) y HCl 4,0 M en dioxano (0,8 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (65 mg, 0,159 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

^{1}H RMN (d_6-DMSO): δ 12,81 (s, 1H), 10,77 (s, 1H), 10,53 (s, 1H), 8,30 (s a, 3H), 8,03 (d, 1H, J = 1,70 Hz), 7,70 (d, 1H, *J* = 1,70 Hz), 7,39 (s, 1H), 3,73 (m, 1H), 1,93-1,55 (m, 6H), 1,27-1,01 (m, 5H).

EMCL: (M+H+) 374,0; (M-H)$^-$ 372,2.

EMAR: (M+H$^+$) calculado para $C_{18}H_{21}N_5O_2Cl$, 374,1384, encontrado 374,1369.

Ejemplo 199: 2-(3,4-Dihidro-1*H*-isoquinolin-2-il)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



Etapa 1. Preparación de éster etílico del ácido (3,4-dihidro-1*H*-isoquinolin-2-il)-acético 199(a)

A una solución de 1,2,3,4-tetra-hidroisoquinolina (2,664 g, 20 mmol) y bromoacetato de etilo (3,647 g, 22 mmol) en *N,N*-dimetilformamida (23 ml) se le añadió Cs_2CO_3 (7,168 g, 22 mmol) en una atmósfera de N_2. La mezcla se agitó a temperatura ambiente durante 4 horas. El disolvente se retiró a presión reducida y el residuo restante se sometió a cromatografía sobre gel de sílice, eluyendo con acetato de etilo/hexanos (33:66), proporcionando el Intermedio 199(a) (3,39 g, 15,5 mmol) en forma de un aceite amarillo con un rendimiento del 77%.

^{1}H RMN ($CDCl_3$): δ 7,13-7,09 (m, 3H), 6,99 (t, 1H), 4,22 (c, 2H), 3,84 (s, 2H), 3,44 (s, 2H), 2,94 (s,4H), 1,29 (t, 3H).

EMCL: ($M+H^+$) 220,3.

Etapa 2. Preparación de ácido (3,4-dihidro-1*H*-isoquinolin-2-il)-acético 199(b)

A una suspensión del Intermedio 199(a) (1,643 g, 7,5 mmol) en metanol (20 ml) se le añadió NaOH 2,5 N (7,8 ml). La solución de reacción se calentó a 48°C y se agitó durante una noche. Con refrigeración, el pH se ajustó a 8 mediante la adición de HCl 1 M. Los componentes volátiles se retiraron al vacío y la mezcla resultante se suspendió en metanol. Después de la filtración para retirar los sólidos insolubles, el filtrado se evaporó, dando el Intermedio 199(b) (1,4 g, 7,3 mmol) en forma de una espuma blanca con un rendimiento del 98%.

^{1}H RMN (d_6-DMSO): δ 7,13-7,09 (m, 3H), 7,02 (t, 1H), 3,76 (s, 2H), 3,27 (s, 2H), 2,88-2,82 (m, 4H).

EMCL: ($M+H^+$) 192,2.

Etapa 3. Preparación del compuesto del título: 2-(3,4-Dihidro-1*H*-isoquinolin-2-il)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida

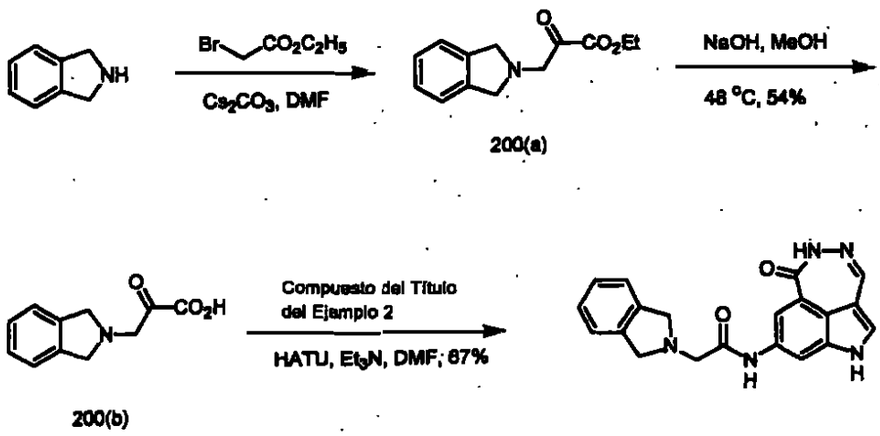
La preparación del compuesto del título a partir del compuesto del título del Ejemplo 2 (185 mg, 0,79 mmol), el Intermedio 199(b) (150 mg, 0,79 mmol), trietilamina (0,274 ml, 1,98 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (330 mg, 0,879 mmol) y *N,N*-dimetilformamida (3 ml) se realizó de manera análoga al **11**. Después de la evaporación de los componentes volátiles, el residuo resultante se trituró con una pequeña

cantidad de *N,N*-dimetilformamida y agua, dando el compuesto del título (123,5 mg, 0,331 mmol) en forma de un sólido amarillo con un rendimiento del 42%.

^{1}H RMN (d_6-DMSO): δ 11,73 (s, 1H), 10,22 (s, 1H), 9,97 (s, 1H), 8,13(8, 1H),7,62 (s, 1H),7,55 (s, 1H), 7,45 (s, 1H), 7,12-7,04 (m, 4H), 3,72 (s, 2H), 2,88-2,80 (m, 6H).

EMCL: ($M+H^+$) 374,4

Ejemplo 200: 2-(1,3-Dihidro-isoindol-2-il)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



Etapa 1. Preparación de éster etílico del ácido (1,3-dihidro-isoindol-2-il)-acético 200(a)

En una solución de isoindolina (1,788 g, 15 mmol) y bromoacetato de etilo (2,756 g, 16,5 mmol) en *N,N*-dimetilformamida (20 ml) se añadió Cs_2CO_3 (5,376 g, 16,5 mmol) en una atmósfera de N_2. La mezcla se agitó a temperatura ambiente durante 4 horas. El disolvente se retiró a presión reducida y la mezcla resultante se sometió a cromatografía sobre gel de sílice, eluyendo con 33:66 de acetato de etilo:hexano, proporcionando el Intermedio

200(a) (1,14 g, 5,56 mmol) en forma de un aceite amarillo con un rendimiento del 37%.

^{1}H RMN ($CDCl_3$): δ 7,20 (s, 4H), 4,22 (c, 6H), 3,66 (s, 2H), 1,29 (t, 3H).

EMCL: ($M+H^+$) 206,3.

Etapa 2. Preparación de ácido (1,3-dihidro-isoindol-2-il)-acético 200(b)

A una suspensión del Intermedio 200(a) (1,14 g, 5,56 mmol) en metanol (20 ml) se le añadió NaOH 2,5 N (5,78 ml). La solución de reacción se calentó a 48°C y se agitó durante una noche. Con refrigeración, el pH se ajustó a 8 mediante la adición de HCl 1 M. Los componentes volátiles se retiraron al vacío y la mezcla resultante se suspendió en metanol. Después de la filtración para retirar los sólidos insolubles, el filtrado se evaporó, dando el Intermedio 200(b) (531 mg, 3 mmol) en forma de sólidos pálidos con un rendimiento del 54%.

EMCL: ($M+H^+$) 178,2.

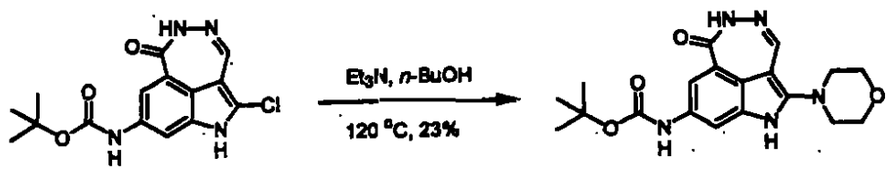
Etapa 3. Preparación del compuesto del título: 2-(1,3-dihidro-isoindol-2-il)-N-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida

La preparación del compuesto del título a partir del compuesto del título del Ejemplo 2 (118 mg, 0,5 mmol), el Intermedio 200(b) (88,5 mg, 0,5 mmol), trietilamina (0,274 ml, 1,98 mmol), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (209 mg, 0,55 mmol) y *N,N*-dimetilformamida (5 ml) se realizó de forma análoga al Ejemplo **11**. Después de la evaporación de los componentes volátiles, el residuo resultante se trituró con una pequeña cantidad de *N,N*-dimetilformamida y agua, dando el compuesto del título (121 mg, 0,337 mmol) en forma de un sólido amarillo con un rendimiento del 67%.

^{1}H RMN (d_6-DMSO): δ 11,73 (s, 1H), 10,21 (s, 1H), 10,02 (s, 1H), 8,13 (s, 1H), 7,66(s, 1H), 7,55 (s, 1H), 7,46 (s, 1H), 7,22 (d, 4H), 4,07 (s, 4H), 3,56 (s, 2H).

EMCL: ($M+H^+$) 360,4

Ejemplo 201: Éster *terc*-butílico del ácido (2-morfolin-4-il-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico

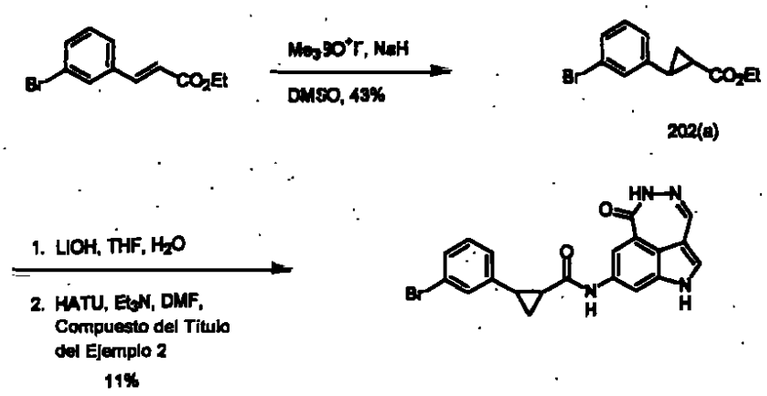


Se agitaron trietilamina (0,039 ml, 0,28 mmol), el compuesto del título del Ejemplo **187** (46 mg, 0,14 mmol), morfolina (96 mg, 1,1 mmol) y *n*-butanol (5 ml) en un matraz con un condensador a 120°C durante una noche. La mezcla se dejó en reposo a temperatura ambiente durante dos días más. Los componentes volátiles se retiraron al vacío y la mezcla resultante se sometió a cromatografía sobre gel de sílice, eluyendo con 95:5 de diclorometano:metanol, proporcionando el compuesto del título (12,5 mg, 0,032 mmol) en forma de un sólido amarillo con un rendimiento del 23%.

^{1}H RMN (d_6-DMSO): δ 9,53 (s, 1H), 8,47 (s, 1H), 7,80 (s, 1H), 7,28 (s, 1H), 6,06 (s, 2H), 3,74 (s, 8H), 1,48 (s, 9H).

EMCL: ($M+H^+$) 386,4.

Ejemplo 202: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-bromo-fenil)-ciclopropanocarboxílico



Etapa 1. Preparación de éster etílico del ácido (1,2-*trans*)-2-(3-bromo-fenil)-ciclopropanocarboxílico 202(a)

A una mezcla de NaH (186 mg, 4,65 mmol) y yoduro de trimetilsulfoxonio (1,02 g, 4,65 mmol) se le añadió DMSO (5 ml). Después de agitar durante 30 min, se añadió gota a gota una solución de éster etílico del ácido *trans*-3-(bromo-fenil)-acrílico (933 mg, 3,57 mmol) en DMSO (2 ml). Después de agitar durante una noche, la mezcla se repartió entre acetato de etilo y agua. La fase acuosa se extrajo con acetato de etilo. Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se sometió a cromatografía sobre gel de sílice, eluyendo con acetato de etilo al 10%/hexano, formando el Intermedio 202(a) en forma de un aceite incoloro (408 mg, 1,52 mmol) con un rendimiento del 43%.

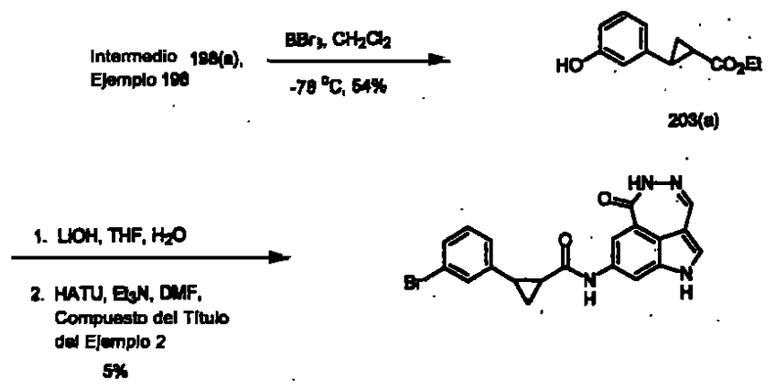
Etapa 2. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-Bromo-fenil)-ciclopropanocarboxílico

A una solución agitada del Intermedio 202(a) (505 mg, 2,25 mmol) en MeOH (10 ml) se le añadió LiOH acuoso 10 M (10 ml). La mezcla se agitó a

23°C durante 12 horas, se acidificó con HCl 1 M a pH 1 y se extrajo con acetato de etilo. Después, las fases orgánicas combinadas se lavaron con salmuera y se concentraron, dando ácido (2,3-*trans*)-3-(3'-bromo-fenil)-cicloprapanecarboxílico bruto (632 mg), que se combinó con el compuesto del título del Ejemplo 2 (111 mg, 0,49 mmol), trietilamina (0,273 ml, 1,96 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (278 mg, 0,73 mmol) en *N,N*-dimetilformamida (4 ml) de manera análoga al Ejemplo **11.** El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso seguido de la cromatografía sobre gel de sílice proporcionó el compuesto del título (100 mg, 0,24 mmol) en forma de un sólido amarillo con un rendimiento del 11%.

^{1}H RMN (d_6-DMSO): 11,85 (d, 1H, J = 2,26 Hz), 10,50 (s, 1H), 10,35 (s, 1H), 8,23 (s, 1H), 7,69 (s, 1H), 7,67 (d, 1H, *J* = 4,0 Hz), 7,58 (s, 1H), 7,53-7,51 (m, 2H), 7,40-7,33 (m, 2H), 2,53 (m, 1H), 2,23 (m, 1H), 1,62 (m, 1H), 1,54 (m, 1H).

Ejemplo 203: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-hidroxi-fenil)-ciclopropanocarboxílico



Etapa 1. Preparación de éster etílico del ácido 2-(3-hidroxi-fenil)-ciclopropanocarboxílico 203(a)

A una solución agitada del Intermedio 196(a) del Ejemplo **196** (1,56 g, 7,12 mmol) en CH_2Cl_2 a -78°C se le añadió BBr_3 1,0 M en CH_2Cl_2 (8,56 ml, 8,56 mmol). La mezcla se calentó a temperatura ambiente y se agitó durante 1 hora. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso seguido de la cromatografía sobre gel de sílice proporcionó el Intermedio 203(a) en forma de un sólido pardo pálido (795 mg, 3,86 mmol) con un rendimiento del 54%.

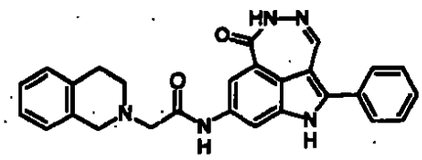
Etapa 2. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-hidroxi-fenil)-ciclopropanocarboxílico

A una solución del Intermedio 203(a) (271 mg, 1,32 mmol) en tetrahidrofurano (2 ml) se le añadió LiOH acuoso 1 M (6 ml, 6 mmol). La mezcla se agitó durante una noche. Después de acidificar a pH 2, la mezcla se extrajo con acetato de etilo. La concentración de la fase orgánica dio ácido 3-(3-hidroxi-fenil)-cicloprapanecarboxílico bruto (235 mg), del que una porción (155 mg, 0,57 mmol) se combinó con el compuesto del título del Ejemplo **2** (137 mg, 0,58 mmol), trietilamina (0,24 ml, 1,72 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (331 mg, 0,87 mmol) en *N,N*-dimetilformamida (3 ml) de manera análoga al Ejemplo **11**. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso seguido de cromatografía sobre gel de sílice produjo el compuesto del título (10 mg, 0,028 mmol) en forma de un sólido castaño con un rendimiento del 5%.

^{1}H RMN (d_6-DMSO): δ 10,35 (s, 1H), 10,27 (s, 1H), 9,35 (s, 1H), 8,12 (s, 1H), 7,67 (dd, 1H, *J* = 3,20, 1,51 Hz), 7,55 (s, 1H), 7,48(8, 1H), 7,15 (t, J = 8,0 Hz, 1H), 6,77-6,74 (m, 3H), 2,32 (m, 1H), 2,09 (m, 1H), 1,45 (m, 1H), 1,38 (m, 1H).

EMCL: ($M-H^+$) 359,1

Ejemplo 204: 2-(3,4-Dihidroisoquinolin-2(1*H*)-il)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida

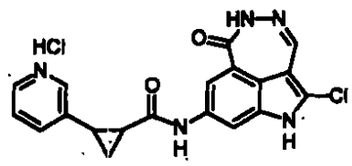


De manera análoga a la del Ejemplo **11**, a una solución agitada de 8-amino-1,5-dihidro-6H-[1,2]diazepino[4,5,6-*cd*]indol-6-ona en *N,N*-dimetilformamida anhidra (6 ml) se le añadió ácido 3,4-dihidroisoquinolin-2(1*H*)-ilacético (62 mg, 0,33 mmol) seguido de trietilamina (0,14 ml, 0,98 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*- (372 mg, 0,98 mmol). La reacción se agitó a temperatura ambiente durante 17 horas. Después de concentrar, se añadió agua y el sólido precipitado se recogió por filtración. Después de HPLC preparativa, se obtuvo el compuesto del título (50 mg) en forma de un polvo amarillo con un rendimiento del 34%.

^{1}H RMN (metanol-d_4) δ: 3,25 (2H, m), 3,72 (2H, s a), 4,27 (2H, s), 4,58 (2H, s), 7,22 (1H, d, J = 7,58 Hz), 7,32 (3H, m), 7,52 (4H, m), 7,63 (3H, m), 8,13 (1H, d, *J* = 1,52 Hz).

EMCL: ($M+H^+$) 450,1.

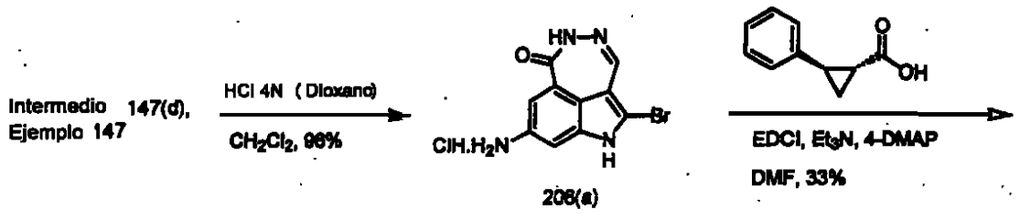
Ejemplo 205: (2-Cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico (sal clorhidrato)

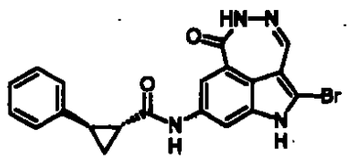


El compuesto de título del Ejemplo **191** (20 mg, 0,053 mmol) se convirtió en una sal HCl en CH_2Cl_2 anhidro (2 ml) con HCl 4,0 M en dioxano (0,026 ml). La mezcla se agitó a temperatura ambiente durante 1 hora. El sólido se recogió por filtración y se lavó con CH_2Cl_2 y éter dietílico. Después de secar, se obtuvo el compuesto del título (20,4 mg, 0,049 mmol) en forma de un polvo amarillo con un rendimiento del 93%.

^{1}H RMN (d_6-DMSO): δ 12,70 (s, 1H), 10,59 (s, 1H), 10,46 (s, 1H), 8,85 (s, 1H), 8,72 (d, 1H, *J* = 5,84 Hz), 8,25 (d, 1H, *J* = 8,29 Hz), 8,07 (d, 1H, *J* = 1,70 Hz), 7,91 (dd, 1H, *J* = 5,27, 5,27 Hz), 7,63 (d, 1H, *J* = 1,70 Hz), 7,35 (s, 1H), 2,75-2,59 (m, 1H), 2,33-2,21 (m, 1H), 1,67-1,56 (m, 2H).

Ejemplo 206: (2-Bromo-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico





Etapa 1. Preparación de 8-amino-2-bromo-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona (sal clorhidrato) 206(a)

La preparación del intermedio 206(a) a partir del Intermedio 147(d) del Ejemplo **147** (2 g, 5,29 mmol) y HCl 4,0 M en dioxano (26,4 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el Intermedio 206(a) (1,59 g, 5,04 mmol) en forma de un polvo amarillo con un rendimiento del 96%.

^{1}H RMN (d_6-DMSO): δ 13,13 (s, 1H), 10,67 (s, 1H), 7,52 (s, 1H), 7,51 (s, 1H), 7,35 (s, 1H).

EMCL: $(M+H^+)$ 279,0, 281,1, $(M+Na^+)$ 401,0, 403,0; $(M-H)^-$ 277,0, 279,0.

Etapa 2. Preparación del compuesto del título: (2-Bromo-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

Preparación del compuesto del título a partir del Intermedio 206(a) (120 mg, 0,380 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (74,0 mg, 0,457 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (88 mg, 0,461 mmol) y 4-dimetilaminopiridina (56 mg, 0,459 mmol) en *N,N*-dimetilformamida (15,0 ml) se realizó de forma análoga al Ejemplo **190**, etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1,2:1 de diclorometano:acetato de etilo, proporcionando el compuesto del título (52,4 mg, 0,124 mmol) en forma de un sólido amarillo con un rendimiento del 33%.

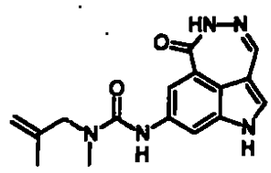
^{1}H RMN (d_6-DMSO): δ 12,59 (s, 1H), 10,45 (s, 1H), 10,44 (s, 1H), 8,08 (d, 1H, J = 1,51 Hz), 7,60 (d, 1H, *J* = 1,70 Hz), 7,33-7,24 (m, 3H), 7,24-7,13 (m,

3H), 2,42-2,32 (m, 1H), 2,11-2,00 (m, 1H), 1,54-1,42 (m, 1H), 1,42-1,30 (m, 1H).

EMCL: ($M+H^+$) 423,0, 425,0, ($M+Na^+$) 445,0, 447,0; $(M-H)^-$ 421,0, 423,0,

EMAR: ($M+H^+$) calculado para $C_{20}H_{16}N_4O_2Br$, 423,0457, encontrado 423,0471.

Ejemplo 207: *N*-Metil-*N*-(2-metilprop-2-enil)-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)urea



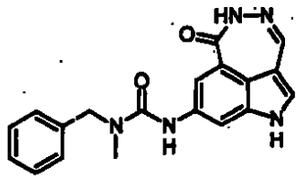
Usando una vía similar a la indicada en el Ejemplo **192**, el compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol) y carbonato de *N,N*-disuccinimidilo (27 mg, 0,11 mmol) se agitaron juntos en *N,N*-dimetilformamida (1 ml) mientras se añadía *N,N*-diisopropiletilamina (0,024 ml, 0,21 mmol). Después de agitar durante tres minutos, se añadió *N*-2-dimetilprop-2-en-1-amina (0,046 ml, 0,21 mmol) dando el producto puro. A la mezcla se la añadió directamente resina eliminadora de poliestireno de intercambio de cationes (Argonaut Technologies™, MP-TsOH). Después de agitar durante 2 horas, la resina se retiró por filtración y se lavó dos veces con *N,N*-dimetilformamida (1 ml). Después, las soluciones de *N,N*-dimetilformamida combinadas se trataron con resina de eliminación de poliestireno de intercambio de aniones (Argonaut Technologies™, MP-carbonato) y se agitó durante 2 horas. De nuevo, la resina se retiró por filtración y se lavó dos veces con *N,N*-dimetilformamida (1 ml). Después, las soluciones de *N,N*-dimetilformamida combinadas se redujeron al vacío y se sometieron a RPHPLC preparativa (Peeke Scientific HI-Q, C18 fase

inversa, 5 µM, 100A, columna de 150 x 20 mm) eluyendo con ácido acético al 0,1% en CH_3CN y ácido acético al 0,1% en H_2O a un caudal de 20 ml/min usando un gradiente de 30-70% de ácido acético al 0,1% en CH_3CN durante 30 min. Las fracciones juzgadas puras se reunieron y los componentes volátiles se retiraron al vacío. Después de una trituración final con acetato de etilo, se obtuvo el compuesto del título (6 mg, 0,019 mmol) en forma de un polvo pardo con un rendimiento del 18%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,90 (s, 1H), 7,42 (s, 1H), 7,30 (s, 1H), 7,28 (s, 1H), 4,98 (s, 1H), 4,90 (s, 1H), 3,95 (s, 2H), 3,03 (s, 3H), 1,77 (s, 3H).

EMCL: ($M+H^+$) 312,2, ($M+Na^+$) 334,1.

Ejemplo 208: *N*-Metil-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-*N*-(fenilmetil)urea

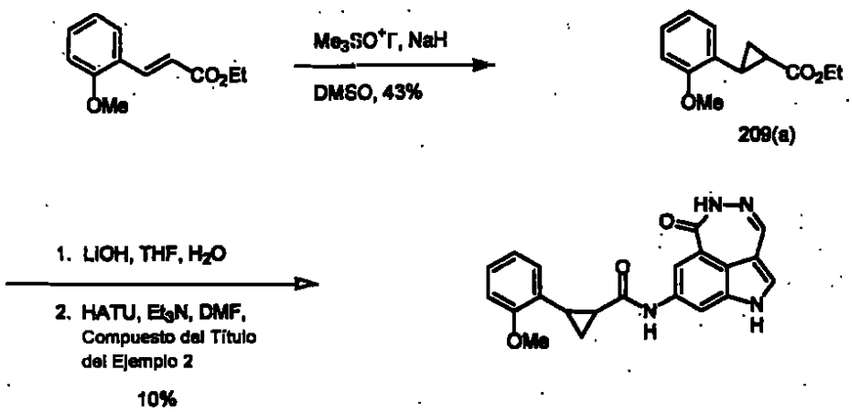


La preparación del ejemplo 208 a partir del compuesto del título del Ejemplo 2 (48 mg, 0,20 mmol), carbonato de *N,N'*-disuccinimidilo (52 mg, 0,20 mmol), trietilamina (0,084 ml, 0,60 mmol) y *N*-metil-1-fenilmetanamina (0,052 ml, 0,40 mmol) en *N,N*-dimetilformamida (0,5 ml) se realizó de forma análoga al Ejemplo **192**. La purificación, también de manera análoga, proporcionó el compuesto del título (8 mg, 0,023 mmol) en forma de un polvo pardo con un rendimiento del 12%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,88 (s, 1H), 7,46-7,23 (m, 8H), 4,64 (s, 2H, oscurecido), 3,03 (s, 3H).

EMCL: ($M+H^+$) 348,4, ($M+Na^+$) 370,4.

Ejemplo 209: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(2'-metoxi-fenil)-ciclopropanocarboxílico



Etapa 1: Preparación de éster etílico del ácido (1,2-*trans*)-2-(2'-metoxi-fenil)-ciclopropanocarboxílico 209(a)

La preparación del intermedio 209(a) a partir de NaH (1,04 g, 26 mmol) y yoduro de trimetilsulfoxonio (5,72 g, 26 mmol) y éster etílico del ácido 2-(metoxi-fenil)-acrílico (4,12 g, 20 mmol) en dimetilsulfóxido (30 ml) se realizó de manera análoga al etapa 2 del Ejemplo **113.** Se obtuvo el Intermedio 209(a) (1,89 g, 8,6 mmol) con un rendimiento del 43%.

Etapa 2: Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(2'-metoxi-fenil)-ciclopropanocarboxílico

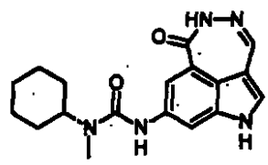
La preparación del compuesto del título se realizó de manera análoga al etapa 3 del Ejemplo **172** con la excepción de que se usó el Intermedio 209(a) en lugar del Intermedio 172(b). Se obtuvo el compuesto del título con un rendimiento del 10%.

^{1}H RMN (d_6-DMSO): δ 11,74 (d, 1H, J = 2,26 Hz), 10,35 (s, 1H), 10,24 (s, 1H), 8,14 (s, 1H), 7,57 (dd, 1H, J = 3,20, 1,51 Hz), 7,46 (s, 2H), 7,20 (t, J = 8,0

Hz, 1H), 6,77-6,74 (m, 3H), 3,80 (s, 3H), 2,36 (m, 1H), 2,02 (m, 1H), 1,44 (m, 1H), 1,34 (m, 1H).

EMCL: ($M-H^+$) 373,1.

Ejemplo 210: *N*-Ciclohexil-*N*-metil-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)urea

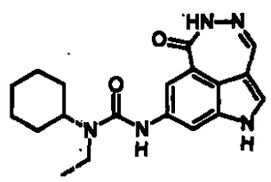


La preparación del ejemplo 210 a partir del compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol), carbonato de *N,N'*-disuccinimidilo (27 mg, 0,11 mmol), *N,N*-diisopropiletilamina (0,024 ml, 0,21 mmol) y *N*-ciclohexil-*N'*-metilamina (0,028 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo 207. La purificación, también de manera análoga, proporcionó el compuesto del título (7 mg, 0,021 mmol) en forma de un polvo amarillo con un rendimiento del 19%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,90 (s, 1H), 7,41 (s, 1H), 7,33 (s, 1H), 7,27 (s, 1H), 4,09 (m, 1H), 2,92 (s, 3H), 1,91-1,80 (m, 2H), 1,79-1,65 (m, 3H), 1,56-1,37 (m, 4H), 1,14 (m, 1H).

EMCL: ($M+H^+$) 340,2, ($M+Na^+$) 362,1.

Ejemplo 211: *N*-Ciclohexil-*N*-etil-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)urea

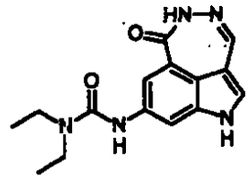


La preparación del ejemplo 211 a partir del compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol), carbonato de *N,N'*-disuccinimidilo (27 mg, 0,11 mmol), *N,N'*-diisopropiletilamina (0,024 ml, 0,21 mmol) y *N*-ciclohexil-*N*-metilamina (0,032 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **207**. La purificación, también de manera análoga, proporcionó el compuesto del título (7 mg, 0,020 mmol) en forma de un polvo amarillo con un rendimiento del 20%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,94 (s, 1H), 7,40 (s, 1H, oscurecido), 7,30 (s, 1H, parcialmente oscurecido), 7,26 (s, 1H), 4,05 (m, 1H, parcialmente oscurecido), 3,36 (m, 2H, parcialmente oscurecido), 1,90-1,74 (m, 4H), 1,71 (m, 1H), 1,58-1,33 (m, 4H), 1,26 (t, 3H, J = 7,16 Hz), 1,14 (m, 1H).

EMCL: ($M+H^+$) 354,2, ($M+Na^+$) 376,1.

Ejemplo 212: *N,N*-Dietil-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)urea

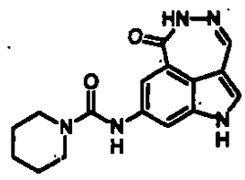


La preparación del ejemplo 212 a partir del compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol), carbonato de *N,N'*-disuccinimidilo (27 mg, 0,11 mmol), *N,N*-diisopropiletilamina (0,024 ml, 0,21 mmol) y *N,N*-dietilamina (0,022 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **207**. La purificación, también de manera análoga, proporcionó el compuesto del título (5 mg, 0,016 mmol) en forma de un polvo amarillo con un rendimiento del 15%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,91 (s, 1H), 7,41 (s, 1H), 7,32 (s, 1H), 7,27 (s, 1H), 3,42 (c, 4H, J = 7,16 Hz), 1,24 (t, 6H, J = 7,16 Hz).

EMCL: ($M+H^+$) 300,2, ($M+Na^+$) 322,1.

Ejemplo 213: *N*-(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-piperidin-1-carboxamida

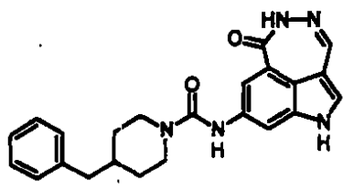


La preparación del ejemplo 213 a partir del compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol), carbonato de *N,N*-disuccinimidilo (27 mg, 0,11 mmol), *N,N*-diisopropiletilamina (0,024 ml, 0,21 mmol) y piperidina (0,021 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **207**. La purificación, también de manera análoga, proporcionó el compuesto del título (7 mg, 0,022 mmol) en forma de un polvo amarillo con un rendimiento del 20%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,77 (s, 1H), 7,65 (s, 1H), 7,43 (s, 1H, parcialmente oscurecido), 7,32 (s, 1H), 3,57-3,47 (m, 4H), 1,76-1,56 (m, 6H).

EMCL: ($M+H^+$) 312,1, ($M+Na^+$) 334,1.

Ejemplo 214: *N*-(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-(fenilmetil)piperidin-1-carboxamida

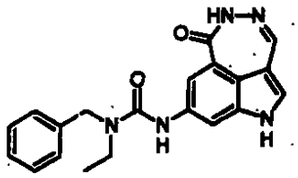


La preparación del ejemplo 214 a partir del compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol), carbonato de *N,N'*-disuccinimidilo (27 mg, 0,11 mmol), *N,N'*-diisopropiletilamina (0,024 ml, 0,21 mmol) y 4-(fenilmetil)piperidina (0,037 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **207.** La purificación, también de manera análoga, proporcionó el compuesto del título (7 mg, 0,017 mmol) en forma de un polvo amarillo con un rendimiento del 16%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,88 (s, 1H), 7,44-7,39 (m, 2H, parcialmente oscurecido), 7,34-7,12 (m, 6H), 4,16 (d, 2H, *J* = 13,75 Hz), 2,91-2,78 (m, 2H), 2,62-2,57 (m, 2H), 1,80-1,69 (m, 3H), 1,36-1,14 (m, 2H).

EMCL: ($M+H^+$) 402,2, ($M+Na^+$) 424,1.

Ejemplo 215: *N*-Etil-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-*N*-(fenilmetil)urea

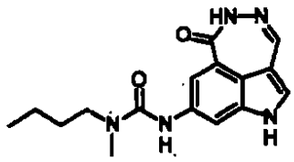


La preparación del ejemplo 215 a partir del compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol), carbonato de *N,N*-disuccinimidilo (27 mg, 0,11 mmol), *N,N*-diisopropiletilamina (0,024 ml, 0,21 mmol) y *N*-(fenilmetil)etanamina (0,032 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **207.** La purificación, también de manera análoga, proporcionó el compuesto del título (7 mg, 0,019 mmol) en forma de un polvo amarillo con un rendimiento del 18%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,94 (s, 1H), 7,46-7,21 (m, 8H, parcialmente oscurecido), 4,63 (s, 2H), 3,51-3,34 (m, 2H, parcialmente oscurecido), 1,28-1,19 (m, 3H).

EMCL: ($M+H^+$) 362,1, ($M+Na^+$) 384,0.

Ejemplo 216: *N*-Butil-*N*-metil-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)urea

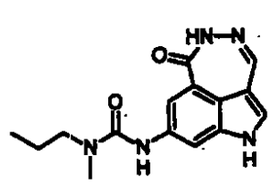


La preparación del ejemplo 216 a partir del compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol), carbonato de *N,N'*-disuccinimidilo (27 mg, 0,11 mmol), *N,N*-diisopropiletilamina (0,024 ml, 0,21 mmol) y *N*-etil-*N*-propilamina (0,025 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **207.** La purificación, también de manera análoga, proporcionó el compuesto del título (4 mg, 0,013 mmol) en forma de un polvo amarillo con un rendimiento del 12%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,92 (s, 1H), 7,41 (s, 1H, parcialmente oscurecido), 7,29 (s, 1H), 7,26 (s, 1H), 3,04 (s, 3H), 1,66-1,55 (m, 2H), 1,45-1,21 (m, 4H), 0,97 (t, 3H, J = 7,35 Hz).

EMCL: ($M+H^+$) 314,1, ($M+Na^+$) 336,2.

Ejemplo 217: *N*-Metil-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-*N*-propilurea

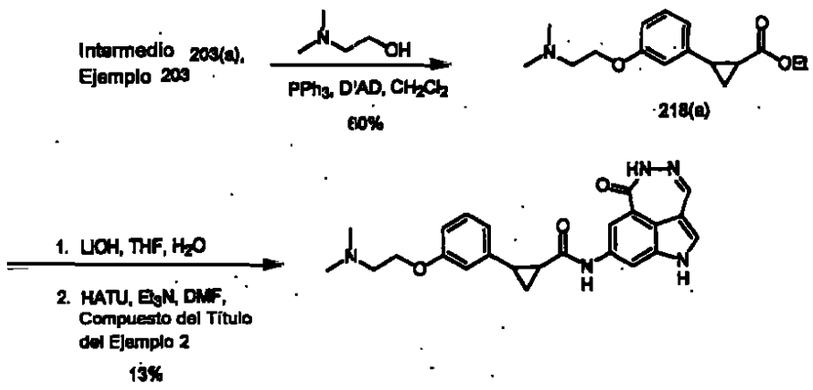


La preparación del ejemplo 217 a partir del compuesto del título del Ejemplo 2 (25 mg, 0,11 mmol), carbonato de *N,N*-disuccinimidilo (27 mg, 0,11 mmol), *N,N*-diisopropiletilamina (0,024 ml, 0,21 mmol) y *N*-etil-*N*-propilamina (0,022 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de forma análoga al Ejemplo **207**. La purificación, también de manera análoga, proporcionó el compuesto del título (4 mg, 0,013 mmol) en forma de un polvo amarillo con un rendimiento del 12%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 7,87 (s, 1H), 7,43 (s, 1H), 7,36 (s, 1H), 7,29 (s, 1H), 3,05 (s, 3H), 1,72-1,58 (m, 2H), 1,37-1,21 (m, 2H), 0,96 (t, 3H, J = 7,25 Hz).

EMCL: ($M+H^+$) 300,2, ($M+Na^+$) 322,1.

Ejemplo 218: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-[3-(2-dimetilamino-etoxi)-fenil]-ciclopropanocarboxílico



Etapa 1. Preparación de ácido (1,2-*trans*)-2-[3-(2-dimetilamino-etoxi)-fenil]-ciclopropanocarboxílico 218(a)

A una solución agitada del Intermedio 203(a) del Ejemplo **203** (125 mg, 0,607 mmol), 2-dimetiletanol (81 mg, 0,91 mmol) y trifenilfosfina (239 mg, 0,91 mmol) en CH_2Cl_2 se le añadió azodicarboxilato de diisopropilo (184 mg, 0,91

mmol). La mezcla se agitó a temperatura ambiente durante 4 horas, se concentró y se sometió a cromatografía sobre gel de sílice, eluyendo con acetato de etilo al 20-30%/hexano, formando el Intermedio 218(a) en forma de un aceite incoloro (101 mg, 0,36 mmol) con un rendimiento del 60%.

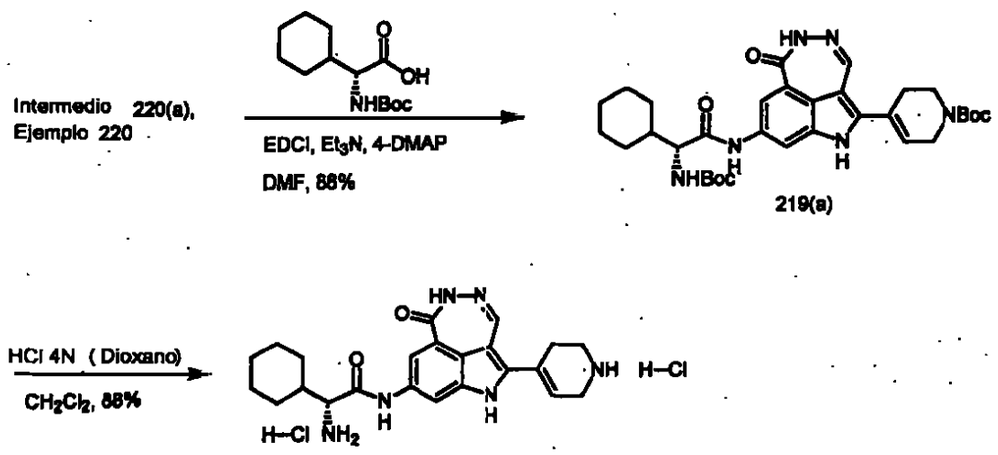
Etapa 2. Preparación del compuesto del título: (6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-[3-(2-dimetilamino-etoxi)-fenil]-ciclopropanocarboxílico

La preparación del compuesto del título se realizó de manera análoga a la etapa 3 del Ejemplo **172** con la excepción de que se usó el Intermedio 218(a) en lugar del Intermedio 172(b). Se obtuvo el compuesto del título con un rendimiento del 13%.

^{1}H RMN (d_6-DMSO): δ 11,56 (d, 1H, *J* = 2,26 Hz), 10,20 (s, 1H), 10,06 (s, 1H), 7,95 (d, 1H, J = 1,88 Hz), 7,38 (dd, 1H, J = 3,20, 1,51 Hz), 7,29 (s, 1H), 7,04 (t, 1H, J = 8,0 Hz), 6,62-6,58 (m, 3H), 6,36 (s, 1H), 3,96-3,94 (m, 2H), 3,12-3,10 (m, 2H), 2,29 (m, 1H), 1,91 (m, 1H), 1,31 (m, 1H), 1,20 (m, 1H).

EMCL: ($M+H^+$) 432,2.

Ejemplo 219: (*R*)-2-Amino-2-ciclohexil-*N*-[6-oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida; diclorhidrato



Etapa 1. Preparación de éster *terc*-butílico del ácido (*R*)-4-[8-(2-*terc*-butoxicarbonilamino-2-ciclohexil-acetilamino)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il]-3,6-dihidro-2H-piridina-1-carboxílico 219(a)

La preparación del intermedio 219(a) a partir del Intermedio 220(a) del Ejemplo **220** (100 mg, 0,262 mmol), ácido (R)-*terc*-butoxicarbonilamino-ciclohexil-acético (74,3 mg, 0,289 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (55 mg, 0,288 mmol) y 4-dimetilaminopiridina (35,2 mg, 0,288 mmol) en *N,N*-dimetilformamida (6,0 ml) se realizó de forma análoga al Ejemplo **190**, etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1:1 de diclorometano:acetato de etilo, proporcionando el Intermedio 219(a) (143 mg, 0,231 mmol) en forma de un sólido amarillo con un rendimiento del 88%.

^{1}H RMN (d_6-DMSO): δ 11,70 (s, 1H), 10,27 (s, 1H), 10,09 (s, 1H), 8,06 (d, 1H, J = 1,51 Hz), 7,59 (s, 1H), 7,51 (s, 1H), 6,88 (d, 1H, *J* = 8,10 Hz), 6,17

(s, 1H), 4,06 (s a, 2H), 3,92 (dd, 1H, *J* = 8,48, 7,72 Hz), 3,55 (t, 2H, *J* = 5,65, 5,27 Hz), 3,32 (m, 2H, oscurecido), 1,76-1,46 (m, 6H), 1,43 (s, 9H), 1,37 (s, 9H), 1,19-0,94 (m, 5H).

EMCL: $(M-H)^-$ 619,2.

Etapa 2. Preparación del compuesto del título: (R)-2-Amino-2-ciclohexil-*N*-[6-oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida; diclorhidrato

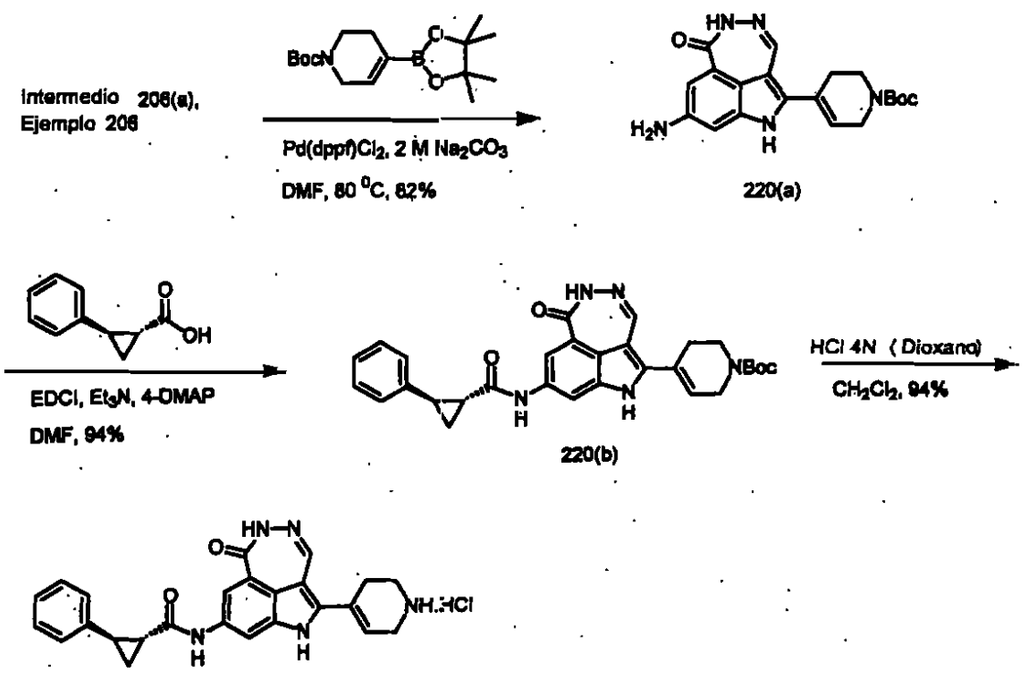
La preparación del compuesto del título a partir del Intermedio 219(a) (143 mg, 0,231 mmol) y HCl 4,0 M en dioxano (2,3 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (100 mg, 0,203 mmol) en forma de un polvo rojo con un rendimiento del 88%.

^{1}H RMN (d_6-DMSO): δ 12,18 (s, 1H), 10,87 (s, 1H), 10,39 (s, 1H), 9,32 (s a, 2H), 8,35 (s a, 3H), 8,07 (d, 1H, *J* = 1,51 Hz), 7,70 (d, 1H, J = 1,51 Hz), 7,55 (d, 1H, J = 1,51 Hz), 6,19 (s, 1H), 3,87-3,74 (m, 3H), 3,41-3,26 (m, 2H), 2,81-2,69 (m, 2H), 1,90-1,55 (m, 6H), 1,28-0,97 (m, 5H).

EMCL: $(M+H^+)$ 421,1, $(M+Na^+)$ 443,1; $(M-H)^-$ 419,1.

EMAR: $(M+H^+)$ calculado para $C_{23}H_{29}N_6O_2$, 421,2352, encontrado 421,2338.

Ejemplo 220: [6-Oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)



Etapa 1. Preparación de éster *terc*-butílico del ácido 4-(8-amino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il)-3,6-dihidro-2*H*-piridina-1-carboxílico 220(a)

De manera análoga a la del Ejemplo **184,** se añadió Na_2CO_3 acuoso 2,0 M (0,66 ml) a una mezcla del Intermedio 206(a) del Ejemplo **206** (1 g, 3,17 mmol), éster *terc*-butílico del ácido 4-(4,4,5,5-tetrametil-[1,2]dioxaborolan-2-il)-3,6-dihidro-2H-piridina-1-carboxílico (1,18 g, 3,82 mmol) y [1,1'-*bis*(difenilfosfino)ferroceno]dicloropaladio (II) (0,13 g, 0,159 mmol) en *N,N*-dimetilformamida anhidra (50 ml) y la reacción se calentó a 80°C durante 16 horas. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío. Se añadieron acetato de etilo (50 ml), metanol (5 ml) y H_2O (500 ml) y la fase acuosa se extrajo con acetato de etilo (3 x 20 ml). Los extractos de acetato de etilo combinados se lavaron con H_2O (2 x 50 ml) y salmuera (50 ml) y se dejaron secar sobre Na_2SO_4. Después de la filtración, los

componentes volátiles se retiraron al vacío y al residuo se le añadió CH_2Cl_2. El sólido resultante se recogió por filtración y se lavó con CH_2Cl_2 y éter dietílico, proporcionando el Intermedio 220(a) (1 g, 2,62 mmol) en forma de un sólido rojo con un rendimiento del 82%.

^{1}H RMN (d_6-DMSO): δ 11,15 (s, 1H), 10,04 (s, 1H), 7,42 (s, 1H), 6,92 (d, 1H, *J* = 1,88 Hz), 6,56 (d, 1H, J = 1,88 Hz), 6,05 (s a, 1H), 5,17 (s, 2H), 4,03 (s, 2H), 3,53 (t, 2H, *J* = 5,65, 5,27 Hz), 3,36 (m, 2H, parcialmente oscurecido), 1,42 (s, 9H).

EMCL: $(M+H^+)$ 382,1, $(M+Na^+)$ 404,3; $(M-H)^-$ 380,1.

Etapa 2. Preparación de éster *terc*-butílico del ácido (1*R*,2*R*)-4-{6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-3,6-dihidro-2*H*-piridina-1-carboxílico 220(b)

La preparación del intermedio 220(b) a partir del Intermedio 220(a) (100 mg, 0,262 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (47,0 mg, 0,290 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (55 mg, 0,288 mmol) y 4-dimetilaminopiridina (35,2 mg, 0,288 mmol) en *N,N*-dimetilformamida (6,0 ml) se realizó de forma análoga al Ejemplo **190**, etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1:1 de diclorometano:acetato de etilo, proporcionando el Intermedio 220(b) (130 mg, 0,248 mmol) en forma de un sólido amarillo con un rendimiento del 94%.

^{1}H RMN (d_6-DMSO): δ 11,71 (s, 1H), 10,39 (s, 1H), 10,26 (s, 1H), 8,07 (d, 1H, J = 1,70 Hz), 7,57 (d, 1H, J = 1,70 Hz), 7,50 (s, 1H), 7,33-7,25 (m, 2H), 7,23-7,15 (m, 3H), 6,16 (s, 1H), 4,08-4,04 (m, 2H), 3,55 (t, 2H, J = 5,65, 5,27 Hz), 3,35 (m, 2H, oscurecido), 2,41-2,33 (m, 1H), 2,11-2,02 (m, 1H), 1,53-1,46 (m, 1H), 1,43 (s, 9H), 1,40-1,30 (m, 1H).

EMCL: $(M-H)^-$ 524,1.

Etapa 3. Preparación del compuesto del título: [6-oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)

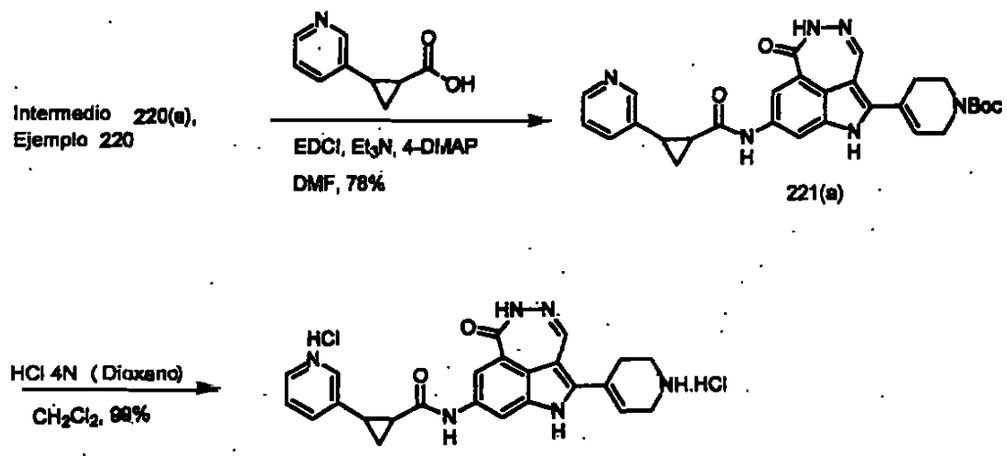
La preparación del compuesto del título a partir del Intermedio 220(b) (130 mg, 0,248 mmol) y HCl 4,0 M en dioxano (1,24 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, proporcionó el compuesto del título (107 mg, 0,232 mmol) en forma de un polvo rojo con un rendimiento del 94%.

^{1}H RMN (d_6-DMSO): δ 11,97 (s, 1H), 10,47 (s, 1H), 10,33 (s, 1H), 9,31-9,10 (s a, 2H), 8,11 (d, 1H, J = 1,70 Hz), 7,61 (d, 2H, J = 1,70 Hz), 7,53 (s, 1H), 7,34-7,24 (m, 2H), 7,24-7,12 (m, 3H), 6,17 (s, 1H), 3,87-3,72 (m, 2H), 3,40-3,25 (m, 2H), 2,80-2,66 (m, 2H), 2,42-2,31 (m, 1H), 2,15-2,04 (m, 1H), 1,55-1,42 (m, 1H), 1,42-1,29 (m, 1H).

EMCL: $(M+H^+)$ 426,0, $(M+Na^+)$ 448,1; $(M-H)^-$ 424,1.

EMAR: $(M+H^+)$ calculado para $C_{25}H_{24}N_5O_2$, 426,1930, encontrado 426,1924.

Ejemplo 221: [6-Oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico; diclorhidrato



Etapa 1. Preparación de éster *terc*-butílico del ácido (1,2-*trans*)-4-{6-oxo-8-[(2-piridin-3-il-ciclopropanocarbonil)amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-3,6-dihidro-2H-piridina-1-carboxílico 221(a)

La preparación del intermedio 221 (a) a partir del Intermedio 220(a) del Ejemplo **220** (100 mg, 0,262 mmol), ácido 2-piridin-3-il-ciclopropanocarboxílico bruto (pureza estimada de aprox. 75%) (67,3 mg, aprox. 0,289 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (55 mg, 0,288 mmol) y 4-dimetilaminopiridina (35,2 mg, 0,288 mmol) en *N,N*-dimetilformamida (10,0 ml) se realizó de forma análoga al Ejemplo **190**, etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 20:1 de diclorometano:metanol, proporcionando el Intermedio 221 (a) (107,6 mg, 0,204 mmol) en forma de un sólido amarillo con un rendimiento del 78%.

^{1}H RMN (d_6-DMSO): δ 11,72 (s, 1H), 10,42 (s, 1H), 10,26 (s, 1H), 8,50 (s, 1H), 8,40 (d, 1H, *J* = 4,71 Hz), 8,07 (s, 1H), 7,57 (s, 1H), 7,55 (d, 1H, J = 7,91 Hz), 7,50 (s, 1H), 7,32 (dd, 1H, *J* = 4,71, 3,77 Hz), 6,16 (s, 1H), 4,05 (s a, 2H), 3,55 (t, 2H, *J* = 4,52, 4,71 Hz), 3,35 (m, 2H, oscurecido), 2,46-2,37 (m, 1H), 2,16-2,06 (m, 1H), 1,57-1,48 (m, 1H), 1,43 (s, 9H), 1,48-1,38(m, 1H).

EMCL: $(M+H^+)$ 527,2; $(M-H)^-$ 525,0.

Etapa 2. Preparación del compuesto del título: [6-oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico; diclorhidrato

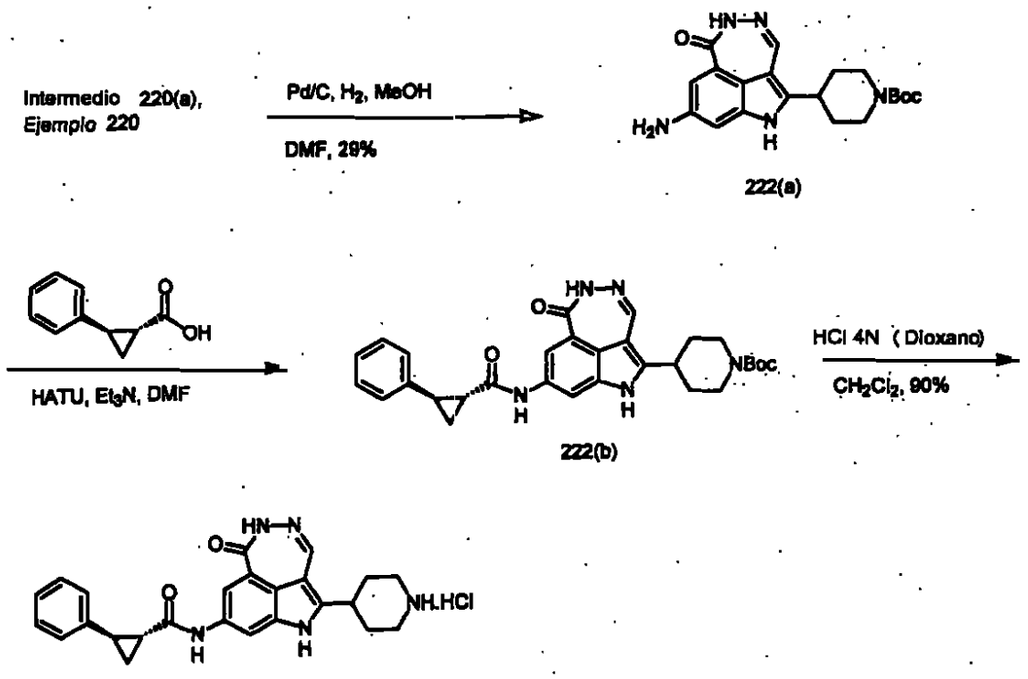
La preparación del compuesto del título a partir del Intermedio 221(a) (100 mg, 0,190 mmol) y HCl 4,0 M en dioxano (0,95 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (95 mg, 0,190 mmol) en forma de un polvo rojo con un rendimiento del 99%.

^{1}H RMN (d_6-DMSO): δ 12,05 (s, 1H), 10,66 (s, 1H), 10,34 (s, 1H), 9,29 (s a, 2H), 8,89 (d, 1H, J = 1,51 Hz), 8,74 (d, 1H, *J* = 5,27 Hz), 8,32 (d, 1H, J = 8,48 Hz), 8,10 (d, 1H, J = 1,51 Hz), 7,94 (dd, 1H, J = 6,03, 5,65 Hz), 7,65 (d, 1H, J = 1,51 Hz), 7,53 (s, 1H), 6,17 (s, 1H), 3,85-3,74 (m, 2H), 3,38-3,25 (m, 2H), 2,80-2,70 (m, 2H), 2,70-2,59 (m, 1H), 2,40-2,29 (m, 1H), 1,69-1,55 (m, 2H).

EMCL: $(M+H^+)$ 427,1, $(M+Na^+)$ 449,1; $(M-H)^-$ 425,0.

EMAR: $(M+H^+)$ calculado para $C_{24}H_{23}N_6O_2$, 427,1882, encontrado 427,1895.

Ejemplo 222: (6-Oxo-2-piperidin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)



Etapa 1. Preparación de éster *terc*-butílico del ácido 4-(8-amino-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il)-piperidin-1-carboxílico 222(a)

De manera análoga a la del Ejemplo **183,** se añadió paladio (al 10% sobre carbono activado) (0,186 g) a una solución del Intermedio 220(a) del Ejemplo **220** (0,61 g, 1,60 mmol) en 9:1 de metanol:*N,N*-dimetilformamida (50 ml). La mezcla de reacción se purgó con H_2 y se agitó a temperatura ambiente en una atmósfera de H_2 (1 atm) durante 6,5 horas. La mezcla se filtró y el filtrado se evaporó. El residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 50:3 de diclorometano:metanol, dando el

Intermedio 222(a) (0,18 g, 0,470 mmol) en forma de un sólido amarillo con un rendimiento del 29%.

^{1}H RMN (d_6-DMSO): δ 11,03 (s, 1H), 9,88 (s, 1H), 7,43 (s, 1H), 6,86 (s, 1H), 6,54 (s, 1H), 5,04 (s a, 2H), 4,16-3,99 (m, 3H), 2,95-2,67 (m, 2H), 1,73-1,54 (m, 4H), 1,42 (s, 9H).

EMCL: $(M+H^+)$ 384,1, $(M+Na^+)$ 406,2; $(M-H)^-$ 382,1.

Etapa 2. Preparación de éster *terc*-butílico del ácido (1*R*,2*R*)-4-[6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il]-piperidin-1-carboxílico 222(b)

La preparación del intermedio 222(b) a partir del Intermedio 222(a) (60 mg, 0,157 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (27,9 mg, 0,172 mmol), trietilamina (0,086 ml, 0,617 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (71,5 mg, 0,188 mmol) en *N,N*-dimetilformamida (5,0 ml) se realizó de forma análoga al Ejemplo **11.** Los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1:1 de diclorometano:acetato de etilo, proporcionando el Intermedio 222(b) (104 mg) en forma de un sólido amarillo contaminado con *N,N*-dimetilformamida que se lleva a continuación directamente a la siguiente etapa.

^{1}H RMN (d_6-DMSO): δ 11,57 (s, 1H), 10,32 (s, 1H), 10,12 (s, 1H), 7,98 (s, 1H), 7,55 (d, 1H, J = 1,32 Hz), 7,54 (s, 1H), 7,33-7,25 (m, 2H), 7,22-7,15 (m, 3H), 4,19-4,00 (m, 3H), 2,92-2,77 (m, 2H), 2,41-2,30 (m, 1H), 2,12-2,00 (m, 1H), 1,80-1,56 (m, 4H), 1,53-1,45 (m, 1H), 1,42 (s, 9H), 1,38-1,29 (m, 1H).

EMCL: $(M+H^+)$ 528,2, $(M+Na^+)$ 550,1; $(M-H)^-$ 526,1.

Etapa 3. Preparación del compuesto del título: (6-oxo-2-piperidin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)

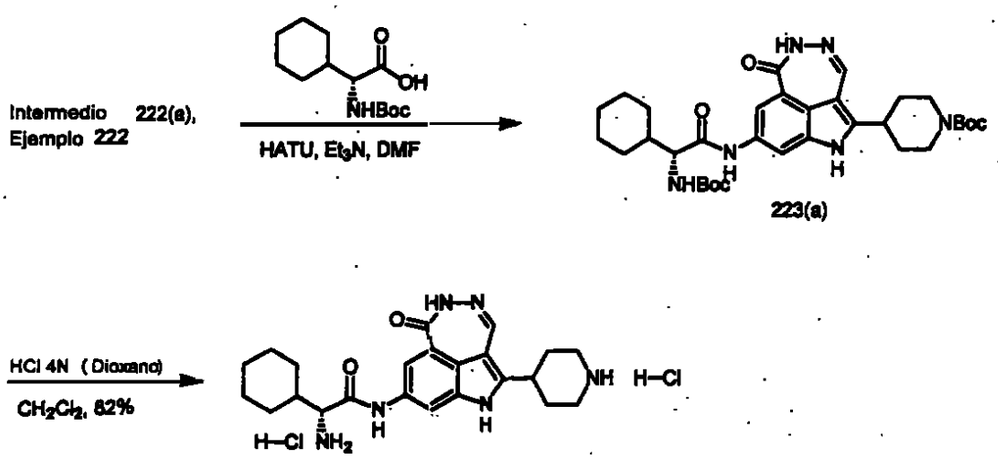
La preparación del compuesto del título a partir del Intermedio 222(b) (100 mg) y HCl 4,0 M en dioxano (1 ml) se realizó de forma análoga al Ejemplo 91. El aislamiento, también de manera análoga, proporcionó el compuesto del título (65,3 mg, 0,141 mmol) en forma de un polvo amarillo con un rendimiento combinado del 90% para las etapas 2 y 3.

^{1}H RMN (d_6-DMSO): δ 11,82 (s, 1H), 10,41 (s, 1H), 10,18 (s, 1H), 9,16-9,00 (m, 1H), 8,93-8,73 (m, 1H), 8,07 (s, 1H), 7,58 (s, 2H), 7,34-7,23 (m, 2H), 7,23-7,09 (m, 3H), 3,46-3,26 (m, 3H), 3,10-2,90 (m, 2H), 2,41-2,29 (m, 1H), 2,15-2,03 (m, 1H), 2,03-1,85 (m, 4H), 1,53-1,40 (m, 1H), 1,40-1,27 (m, 1H).

EMCL: ($M+H^+$) 428,1, ($M+Na^+$) 450,2; $(M-H)^-$ 426,2.

EMAR: ($M+H^+$) calculado para $C_{25}H_{26}N_5O_2$, 428,2087, encontrado 428,2086.

Ejemplo 223: (*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-piperidin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida; diclorhidrato



Etapa 1. Preparación de éster *terc*-butílico del ácido (*R*)-4-[8-(2-*terc*-butoxicarbonilamino-2-ciclohexil-acetilamino)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il]-piperidin-1-carboxílico 223(a)

La preparación del intermedio 223(a) a partir del Intermedio 222(a) del Ejemplo **222** (60 mg, 0,157 mmol), ácido (*R*)-*terc*-butoxicarbonilamino-ciclohexil-acético (44,3 mg, 0,172 mmol), trietilamina (0,086 ml, 0,617 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (71,5 mg, 0,188 mmol) en *N,N*-dimetilformamida (8,0 ml) se realizó de forma análoga al Ejemplo **11**. Los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1:1 de diclorometano:acetato de etilo, proporcionando el Intermedio 223(a) (107 mg) en forma de un sólido amarillo contaminado con *N,N*-dimetilformamida que se lleva a continuación directamente a la siguiente etapa.

^{1}H RMN (d_6-DMSO): δ 11,57 (s, 1H), 10,14 (s, 1H), 10,03 (s, 1H), 7,98 (s, 1H), 7,94 (s, 1H), 7,56 (s, 1H), 7,54 (s, 1H), 6,85 (d, 1H, *J* = 8,48 Hz), 4,15-3,99 (m, 2H), 3,99-3,85 (m, 1H), 2,92-2,76 (m, 2H), 1,78-1,45 (m, 10H), 1,42 (s, 9H), 1,37 (s, 9H), 1,22-0,97 (m, 5H).

EMCL: $(M+H^+)$ 623,2, $(M+Na^+)$ 645,2; $(M-H)^-$ 621,2.

Etapa 2. Preparación del compuesto del título: (*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-piperidin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida; diclorhidrato

La preparación del compuesto del título a partir del Intermedio 223(a) (100 mg, 0,161 mmol) y HCl 4,0 M en dioxano (1,6 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga,

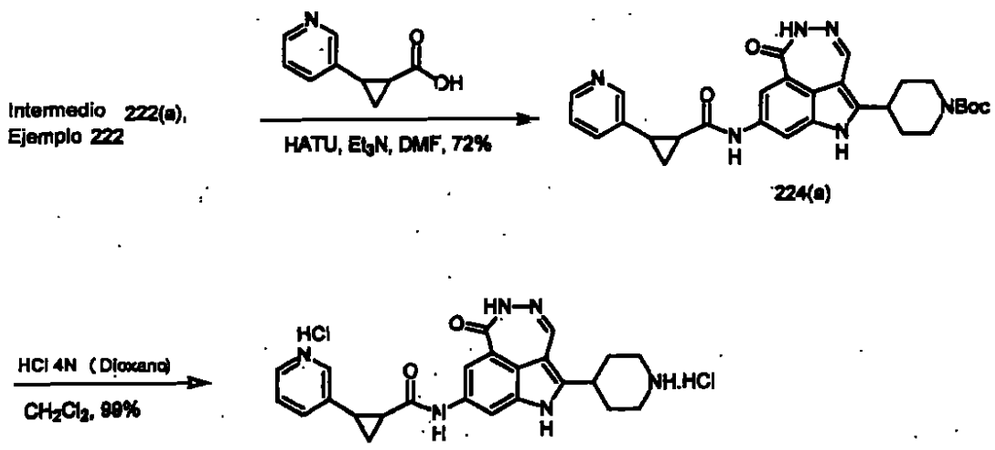
proporcionó el compuesto del título (63,2 mg, 0,128 mmol) en forma de un polvo amarillo con un rendimiento combinado del 82% para las etapas 1 y 2.

^{1}H RMN (d_6-DMSO): δ 11,98 (s, 1H), 10,82 (s, 1H), 10,24 (s, 1H), 9,21-9,06 (m, 1H), 9,06-8,87 (m, 1H), 8,35 (s, 3H), 8,04 (s, 1H), 7,64 (d, 1H, J = 1,70 Hz), 7,60(s, 1H), 3,47-3,28 (m, 4H), 3,10-3,29 (m, 2H), 2,10-1,86 (m, 4H), 1,86-1,52 (m, 6H), 1,28-0,94 (m, 5H).

EMCL: $(M+H^+)$ 423,2, $(M+Na^+)$ 445,1; $(M-H)^-$ 421,3.

EMAR: $(M+H^+)$ calculado para $C_{23}H_{31}N_6O_2$, 423,2508, encontrado 423,2492.

Ejemplo 224: Diclorhidrato de (6-oxo-2-piperidin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico



Etapa 1. Preparación de éster *terc*-butílico del ácido 4-{6-oxo-8-[(1,2-*trans*)-(2-piridin-3-il-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-piperidin-1-carboxílico 224(a)

La preparación del intermedio 224(a) a partir del Intermedio 222(a) del Ejemplo **222** (60 mg, 0,157 mmol), ácido (1,2-*trans*)-2-piridin-3'-il-

ciclopropanocarboxílico (40,2 mg, 75%, 0,172 mmol), trietilamina (0,086 ml, 0,617 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (71,5 mg, 0,188 mmol) en *N,N*-dimetilformamida (8,0 ml) se realizó de forma análoga al Ejemplo **11.** Los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 25:1 de diclorometano:metanol, proporcionando el Intermedio 224(a) (59,2 mg, 0,112 mmol) en forma de un sólido amarillo con un rendimiento del 72%.

^{1}H RMN (d_6-DMSO): δ 11,59 (s, 1H), 10,39 (s, 1H), 10,14 (s, 1H), 8,65 (d, 1H, J = 2,07 Hz), 8,53 (dd, 1H, *J* = 4,99, 1,41 Hz), 7,98 (d, 1H, *J* = 1,70 Hz), 7,84 (d, 1H, *J* = 7,91 Hz), 7,59-7,53 (m, 3H), 4,16-4,02 (m, 3H), 2,95-2,74 (m, 2H), 2,22-2,13 (m, 1H), 1,78-1,45 (m, 7H), 1,42 (s, 9H).

EMCL: $(M+H^+)$ 529,1; $(M-H)^-$ 527,2.

Etapa 2. Preparación del compuesto del título: (6-oxo-2-piperidin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-(2-piridin-3-il-ciclopropanocarboxílico); diclorhidrato

La preparación del compuesto del título a partir del Intermedio 224(a) (50 mg, 0,095 mmol) y HCl 4,0 M en dioxano (0,5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (47,4 mg, 0,095 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

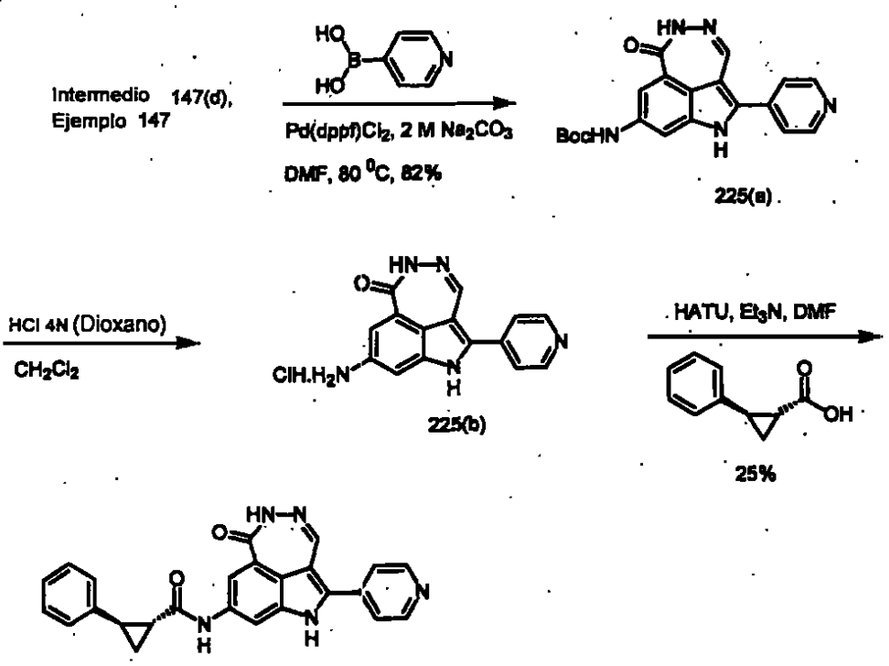
^{1}H RMN (d_6-DMSO): δ 11,87 (s, 1H), 10,59 (s, 1H), 10,20 (s, 1H), 9,18-9,00 (m, 2H), 8,89 (s a, 2H), 8,72 (d, 1H, J = 5,09 Hz), 8,33 (d, 1H, *J* = 8,10 Hz), 8,07 (s, 1H), 7,96 (dd, 1H, J = 8,10, 7,72 Hz), 7,60 (d, 2H, *J* = 5,09 Hz), 3,47-

3,29 (m, 3H), 3,11-2,84 (m, 2H), 2,75-2,61 (m, 1H), 2,40-2,29 (m, 1H), 2,09-1,84 (m, 4H), 1,70-1,54 (m, 2H).

EMCL: $(M+H^+)$ 429,2, $(M+Na^+)$ 451,1; $(M-H)^-$ 427,1.

EMAR: $(M+H^+)$ calculado para $C_{24}H_{25}N_6O_2$, 429,2039, encontrado 429,2021.

Ejemplo 225: (1*R*,2*R*)-*N*-(6-Oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida



Etapa 1. Preparación de 6-oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamato de *terc*-butilo 225(a)

Una mezcla del Intermedio 147(d) del Ejemplo **147** (0,50 g, 1,3 mmol), ácido 4-piridil-bórico (0,25 g, 2,0 mmol), [1,1-*bis*(difenilfosfino)ferroceno]dicloropaladio (II) (106 mg, 0,13 mmol) y carbonato sódico acuoso 3,0 M (3,3 ml) en *N,N*-dimetilformamida (20 ml) se agitó a 100°C

durante 4 horas. Los componentes volátiles se retiraron al vacío y el residuo se sometió a cromatografía sobre gel de sílice, eluyendo con CH_2Cl_2:metanol (95:5 aumentando a 90:10). Se obtuvo el Intermedio 225(a) (0,41 g) con un rendimiento del 82%.

^{1}H RMN (d_6-DMSO): δ 12,22 (s, 1H), 10,52 (s, 1H), 9,60 (s, 1H), 8,74 (s, 1H), 8,72 (s, 1H), 7,85 (d, 1H, *J* = 1,7 Hz), 7,75 (d, 1H, *J* = 1,7 Hz), 7,60-7,72 (m, 3H), 1,51 (s, 9H).

EMCL (M^++1): 378,1

Etapa 2. Preparación de clorhidrato de 8-amino-2-piridin-4-il-1,5-dihidro-6H-[1,2]diazepino[4,5,6-*cd*]indol-6-ona 225(b)

A una mezcla del Intermedio 225(a) (0,38 g, 1,0 mmol) en CH_2Cl_2 (30 ml), se le añadió HCl 1 M en éter dietílico (20 ml). Después, la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se retiraron al vacío, proporcionando el Intermedio 225(b) que se lleva a continuación directamente a la siguiente etapa sin purificación adicional.

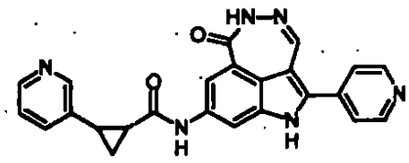
Etapa 3. Preparación del compuesto del título: (1*R*,2*R*)-*N*-(6-oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-cd]indol-8-il)-2-fenilciclopropanocarboxamida

Una solución del Intermedio 225(b) (aprox. 0,5 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (113 mg, 0,7 mmol), trietilamina (0,4 ml) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (0,23 g, 0,6 mmol) en 10 ml de *N,N*-dimetilformamida se agitó a temperatura ambiente durante 3 horas. La mezcla se sometió a HPLC preparativa, proporcionando el compuesto del título (107 mg, 0,25 mmol) con un rendimiento del 25% para las etapas 2 y 3.

^{1}H RMN (d_6-DMSO): δ 12,25 (s, 1H), 10,49 (s, 1H), 10,44 (s, 1H), 8,67 (s, 1H), 8,65 (s, 1H), 8,16 (s, 1H), 7,48-7,91 (m, 4H), 7,20-7,46 (m, 2H), 6,96-7,20 (m, 3H), 2,26-2,40 (m, 1H), 1,94-2,13 (m, 1H) 1,39-1,60 (m, 1H), 1,22-1,39 (m, 1H).

EMAR calculado para $C_{25}H_{19}N_5O_2$, 422,1617 (M+H), encontrado 422,1626.

Ejemplo 226: *N*-(6-Oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,2-*trans*)-2-piridin-3-ilciclopropanocarboxamida

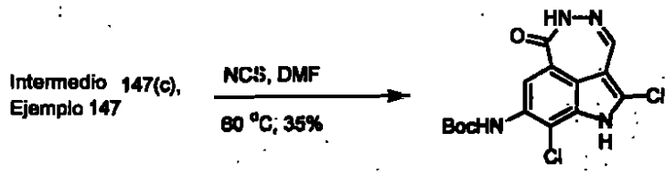


La preparación del ejemplo 226 a partir del Intermedio 147(d) del Ejemplo **147** (200 mg, 0,529 mmol) se realizó de manera análoga a la preparación del Ejemplo **225** en tres etapas con la excepción de que se usó ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico en lugar de ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico en la etapa 3. El aislamiento, también de manera análoga, proporcionó el compuesto del título (54 mg) en forma de un polvo amarillo con un rendimiento total del 25%.

^{1}H RMN (d_6-DMSO): δ 12,26 (s, 1H), 10,49 (s, 1H), 10,47 (s, 1H), 8,67 (s, 1H), 8,65 (s, 1H), 8,46 (s, 1H), 8,30-8,43 (d, 1H, *J* = 4,7 Hz), 8,16 (s, 1H), 7,57-7,88 (m, 4H), 7,45-7,57 (m, 1H), 7,19-7,41 (m, 1H), 2,32-2,42 (m, 1H), 2,01-2,20 (m, 1H), 1,46-1,65 (m, 1H), 1,32-1,46 (m, 1H).

EMAR calculado para $C_{24}H_{18}N_6O_2$ 423,1569 (M+H), encontrado 423,1598.

Ejemplo 227: Éster *terc*-butílico del ácido (2,9-dicloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico

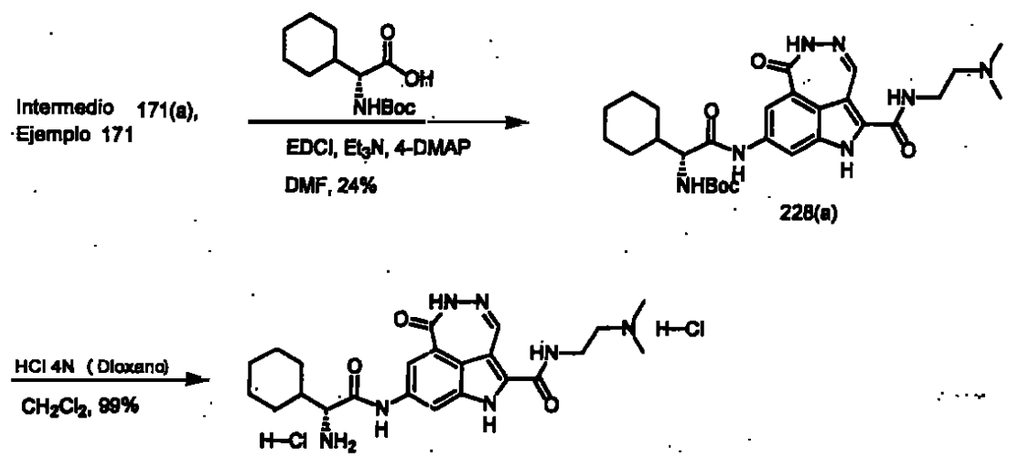


A una solución del Intermedio 147(c) del Ejemplo **147** (1,5 g, 5 mmol) en $CHCl_3$ (10 ml) y *N,N*-dimetilformamida (15 ml) se le añadió *N*-clorosuccinimida (701 mg, 5,25 mmol). La mezcla se calentó a 60°C y se agitó durante 3 horas. Se añadieron cloroformo, *N,N*-dimetilformamida y agua. Después del tratamiento de extracción con cloroformo, la fase orgánica se secó sobre Na_2SO_4 y se filtró. La evaporación de los componentes volátiles dio un residuo pardo oscuro al que se le añadió metanol. La filtración y la recolección de los sólidos dieron el compuesto del título (648 mg) en forma de un sólido pardo oscuro cuya pureza por RMN y HPLC se estimó en aproximadamente un 70%.

^{1}H RMN (d_6-DMSO): δ 13,15 (s, 1H), 10,62 (s, 1H), 8,90 (s, 1H), 7,65 (s, 1H), 7,39 (s, 1H), 1,47 (s, 9H).

EMCL: ($M+H^+$) 370,2.

Ejemplo 228: (2-Dimetilamino-etil)-amida del ácido (*R*)-8-(2-amino-2-ciclohexil-acetilamino)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico; diclorhidrato



Etapa 1. Preparación de éster *terc*-butílico del ácido (*R*)-{ciclohexil-[2-(2-dimetilamino-etilcarbamoil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil]-metil}-carbámico 228(a)

La preparación del intermedio 228(a) a partir del Intermedio 171 (a) del Ejemplo **171** (200 mg, 0,571 mmol), ácido (*R*)-*terc*-butoxicarbonilamino-ciclohexil-acético (147 mg, 0,571 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (131 mg, 0,686 mmol) y 4-dimetilaminopiridina (84 mg, 0,688 mmol) en *N,N*-dimetilformamida (8,0 ml) se realizó de forma análoga al Ejemplo **190,** etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 40:3:0,3 de diclorometano:metanol:hidróxido amónico, proporcionando el Intermedio 228(a) (77 mg, 0,139 mmol) en forma de un sólido amarillo con un rendimiento del 24%.

^{1}H RMN (d_6-DMSO): δ 12,65 (s, 1H), 10,66 (s, 1H), 10,26 (s, 1H), 9,83 (s a, 1H), 8,98 (s a, 1H), 8,16 (s, 2H), 7,76 (s, 1H), 6,93 (d, 1H, *J* = 9,23 Hz), 4,18-

4,03 (m, 1H), 4,01-3,85 (m, 1H), 3,71-3,56 (m, 2H), 2,83 (s, 6H), 1,78-1,45 (m, 6H), 1,37 (s, 9H), 1,21-0,93 (m, 5H).

EMCL: $(M+H^+)$ 554,2, $(M+Na^+)$ 576,1; $(M-H)^-$ 552,2.

Etapa 2. Preparación del compuesto del título: (2-dimetilamino-etil)-amida del ácido (*R*)-8-(2-amino-2-ciclohexil-acetilamino)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico; diclorhidrato

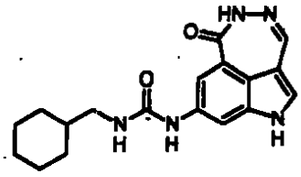
La preparación del compuesto del título a partir del Intermedio 228(a) (75 mg, 0,136 mmol) y HCl 4,0 M en dioxano (1,36 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el compuesto del título (71,3 mg, 0,136 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

^{1}H RMN (d_6-DMSO): δ 12,95 (s, 1H), 10,98 (s, 1H), 10,70 (s, 1H), 10,08 (s a, 1H), 9,16 (s, 1H), 8,37 (s, 3H), 8,21 (s, 1H), 8,13 (d, 1H, *J* = 1,32 Hz), 7,79 (d, 1H, J = 1,51 Hz), 3,85-3,74 (m, 1H), 3,65 (d, 2H, *J* = 5,84 Hz), 3,30 (d, 2H, J = 6,41 Hz), 2,83 (d, 6H, J = 4,71 Hz), 1,93-1,52 (m, 6H), 1,29-0,97 (m, 5H).

EMCL: $(M+H^+)$ 454,2, $(M+Na^+)$ 476,1; $(M-H)^-$ 452,1.

EMAR: $(M+H^+)$ calculado para $C_{23}H_{32}N_7O_3$, 454,2567, encontrado 454,2574.

Ejemplo 229: *N*-(Ciclohexilmetil)-*N'*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)urea

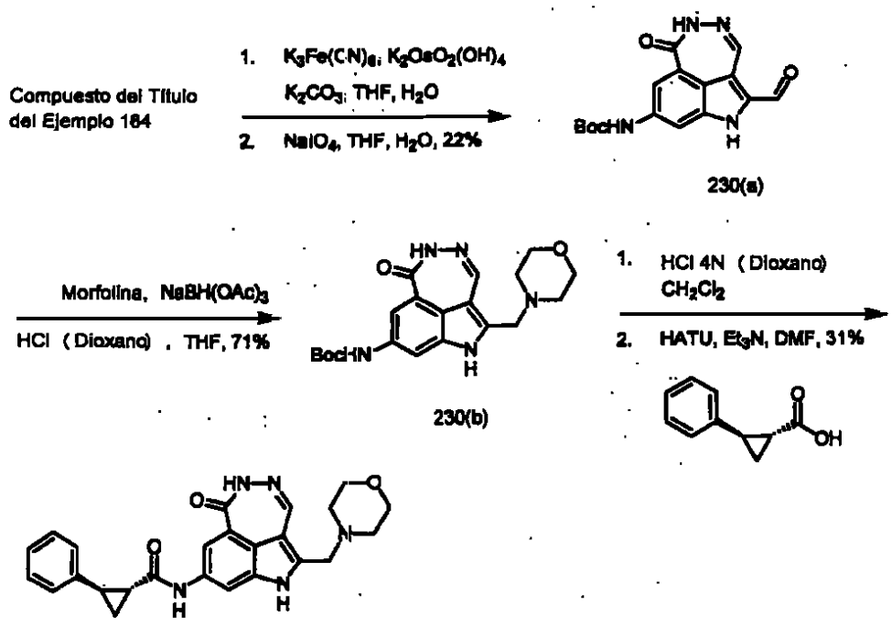


La preparación del ejemplo 229 a partir del compuesto del título del Ejemplo **2** (25 mg, 0,11 mmol), carbonato de *N,N*-disuccinimidilo (27 mg, 0,11 mmol), *N,N'*-diisopropiletilamina (0,024 ml, 0,21 mmol) y 1-ciclohexilmetanamina (0,028 ml, 0,021 mmol) en *N,N*-dimetilformamida (1,0 ml) se realizó de manera análoga al Ejemplo **207**. La purificación, también de manera análoga, proporcionó el compuesto del título (4 mg, 0,009 mmol) en forma de un polvo amarillo con un rendimiento del 8%.

^{1}H RMN ($CDCl_3$/metanol-d_4): δ 8,02 (s, 1H), 7,42 (s, 1H), 7,28 (s, 1H), 7,18 (s, 1H), 3,06 (d, 2H, J = 5,84 Hz), 1,82-1,71 (m, 5H), 1,34-1,18 (m, 5H), 0,97 (m, 1H).

EMCL: $(M-H)^-$ 338,1, $(M+Na^+)$ 362,1.

Ejemplo 230: (2-Morfolin-4-ilmetil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico compuesta con ácido acético



Etapa 1. Preparación de éster *terc*-butílico del ácido (2-formil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico 230(a)

A una solución del compuesto del título del Ejemplo **164** (48 mg, 0,146 mmol) en 1:1 de tetrahidrofurano:H_2O (4 ml) se le añadieron K_2CO_3 (30 mg, 0,219 mmol), $K_2OsO_2(OH)_4$ (7 mg) y $K_3Fe(CN)_6$ (72 mg, 0,219 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas tras lo cual se añadieron agua y acetato de etilo. Después del tratamiento de extracción, la fase orgánica se secó, se filtró y se concentró. El residuo se disolvió en 1:1 de tetrahidrofurano:H_2O (2 ml) y peryodato sódico (156 mg, 50,73 mmol). La mezcla se agitó a temperatura ambiente durante 30 min, tras lo cual se añadieron agua y acetato de etilo. Después del tratamiento de extracción, la fase orgánica se secó, se filtró y se concentró. La cromatografía sobre gel de sílice del residuo, eluyendo con acetato de etilo al 30% en hexano dio el Intermedio 230(a) en forma de un sólido amarillo pálido (11 mg, 0,034 mmol) con un rendimiento del 22%.

Etapa 2. Preparación de éster *terc*-butílico del ácido (2-morfolin-4-ilmetil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico 230(b)

A una solución de morfolina (0,32 ml, 3,64 mmol) y tamices moleculares 4 Å en polvo (1,0 g) en tetrahidrofurano (5 ml) se le añadió HCl 4 M en dioxano (0,91 ml, 3,64 mmol). Después de 10 min, se añadió gota a gota una solución del Intermedio 230(a) (199 mg, 0,607 mmol) en tetrahidrofurano (2 ml) seguido de $NaBH(OAc)_3$ (254 mg, 1,2 mmol). La suspensión resultante se agitó a temperatura ambiente durante 24 horas. La mezcla se inactivó con bicarbonato sódico saturado acuoso y se filtró a través de tierra diatomácea, que después

se lavó con acetato de etilo. Al filtrado se le añadió más acetato de etilo y la fase acuosa se extrajo. Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se sometió a cromatografía sobre gel de sílice eluyendo con MeOH al 5%/acetato de etilo, dando el Intermedio 230(b) en forma de un polvo amarillo pálido (173 mg, 0,43 mmol) con un rendimiento del 71%.

^{1}H RMN (d_6-DMSO): 11,71 (s, 1H), 10,21 (s, 1H), 7,73 (s, 1H), 7,62 (s, 2H), 3,74 (s, 2H), 3,63-3,61 (m, 4H), 2,43-2,41 (m, 4H), 1,52 (s, 9H).

EMCL: ($M+H^+$) 400.

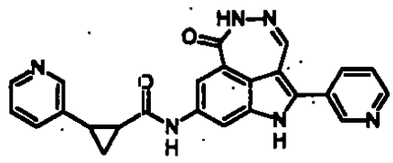
Etapa 3. Preparación del compuesto del título: (2-morfolin-4-ilmetil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico compuesta con ácido acético

La preparación del compuesto del título a partir del Intermedio 230(b) (173 mg, 0,433 mmol) en CH_2Cl_2 (2 ml) y HCl 4 M en dioxano (2 ml) se realizó de manera análoga a la preparación del Ejemplo **91**. Después de la concentración, el residuo se disolvió en *N,N*-dimetilformamida (5 ml). Se añadieron ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (84 mg, 0,52 mmol), trietilamina (0,18 ml, 1,3 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (247 mg, 0,65 mmol). Después de 12 horas, la mezcla se concentró y se sometió a HPLC preparativa de manera análoga al Ejemplo **146**, Etapa 2. Se obtuvo el compuesto del título (59 mg, 0,13 mmol) en forma de un polvo amarillo pálido con un rendimiento del 31%.

^{1}H RMN (d_6-DMSO): 11,84 (s, 1H), 10,42 (s, 1H), 10,28 (s, 1H), 8,10 (s, 1H), 7,67 (s, 1H), 7,64 (s, 1H), 7,39-7,24 (m, 5H), 3,78 (s, 2H), 3,68-3,64 (m,

4H), 2,49-2,47 (m, 4H), 2,14 (m, 1H), 1,56 (m, 1H), 1,42 (m, 1H) EMCL: ($M+H^+$) 444,1

Ejemplo 231: *N*-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,2-*trans*)-2-piridin-3-ilciclopropanocarboxamida

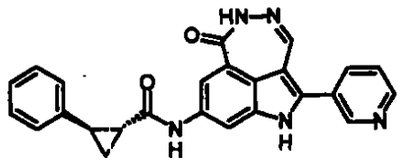


La preparación del ejemplo 231 a partir del Intermedio 147(d) del Ejemplo **147** se realizó de forma análoga a la preparación del Ejemplo 225 en tres etapas con la excepción de que se usó ácido 3-piridil-bórico en lugar de ácido 4-piridil-bórico en la etapa 1 y ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico en lugar de ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico en etapa 3. El aislamiento, también de manera análoga, proporcionó el compuesto del título (69 mg) en forma de un polvo amarillo con un rendimiento total del 33%.

^{1}H RMN (d_6-DMSO): δ 12,19 (s, 1H), 10,30-10,50 (m, 2H), 8,81 (m, 1H), 8,60 (m, 1H), 8,46 (m, 1H), 8,36 (m, 1H), 8,13 (m, 1H), 7,93-8,08 (m, 1H), 7,37-7,69 (m, 4H), 7,27 (m, 1H), 2,40 (m, 1H), 2,08 (m, 1H), 1,28-1,60 (m, 2H).

EMAR calculado para $C_{24}H_{18}N_6O_2$, 423,1569 (M+H), encontrado 423,1590.

Ejemplo 232: (1*R*,2*R*)-*N*-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida

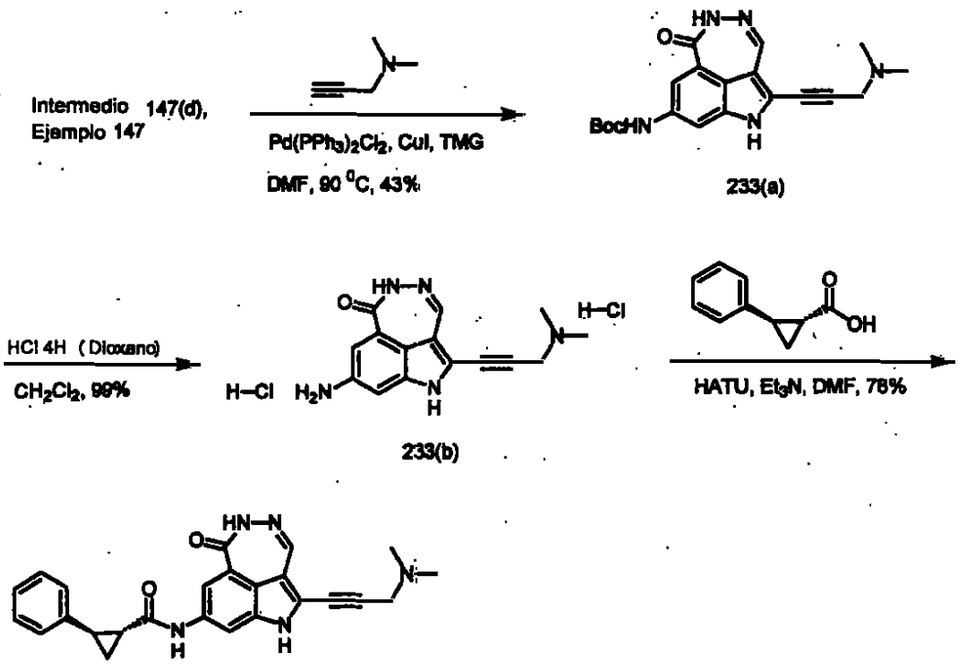


La preparación del ejemplo 232 a partir del Intermedio 147(d) del Ejemplo **147** se realizó de manera análoga a la preparación del Ejemplo **225** en tres etapas con la excepción de que se usó ácido 3-piridil-bórico en lugar de ácido 4-piridil-bórico en la etapa 1. El aislamiento, también de manera análoga, proporcionó el compuesto del título (18 mg) en forma de un polvo amarillo con un rendimiento total del 8%.

^{1}H RMN (d_6-DMSO): δ 12,18 (s, 1H), 10,28-10,54 (m, 2H), 8,81 (m, 1H), 8,60 (m, 1H), 8,13 (m, 1H), 7,95-8,08 (m, 1H), 7,57-7,70 (m, 1H), 7,49-7,57 (m, 1H), 7,38-7,48 (m, 1H), 7,01-7,34 (m, 3H) 4,05 (m, 1H), 2,32 (m, 1H), 2,03 (m, 1H), 1,46 (m, 1H), 1,32 (m, 1H).

EMAR calculado para $C_{25}H_{19}N_5O_2$, 422,1617 (M+H), encontrado 422,1598.

Ejemplo 233: [2-(3-Dimetilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



Etapa 1. Preparación de éster *terc*-butílico del ácido [2-(3-dimetilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-carbámico 233(a)

En una atmósfera de argón, se añadieron dimetil-prop-2-inil-amina (198 mg, 2,38 mmol), dicloro*bis*(trifenilfosfina)paladio (II) (27,6 mg, 0,039 mmol), yoduro de cobre (7,8 mg, 0,041 mmol) y *N,N,N',N'*-tetrametilguanidina (912 mg, 7,93 mmol) a una solución del Intermedio 147(d) del Ejemplo **147** (300 mg, 0,794 mmol) en *N,N*-dimetilformamida (3 ml) y dioxano (12 ml). La reacción se calentó a 90°C durante 4 horas, momento en el que los componentes volátiles se retiraron al vacío. El residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna

de gel de sílice y se eluyó con 20:1:0,1 de diclorometano:metanol:hidróxido amónico, proporcionando el Intermedio 233(a) (130 mg, 0,341 mmol) en forma de un sólido amarillo con un rendimiento del 43%.

^{1}H RMN (d_6-DMSO): δ 12,09 (s, 1H), 10,45 (s, 1H), 9,54 (s, 1H), 7,71 (s, 1H), 7,65 (d, 1H, *J* = 1,51 Hz), 7,40 (s, 1H), 3,61 (s, 2H), 2,27 (s, 6H), 1,47 (s, 9H).

EMCL: ($M+H^+$) 382,1, ($M+Na^+$) 404,1; ($M-H)^-$ 380,1.

Etapa 2. Preparación de 8-amino-2-(3-dimetilamino-prop-1-inil)-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona; diclorhidrato 233(b)

La preparación del intermedio 233(b) a partir del Intermedio 233(a) (126 mg, 0,331 mmol) y HCl 4 M en dioxano (1,68 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, proporcionó el Intermedio 233(b) (117 mg, 0,331 mmol) en forma de un polvo amarillo con un rendimiento del 99%.

^{1}H RMN (d_6-DMSO): δ 12,56 (s a, 1H), 10,68 (s, 1H), 7,58 (s, 1H), 7,36 (s, 1H), 7,24 (s, 1H), 4,46 (s, 2H), 2,88 (s, 6H).

EMCL: ($M+Na^+$) 304,1; ($M-H)^-$ 280,1.

Etapa 3. Preparación del compuesto del título: [2-(3-dimetilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-cd]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

La preparación del compuesto del título a partir del Intermedio 233(b) (110 mg, 0,312 mmol), ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (55 mg, 0,339 mmol), trietilamina (0,189 ml, 1,36 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (155 mg, 0,408 mmol) en *N,N*-dimetilformamida (10,0 ml) se realizó de forma análoga al Ejemplo **11**. Los

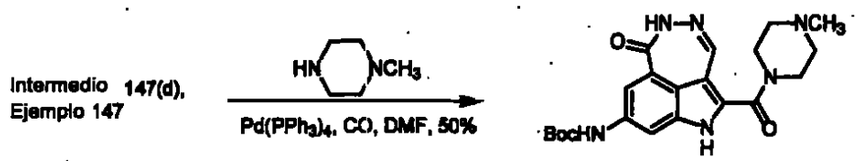
componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 40:3:0,3 de diclorometano:metanol:hidróxido amónico,, proporcionando el compuesto del título (100 mg, 0,235 mmol) en forma de un sólido amarillo-pardo con un rendimiento del 76%.

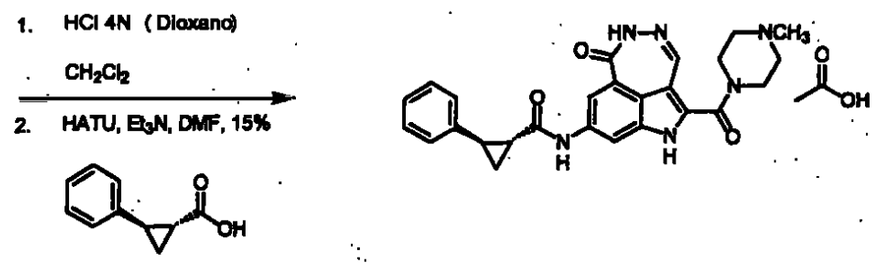
^{1}H RMN (d_6-DMSO): δ 12,24 (s, 1H), 10,53 (s, 1H), 10,47 (s, 1H), 8,10 (d, 1H, *J* = 1,32 Hz), 7,62 (d, 1H, J = 1,51 Hz), 7,45 (s, 1H), 7,33-7,25 (m, 2H), 7,23-7,15 (m, 3H), 3,84 (s, 2H), 2,44 (s, 6H), 2,42-2,32 (m, 1H), 2,12-2,02 (m, 1H), 1,55-1,45 (m, 1H), 1,42-1,32 (m, 1H).

EMCL: $(M+H^+)$ 426,0, $(M+Na^+)$ 448,1; $(M-H)^-$ 424,1.

EMAR: $(M+H^+)$ calculado para $C_{25}H_{24}N_5O_2$, 426,1930, encontrado 426,1911.

Ejemplo 234: [2-(4-Metil-piperazina-1-carbonil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal del ácido acético)





Etapa 1. Preparación de éster *terc*-butílico del ácido [2-(4-metil-piperazina-1-carbonil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-carbámico; compuesto con ácido acético 234(a)

La preparación del intermedio 234(a) a partir del Intermedio 147(d) del Ejemplo **147** (453 mg, 1,2 mmol), *N*-metilpiperazina (0,66 ml, 6 mmol) y *tetraquis*(trifenilfosfina)paladio (0) (105 mg, 0,09 mmol) en *N,N*-dimetilformamida (7 ml) se realizó de manera análoga a la preparación del Ejemplo **161** con la excepción de que se usó *tetraquis*(trifenilfosfina)paladio (0) como catalizador en lugar de *bis*(difenilfosfino)ferrocenodicloropaladio (II). Después de la concentración, el residuo se sometió a HPLC preparativa (Peeke Scientific, HI-Q C18 fase inversa 5 µ, 100A, columna de 250 x 21,2) eluyendo con CH_3CN y ácido acético al 0,1% en agua a un caudal de 20 ml/min usando

un gradiente de CH_3CN al 5-95% durante 40 min, dando el Intermedio 234(a) (254 mg, 0,6 mmol) en forma de un polvo verde pálido con un rendimiento del 50%.

^1H RMN (d_6-DMSO): 12,06 (s, 1H), 10,46 (s, 1H), 9,52 (s, 1H), 7,74 (s, 1H), 7,64 (s, 1H), 7,37 (s, 1H), 3,49-3,48 (m, 4H), 2,29-2,28 (m, 4H), 2,20 (s, 3H), 1,42 (s, 9H).

EMCL: $(M+H^+)$ 426,1

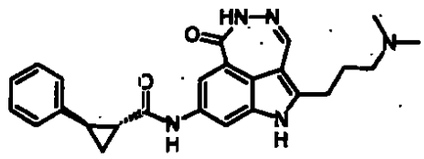
Etapa 2. Preparación del compuesto del título: [2-(4-metil-piperazina-1-carbonil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal del ácido acético)

La preparación del compuesto del título a partir del Intermedio 234(a) (445 mg, 1,06 mmol) en CH_2Cl_2 (5 ml) y HCl 4 M en dioxano (5 ml) se realizó de forma análoga al Ejemplo **91**. Después de la concentración, el residuo se disolvió en *N,N*-dimetilformamida (5 ml). Se añadieron secuencialmente ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (162 mg, 1,0 mmol), trietilamina (0,42 ml, 3 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (456 mg, 1,2 mmol). Después de 12 horas, la mezcla se concentró. El producto bruto se purificó por HPLC preparativa de manera análoga al Ejemplo 146, Etapa 2, dando el compuesto del título en forma de un polvo amarillo pálido (74 mg, 0,16 mmol) con un rendimiento del 15%.

^1H RMN (d_6-DMSO): 12,25 (s, 1H), 10,59(s, 1H), 10,51 (s, 1H), 8,18 (s, 1H), 7,69 (s, 1H), 7,49 (s, 1H), 7,34-7,19 (m, 5H), 3,63 (s a, 4H), 2,56 (s, 3H), 2,40-2,30 (m, 4H), 2,11 (m, 1H), 1,56 (m, 1H), 1,42 (m, 1H).

EMCL: $(M+H^+)$ 444,1

Ejemplo 235: [2-(3-Dimetilamino-propil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



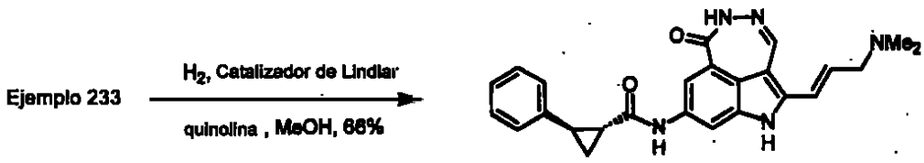
De manera análoga a la del Ejemplo **183**, se añadió paladio al 10% sobre carbono activado (20 mg) a una solución del compuesto del título del Ejemplo **233** (20 mg, 0,047 mmol) en metanol (3 ml). La mezcla de reacción se purgó con H_2 y se agitó a temperatura ambiente en una atmósfera de H_2 (1 atm) durante 1 hora. La mezcla de reacción se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 20:1:0,1 de diclorometano:metanol:hidróxido amónico, proporcionando el compuesto del título (8 mg, 0,0186 mmol) en forma de un sólido amarillo con un rendimiento del 40%.

^{1}H RMN (d_6-DMSO): δ 11,70 (s, 1H), 10,34 (s, 1H), 10,17 (s, 1H), 8,04 (d, 1H, J = 1,51 Hz), 7,52 (d, 1H, *J* = 1,51 Hz), 7,48 (s, 1H), 7,33-7,25 (m, 2H), 7,23-7,14 (m, 3H), 2,98-2,81 (m, 4H), 2,66 (s a, 6H), 2,41-2,31 (m, 1H), 2,11-2,02 (m, 1H), 2,01-1,87 (m, 2H), 1,53-1,43 (m, 1H), 1,41-1,31 (m, 1H).

EMCL: $(M+H^+)$ 430,1, $(M+Na^+)$ 452,1; $(M-H)^-$ 428,1.

EMAR: $(M+H^+)$ calculado para $C_{25}H_{28}N_5O_2$, 430,2243, encontrado 430,2240.

Ejemplo 236: [2-(3-Dimetilamino-propenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



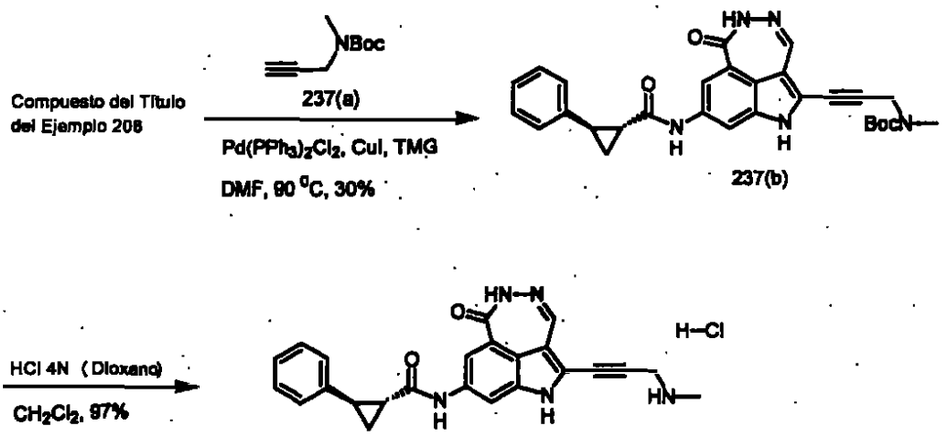
A una mezcla del compuesto del título del Ejemplo **233** (45 mg, 0,106 mmol), catalizador de Lindlar (45 mg) y quinolina (4,1 mg, 0,032 mmol) se le añadió metanol anhidro (3 ml). La mezcla de reacción se purgó con H_2 y se agitó a temperatura ambiente en una atmósfera de H_2 (1 atm) durante 2,5 horas. La mezcla de reacción se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 20:1:0,1 de diclorometano:metanol:hidróxido amónico, proporcionando el compuesto del título (30 g, 0,070 mmol) en forma de un sólido amarillo con un rendimiento del 66%.

^{1}H RMN (d_6-DMSO): δ 13,07 (s, 1H), 10,41 (s, 1H), 10,32 (s, 1H), 8,11 (d, 1H, *J* = 1,70 Hz), 7,57 (s, 1H), 7,54 (d, 1H, *J* = 1,70 Hz), 7,33-7,25 (m, 2H), 7,23-7,14 (m, 3H), 6,88 (d, 1H, *J* = 12,25 Hz), 5,91 (dt, 1H, *J* = 12,06, 6,22), 3,16 (d, 2H, *J* = 5,65 Hz), 2,42-2,33 (m, 1H), 2,28 (s, 6H), 2,12-2,03 (m, 1H), 1,53-1,44 (m, 1H), 1,41-1,31 (m, 1H).

EMCL: $(M+H^+)$ 428,1, $(M+Na^+)$ 450,0; $(M-H)^-$ 426,0.

EMAR: $(M+H^+)$ calculado para $C_{25}H_{26}N_5O_2$, 428,2087, encontrado 428,2082.

<u>Ejemplo 237: [2-(3-Metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)</u>



Etapa 1. Preparación de éster *terc*-butílico del ácido (1*R*,2*R*)-metil-(3-{6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-prop-2-inil)-carbámico 237(b)

El Intermedio 237(a) se preparó agitando metil-prop-2-inil-amina (0,5 g, 7,23 mmol), dicarbonato de di-*terc*-butilo (1,74 g, 7,97 mmol) y 2,6-dimetil-piridina (0,088 g, 0,72 mmol) en acetonitrilo anhidro (10 ml) a temperatura ambiente durante 16 horas. El disolvente se evaporó y el residuo se sometió a cromatografía sobre gel de sílice eluyendo con acetato de etilo, proporcionando el Intermedio 237(a) (1 g, 5,91 mmol) en forma de un aceite incoloro con un rendimiento del 82%. De manera análoga a la del Ejemplo **233**, Etapa 1, en una atmósfera de argón, se añadieron el intermedio 237(a) (66 mg, 0,39 mmol), diclorobis(trifenilfosfina)paladio (II) (4,6 mg, 0,0066 mmol), yoduro de cobre (1,2 mg, 0,0063 mmol) y *N,N,N,N*-tetrametilguanidina (150 mg, 1,30 mmol) a una solución del compuesto del título del Ejemplo **206** (55 mg, 0,13 mmol) en *N,N*-dimetilformamida (0,5 ml) y dioxano (2 ml). La reacción se calentó a 90°C durante 3 horas, momento en el que los componentes volátiles se retiraron al vacío. El residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y

se eluyó con 3:2 de diclorometano:acetato de etilo, proporcionando el Intermedio 237(b) (20 mg, 0,039 mmol) en forma de un sólido amarillo con un rendimiento del 30%.

^{1}H RMN (d_6-DMSO): δ 12,22 (s, 1H), 10,51 (s, 1H), 10,46 (s, 1H), 8,08 (d, 1H, J = 1,51 Hz), 7,61 (d, 1H, *J* = 1,70 Hz), 7,41 (s, 1H), 7,33-7,25 (m, 2H), 7,22-7,15 (m, 3H), 4,37 (s, 2H), 2,90 (s, 3H), 2,41-2,33 (m, 1H), 2,11-2,02 (m, 1H), 1,54-1,45 (m, 1H), 1,42 (s, 9H), 1,39-1,32 (m, 1H).

EMCL: $(M-H)^-$ 510,0.

Etapa 2. Preparación del compuesto del título: [2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato)

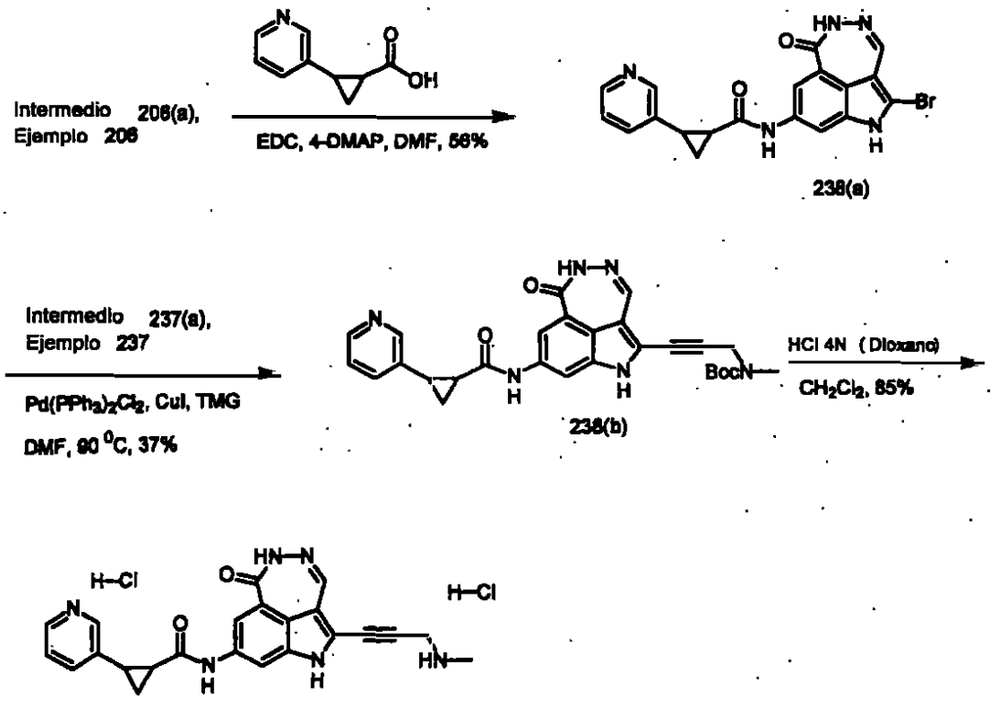
La preparación del compuesto del título a partir del Intermedio 237(b) (20 mg, 0,039 mmol) y HCl 4,0 M en dioxano (0,5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga proporcionó el compuesto del título (17 mg, 0,038 mmol) en forma de un polvo amarillo con un rendimiento del 97%.

^{1}H RMN (d_6-DMSO): 8 12,37 (s, 1H), 10,59 (s, 1H), 10,55 (s, 1H), 9,30 (s a, 2H), 8,14 (s, 1H), 7,65 (s, 1H), 7,58 (s, 1H), 7,36-7,24 (m, 2H), 7,24-7,12 (m, 3H), 4,27 (s, 2H), 2,66 (s, 3H), 2,41-2,29 (m, 1H, parcialmente oscurecido), 2,17-2,03 (m, 1H), 1,56-1,44 (m, 1H), 1,43-1,31 (m, 1H).

EMCL: $(M-H)^-$ 410,1.

EMAR: $(M+H^+)$ calculado para $C_{24}H_{22}N_5O_2$, 412,1774, encontrado 412,1768.

Ejemplo 238: [2-(3-Metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico; diclorhidrato



Etapa 1. Preparación de (2-bromo-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico 238(a)

La preparación del intermedio 238(a) a partir del Intermedio 206(a) del Ejemplo **206** (120 mg, 0,38 mmol), ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico (106 mg, aprox. 0,487 mmol, pureza aprox. del 75%), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (88 mg, 0,461 mmol) y 4-dimetilaminopiridina (56 mg, 0,459 mmol) en *N,N*-dimetilformamida (15,0 ml) se realizó de manera análoga a la preparación del Ejemplo **190**, etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se

retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 50:3 de diclorometano:metanol, proporcionando el Intermedio 238(a) (90 mg, 0,212 mmol) en forma de un sólido amarillo con un rendimiento del 56%.

^{1}H RMN (d_6-DMSO): δ 12,60 (s, 1H), 10,46 (s, 1H), 10,45 (s, 1H), 8,50 (d, 1H, J = 1,88 Hz), 8,40 (dd, 1H, J = 4,62, 1,41 Hz), 8,08 (d, 1H, J = 1,70 Hz), 7,60 (d, 1H, J = 1,51 Hz), 7,56 (dt, 1H, J = 7,96, 1,86 Hz), 7,32 (dd, 1H, J = 7,91, 4,90 Hz), 7,27 (s, 1H), 2,45-2,37 (m, 1H), 2,16-2,06 (m, 1H), 1,57-1,49 (m, 1H), 1,49-1,40 (m, 1H).

EMCL: $(M-H)^-$ 422,0, 424,0.

Etapa 2. Preparación de éster *terc*-butílico del ácido metil-(3-{6-oxo-8-[(2-piridin-3-il-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-prop-2-inil)-carbámico 238(b)

En una atmósfera de argón de manera análoga a la del Ejemplo **233,** etapa 1, se añadieron el Intermedio 237(a) del Ejemplo 237 (54 mg, 0,32 mmol), dicloro*bis*(trifenilfosfina)paladio (II) (3,7 mg, 0,0053 mmol), yoduro de cobre (1,0 mg, 0,0053 mmol) y *N,N,N,N*-tetrametilguanidina (122 mg, 1,06 mmol) a una solución del Intermedio 238(a) (45 mg, 0,106 mmol) en *N,N*-dimetilformamida (1 ml) y dioxano (2 ml). La reacción se calentó a 90°C durante 2 horas, momento en el que los componentes volátiles se retiraron al vacío. El residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 20:1:0,1 de diclorometano:metanol:hidróxido amónico, proporcionando el

Intermedio 238(b) (20 mg, 0,039 mmol) en forma de un sólido amarillo con un rendimiento del 37%.

^{1}H RMN (d_6-DMSO): δ 12,23 (s, 1H), 10,52 (s, 1H), 10,50 (s, 1H), 8,45 (s a, 1H), 8,08 (s, 1H), 7,61 (s, 1H), 7,56 (d, 1H, J = 7,91 Hz), 7,41 (s, 1H), 7,35 (s a, 1H), 4,37 (s, 2H), 2,90 (s, 3H), 2,45-2,38 (m, 1H, parcialmente oscurecido), 2,16-2,07 (m, 1H), 1,59-1,49 (m, 1H), 1,50-1,44 (m, 1H, parcialmente oscurecido), 1,42 (s, 9H).

EMCL: ($M+H^+$) 513,2, ($M+Na^+$) 535,1; ($M-H)^-$511,1.

Etapa 3. Preparación del compuesto del título: [2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico; diclorhidrato

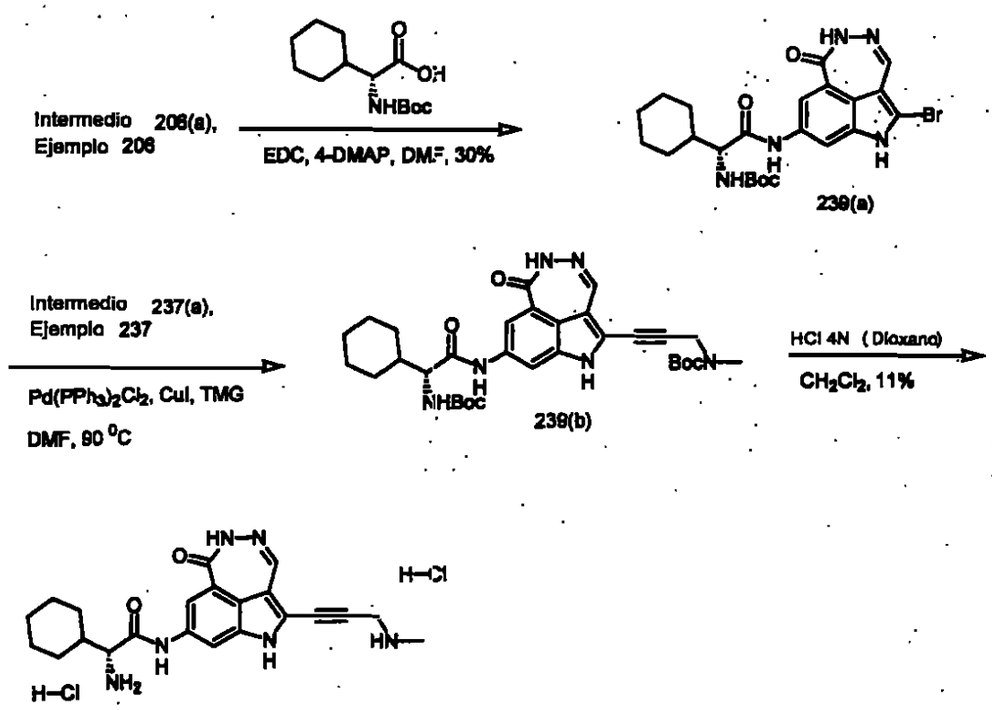
La preparación del compuesto del título a partir del Intermedio 238(b) (20 mg, 0,039 mmol) y HCl 4 M en dioxano (0,5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga proporcionó el compuesto del título (16 mg, 0,033 mmol) en forma de un sólido rojo oscuro con un rendimiento del 85%.

^{1}H RMN (d_6-DMSO): δ 12,46 (s, 1H), 10,77 (s, 1H), 10,59 (s, 1H), 9,46 (s a, 2H), 8,90 (s, 1H), 8,76 (d, 1H, J = 3,77 Hz), 8,34 (d, 1H, *J* = 7,35 Hz), 8,11 (s, 1H), 8,03-7,90 (m, 1H), 7,69 (s, 1H), 7,59 (s, 1H), 4,25 (s, 2H), 2,65 (s, 3H), 2,49 (m, 1H, oscurecido), 2,41-2,29 (m, 1H, parcialmente oscurecido), 1,73-1,55 (m, 2H).

EMCL: ($M-H)^-$ 411,1.

EMAR: ($M+H^+$) calculado para $C_{23}H_{21}N_6O_2$, 413,1726, encontrado 413,1753.

Ejemplo 239: (2*R*)-2-Amino-2-ciclohexil-*N*-[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida: diclorhidrato



Etapa 1. Preparación de éster *terc*-butílico del ácido (*R*)-[(2-bromo-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-ilcarbamoil)-ciclohexil-metil]-carbámico 239(a)

La preparación del intermedio 239(a) a partir del Intermedio 206(a) del Ejemplo **206** (120 mg, 0,38 mmol), ácido (*R*)-*terc*-butoxicarbonilamino-ciclohexil-acético (120 mg, 0,466 mmol), clorhidrato de (3-dimetilamino-propil)-etil-carbodiimida (87 mg, 0,455 mmol) y 4-dimetilaminopiridina (56 mg, 0,459 mmol) en *N,N*-dimetilformamida (7,0 ml) se realizó de manera análoga a la preparación del Ejemplo **190**, etapa 2. Cuando se juzgó que la reacción se había completado, los componentes volátiles se retiraron al vacío y el residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice.

Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 1,2:1 de diclorometano:acetato de etilo, proporcionando el Intermedio 239(a) (60 mg, 0,116 mmol) en forma de un sólido amarillo con un rendimiento del 30%.

^{1}H RMN (d_6-DMSO): δ 12,59 (s, 1H), 10,46 (s, 1H), 10,14 (s, 1H), 8,06 (s, 1H), 7,64 (s, 1H), 7,27 (s, 1H), 6,90 (d, 1H, *J* = 8,85 Hz), 3,91 (t, 1H, *J* = 8,29 Hz), 1,76-1,44 (m, 6H), 1,37 (s, 9H), 1,20-0,93 (m, 5H).

EMCL: $(M-H)^-$ 518,0, 516,0.

Etapa 2. Preparación de éster *terc*-butílico del ácido (*R*)-{3-[8-(2-*terc*-butoxicarbonilamino-2-ciclohexil-acetilamino)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il]-prop-2-inil}-metil-carbámico 239(b)

En una atmósfera de argón de manera análoga a la del Ejemplo **233** etapa 1, se añadieron el Intermedio 237(a) del Ejemplo **237** (65 mg, 0,38 mmol), dicloro*bis*(trifenilfosfina)paladio (II) (4,5 mg, 0,0064 mmol), yoduro de cobre (1,2 mg, 0,0063 mmol) y *N,N,N,N'*-tetrametilguanidina (146 mg, 1,27 mmol) a una solución del Intermedio 239(a) (66 mg, 0,127 mmol) en *N,N*-dimetilformamida (0,5 ml) y dioxano (2 ml). La mezcla de reacción se calentó a 90°C durante 3 horas, momento en el que los componentes volátiles se retiraron al vacío. El residuo resultante se disolvió en metanol y se cargó sobre un lecho de gel de sílice. Después, el lecho se cargó sobre una columna de gel de sílice y se eluyó con 4:1 de diclorometano:acetato de etilo, proporcionando el Intermedio 239(b) (10 mg) en forma de un sólido amarillo contaminado con una impureza desconocida.

EMCL: $(M+H^+)$ 607,2, $(M+Na^+)$ 629,3; $(M-H)^-$ 605,2.

Etapa 3. Preparación del compuesto del título: (2*R*)-2-amino-2-ciclohexil-*N*-[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida; diclorhidrato

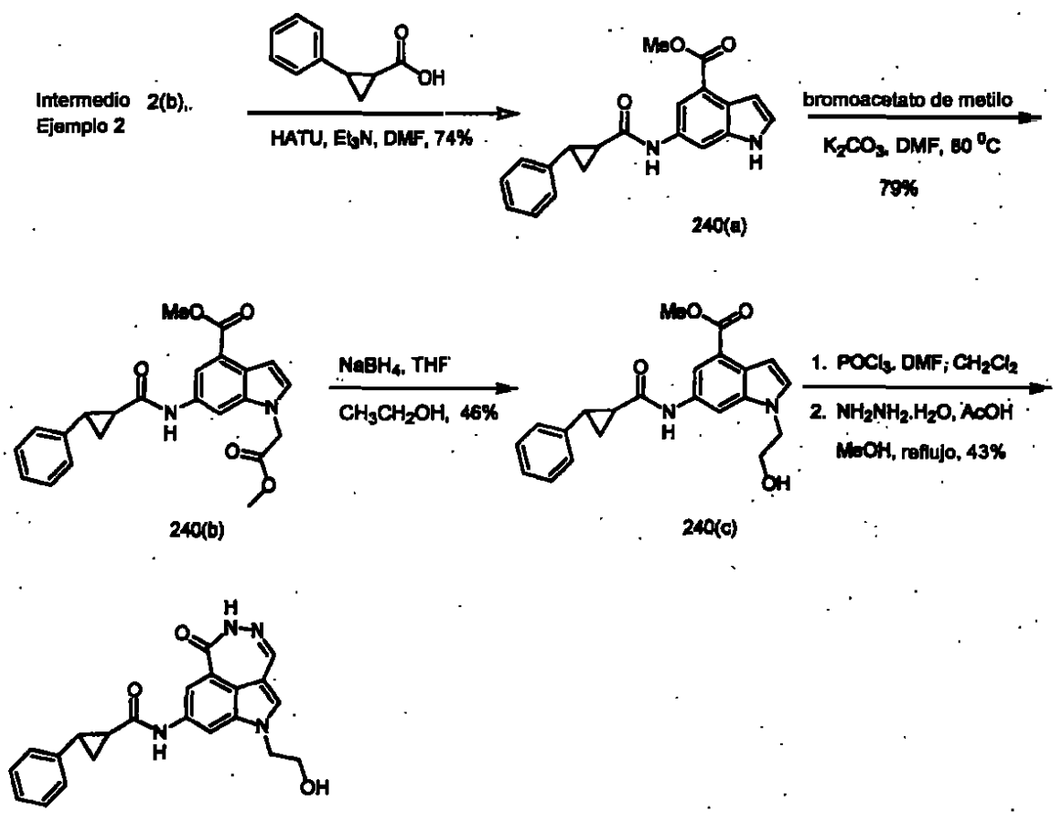
La preparación del compuesto del título a partir del Intermedio 239(b) (10 mg) y 4 M HCl en dioxano (0,5 ml) se realizó de forma análoga al Ejemplo **91**. El aislamiento, también de manera análoga, incluyó otra trituración con CH_2Cl_2 que retiró la impureza llevada de la etapa 2. Se obtuvo el compuesto del título (6 mg, 0,013 mmol) en forma de un polvo amarillo con un rendimiento combinado del 11% para las etapas 2 y 3.

^{1}H RMN (d_6-DMSO): δ 12,52 (s, 1H), 10,90 (s, 1H), 10,66 (s, 1H), 9,37 (s a, 2H), 8,33 (s a, 3H), 8,08 (s, 1H), 7,73 (d, 1H, J = 0,9 Hz), 7,61 (s, 1H), 4,27 (s, 2H), 3,84-3,74 (m, 1H), 2,67 (s, 3H), 1,90-1,54 (m, 6H), 1,27-0,97 (m, 5H).

EMCL: $(M+Na^+)$ 429,2; $(M-H)^-$ 405,2.

EMAR: $(M+H^+)$ calculado para $C_{22}H_{27}N_6O_2$, 407,2195, encontrado 407,2209.

Ejemplo 240: (1,2-*trans*)-*N*-[1-(2-hidroxietil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fenilciclopropanocarboxamida



Etapa 1. Preparación de 6-{[(2-fenilciclopropil)carbonil]amino}-1*H*-indol-4-carboxilato de metilo 240(a)

La preparación del intermedio 240(a) a partir del Intermedio 2(b) del Ejemplo 2 (2,27 g, 10 mmol), ácido (1,2-*trans*)-2-fenil-ciclopropanocarboxílico (1,79 g, 11 mmol), trietilamina (3,0 g, 30 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (4,18 g, 11 mmol) en *N,N*-dimetilformamida (20 ml) se realizó de forma análoga al Ejemplo **11.** El tratamiento de extracción en acetato de etilo, seguido de purificación sobre una

columna de gel de sílice eluyendo con CH_2Cl_2/acetato de etilo proporcionó el Intermedio 240(a) (2,47 g) con un rendimiento del 74%.

^{1}H RMN (d_6-DMSO): δ 11,39 (s, 1H), 10,39 (s, 1H), 8,25 (s, 1H), 7,88 (s, 1H), 7,47 (s, 1H), 7,10-7,40 (m, 5H), 6,86 (s, 1H), 3,89 (s, 3H), 2,33-2,48 (m, 1H), 2,04-2,21 (m, 1H), 1,46-1,63 (m, 1H), 1,29-1,45 (m, 1H).

EMCL (M+H): 335,1.

Etapa 2. Preparación de 1-(2-metoxi-2-oxoetil)-6-{[(2-fenilciclopropil)carbonil]amino}-1*H*-indol-4-carboxilato de metilo 240(b)

Se mezclaron el Intermedio 240(a) (2,40 g, 7,2 mmol), bromoacetato de metilo (1,32 g, 8,6 mmol) y K_2CO_3 (2,0 g, 14,4 mmol) en *N,N*-dimetilformamida (25 ml) y se agitaron a 80°C durante 3 horas. Después de la filtración, el filtrado se evaporó y el residuo se sometió a cromatografía sobre gel de sílice eluyendo con CH_2Cl_2/acetato de etilo, proporcionando el Intermedio 240(b) (2,31 g) con un rendimiento del 79%.

^{1}H RMN (d_6-DMSO): δ 10,50 (s, 1H), 8,09 (s, 1H), 7,95 (s, 1H), 7,48 (m, 1H), 7,10-7,38 (m, 5H), 6,90 (m, 1H), 5,16 (s, 2H), 3,91 (s, 3H), 3,70 (s, 3H), 2,30-2,44 (m, 1H), 2,03-2,21 (m, 1H), 1,44- 1,58 (m, 1H), 1,30-1,43 (m, 1H).

EMCL (M+H): 407,1.

Etapa 3. Preparación de 1-(2-hidroxietil)-6-{[(2-fenilciclopropil)carbonil]amino}-1*H*-indol-4-carboxilato de metilo 240(c)

Al Intermedio 240(b) (2,0 g, 49 mmol) en 1:1 de etanol:tetrahidrofurano (80 ml) se le añadió $NaBH_4$ (2,0 g, 53 mmol). La mezcla se agitó a temperatura ambiente durante una noche. La purificación por cromatografía sobre gel de sílice produjo el Intermedio 240(c) (0,85 g) con un rendimiento del 46%.

^{1}H RMN (d_6-DMSO): δ 10,45 (s, 1H), 8,27 (s, 1H), 7,89 (d, 1H, *J* = 1,7 Hz), 7,49 (d, 1H, *J* = 1,5 Hz), 7,15-7,35 (m, 5H), 6,87 (d, 1H, *J* = 3,0 Hz), 4,95 (t, 1H. *J* = 5,2 Hz), 4,20 (t, 2H, *J* = 5,7 Hz), 3,91 (s, 3H), 3,60-3,80 (m, 2H), 2,33-2,46 (m, 1H), 2,05-2,18 (m, 1H), 1,43-1,65 (m, 1H), 1,30- 1,43 (m, 1H).

EMCL (M+H): 379,1.

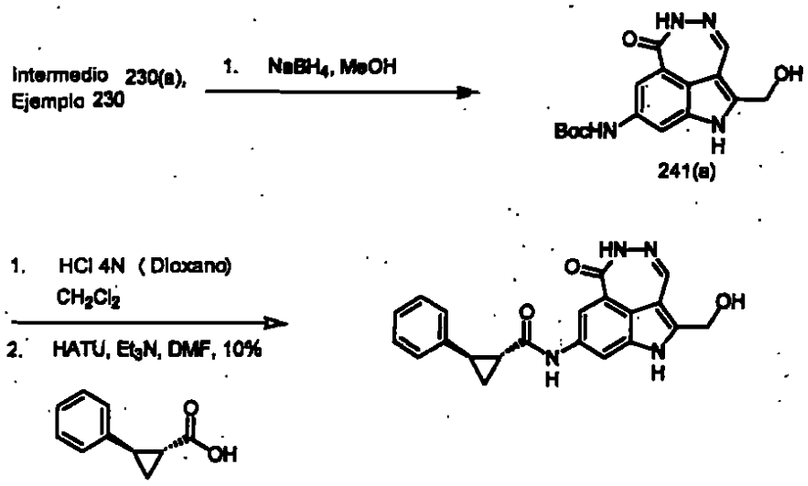
Etapa 4. Preparación del compuesto del título: (1,2-*trans*)-*N*-[1-(2-hidroxietil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fenilciclopropanocarboxamida

Con agitación, se añadió el Intermedio 240(c) en *N,N*-dimetilformamida (7 ml) a una mezcla de $POCl_3$ (0,6 ml) y *N,N*-dimetilformamida (5 ml) a 0°C. Después de 1 hora, la reacción se interrumpió con agua y se extrajo con acetato de etilo. La fase orgánica se secó con Na_2SO_4 y se filtró. Después de la evaporación de los componentes volátiles, el residuo se mezcló con metanol (50 ml) que contenía hidrazina (1 ml) y se calentó a reflujo durante 5 horas. Después de que la mezcla se enfriara a temperatura ambiente, el precipitado amarillo resultante se recogió por filtración y se lavó con metanol, proporcionando el compuesto del título (0,37 g) con un rendimiento del 43%.

^{1}H RMN (d_6-DMSO): δ 10,41 (s, 1H), 10,25 (s, 1H), 8,12 (d, 1H, *J* = 1,6 Hz), 7,55 (s, 2H), 7,45 (s, 1H), 7,10-7,33 (m, 5H), 4,12 (t, 2H, *J* = 5,1 Hz), 3,67 (t, 2H, *J* = 5,2 Hz), 2,29-2,40 (m, 1H), 1,99-2,10 (m, 1H), 1,41-1,52 (m, 1H), 1,28-1,39 (m, 1H).

EMAR calculado para $C_{22}H_{21}N_5O_3$, 389,1614 (M+H), encontrado 389,1627.

Ejemplo 241: (2-Hidroximetil-6-oxo-5,6-dihidro-1*H*-[1,2-*cd*]diazepino[4,5,6]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



Etapa 1. Preparación de éster *terc*-butílico del ácido (2-hidroximetil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico 241 (a)

Una solución del intermedio 230(a) del Ejemplo **230** (26 mg, 0,079 mmol) en metanol (2 ml) se trató con $NaBH_4$ (6 mg, 0,16 mmol) a 0°C durante 15 min. La solución se inactivó con NH_4Cl saturado acuoso y se diluyó con acetato de etilo. Después de la extracción, la fase orgánica se lavó con salmuera, se secó (Na_2SO_4), se filtró y se concentró. La cromatografía sobre gel de sílice del residuo (3:1 de acetato de etilo:hexano) dio el intermedio 241 (a) (13 mg) con un rendimiento del 50%.

Etapa 2. Preparación del compuesto del título: (2-hidroximetil-6-oxo-5,6-dihidro-1*H*-[1,2-*cd*]diazepino[4,5,6]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

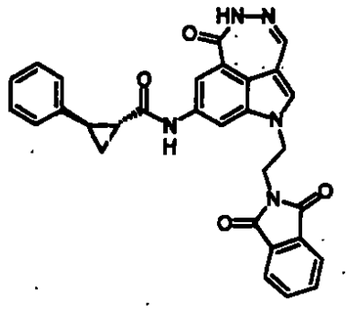
A una suspensión del Intermedio 241 (a) (76 mg, 0,23 mmol) en CH_2Cl_2 (2 ml) se le añadió HCl 4 M en dioxano (2 ml, 8 mmol). Después de agitar a temperatura ambiente durante 2 horas, la mezcla se concentró y el residuo se disolvió en *N,N*-dimetilformamida (2 ml). Se añadieron ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (33,6 mg, 0,21 mmol), trietilamina (0,1 ml, 0,69 mmol) y

hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (131 mg, 0,345 mmol). Después de agitar a temperatura ambiente durante 2 horas, la mezcla se concentró y el residuo se sometió a HPLC preparativa de manera análoga al Ejemplo **146,** etapa 2. Se obtuvo el compuesto del título en forma de un polvo amarillo pálido (9 mg, 0,024 mmol) con un rendimiento del 10%.

^{1}H RMN (d_6-DMSO): δ 11,79 (s, 1H), 10,36 (s, 1H), 10,19 (s, 1H), 8,05 (d, 1H, *J* = 1,88 Hz), 7,57 (s, 1H), 7,56 (s, 1H), 7,32-7,19 (m, 5H), 5,70 (t, 1H, *J* = 4,0 Hz), 4,70 (d, 2H, *J* = 5,4 Hz), 2,35 (m, 1H), 2,07 (m, 1H), 1,50 (m, 1H), 1,36 (m, 1H).

EMCL: ($M+H^+$) 375,2

Ejemplo 242: {1-[2-(1,3-Dioxo-1,3-dihidro-isoindol-2-il)-etil]-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il}-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

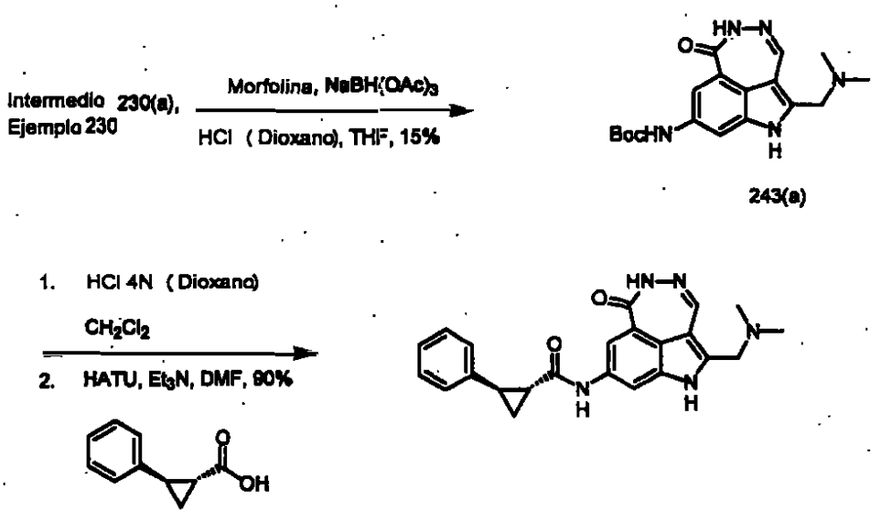


El compuesto de título del Ejemplo 100 (130 mg, 0,38 mmol), 2-(2'-bromo-etil)-isoindol-1,3-diona (0,48 g, 1,9 mmol) y K_2CO_3 (0,28 g, 2,0 mmol) se agitaron en *N,N*-dimetilformamida (6 ml) a 80°C durante 20 horas. Después de la evaporación de los componentes volátiles, el residuo se sometió a cromatografía sobre gel de sílice eluyendo con CH_2Cl_2/MeOH, proporcionando el compuesto del título (130 mg) con un rendimiento del 67%.

^{1}H RMN (d_6-DMSO): δ 10,33 (s, 1H), 10,31 (s, 1H), 8,07-8,15 (d, 1H, J = 1,5 Hz), 7,72-7,85 (m, 4H), 7,58 (s, 1H), 7,46-7,53 (d, 1H, *J* = 1,5 Hz), 7,40 (s, 1H), 7,27-7,37 (m, 2H), 7,12-7,27 (m, 3H), 4,41 (t, 2H, *J* = 4,7 Hz), 3,95 (t, 2H, J = 4,9 Hz), 2,31-2,42 (m, 1H), 1,96-2,07 (m, 1H), 1,43-1,55 (m, 1H), 1,30-1,42 (m, 1H).

EMAR calculado para $C_{30}H_{24}N_5O_4$, 518,1828 (M+H), encontrado 518,1852.

Ejemplo 243: (2-Dimetilaminometil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



Etapa 1. Preparación de éster *terc*-butílico del ácido (2,2-dimetilaminometil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-carbámico 243(a)

La preparación del intermedio 243(a) a partir del Intermedio 230(a) del Ejemplo **230** (707 mg, 2,16 mmol), dimetilamina 2 M en tetrahidrofurano (5,4 ml, 10,8 mmol), HCl 4 M en dioxano (10,8 ml; 10,8 mmol) y $NaBH(OAc)_3$ (2,29 g, 10,8 mmol) en tetrahidrofurano (5 ml) con tamices moleculares 4 Å en polvo

(400 mg) se realizó de forma análoga al Ejemplo **230**, etapa 2. La cromatografía sobre gel de sílice (eluida con metanol al 2% en CH_2Cl_2), también de manera análoga, proporcionó el Intermedio 243(a) en forma de un polvo amarillo pálido (112 mg, 0,31 mmol) con un rendimiento del 15%.

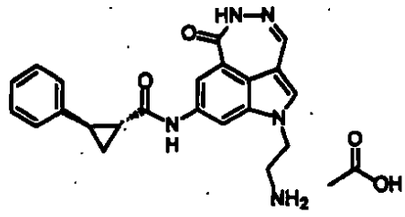
Etapa 2. Preparación del compuesto del título: (2-dimetilaminometil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico

La preparación del compuesto del título a partir del Intermedio 243(a) (112 mg, 0,31 mmol) se realizó de manera análoga al etapa 3 del Ejemplo **230**. La cromatografía sobre gel de sílice (eluida con metanol al 2% en acetato de etilo), también de manera análoga, proporcionó el compuesto del título (113 mg, 0,28 mmol) en forma de un polvo amarillo con un rendimiento del 90%.

^{1}H RMN (d_6-DMSO): 11,84 (s, 1H), 10,38 (s, 1H), 10,28 (s, 1H), 8,75 (d, J = 4 Hz, 1H), 8,53 (d, *J* = 4 Hz, 1H), 8,07 (s, 1H), 7,62 (s, 1H), 7,60 (m, 1H), 7,51 (m, 1H), 7,32-7,18 (m, 3H), 3,31 (s, 2H), 2,49 (s, 6H), 2,33 (m, 4H), 2,09 (m, 1H), 1,50 (m, 1H), 1,36 (m, 1H).

EMCL: $(M-H)^-$ 400.

Ejemplo 244: [1-(2-Amino-etil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; compuesto con ácido acético

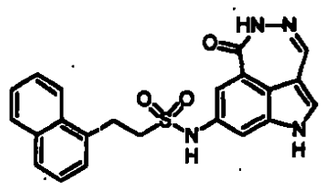


El compuesto de título del Ejemplo **242** (92 mg, 0,18 mmol) e hidrazina (0,2 ml) se calentaron a reflujo en etanol (14 ml) 3 horas. Después de la evaporación de los componentes volátiles, el residuo se sometió a HPLC preparativa que proporcionó el compuesto del título (71,4 mg) en forma de una sal del ácido acético con un rendimiento del 89%.

^{1}H RMN (d_6-DMSO): δ 10,44 (s, 1H), 10,27 (s, 1H), 8,15 (s, 1H), 7,58 (s, 1H), 7,56 (s, 1H), 7,46 (s, 1H), 7,26-7,34 (m, 2H), 7,12-7,23 (m, 3H), 3,99-4,13 (m, 2H), 2,88 (m, 2H), 2,33-2,42 (m, 1H), 2,02-2,12 (m, 1H), 1,43-1,55 (m, 1H), 1,30-1,41 (m, 1H).

EMAR calculado para $C_{22}H_{22}N_5O_2$, 388,1774 (M+H), encontrado 388,1797.

Ejemplo 245: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 2-naftalen-1-il-etanosulfónico

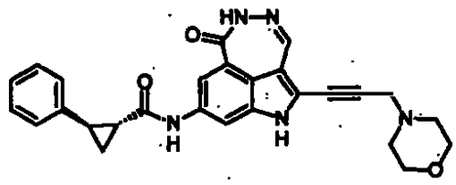


En una atmósfera de nitrógeno, el compuesto del título del Ejemplo 2 (260 mg, 1,1 mmol), cloruro de 2-(1-naftil)etanosulfonilo (300 mg, 1,18 mmol) y trietilamina (0,68 ml, 4,89 mmol) se calentaron a reflujo en tetrahidrofurano (5 ml) durante 12 horas. Los componentes volátiles se evaporaron y la cromatografía sobre gel de sílice (eluida con metanol al 2% en CH_2Cl_2) del residuo produjo el compuesto del título (61 mg, 0,15 mmol) en forma de un polvo amarillo con un rendimiento del 13%.

^{1}H RMN (DMSO): δ 11,58 (s, 1H), 10,13 (s, 1H), 9,85 (s, 1H), 7,67 (d, *J* = 8,0 Hz, 1H), 7,56 (dd, *J* = 8,0, 4,0 Hz, 1H), 7,43-7,17 (m, 8H), 7,06 (m, 1H), 3,22-3,15 (m, 4H).

EMCL: (M+H$^+$) 417,0.

Ejemplo 246: [2-(3-Morfolin-4-il-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



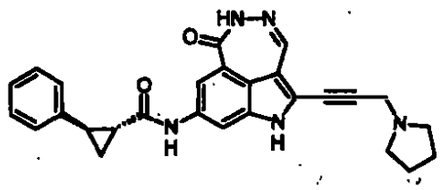
La preparación del ejemplo 246 a partir del Intermedio 147(d) del Ejemplo **147** (300 mg, 0,794 mmol) se realizó en tres etapas de manera similar a la descrita para la preparación de Ejemplo 233 con la excepción de que se usó 4-prop-2-inil-morfolina en lugar de dimetil-prop-2-inil-amina en la etapa 1. Se preparó 4-prop-2-inil-morfolina calentando a reflujo 3-bromo-propina, morfolina y K_2CO_3 en tetrahidrofurano durante 1 hora. Se obtuvo el compuesto del título (34 mg, 0,073 mmol) en forma de un polvo amarillo con un rendimiento total del 18%.

^{1}H RMN (d_6-DMSO): δ 12,21 (s, 1H), 10,49 (s, 1H), 10,46 (s, 1H), 8,08 (s, 1H), 7,61 (s, 1H), 7,41 (s, 1H), 7,33-7,24 (m, 2H), 7,23-7,13 (m, 3H), 3,66 (s, 2H), 3,62 (s a, 4H), 2,54 (s a, 4H), 2,42-2,33 (m, 1H), 2,11-2,02 (m, 1H), 1,54-1,44 (m, 1H), 1,42-1,32 (m, 1H).

EMCL: (M+H$^+$) 468,2, (M+Na$^+$) 490,1; (M-H)$^-$ 466,1.

EMAR: (M+H$^+$) calculado para $C_{27}H_{26}N_5O_3$, 468,2036, encontrado 468,2049.

Ejemplo 247: [6-Oxo-2-(3-pirrolidin-1-il-prop-1-inil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-arnida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



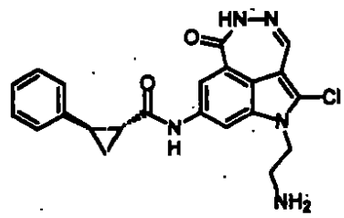
La preparación del ejemplo 247 a partir del Intermedio 147(d) del Ejemplo **147** (300 mg, 0,794 mmol) se realizó en tres etapas de manera similar a la descrita para la preparación de Ejemplo **233** con la excepción de que se usó 1-prop-2-inil-pirrolidina en lugar de dimetil-prop-2-inil-amina en la etapa 1. Se preparó 1-prop-2-inil-pirrolidina agitando 3-bromo-propina, pirrolidina y trietilamina a temperatura ambiente en tetrahidrofurano durante 2 horas. Se obtuvo el compuesto del título (80 mg, 0,177 mmol) en forma de un polvo amarillo con un rendimiento total del 36%.

^{1}H RMN (d_6-DMSO): δ 12,18 (s, 1H), 10,48 (s, 1H), 10,45 (s, 1H), 8,07 (d, 1H, *J* = 1,77 Hz), 7,61 (d, 1H, *J* = 1,52 Hz), 7,39 (s, 1H), 7,32-7,25 (m, 2H), 7,23-7,14 (m, 3H), 3,75 (s, 2H), 2,60 (s a, 4H), 2,41-2,33 (m, 1H), 2,10-2,03 (m, 1H); 1,73 (s a, 4H), 1,52-1,46 (m, 1H), 1,40-1,33 (m, 1H).

EMCL: ($M+H^+$) 452,1, ($M+Na^+$) 474,1; $(M-H)^-$ 450,2.

EMAR: ($M+H^+$) calculado para $C_{27}H_{26}N_5O_2$, 452,2087, encontrado 452,2102.

Ejemplo 248: [1-(2-Amino-etil)-2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-Fenil-ciclopropanocarboxílico

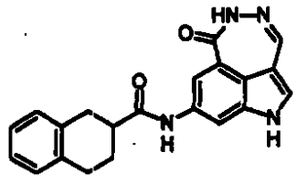


La preparación del ejemplo 248 se realizó en dos etapas. La primera etapa se realizó de manera idéntica a la descrita para la preparación de Ejemplo **242** con la excepción de que se usó el compuesto del título del Ejemplo 190 en lugar del compuesto del título del Ejemplo **100.** Esto dio el intermedio protegido con ftaloílo. La segunda etapa consistió en desprotección de ftaloílo y las condiciones fueron idénticas a las descritas en el Ejemplo **244.** La purificación, análoga a la descrita para el Ejemplo **244,** dio el compuesto del título (0,054 g) en forma de un polvo amarillo con un rendimiento total del 49%.

^{1}H RMN (d_6-DMSO): δ 10,56 (s, 1H), 10,53 (s, 1H), 8,22 (s, 1H), 8,00-8,18 (d a, 2H), 7,57 (s, 1H), 7,36 (s, 1H), 7,19-7,29 (m, 2H), 7,05-7,18 (m, 3H), 4,39 (t, 2H, *J* = 6,6 Hz), 3,06 (t, 2H, *J* = 6,5 Hz), 2,28-2,37 (m, 1H), 2,00-2,13(m, 1H), 1,39-1,51 (m, 1H), 1,26-1,38 (m, 1H).

EMAR calculado para $C_{22}H_{22}N_5O_2$, 422,1384 (M+H), encontrado 422,1403.

Ejemplo 249: (6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 1,2,3,4-tetrahidro-naftaleno-2-carboxílico



La preparación del ejemplo 249 a partir del compuesto del título del Ejemplo 2 (base libre) (100 mg, 0,500 mmol), ácido 1,2,3,4-tetrahidro-naftaleno-2-carboxílico (100 mg, 0,567 mmol), trietilamina (0,278 ml, 2,00 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N*-tetrametiluronio (285 mg, 0,750 mmol) en *N,N*-dimetilformamida (4,0 ml) se realizó de manera análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con acetato de etilo), también de manera análoga, proporcionó el compuesto del título (87 mg, 0,243 mmol) en forma de un polvo amarillo con un rendimiento del 48%.

^{1}H RMN (d_6-DMSO): δ 11,73 (d, 1H, J = 2,26 Hz), 10,23 (s, 1H), 10,11 (s, 1H), 8,16 (d, 1H, *J* = 1,51 Hz), 7,60 (d, 1H, *J* = 1,70 Hz), 7,55 (d, 1H, *J* = 2,64 Hz), 7,46 (s, 1H), 7,14-7,06 (m, 4H), 2,97-2,88 (m, 2H), 2,86-2,70 (m, 3H), 2,14-2,02 (m, 1H), 1,86-1,68 (m, 1H).

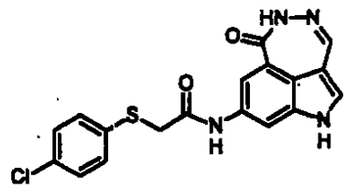
EMCL: $(M+H^+)$ 359,1, $(M+Na^+)$ 381,0; $(M-H)^-$ 357,2.

EMAR: $(M+H^+)$ calculado para $C_{21}H_{19}N_4O_2$, 359,1481, encontrado 359,1484.

Anál. calc. para $C_{21}H_{18}N_4O_2$: C, 70,38; H, 5,06; N, 15,63.

Encontrado: C, 69,36; H, 5,07; N, 15,21.

Ejemplo 250: 2-(4-Cloro-fenilsulfanil)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



La preparación del ejemplo 250 a partir del compuesto del título del Ejemplo 2 (base libre) (100 mg, 0,500 mmol), ácido (4-cloro-fenilsulfanil)-

acético (110 mg, 0,543 mmol), trietilamina (0,278 ml, 2,00 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (285 mg, 0,750 mmol) en *N,N*-dimetilformamida (4,0 ml) se realizó de forma análoga al Ejemplo **11**. Cuando se juzgó que la reacción se había completado, la *N,N*-dimetilformamida se evaporó y se añadió metanol. La mezcla se filtró para recoger los sólidos, que después se lavaron con metanol, diclorometano y éter dietílico. Después de secar al vacío, se obtuvo el compuesto del título (115 mg, 0,321 mmol) en forma de un polvo amarillo con un rendimiento del 72%.

^{1}H RMN (d_6-DMSO): δ 11,73 (d, 1H, *J* = 1,70 Hz), 10,35 (s, 1H), 10,26 (s, 1H), 8,06 (d, 1H, *J* = 1,51 Hz), 7,56 (d, 1H, J = 2,64 Hz), 7,52 (d, 1H, *J* = 1,51 Hz), 7,48-7,34 (m, 5H), 3,86 (s, 2H).

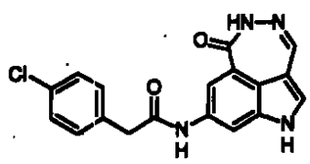
EMCL: $(M-H)^-$ 383,0.

EMAR: ($M+H^+$) calculado para $C_{18}H_{14}ClN_4O_2S$, 385,0526, encontrado 385,0538.

Análisis calculado para $C_{18}H_{13}ClN_4O_2S \cdot 0,25\ CH_3OH$: C, 55,79; H, 3,59; N, 14,26; Cl, 9,02.

Encontrado: C, 55,49; H, 3,65; N, 14,57, Cl, 8,87.

Ejemplo 251: 2-(4-Cloro-fenil)-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida



La preparación del ejemplo 251 a partir del compuesto del título del Ejemplo 2 (106 mg, 0,448 mmol), ácido (4-cloro-fenil)-acético (85,0 mg, 0,498 mmol), trietilamina (0,313 ml, 2,25 mmol) y hexafluorofosfato de *O*-(7-

azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (257 mg, 0,676 mmol) en *N,N*-dimetilformamida (4,0 ml) se realizó de forma análoga al Ejemplo **11**. La cromatografía sobre gel de sílice (eluida con 1:1 de acetato de etilo:hexano), también de manera análoga, proporcionó el compuesto del título (130 mg, 0,369 mmol) en forma de un polvo amarillo con un rendimiento del 82%.

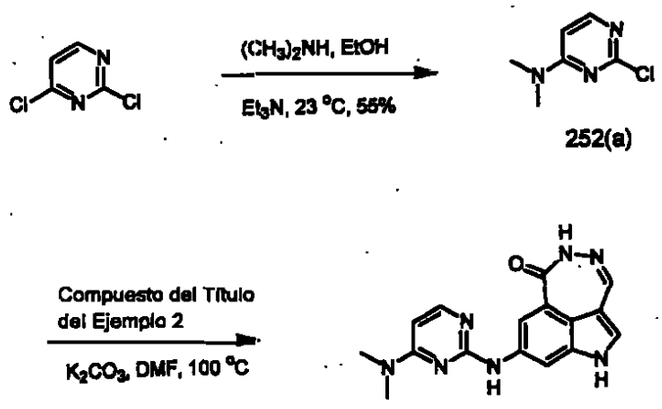
^{1}H RMN (d_6-DMSO): δ 11,73 (d, 1H, *J* = 1,70 Hz), 10,31 (s, 1H), 10,24 (s, 1H), 8,10 (d, 1H, *J* = 1,51 Hz), 7,57-7,53 (m, 2H), 7,45 (s, 1H), 7,37 (ddd, 4H, J = 8,67, 8,67, 2,64 Hz), 3,64 (s, 2H).

EMCL: $(M+H^+)$ 353,2; $(M-H)^-$ 351,2.

Análisis calculado para $C_{18}H_{13}ClN_4O_2$: C, 61,28; H, 3,71; N, 15,88; Cl, 10,05.

Encontrado: C, 62,22; H, 3,88; N, 15,80; Cl, 10,13.

Ejemplo 252: 8-(4-Dimetilamino-pirimidin-2-ilamino)-1,5-dihidro-[1,2]diazepino[4,5,6-*cd*]indol-6-ona



Etapa 1. 2-Cloro-4-Dimetilaminopirimidina 252(a)

A una solución de 2,4-dicloropiridina (2,24 g, 15 mmol) en etanol (45 ml) se le añadió trietilamina (2,1 ml, 15 mmol) seguido de dimetilamina (7,5 ml, 1,0 M en THF). La mezcla resultante se agitó a 23°C durante 2 h. El tratamiento de

extracción en acetato de etilo y $NaHCO_3$ saturado acuoso produjo el producto bruto, que se purificó por cromatografía sobre gel de sílice, eluyendo con 30% acetato de etilo/hexano, formando el Intermedio 252(a) (1,4 g, 8,2 mmol) con un rendimiento del 55%.

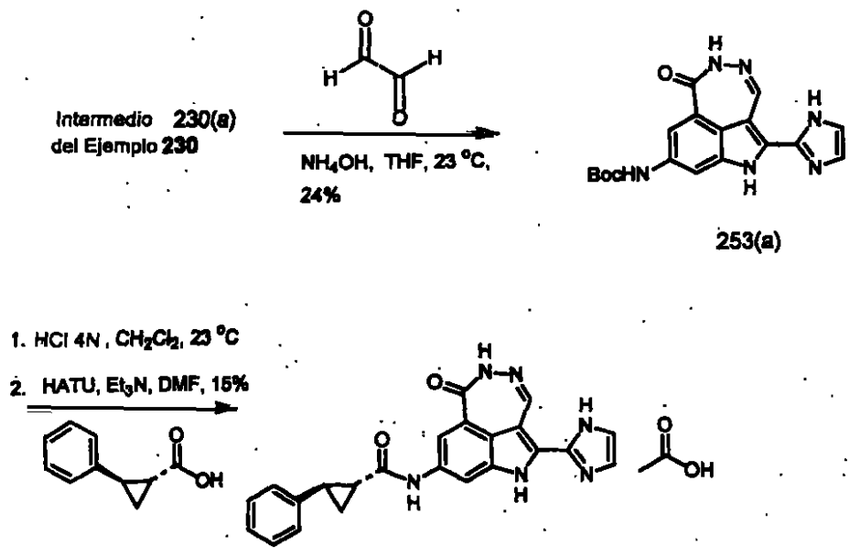
Etapa 2. Preparación del compuesto del título: 8-(4-dimetilamino-pirimidin-2-ilamino)-1,5-dihidro-[1,2]diazepino[4,5,6]indol-6-ona

Una mezcla del Intermedio 252(a) (212 mg, 1,35 mmol), el compuesto del título del Ejemplo 2 (base libre) (320 mg, 1,6 mmol), K_2CO_3 (560 mg, 4,05 mmol) en *N,N*-dimetilformamida (5 ml) se calentó a 100°C durante 4 h. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso produjo el producto bruto, que se trituró con metanol. La mezcla se recogió por filtración y se lavó con metanol, dando el compuesto del título en forma de un sólido amarillo (83 mg, 0,26 mmol) con un rendimiento del 19%.

^{1}H RMN (d_6-DMSO): δ 11,63 (s, 1H), 10,12 (s, 1H), 9,15 (s, 1H), 8,15 (d, 1H, J = 1,8 Hz), 7,94 (d, 1H, J = 6,1 Hz), 7,92 (d, 1H, J = 1,6 Hz), 7,46 (d, 1H, J = 2,5 Hz), 7,43 (s, 1H), 6,11 (d, 1H, J = 6,1 Hz), 3,08 (s, 6H).

EMCL: ($M+H^+$) 322,3.

Ejemplo 253: [2-(1*H*-Imidazol-2-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico



Etapa 1. Éster *terc*-butílico del ácido [2-(1*H*-imidazol-2-il)-6-oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-]indol-8-il]-carbámico 253(a)

A una solución del Intermedio 230(a) del Ejemplo 230 (274 mg, 0,835 mmol) en tetrahidrofurano (5 ml) y etanol (1 ml) se le añadió hidróxido amónico 15 N (0,5 ml) seguido de glicol al 40% en agua (0,5 ml). La mezcla resultante se agitó a 23°C durante una noche. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso produjo el producto bruto, que se purificó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo al 50%/hexano, formando el intermedio 253(a) (75 mg, 0,2 mmol) con un rendimiento del 24%.

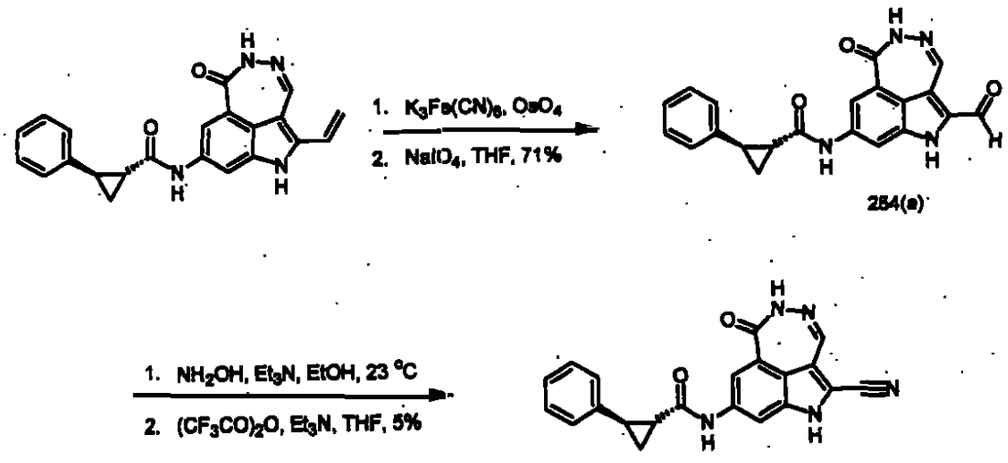
Etapa 2. Preparación del compuesto del título: [2-(1*H*-imidazol-2-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6]indol-8-il]-amida del ácido 2-fenil-ciclopropanocarboxílico; compuesta con ácido acético.

La desprotección del Intermedio 253(a) (41 mg, 0,11 mmol) en CH_2Cl_2 (2 ml) usando HCl 4 M en dioxano (2 ml) se realizó de forma análoga al Ejemplo **91**. Después de la concentración, el residuo se disolvió en *N,N*-dimetilformamida (5 ml). Se añadieron secuencialmente ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (35,6 mg, 0,22 mmol), trietilamina (0,046 ml, 0,33 mmol) y hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (51 mg, 0,13 mmol). Después de 12 h, la mezcla se concentró. El producto bruto se purificó por HPLC preparativa de manera análoga al Ejemplo **146**, Etapa 2, dando el compuesto del título en forma de un polvo amarillo pálido (7 mg, 0,017 mmol) con un rendimiento del 15%.

^{1}H RMN (d_6-DMSO): 12,27 (s, 1H), 11,79 (s, 1H), 10,25 (s, 1H), 10,21 (s, 1H), 7,93 (d, 1H, J = 1,7 Hz), 7,90 (s, 1H), 7,45 (d, 1H, J = 1,7 Hz), 7,20 (s, 1H), 7,13-6,99 (m, 5H), 2,19 (m, 1H), 1,89 (m, 1H), 1,31 (m, 1H), 1,18 (m, 1H).

EMCL: ($M+H^+$) 409.

Ejemplo 254: (2-Ciano-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; compuesta con sal HOAc.



Etapa 1: (2-Formil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 2-fenil-ciclopropanocarboxílico 254(a)

La preparación del material de partida, (6-oxo-2-vinil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 2-fenil-ciclopropanocarboxílico, se realizó desprotegiendo el compuesto del título del Ejemplo **164** de manera análoga al Ejemplo 91 y después acoplándolo a la amida de manera análoga al Ejemplo **61**. Después, la (6-oxo-2-vinil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido 2-fenil-ciclopropanocarboxílico (542 mg, 1,46 mmol) se trató con $K_3Fe(CN)_6$ (483 mg, 1,46 mmol) y $NaIO_4$ (1,25 g, 5,84 mmol) en tetrahidrofurano (5 ml) y agua (2 ml) de forma análoga al Ejemplo **230**, etapa 1. El tratamiento de extracción en acetato de etilo y $NaHCO_3$ saturado acuoso produjo el producto bruto, que se purificó por cromatografía sobre gel de sílice, eluyendo con acetato de etilo al 50%/hexano, formando el intermedio 254(a) (384 mg, 1,17 mmol) con un rendimiento del 71%.

Etapa 2. Compuesto del título: (2-ciano-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido 2-fenil-ciclopropanocarboxílico, compuesta con la sal HOAc.

Una mezcla del Intermedio 254(a) (103 mg, 0,276 mmol), $NH_2OH{\cdot}HCl$ (38 mg, 0,55 mmol) y trietilamina (0,15 ml, 1,1 mmol) en etanol (2 ml) se agitó a 23°C durante 1 h. El tratamiento de extracción con acetato de etilo y $NaHCO_3$ saturado acuoso produjo el producto bruto, que se disolvió en tetrahidrofurano (2 ml) y trietilamina (0,077 ml, 0,55 mmol). Después, se añadió gota a gota anhídrido trifluoroacético (0,046 ml, 0,33 ml). La mezcla resultante se agitó durante una noche. El tratamiento de extracción en acetato de etilo y $NaHCO_3$

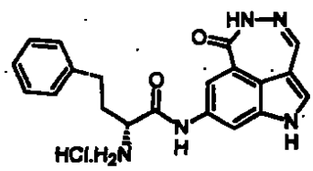
saturado acuoso produjo el producto bruto, que se purificó por HPLC preparativa de manera análoga al Ejemplo **146,** Etapa 2, dando el compuesto del título (5 mg, 0,014 mmol) con un rendimiento del 5%.

^{1}H RMN (d_6-DMSO): 9,05 (s, 1H), 8,74 (s, 1H), 8,09 (s, 1H), 7,58 (s, 1H), 7,47 (s, 1H), 7,24-7,12 (m, 5H), 2,19 (m, 1H), 1,89 (m, 1H), 1,52 (m, 1H), 1,11 (m, 1H).

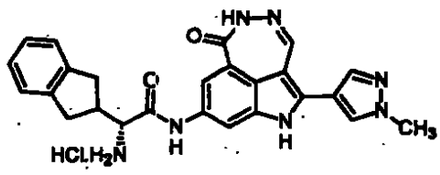
EMCL: ($M+H^+$) 369,1.

Otros compuestos que se prepararon a partir de los materiales de partida apropiados incluyen los siguientes:

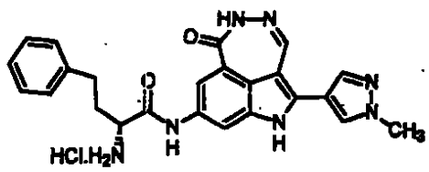
Ejemplo 255: (2*R*)-2-Amino-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida (sal clorhidrato):



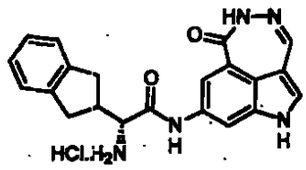
Ejemplo 256: (2*R*)-2-Amino-2-indan-2-il-*N*-[2-(1-metil-1*H*-pirazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal clorhidrato):



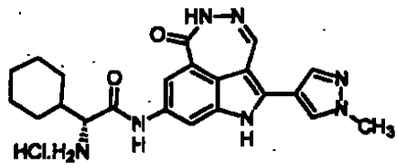
Ejemplo 257: (2*R*)-2-Amino-*N*-[2-(1-metil-1*H*-pirazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-4-fenil-butiramida (sal clorhidrato):



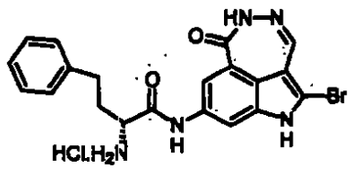
Ejemplo 258: (2*R*)-2-Amino-2-indan-2-il-*N*-(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (sal clorhidrato):



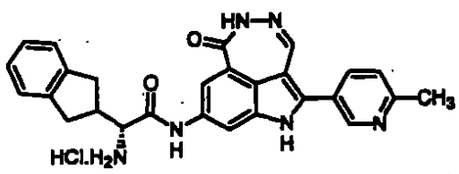
Ejemplo 259: [2-(1-metil-1*H*-pirazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (2*R*)-2-amino-3-etil-heptanoico (sal clorhidrato):



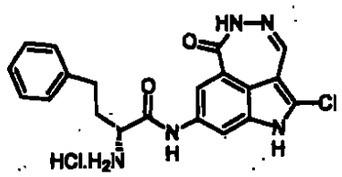
Ejemplo 260: (2*R*)-2-Amino-*N*-(2-bromo-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida (sal clorhidrato):



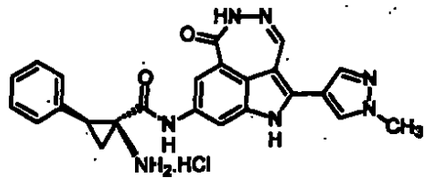
Ejemplo 261: (2*R*)-2-Amino-2-indan-2-il-*N*-[2-(6-metil-piridin-3-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal clorhidrato):



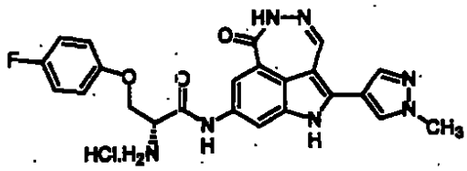
Ejemplo 262: (2*R*)-2-Amino-*N*-(2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida (sal clorhidrato):



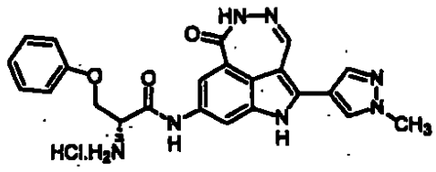
Ejemplo 263: [2-(1-Metil-1*H*-pirazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*S*,2*R*)-1-amino-2-fenil-ciclopropanocarboxílico (sal clorhidrato):



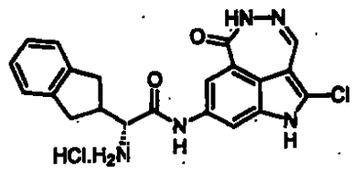
Ejemplo 264: (2*R*)-2-Amino-3-(4-fluoro-fenoxi)-*N*-[2-(1-metil-1*H*-pirazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-propionamida (sal clorhidrato):



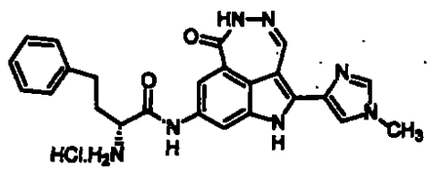
Ejemplo 265: (2*R*)-2-Amino-*N*-[2-(1-metil-1*H*-pirazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-3-fenoxi-propionamida (sal clorhidrato):



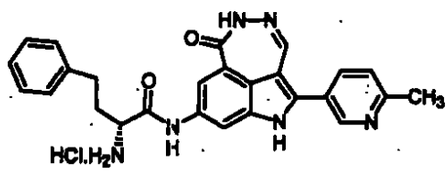
Ejemplo 266: (2*R*)-2-Amino-*N*-(2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-indan-2-il-acetamida (sal clorhidrato):



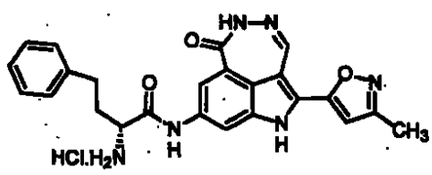
Ejemplo 267: (2*R*)-2-Amino-*N*-[2-(1-metil-1*H*-imidazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-4-fenil-butiramida (sal clorhidrato):



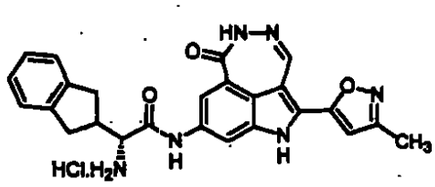
Ejemplo 268: (2*R*)-2-Amino-*N*-[2-(6-metil-piridin-3-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-4-fenil-butiramida (sal clorhidrato):



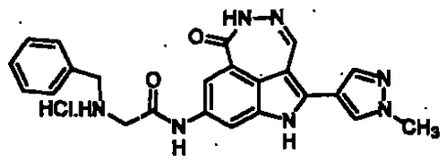
Ejemplo 269: (2*R*)-2-Amino-*N*-[2-(3-metil-isoxazol-5-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-4-fenil-butiramida (sal clorhidrato):



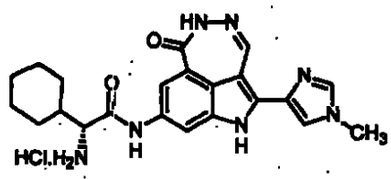
Ejemplo 270: (2*R*)-Amino-2-indan-2-il-*N*-[2-(3-metil-isoxazol-5-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal clorhidrato):



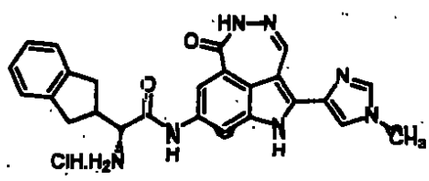
Ejemplo 271: 2-Bencilamino-*N*-[2-(1-metil-1*H*-pirazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal clorhidrato):



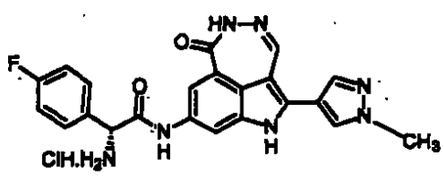
Ejemplo 272: (2*R*)-2-Amino-2-ciclohexil-*N*-[2-(1-metil-1*H*-imidazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal clorhidrato):



Ejemplo 273: (2*R*)-2-Amino-2-indan-2-il-*N*-[2-(1-metil-1*H*-imidazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal clorhidrato):



Ejemplo 274: (2*R*)-2-Amino-2-(4-fluoro-fenil)-*N*-[2-(1-metil-1*H*-pirazol-4-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal clorhidrato):



Ejemplo 275: **Estudios de combinación in vitro**

Pueden incubarse células cancerígenas con un agente antineoplástico sólo o junto con un inhibidor de CHK-1 de fórmula 1. Los datos del crecimiento

celular de un estudio de combinación (agente antineoplástico junto con una concentración fijada de compuesto de ensayo) pueden compararse con los datos correspondientes obtenidos de un estudio de agente unitario (agente antineoplástico sin compuesto de ensayo). La concentración de agente antineoplástico que provoca una inhibición del crecimiento celular del 50% (CI_{50}) puede determinarse para el tratamiento con un agente unitario y para el tratamiento de combinación. Los valores CI_{50} pueden calcularse usando la porción lineal de una representación semi-log de concentración de agente antineoplástico frente al porcentaje de la inhibición del crecimiento celular. La relación entre el CI_{50} del agente antineoplástico sólo y el CI_{50} del agente antineoplástico junto con el compuesto de ensayo representa el Factor de Potenciación 50 (FP_{50}). El FP_{50} puede usarse para medir la eficacia del tratamiento de combinación. El tratamiento de combinación con un agente antineoplástico y compuestos de ensayo de fórmula 1 puede proporcionar valores FP_{50} que varían de 2 a 8 en las células cancerígenas.

La viabilidad de las células cancerígenas y la proliferación pueden evaluarse usando un ensayo de reducción de sal tetrazolio (ensayo MTT). En las células viables, este ensayo colorimétrico puede medir la reducción mitocondrial de un componente tetrazolio en un producto de formazán insoluble. A la inversa, este ensayo puede usarse para determinar si se impide o no una función mitocondrial, por ejemplo, por los eventos metabólicos que conducen a la apoptosis o necrosis. Las líneas celulares cancerígenas pueden dejarse crecer en placas de 96 pocillos y pueden ponerse en placas en el medio apropiado a un volumen de 100 µl/pocillo. Las placas pueden incubarse durante cuatro horas antes de la adición de los compuestos de ensayo. En la

parte del fondo de la placa de 96 pocillos, la células pueden tratarse con concentraciones en aumento de agente antineoplástico. En la parte superior de la placa, las células pueden tratarse con concentraciones en aumento de agente antineoplástico combinado con una concentración fijada de compuesto de ensayo. Las células pueden incubarse a 37°C (CO_2 al 5%) durante de cuatro a seis días (dependiendo del tipo de célula). Al final de la incubación, el componente tetrazolio puede añadirse a una concentración final de 0,2 mg/ml, y las células pueden incubarse durante 4 horas a 37°C. Después de la centrifugación de las placas y la retirada del medio, la absorción del formazán (solubilizado en dimetilsulfóxido) puede medirse a 540 nm.

Los agentes antineoplásticos puede incluir cisplantina, hidroxiurea, gemcitibina, carboplatina, 7-etil-10-hidroxicamptotecina (SN-38) y citosina β-*D*-arabinoside.

Las células cancerígenas pueden referirse a las siguientes:

Línea celular	Tipo de cáncer
CA-46	linfoma (humano)
HT-29	colon (humano)
Colo205	colon (humano)
MV522	pulmón (humano)
SW620	colon (humano)
L1210	leucemia (murina)
PANC-1	páncreas (humano)
BXPC-3	páncreas (humano)
MCF-7	pecho (humano)
HCT116	colon (humano)

H23	pulmón (humano)

Ejemplo 276: **Modelos de tumor in vivo**

Para valorar la capacidad de los inhibidores de CHK-1 de fórmula 1 para aumentar la reducción del volumen tumoral junto con gemcitibina en ratones, pueden establecerse modelos de tumor de xenoinjerto usando líneas celulares tumorales HT-29, MV522 o Colo205.

Los ratones pueden agruparse al azar (12 ratones/grupo) en grupos de tratamiento y usarse cuando el tumor alcanza un volumen de 150-200 mm^3. Los ratones pueden experimentar un transcurso de inyecciones intraperitoneales (i.p.) compuestas sólo por vehículo, sólo gemcitibina o gemcitibina junto con el compuesto de ensayo de fórmula I. Los volúmenes tumorales pueden medirse en momentos que varían de 2 a 25 días. El control puede consistir en una inyección i.p. de vehículo a intervalos apropiados. El control paralelo puede constar de una inyección i.p. de gemcitibina sola de 15 mg/kg a 240 mg/kg a intervalos apropiados. El tratamiento puede constar de una inyección i.p. de gemcitibina (de 5 mg/kg a 240 mg/kg) a intervalos apropiados junto con una inyección i.p. del compuesto de ensayo de fórmula I (de 1 mg/kg a 100 mg/kg) a intervalos apropiados. Al final del estudio, puede medirse el volumen del tumor (mm^3). Puede observarse una mejora en el retardo del crecimiento tumoral en los ratones tratados con gemcitibina junto con el compuesto de ensayo de fórmula I frente al tratado sólo con gemcitibina.

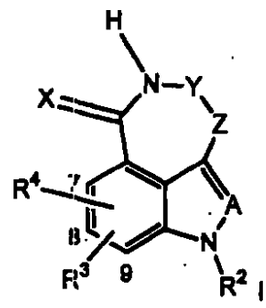
Aunque la invención se ha ilustrado haciendo referencia a realizaciones específicas y preferidas, los especialistas en la técnica reconocerán que pueden realizarse variaciones y modificaciones a través de la experimentación y práctica rutinaria de la invención. De esta manera, la invención no pretende

limitarse por la descripción anterior, pero sí definirse por las reivindicaciones adjuntas y sus equivalentes.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de fórmula:



en la que:

X es =O o =S;

A es $=CR^1-$ o =N-;

El grupo -Y-Z- tiene la fórmula $-O-CH_2-$ o -N=CH-;

R^1 es:

(a) alquilo (C_1-C_8);

(b) $-C(=O)-R^5$;

(c) $-C(=O)-NR^6R^7$; o

(d) R^{35} o R^{36}, alquenilo (C_2-C_8) o alquinilo (C_2-C_8) {donde cada uno de dichos alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por F, Cl, OH, $-NH_2$, R^{40} y R^{42}};

R^2 es

(a) H, OH o alquilo (C_1-C_8);

(b) -C(=O)-R^8;

(c) -(C=S)-R^9 o -(C=S)-N $R^{10}R^{11}$; o

(d) R^{38} o R^{39};

R^3 es

(a) alquilo (C_1-C_8);

(b) -C(=O)-R^{12};

(c) -C(=O)-$NR^{13}R^{14}$;

(d) -NR^{15}-C(=O)-R^{16};

(e) -NR^{17}-SO_2R^{18};

(f) -NR^{19}-SO_n-$NR^{20}R^{21}$ {donde n es 1 ó 2};

(g) -NR^{22}-(C=S)-R^{23} o -NR^{22}-(C=S)-$NR^{23}R^{24}$;

(h) R^{36}, alquenilo (C_2-C_8) o alquinilo (C_2-C_8) {donde cada uno de dichos R^3 alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por -(C=O)-O-alquilo (C_1-C_8), -O-(C=O)-alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), R^{40}, R^{41} y R^{42}};

(i) R^{37}, -NH_2, -NH(alquenilo (C_2-C_8)), -NH(alquinilo (C_2-C_8)), -N(alquil (C_1-C_8))(alquenilo (C_2-C_8)) o -N(alquil (C_1-C_8))(alquinilo (C_2-C_8)) {donde cada uno de dichos R^{26} alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{40}, R^{41} y R^{42}}; o

(j) R^{38};

R^4 se selecciona entre el grupo compuesto por H, F, Br, Cl y alquilo (C_1-C_8);

R^5 se selecciona entre el grupo compuesto por H, alquilo (C_1-C_8), alquil (C_1-C_8)-O- y R^{36};

Cada R^6 y R^7 se selecciona independientemente entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^8 se selecciona entre el grupo compuesto por alquilo (C_1-C_8), alquenilo (C_2-C_8), alquinilo (C_2-C_8), -NH_2, R^{36} y R^{37};

Cada uno de R^9, R^{10} y R^{11} se selecciona independientemente entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^{12} se selecciona entre el grupo compuesto por H, OH, alquilo (C_1-C_8), alquil (C_1-C_8)-O- y R^{36};

R^{13} es H o alquilo (C_1-C_8);

R^{14} se selecciona entre el grupo compuesto por H, alquilo (C_1-C_8), -CH_2-(C=O)-O-alquilo (C_1-C_8) y R^{36};

R^{15} es H o alquilo (C_1-C_8);

R^{16} se selecciona entre el grupo compuesto por H, alquilo (C_1-C_8), alquenilo (C_2-C_8), alquinilo (C_2-C_8), -NH_2, R^{36} y R^{37};

donde cada uno de dichos R^{15} y R^{16}, alquenilo (C_2-C_8) o alquinilo (C_2-C_8) está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{40}, R^{41} y R^{42};

R^{17} se selecciona entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^{18} es alquilo (C_1-C_8) o R^{36};

R^{19}, R^{20} y R^{21} se seleccionan independientemente entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^{22}, R^{23} y R^{24} se seleccionan independientemente entre el grupo compuesto por H, alquilo (C_1-C_8) y R^{36};

R^{25} es H o alquilo (C_1-C_8);

R^{26} se selecciona entre el grupo compuesto por -C(=O)-O-C(CH_3)$_3$, alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

o R^{25} y R^{26} pueden tomarse opcionalmente junto con el nitrógeno al que están unidos para formar un anillo heteroarilo o heterociclilo de 5 a 8 miembros;

R^{27} se selecciona entre el grupo compuesto por alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

R^{28} se selecciona entre el grupo compuesto por alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

R^{29} es H o alquilo (C_1-C_8);

R^{30} es alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10});

o R^{29} y R^{30} pueden tomarse opcionalmente junto con el nitrógeno al que están unidos para formar un anillo heteroarilo o heterociclilo de 5 a 8 miembros;

R^{31} es H o alquilo (C_1-C_8);

R^{32} se selecciona independientemente entre el grupo compuesto por alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

o R^{31} y R^{32} pueden tomarse opcionalmente junto con el átomo de nitrógeno al que están unidos para formar un anillo heteroarilo o heterociclilo de 5 a 8 miembros;

R^{33} es alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10});

R^{34} es alquilo (C_1-C_8), cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10});

Cada R^{35} se selecciona independientemente entre el grupo compuesto por H, F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, -NH-C(=O)-O-$C(CH_3)_3$ y CF_3;

Cada R^{36} se selecciona independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

Cada R^{37} se selecciona independientemente entre el grupo compuesto por:

(a) $-NR^{25}R^{26}$; y

(b) R^{27}-O-;

R^{38} es R^{28}-SO_n-; donde n es 0, 1 ó 2 cuando -SO_n- se une a R^{28} mediante un átomo de carbono R^{28} o donde n es 1 ó 2 cuando -SO_n- se une a R^{28} mediante un átomo de nitrógeno del anillo R^{28};

R^{39} es $R^{29}R^{30}$N-SO_n-; donde n es 1 ó 2;

donde cada uno de dichos alquilo (C_1-C_8), cuando aparezca en cualquiera de dichos R^1(a)-(d), R^2(a)-(d), R^3(a)-(j), R^4, R^{37}, R^{38} o R^{39}, está no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquenilo (C_2-C_8), R^{40}, R^{41} y R^{42};

donde cada uno de dichos cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10}), cuando aparezca en dichos R^{36}, R^{37}, R^{38} o R^{39}, está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre R^{40};

R^{40} se selecciona entre el grupo compuesto por alquilo (C_1-C_8), R^{41}, R^{42} y R^{43};

Cada R^{41} se selecciona independientemente entre el grupo compuesto por F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-NH-C(=O)-O-C(CH_3)_3$, COOH, $-C(=O)$alquilo (C_1-C_8), $-C(=O)-O-$alquilo (C_1-C_8), $-NH-SO_2-$alquilo (C_1-C_8), $-NH-SO_2-$arilo (C_6-C_{10}) y CF_3;

Cada R^{42} se selecciona independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

Cada R^{43} se selecciona independientemente entre el grupo compuesto por:

(a) $-NR^{31}R^{32}$;

(b) $R^{33}-O-$; y

(c) $R^{34}-SO_n-$; donde n es 0,1 ó 2 cuando $-SO_n-$ se une a R^{34} mediante un átomo de carbono R^{34} o donde n es 1 ó 2 cuando $-SO_n-$ se une a R^{34} mediante un átomo de nitrógeno del anillo R^{34};

donde cada uno de dichos alquilo (C_1-C_8), cuando aparezca en cualquiera de R^{40} está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{44} y R^{45};

donde cada uno de dichos cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10}), cuando aparezca en cualquiera de dichos R^{42} o R^{43}, está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{47} seleccionado entre el grupo compuesto por alquilo (C_1-C_8), R^{44} y R^{45};

Cada R^{44} se selecciona independientemente entre el grupo compuesto por F, Cl, Br, I, CN, OH, NO_2, $-NH_2$, $-CF_3$, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O$-alquilo (C_1-C_8), $-(C=O)-O$-alquilo (C_1-C_8), $-O-(C=O)$-alquilo (C_1-C_8), $-(C=O)$-alquilo (C_1-C_8), $-(C=O)-NH_2$, $-(C=O)-NH$-alquilo (C_1-C_8), $-(C=O)-N<$[alquilo (C_1-C_8)]$_2$, $-NH-(C=O)$-alquilo (C_1-C_8), R^{37} y R^{38};

Cada R^{45} se selecciona independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

donde cada uno de dichos alquilo (C_1-C_8) cuando aparezca en cualquiera de dichos R^{44} o R^{45} está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por R^{46} y R^{47};

donde cada uno de dichos cicloalquilo (C_3-C_{10}), heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) o heteroarilo (C_1-C_{10}), cuando aparezca en cualquiera de dichos R^{43} o R^{44} está independientemente no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), R^{46} y R^{47};

Cada R^{46} se selecciona independientemente entre el grupo compuesto por F, Cl, Br, I, CN, OH, NO_2, $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O$-alquilo (C_1-C_8), $-(C=O)-O$-alquilo (C_1-C_8), $-O-(C=O)$-alquilo (C_1-C_8), $-(C=O)$-alquilo (C_1-C_8), $-(C=O)-NH_2$, $-(C=O)-NH$-alquilo (C_1-C_8), $-(C=O)-N<$[alquilo (C_1-C_8)]$_2$, $-NH-(C=O)$-alquilo (C_1-C_8), $-C(=NH)-NH_2$, $-C(=NH)-NH-OH$, $-C(=NH)-NH-O$-alquilo (C_1-C_8), $-(C=O)-O$-alquilo (C_1-C_8), $-O-(C=O)$-alquilo (C_1-C_8), $-(C=O)$-alquilo (C_1-C_8), $-(C=O)-NH_2$, $-(C=O)-NH$-alquilo (C_1-C_8), $-(C=O)-N>$[alquilo (C_1-C_8)]$_2$, $-NH-(C=O)$-alquilo (C_1-C_8), R^{37} y R^{38}; y

Cada R^{47} se selecciona independientemente entre el grupo compuesto por cicloalquilo (C_3-C_{10}); heterociclilo (C_2-C_{10}), arilo (C_6-C_{10}) y heteroarilo (C_1-C_{10});

o una sal farmacéuticamente aceptable del mismo.

2. Un compuesto de acuerdo con la reivindicación 1 en el que R^3 es -NR^{15}-C(=O)-R^{16}, donde R^{16} es cicloalquilo (C_3-C_{10}) no sustituido o sustituido con uno o dos sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, Cl, CN, OH, NH_2, CF_3, heteterociclilo (C_2-C_{10}), arilo (C_6-C_{10}), y heteroarilo (C_1-C_{10}); donde dicho sustituyente arilo (C_6-C_{10}) no está sustituido o está sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), F, Cl, Br, CN, OH y CF_3; y donde dicho sustituyente heterociclilo (C_2-C_{10}) no está sustituido o está sustituido con uno o dos sustituyentes seleccionados independientemente entre el grupo compuesto por alquilo (C_1-C_8), -(C=O)-alquilo (C_1-C_8), -(C=O)-O-alquilo (C_1-C_8), -S-alquilo (C_1-C_8), F, Br, OH, y CF_3.

3. Un compuesto de acuerdo con la reivindicación 1 en el que R^2 es H o alquilo (C_1-C_8) no sustituido o sustituido con uno a cuatro sustituyentes seleccionados independientemente entre el grupo compuesto por OH, -NH_2, alquil (C_1-C_8)-NH-, [alquil (C_1-C_8)]$_2$>N-, heterociclilo (C_2-C_{10}) y heteroarilo (C_1-C_{10}).

4. Un compuesto de acuerdo con la reivindicación 1 en el que X es = O.

5. Un compuesto de acuerdo con la reivindicación 1 en el que el grupo -Y-Z- tiene la fórmula -N=CH-.

6. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre el grupo compuesto por:

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenil-acetamida;

2-Ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida;

3-Fluoro-2-metil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida;

2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-trifluorometil-benzamida;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-Fenil-ciclopropanocarboxílico;

2-(3-Clorofenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida;

1-Acetil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)piperidin-4-carboxamida;

3-(2-Metilfenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida;

(2*S*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-fenil-butiramida compuesto con ácido trifluoroacético;

Trifluoroacetato de (2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

2-Etilsulfanil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-nicotinamida;

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

N-[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fluoro-3-trifluorometil-benzamida;

6-Oxo-2-fenil-*N*-(2-fenilciclopropil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

N-[1-(4-Fluorofenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

3-{6-Oxo-8-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-bencil éster del ácido acético;

[2-(3-hidroximetil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1R,2R)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (sal clorhidrato);

N-[1-(4-Hidroxifenil)etil]-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

2,3-Difluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida;

(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

N-(4-Fluorobencil)-6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

[2-(3-ciclobutilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

[6-oxo-2-(3-pirrolidin-1-ilmetil-fenil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

Trifluoroacetato de *N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,2-*trans*)-2-[6-(trifluorometil)piridin-3-il]ciclopropanocarboxamida;

(2*R*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenil-acetamida (sal clorhidrato);

(2*R*)-2-Amino-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-fenil-propionamida (sal clorhidrato);

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (3*E*)-4-fenil-but-3-enoico;

2-Indan-2-il-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-fluoro-fenil)-ciclopropanocarboxílico;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico (sal clorhidrato);

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-metoxi-fenil)-ciclopropanocarboxílico;

2-Indan-2-il-(6-oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

(2*R*)-2-Hidroxi-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-feniletanamida;

Ácido acético de (6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-2-il-ciclopropanocarboxílico;

Ácido acético de (6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(1*H*-imidazol-4-il)-ciclopropanocarboxílico;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*)-piperidin-2-carboxílico (sal clorhidrato);

Ácido acético de (2*S*)-2-amino-3-ciano-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-propionamida;

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(2*R*)-2-amino-3-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida (sal clorhidrato);

Éster metílico del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2*R*)-3-(4-Hidroxifenil)-2-(metilamino)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida (sal clorhidrato);

(2*R*)-2-Amino-3-(4-fluorofenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida (sal clorhidrato);

Metilamida del ácido (1R,2R)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2-Hidroxi-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2-Dimetilamino-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2*R*)-2-Amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida (sal clorhidrato);

(6-Oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-bromo-fenil)-ciclopropanocarboxílico;

(6-Oxo-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(3-hidroxi-fenil)-ciclopropanocarboxílico;

2-(3,4-Dihidroisoquinolin-2(1H)-il)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida;

(2-Bromo-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[6-Oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida;

N-(6-Oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,2-*trans*)-2-piridin-3-ilciclopropanocarboxamida;

N-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-(1,2-*trans*)-2-piridin-3-ilciclopropanocarboxamida;

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida;

[2-(3-dimetilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-dimetilamino-propil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-dimetilamino-propenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico (sal clorhidrato);

[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1,2-*trans*)-2-piridin-3-il-ciclopropanocarboxílico (sal diclorhidrato);

(2*R*)-2-Amino-2-ciclohexil-*N*-[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida (sal diclorhidrato);

(1,2-*trans*)-*N*-[1-(2-Hidroxietil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fenilciclopropanocarboxamida;

(2-dimetilaminometil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[1-(2-amino-etil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-morfolin-4-il-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[6-oxo-2-(3-pirrolidin-1-il-prop-1-inil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; y

[1-(2-amino-etil)-2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(1*H*-imidazol-2-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Ciano-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; y

[2-(1*H*-imidazol-2-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]-indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; o

una sal o solvato farmacéuticamente aceptable del mismo.

7. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre el grupo compuesto por:

3-Fluoro-2-metil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-benzamida;

2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida;

(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

3-{6-oxo-8-[((1*R*,2*R*)-2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-il}-bencil éster del ácido acético;

[2-(3-hidroximetil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

(6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-ciclobutilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[6-oxo-2-(3-pirrolidin-1-ilmetil-fenil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

2-Indan-2-il-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida;

(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-fluoro-fenil)-ciclopropanocarboxílico;

(2*R*)-2-Amino-3-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida;

Éster metílico del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

Metilamida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2-Hidroxi-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2-Hidroxi-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(2*R*)-2-Amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida;

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido

(1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

2-(3,4-Dihidroisoquinolin-2(1*H*)-il)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida;

2-(3,4-Dihidroisoquinolin-2(1H)-il)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)acetamida;

[6-oxo-2-(1,2,3,6-tetrahidro-piridin-4-il)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-4-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida;

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida;

[2-(3-Dimetilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-Dimetilamino-propenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(3-Metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Amino-2-ciclohexil-*N*-[2-(3-metilamino-prop-1-inil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-acetamida;

(2-Hidroximetil-6-oxo-5,6-dihidro-1*H*-[1,2-*cd*]diazepino[4,5,6]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[6-Oxo-2-(3-pirrolidin-1-il-prop-1-inil)-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

[2-(1*H*-Imidazol-2-il)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Ciano-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; y

Clorhidrato de (2*R*)-2-amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida; o

una sal o solvato farmacéuticamente aceptable del mismo.

8. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre el grupo compuesto por:

2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida;

[2-(3-Hidroximetil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (clorhidrato);

6-Oxo-2-fenil-*N*-[(1*R*)-1-feniletil]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-carboxamida;

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2*R*)-2-Hidroxi-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-feniletanamida;

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-piridin-2-il-ciclopropanocarboxílico (sal del ácido acético);

(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1,2-*trans*)-2-(1*H*-Imidazol-4-il)-ciclopropanocarboxílico (sal del ácido acético);

(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (2*R*)-piperidin-2-carboxílico (sal clorhidrato);

Clorhidrato de (2*R*)-2-amino-3-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)propanamida;

(2-Dimetilamino-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

(6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-hidroxi-fenil)-ciclopropanocarboxílico;

(2-Etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(1*R*,2*R*)-*N*-(6-Oxo-2-piridin-3-il-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-fenilciclopropanocarboxamida; y

[1-(2-Amino-etil)-2-cloro-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; o una sal o solvato farmacéuticamente aceptable del mismo.

9. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre el grupo compuesto por:

2-Fluoro-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-3-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-2-trifluorometil-benzamida;

N-(6-Oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-4-tien-2-ilbutanamida;

N-[2-(3-Dimetilaminometil-fenil)-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il]-2-fluoro-3-trifluorometil-benzamida;

(2*R*)-2-Amino-2-ciclohexil-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-acetamida (clorhidrato);

(6-Oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico;

(2-Dimetilamino-etil)-amida del ácido (1*R*,2*R*)-6-oxo-8-[(2-fenil-ciclopropanocarbonil)-amino]-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-2-carboxílico;

Clorhidrato de (2*R*)-2-amino-2-(4-hidroxifenil)-*N*-(6-oxo-2-fenil-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)etanamida;

(6-Oxo-2-fenil-5,6-dihidro-1-[1,2]diazepino[4,5,6]indol-8-il)-amida del ácido (1,2-*trans*)-2-(4-Hidroxi-fenil)-ciclopropanocarboxílico; y

(2-etil-6-oxo-5,6-dihidro-1*H*-[1,2]diazepino[4,5,6-*cd*]indol-8-il)-amida del ácido (1*R*,2*R*)-2-fenil-ciclopropanocarboxílico; o

una sal o solvato farmacéuticamente aceptable del mismo.

10. Una composición farmacéutica que comprende:

(a) una cantidad eficaz de un agente que inhibe CHK-1 que es un compuesto de acuerdo con la reivindicación 1; o una sal farmacéuticamente aceptable del mismo;

(b) una cantidad eficaz de un agente anti-neoplásico o radiación terapéutica; y

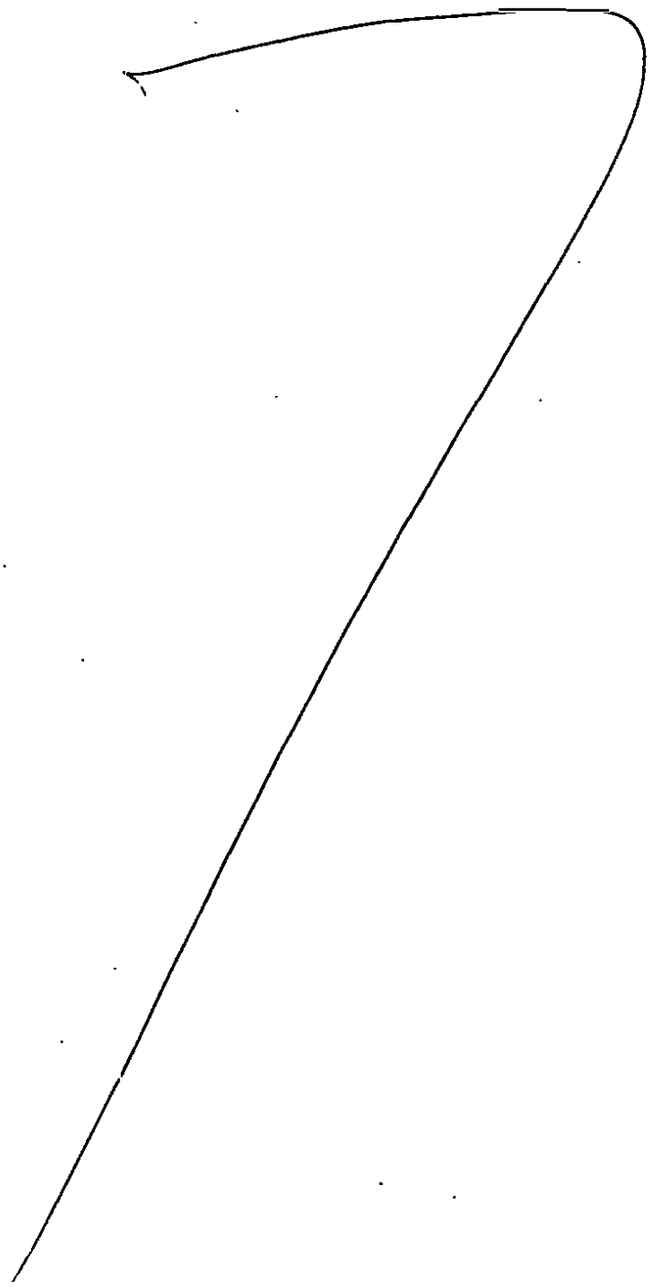
(c) un vehículo farmacéuticamente aceptable para dicho agente que inhibe CHK-1.

11. Una composición que contiene un compuesto de acuerdo con la reivindicación 1 o una sal o solvato farmacéuticamente aceptable del mismo y un agente anti-neoplásico en forma de una preparación combinada para uso simultáneo, separado o secuencial en el tratamiento de un neoplasma.

12. Uso de un agente anti-neoplásico o radiación terapéutica que tiene un efecto anti-neoplásico en combinación con un compuesto de acuerdo con la reivindicación 1 o una sal o solvato farmacéuticamente aceptable del mismo para el tratamiento de un neoplasma en un mamífero.

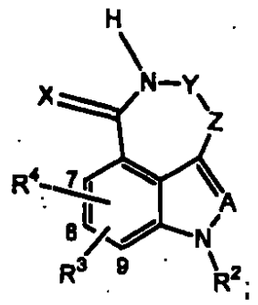
13. Uso de un compuesto de acuerdo con la reivindicación 1 o una sal o solvato farmacéuticamente aceptable del mismo, para el tratamiento de una

afección que puede tratarse mediante la inhibición de proteína quinasas en un mamífero, incluyendo un ser humano.



RESUMEN DE LA DESCRIPCIÓN

Proteína quinasas, tales como CHK-1, que inhiben compuestos tricíclicos de la siguiente fórmula (en la que R^2, R^3 y R^4 son como se han definido en la memoria descriptiva)



composiciones farmacéuticas que contienen cantidades eficaces de dichos compuestos o sus sales son útiles como un único agente o en combinación con un agente anti-neoplásico o radiación terapéutica que tienen un efecto anti-neoplásico para tratar enfermedades o afecciones tales como cánceres.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LUMB, J., Trevor
Pfizer Inc.
201 Tabor Road
Morris Plains, NJ07950
ETATS-UNIS D'AMERIQUE

RECEIVED
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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14.01.2005
Applicant's or agent's file reference: PC25144A	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/000026	05.01.2004	09.01.2003

Applicant
PFIZER INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Ullrich, J

Tel. +49 89 2399-8048

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC25144A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB2004/000026	International filing date *(day/month/year)* 05.01.2004	Priority date *(day/month/year)* 09.01.2003
International Patent Classification (IPC) or both national classification and IPC C07D487/00		
Applicant PFIZER INC. et al.		

1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.02.2004	14.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fritz, M Telephone No. +49 89 2399-2792

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB2004/000026

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-262 as originally filed

Claims, Numbers

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/IB2004/000026

II. Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☒ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12-13

   because:

   ☒ the said international application, or the said claims Nos. 12-13 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	

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Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO A 02/44183
D2: WO A 00/42040

The present application relates to compounds of the general formula I (claims 1-9), pharmaceutical compositions thereof (claims 10-11) and a method of treatment by administering the compounds I (claims 12-13).

For the assessment of the present claims 12-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The compounds I belong to a known class of substances representatives of which are known from e.g. D1 and D2.

The compounds according to ex. 1-1 to 6-1 of D2 (which are themselves representatives of the compounds I-1 according to claim 5 of D2) have a substitution system which is different from the compounds I according to the present case (e.g. the benzo-moiety of the latter is substituted by a group R^3; this is not the case in the known compounds).

The compound according to ex. AAAA of D2 is structurally extremely close to the com-

pounds I of the present case; the only diference is the absence of a substituent at the benzo-moiety.

The subject-matter of claims 1-11 according to the present case is therefore novel in the sense of Article 33(2) PCT.

The problem of the present application was to provide further compounds inhibiting protein kinases, preferably CHK-1.

This problem has been solved, as is evident from the descripion.

The compounds disclosed in D1 and D2 are - as the compounds I of the present case - useful against cancer, they are - however - characterized as being PARP inhibitors. By consequence the compounds I according to the present case cannot be considered obvious over D1 and D2, and an inventive step in the sense of Article 33(3) PCT is acknowledged for the subject-matter of claims 1-11.

Furthermore the following objections are raised:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 is not mentioned in the description, nor are these documents identified therein.

The terms "(C_2-C_{10})heterocyclyl" and "(C_1-C_{10})heteroaryl" used in the claims are chemically not reasonable and should be corrected (Article 6 PCT).

The definitions of "cycloalkyl" and "heterocyclyl" found in he description on p. 22 ff. should be inserted in the claims (Art. 6 PCT).

The vague and imprecise expression "equivalents" employed in the description on page 262 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

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UNDER THE PATENT COOPERATION TREATY
IN THE INTERNATIONAL BUREAU

IN RE APPLICATION OF: PFIZER INC.
INTERNATIONAL APPLICATION NO: PCT/IB2004/000026
INTERNATIONAL FILING DATE: 05 JANUARY 2004 (05.01.04)
PRIORITY DATE(S) CLAIMED: 09 JANUARY 2003 (09.01.2003)
FOR: TRICYCLIC COMPOUNDS PROTEIN KINASE INHIBITORS FOR ENHANCING THE EFFICACY OF ANTINEOPLASTIC AGENTS AND RADIATION THERAPY
OUR REF.: PC25144A

World Intellectual Property Organization
34 chemin des Colombettes
CH-1211 Geneva 20
Switzerland

RE: Adding Inventor(s) to the International Application

The Applicant, Pfizer Inc., of 235 East 42nd Street, New York, New York 10017, United States of America, respectfully requests that two additional inventors, Yong WANG and Jinjiang ZHU, of Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive, San Diego, California 92121, United States of America, be added to the above-identified International Patent Application. We enclose a new sheet no.2 and 3 of the PCT Request giving full details of the additional inventors.

We are enclosing a case specific Power of Attorney for Yong WANG and Jinjiang ZHU.

Should additional fees be payable in respect to the addition of the above-identified inventor, we would be grateful if you would debit Deposit Account No. 17992 in the name of Pfizer Inc.

If you have any questions or need further assistance, please feel free to contact me at:

Tel: (212) 573-1390 Fax: (973) 385-7330 Email: grover.f.fuller@pfizer.com

Respectfully submitted,

Date 28 June 2005 (28.06.2005)

Grover F. Fuller Jr.
For and on behalf of PFIZER INC.
And as agent for all other applicants

Pfizer Inc.
201 Tabor Road
Morris Plains, New Jersey 07950
United States of America

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Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address:

BENNETT, Michael John
Agouron Pharmaceuticals, Inc.,
A Pfizer Company, 10777 Science Center Drive
San Diego, California 92121
United States of America

This person is:

☐ applicant only
☒ applicant and inventor
☐ inventor only

State of nationality: US

State of residence: US

This person is applicant for the purposes of:

☐ all designated States
☐ all designated States except the United States of America
☒ the United States of America only
☐ the States indicated in the Supplemental Box

Name and address:

RUI, Yuanjin
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United States of America

This person is:

☐ applicant only
☒ applicant and inventor
☐ inventor only

State of nationality: CN

State of residence: US

This person is applicant for the purposes of:

☐ all designated States
☐ all designated States except the United States of America
☒ the United States of America only
☐ the States indicated in the Supplemental Box

Name and address:

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San Diego, California 92121
United States of America

This person is:

☐ applicant only
☒ applicant and inventor
☐ inventor only

State of nationality: CN

State of residence: US

This person is applicant for the purposes of:

☐ all designated States
☐ all designated States except the United States of America
☒ the United States of America only
☐ the States indicated in the Supplemental Box

Name and address:

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United States of America

This person is:

☐ applicant only
☒ applicant and inventor
☐ inventor only

State of nationality: US

State of residence: US

This person is applicant for the purposes of:

☐ all designated States
☐ all designated States except the United States of America
☒ the United States of America only
☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

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Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address:	This person is:
TENG, Min Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive San Diego, California 92121 United States of America	☐ applicant only ☒ applicant and inventor ☐ inventor only

State of nationality:	State of residence:
US	US

This person is applicant for the purposes of:	☐ all designated States	☐ all designated States except the United States of America	☒ the United States of America only	☐ the States indicated in the Supplemental Box

Name and address:	This person is:
WANG, Yong Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive San Diego, California 92121 United States of America	☐ applicant only ☒ applicant and inventor ☐ inventor only

State of nationality:	State of residence:
CN	US

This person is applicant for the purposes of:	☐ all designated States	☐ all designated States except the United States of America	☒ the United States of America only	☐ the States indicated in the Supplemental Box

Name and address:	This person is:
ZHU, Jinjiang Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive San Diego, California 92121 United States of America	☐ applicant only ☒ applicant and inventor ☐ inventor only

State of nationality:	State of residence:
CA	US

This person is applicant for the purposes of:	☐ all designated States	☐ all designated States except the United States of America	☒ the United States of America only	☐ the States indicated in the Supplemental Box

Name and address:	This person is:
	☐ applicant only ☐ applicant and inventor ☐ inventor only

State of nationality:	State of residence:

This person is applicant for the purposes of:	☐ all designated States	☐ all designated States except the United States of America	☐ the United States of America only	☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

LUMB, J., Trevor
Pfizer Inc.
201 Tabor Road
Morris Plains, NJ 07950
United States of America

RECEIVED
MAY 2004
PATENT DEPT

Date of mailing (day/month/year) 22 April 2004 (22.04.2004)	
Applicant's or agent's file reference PC25144A	**IMPORTANT NOTIFICATION**
International application No. PCT/IB2004/000026	**International filing date** (day/month/year) 05 January 2004 (05.01.2004)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
TENG, Min Agouron Pharmaceuticals, Inc. A Pfizer Company 10777 Science Center Drive San Diego, CA 92121 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Additional inventor and applicant for US only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Fabienne SOCIÉ
Facsimile No. (41-22) 338.70.60	Telephone No. (41-22) 338 9175

Form PCT/IB/306 (March 1994) 006217421

INTERNATIONAL SEARCH REPORT

PCT/IB2004/000026

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/06 A61P35/00 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/44183 A (LI JIA HE ;ZHANG JIE (US); FERRARIS DANA V (US); GUILFORD PHARM IN) 6 June 2002 (2002-06-06) Cpds. I-1; ex. 1-1 to 6-1 claim 5	1-13
A	WO 00/42040 A (CANCER RES CAMPAIGN TECH ;CANAN KOCH STACIE S (US); WEBBER STEPHEN) 20 July 2000 (2000-07-20) Cpds. (III); ex. AAAA	1-13

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

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 2004	07/05/2004

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL – 2280 HV Rijswijk
Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,
Fax: (+31–70) 340–3016

Authorized officer
Fritz, M

INTERNATIONAL SEARCH REPORT

PCT/IB2004/000026

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0244183 A	06-06--2002	AU 3652102 A	11-06-2002
		CA 2430363 A1	06-06-2002
		EP 1339402 A2	03-09-2003
		WO 0244183 A2	06-06-2002
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		LV 12770 A ,B	20-12-2001
		NO 20013313 A	10-09-2001
		NZ 512731 A	30-01-2004
		SI 20691 A	30-04-2002
		SK 9662001 A3	04-04-2002
		TR 200102005 T2	21-12-2001
		WO 0042040 A1	20-07-2000
		US 2003078254 A1	24-04-2003
		US 6495541 B1	17-12-2002
		ZA 200105399 A	01-07-2002

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADO
PATENTE DE INVENCIÓN . MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	( )	( )
- Representación gráfica o fotográfice del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
- Representación gráfica del esquema de trazado	( )	( )
- Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05065794 00000000 Folios: 758
Fecha (ANO): 2005-07-05 15:58:37
Tramite : 011 PCT-PATENT 3/9 FASE NACI 411 PRESENTAC
Dependencia: 3020 DIVISION DE NUEVAS CREACIONES

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760

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO

REFERENCIA	Radicación No.	5 65794
	Solicitud internacional	IB2004/000026
	Fecha inicio fase nacional	09/08/2005
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	09717

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. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

3. Aclarar el motivo por el cual el Señor J. Trevor Lumb aparece con diferentes cargos en distintas compañías: Secretario Asistente con Pharmacia & Upjohn Company, Vicepresidente con Pfizer Products Inc, Asistente General Consejero de Patentes en Pfizer Inc, Secretario Asistente con Warner Lambert Company LLC.

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 DESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 28 OCT 2005
adpa1